Novel Cyclisations of Nitro Compounds for Heterocyclic Synthesis

by

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Research Supervisor : Dr G. W. Weaver

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Dedication

This research work is dedicated to my late Father

and my dear Mother

Acknowledgements

My sincere gratitude to Dr. G. W. Weaver for his guidance, encouragement, enthusiastic supervision, invaluable advice and friendship throughout the duration of this research project.

I am thankful to EPSRC for the studentship.

An immeasurable debt of appreciation is due to past and present occupants of laboratories F001, F009 and F401, which include members of the Marples, Page, Bowman, Christie and Allin research groups for their help and generous supplies of apparatus and reagents. I am grateful to my group members for their friendship and humour.

I would like to thank my family for their support and patience throughout these studies.

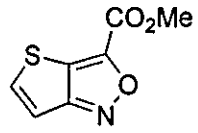
I would like to record a special thanks to the technical staff for all their assistance. They include Dr A.M.Z Slawin (University of St. Andrews) for X-ray crystallography, Dr T.A.D. Smith for NMR spectroscopy, Mr A. Daley for elemental analysis and Mr J. Kershaw for mass spectrometry. I would also like to thank Miss V. Coote for proof reading this thesis.

Abstract

The research described in this thesis is aimed at developing novel methods of synthesis for heterocyclic compounds, in particular cyclisation reactions involving the nitro functional group.

The first chapter describes investigations into the Wallach imidazole synthesis. A number of chloroimidazoles were prepared, but the possible extension to highly functionalised imidazoles proved elusive.

The second chapter describes studies on the successful conversion of nitroimidazolyl malonates **1** into imidazo[4,5-*c*]isoxazoles **2, Scheme 1**. Related cyclisations are described in chapter three and the thiophene fused isoxazole **3** was successfully prepared.



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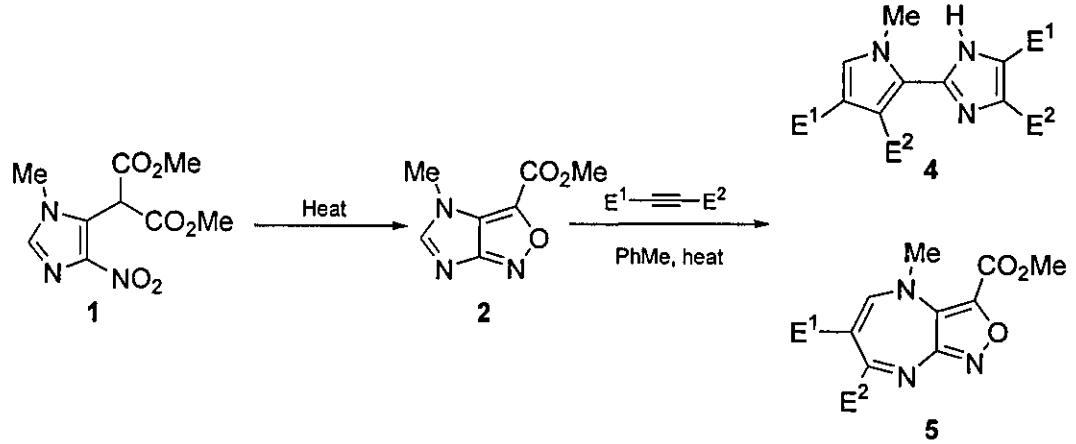
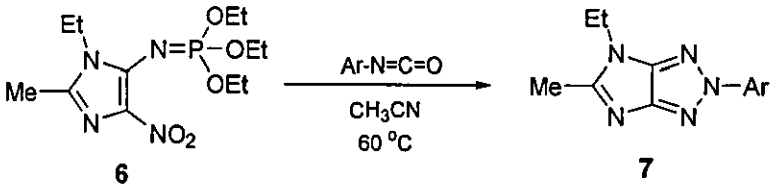
Chapter four investigates the reactivity of the strained imidazo[4,5-*c*]isoxazole heterocycles. Ring opening of the isoxazole occurred on reaction with phosphines to give iminophosphorane derivatives. Reactions with electron deficient acetylenes led to pyrrolyl imidazoles **4**, and a novel [1,4]diazepino[2,3-*c*]isoxazole **5**, **Scheme 1** but no reaction was observed with alkenes.



Scheme 1

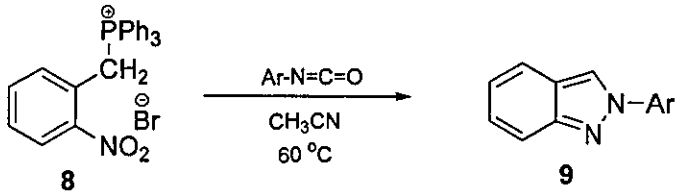
Chapter five entails synthesis of a series of 5-aryl-2*H*,1*H*-imidazo[4,5-*d*][1,2,3]triazole derivatives **7**. Triethyl *N*-1-ethyl-2-methyl-4-nitro-1*H*-imidazol-5-yl phosphoramidate compound **6** was treated with a range of aryl isocyanates which gave imidazo[4,5-*c*]triazoles **7** in moderate to good yields. A mechanism involving carbodiimide formation was postulated and was supported using infra-red spectroscopy, **Scheme 2**.



6 **7**

Scheme 2

Chapter six reports a new synthesis of 5-aryl-2*H* indazole derivatives **9** by base catalysed reaction of 2-nitrobenzyl triphenylphosphonium bromide salts **8** with a range of aryl isocyanates. A mechanism of this reaction was proposed and investigated by infra-red spectroscopy, **Scheme 3**.



8 **9**

Scheme 3

Abbreviations

- **A.I.B.N** -2,2 Azobisisobutyronitrile
- **Aq.** -Aqueous
- **b.p** -Boiling point
- ***n*-BuLi** -*normal*-Butyl lithium
- ***t*-Bu** -*tertiary*-Butyl
- **$CDCl_3$** -Deutrated chloroform
- **cm^3** -Cubic centimetres
- **Conc** -Concentrated
- **DAST** -Diethyl aminosulphur trifluoride
- **DCM** -Dichloromethane
- **DBU** -1,5-Diazabicyclo[4.3.0]non-5-ene
- **DMAD** -Dimethyl acetylenedicarboxylate
- **DMF** -Dimethylformamide
- **DMSO** -Dimethylsulphoxide
- **DNA** -Deoxyribose nucleic acid
- **EI** -Electron Impact
- **eq.** -Equivalents
- **Et** -Ethyl
- **EtOAc** -Ethyl Acetate
- **EtOH** -Ethanol
- **h** -Hour(s)
- **HOMO** -Highest Occupied Molecular Orbital

- **Hz** -Hertz
- **I.R** -Infrared Spectroscopy
- **Lit** -Literature
- **g** -Grams
- **MeOH** -Methanol
- **Me** -Methyl
- **MCPBA** -*meta*-Chloroperoxybenzoic acid
- **min** -Minute(s)
- **ml** -Millilitre(s)
- **mmol** -Millimole(s)
- **m.p** -Melting Point
- **NBS** -N-bromosuccinimide
- **N.M.R** -Nuclear Magnetic Resonance Spectroscopy
- **P.E** -Petroleum Ether(40/60)
- **Ph** -Phenyl
- **R.T** -Room Temperature
- **TFA** -Trifluoroacetic acid
- **TFAA** -Trifluoroacetic acid anhydride
- **THF** -Tetrahydrofuran
- **T.L.C** -Thin layer chromatography
- **TMS** -Trimethylsilyl

Contents

Chapter 1

Introduction and Studies on the Wallach imidazole synthesis

1.0 Introduction

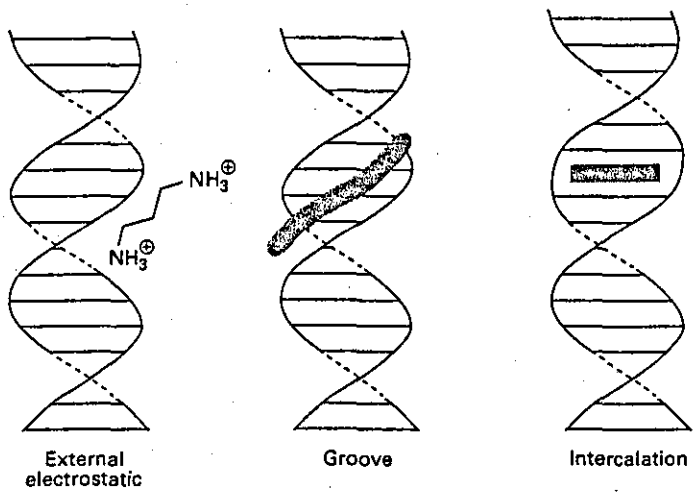
1.1 General introduction

Molecules that bind to nucleic acids by non-covalent interactions have potential as therapeutic agents, tools for molecular biology and probing the structure of DNA coiling and packing[1]. Molecules and ions in this group represent a wide range of chemical types from simple to complex, metal species, a variety of drugs, carcinogens, and complex antibiotics.

One important feature of reversible interactions on nucleic acid structure and function is drug development and chemotherapy against cancers, viral, and parasitic diseases. This involves drugs interacting reversibly with nucleic acids. Natural antibiotics such as adriamycin and synthetic drugs such as amsacrine which interact with DNA are widely used in clinical treatment of a range of neoplastic diseases. Further knowledge of the mode of action of medicinal agents may help develop a new generation of superior selective drugs. New approaches to drug design is focused on synthetic heterocyclic chemistry as nucleic acid recognising drugs.

1.2 Reversible interactions with nucleic acids

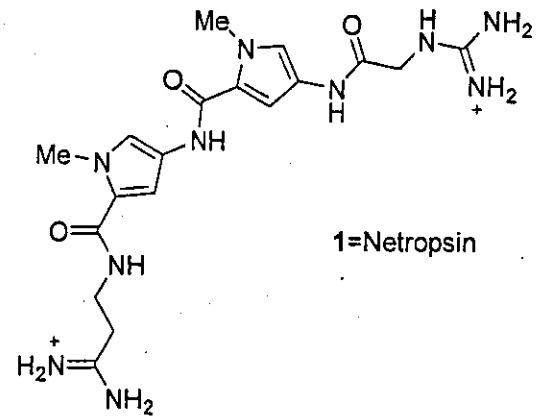
Many heterocyclic molecules interact with duplex nucleic acids by either covalent interactions or reversible interactions. Reversible interactions include external electrostatic interactions, binding on the exterior of the DNA helix such as groove binding, involving direct interactions of the bound molecule with edges of the base-pairs in either of the major and minor grooves of the nucleic acids, and intercalation of planar aromatic rings between base pairs of the DNA. **Figure 1.1**, shows three modes of reversible interactions and examples of cations that bind by the three modes.



a) External, electrostatic interations

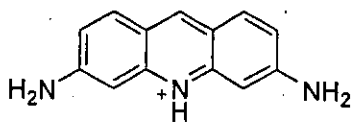
Na^+ Mg^{2+} $H_3\overset{+}{N}CH_2CH_2CH_2\overset{+}{N}H_3$

b) Groove-binding



1=Netropsin

c) Intercalation



2=Proflavine

Figure 1.1

Groove binding molecules

Distamycin **3** is a typical molecule which interacts with DNA by this mechanism, **Figure 1.2**. The major and minor grooves differ in electrostatic potential, hydrogen bonding characteristics, steric effects, and hydration. Binding in this manner can affect the three dimensional structure of DNA and the ease with which the DNA chains can separate.

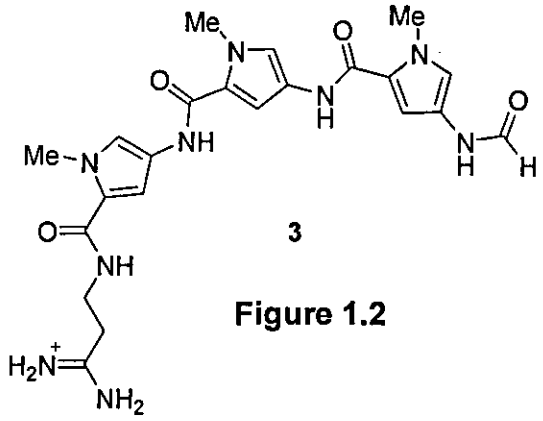


Figure 1.2

DNA cleavage reagents

Molecules that cleave nucleic acids are well known. One DNA cleavage compound is the glycopeptide antibiotic and anti-cancer drug bleomycin A2, **4**, **Figure 1.3**. The 2,4'-bithiazole rings and the cationic side chain direct the binding of the bleomycin to DNA and the remaining portion of the molecule provides a metal complexing domain which is responsible for DNA strand cleavage.

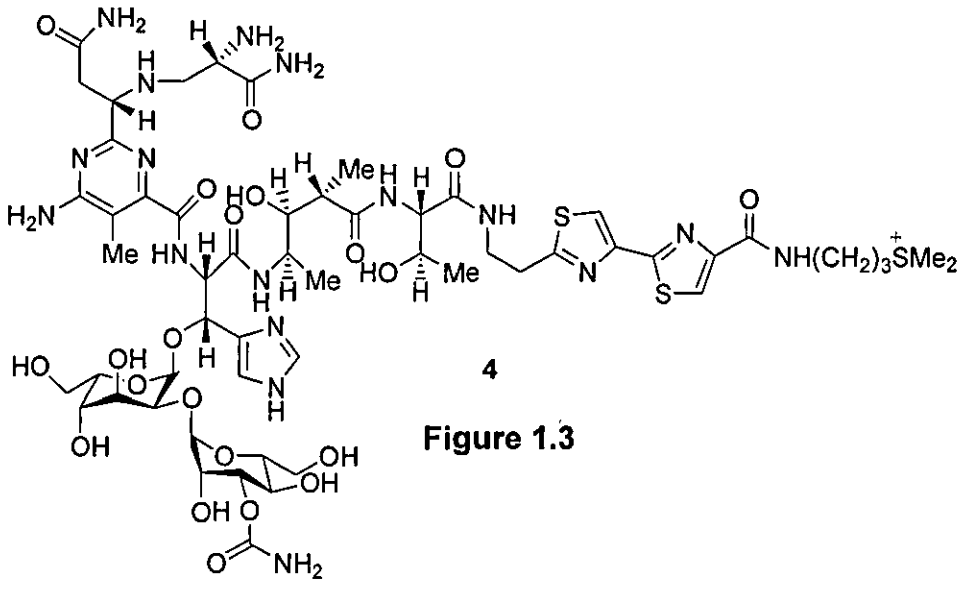


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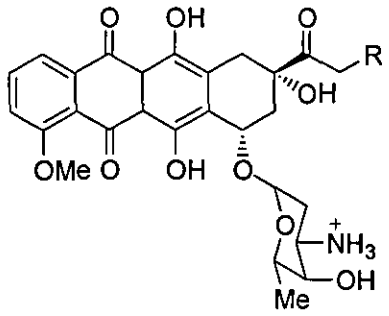
Figure 1.3

Intercalation

Planar aromatic molecules can bind to DNA by a process of intercalation in which the molecule is accommodated between nucleic acid base-pairs. They may have non-planar counterparts, either cationic or neutral, which protrude into one of the DNA grooves. The generation of the site extends the DNA duplex and causes unwinding of the base-pairs and other distortions. Examples of natural anthracycline intercalators are the antibiotics, daunomycin **5** and adriamycin **6**, **Figure 1.4** and synthetic intercalators such as proflavine **2**, **Figure 1.1**.

Bisintercalators are two covalently linked intercalating ring systems with connecting chains of variable length and rigidity. The interaction of the ring systems with DNA base-pairs is controlled to a large extent by the characteristics of the linker. Synthetic bisintercalators with short linkers, can bind to DNA in violation of neighbour exclusion. An example of such a molecule is the acridine bis-intercalator **7**, **Figure 1.5**.



R=H, Daunomycin **5**
R=OH, Adriamycin **6**

Figure 1.4

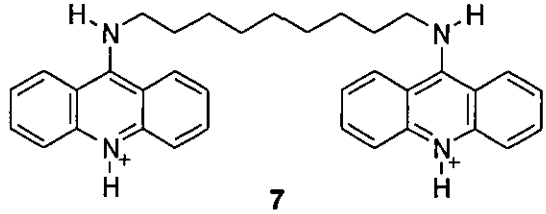


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Figure 1.5

There has been recent interest[2] in construction of intercalators bearing more than one heterocyclic binding domains, linked by rigid or flexible chains of various lengths. These molecules have a greater advantage for tighter binding to DNA due to the chelate effect. Variation of chain length allows spanning of base pairs, or linking into more than one DNA strand. This allows investigation into sequence binding specificity and into three dimensional structure of DNA.

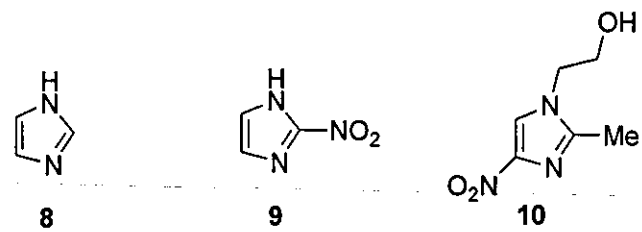
Molecules that are sequence specific and exhibit tighter binding have a great potential in cancer chemotherapy as lower doses can be administered, reducing the undesirable side effects associated with most treatments. The majority of such molecules are heterocyclic, and the importance of those biologically active compounds provides a driving force for the continued investigation into new and improved methods of heterocyclic synthesis-the broad topic of this thesis.

1.3 Imidazole synthesis

Our work is primarily related to synthesis of substituted imidazoles. Imidazoles[3] are planar heterocycles containing two non adjacent nitrogen atoms and having considerable resonance energy. The ring is present in many natural products such as the essential amino acid, histidine and histamine. Imidazole **8, Figure 1.6** can both act as an acid and a base. Imidazole is a moderately strong organic base (pK_a 7.0) and also a weak acid (pK_a 14.5).

The imidazole ring system has a broad range of uses. These include the drug cimetidine which was designed around the structure of histamine that would selectively block H_2 receptor sites for the treatment of peptic ulcer.

Several other classes of drugs are based on the imidazole ring. 2-Nitroimidazole (azomycin) **9** is a naturally occurring antibiotic. Nitroimidazoles[4] are antibiotics used clinically for anaerobic bacterial and protozoal intestinal infections, and anticancer chemotherapy. The biological mode of action of these compounds has not been proven, though nitroimidazoles are believed to be reduced *in vivo* prior to the reaction between the drug and the biological target. There are three possible structural isomers with the nitro group at *C*-2, *C*-4, or *C*-5 of the imidazole ring. In the 1960's there was a great advance in the field of chemotherapy of microbial infections as the compound metronidiazole **10**, a drug used for protozoal infections and as a radiosensitiser in X-ray therapy was introduced. Metronidiazole is still in wide use today because of its effectiveness, short duration of therapy and selective toxicity. However many other 2- or 5-nitroimidazoles have been developed. There are more 5-nitroimidazole drugs than there are 2-nitroimidazoles due to the greater therapeutic activity of the former.



8 **9** **10**

Figure 1.6

Other examples of drugs incorporating the imidazole nucleus are antifungal agents; these include bifonazole **11** and clotrimazole **12**, **Figure 1.7**.

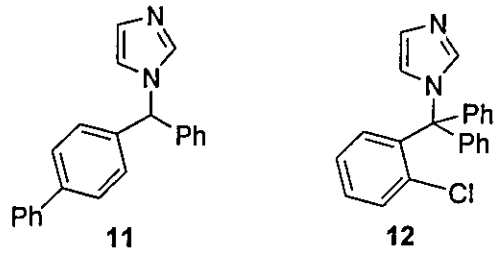
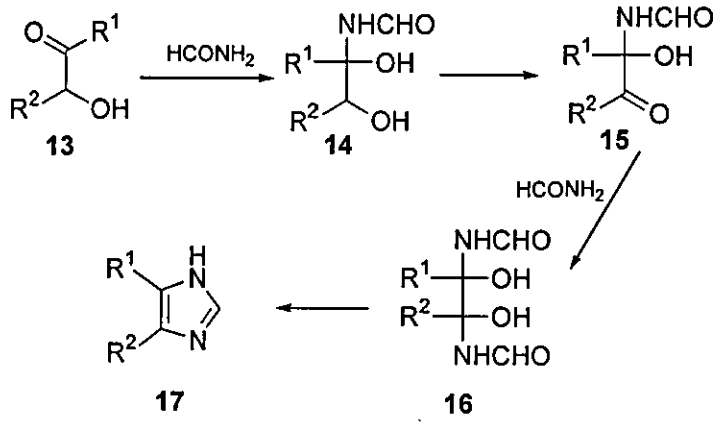


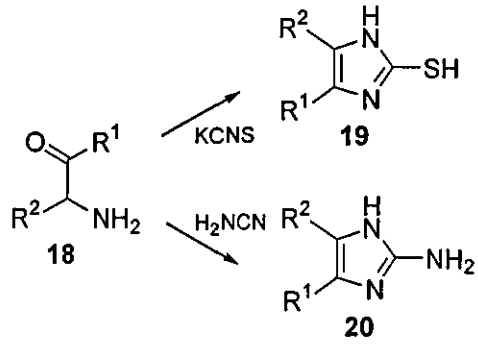
Figure 1.7

1.4 Examples of imidazole ring synthesis

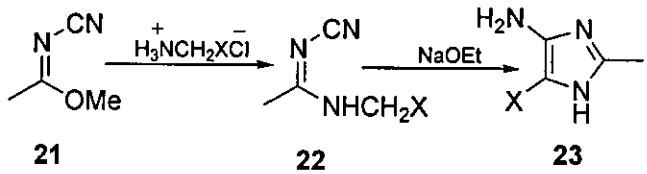
There are several methods of preparing imidazoles and a variety of cyclisation reactions are known to produce specifically substituted imidazoles. Examples include the Bredereck reaction[5], in which an α-hydroxyketone **13** or an α-haloketone is heated with formamide to give a 2-unsubstituted imidazole **17**, **Scheme 1**. α-Aminoketones **18** are intermediates in the synthesis of several types of imidazoles; reactions with thiocyanates and cyanamide give imidazole-2-thiols **19** (the *Marchwald* synthesis[6]) and 2-aminoimidazoles **20** respectively, **Scheme 2**. Another cyclisation route to 4-aminoimidazoles[6] **23** is shown in **Scheme 3**.



Scheme 1



Scheme 2



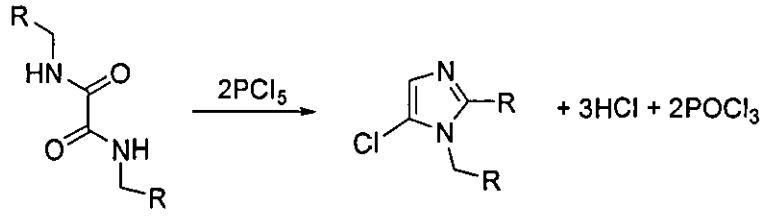
X= CN or CO_2Et

Scheme 3

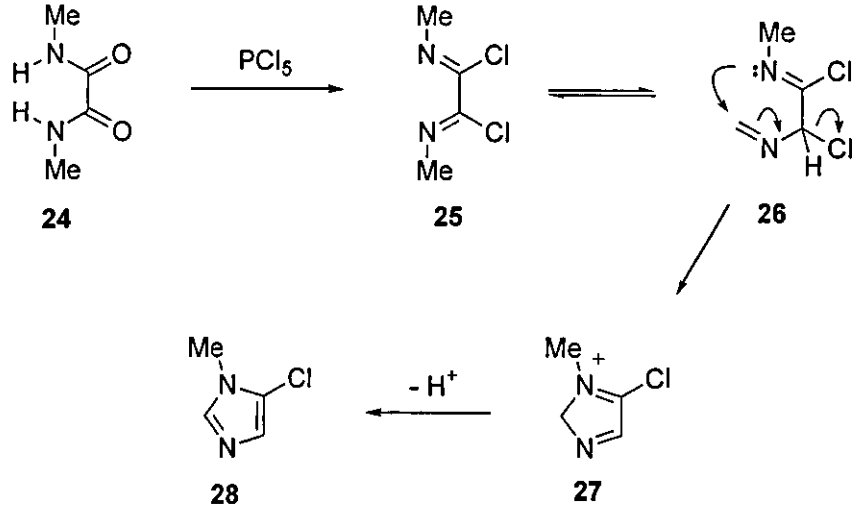
1.5 Wallach Imidazole synthesis

The synthesis of the imidazole derivatives studied in this work is based around the reaction shown in **Scheme 4**. This unusual reaction was first described by Wallach as long ago as 1882 and has received little attention in the literature. The mechanism is still not clearly understood although recent work[7] has shown nitrile ylides to be involved at least in the case of aryl substituted compounds. The reaction has not fully been exploited for the synthesis of heterocyclic compounds. Importantly, no examples have been described which incorporate more than one imidazole ring into a molecule by this reaction. Studying the full scope and developing an understanding of the basic mechanism of the Wallach cyclisation was one of the aims of research described in this chapter. One proposed mechanism for this reaction is detailed in **Scheme 5**. This involves formation of the bis iminoyl chloride **25**. If this is in tautomeric equilibrium with **26,** 5-*endo*-trig cyclisation can occur by attack of the methyl imine nitrogen on to

the methylene imine carbon atom. This in turn leads to loss of chloride from what became *C*-4 of the imidazole product. Loss of a proton from **27** then allows aromatisation of the 5-chloroimidazole product **28**.



Scheme 4



Scheme 5

Early investigations into this imidazole synthesis dealt with the chemistry of the chloroimidazoles which result when symmetrical oxamides are subjected to phosphorus pentachloride. Wallach, the founder of this reaction, named the compound resulting from the reaction of *sym*-dimethyloxamide and phosphorus pentachloride "chloroxalmethylin" and that resulting from *sym*-diethyloxamide "chloroxalethylin".[8-14] Chloroxalmethylin is 1-methyl-5-chloro-1*H*-imidazole and chloroxalethylin is 1-ethyl-5-chloro-1*H*-imidazole[15,16] which have recently become of some importance as useful

starting materials for the preparation of certain purines.[16,17] The position of the chlorine atoms was established[15] in 1924, although the compounds had been known since 1882. The Wallach procedure for the preparation of chloroimidazoles is limited to these two cases. Higher oxamides either failed to give imidazoles on treatment with phosphorus pentachloride, or they give extremely poor yields.[8]

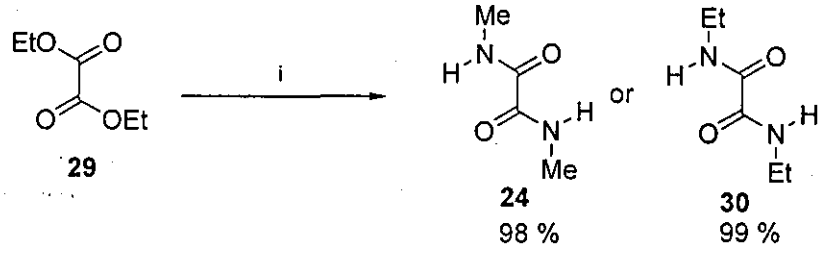
Another route to chloroimidazoles involved treating acylated glycine derivatives with phosphorus pentachloride. Benzoyl-glycine ethylamide and benzoylglycine anilide afford 1-ethyl-2-phenyl-5-chloroimidazole and 1,2 diphenyl-5-chloroimidazole[17,18] respectively.

1.6 Results and Discussion

1.6.1 Wallach imidazole synthesis

In order to study the Wallach imidazole synthesis and to investigate the use of solvents and other reagents to affect imidazole formation a range of substituted oxamides were first prepared.

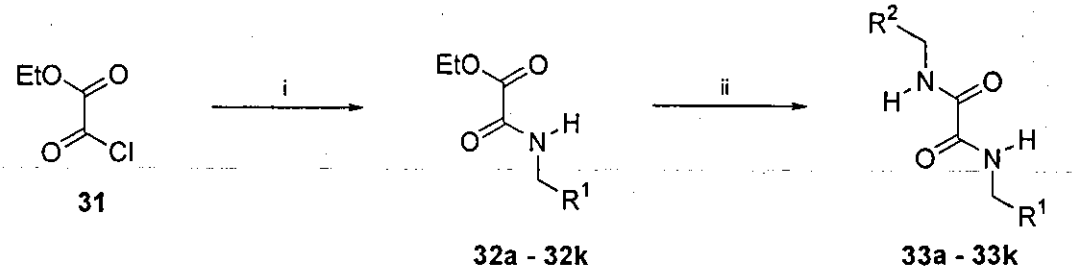
Dimethyloxamide **24** or diethyl oxamide **30** were prepared in excellent yield by the reaction of diethyl oxalate **29** with aqueous methylamine or ethylamine solution at 0 °C by simple addition of the ester and collection of the precipitated product. This yielded the oxamides **24** or **30** in excellent yield, **Scheme 6**.



Reagents and conditions: i, $MeNH_2$ (aq) or $EtNH_2$ (aq), H_2O.

Scheme 6

Substituted oxamides were also prepared in excellent yields ranging from 47-100 %. Some of the samples prepared existed as rotamers. These were prepared by reacting ethyl oxalyl chloride **31** with substituted amines in dichloromethane at 0 °C. This gave the oxamate products **32a–32k**. Subsequently these were reacted in either dichloromethane, or methanol at 0 °C with a second amine to give the oxamides (**33a-33k**) in excellent yield, **Scheme 7** and **Table 1.1**.



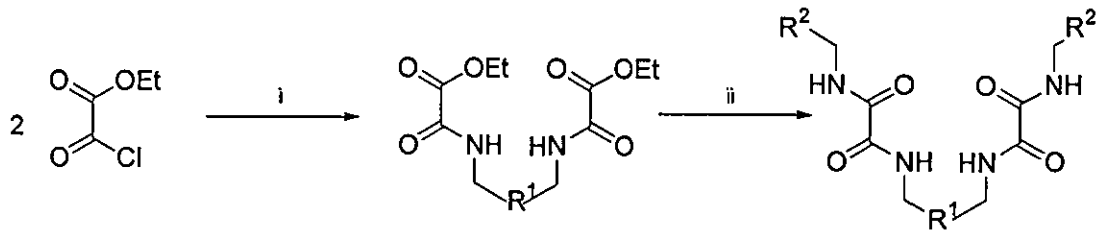
Reagents and conditions: i, R^1NH_2, Et_3N, DCM; ii, R^2NH_2, DCM or MeOH.

Scheme 7

R^1	Yield (%)	R^2	Yield (%)
32a phenyl	100	**33a** H	89
32b 2-pyridyl	100	**33b** H	94
32c 3-pyridyl	96	**33c** H	84
32d 4-pyridyl	100	**33d** H	95
32e trifluoromethyl	100	**33e** H	100
32f *t*-butyl	99	**33f** H	87
32g nitrile	100	**33g** H	100
32h *t*-butyl	99	**33h** phenyl	66
32i trifluoromethyl	100	**33i** phenyl	100
32j trifluromethyl	100	**33j** 2-pyridyl	47
32k 2-pyridyl	100	**33k** methanol	98

Table 1.1

In order to prepare a range of chloroimidazoles linked together, ethyl oxalyl chloride was also treated with 1,6 diaminohexane to give the bis oxamate derivative **34** in good yield. Treatment with a second amine gave the linked oxamides **35a** and **35b** in good yield, **Scheme 8** and **Table 1.2.**



Reagents and conditions: i, $H_2NR^1NH_2$, Et_3N, DCM; ii, R^2NH_2, DCM or MeOH.

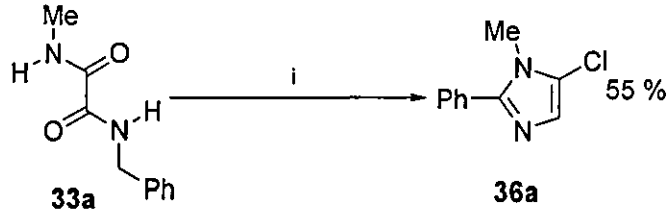
Scheme 8

R^1	Yield (%)	R^2	Yield (%)
hex-1,6-diyl **34**	89	**35a** methyl	99
hex-1,6-diyl **34**	89	**35b** methyl-2-pyridyl	97

Table 1.2

Oxamides compounds such as **33a-33k** were subjected to the Wallach cyclisation to form substituted imidazoles as reported by Wallach,[8-14] Kochergin,[19] Godefroi[20] and Trout.[21] Wallach's original procedure involved grinding the oxamide with solid phosphorus pentachloride with no solvent. This initiated an exothermic reaction which generated phosphorus oxychloride which causes the mixture to liquify. It was then heated at 100 °C for 6 h. This process however results in considerable tar formation. Higher un-symmetrical substituted imidazoles could not be prepared by this method. Later reports[7,19] suggested that using phosphorus pentachloride with phosphorus oxychloride as a solvent improved yields of the preparation of higher substituted imidazoles from higher un-symmetrical oxamides.

We first carried out the Wallach cyclisation on compound **33a** using the methodology adopted by Godefroi,[20] using phosphorus pentachloride with phosphorus oxychloride as the solvent and heating under reflux. This gave product **36a** in 55 % yield, **Scheme 9**.



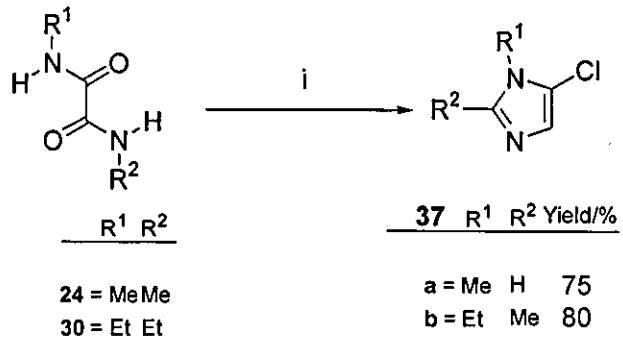
33a **36a**

Reagents and conditions: i, 2.1 PCl_5, $POCl_3$, Reflux.

Scheme 9

It was then decided to investigate other solvents for the reaction to try to improve the yields and the convenience of the procedure, and to minimise tar formation. We tried initially the use of acetonitrile as an alternative solvent in place of the high boiling, toxic

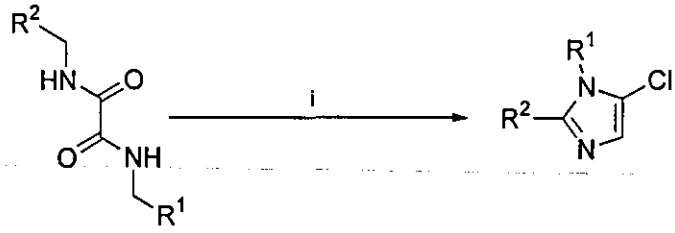
and corrosive phosphorus oxychloride. Oxamides **24** and **30** was treated with 2.5 eq. of phosphorus pentachloride in dry acetonitrile. Refluxing for 3 h and purification by distillation under reduced pressure gave imidazoles **37a** and **37b, Scheme 10**. This reaction was carried out several times to produce **37a** and **37b** on a large scale as this was an important compound that was used and exploited throughout the research to prepare many novel heterocycles. The yields for these reactions, **Scheme 10** were 75 % and 80 % respectively.



Reagents and conditions: i, 2.5 PCl_5, CH_3CN, Reflux.

Scheme 10

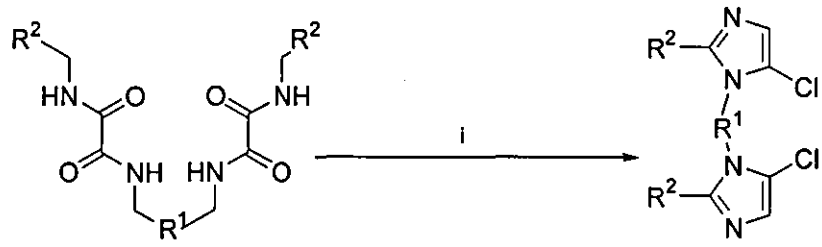
This modified Wallach reaction was utilised for the reaction with phosphorus pentachloride with the higher oxamides **33a - 33k** and **35a - 35b** prepared. However disappointingly under the new conditions used, only a few of the functionalised oxamides under went cyclisation to afford substituted imidazoles. In most cases starting material were recovered. **Schemes 11, 12** and **Table 1.3** show the outcome of the cyclisation reactions. This may infer that higher un-symmetrical di-amides does not work effectively under the conditions we have described.



33a - 33k **36a - 36k**

Reagents and conditions: i, 2.5 PCl_5, CH_3CN, Reflux.

Scheme 11



35a and **35b** **38a** and **38b**

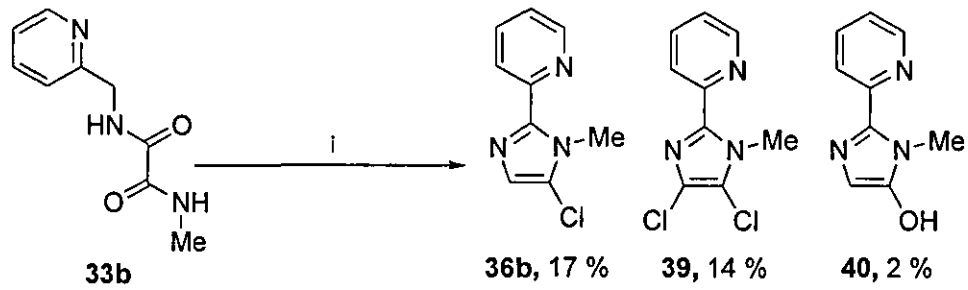
Reagents and conditions: i, 4.5 PCl_5, CH_3CN, Reflux.

Scheme 12

Compound	R^1	R^2	Wallach cyclisation (Y/N)
33a	Phenyl	H	Y 63 %
33b	2-pyridyl	H	Y 17 %
33c	3-pyridyl	H	Y 2 %
33d	4-pyridyl	H	N
33e	trifluoromethyl	H	N
33f	*t*-butyl	H	N
33g	nitrile	H	N
33h	*t*-butyl	phenyl	N
33i	trifluoromethyl	phenyl	N
33j	trifluromethyl	2-pyridyl	N
33k	2-pyridyl	methanol	?
35b	hex-1,6-diyl	2-pyridyl	Y 6 %

Table 1.3

Imidazole **36a** was prepared in 63 % yield under these conditions. However, compound **33b** under went cyclisation to furnish three compounds **36b**, **39** and **40** in low yield also with the recovery of starting material, **Scheme 13**.



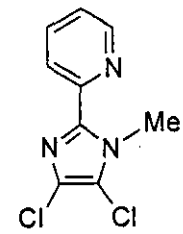
33b **36b, 17 %** **39, 14 %** **40, 2 %**

Reagents and conditions: i, 2.5 PCl_5, CH_3CN, Reflux.

Scheme 13

Compounds **39** and **40** are interesting, as the presence of 4,5-dichloro or hydroxyl substituted imidazoles have never been reported as products from the Wallach reaction. The structure of compound **39** was confirmed by X-ray crystallography, **Figure 1.8** and **Appendix 8**. This confirmed the compound **39** as having two chlorine substituents at the 4 and 5 positions and to be a planar aromatic heterocycle having a dihedral angle of zero between the pyridine and imidazole rings. In its crystal form the nitrogen atom of the pyridine ring is on the same side as the methyl substituent on the imidazole ring. This may be due to a lone pair interaction with the nitrogen at position 3 of the imidazole ring.

This may suggest that more than one mechanism is operating in the Wallach reaction. A possible mechanism can be put forward to account for the formation of **39**. Protonation of the intermediate **41**, leads to the intermediate **42**. Loss of a proton from the adjacent carbon atom gives the betaine intermediate **43**. This undergoes cyclisation to give the dichloro, dihydroimidazole **44**. Subsequent oxidation must then be invoked to give the dichloro substituted imidazole **39**, **Scheme 14**.



39

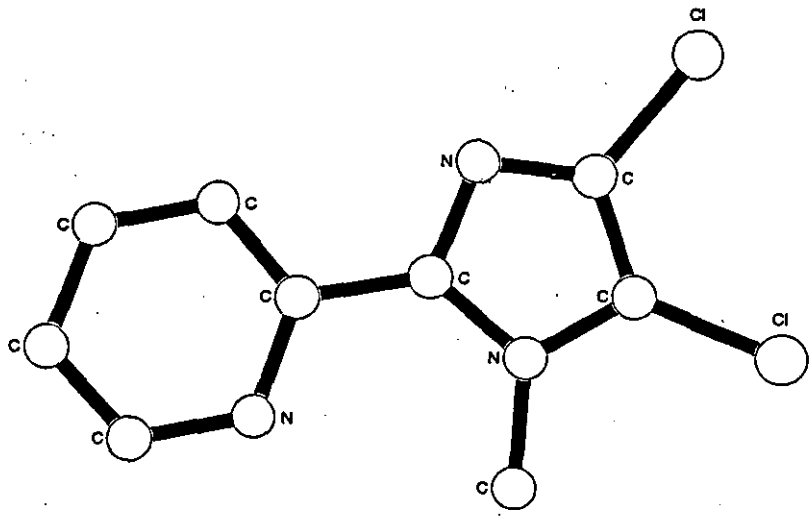
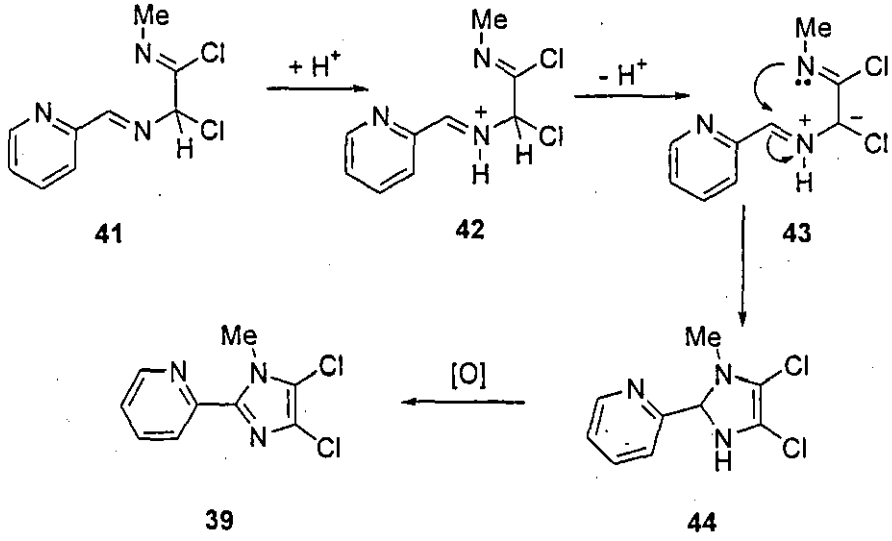


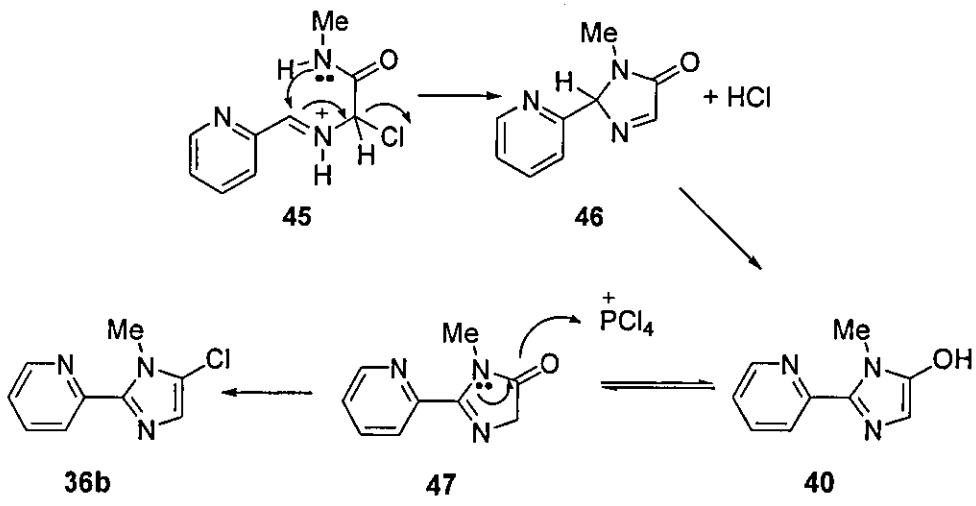
Figure 1.8, X-ray crystal structure of 2-(4,5-dichloro-1-methyl-1*H*-imidazol-2-yl)pyridine (39).



Possible mechanism for formation of dichloroimidazoles

Scheme 14

A mechanism can also be postulated for the creation of the hydroxy imidazole **40**. Protonation of a half chlorinated oxamide will give **45**. Nucleophilic displacement of the chlorine atom by the oxamide nitrogen can give the dihydroimidazolone **46** and hydrogen chloride. Tautomerisation then produces the hydroxy imidazole **40**. The isolation of the 5-hydroxyimidazole suggests another mechanism may be operating to produce the 5-chloro compounds since a further chlorination can take place to give the chloro product **36b, Scheme 15**.

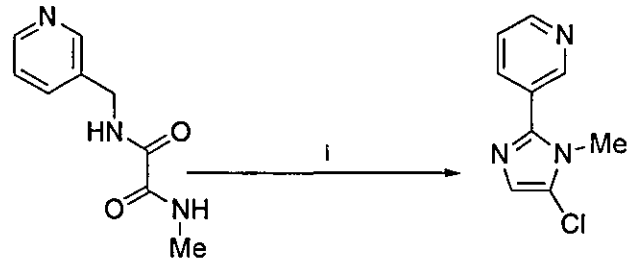


Possible mechanism for formation of hydroximidazoles

Scheme 15

These results show that more than one mechanism may be operating in the Wallach cyclisation.

The 3-pyridylmethyl oxamide **33c** was cyclised, affording a low yield of only 2 % of the substituted imidazole **36c**. No other identifiable product was isolated except for starting material, **Scheme 16.**

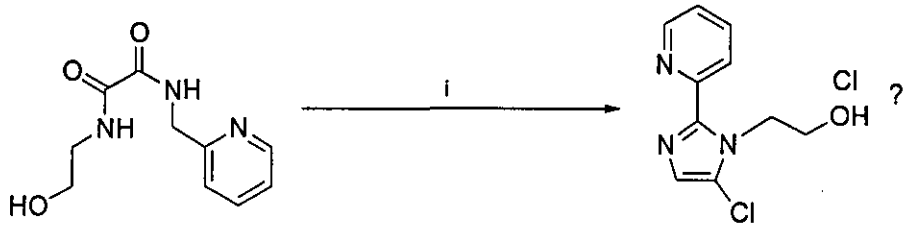


33c **36c**, 2 %

Reagents and conditions: i, 2.5 PCl_5, CH_3CN, Reflux.

Scheme 16

Compounds **33k** and **35b** had also under gone the Wallach reaction to give **36k** and **38b** respectively in very low yield with the recovery of starting material, **Scheme 17** and **18**. The outcome of the reaction between **33k** and phosphorus pentachloride is thought to have afforded the speculative product **36k, Scheme 17**. We have no comprehensive evidence to confirm this due to lack of material. Three other products have also been isolated in the same reaction but could not be fully characterised.

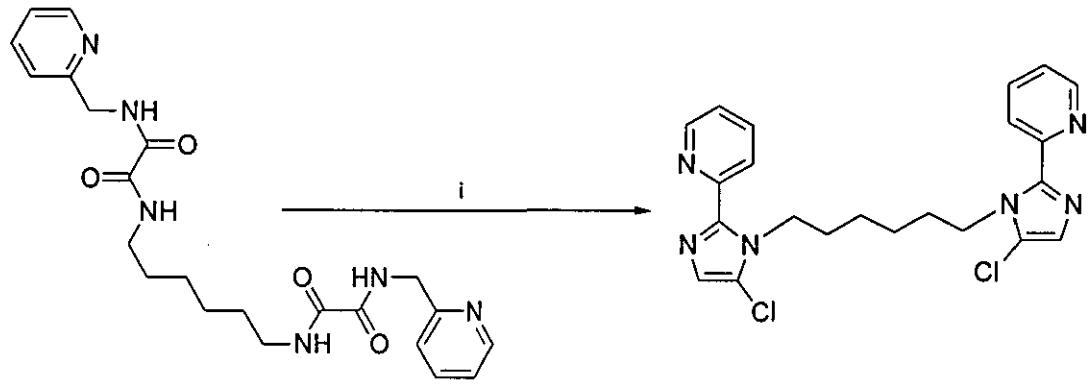


33k **36k**

Reagents and conditions: i, 3.1 PCl_5, CH_3CN, Reflux.

Scheme 17

The reaction of **35b** with phosphorus pentachloride gave **38b** and also two other products that have been isolated but not fully characterised, **Scheme 18**.



35b **38b**, 6 %

Reagents and conditions: i, 4.1 PCl_5, CH_3CN, Reflux.

Scheme 18

1.6.2 Investigation into the use of other reagents for effecting the Wallach cyclisation

Due to the very low yields encountered using phosphorus pentachloride, it was decided to study the reaction of other halogenating agents with oxamides to see if the formation of the reaction of substituted imidazoles could be effected using milder conditions. The use of brominating agents in particular was of interest because if bromoimidazoles could be produced, this would then open up the scope of the chemistry to include the use of palladium catalysed coupling reactions.

Use of thionyl chloride

Benzyl oxamide **33a, Scheme 7, Table 1.1** was treated with excess of thionyl chloride and heated under reflux in an attempt to prepare **36a**. However this was not achieved and only starting material was recovered.

Use of thionyl bromide

2-Pyridyl oxamide **33b, Scheme 7, Table 1.1** was treated with 2.1 equivalents of thionyl bromide and heated under reflux to try and synthesise bromo substituted imidazole **36b.** However, this was not achieved as only starting material was recovered.

Use of phosphorus oxychloride

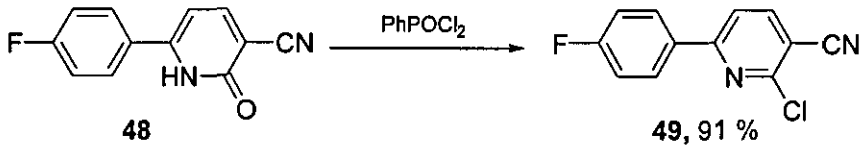
2-Pyridyl oxamide **33b, Scheme 7, Table 1.1** was treated with an excess of phosphorus oxychloride and heated at 100°C to try to afford **36b**. However this was unsuccessful as only starting material was recovered.

Use of Phosphorus pentabromide

Oxamide compounds **33a, 33b** and **24** were treated with 2.1 equivalents of phosphorus pentabromide (PBr_5) in acetonitrile under reflux, to try to prepare the bromo derivatives of **36a, 36b** and **37a**. However these reactions did not proceed, and starting material was recovered. It has been reported[19] that PBr_5 has been used to prepare substituted imidazoles incorporating a bromine atom. However, the reaction gave a very poor yield of 4,5-dibromo substituted imidazole.

Use of phenylphosphonic dichloride

It has been reported[22] that phenylphosphonic dichloride is an effective reagent for chlorinative dehydration of some heterocycles, such as **48** to give **49** in excellent yield, as shown in **Scheme 19**. This reagent is used in cases where conventional reagents which include phosphorus oxychloride and phosphorus pentachloride fail. Thus it was decided to investigate its use to prepare **36b**, **(Scheme 11)** from oxamide compound **33b** under inert and dry conditions. However, this reaction disappointingly failed to give the desired product.



48 **49**, 91 %

Scheme 19

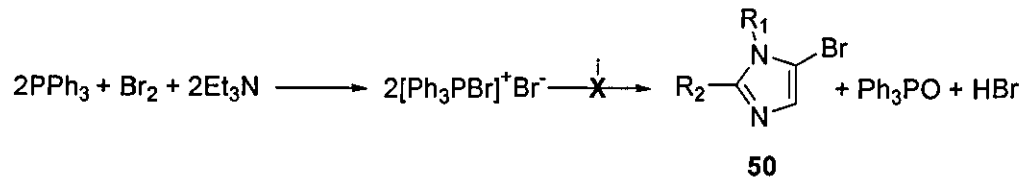
Use of carbon tetrabromide and triphenylphosphine

Carbon tetrabromide and triphenyl phosphine are commonly used in the Mitsunobu reaction to convert alcohols to alkyl bromides. It was therefore considered that this combination of reagents might be effective for cyclising oxamides to bromoimidazoles. Compound **24** **(Scheme 10)** was treated with two equivalents of carbon tetrabromide and two equivalents of triphenyl phosphine in acetonitrile. The mixture was heated under reflux. However, the reaction was unsuccessful as starting material was recovered and none of the desired imidazole **37a** was formed.

Synthesis and use of halo-phosphonium salts

Under inert and dry conditions triphenylphosphine was treated with bromine and triethylamine at 0 °C to give bromo-triphenylphosphonium bromide salt. This was reacted with oxamides **33a** or **33b** to try and form the bromo substituted imidazole **50**, **Scheme 20**. Thus forming the energetically favourable triphenylphosphine oxide and hydrogen bromide gas. However, so far this has not been successful. The solvents were varied using dichloromethane, acetonitrile and benzonitrile. This did not improve the

reaction to form the bromo-substituted imidazoles. At the end of each of the reactions only starting material was recovered.

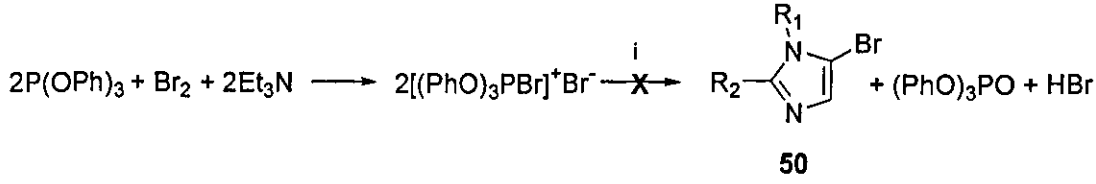


50

*Reagents and conditions: i, Oxamide **33a** or **33b**, Reflux.*

Scheme 20

In a similar set of reactions triphenylphosphite was treated with bromine to afford the bromo triphenylphosphonium bromide salt. The salt was treated with benzyl oxamide **33a** or 2-pyridyl oxamide **33b** in a range of solvents to try to give the bromo substituted imidazoles but none of these experiments were successful, **Scheme 21**.

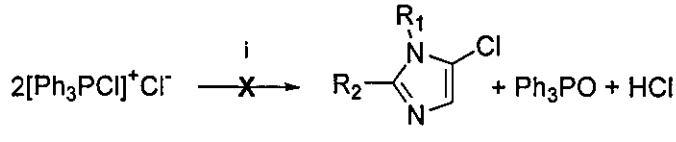


50

*Reagents and conditions: i, Oxamide **33a** or **33b**, Reflux.*

Scheme 21

Finally the chloro triphenylphonium chloride salt in acetonitrile was investigated as a reagent to convert oxamide **30** into the chloro substituted imidazole **37b, Scheme 22.** Thus, again forming the favourable triphenylphosphine oxide and hydrogen chloride gas. Disappointingly only starting material was again recovered and it was decided to discontinue work on the Wallach reaction and investigate other areas of imidazole chemistry.



37b

*Reagents and conditions: i, Diamide **30**, Reflux.*

Scheme 22

1.7 Conclusion

The synthesis of various substituted oxamides was straight forward and a number of new compounds were prepared in high yield. The Wallach imidazole synthesis was found to work well in acetonitrile as solvent for simple oxamides. However, the modified conditions failed to work with more functionally substituted oxamides. Several new chlorinated imidazoles were prepared but in poor yield. It was discovered that there is probably more than one mechanism operating in the Wallach reaction to form 5-chloroimidazoles.

Variation of the Wallach reaction was carried out using other reagents. None of these worked with the oxamides that were studied. Other reagents and conditions can still be sought, or existing methods can be modified, and there remains a need to prepare halogenated substituted imidazoles more easily.

1.8 Experimental

1.8.1 General experimental procedures :

1.8.2 Purification of reagents and solvents

Commercially available reagents were used as supplied from Aldrich, Lancaster, Maybridge, Fluka, Avocado, and Fisher Scientific chemical companies without purification unless otherwise stated. Air and moisture sensitive compounds were stored in a dessicator over self-indicating silica gel, under a nitrogen atmosphere.
Light petroleum ether refers to the fractions boiling between 40 °C and 60 °C. Ethyl acetate, light petroleum ether were distilled from calcium chloride. Dichloromethane and chloroform were distilled from phosphorus pentoxide or calcium hydride. Methanol was distilled from magnesium turnings and iodine after reaction overnight to form magnesium methoxide. Tetrahydrofuran was distilled from the sodium/benzophenone ketyl radical before use. Triethylamine was stored over potassium hydroxide pellets. Other solvents such as dimethylformamide, acetonitrile and toluene were purchased as anhydrous solvents from the chemical companies stated above.

1.8.3 Chromatography techniques

Analytical thin layer chromatography was carried out using either aluminium, plastic or glass based plates coated with silica Merck Kieselgel 60 GF_{254} or alumina Merck neutral type E F_{254} were visualised under UV light (at 254 and/or 360 nm) or by staining with visualising agents such as potasssium permanganate solution followed by heating. Flash chromatography was carried out using Merck 9385 Kieselgel 60-45 (230-400 mesh) silica and hand bellows to apply pressure to the column.

1.8.4 Preparation of Glassware

Air and moisture sensitive reactions were carried out using glassware that had been dried overnight in an oven at 150 °C. These were allowed to cool in a dessicator over self indicating silica gel. All moisture and air sensitive reactions were carried out under

a positive pressure of nitrogen. Reagents and solvents were introduced using syringe or cannula techniques, through a septum cap.

1.8.5 Melting point and Elemental Analysis

Elemental analysis were performed on a Perkin-Elmer 2400 CHN elemental analyser. Melting points were carried out on a Leica Gallin hot plate melting apparatus or an Electrothermal-IA 9100 apparatus and are uncorrected.

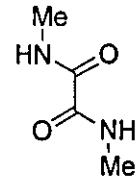
1.8.6 Spectroscopic Techniques

Infra-red (IR) spectroscopy was recorded on a Perkin-Elmer Fourier transform paragon 1000 spectrophotometer. I.R. spectra were recorded in the range 4000-600 cm^{-1}. Samples were run as thin film in dichloromethane solution, neat or nujol mulls on sodium chloride discs.

High and low resolution mass spectrometry (MS) was undertaken on a Kratos MS80 instrument or Jeol (JMX)SX102 instrument using electron impact (EI) or fast atom bombardment (FAB) ionisation techniques. Gas chromatography-mass spectrometry (GC-MS) was carried out on a Fisons GC-MS MD/AS-800 instrument.

^{1}H, ^{13}C and ^{31}P nuclear magnetic resonance spectra were recorded using a Bruker AC-250 instrument operating at 250.13, 62.85 and 100.20 MHz respectively, or using a Bruker DPX-400 instrument operating at 400.13, 100.59 and 161.97 MHz respectively. The experiments were conducted in deuteriated solvents with reference to tetramethylsilane (TMS) as the internal standard. Chemical shifts are quoted in ppm. The coupling constants *J* are recorded in Hz. Spectroscopic data is annotated with the following notations: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet. DEPT and COSY experiments were also recorded on the same instruments.

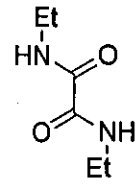
***N1-N2*-Dimethyloxamide (37a)**



Diethyl oxalate (85.5 cm^3, 0.63 mol) was added dropwise to 40% methylamine solution in water (400 cm^3) stirred at 0 °C. After 1 h the reaction was left to stand at R.T for a further 1 h. The solid was filtered under vacuum to yield a white crystalline solid. The solid was washed with cold methanol and dried under vacuum to yield the title compound (53.5 g, 96 %).

White solid, yield 96 %, m.p. 215-216 °C (lit.,[23] 215-217 °C); (m/z, 116.0, 30 % $C_4H_8N_2O_2$); ν_{max} 3304, 2900 and 1656 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 2.89 (6H, d, *J* 0.5, CH_3) and 7.49 (2H, br s, NH); δ_C (62.9 MHz; CF_3CO_2D) 21.79 (CH_3).

***N-1, N-2*-Diethyl oxamide (37b)**

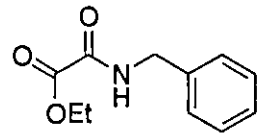


Diethyl oxalate (105 g, 0.72 mol) was added dropwise to 70% ethylamine solution in water (150 cm^3) stirred at 0 °C. After 1 h the reaction was left to stand at R.T for a further 1 h. The solid was filtered under vacuum to yield a white crystalline solid. The

solid was washed with cold methanol and dried under vacuum to yield the title compound (90 g, 87 %).

White solid, yield 87 %, m.p. 180-181 °C (lit.,[21] 180-181 °C); (Found: m/z, 144.0899, $C_6H_{12}N_2O_2$ requires: M, 144.0899); ν_{max} 3295, 2853, 1650, 1378, 1229, 1148, 821 and 775 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.21 (6H, t, *J* 7.6, CH_3), 3.37 (4H, p, *J* 7.6, CH_2) and 8.12 (2H, br s, N-H); δ_C (100 MHz; $CDCl_3$) 14.7 (CH_3), 34.9 (CH_2) and 160.3 (CO).

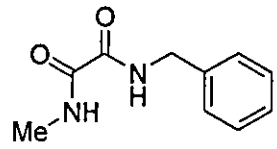
Ethyl 2-(benzylamino)-2-oxoacetate (32a)



Ethyl oxalyl chloride, (3.3 cm^3, 30 mmol) in dichloromethane (30 cm^3) was added dropwise to a stirred mixture of benzylamine (3.33 cm^3, 30 mmol) and triethylamine (4.2 cm^3, 30 mmol) in dichloromethane (15 cm^3). After 3 h the solution was filtered and the solid washed with dichloromethane. The organic filtrate was washed with water (10 cm^3). The aqueous phase was extracted with dichloromethane. The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to dryness. Re-crystallisation of the residue from ethyl acetate afforded the title compound as a pale white solid (6.21 g, 100 %).

White solid, yield 100 %, m.p. 48-49 °C (lit.,[24] 47-50 °C); (Found m/z, 207.0900, $C_{11}H_{13}NO_3$ requires M, 207.0895); ν_{max} 3280, 1651 and 1525 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.38 (3H, t, *J* 7.2, CH_3), 4.38 (2H, q, *J* 7.2, CH_2), 4.53 (2H, d, *J* 6.0, CH_2) and 7.29-7.34 (5H, m, Ar-H); δ_C (62.9 MHz; CF_3CO_2D) 14.1 (CH_3), 47.0 (CH_2), 68.2 (CH_2), 129.8 (Ar-CH), 130.6 (Ar-CH), 131.0 (Ar-CH), 136.6 (Ar-C) and 160.7 (CO).

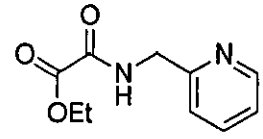
***N1*-Benzyl-*N2*-methylethandiamide (33a)**



40% Methylamine solution in water (32 cm^3, 80 eq.) was added dropwise to stirred solution of ethyl 2-(benzylamino)-2-oxoacetate (3.0 g, 14.4 mmol) in methanol (20 cm^3) at room temperature. After 3 h the solid was filtered and washed with water (10 cm^3). The solution was extracted with dichloromethane. The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to dryness. Re-crystallisation from chloroform yielded *N1*-benzyl-*N2*-methylethandiamide as a white solid (2.47 g, 89 %).

White solid, yield 89 %, m.p. 186-187 °C, (lit.,[20] 184-185 °C); (Found: C, 62.52; H, 6.27; N, 14.67; m/z, 192.0899, $C_{10}H_{12}N_2O_2$ requires M, C, 62.5; H, 6.29; N, 14.5 %; M, 192.0899); ν_{max} 3291, 1652 and 1531 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 2.82 (3H, d, *J* 5.3, CH_3), 4.41 (2H, d, *J* 6.1, CH_2), 7.18-7.29 (5H, m, Ar-H), 7.53 (1H, br s, N-H) and 7.83 (1H, br s, N-H); δ_C (62.9 MHz; CF_3CO_2D) 27.9 (CH_3), 46.5 (CH_2), 129.4 (Ar-CH), 130.4 (Ar-CH), 130.9 (Ar-CH) and 136.9 (Ar-C).

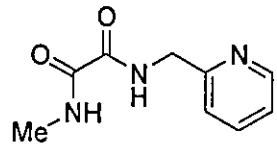
Ethyl 2-oxo-2-[(2-pyridylmethyl)amino]acetate (32b)



Ethyl oxalyl chloride, (13.4 cm^3, 120 mmol) in dichloromethane (45 cm^3) was added dropwise to a stirred mixture of 2-(aminomethyl)pyridine (12.4 cm^3, 120 mmol) and triethylamine (16.7 cm^3, 120 mmol) in dichloromethane (45 cm^3). After 3 h the solution was filtered and the solid washed with dichloromethane. The organic filtrate was washed with water (10 cm^3). The aqueous phase was extracted with dichloromethane. The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to dryness affording the title compound as a pale yellow solid (25.0 g, 100 %).

Pale yellow solid, yield 100 %, m.p. 64-65 °C (lit.,[25] 62-63 °C); (Found: m/z, 208.0846, $C_{10}H_{12}N_2O_3$ requires M, 208.0848); ν_{max} 3286, 1650, 1590, 1569 and 1529 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.32-1.43 (3H, m, CH_3), 4.32-4.42 (2H, m, CH_2), 4.65 (2H, d, *J* 5.3, CH_2), 7.20-7.65 (2H, m, Ar-CH), 7.66-7.74 (1H, m, Ar-CH), 8.38 (1H, br d, N-H) and 8.58 (1H, d, *J* 4.2, Ar-CH); δ_C (62.9 MHz; $CDCl_3$) 8.0 (CH_3), 45.1 (CH_2), 46 (CH_2), 121.2 (Ar-C), 122.0 (Ar-CH), 136.2 (Ar-CH), 148.7 (Ar-CH), 155.0(CO) and 159.2 (CO).

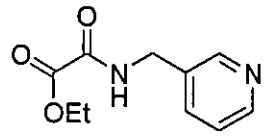
_N1_-Methyl-_N2_-(2-pyridylmethyl)ethane diamide (33b)



40% Methylamine solution in water (300 cm^3) was added dropwise to stirred solution ethyl 2-oxo-2-[(2-pyridylmethyl)amino]acetate (25.0 g, 0.12 mol) in dichloromethane (40 cm^3) at room temperature. After 3 h the organic phase was collected and the aqueous phase was extracted with dichloromethane. The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to dryness. Re-crystallisation from ethanol yielded *N1*-methyl-*N2*-(2-pyridylmethyl)ethane diamide as a pale yellow solid (21.8 g, 94 %).

Yellow solid, yield 94 %, m.p. 126-127 °C; (Found: C, 56.53; H, 5.55; N, 21.74; m/z, 193.0851, $C_9H_{11}N_3O_2$ requires C, 55.93; H, 5.74; N, 21.76 %; M, 193.0851); ν_{max} 3287, 1652, 1592 1570 and 1537 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 2.91 (3H, t, *J* 5.2, CH_3), 4.63 (2H, t, *J* 6.3, CH_2), 7.18-7.29 (2H, m, Ar-CH), 7.61 (1H, br s, N-H), 7.64 (1H, tt, *J* 0.93, 6, Ar-CH), 8.48 (1H, br s, NH) and 8.57 (1H, d, *J* 4.4 Ar-CH); δ_C (100MHz; $CDCl_3$) 26.2 (CH_3), 44.7 (CH_2), 121.8 (Ar-CH), 122.6 (Ar-CH), 136.8 (Ar-CH), 149.4 (Ar-CH), 155.6 (Ar-C), 160.0 (CO) and 160.4 (CO).

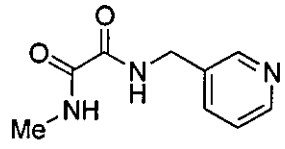
Ethyl 2-oxo-2-[(3-pyridylmethyl)amino]acetate (32c)



Ethyl oxalyl chloride, (13.4 cm^3, 120 mmol) in dichloromethane (45 cm^3) was added dropwise to a stirred mixture of 3-(aminomethyl)pyridine (12.2 cm^3, 120 mmol) and triethylamine (16.7 cm^3, 120 mmol) in dichloromethane (45 cm^3). After 3 h the solution was filtered and the solid washed with dichloromethane. The organic filtrate was washed with water (10 cm^3). The aqueous phase was extracted with dichloromethane. The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to dryness. Re-crystallisation from ethyl acetate yielded the title compound as an orange solid (24.0 g, 96 %).

Orange solid, yield 96 %, m.p. 94-95 °C (lit.,[20] 95-96 °C); (Found: m/z, 208.0848, $C_{10}H_{12}N_2O_3$ requires M, 208.0848); ν_{max} 3159, 2993, 1729, 1682, 1595 and 1579 cm^{-1}; δ_H (250MHz; $CDCl_3$) 1.37 (3H, t, *J* 7.1, CH_3), 4.34 (2H, q, *J* 7.1, CH_2), 4.52 (2H, d, *J* 6.7, CH_2), 7.24-7.31 (1H, m, Ar-CH), 7.66 (1H, tt, *J* 1.8, 8 Ar-CH), 8.05 (1H, br d, *J* 52, N-H) and 8.54 (2H, d, *J* 4.9, Ar-CH); δ_C (62.9 MHz; $CDCl_3$) 13.8 (CH_3), 41.1 (CH_2), 63.2 (CH_2), 123.5 (Ar-CH), 135.4 (Ar-CH), 135.6 (Ar-CH), 149.1 (Ar-CH), 156.7 (Ar-C), 159.5 (CO) and 160.5 (CO).

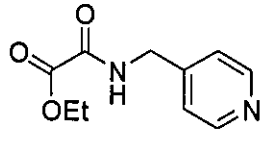
***N1*-Methyl-*N2*-(3-pyridylmethyl)ethane diamide (33c)**



40% Methylamine solution in water (300 cm^3) was added dropwise to stirred solution ethyl 2-oxo-2-[(3-pyridylmethyl)amino]acetate (24.0 g, 0.12 mol) in dichloromethane (20 cm^3) at room temperature. After 3 h the organic phase was collected and the aqueous phase was extracted with dichloromethane. The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to dryness. Re-crystallisation from ethanol yielded *N1*-methyl-*N2*-(3-pyridylmethyl)ethane diamide as a cream coloured solid (19.36 g, 84 %).

Cream solid, yield 84 %, m.p. 133-134 °C (lit.,[20] 157-158 °C); (Found: C, 53.68; H, 5.97; N, 21.41 %; m/z, 193.0853, $C_9H_{11}N_3O_2$ requires C, 55.95; H, 5.74; N, 21.75 %; M, 193.0851); ν_{max} 3302, 1650 and 1535 cm^{-1}; δ_H (250MHz; $CDCl_3$) 2.87 (3H, d, *J* 6.9, CH_3), 4.50 (2H, d, *J* 4.5, CH_2), 7.23-7.28 (1H, m, Ar-CH), 7.65 (1H, d, *J* 7.8, Ar-CH), 8.11 (1H, br s, NH), 8.50 (1H, d, *J* 4.0, Ar-CH), 8.57 (1H, s, Ar-CH) and 8.75 (1H, br s, NH); δ_C (62.89 MHz, CD_3SOCD_3) 30.9 (CH_3), 44.9 (CH_2), 128.5 (Ar-CH), 140.3 (Ar-CH), 153.3 (Ar-CH), 154.0 (Ar-CH), 154.9 (Ar-C), 165.3 (CO) and 165.6 (CO).

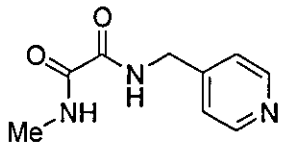
Ethyl 2-oxo-2-[(4-pyridylmethyl)amino]acetate (32d)



Ethyl oxalyl chloride, (13.4 cm^3, 120 mmol) in dichloromethane (45 cm^3) was added dropwise to a stirred mixture of 4-(aminomethyl)pyridine (12.1 cm^3, 120 mmol) and triethylamine (16.7 cm^3, 120 mmol) in dichloromethane (45 cm^3). After 3 h the solution was filtered and the solid washed with dichloromethane. The organic filtrate was washed with water (10 cm^3). The aqueous phase was further extracted with dichloromethane. The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to dryness affording the title compound as a dark red liquid (24.9 g, 99 %).

Red liquid, yield 99 %, (Found: m/z, 208.0849, $C_{10}H_{12}N_2O_3$ requires M, 208.0848); ν_{max} 3300, 2985, 2939, 1736, 1695, 1563 and 1528 cm^{-1}; δ_H (250MHz; $CDCl_3$) 1.38 (3H, t, *J* 7.5, CH_3), 4.34 (2H, q, *J* 6.4, CH_2), 4.54 (2H, d, *J* 6.3, CH_2), 7.21 (2H, d, *J* 6.1 Ar-CH), 8.03 (1H, br s, N-H) and 8.54 (2H, d, *J* 6.0 Ar-CH); δ_C (62.9 MHz; CD_3SOCD_3) 18.9 (CH_3), 46.6 (CH_2), 67.2 (CH_2), 127.5 (Ar-CH), 153.9 (Ar-C), 154.0 (Ar-CH), 164.3 (CO) and 167.2 (CO).

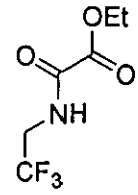
***N1*-Methyl-*N2*-(4-pyridylmethyl)ethane diamide (33d)**



40% Methylamine solution in water (300 cm^3) was added dropwise to stirred solution of ethyl 2-oxo-2-[(4-pyridylmethyl)amino]acetate (24.5 g, 0.12 mol) in dichloromethane (20 cm^3) at room temperature. After 3 h the organic phase was collected and the aqueous phase was extracted with dichloromethane. The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to dryness. Re-crystallisation from ethanol yielded *N*1-methyl-*N*2-(4-pyridylmethyl)ethane diamide as a white coloured solid (23.08 g, 99 %).

White solid, yield 99 %, m.p. 152-153 °C; (Found: C, 56.05; H, 5.58; N, 21.74; m/z, 193.0855, $C_9H_{11}N_3O_2$ requires M, C, 55.95; H, 5.74; N, 21.75 %; M, 193.08512); ν_{max} 3302, 1653, 1602 and 1521 cm^{-1}; δ_H (250MHz; $CDCl_3$) 2.86 (3H, t, *J* 5.2, CH_3), 4.47 (2H, d, *J* 6.5, CH_2), 7.17 (2H, d, *J* 6.0, Ar-CH), 7.96 (1H, br s, NH) 8.53 (2H, d, *J* 6.0, Ar-CH) and 8.66 (1H, br s, NH); δ_C (62.89 MHz, $CDCl_3$) 26.2 (CH_3), 42.4 (CH_2), 122.2 (Ar-CH), 146.3 (Ar-C), 150.0 (Ar-CH), 160.2 (CO) and 160.4 (CO).

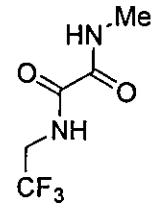
Ethyl 2-oxo-[(2,2,2-trifluoroethyl)amino]acetate (32e)



Ethyl oxalyl chloride, (3.4 cm^3, 30 mmol) in dichloromethane (15 cm^3) was added dropwise to a stirred mixture of 2,2,2-trifluoroethylamine hydrochloride (4.1g, 30 mmol) and triethylamine (8.36 cm^3, 60 mmol) in dichloromethane (15 cm^3) at 0 °C. After 3 h the solution was filtered and the solid washed with dichloromethane. The organic filtrate was washed with water (10 cm^3). The aqueous phase was extracted with dichloromethane. The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to dryness. Re-crystallisation from ethyl acetate yielded the title compound as a red solid (5.97 g, 100 %).

Red solid, yield 100 %, m.p. 53-54 °C, (Found: C, 36.55; H, 4.05; N, 7.01; m/z, 199.0465, $C_6H_8F_3NO_3$ requires, C, 36.20; H, 4.05; N, 7.06 %; M, 199.0456); ν_{max} 3295, 2996, 1742 and 1693 cm^{-1}; δ_H (400MHz; $CDCl_3$) 1.41 (3H, t, *J* 7.1 CH_3), 4.0 (2H, p, *J* 6.7, CH_2), 4.38 (2H, q, *J* 7.1, CH_2) and 7.45 (1H, br s, N-H); δ_C (100.6 MHz; $CDCl_3$) 13.9 (CH_3), 40.9 (q, $^2J_{CF}$ 35, CH_2), 63.7 (CH_2), 123.6 (q, $^1J_{CF}$ 276, CF_3), 156.8 (CO) and 159.8 (CO).

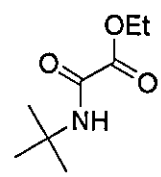
***N1*-Methyl-*N2*-(2,2,2-trifluoroethyl)ethaneamide (33e)**



40% Methylamine solution in water (20 cm^3, 58 eq.) was added dropwise to stirred solution of ethyl 2-oxo-[(2,2,2-trifluoroethyl)amino]acetate (2.00 g, 12.8 mmol) in dichloromethane (20 cm^3) at room temperature. After 3 h the organic phase was collected and the aqueous phase was extracted with dichloromethane. The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to dryness. Re-crystallisation from hot acetone gave a yellow solid (2.38 g, 100 %).

Yellow solid, yield 100 %, m.p. 194-195 °C; (Found: C, 33.33; H, 3.87; N, 15.62; m/z, 184.0460, $C_5H_7F_3N_2O_2$ requires M, C, 32.63; H, 3.83; N, 15.28 % M, 184.0456); ν_{max} 3297, 1659, 1415 and 1165 cm^{-1}; δ_H (400 MHz; CF_3CO_2D) 3.07 (3H, d, *J* 8, CH_3), 4.08 (2H, q, *J* 8.0, CH_2), 8.5 (1H, br s, N-H) and 8.67 (1H, br s, N-H); δ_C (100 MHz; CF_3CO_2D) 27.0 (CH_3), 37.5 (q, $^2J_{CF}$ 30, CH_2), 119.5 (q, $^1J_{CF}$ 280, CF_3), 137.0 (CO) and 161.0 (CO).

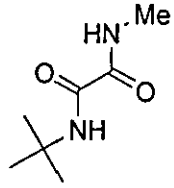
Ethyl 2-(*tert*-butylamino)-2-oxoacetate[26] (32f)



Ethyl oxalyl chloride, (3.4 cm^3, 30 mmol) in dichloromethane (15 cm^3) was added dropwise to *t*-butylamine (3.2 cm^3, 30 mmol) and triethylamine (4.2 cm^3, 30 mmol) in dichloromethane (10 cm^3) at 0 °C. After 3 h the solution was filtered and washed with dichloromethane. The organic filtrate was washed with water (10 cm^3). The aqueous phase was extracted with dichloromethane. The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to dryness yielding the title compound as a pale yellow liquid (5.16 g, 99 %).

Yellow liquid, yield 99 %; (Found: m/z, 173.1054, $C_8H_{15}NO_3$ requires M, 173.1052); ν_{max} 3407, 2933, 1735, 1700 and 1527 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.38 (3H, t, *J* 7.3, CH_3), 1.4 (9H, s, CH_3), 4.31 (2H, q, *J* 7.2, CH_2) and 7.0 (1H, br s, N-H); δ_C (100.6 MHz; $CDCl_3$) 14.0 (CH_3), 28.0 (CH_3), 51.9 (C), 63.1 (CH_2), 155.6 (CO) and 161.3 (CO).

***N1*-(*tert*-Butyl)-*N2*-methyl ethanediamide (33f)**

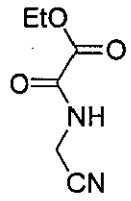


40% aqueous methylamine (32 cm^3, 80 eq.) was added dropwise to stirred ethyl 2-(*tert*-butylamino)-2-oxoacetate (2.0g, 11.5 mmol) in methanol (32 cm^3) at room temperature. After 3 h the homogeneous mixture was extracted with dichloromethane. The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to dryness. Re-crystallisation from ethanol yielded the title compound as a white solid (1.61g, 89 %).

White solid, yield 89 %, m.p. 118.5-119.5 °C (lit.,[27] 119-121 °C); (Found: C, 53.3; H, 8.64; N, 17.94 %; m/z, 158.1056, $C_7H_{14}N_2O_2$ requires: C, 53.17; H, 8.92; N, 17.71 %; M, 158.1055); ν_{max} 3343, 3298, 2933 and 1659 cm^{-1}; δ_H (250MHz; $CDCl_3$) 1.39 (9H, s,

CH_3), 2.89 (3H, d, *J* 4.5, CH_3), 7.40 (1H, br s, N-H) and 7.60 (1H, br s, N-H); δ_C (62.9 MHz; $CDCl_3$) 26.1 (CH_3), 28.2 (CH_3), 51.3 (C), 159.0 (CO) and 161.0 (CO).

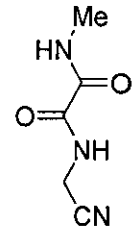
Ethyl 2-[(cyanomethyl)amino]-2-oxoacetate (32g)



Ethyl oxalyl chloride, (3.4 cm^3, 30 mmol) in dichloromethane (15 cm^3) was added dropwise to aminoacetonitrile hydrochloride (4.06g, 30 mmol) and triethylamine (8.4 cm^3, 60 mmol) in dichloromethane (15 cm^3). After 3 h the solution was filtered and the solid washed with dichloromethane. The organic filtrate was washed with water (10 cm^3). The aqueous phase was extracted with dichloromethane. The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to dryness to yield the title compound as a dark red solid (4.68g, 100 %).

Red solid, yield 100 %, m.p. 53-54 °C; (Found: m/z, 156.0538, $C_6H_8N_2O_3$ requires: M, 156.0535); ν_{max} 3331, 2988, 2947, 2267 (CN), 1715 and 1525 cm^{-1}; δ_H (400MHz; $CDCl_3$) 1.39 (3H, t, *J* 7.0, CH_3), 4.31 (2H, d, *J* 6.0, CH_2), 4.38 (2H, q, *J* 7.3, CH_2) and 8.00 (1H, br s, N-H); δ_C (100.6 MHz; $CDCl_3$) 13.9 (CH_3), 27.88 (CH_2), 63.83 (CH_2), 115.11 (CN), 156.9 (CO) and 163.2(CO).

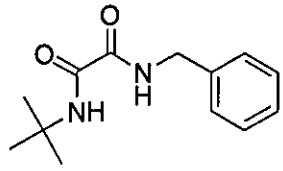
***N1*-Cyanomethyl-*N2*-methylethane diamide (33g)**



40% Methylamine solution in water (20 cm^3, 45 eq.) was added dropwise to a stirred solution of ethyl 2-[(cyanomethyl)amino]-2-oxoacetate (2.00 g, 12.8 mmol) in methanol (20 cm^3) at room temperature. After 3 h the mixture was extracted with dichloromethane. The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to dryness to give a solid. Re-crystallisation from ethanol yielded *N1*-cyanomethyl-*N2*-methylethane diamide as a white coloured solid (1.8 g, 100 %).

White solid, yield 100 %, m.p. 130-131 °C; (Found: m/z, 115.0508, $C_5H_7N_3O_2$ requires: M^+-CN, 115.0508); ν_{max} 3298, 2286 and 1654 cm^{-1}; δ_H (400MHz; CD_3SOCD_3) 2.67 (3H, d, *J* 4.8, CH_3), 3.72 (2H, d, *J* 6.1, CH_2), 7.80 (1H, br s, N-H) and 8.73 (1H, br s, N-H); δ_C (100.6 MHz; CD_3SOCD_3) 25.7 (CH_3), 41.7 (CH_2), 164.3 (CO) and 168.1(CO).

_N1_-Benzyl-_N2_-(_tert_-butyl)ethanediamide (33h)

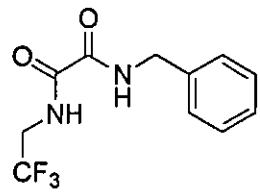


Benzylamine (6.4 cm^3, 60 mmol) was added dropwise to a stirred solution of ethyl 2-(*tert*-butylamino)-2-oxoacetate (5.16 g, 29.8 mmol) in methanol (20 cm^3) at room temperature. After 3 h the mixture was treated with water and was extracted with dichloromethane. The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to dryness to give a solid. Re-crystallisation from ethanol yielded *N1*-benzyl-*N2*-(tert-butyl)ethanediamide as a white coloured solid (4.58 g, 66 %).

White solid, yield 66 %, m.p. 100-102 °C; (Found: C, 66.74; H, 7.60; N, 12.15 %; m/z, 234.1370, $C_{13}H_{18}N_2O_2$ requires: C, 66.68; H, 7.74; N, 11.96 %; M, 234.1368); ν_{max} 3312, 2972, 2932, 1662 and 1513 cm^{-1}; δ_H (250MHz; $CDCl_3$) 1.36 (9H, s, CH_3), 4.4

(2H, d, *J* 6.1, CH_2), 7.24-7.33 (5H, m, Ar-H), 7.47 (1H, br s, N-H) and 8.3 (1H, br s, N-H); δ_C (62.9 MHz; $CDCl_3$) 28.1 (CH_3), 43.5 (CH_2), 51.26 (C), 127.4 (Ar-CH), 127.5 (Ar-CH), 128.5 (Ar-CH), 137.0 (Ar-C), 158.7 (CO) and 160.4 (CO).

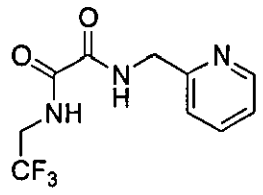
_N1_-Benzyl-_N2_-trifluoromethylethanediamide (33i)



Ethyl 2-(benzylamino)-2-oxoacetate (3.0 g, 14.4 mmol) in methanol (10 cm^3) was added to stirred 2,2,2-trifluoroethylamine hydrochloride (1.95 g, 14.4 mmol) and triethylamine (6.0 cm^3, 43.2 mmol) in methanol (10 cm^3) at room temperature. After 3 h the reaction mixture was filtered and washed with methanol (10 cm^3). The filtrate was concentrated *in vacuo* to remove methanol. The residual aqueous phase was extracted with dichloromethane. The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to dryness. Re-crystallisation from ethanol yielded *N1*-benzyl-*N2*-trifluoromethylethanediamide as a white coloured solid (3.77g, 100 %).

White solid, yield 100 %, m.p. 105-106 °C; (Found: m/z, 260.0776, $C_{11}H_{11}F_3N_2O_2$ requires M, 260.0773); ν_{max} 3357, 3286, 2977, 1684 and 1659 cm^{-1}; δ_H (250MHz; $CDCl_3$) 3.90 (2H, s, CH_2), 4.53 (2H, d, *J* 4.5, CH_2) and 7.29-7.37 (5H, m, Ar-H); δ_C (62.9 MHz; $CDCl_3$) 45.7 (CH_2), 53.6 (CH_2), 127.8 (Ar-CH), 127.9 (Ar-CH) and 128.7 (Ar-CH).

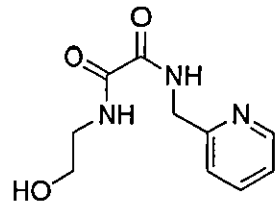
_N1_-(2-Pyridylmethyl)-_N2_-trifluoromethylethanediamide (33j)



Ethyl 2-oxo-2-[(2-pyridylmethyl)amino]acetate (3.0 g, 14.4 mmol) in methanol (10 cm^3) was added to stirred 2,2,2-trifluoroethylamine hydrochloride (1.95 g, 14.4 mmol) and triethylamine (6.01 cm^3, 43.2 mmol) in methanol (10 cm^3) at room temperature. After 3 h the reaction mixture was filtered and washed with methanol (10 cm^3). The filtrate was concentrated *in vacuo* to remove methanol. The residual aqueous phase was extracted with dichloromethane. The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to dryness to give a solid. Re-crystallisation from ethanol yielded *N1*-(2-pyridylmethyl)-*N2*-trifluoromethylethanediamide as a pale yellow solid (1.69g, 47 %).

Yellow solid, yield 47 %, m.p. 147-148 °C; (Found: m/z, 261.0719, $C_{10}H_{10}F_3N_3O_2$ requires M, 261.0725); ν_{max} 3286, 1651, 1591 and 1569 cm^{-1}; δ_H (250MHz; $CDCl_3$) 3.9 (2H, s, CH_2), 4.65 (2H, d, *J* 4.3, CH_2), 7.10-7.28 (2H, m, Ar-H), 7.5-7.68 (1H, m, Ar-H), 8.31 (1H, br s, N-H), 8.44 (1H, br s, N-H) and 8.57 (2H, d, *J* 4.1, Ar-H); δ_C (62.89 MHz, $CDCl_3$) 44.6 (CH_2), 41.5 (CH_2, q, $^2J_{CF}$ 32), 121.7 (Ar-CH), 122.5 (Ar-CH), 122.62 (Ar-C), 136.7 (Ar-CH), 149.3 (Ar-CH), 155.60 (CO) and 159.8 (CO).

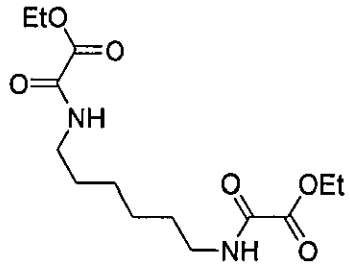
***N1*-(2-Hydroxyethyl)-*N2*-(2-pyridylmethyl)ethanediamide (33k)**



Ethanolamine (0.47 cm^3, 7.7 mmol) was added dropwise to stirred ethyl 2-oxo-2-[(4-pyridylmethyl)amino]acetate (1.5g, 7.8 mmol) in dichloromethane (10 cm^3) at room temperature. After 1 h the precipitate was filtered and washed with diethyl ether to give a white solid. Re-crystallisation from ethanol yielded *N1*-(2-hydroxyethyl)-*N2*-(2-pyridylmethyl) ethanediamide as a cream solid (1.71 g, 98 %).

Cream solid, yield 98 %, m.p. 102-105 °C; (Found: m/z, 223.0955, $C_{10}H_{13}N_3O_3$ requires M, 223.0957); ν_{max} 3284, 3055, 1651, 1597 and 1528 cm^{-1}; δ_H (250MHz; $CDCl_3$) 2.85 (1H, br s, OH), 3.54-3.79 (4H, m, CH_2), 4.61 (2H, d, *J* 4.8, CH_2), 7.2-7.28 (2H, m, Ar-CH), 7.67 (1H, tt, *J* 1.7, 7.6, Ar-CH), 8.55 (1H, br s, N-H) and 8.57 (1H, br s, N-H); δ_C (62.89 MHz; CD_3SOCD_3) 46.8 (CH_2), 49.2 (CH_2), 64.3 (CH_2), 126.1 (Ar-CH), 127.3 (Ar-CH), 141.8 (Ar-CH), 153.9 (Ar-CH), 162.4 (Ar-C), 165.0 (CO) and 165.3 (CO).

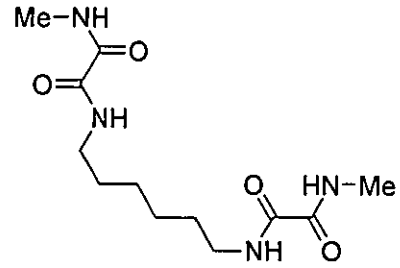
Ethyl 2(6-[(2-ethoxy-2-oxoacetyl)amino]hexyl-3-amino)-2-oxoacetate (34)



Ethyl oxalyl chloride, (3.4 cm^3, 30mmol) in dichloromethane (20 cm^3) was added dropwise to 1,6-diaminohexane (1.74g, 15 mmol) and triethylamine (4.2 cm^3, 30 mmol) in dichloromethane (20 cm^3) at 0 °C. After 3 h the reaction mixture was treated with water (10 cm^3) and diethyl ether (10 cm^3) then filtered. The organic filtrate was extracted with diethyl ether. The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to dryness. Re-crystallisation from ethyl acetate yielded the title compound as a cream coloured solid (4.2 g, 89 %).

Cream solid, yield 89 %, m.p. 90-91 °C (lit.,[28] 89 °C); (Found: C, 53.14; H, 7.54; N, 8.95 %; m/z, 316.1634, $C_{14}H_{24}N_2O_6$ requires: C, 53.18; H, 7.65; N, 8.86 %; M, 316.1634); ν_{max} 3298, 2967, 2928, 2850, 1746, 1735 and 1677 cm^{-1}; δ_H (250MHz; $CDCl_3$) 1.37 (10H, t, *J* 7.15, CH_3CH_2), 1.58 (4H, t, *J* 6.7 CH_2), 3.33 (4H, q, *J* 6.9 CH_2), 4.35 (4H, q, *J* 7.15, CH_2) and 7.2 (2H, br s, N-H); δ_C (62.89 MHz; $CDCl_3$) 13.8 (CH_3), 26.1 (CH_2), 28.8 (CH_2), 39.5 (CH_2), 62.9 (CH_2), 156.5 (CO) and 161.0 (CO).

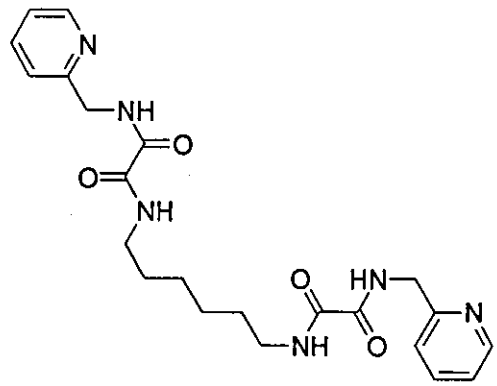
_N1_-Methyl-_N2_-(6-[2-(methylamino)-2-oxoacetyl]aminohexyl)ethaneamide (35a)



40 % Methylamine solution in water (25 cm^3, 115 eq.) was added dropwise to stirred ethyl 2(6-[(2-ethoxy-2-oxoacetyl)amino]hexyl-3-amino)-2-oxoacetate (2.00 g, 6.32 mmol) in methanol (20 cm^3) at 0 °C. After 1 h the resulting solid was filtered and was washed with petroleum ether. The solid was re-crystallised from DMSO and washed with diethyl ether yielding *N1*-methyl-*N2*-(6-[2-(methylamino)-2-oxoacetyl]aminohexyl)ethaneamide as a white solid (1.8 g, 99 %).

White solid, yield 99 %, m.p. 266-267 °C; (Found: C, 49.37; H, 7.52; N, 18.57 %; m/z, 286.1639, $C_{12}H_{22}N_4O_4$ requires: C, 50.36; H, 7.75; N, 19.57 %; M, 286.1641); ν_{max} 3290, 2925, 1684 and 1648 cm^{-1}; δ_H (250MHz; CD_3SOCD_3) at 60 °C, 1.22-1.28 (4H, m, CH_2), 1.46 (4H, t, *J* 6.8, CH_2), 2.68 (6H, d, *J* 4.9, CH_3), 3.13 (4H, t, *J* 6.7, CH_2) and 8.39 (2H, br s, NH); δ_C (62.89 MHz; CF_3CO_2D) 28.2 (CH_3), 28.3 (CH_2), 30.5 (CH_2) and 42.9 CH_2).

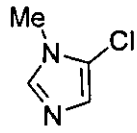
_N1_-[6-({2-Oxo-2-[pyridin-2-yl methyl)amino]acetyl}amino)hexyl]-_N2_-pyridin-2-ylmethylethanediamide (35b)



2-(Aminomethyl)pyridine (6.6 cm^3, 6 mmol) in methanol (5 cm^3) was added dropwise to stirred ethyl 2({6-[(2-ethoxy-2-oxoacetyl)amino]hexyl-3-amino)-2-oxoacetate (0.94g, 3mmol) in methanol (5 cm^3). After 2 h the precipitated solid was filtered and was washed with diethyl ether to reveal the title compound as a white solid (1.28 g, 97 %).

White solid, yield 97 %, m.p. 180-182 °C; (Found: m/z, 440.2180, $C_{22}H_{28}N_6O_4$ requires: M, 440.2172); ν_{max} 3289, 3054, 1647, 1590 and 1515 cm^{-1}; δ_H (250MHz; CD_3SOCD_3) 1.25 (4H, br s, CH_2), 1.47 (4H, br s, CH_2), 3.15 (4H, q, *J* 6.6, CH_2), 4.47 (4H, d, *J* 6.5, CH_2), 7.25-7.28 (4H, m, Ar-CH), 7.76 (2H, tt, *J* 1.7, 7.7, Ar-CH), 8.49-8.51 (2H, m, Ar-CH), 8.79 (2H, t, *J* 6.02, Ar-CH) and 9.22 (2H, t, *J* 6.1, NH); δ_C (62.89 MHz; CF_3CO_2D) 28.5 (CH_2), 30.6 (CH_2), 43.2 (CH_2), 43.6 (CH_2), 129.4 (Ar-CH), 129.8 (Ar-CH), 143.9 (Ar-CH), 151.0 (Ar-CH), 153.9 (Ar-C) and 161.7 (CO).

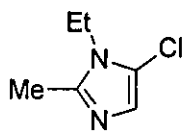
5-Chloro-1-methyl-1*H*-imidazole (37a)



N1-N2-Dimethyloxamide (100 g, 0.861 mol) was added dropwise to phosphorus pentachloride (376.6 g, 1.81 mol) in dry acetonitrile (1000 cm^3) in a modification of Wallach's procedure.[8-14] The mixture was heated under reflux for 14 h. The solvent was removed *in vacuo* to yield a black viscous oil. The oil was cooled to 0 °C and was made alkaline with concentrated ammonium hydroxide solution. The inorganic solid which precipitated (ammonium chloride) was filtered and washed with dichloromethane (4 × 20 cm^3). The filtrate was extracted with dichloromethane (6 × 50 cm^3), the organic extracts combined, dried over $MgSO_4$, filtered and evaporated to dryness to yield a dark brown/black liquid (105 g). The liquid was distilled under reduced pressure at 65 °C to afford the title compound as a colourless oil (75.0 g, 75 %).

Colourless oil, yield 75 %, b.p. 50-52 °C at 6.3 Torr (lit.,[19] 53-54 °C at 6.8 Torr); (Found: m/z, 116.0140, $C_4H_5ClN_2$ requires: M, 116.0141); ν_{max} 2953, 1615, 690 and 659 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.58 (3H, s, N-CH_3), 6.92 (1H, s, H-4) and 7.43 (1H, s, H-2); δ_C (100.6 MHz; $CDCl_3$) 31.3 (N-CH_3), 118.1 (Ar-C), 125.6 (Ar-C) and 137.0 (Ar-CH).

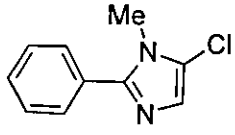
5-Chloro-1-ethyl-2-methyl-1*H*-imidazole (37b)



N1-*N2*-Diethyloxamide (63.2 g, 0.438 mol) was added dropwise to phosphorus pentachloride (191.7 g, 0.92 mol) in dry acetonitrile (1000 cm^3) in a modification of Wallach's procedure.[8-14] The mixture was heated under reflux for 12 h. The solvent was removed *in vacuo* to yield a black viscous oil. The oil was cooled to 0 °C and was made alkaline with concentrated ammonium hydroxide solution. The inorganic solid was filtered and washed with dichloromethane (100 cm^3). The filtrate was extracted with dichloromethane (4 × 100 cm^3), combined, dried over $MgSO_4$, filtered and evaporated to dryness, to yield a dark brown/black liquid. The liquid was distilled under reduced pressure at 53 °C to afford the title compound as a colourless oil (50.68 g, 80 %).

Colourless oil, yield 80 %, b.p. 53 °C at 0.2 Torr (lit.,[19] 68 °C at 0.6 Torr); (Found: m/z, 144.0899, $C_6H_9ClN_2$ requires: M, 144.0899); ν_{max} 2981, 2937, 1672, 1527, 1495, 1410, 1383, 1351, 1260, 1186, 1112, 800 and 626 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.29 (3H, t, *J* 7.2, CH_3), 2.38 (3H, s, CH_3), 3.91 (2H, q, *J* 7.4, CH_2) and 6.79 (1H, s, H-4); δ_C (62.9 MHz; $CDCl_3$) 13.5 (CH_3), 14.8 (CH_3), 38.3 (CH_2), 115.6 (C), 123.3 (CH) and 143.4 (C).

5-Chloro-1-methyl-2-phenyl-1*H*-imidazole (36a)

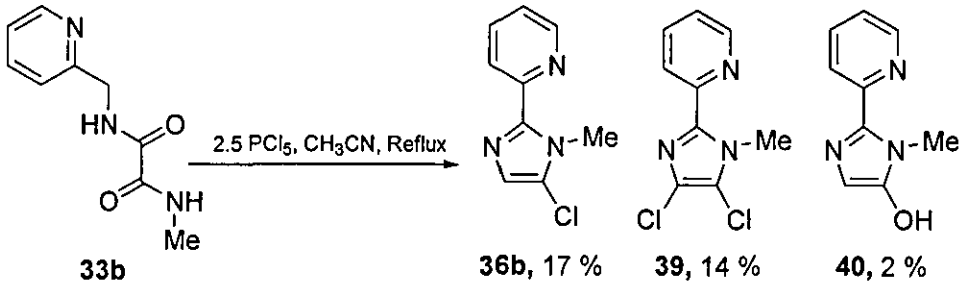


N1-Benzyl-*N2*-methylethandiamide (0.3g, 1.56 mmol) was added dropwise to phosphorus pentachloride (0.68g, 3.2mmol) in dry acetonitrile (10 cm^3) in a modification of Wallach's procedure.[8-14] The mixture was heated under reflux for 3 h. The solvent was removed *in vacuo* to yield a black solid. The solid was cooled to 0 °C and treated with sodium hydroxide solution until the mixture was alkaline. The aqueous

phase was extracted with dichloromethane (4 × 15 cm^3), the extracts combined, dried over $MgSO_4$, filtered and evaporated to dryness to yield a brown solid. Re-crystallisation from dichloromethane and petroleum ether gave the title compound as a cream solid (0.188 g, 63 %).

Cream solid, yield 63 %, m.p. 96-97 °C (lit.,[20] 106-107 °C); (Found: m/z, 192.0425, $C_{10}H_9ClN_2$ requires: M, 192.0454); ν_{max} 3049, 1678, 1502, 1470, 767 and 723 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.66 (3 H, s, N-CH_3), 7.06 (1H, s, Ar-CH), 7.42-7.48 (3H, m, Ar-CH) and 7.06-7.60 (2H, m, Ar-CH); δ_C (100.6 MHz; $CDCl_3$) 32.1 (N- CH_3), 119.2 (Ar-C), 125.0 (Ar-CH), 125.8 (Ar-C), 128.6 (Ar-CH), 129.1 (Ar-CH), 130.4 (Ar-C) and 147.3 (Ar-CH).

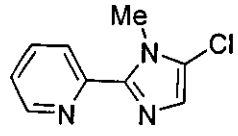
Reaction of *N1*-methyl-*N2*-(2-pyridylmethyl)ethane diamide 33b with phosphorus pentachloride



*N*1-Methyl-*N*2-(2-pyridylmethyl)ethane diamide (3.9g, 20 mmol) was addded dropwise to phosphorus pentachloride (10.5g, 50.5mmol) in dry acetonitrile (100 cm^3) in a modification of Wallach's procedure.[8-14] The mixture was heated under reflux for 3 h. The solvent was removed *in vacuo* to yield a black viscous oil. The oil was cooled to 0 °C and made alkaline with concentrated ammonium hydroxide solution. The inorganic solid formed was filtered and washed with dichloromethane (6 × 20 cm^3). The filtrate was extracted with dichloromethane (6 × 20 cm^3), the extracts combined, dried over $MgSO_4$, filtered and evaporated to dryness, to yield a dark brown/black liquid (5.53 g,

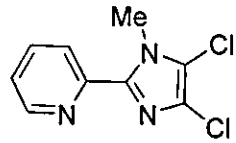
≥100 %). The liquid was distilled under reduced pressure at 3 mbar at 80 °C to afford a colourless oil. The remaining residue was extracted with diethyl ether and the solvent was removed *in vacuo* and combined with the distilled liquid. Flash chromatography on silica eluting with ethyl acetate and petroleum ether (5:95) afforded the title compounds as **36b**, pale white solid (0.662g, 17 %), **39**, yellow plates (0.785g, 14 %) and **40**, yellow solid (0.094g, 2 %). The products were re-crystallised from ethyl acetate and petroleum ether.

2-(5-Chloro-1-methyl-1*H*-imidazol-2-yl)pyridine (36b)



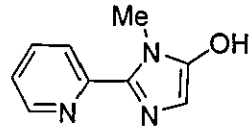
White solid, yield 17 %, m.p. 55-56 °C; (Found: m/z, 193.0372, $C_9H_8ClN_3$ requires: M, 193.0407); ν_{max} 1588 and 789 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 4.08 (3H, s, N-CH_3), 7.07 (1H, s, Ar-CH) 7.22-7.27 (1H, m, Ar-CH), 7.73-7.80 (1H, m, Ar-CH), 8.09-8.13 (1H, m, Ar-CH) and 8.58-8.6 (1H, m, Ar-CH); δ_C (62.9 MHz; $CDCl_3$) 33.03 (N-CH_3), 122.5 (Ar-CH), 122.7(Ar-CH), 125.2 (Ar-CH), 125.8 (Ar-C), 136.6 (Ar-CH), 148.2 (Ar-CH) and 150.5 (Ar-C).

2-(4,5-Dichloro-1-methyl-1*H*-imidazol-2-yl)pyridine (39)



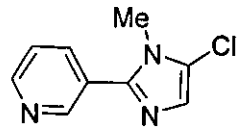
Yellow plates, yield 14 %, m.p. 77-78 °C; (Found: m/z, 227.0012, $C_9H_7Cl_2N_3$ requires: M, 227.0017); ν_{max} 1676, 1526, 1500, 1463, 786 and 739 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 4.10 (3H, s, N-CH_3), 7.23-7.27 (1H, m, Ar-CH), 7.75 (1H, tt, *J* 1.9, 7.8, Ar-CH), 8.10 (1H, dd, *J* 0.9, 6, Ar-CH) and 8.57 (1H, dd, *J* 0.9, 5.3, Ar-CH); δ_C (100.62 MHz; $CDCl_3$) 34.2 (N- CH_3), 116.5 (Ar-C), 121.4 (Ar-C), 123.1 (Ar-CH), 125.8 (Ar-CH), 136.8 (Ar-CH), 142.4 (Ar-C), 148.3 (Ar-CH) and 149.5 (Ar-C).

1-Methyl-2-(2-pyridyl)-1*H*-imidazol-5-ol (40)



Yellow solid, yield 2 %, m.p. 85-86 °C; (Found: C, 61.78; H, 4.99; N, 23.52 %; m/z, 175.0745, $C_9H_9N_3O$ requires: C, 61.7; H, 5.18; N, 23.99 %; M, 175.0746); ν_{max} 3399, 2900, 1658, 1548 and 1503 1548 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 3.03 (3H, d, *J* 7.5, N-CH_3), 6.78 (1H, t, *J* 8.7, Ar-CH), 6.92 (1H, t, *J* 6.6, Ar-CH), 7.37 (1H, br s, OH), 7.43 (1H, s, Ar-CH), 7.54 (1H, d, *J* 9, Ar-CH) and 9.47 (1H, d, *J* 6.2, Ar-CH); δ_C (62.9 MHz; $CDCl_3$) 25.67 (N- CH_3), 114.5 (Ar-CH), 117.8 (Ar-CH), 120.2 (Ar-CH), 121.4 (Ar-CH), 125.5 (Ar-CH), 129.9 (Ar-C), 133.3 (Ar-C) and 160.3 (C-OH).

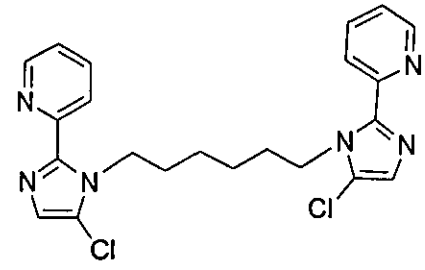
3-(5-Chloro-1-methyl-1*H*-imidazol-2-yl)pyridine (36c)



N1-Methyl-*N2*-(3-pyridylmethyl)ethane diamide (10.0 g, 52 mmol) was addded dropwise to phosphorus pentachloride (23.71g, 0.113 mol) in dry acetonitrile (70 cm^3) in a modification of Wallach's procedure.[8-14] The mixture was heated to reflux under 2 h. The solvent was removed *in vacuo* to yield a black viscous oil. The oil was cooled to 0 °C and was made alkaline with concentrated ammonium hydroxide solution. The inorganic solid was filtered and washed with dichloromethane (4 × 20 cm^3). The filtrate was extracted with dichloromethane (6 × 50 cm^3), the extracts combined, dried over $MgSO_4$, filtered and evaporated to dryness, to yield a dark brown/black solid (4.89 g, 49 %). The solid was extracted with diethyl ether to afford an orange viscous oil (2.01g, 20 %). Flash chromatography of the oil on silica eluting with ethyl acetate and petroleum ether (2:1) afforded three products, one identified as the title compound, a yellow solid (0.234g, 2 %).

Yellow solid, yield 2 %, m.p. 121-122 °C; (Found: m/z, 193.0405, $C_9H_8ClN_3$ requires: M, 193.0407); ν_{max} 2985, 1573, 1520, 739 and 705 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 3.56 (3H, s, N-CH_3), 6.95 (1H, s, Ar-H), 7.28 (1H, t, *J* 4.9, Ar-H), 7.81 (1H, d, *J* 8.0, Ar-CH), 8.5 (1H, br s, Ar-CH) and 8.74 (1H, br s, Ar-CH); δ_C (62.89 MHz; $CDCl_3$) 32.0 (CH_3), 120.0 (Ar-C), 123.4 (Ar-CH), 125.8 (Ar-CH), 126.7 (Ar-C), 135.7 (Ar-CH), 144.0 (Ar-C), 148.9 (Ar-CH) and 149.8 (Ar-CH).

2-{5-Chloro-1-[6-(5-chloro-2-pyridin-2-yl-1*H*-imidazol-1-yl)hexyl]-1*H*-imidazol-2yl}pyridine (38b)



N1-[6-({2-Oxo-2-[pyridin-2-ylmethyl)amino]acetyl}amino)hexyl]-*N2*-pyridin-2-yl methyl ethanediamide (0.881g, 2 mmol) was added portionwise to phosphorus pentachloride (1.71g, 8.2mmol) in dry acetonitrile (20 cm^3) in a modification of Wallach's procedure.[8-14] The mixture was heated under reflux for 3 h. The solvent was removed *in vacuo* to yield a black viscous oil. The oil was cooled to 0 °C and was made alkaline with concentrated ammonium hydroxide solution. The inorganic solids were filtered and washed with dichloromethane (4 × 20 cm^3). The filtrate was extracted with dichloromethane (6 × 50 cm^3), the extracts combined, dried over $MgSO_4$, filtered and evaporated to dryness. To yield a dark brown/black solid (0.392 g, 44 %). The solid was extracted with diethyl ether to afford an orange viscous oil (0.187g, 21 %). Flash chromatography on silica eluting with ethyl acetate and petroleum ether (2:1) afforded four products, one identified as the title compound, a yellow solid (0.050g, 6 %).

Yellow solid, yield 6 %, m.p. 144-145 °C; (Found: m/z, 440.1280, $C_{22}H_{22}Cl_2N_6$ requires 440.1283); ν_{max} 1588 and 789 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.35 (4H, s, CH_2), 1.75 (4H, s, CH_2), 4.58 (4H, t, *J* 7.6, CH_2), 7.15 (2H, s, Ar-CH), 7.19-7.27 (2H, m, Ar-CH) 7.7 (2H, tt, *J*, 1.72, 7.97, Ar-CH), 8.09 (2H, d, *J* 8.1, Ar-CH) and 8.51 (2H, d, *J* 4.9, Ar-CH).

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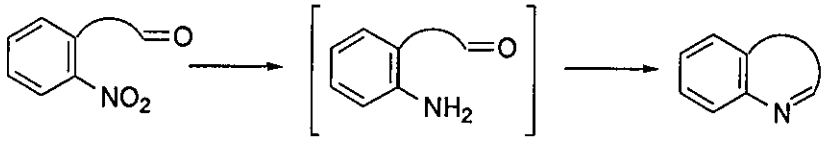
Chapter 2

Substitution Reactions of 5-Chloro-4-nitro-1*H*- imidazole Derivatives and Cyclisation Reactions Involving the Nitro Group

2.1 Introduction

2.1.1 Application of nitro compounds in synthesis

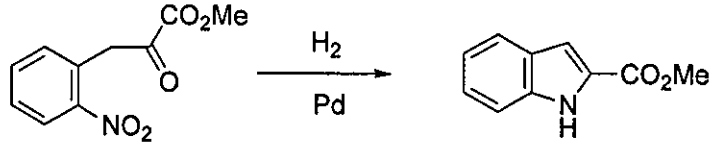
The use of the nitro goup in organic synthesis has been an important tool for incorporating a nitrogen atom into end products. The majority of reactions involve reduction of the nitro group to an amine which then participates in a condensation reaction often to form a ring, **Scheme 23.**



Reductive cyclisation

Scheme 23

One interesting example of this process is the Reissert indole synthesis. The nitro group is reduced by hydrogen over a palladium catalyst to the amine functionality. This is then trapped by the keto ester side chain affording the indole nucleus, **Scheme 24.**

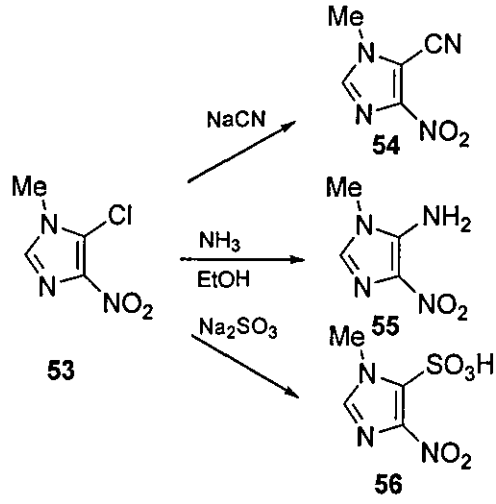


51 **52**

Scheme 24

Early work on reductive cyclisations involving 4-nitroimidazoles relevant to the compounds under investigation in this thesis include chemistry of 1-methyl-5-chloro -1*H*-imidazole **53**. The introduction of a nitro group to the 4 position of the chloroimidazole **53** renders the halogen atom susceptible to displacement by a variety of nucleophiles including cyanide ions[1], sulphite ions[2] and amines[3]. These reactions are typical examples of S_NAR substitutions involving addition and elimination, with the nitro group stabilising the negative charge in the intermediate. Examples include the conversion of the chloronitroimidazole **53** to the nitrile **54** when heated with sodium or potassium cyanide.

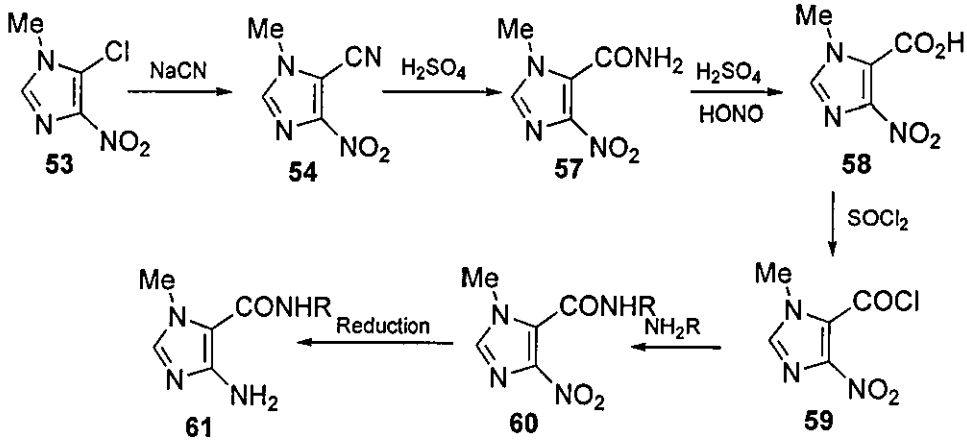
Treatment of **53** with ethanolic ammonia at 140 °C, or with sodium sulphite, affords the amine **55** and sulphonic acid **56**, respectively, **Scheme 25**.



Scheme 25

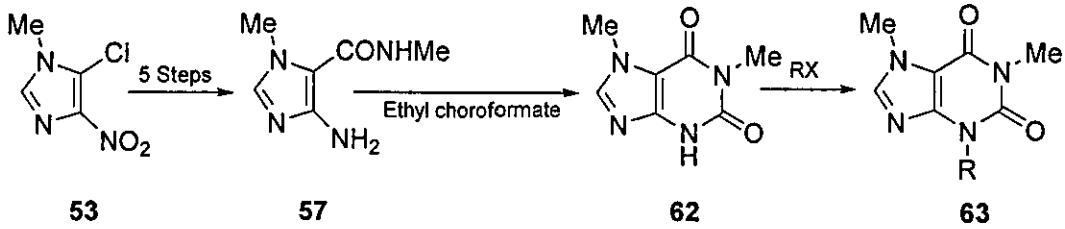
1-Methyl-5-chloro-4-nitro-imidazole **53** has been used as a starting material for the preparation of 1-methyl-4-amino-5-imidazolecarboxylic acid and its esters and amides.[4,5] Acid hydrolysis of the nitrile **54** converts it into 1-methyl-4-nitro-5-imidazolecarboxamide **57** which is resistant to acid hydrolysis. Treatment of **57** with concentrated sulphuric acid and sodium nitrite however has been used to convert the amide into the imidazolecarboxylic acid **58**. Subsequent treatment with thionyl chloride affords the acid chloride **59**, which is readily converted into substituted amides **60** and these, on reduction, gave 1- methyl-4-amino-5-imidazole carboxamides **61**, **Scheme 26**.

Blicke has reported the use of **53** to prepare 3-substituted paraxanthines[5] by alkylation of



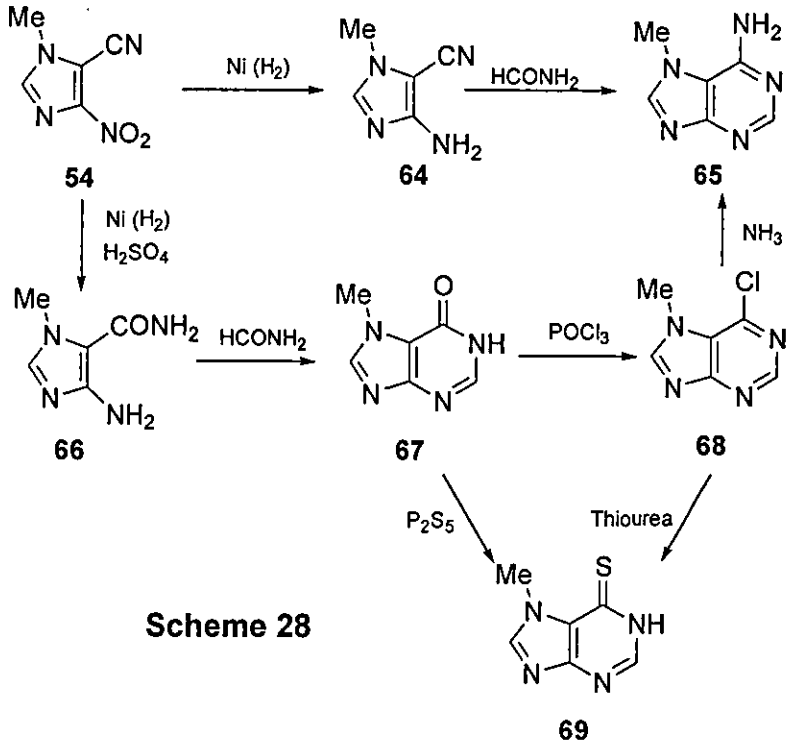
Scheme 26

the paraxanthines. Their potency as diuretics was also determined. Compound **53** has been converted to **63** by the steps shown in **Scheme 27**. 1-Methyl-4-amino-5-imidazole carboxamide **57** was condensed with ethyl chloroformate to produce 1,7 dimethylxanthine **62**. Treatment of **62** with electrophiles such alkyl or aryl halides produced 3-substituted paraxanthines **63, Scheme 27.**



Scheme 27

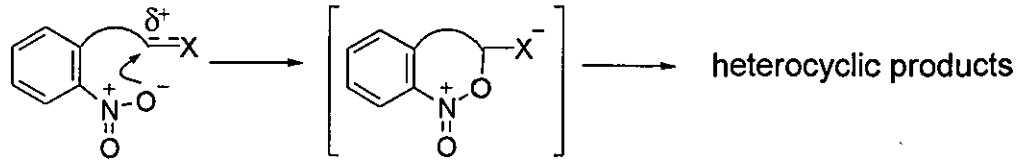
1-Methyl-5-chloro-4-nitro-imidazole **53** has been employed as a starting material in the preparation of purines[6] and thiapurines[7] as potential purine antagonists and anti-tumour agents. The purines that were synthesised were 7-methyladenine **65**, 7-methylhypoxanthine **67** from 4-amino-1-methyl-5-imidazole carbonitrile **64** and 4-amino-1-methyl-5-imidazole carboxamide **66** respectively. Chlorination yielded 6-chloro-7-methylpurine **68** as a potential candidate for an anti-tumour agent. Treatment with thiourea gave 7-methyl-6-purine thiol **69, Scheme 28.**



Scheme 28

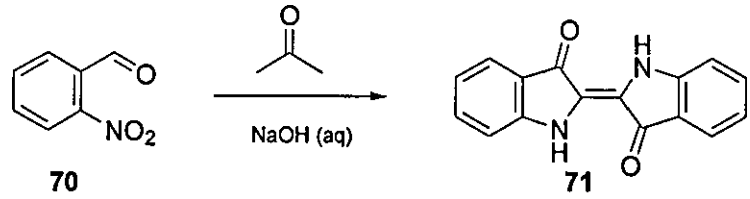
Our research is aimed at developing cyclisation reactions which involve attack by the nitro group itself onto neighbouring substituents leading to the formation of a new heterocyclic ring, **Scheme 29.**

Intramolecular reactions of the nitro group



Scheme 29

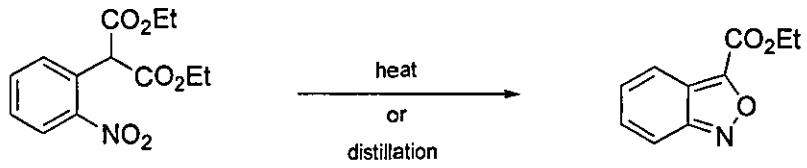
One classical example of the use of the nitro group functionality in direct nucleophilic intramolecular heterocyclisation reaction is the formation of indigo from *ortho*-nitrobenzaldehyde **70**. Indigo is a dye, a product that is used commercially in the clothes industry to dye jeans. This reaction involves the reaction of *ortho*-nitrobenzaldehyde **70** with acetone and the use of a base such as sodium hydroxide to form the acetone enolate. After a complex sequence of reactions involving 2-nitrobenzylidene acetone and a series of ring closures leading to indole derivatives, the indigo dye **71** is formed in a dimerisation process, **Scheme 30.**



70 **71**

Scheme 30

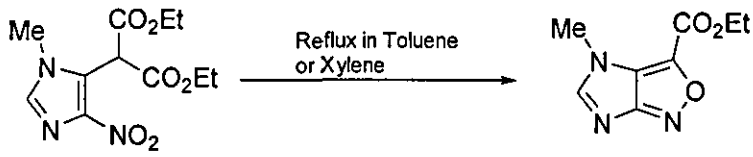
The interaction of an aromatic nitro group with *ortho* electrophilic side chains is a convenient, but a little studied way of preparing heterocycles.[8] A report[9] by Grob and Weissbach in 1961, described how 2-(2-nitrophenyl)malonate derivative, **72** was cyclised to diethyl 2,1-benzisoxazole-3-carboxylate **73** on heating or distillation in an unspecified yield, **Scheme 31.**



72 73

Scheme 31

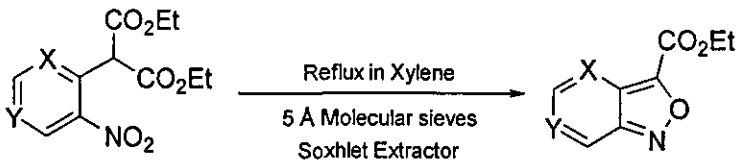
This unusual heterocyclisation reaction prompted Tennant[10] and Weaver to prepare imidazo[4,5-*c*]isoxazole heterocycles **75** in good to excellent yields by a similar method employing nitroimidazolyl malonates **74**, **Scheme 32**. More recently Duffy and Tennant[11] have extended this reaction and constructed isoxazolo[3,4-*b*]pyridines **77** and isoxazolo[3,4-*d*]pyrimidines **79** heterocyclic ring systems, by employing molecular sieves to displace the reaction equilibrium in favour of the fused isoxazole products **Scheme 33.**



74 75

Scheme 32

These reactions have inspired us to attempt to understand the chemistry involved in these reactions, and to extend the scope of the process preparing various nitro substituted heterocyclic malonate derivatives and investigating their thermolytic conversion into the corresponding fused isoxazoles.



76 X=N, Y=C
78 X=N, Y=N

77 X=N, Y=C
79 X=N, Y=N

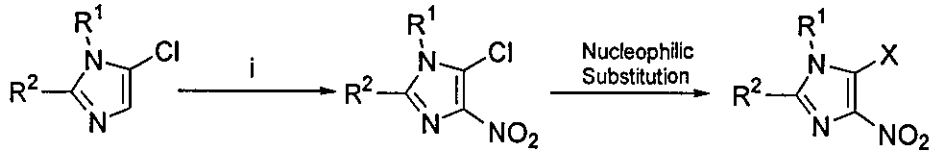
Scheme 33

2.2 Results and Discussion

2.2.1 Chemistry of 5-Chloro-4-Nitro-imidazoles

As part of an investigation into preparing substituted imidazole compounds as useful intermediates for further elaboration we have investigated the displacement of chloride from 5-chloro-4-nitroimidazoles, **53** and **80**.

5-Chloro-1*H*-imidazole derivatives **53** and **80** are synthetically useful intermediates and can be prepared by the Wallach reaction discussed in Chapter 1. Compounds **53** and **80** was nitrated under classical conditions[1] to give **53** and **80** in 88 % and 98 % yields respectively, **Scheme 34**.



37 R^1 R^2

a = Me H
b = Et Me

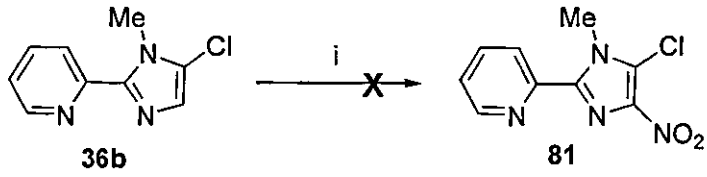
R^1 R^2 Yield/%

53 = Me H 88
80 = Et Me 98

Reagents and conditions: i, HNO_3, H_2SO_4, 100 °C.

Scheme 34

Nitration was carried out on 2-(5-chloro-1-methyl-1*H*-imidazol-2-yl)pyridine **36b** using classical nitration conditions of three equivalents of concentrated sulphuric acid and fuming nitric acid, **Scheme 35**. However this did not give the nitrated product **81** and starting material was recovered unchanged. Nitration using nitronium tetrafluoroborate in dichloromethane under inert and dry conditions dissappointingly failed to give the desired product. This may be due to the pyridine substituent removing the electron density from the imidazole ring, making it less susceptible to electrophilic attack.

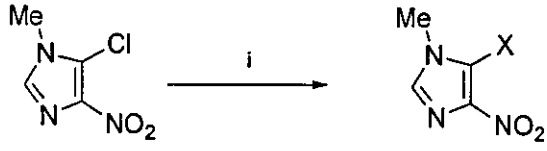


36b 81

Reagents and conditions: i, HNO_3, H_2SO_4, 100 °C.

Scheme 35

The chlorine substituent is activated by the single nitro group (electron acceptor) in the *ortho* position which undergoes nucleophilic displacement by a variety of nucleophiles. Nucleophilic displacement reactions with various amine compounds were investigated, **Scheme 36, Table 2.1** and with a range of other nucleophiles, **Scheme 37.** The products were prepared in very good yields. Methanol was found to be an effective solvent for the reaction with amines and ethanolamine, diethanolamine and cyclopropylamine all reacted successfully to give the substituted imidazole **85, 86** and **87** shown in **Table 2.1.** DMF on the other hand was a good solvent for the reaction with anionic nucleophiles such as azide and cyanide, **Scheme 37.**



53 85-87

*Reagents and conditions: i, Substrates **82-84**, Methanol, Reflux.*

Scheme 36

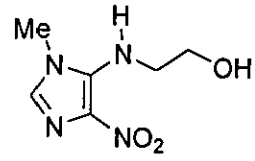
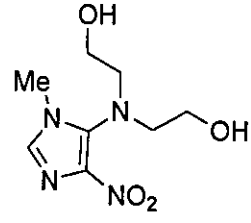
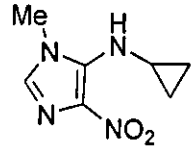
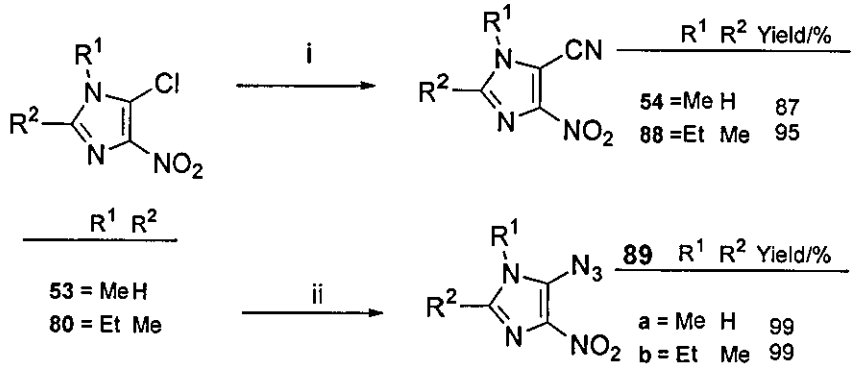
Substrates	Product	Yield (%)
Ethanolamine **82**	 **85**	71
Di-ethanolamine **83**	 **86**	70
Cyclopropylamine **84**	 **87**	86

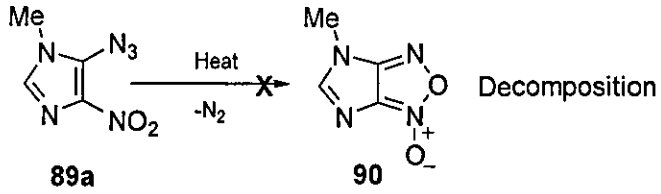
Table 2.1



Reagents and conditions: i,NaCN , DMF, R.T. ii, NaN_3, DMF, R.T.

Scheme 37

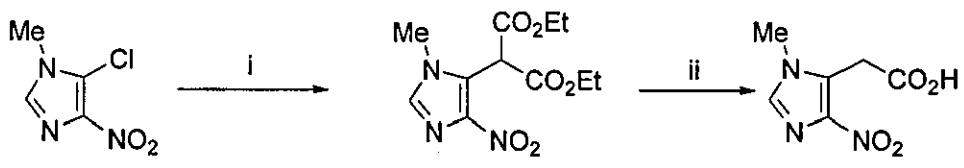
The azide[25] **89a** was of interest as it was thought thermolysis by attack of the nitro group oxygen would lead to the liberation of nitrogen and cyclisation to give the imidazo fused furazan N-oxide, **90**. Such a reaction is known in the benzene series.[12] However, disappointingly this was unsuccessful on heating the azide **89a** in either acetonitrile or tetrachloroethane as the compound decomposed and complex gums were obtained. The azide was stable in boiling dichloromethane and compound **89a** was treated with rhodium di-acetate in dichloromethane in an attempt to generate **90** by a hoped for milder catalytic decomposition of the azide by the metal. However this was again unsuccessful, **Scheme 38**.



89a **90**

Scheme 38

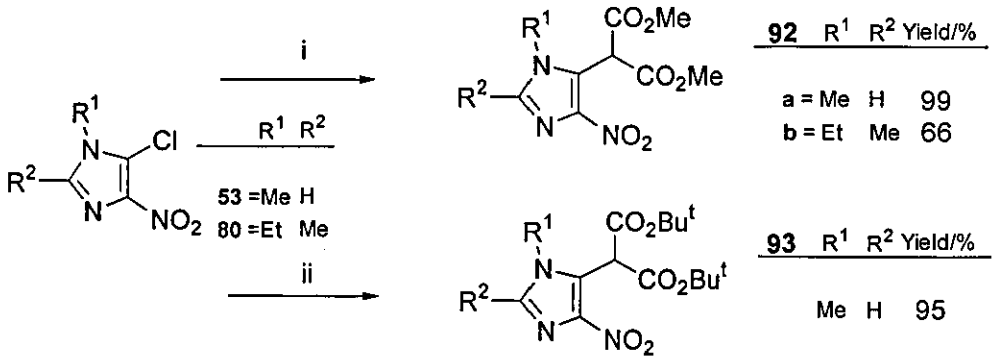
It was then decided to investigate the displacement of chloride from substituted 5-chloro-4-nitroimidazoles by stabilised carbanions derived from active methylene compounds to generate synthetically useful side chain functionalised imidazole derivatives. One report[13] described the anion of diethyl malonate displacing the chloride in **53** to give **74**. Acid hydrolysis and decarboxylation then gave **91**, **Scheme 39**. This methodology was adopted using various active carbanions. The use of sodium methoxide in methanol was found to be effective and the dimethyl malonate derivatives **92a** and **92b** were successfully prepared. Treatment of **53** with potassium tertiary butoxide and tertiary butanol also proved effective in preparing di-*t*-butyl malonate derivative **93** in good yield, **Scheme 40**.



53 **74** 82 % **91** 87 %

Reagents and conditions: i, Diethyl malonate, NaOEt, Ethanol, Reflux, Soxhlet. ii,HCl, Reflux.

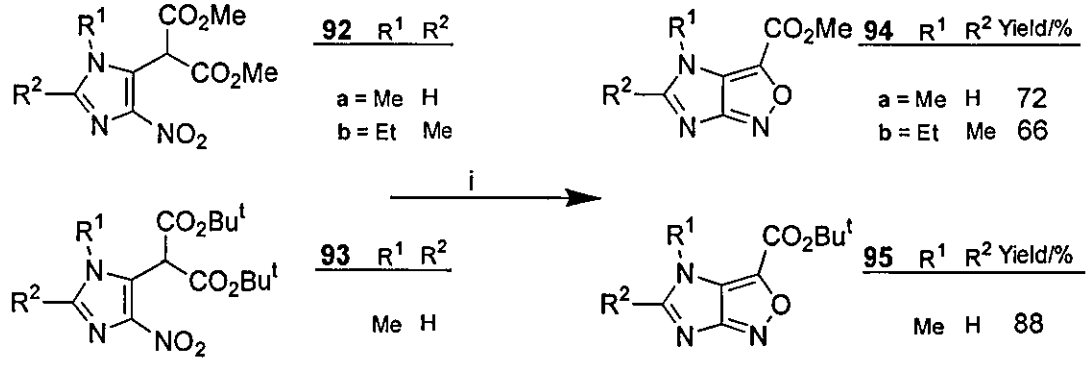
Scheme 39



Reagents and conditions: i, Dimethyl malonate, NaOMe, MeOH, Reflux, Soxhlet.
ii, Di-tert-butyl malonate, KOBu^t, tert-butanol, Reflux, Soxhlet.

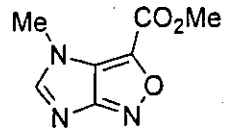
Scheme 40

In order to study the reactivity of these compounds towards cyclisation we have heated them in toluene under high dilution to try to prevent tar formation, and in the presence of molecular sieves to remove methanol. This led to smooth conversion to the 4*H*-imidazo[4,5-*c*]isoxazole derivatives **94a**, **94b** and **95** in high yields, **Scheme 41**. The structures of the imidazo[4,5-*c*]isoxazoles were supported by NMR spectroscopy, mass spectrometric and analytical data. Crystals suitable for X-ray diffraction were prepared for **94a**, and an X-ray crystal structure of **94a** has been obtained, the first for an imidazo[4,5-*c*]isoxazole. This is shown in **Figure 2.1**, (see also **Appendix 8**). This firmly establishes the structural identity of this fused aromatic compound.



Reagents and conditions: i, Tofuene, Molecular sieves, Reflux, Soxhlet.

Scheme 41



94a

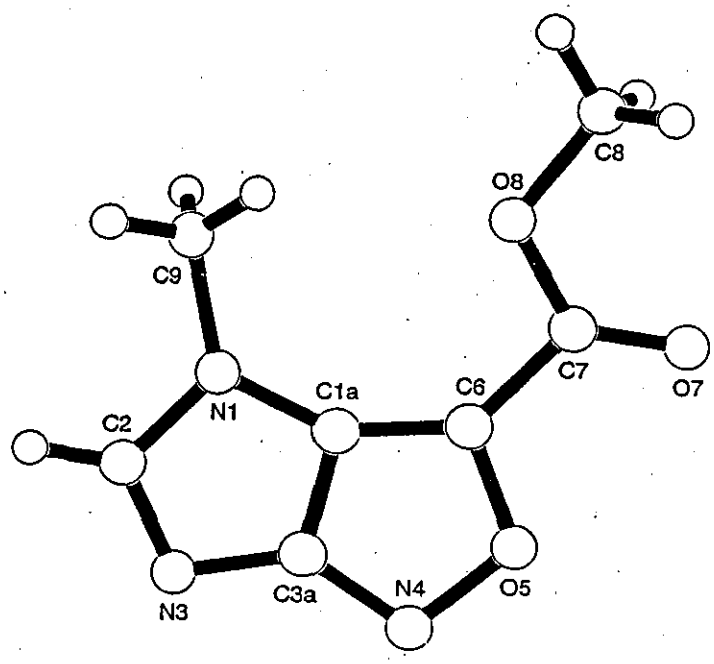
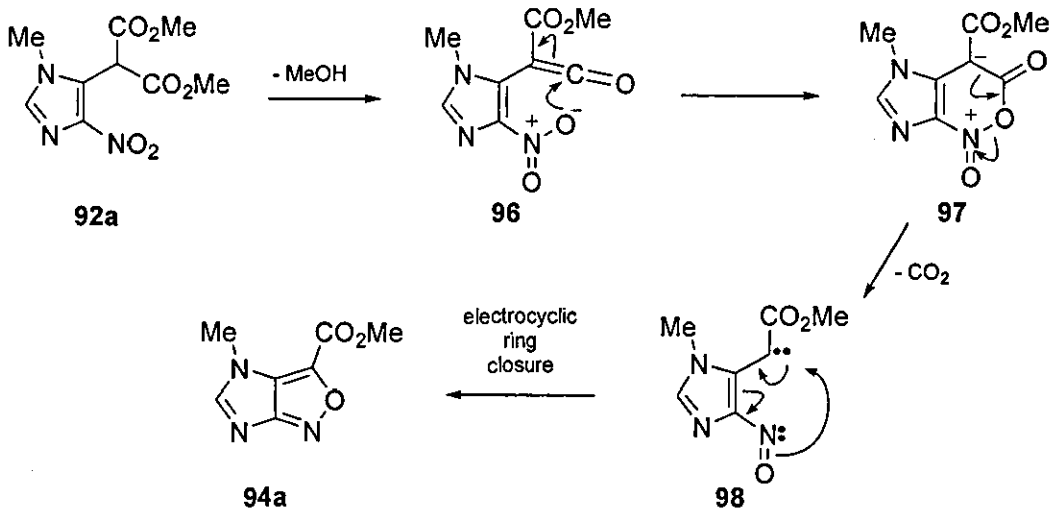


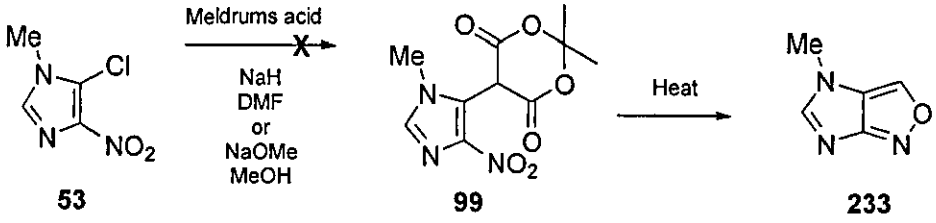
Figure 2.1, X-ray crystal structure of methyl 4-methyl-4*H*-imidazo[4,5-c]isoxazole-3-carboxylate (94a).

The thermal transformation of the malonate derivative **92a**, into the corresponding imidazo fused isoxazole **94a** can be rationalised by the mechanism postulated by Tennant[10] and Weaver and in later further studies by Tennant[11] and Duffy. The cyclisation reaction involves the participation of the nitro substituent as first demonstrated by Grob and Weissbach.[9] Initial expulsion of methanol, generates a reactive ketene intermediate **96**. Nucleophilic interaction of the nitro group with the ketene intermediate afffords the cyclic oxoimidazo[4,5-*c*]-1,2-oxazin-*N*-oxide betaine **97**. Transformation by carbon dioxide extrusion generates the nitroso carbene **98**, and subsequent electrocyclic ring closure produces the isoxazole ring, **Scheme 42**.



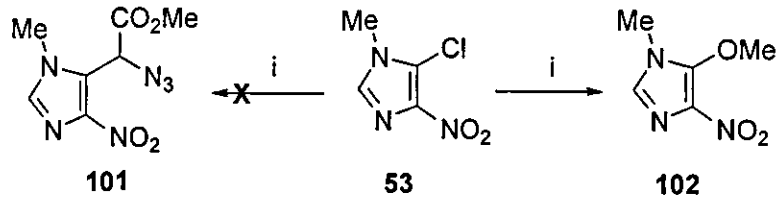
Scheme 42

If this mechanism is correct, it should be possible to use a variation of the reaction to prepare the 3-unsubstituted imidazo[4,5-*c*]isoxazole **233**. This would involve treatment of the anion of Meldrums acid (isopropylidene malonate) with the chloro nitro imidazole **53** to give the adduct **99, Scheme 43**. Thermolysis of compound **99** may then liberate acetone and carbon dioxide to give a ketene intermediate which could cyclise to the 3-unsubstituted isoxazole **233, Scheme 43**. Disappointingly, this approach was not very successful and the nitroimidazolyl Meldrum's acid adduct **99** could not be formed either by carrying the reaction out with sodium hydride in DMF, or using sodium methoxide in methanol. In both cases only starting materials were recovered. This lack of reaction may be due to the anion of Meldrum's acid being too stabilised to react, or since it is a more rigid molecule than dimethyl malonate, for steric reasons.



Scheme 43

Other nucleophilic displacement reactions of chloro nitro imidazole **53** were carried out with simple carbanions. One experiment involved the anion of ethyl nitroacetate, under the same conditions as for the synthesis of **99**. However, this reaction failed to give the product and led to the recovery of starting material. Another reaction was investigated which employed methyl azidoacetate, **100** with chloro-nitro imidazole **53**. Methyl azidoacetate, **100** was prepared successfully by the reaction of methyl bromoacetate and sodium azide. The reaction between the chloro-nitroimidazole **53** and methyl azidoacetate, **100** was then investigated using sodium methoxide as base in methanol. Instead of the expected addition product **101**, methoxy nitro imidazole **102** was formed in 56 % yield. The product formed lacked an azide band in its I.R spectrum and the mass spectrum showed a parent ion signal at m/z 157.0487 consistent with the molecular formula $C_5H_7N_3O_3$, indicating the presence of only three nitrogen and three oxygen atoms in the molecule. The reaction had led only to the unwanted methoxy substituted imidazole, which must have arisen by direct reaction of methoxide with chloro-nitroimidazole **53**, **Scheme 44**.

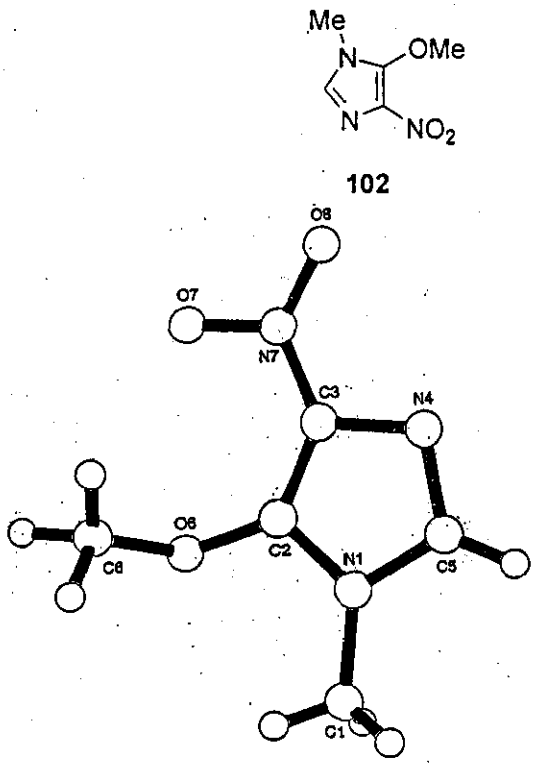


101 **53** **102**

Reagents and conditions: i, Methyl azidoacetate (100), NaOMe, MeOH.

Scheme 44

The absolute structure of compound **102** was determined by X-ray crystallography. The structure is shown in **Figure 2.2** and **Appendix 8.** The use of sodium hydride in DMF was also investigated to affect this reaction. Again, led to only recovery of starting material. Another method using *n*BuLi as a base in THF at -78 °C to form **101**, also failed to give the required product, and starting material was recovered. This suggests that the anion used for displacement may have been too stabilised, or may be too bulky for the reaction to take place.



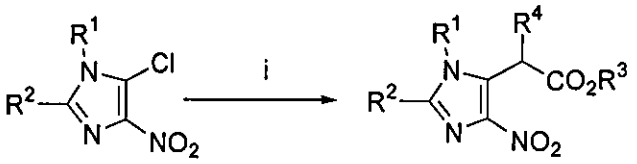
102

Figure 2.2, X-ray structure of 5-methoxy-1-methyl-4-nitro-1*H*-imidazole (102).

2.2.2 Synthesis of functionalised imidazoles

The successful development of the procedure for imidazo-isoxazole synthesis using 2.2 equivalents of sodium hydride in dry DMF under heating in inert and dry conditions prompted an investigation into extending the reaction to heteroaromatic carbanions to carry out nucleophilic displacement reactions with chloro-nitroimidazole **53** to prepare functionally substituted imidazoles. Treatment of heteroaromatic substrates **103-108** with sodium hydride in DMF at 0 °C, followed by addition of chloro-nitroimidazole gave a number of bright coloured compounds in very good yields as shown in **Scheme 45** and **Table 2.2** and **2.3**. Thermolysis of these compounds in toluene was expected to allow access to more interesting substituted imidazo[4,5-*c*]isoxazole derivatives. **Table 2.2** and **2.3** show the substrates and yields of the heteroaromatic substituted nitro-imidazoles. The reaction involved formation of the anion of the methylene substrates and a nucleophilic displacement of the chloride atom at *C*-5 of the imidazole **53.** Formation of the products were easily observed by the production of bright orange or red colours due to the highly

delocalised anion of the adducts. Some of the substrates were not commercially available, so they were prepared by known methods.



R1	R2	Products	R1	R2	R3	R4
53 Me	H	**109-114**	Me	H	Me or Et	CN or Heteroaryl

*Reagents and conditions: i, 2.2 NaH, Substrates **103- 109**, DMF, 0 °C - R.T.*

Scheme 45

Methyl 2-(phenylsulphonyl)ethanoate[14] **107** was prepared from methyl bromoacetate and benzenesulfinic acid sodium salt **115** in 81 % yield, **Scheme 46**. Methyl 2-pyridin-2-yl ethanoate[15] **103** and methyl 3-indole-2-yl-ethanoate[16] **118** were prepared from the reaction of carboxylic acid derivatives **116** and **117** with thionyl chloride in methanol. The yields were 75 % and 99 % respectively, **Schemes 47** and **48**.

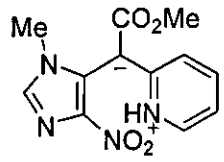
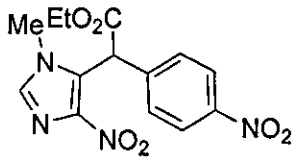
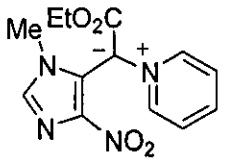
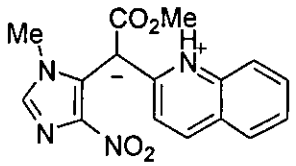
Substrates	Products	Yield (%)
Methyl 2-pyridin-2-yl ethanoate **103**	 **109**	100
Ethyl 4-nitrophenyl acetate **104**	 **110**	100
Ethyl 2-pyridinium-1-yl ethanoate bromide **105**	 **111**	86
Methyl 2-quinolin-2-yl ethanoate **106**	 **112**	96

Table 2.2, showing substrates used in preparing the substituted imidazoles with their corresponding yields.

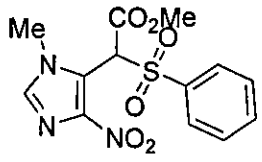
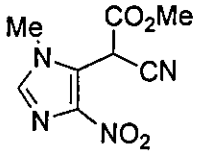
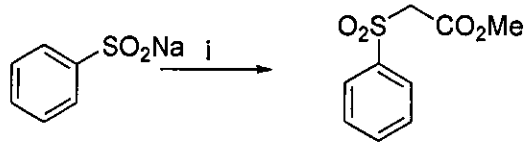
Substrates	Products	Yield (%)
Methyl 2-(phenyl sulphonyl) ethanoate **107**	 **113**	85
Methyl cyanoacetate **108**	 **114**	100

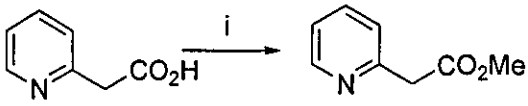
Table 2.3, showing substrates used in preparing the substituted nitroimidazolyl acetates with their corresponding yields.



115 **107**

Reagents and conditions : i) Methyl bromoacetate, methanol, Reflux.

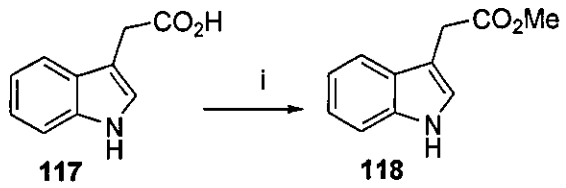
Scheme 46



116 **103**

Reagents and condition: i) Thionyl chloride, methanol -10 °C then Reflux.

Scheme 47

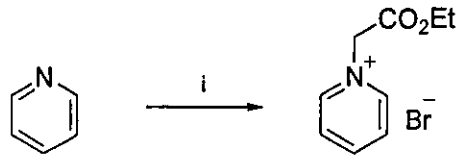


117 118

Reagents and conditions: i) Thionyl chloride, methanol -10 °C then Reflux.

Scheme 48

Ethyl bromoacetate was treated with pyridine **119** in toluene under reflux to give ethyl 2-pyridinium-1-yl ethanoate bromide[17] **105** in 78 % yield, **Scheme 49**.

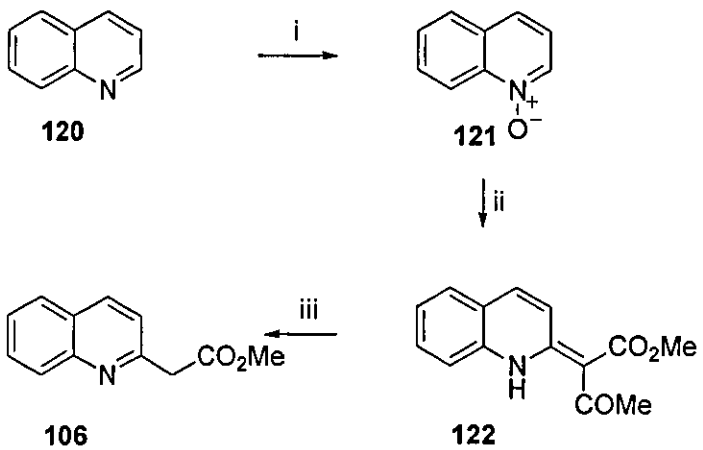


119 **105**

Reagents and conditions : i) Ethyl bromoacetate, toluene, Reflux.

Scheme 49

Methyl 2-quinolin-2-yl ethanoate **106** was prepared from a known procedure.[18] Three steps from quinoline **120** gave **106** in 87 % yield as shown in **Scheme 50**.

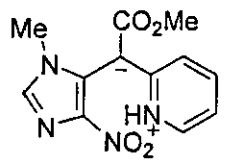


120 **121** **106** **122**

Reagents and conditions: i) mCPBA, ii) Methyl acetoacetate, Ac_2O, iii) 10 % HCl.

Scheme 50

Reaction of ethyl pyridinium-1-acetate **105** with the chloronitroimidazole **53** was also studied and was carried out using sodium hydride in DMF. This afforded a good yield of a bright red crystalline product that showed a peak at m/z 291.1092 in its high resolution mass spectrum consistent with a cation of molecular formula $C_{13}H_{14}N_4O_4$. Methyl 2-(1-methyl-4-nitro-1*H*-imidazol-5-yl)-2-pyridin-2-yl ethanoate **109** showed an interesting ^1H NMR spectrum with the signals in duplicate, **Appendix 8**. This result demonstrates compound **109** is in equilibrium with the betaine. Crystals of this compound were prepared for X-ray crystallography and showed its zwitterionic structure. The pyridine substiuent on compound **109** is behaving as a base by removing the acidic proton adjacent to the ester functionality. There is also evidence of intramolecular hydrogen bonding, **Figure 2.3** and **Appendix 8**.



109

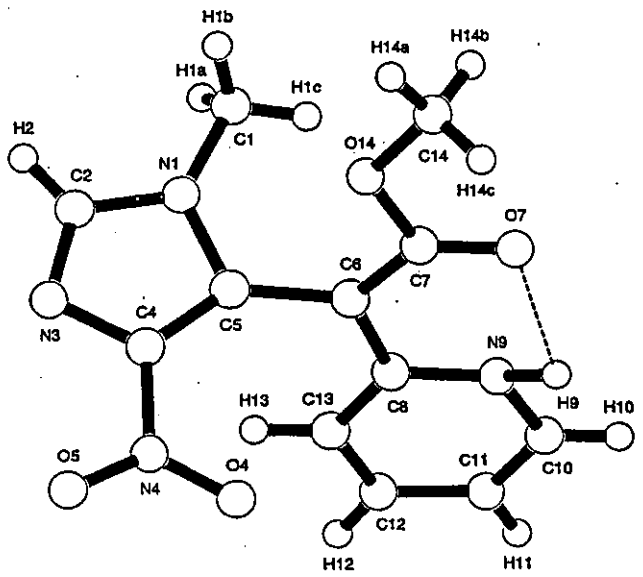
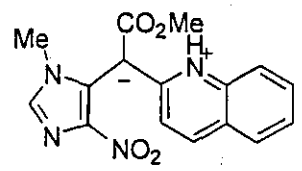


Figure 2.3, An X-ray crystal structure of methyl 2-(1-methyl-4-nitro-1*H*-imidazol-5-yl)-2-pyridin-2-yl ethanoate (109), showing it exists as a betaine.

A bright red crystalline compound with analytical and spectroscopic properties consistent with the methyl 2-(1-methyl-4-nitro-1*H*-imidazol-5-yl)-2-quinolin-2-yl ethanoate **112** was obtained when methyl 2-quinolin-2-yl ethanoate **106** was reacted with **53** under analogous conditions. Crystals were also obtained for this product and an X-ray crystallographic structure obtained, **Figure 2.4** and **Appendix 8.** The result of this shows compound **112** also behaves as a betaine in crystalline form.



112

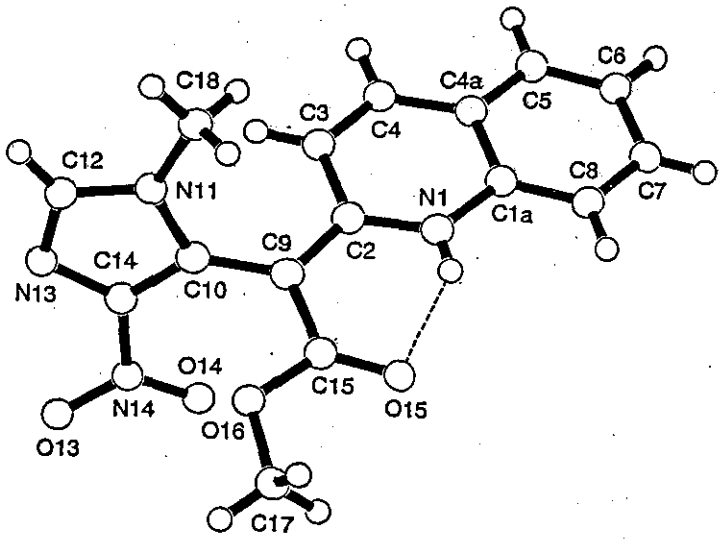
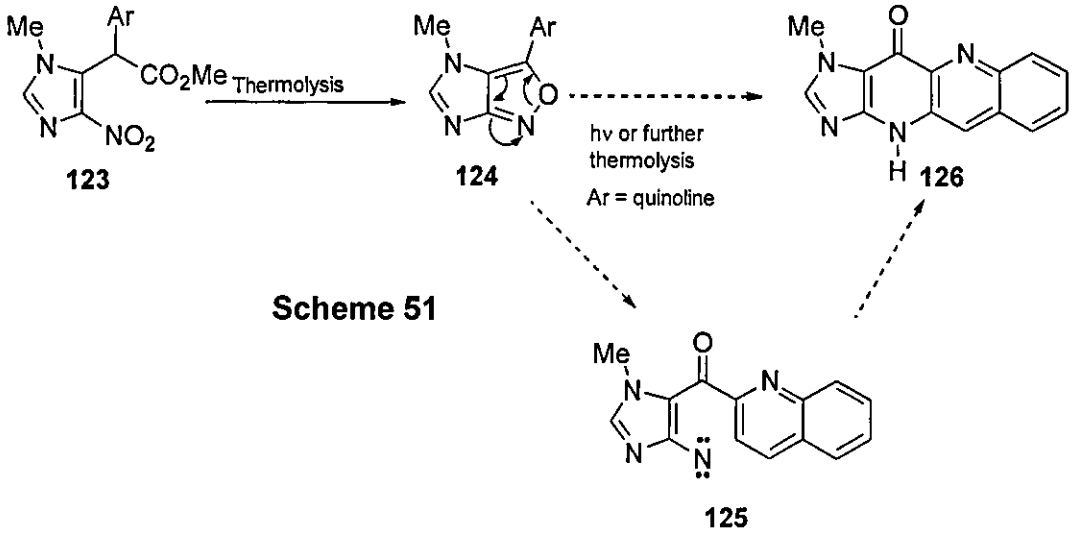


Figure 2.4, X-ray crystal structure of methyl 2-(1-methyl-4-nitro-1*H*-imidazol-5-yl)-2-quinolin-2-yl ethanoate (112), showing it exists as a betaine.

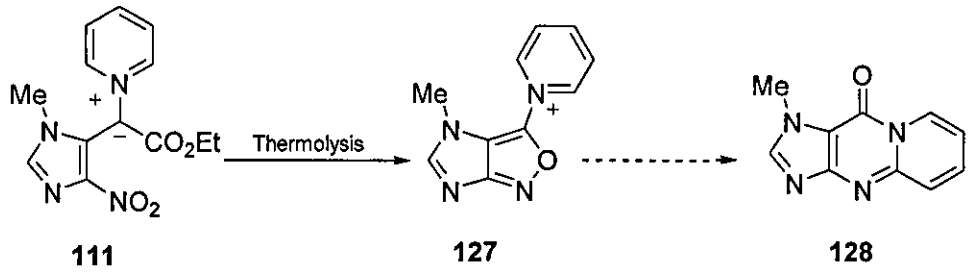
2.2.3 Thermolysis of substituted imidazoles to imidazo fused isoxazoles

It was next decided to study the thermolysis of the nitroimidazolyl heteroaryl substituted acetates **109-113** and **114** and their possible conversion into heteroaryl imidazo[4,5-*c*]isoxazoles of type **124**. These compounds were of interest as it was planned to exploit the ring strain in the isoxazole and to induce ring opening by thermal or photochemical means to generate nitrenes of type **125, Scheme 51**. These could be expected to insert into the aryl substituent at the 5-position and lead to the formation of a series of novel tetracyclic fused imidazopyridinones such as **126**. These compounds are of interest as possible DNA intercalators. Two reactions provide precedent for this work; the thermal rearrangement of 3-aryl-2,1-benzisoxazoles[19] to acridones, and a single low yielding example of the thermolysis[10] of a substituted imidazo[4,5-*c*]isoxazole to a fused pyridinone.



Scheme 51

Our first attempt in this study was to heat compound **111** with the intention of forming **128.** After heating **111** in toluene under reflux disappointingly only decomposition products were obtained. None of the isoxazole **127** or the pyridinone **128** was isolated, **Scheme 52.**

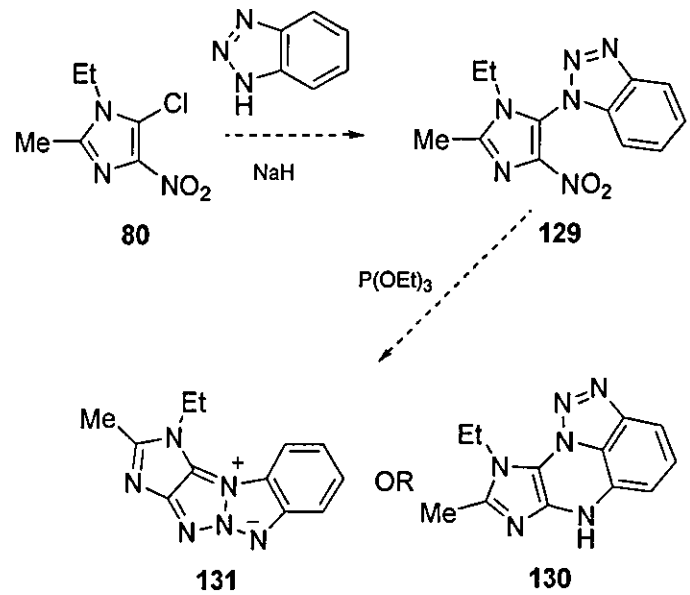


111 127 128

Scheme 52

2.2.4 Synthesis and a reaction of nitroimidazolyl benzotriazole 129

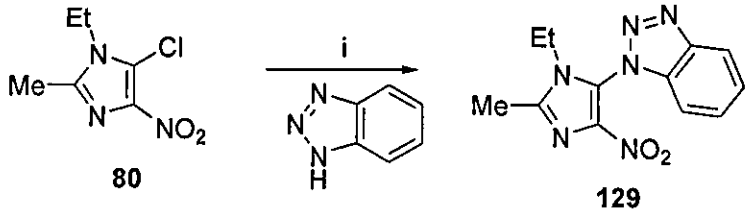
In another approach to build polycyclic heterocycle structures from the chloro-nitroimidazole, it was decided to investigate the displacement of the chlorine atom by benzotriazole anion to form nitroimidazolyl benzotriazole derivatives of the type **129**. The intention was then to study if deoxygenation of the nitro group of the imidazole could be effected leading to ring closure to form tetracyclic mesomeric betaines such as **131**. Deoxygenation of nitro group compounds has been extensively studied by Ollis[20] to form mesoionic compounds. Phosphines and phosphites are frequently employed as deoxygenation reagents to generate nitrenes from the nitro compounds[21], **Scheme 53.**



80 129 131 130

Scheme 53

Commercially available benzotriazole was treated with sodium hydride in DMF generating benzotriazole anion, followed by addition of chloro-nitroimidazole **80**. Displacement of the chlorine atom from chloro-nitroimidazole **80** gave the benzotriazolyl substituted imidazole **129** in 64 % yield, **Scheme 54**.



Reagents and condition: i) NaH, DMF, 0 ° C-R.T.

Scheme 54

This compound satisfied all expected spectroscopic data for a compound of molecular formula $C_{12}H_{12}N_6O_2$. Although, ^1H NMR spectrum of this compound showed two broad singlet signals for the methylene protons of the imidazole ethyl substituent rather than the expected quartet splitting pattern. However a variable temperature ^1H NMR study in deuterated DMSO demonstrated that the two broad singlet signals transforms into a quartet signal on heating to 100 °C, **Figure 2.5** and **2.6**. This spectroscopic experiment suggests steric hindrance is causing the two broad singlet pattern to appear due to lack of free rotation of the ethyl group.

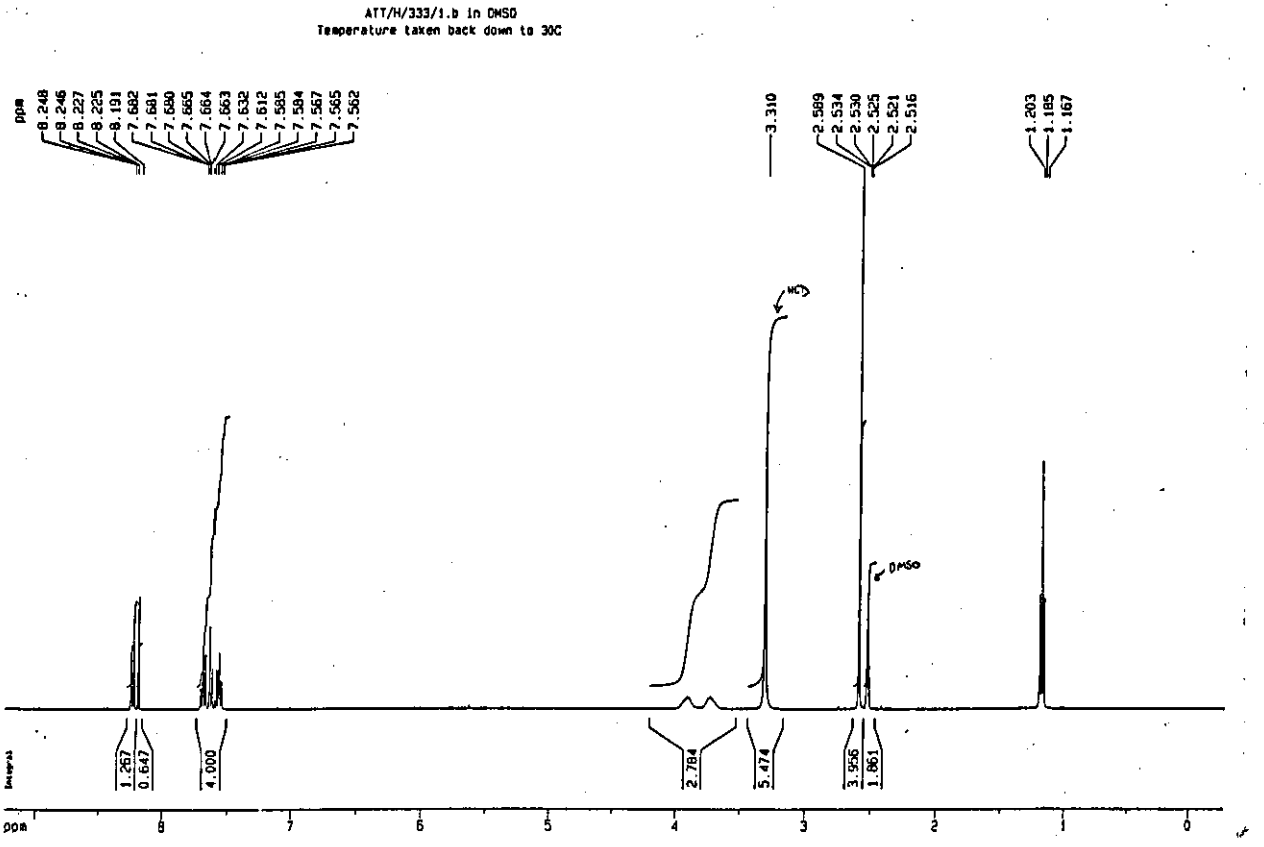


Figure 2.5, ^{1}H NMR spectrum at 400 MHz, showing 1-(1-ethyl-4-methyl-4-nitro-1*H*-imidazol-5-yl)-1*H*-1,2,3-benzotriazole (129) at 30 °C in deuterated DMSO.

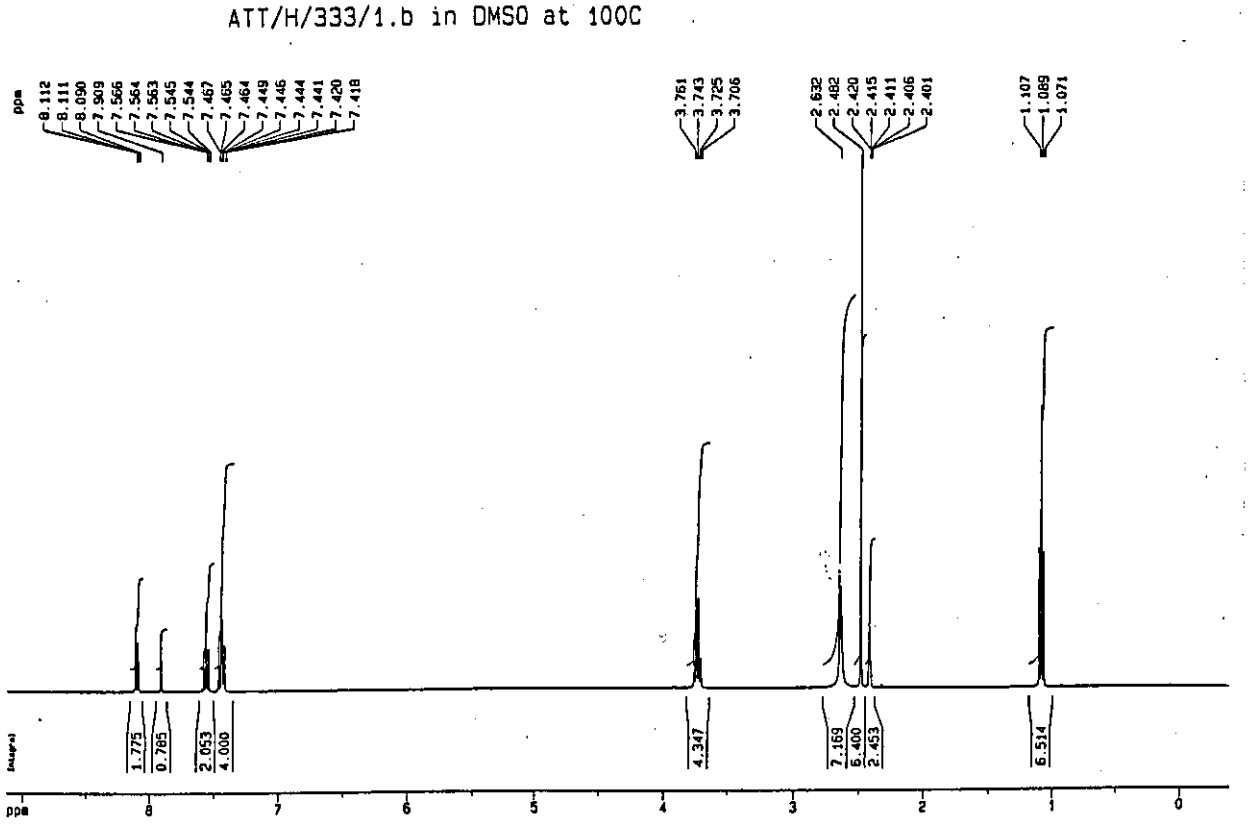
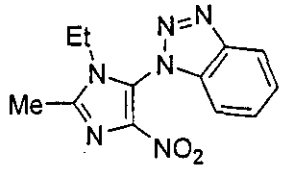


Figure 2.6, ^{1}H NMR spectrum at 400 MHz, showing 1-(1-ethyl-4-methyl-4-nitro-1*H*-imidazol-5-yl)-1*H*-1,2,3-benzotriazole (129) at 100 °C in deuterated DMSO.

In order to determine which nitrogen atom of the benzotriazole was substituted an X-ray crystallography study was carried out, **Figure 2.7 (Appendix 8)** shows the benzotriazole is substituted on the 1 position. Substitution on the 1-position is probably preferred as this shows the benzotriazole to retain a fully aromatic benzene ring. This is not possible for the alternative 2-substituted benzotriazole isomer.



129

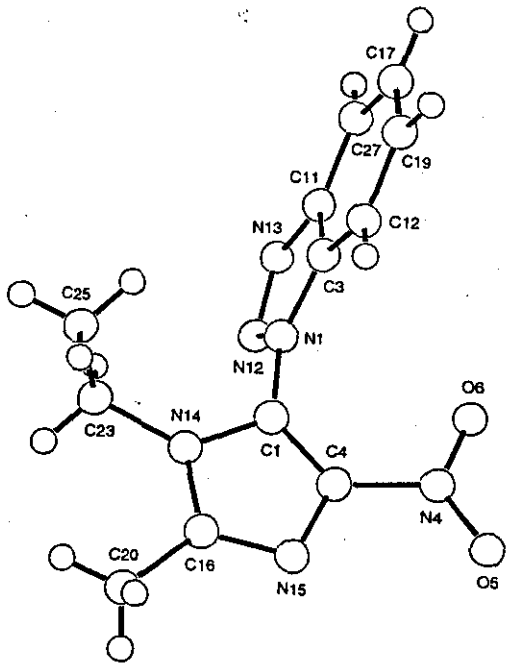
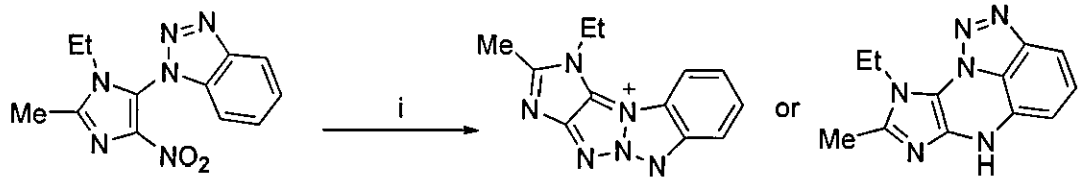


Figure 2.7, X-ray crystal structure of 1-(1-ethyl-4-methyl-4-nitro-1*H*-imidazol-5-yl)-1*H*-1,2,3-benzotriazole (129).

Benzotriazole **129**, was treated with triethyl phosphite in refluxing acetonitrile to chemically generate the nitrene by deoxygenation of the nitro group. Which can insert into the heteroaromatic ring to generate the mesomeric betaine **132** and or the fused pyrazine compound **133.** This did not facilitate the formation of these products and starting material was recovered unchanged. However, using neat triethyl phosphite as the solvent and heating under reflux conditions led to the consumption of starting material **129, Scheme 55**. A yellow solid in 67 % yield was isolated after separation and purification by flash column chromatography. This product is tentatively assigned to be **132** by evidence of methyl, ethyl and aromatic signals in ^{1}H NMR. Mass spectrometry had shown the product to have a mass of 240 corresponding to the molecular formula $C_{12}H_{12}N_6$ of product **132.** Further work is needed to understand this reaction and time constraints have prevented this.



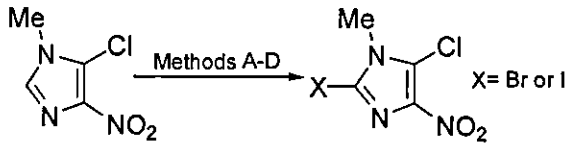
129 **132** **133**

Reagents and conditions: i) Triethylphosphite, reflux.

Scheme 55

2.2.5 Attempted synthesis of 2-substituted imidazoles

As difficulty had been encountered in preparing 2 substituted 5-chloro imidazoles by the Wallach reaction, as discussed in chapter one, it was thought to prepare halogenated imidazoles substituted on the two position. Reports[22, 23] have shown the 2-position of various substituted imidazoles can be halogenated. If the 2-position of imidazole derivative **53** could be halogenated, this would allow further elaboration to give another heterocyclic ring for example by palladium coupling reactions. Several approaches were investigated to prepare 2-bromo or 2-iodo substituted imidazoles **134, Scheme 56** by known methods.[22-25]



53 134

Scheme 56

Treatment of the chloro-nitroimidazole **53** with iodine, or NBS under both anionic and radical forming reactions all failed to give the expected 2-substituted compounds **134** as only starting material was recovered in each case, **Table 2.4.**

Method	Reagent and conditions	X
a	1.1 eq. NaH, NBS and DMF. 0°C-R.T under N_2	Br
b	1.1 eq. nBuLi, Br_2 and THF -78°C under N_2	Br
c	AIBN, NBS, CCl_4	Br
d	1.1 eq. nBuLi, I_2 and THF -78°C under N_2	I

Table 2.4, Methods of preparing 2-Halogenated imidazoles.

The reason for un-reactivity of **53** under the conditions examined may be due to the stability of the *C*-2 anion of **53** which may be too stabilised due to the influence of the nitro group. Substitution at *C*-2 by this approach would require further detailed and systematic study and was not carried out in the present research.

2.3 Conclusion

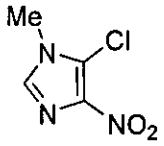
The chloro-nitroimidazoles **53** was shown to be an important intermediate in heterocyclic synthesis. The chlorine atom was displaced by a variety of nucleophiles, including substituted amines and azide, affording various novel distinct functional imidazoles. Displacement reactions with the anions of malonate esters provided a very good route to imidazo fused isoxazoles by thermolysis involving a cyclisation reaction of the nitro group. The first X-ray structure of a derivative of the imidazo[4,5-*c*]isoxazole ring system was obtained.

Active heteroaromatic methylene compounds were prepared and successful displacement reactions were carried with their carbanions with the chloro-nitroimidazole **53** to give nitro imidazolyl heteroaryl acetate derivatives. Spectroscopic and X-ray analysis confirmed their precise structures. Attempts to thermolyse one of these compounds to form imidazo fused isoxazoles, were carried out, however without success. Time prevented a full study on the thermolysis of all the heteroaryl acetates prepared. A nitroimidazolyl benzotriazole derivative **129**, was successfully prepared, and experiments to reductively cyclise it with triethyl phosphite were studied. A product was isolated and speculatively thought to be the mesomeric betaine **132**. The reaction was not investigated further as other areas of chemistry were proving more fruitful.

2.4 Experimental

For general experimental procedures see Chapter 1, section 1.8.1.

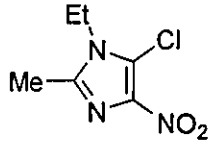
5-Chloro-1-methyl-4-nitro-1*H*-imidazole (53)



Concentrated sulphuric acid (20.6 g, 0.21 mol) was added dropwise to 5-chloro-1-methyl-1*H*-imidazole **37a** (8.16g, 0.070 mol) at 0 °C. Fuming nitric acid (13.2 g, 0.21 mol) was added dropwise to the reaction mixture. The mixture was heated at 100 °C for 3 h. The reaction was cooled to room temperature and poured over ice. The solid and the aqueous phase were extracted with dichloromethane (30 cm^3) and the organic layer washed with saturated sodium hydrogen carbonate (3 × 20 cm^3). The organic layer was separated and the aqueous phase was extracted with dichloromethane (4 × 20 cm^3). The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to dryness to yield a white solid, which was dried under vacuum (10.6 g, 94 %).

White solid, yield 94 %, m.p. 147-148 °C (lit.,[1] 145-146 °C); (Found: m/z, 160.9992, $C_4H_4ClN_3O_2$, requires 160.9992); ν_{max} 1678, 1528, 1504, 1384 and 1353 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.76 (3H, s, N-CH_3) and 7.52 (1H, S, Ar-CH); δ_C (100.61 MHz; $CDCl_3$) 32.8 (N- CH_3), 53.5 (Ar-C), 119.6 (Ar-C) and 134.6 (Ar-CH).

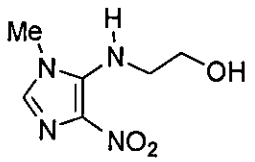
5-Chloro-1-ethyl-2-methyl-4-nitro-1*H*-imidazole (80)



Concentrated sulphuric acid (16.3 g, 0.17 mol) was added dropwise to 5-chloro-1-ethyl-2-methyl-4-nitro-1*H*-imidazole **37b** (8.0 g, 0.055 mol) at 0 °C. Fuming nitric acid (10.5 g, 0.17 mol) was added dropwise to the reaction mixture. The mixture was heated at 100 °C for 3 h. The reaction was cooled to room temperature and poured over ice. The mixture was extracted with dichloromethane (30 cm^3) and the organic layer washed with saturated sodium hydrogen carbonate solution (3 × 20 cm^3). The aqueous phase was further extracted with dichloromethane (4 × 20 cm^3). The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to dryness to yield a white solid, which was dried under vacuum (10.3 g, 98 %).

White solid, yield 98 %, m.p. 92-93 °C (lit.,[1] 88 °C); (Found: m/z, 189.0305, $C_6H_8ClN_3O_2$ requires: M, 189.0305); ν_{max} 2988, 2942, 1531, 1484, 1414, 1403, 1350, 1288, 1260, 1189, 1043, 856 and cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.40 (3H, t, *J* 7.3, CH_3), 2.48 (3H, s, CH_3) and 4.06 (2H, q, *J* 7.2, CH_2); δ_C (62.9 MHz; $CDCl_3$) 13.5 (CH_3), 14.4 (CH_3), 40.2 (CH_2), 117.9 (C) and 142.5 (C).

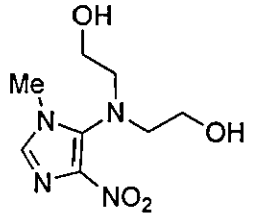
2-[(1-Methyl-4-nitro-1*H*-imidazol-5yl)amino]ethan-1-ol (85)



Ethanolamine (0.25 g, 4.2 mmol) was added to 5-chloro-1-methyl-4-nitro-1*H*-imidazole (0.32 g, 2 mmol) in dry methanol (5 cm^3). The reaction mixture was heated under reflux for 12 h. The reaction mixture was cooled to room temperature evaporated to dryness. The yellow solid was re-crystallised from hot ethanol to afford yellow crystals (0.26 g, 71 %).

Yellow crystals, yield 71 %, m.p. 156-157 °C (lit.,[26] 156-157 °C); (Found: C, 38.98; H, 5.05; N, 29.35 %; m/z, 186.0753, $C_6H_{10}N_4O_3$ requires: C, 38.71; H, 5.41; N, 30.09 %; M, 186.0753); ν_{max} 3440, 1660 and 1381 cm^{-1}; δ_H (250MHz; CD_3SOCD_3) 3.7 (3H, s, CH_3), 3.61 (4H, m, CH_2), 5.04 (1H, t, *J* 4.9 OH), 7.27 (1H, S, Ar-CH) and 7.68 (1H, t, *J* 5.8, CH_2); δ_C (62.9 MHz; CD_3SOCD_3) 34.5 (N- CH_3), 46.8 (CH_2), 61.2 (CH_2), 79.9 (Ar-C), 134.8 (Ar-C) and 145.0 (Ar-CH).

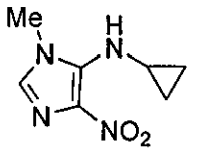
2-[(2-Hydroxyethyl)(1-methyl-4-nitro-1H-imidazol-5-yl)amino] ethano-1-ol (86)



Diethanolamine (0.44 g, 4.2 mmol) was added to 5-chloro-1-methyl-4-nitro-1*H*-imidazole (0.32 g, 2 mmol) in dry methanol (5 cm^3). The reaction mixture was heated under reflux for 12 h. The reaction was cooled and evaporated to dryness. The yellow solid was re-crystallised from hot ethanol to afford yellow crystals (0.36 g, 71 %).

Yellow crystals, yield 71 %, m.p. 148-149°C; (Found: m/z, 230.1016, $C_8H_{14}N_4O_4$ requires: M, 230.1015); ν_{max} 3294, 2987, 1651, 1573 and 1360 cm^{-1}; δ_H (250MHz; CD_3CN) 3.04 (2H, br s, OH), 3.25 (4H, t, *J* 5.6 CH_2), 3.50 (4H, t, *J* 4.7 CH_2), 3.58 (3H, s, N-CH_3) and 7.32 (1H, s, Ar-H); δ_C (62.9 MHz; CH_3OD) 31.0 (N- CH_3), 49.9 (Ar-C), 55.8 (CH_2), 60.5 (CH_2), 133.4 (Ar-CH) and 140.6 (Ar-C).

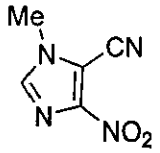
_N_-Cyclopropyl-N-(1-methyl-4-nitro-1_H_-imidazol-5-yl) amine (87)



Cyclopropylamine (0.23 g, 4 mmol) was added to 5-chloro-1-methyl-4-nitro-1*H*-imidazole (0.32 g, 2 mmol) in dry methanol (10 cm^3). The reaction mixture was heated under reflux for 12 h. The reaction was cooled and solvent evaporated. The residue was treated with water (10 cm^3) and extracted with Ethyl acetate (4 × 10 cm^3). The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to dryness to yield a yellow solid. Re-crystallisation from dichloromethane and petroleum ether affording a yellow solid (0.31 g, 86 %).

Yellow solid, yield 86 %, m.p. 171-173°C; (Found: m/z, 182.0806, $C_7H_{10}N_4O_2$ requires: M, 182.0804); ν_{max} 3350, 3082, 2987, 1601, 1560, 1433, 1386 and 1361 cm^{-1}; δ_H (250MHz; $CDCl_3$) 0.82-0.88 (2H, m, CH_2), 0.91-1.01 (2H, m, CH_2), 2.92-2.98 (1H, m, CH), 3.95 (3H, s, N-CH_3), 6.92 (1H, s, Ar-H) and 7.37 (1H, br s, N-H); δ_C (62.9 MHz; $CDCl_3$) 9.9 (CH_2), 25.8 (CH), 33.9 (N- CH_3), 132.5 (Ar-CH) and 134.5 (Ar-C).

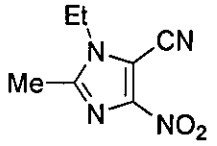
5-Cyano-1-methyl-4-nitro-1_H_-imidazole (54)



Sodium cyanide (0.303 g, 6.2 mmol) was added portionwise to stirred 5-chloro-1-methyl-4-nitro-1*H*-imidazole (1.0 g, 6.2 mmol) in dry DMF (10 cm^3). After 12 h the solvent was removed *in vacuo*. The residue was treated with water (10 cm^3). The aqueous phase was extracted with dichloromethane (3 × 15 cm^3), the organic extracts combined, dried over $MgSO_4$, filtered and evaporated to dryness to yield a white solid. Re-crystallisation from acetone/petroleum ether gave white crystals (0.82 g, 87 %).

White crystals, yield 87 %, m.p. 119-120 °C (lit.,[27] 121-122 °C); (Found: m/z, 152.0333, $C_5H_4N_4O_2$ requires M, 152.0334); ν_{max} 2853, 2238 (CN), 1514, 1497, 1337, 1310, 836, 722 and 641 cm^{-1}; δ_H (400MHz; CD_3COCD_3) 4.08 (3H, s, N-CH_3) and 8.08 (1H, s, Ar-H); δ_C (100MHz; CD_3COCD_3) 34.03 (3H, s, N-CH_3), 104.7 (CN), 108.5 (Ar-C), 140.2 (Ar-CH) and 150.9 (Ar-C).

1-Ethyl-2-methyl-4-nitro-1*H*-imidazol-5-yl cyanide (88b)



Sodium cyanide (0.78 g, 15.8 mmol) was added to stirred 5-chloro-1-ethyl-2-methyl-4-nitro-1*H*-imidazole (3.00 g, 16 mmol) in dry DMF (10 cm^3) was added dropwise. After 12 h the solvent was removed *in vacuo*. The residue was treated with water (10 cm^3). The aqueous phase was extracted with dichloromethane (3 × 15 cm^3), the organic extracts combined, dried over $MgSO_4$, filtered and evaporated to dryness to yield a viscous oil. Dry flash column chromatography eluting with dichloromethane gave an orange oil (2.7 g, 95 %). The oil did not crystallise and was used directly in the next step without further purification, (lit.,[4] m.p. 78-79 °C).

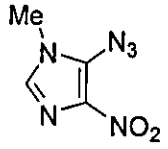
Orange oil, yield 95 %; (Found: m/z, 180.0647, $C_7H_8N_4O_2$ requires M, 180.0647); ν_{max} 2985, 2236 (CN), 1566, 1518, 1410, 1346, 1313, 1216, 1089, 968, 870, 800 and 651 cm^{-1}; δ_H (400MHz; $CDCl_3$) 1.55 (3H, t, *J* 7.2, CH_3), 2.59 (3H, s, CH_3) and 4.23 (2H, q, *J* 7.2,

CH_2); δ_C (100MHz; CD_3COCD_3) 13.8 (CH_3), 15.8 (CH_3), 42.8 (CH_3), 103.3 (CN), 108.7 (Ar-C), 148.2 (Ar-C) and 150.3 (Ar-C).

5-Azido-4-nitro-1*H*-imidazoles (89a and **89b)**

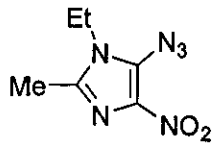
A solution of the chloronitroimidazole **53** or **80** (0.02 mol) in anhydrous dimethylformamide (25 ml) was treated with sodium azide (1.4 g, 0.022 mol) and the mixture stirred at room temperature, with the exclusion of light, for 17 h. The solvent was evaporated under vacuum and the residue treated with water (20 cm^3). The light brown insoluble solid was collected by suction filtration, washed with water and dried *in vacuo* to give the following compounds in essentially quantitative yield.

5-Azido-1-methyl-4-nitro-1*H*-imidazole (89a)



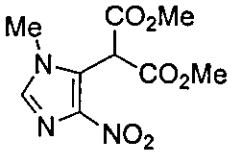
Light brown crystals, yield 99 %, m.p. 111-112 °C (lit.,[27] 102-103 °C); (Found: m/z, 168.0395, $C_4H_4N_6O_2$ requires: M, 168.0396); ν_{max} 2152 (N_3), 1551 (NO_2), 1522, 1485, and 1379 (NO_2) cm^{-1}; δ_H (250MHz; CD_3CN) 3.48 (3H, s, CH_3) and 7.35 (1H, s, H-2); δ_C (62.89 MHz; $CDCl_3$) 15.1 (CH_3), 14.0 (CH_3), 39.6 (CH_2), 129.3 (C), 135.7 (C) and 140.7 (C).

5-Azido-1-ethyl-2-methyl-4-nitro-1*H*-imidazole (89b)



Pale brown needles, yield 99 %, m.p. 72-73 °C, (Found: m/z, 196.0719, $C_6H_8N_6O_2$ requires: M, 196.0709); ν_{max} 2150 (N_3), 1550 (NO_2) and 1360 (NO_2) cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.34 (3H, t, *J* 7, CH_3CH_2), 2.39 (3H, s, CH_3) and 3.90 (3H, q, *J* 7, CH_3CH_2); δ_C (100.6 MHz; $CDCl_3$) 15.1 (CH_3), 14.0 (CH_3), 39.6 (CH_2), 129.3 (C), 135.7 (C) and 140.7 (C).

Dimethyl 2-(1-methyl-4-nitro-1*H*-imidazol-5-yl)propanedioate (92a)

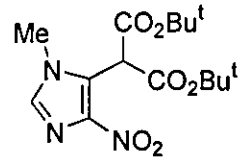


Dimethyl malonate (3.1 cm^3, 27 mmol) was added dropwise to a stirred solution of sodium methoxide (1.22g, 22.5 mmol) in dry methanol (60 cm^3). A Soxhlet extractor, containing 5-chloro-1-methyl-4-nitro-1*H*-imidazole (1.455g, 9 mmol) in its thimble was attached to the reaction flask and reaction mixture was heated under reflux for 12 h. The solvent was removed *in vacuo*. The residue was treated with water (10 cm^3) and extracted with diethyl ether (3 × 15 cm^3). The organic extract was separated. The aqueous phase was acidified with concentrated hydrochloric acid. The aqueous phase was extracted with chloroform (3 × 15 cm^3). The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated

to dryness to yield an orange solid. Re-crystallisation from ethanol/ diethyl ether gave white crystals (2.3g, 99 %).

White solid, yield 99 %, m.p. 97-98°C; (Found: m/z, 257.0636, $C_9H_{11}N_3O_6$ requires: M, 257.0648); ν_{max} 2956, 1743, 1583, 1509, 1583 and 1350 cm^{-1}; δ_H (250MHz; $CDCl_3$) 3.77 (1H, s, N-CH_3), 3.84 (3H, s, CO_2CH_3), 6.17 (1H, s, CH) and 7.49 (1H, s, Ar-H); δ_C (62.9 MHz; $CDCl_3$) 33.9 (CH_3), 47.5 (CH), 53.5 (NCH_3), 124.0 (Ar-C), 137.0 (Ar-CH) and 166.0 (CO).

Di-*t*-butyl 2-(1-methyl-4-nitro-1*H*-imidazol-5-yl)propanedioate (93)

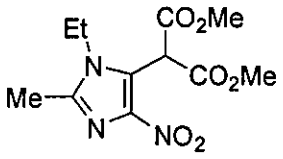


Di-*tert*-butyl malonate (8.1 g, 37 mmol) was added dropwise to a stirred solution of potassium *tert* butoxide (3.47 g, 30.9 mmol) in dry tert butanol (70 cm^3). A Soxhlet extractor, containing 5-chloro-1-methyl-4-nitro-1*H*-imidazole (2.0 g, 12.4 mmol) in its thimble was attached to the reaction flask and reaction mixture was heated under reflux for 12 h. The solvent was removed *in vacuo*. The residue was treated with water (10 cm^3) and extracted with diethyl ether (3 × 15 cm^3). The organic extract was separated. The aqueous phase was acidified with concentrated hydrochloric acid. The aqueous phase was extracted with dichloromethane (3 × 15 cm^3). The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to dryness to yield an orange solid. Re-crystallisation from ethanol gave a white solid (2.53 g, 95 %).

White crystalline solid, yield 95 %, m.p. 119.5-120.5 °C; (Found: C, 52.51; H, 6.72; N, 12.35 %; m/z, 341.1594, $C_{15}H_{23}N_3O_6$ requires: C, 52.77; H, 6.49; N, 12.3 %; M, 341.1587); ν_{max} 2992, 1715, 1498, 1359, 1524, 1144, 1098 and 745 cm^{-1}; δ_H (400 MHz;

$CDCl_3$) 1.50 (18H, s, CH_3) 3.80 (H, s, CH_3) 5.98 (1H, s, CH) and 7.46 (H, s, Ar-H); δ_C (100 MHz; $CDCl_3$) 28.2 (CH_3), 34.6 (CH), 50.6 (NCH_3), 84.4 (C), 125.4 (Ar-C), 137.38 (Ar-CH), 146.12 (C) and 164.9 (CO).

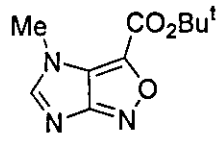
Dimethyl 2-(1-ethyl-2-methyl-4-nitro-1*H*-imidazol-5-yl)propanedioate (92b)



Dimethyl malonate (10.4 g, 79 mmol) was added dropwise to a stirred solution of sodium methoxide (3.56 g, 66 mmol) in dry methanol (100 cm^3). A Soxhlet extractor, containing 5-chloro-1-ethyl-2-methyl-4-nitro-1*H*-imidazole (5.0 g, 26.4 mmol) in its thimble was attached to the reaction flask and reaction mixture was heated under reflux for 12 h. The solvent was removed *in vacuo*. The residue was treated with water (15 cm^3) and extracted with diethyl ether (3 × 25 cm^3). The organic extract was separated. The aqueous phase was acidified with concentrated hydrochloric acid. The aqueous phase was extracted with chloroform (3 × 25 cm^3). The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to dryness to yield an orange solid. Re-crystallisation from ethanol/diethyl ether gave white crystals (5.0 g, 66 %).

White solid, yield 66 %, m.p. 118-119 °C; (Found: C, 46.22; H, 5.13; N, 14.59 %; m/z, 285.0958, $C_{11}H_{15}N_3O_6$ requires: C, 46.32; H, 5.29; N, 14.73 %; M, 285.0961); ν_{max} 2956, 1754, 1537, 1506, 1435, 1395, 1349, 1315, 1295, 1246, 1163, 1029 and 797 cm^{-1}; δ_H (250MHz; $CDCl_3$) 1.34 (3H, t, *J* 7.23, CH_3), 2.49 (3H, s, CH_3), 3.82 (6H, s, CH_3), 4.04 (3H, q, *J* 7.23, CH_2) and 5.88 (1H, s, CH); δ_C (62.89 MHz; $CDCl_3$) 13.5 (CH_3), 14.5 (CH_3), 40.6 (CH), 47.6 (CH_3), 53.3 (CH_2), 123.3 (Ar-C), 143.9 (Ar-C), 144.4 (Ar-C) and 165.5 (CO).

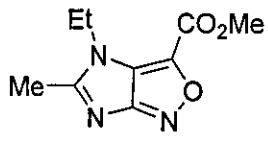
t-Butyl 4-methyl-4*H*-imidazo[4,5-c]isoxazole-3-carboxylate (95)



Di-*t*-butyl 2-(1-methyl-4-nitro-1*H*-imidazol-5-yl)propanedioate (2.39 g, 7 mmol) was dissolved in dry toluene (70 cm^3). A Soxhlet extractor, containing molecular sieves in its thimble was attached to the reaction flask and reaction mixture was refluxed for 16 h. The reaction mixture was cooled to room temperature. The solvent was evaporated to reveal a pale orange solid. The solid was re-crystallised from hot ethanol to afford a cream coloured solid (1. 26 g, 81 %).

Cream crystalline solid, yield 81 %, m.p. 119.5-120.5 °C; (Found: m/z, 223.0957, $C_{10}H_{13}N_3O_3$ requires: M, 223.0957); ν_{max} 2980, 1731, 1506, 1369, 1341, 1249, 1139, 957, 836, 764 and 651 cm^{-1}; δ_H (250MHz; $CDCl_3$) 1.63 (9H, s, CH_3), 3.90 (3H, s, CH_3) and 7.86 (H, s, Ar-H); δ_C (100 MHz; $CDCl_3$) 28.6 (CH_3), 34.0 (N-CH_3), 84.7 (C), 125.3 (Ar-C), 140.5 (Ar-C), 155.9 (Ar-C), 158.0 (Ar-CH) and 174.8 (CO).

Methyl 1-ethyl-4-methyl-4*H*-imidazo[4,5-c]isoxazole-3-carboxylate (94b)

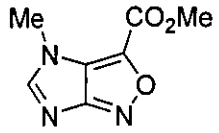


Dimethyl 2-(1-ethyl-2-methyl-4-nitro-1*H*-imidazol-5-yl)propanedioate (0.257g, 1 mmol) was dissolved in dry toluene (10 cm^3). The reaction mixture was heated under reflux for 16 h. The reaction mixture was cooled to room temperature. The solvent was evaporated

to dryness to reveal a pale orange solid. The solid was re-crystallised from hot ethanol to afford a cream solid (0.13g, 72 %).

Cream crystalline solid, yield 88 %, m.p. 94-95 °C; (Found: C, 51.58; H, 5.12; N, 19.9 %; m/z, 209.0801, $C_9H_{11}N_3O_3$ requires: C, 51.67; H, 5.29; N, 20.0 %; M, 209.0800); ν_{max} 2981, 2958, 1738, 1546, 1493, 1427, 1389, 1352, 1280, 1238, 1152, 1098, 1004, 962, 898 and 748 cm^{-1}; δ_H (250MHz; $CDCl_3$) 1.40 (3H, t, *J* 7.2, CH_3), 2.58 (3H, s, CH_3), 4.01 (3H, s, CH_3) and 4.23 (2H, q, *J* 7.2, CH_2); δ_C (100 MHz; $CDCl_3$) 14.6 (CH_3), 15.3 (CH_3), 40.7 (CH_2), 52.4 (CH_3), 126.0 (C), 136.5 (Ar-C), 156.7 (Ar-C), 167.4 (Ar-C) and 172.9 (CO).

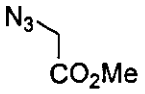
Methyl 4-methyl-4*H*-imidazo[4, 5-c]isoxazole-3-carboxylate (94a)



Dimethyl 2-(1-methyl-4-nitro-1*H*-imidazol-5-yl)propanedioate (0.257g, 1 mmol) was dissolved in dry toluene (10 cm^3). The reaction mixture was heated under reflux for 16 h. The reaction mixture was cooled and evaporated to dryness to reveal a pale orange solid. The solid was re-crystallised from hot ethanol to afford a cream solid (0.13g, 72 %).

Cream solid, yield 72 %, m.p. 180-182 °C; (Found: C, 46.31; H, 3.85; N, 22.93; m/z, 181.0489, $C_7H_7N_3O_3$ requires, C, 46.41; H, 3.89; N, 23.19 %; M, 181.0487); ν_{max} 2978, 1737 and 1586 cm^{-1}; δ_H (250MHz; CD_3SOCD_3) 3.80 (3H, s, CO_2CH_3), 3.95 (3H, s, N-CH_3) and 8.48 (H, s, Ar-H); δ_C (62.9 MHz; CD_3SOCD_3) 38.3 (CO_2CH_3), 57.9 (N-CH_3), 131.0 (Ar-C), 143.0 (Ar-C), 161.3 (Ar-C), 165.6 (Ar-CH) and 179.5 (CO).

Methyl (2-azido)ethanoate (100)

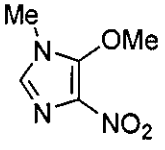


Methyl bromoacetate (6.04g, 65.3 mmol) was added to sodium azide (4.25 g, 65.3 mmol) in dry methanol (20 cm^3). The reaction mixture was stirred at room temperature for 3 h. The solvation was evaporated to dryness. The residue was treated with water (15 cm^3) and extracted with diethyl ether (3 × 20 cm^3), the organic extracts combined, dried over $MgSO_4$, filtered and evaporated to yield a colourless liquid (6.26 g, 83 %).

Colourless liquid, yield 83 %; (Found: m/z, 115.0382, $C_3H_5N_3O_2$ requires: M, 115.0383); ν_{max} 2959, 2108 (N_3) and 1748 cm^{-1}; δ_H (250MHz; $CDCl_3$) 3.79 (3H, s, CO_2CH_3) and 3.89 (2H, s, CH_2); δ_C (62.9 MHz; $CDCl_3$) 50.1 (CH_2), 52.4 (CH_3) and 169.0 (CO).

Attempted reaction of methyl 2-azidoethanoate (100) with 5-chloro-1-methyl-4-nitro-1*H*-imidazole (53)

5-Methoxy-1-methyl-4-nitro-1*H*-imidazole (102)

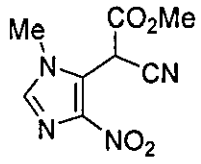


Methyl (2-azido)ethanoate (0.305g, 2mmol) in methanol was added dropwise to a stirred solution of sodium methoxide (0.226g, 4.2mmol) in dry methanol (6 cm^3) at 0 °C. After 10 min. 5-chloro-1-methyl-4-nitro-1*H*-imidazole (0.323g, 2 mmol) in methanol (3 cm^3) was added and the reaction mixture was stirred at room temperature for 1 h. The reaction

was then heated for 1 h at 70-80 °C. The solvent was removed *in vacuo*. The residue was treated with water (10 cm^3) and extracted with ethyl acetate (4 × 20 cm^3). The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to dryness to yield an orange solid (0.27.3g, 56 %), re-crystallisation from ethyl acetate and petroleum ether gave pale yellow crystals.

Yellow crystals, yield 56 %, m.p. 131-132 °C (lit.,[28] 134-135 °C); (Found: m/z, 157.0487, $C_5H_7N_3O_3$ requires: M, 157.0487); ν_{max} 2987, 1585, 1523 and 1371 cm^{-1}; δ_H (250MHz; $CDCl_3$) 3.56 (3H, s, OCH_3), 4.20 (3H, s, N-CH_3) and 7.11 (1H, s, Ar-H); δ_C (62.9 MHz; $CDCl_3$) 30.3 (CH_3), 41.8 (NCH_3), 129.0 (Ar-CH) and 131.5 (Ar-C).

Methyl 2-cyano-2-(1-methyl-4-nitro-1*H*-imidazol-5-yl)ethanoate (114)

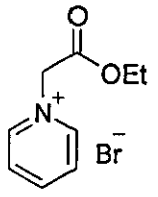


Methyl cyanoacetate (0.198g, 2 mmol) in dry DMF (5 cm^3) was added to stirred NaH in oil (0.176g, 4.4 mmol) in dry DMF (5 cm^3) at 0 °C under N_2. After 10 min 5-chloro-1-methyl-4-nitro-1*H*-imidazole (0.323g, 2 mmol) in dry DMF (5 cm^3) was added dropwise. After 1 h the solvent was removed *in vacuo*. The residue was treated with water (10 cm^3) and acidified with concentrated hydrochloric acid until neutral to pH paper. The aqueous phase was extracted with dichloromethane (3 × 15 cm^3), the extracts combined, dried over $MgSO_4$, filtered and evaporated to dryness to yield an orange solid (0.44g, 100 %). The orange solid was re-crystallised from ethanol to yield an orange solid.

Orange solid, yield 100 %, m.p. 144-145 °C; (Found: C, 42.97; H, 3.50; N, 25.04 %; m/z, 224.0548, $C_8H_8N_4O_4$ requires, C, 42.86; H, 3.59; N, 24.99 %; M, 224.0546); ν_{max} 2924, 2853, 2250 (CN), 1743, 1610, 1536, 1508, 1383 and 1353 cm^{-1}; δ_H (250MHz; $CDCl_3$) 3.87

(3H, s, CO_2CH_3), 3.93 (3H, s, N-CH_3) 6.34 (1H, s, C-H) and 7.53 (1H, s, Ar-H); δ_C (62.9 MHz; CD_3SOCD_3) 38.0 (N-CH_3), 38.7 (CH_3), 59.2 (CH), 118.5 (Ar-C), 128.5 (Ar-C), 143.2 (Ar-CH), 149.0 (Ar-C) and 168.5 (CO).

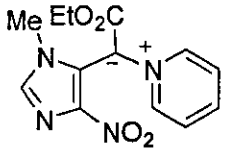
Ethyl 2-pyridinium-1-yl ethanoate bromide (105)



Ethyl bromoacetate (5.54 cm^3, 50mmol) was added to stirred pyridine (4.04 cm^3, 50mmol) in toluene (10 cm^3) at 0 °C. After 10 min. the reaction mixture was allowed to warm to room temperature and heated under reflux for 10 min. The reaction mixture was allowed to cool, the brown solid was filtered, washed with diethyl ether (3 × 10 cm^3) and dried under vacuum (9.52g, 78 %).

Brown solid, yield 78 %, m.p. 133-135 °C (lit.,[17] 135-136 °C); ν_{max} 2978, 2894, 1740, 1636 and 1578 cm^{-1}; δ_H (250MHz; CD_3OH) 1.38 (3H, t, *J* 6.6, CH_3), 4.36 (2H, q, *J* 6.3 CH_2), 5.67 (2H, br s, CH_2), 8.22 (2H, br s, Ar-H), 8.70 (1H, br s, Ar-H) and 9.02 (2H, br s, Ar-H).

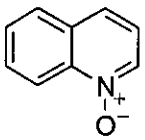
Ethyl 2-(1-methyl-4-nitro-1*H*-imidazol-5-yl)-2-pyridinium-1-yl-acetate (111)



Ethyl 2-pyridinium-1-yl ethanoate bromide (0.98g, 4 mmol) in dry DMF (5 cm^3) was added stirred NaH in oil (0.352g, 8.8 mmol) in dry DMF (5 cm^3) at 0 °C under N_2. After 10 min 5-chloro-1-methyl-4-nitro-1*H*-imidazole (0.64g, 4 mmol) in dry DMF (5 cm^3) was added dropwise. After 1 h the solvent was removed *in vacuo*. The residue was treated with water (10 cm^3) and acidified with concentrated hydrochloric acid until neutral to pH paper. The aqueous phase was extracted with dichloromethane (4 × 15 cm^3), combined, dried over $MgSO_4$, filtered and evaporated to dryness to yield a red solid (1.0 g, 86 %), the solid was re-crystallised from dichloromethane and petroleum ether.

Red solid, yield 86 %, m.p. 179-180 °C; (Found: m/z, 291.1092, $C_{13}H_{15}N_4O_4$ requires: M, 291.10932); ν_{max} 2924, 2852, 1745, 1631, 1600, 1538, 1371 and 1351 cm^{-1}; δ_H (250MHz; $CDCl_3$) 1.23 (3H, t, *J* 7.0, CH_3), 3.62 (3H, s, N-CH_3), 4.18 (2H, q, *J* 7.2 Ar-H), 7.49-7.76 (4H, m, Ar-H) and 8.66 (1H, br s, Ar-H); δ_C (62.9 MHz; $CDCl_3$) 14.9 (CH_3), 33.2 (N-CH_3), 58.6 (CH_2), 125.8 (Ar-CH), 133.6 (Ar-CH), 136.0 (Ar-CH) and 139.8 (Ar-CH).

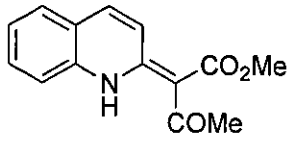
Quinoline-1-oxide (121)



Quinoline (5 cm^3, 50 mmol) was added dropwise to a stirred mixture of *m*CPBA (17.3g, 100 mmol) in chloroform (50 cm^3). After 2 h the reaction mixture was treated with 5% sodium hydrogen carbonate solution. The organic layer was separated. The aqueous phase was extracted with dichloromethane (3 × 20 cm^3). The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to dryness to yield a brown solid. Recrystallisation from ethyl acetate afforded a cream coloured solid (7.25g 100 %).

Cream solid, yield 100 %, m.p. 59-60 °C (lit.,[29] 52-55 °C); m/z, 145 (100%) and 90 (85 %); ν_{max} 2987, 1575, 1514, 1291, 1265, 1225 and 1207 cm^{-1}; δ_H (400MHz; $CDCl_3$) 7.28-7.49 (2H, m, Ar-H), 7.65 (1H, t, *J* 7.0 Ar-H), 7.79-8.03 (3H, m, Ar-H) and 8.78 (1H, dd, *J* 6, 8.7, Ar-H); δ_C (62.9 MHz; $CDCl_3$) 119.1 (Ar-CH), 120.7 (Ar-CH), 126.6 (Ar-CH), 127.6 (Ar-CH), 129.2 (Ar-CH), 131.9 (Ar-CH), 140.8 (Ar-CH), 141.0 (Ar-C) and 167.9 (Ar-C).

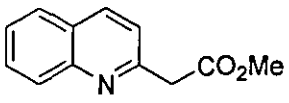
Methyl 1,2-Dihydro-2-quinolylideneacetoacetate (122)



Methyl acetoacetate (6.56 cm^3, 60.8 mmol) was added dropwise to a stirred solution of quinoline-1-oxide (7.0g, 47.8 mmol) in acetic anhydride (14 cm^3). After the addition the reaction was heated to 35-45 °C for 12 h. The reaction was allowed cool to room temperature and then poured on ice. The yellow solid was filtered, washed with water (10 cm^3) and cold methanol (10 cm^3). The solid was dried under vacuum. Re-crystallisation from hot methanol afforded a yellow solid (8.11g, 71 %).

Yellow solid, yield 71 %, m.p. 118-119 °C (lit.,[18] 119.5-120.5); m/z, 201 (M^+ 10%) and 143 (90 %); ν_{max} 2987, 1685, 1630, 1587 cm^{-1}; δ_H (400MHz; $CDCl_3$) 2.45 (3H, s, $COCH_3$), 3.85 (3H, s, CO_2CH_3), 7.35 (1H, t, *J* 7.0 Ar-H), 7.52 (1H, d, *J* 8.1 Ar-H), 7.57-7.61 (2H, m, Ar-H), 7.85 (1H, d, *J* 9.5, Ar-H) and 7.92 (1H, d, *J* 9.5, Ar-H); δ_C (62.9 MHz; $CDCl_3$) 29.9 ($COCH_3$), 51.0 (CO_2CH_3), 98.0 (Ar-C), 116.5 (Ar-CH), 123.1 (Ar-C), 120.1 (Ar-CH), 124.7 (Ar-CH), 127.4 (Ar-CH), 131.2 (Ar-CH), 136.1 (Ar-C), 137.5 (Ar-CH), 154.5 (Ar-C), 170.0 (CO) and 195.5 (CO).

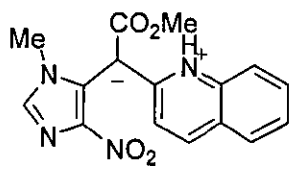
Methyl 2-quinolin-2-yl ethanoate (106)



10 % Hydrochloric acid (100 cm^3) was added dropwise to stirred methyl 1,2-dihydro-2-quinolylideneacetoacetate (8.0g, 40 mmol) over 10 min. After a further 10 min stirring at room temperature the reaction mixture was basified with saturated sodium hydrogen carbonate solution. The mixture was extracted with chloroform (3 × 20 cm^3). The organic extracts were combined and washed with water (20 cm^3). The organic phase was dried over $MgSO_4$, filtered and evaporated to dryness to yield a red/orange oil (10.4g). The oil was distilled under reduced pressure at 200 °C at 9 mbar to afford an orange oil (8.4g, 87 %).

Orange oil, yield 87 %, b.p. 200°C at 9 mbar (lit.,[18] 133-137 °C at 1mm); m/z, 201 ($M,^+$ 50%) and 143 (100 %); ν_{max} 2924, 1740 and 1621 cm^{-1}; δ_H (250MHz; $CDCl_3$) 3.72 (3H, s, OCH_3), 4.07 (2H, s, CH_2), 7.42 (1H, d, *J* 8.4 Ar-H), 7.50 (1H, t, *J* 7.23, Ar-H), 7.69 (1H, t, *J* 2.85, Ar-H) 7.78 (1H, d, *J* 8, Ar-H) and 8.1 (1H, t, *J* 8.5, Ar-H); δ_C (62.9 MHz; $CDCl_3$) 44.3 (CH_2), 52.1 (O-CH_3), 121.7 (Ar-CH), 126.3 (Ar-CH), 127.5 (Ar-CH), 128.7 (Ar-CH), 129.1 (Ar-CH), 136.7 (Ar-CH), 148.0 (Ar-C), 150.0 (Ar-C), 155.0 (Ar-C) and 171.0 (CO).

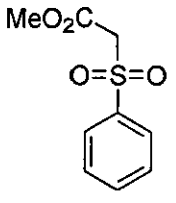
Methyl 2-(1-methyl-4-nitro-1*H*-imidazol-5-yl)-2-quinolin-2-yl ethanoate (112)



Methyl 2-quinolin-2-yl ethanoate (0.40g, 2 mmol) in dry DMF (5 cm^3) was added to stirred NaH in oil (0.176g, 4.4 mmol) in dry DMF (5 cm^3) at 0 °C under nitrogen. After 10 min. 5-chloro-1-methyl-4-nitro-1*H*-imidazole (0.323g, 2mmol) in dry DMF (5 cm^3) was added dropwise. After 1 h the solvent was removed *in vacuo*. The residue was treated with water (10 cm^3) and acidified with concentrated hydrochloric acid until neutral to pH paper. The aqueous phase was extracted with dichloromethane (3 × 15 cm^3), the extracts combined, dried over $MgSO_4$, filtered and evaporated to dryness to yield a dark red solid. Re-crystallisation from dichloromethane and petroleum ether gave a bright red crystalline solid, (0.63g, 96 %).

Red solid, yield 96 %, m.p. 194-196 °C; (Found: m/z, 326.1018, $C_{16}H_{14}N_4O_4$ requires M, 326.1015); ν_{max} 3409, 2951, 1731, 1554, 1458 and 1435 cm^{-1}; δ_H (250MHz; $CDCl_3$) 3.53 (3H, s, OCH_3), 3.68 (3H, s, N-CH_3), 6.33 (1H, dd, *J* 1.72, 9.48, Ar-H), 7.205-7.36 (2H, m, Ar-H), 7.47 (1H, s, Ar-H), 7.50-7.51 (1H, m, Ar-H), 7.53 (1H, t, *J* 1.2, Ar-H), 7.56 (1H, s, Ar-H) and 13.57 (1H, br s, N-H); δ_C (62.9 MHz; $CDCl_3$) 32.1 (N-CH_3), 51.0 (CH_3), 76.0 (C), 116.4 (Ar-CH), 116.6 (Ar-CH), 121.5 (Ar-C), 123.6 (Ar-CH), 127.6 (Ar-CH), 129.0 (Ar-C), 131.4 (Ar-CH), 135.5 (Ar-CH), 136.7 (Ar-CH), 136.8 (Ar-C), 146.0 (Ar-C), 152.2 (Ar-C) and 169.0 (CO).

Methyl 2-(phenyl sulphonyl) ethanoate[14] (107)

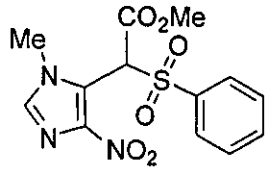


Methyl bromoacetate (0.185 cm^3, 20 mmol) was added to stirred benzenesulfinic acid sodium salt (3.28g, 20 mmol) in dry methanol (10 cm^3). The reaction mixture was heated under reflux for 12 h. The reaction mixture was cooled and the solvent removed *in vacuo* to yield a white solid. The residue was treated with water (5 cm^3). The aqueous phase was

extracted with dichloromethane (3 × 15 cm^3), the extracts combined, dried over $MgSO_4$, filtered and evaporated to dryness to yield a viscous colourless oil (2.60g, 81 %).

Colourless oil, yield 81 %, (Found: m/z, 214.0305 $C_9H_{10}O_4S$ requires M, 214.0300); ν_{max} 2953, 1743, 1584, 1447, 1325 and 1151 cm^{-1}; δ_H (250MHz; $CDCl_3$) 3.7 (3H, s, CO_2Me), 4.14 (2H, s, CH_2), 7.56-7.63 (2H, m, Ar-H), 7.67-7.74 (1H, m, Ar-H) and 7.93-7.98 (2H, m, Ar-H); δ_C (62.9 MHz; $CDCl_3$) 52.0 (O-CH_3), 60.6 (CH_2), 128.3 (Ar-CH), 129.2 (Ar-CH), 134.3 (Ar-CH), 139.0 (Ar-C) and 163.0 (CO).

Methyl 2-(1-methyl-4-nitro-1*H*-imidazol-5-yl)-2-(phenylsulphonyl)ethanoate (113)

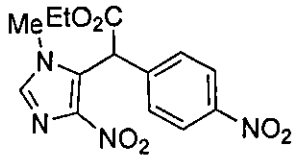


Methyl 2-(phenylsulphonyl)ethanoate (0.43g, 2 mmol) in dry DMF (5 cm^3) was added to stirred NaH in oil (0.176g, 4.4 mmol) in dry DMF (5 cm^3) at 0 °C under N_2. After 10 min 5-chloro-1-methyl-4-nitro-1*H*-imidazole (0.323g, 2mmol) in dry DMF (5 cm^3) was added dropwise. After 1 h the solvent was removed *in vacuo*. The residue was treated with water (10 cm^3) and acidified with concentrated hydrochloric acid until neutral to pH paper. The aqueous phase was extracted with dichloromethane (3 × 15 cm^3), the extracts combined, dried over $MgSO_4$, filtered and evaporated to dryness to yield a yellow solid (0.65 g). Re-crystallisation from dichloromethane and petroleum ether afforded a cream coloured solid (0.58g, 85 %).

Cream solid, yield 85 %, m.p. 130-132 °C; (Found: C, 45.07; H, 3.90; N, 12.49; m/z, 339.0522, $C_{13}H_{13}N_3O_6S$ requires, C, 46.01; H, 3.86; N, 12.38 %; M, 339.0525); ν_{max} 1751, 1560, 1508, 1448, 1330 and 1151 cm^{-1}; δ_H (250MHz; $CDCl_3$) 3.83 (3H, s, OCH_3), 4.00 (3H, s, N-CH_3), 6.8 (1H, br s, C-H), 7.53-7.63 (3H, m, Ar-H), 7.68-7.74 (1H, m, Ar-H) and 7.86-7.93 (2H, m, Ar-H); δ_C (62.9 MHz; $CDCl_3$) 35.0 (CH), 53.7 (N-CH_3), 65.2 (O-CH_3),

120.0 (Ar-C), 125.6 (Ar-C), 128.3 (Ar-CH), 129.4 (Ar-CH), 131.0 (Ar-C), 134.6 (Ar-CH), 138.4 (Ar-CH) and 163.0 (CO).

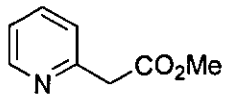
Ethyl 2-(1-methyl-4-nitro-1*H*-imidazol-5-yl)-2-(4-nitrophenyl) ethanoate (110)



Ethyl 4-nitrophenylacetate (0.42g, 2 mmol) in dry DMF (5 cm^3) was added to stirred NaH in oil (0.176g, 4.4 mmol) in dry DMF (5 cm^3) at 0 °C under N_2. After 10 min 5-chloro-1-methyl-4-nitro-1*H*-imidazole (0.323g, 2mmol) in dry DMF (5 cm^3) was added dropwise. After 1 h the solvent was removed *in vacuo*. The residue was treated with water (10 cm^3) and acidified with concentrated hydrochloric acid until neutral to pH paper. The aqueous phase was extracted with dichloromethane (3 × 15 cm^3), combined, dried over $MgSO_4$, filtered and evaporated to yield a brown solid (0.77 g). Re-crystallisation from dichloromethane and petroleum ether afforded a cream coloured solid (0.66 g, 100 %).

Cream solid, yield 100 %, m.p. 182-184 °C; (Found: C, 50.21; H, 4.10; N, 16.57; m/z, 334.0915, $C_{14}H_{14}N_4O_6$ requires, C, 50.30; H, 4.22; N, 16.76 %; M, 334.0913); ν_{max} 3409, 2951, 1731, 1554, 1458, 1435 and 1330 cm^{-1}; δ_H (250MHz; CD_3SOCD_3) 1.2 (3H, t, *J* 7.1, CH_3), 3.65 (3H, s, N-CH_3), 4.11-4.22 (2H, m, CH_2), 6.09 (1H, s, C-H), 7.61 (2H, d, *J* 8.0, Ar-H), 7.8 (1H, s, Ar-H) and 8.2 (2H, d, *J* 8.2, Ar-H); δ_C (62.9 MHz; CD_3SOCD_3) 18.9 (CH), 37.9 (N-CH_3), 50.7 (CH_3), 66.7 (CH_2), 128.4 (Ar-CH), 139.0 (Ar-C), 135.3 (Ar-CH), 142.3 (Ar-CH), 146.6 (Ar-C), 149.5 (Ar-C), 152.0 (Ar-C) and 172.5 (CO).

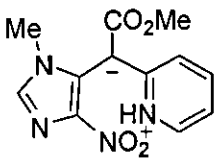
Methyl 2-pyridin-2-yl ethanoate[15] (103)



Thionyl chloride (2.1 cm^3, 29 mmol) was added dropwise to a stirred methanol (20 cm^3) at -10°C. 2-Pyridylacetic acid hydrochloride (3.30 g, 19 mmol) was added after 5 min. The reaction mixture was stirred for 2 h at -10°C. The reaction mixture was allowed to warm to room temperature and then heated under reflux for 2 h. The solvent was removed *in vacuo* to yield a brown solid. This was treated with saturated sodium hydrogen carbonate solution. The residue was extracted with dichloromethane (3 × 15 cm^3), the extracts combined and dried over $MgSO_4$, filtered and evaporated to afford an orange liquid (2.16g, 76 %).

Orange liquid, yield 76 %; m/z, 151 (M^+ 20%) and 92 (100 %); ν_{max} 2954, 1740 and 1572 cm^{-1}; δ_H (250MHz; $CDCl_3$) 3.72 (3H, s, OCH_3), 3.86 (2H, s, CH_2), 7.19 (1H, t, *J* 4.9 Ar-H), 7.29 (1H, d, *J* 7.5, Ar-H), 7.67 (1H, tt, *J* 1.9, 7.8, Ar-H) and 8.56 (1H, d, *J* 4.9, Ar-H); δ_C (62.9 MHz; $CDCl_3$) 43.6 (CH_2), 52.0 (O-CH_3), 122.0 (Ar-CH), 123.7 (Ar-CH), 136.5 (Ar-CH), 149.4 (Ar-CH), 154.2 (Ar-C) and 170.9 (CO).

Methyl 2-(1-methyl-4-nitro-1*H*-imidazol-5-yl)-2-pyridin-2-yl ethanoate (109)

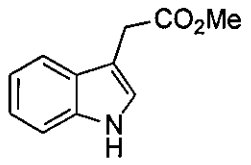


Methyl 2-pyridin-2-ylethanoate (0.30g, 2 mmol) in dry DMF (5 cm^3) was added to stirred NaH in oil (0.176g, 4.4 mmol) in dry DMF (5 cm^3) at 0 °C under N_2. After 10 min 5-

chloro-1-methyl-4-nitro-1*H*-imidazole (0.323g, 2 mmol) in dry DMF (5 cm^3) was added dropwise. After 1 h the solvent was removed *in vacuo*. The residue was treated with water (10 cm^3) and acidified with concentrated hydrochloric acid until neutral to pH paper. The aqueous phase was extracted with dichloromethane (3 × 15 cm^3), combined, dried over $MgSO_4$, filtered and evaporated to dryness. Re-crystallisation yielded an orange solid (0.55g, 100 %).

Orange solid, yield 100 %, m.p. 150-151 °C; (Found: C, 51.91; H, 4.32; N, 20.26 %; m/z, 276.0858, $C_{12}H_{12}N_4O_4$ requires, C, 52.16; H, 4.38; N, 20.29 %; M, 276.0856); ν_{max} 2924, 1743, 1633, 1587, 1495, 1395, 1380 and 1357 cm^{-1}; δ_H (250MHz; $CDCl_3$) 3.50 (3H, s, OCH_3), 3.78 (3H, s, CH_3), 6.48 (1H, s, C-H), 7.22-7.28 (2H, m, Ar-H), 7.38 (1H, s, Ar-H). 7.71 (1H, tt, *J* 1.9, 7.7, Ar-H) and 8.5 (1H, d, *J* 3.9, N-H); δ_C (62.9 MHz; $CDCl_3$) 32.0 ($N-CH_3$), 49.0 (C-H), 53.0 (CH_3), 71.4 (Ar-C), 123.1 (Ar-CH), 124.4 (Ar-CH), 135.3 (Ar-CH), 137.9 (Ar-C), 136.8 (Ar-CH), 149.2 (Ar-CH), 153.5 (Ar-C) and 169.0 (CO).

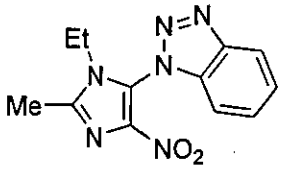
Methyl 3-indole-2-yl ethanoate[16] (118)



Thionyl chloride (3.2 cm^3, 43 mmol) was added dropwise to stirred methanol (20 cm^3) at -10°C. Indole-3-acetic acid (5.0g, 26 mmol) in methanol (5 cm^3) was added after 5 min. The reaction was stirred for 1 h at -10°C. The reaction mixture was allowed to warm to room temperature and then heated under reflux for 2 h. The solvent was removed *in vacuo* to yield a brown liquid. This was treated with saturated sodium hydrogen carbonate solution. The residue was extracted with dichloromethane (3 × 15 cm^3), the extracts combined, dried over $MgSO_4$, filtered and evaporated to dryness to afford a red viscous liquid (5.38g, 99 %).

Red liquid, yield 99 %, m/z, 189 (M^+, 40%) and 130 (100 %); ν_{max} 3409, 2951, 1731, 1554, 1458, and 1435 cm^{-1}; δ_H (250MHz; $CDCl_3$) 3.62 (3H, s, OCH_3), 3.72 (2H, s, CH_2), 6.80 (1H, d, *J* 2.5 Ar-H), 7.05-7.14 (3H, m, Ar-H), 7.53-7.58 (1H, m, Ar-H) and 8.09 (1H, br s, N-H); δ_C (62.9 MHz; $CDCl_3$) 31.2 (CH_2), 52.0 (O-CH_3), 107.8 (Ar-C), 111.0 (Ar-CH), 118.7 (Ar-CH), 119.6 (Ar-CH), 122.0 (Ar-CH), 123.5 (Ar-CH), 127.5 (Ar-C), 136.5 (Ar-C) and 173.5 (CO).

1-(1-ethyl-4-methyl-4-nitro-1*H*-imidazol-5-yl)-1*H*-1, 2,3-benzotriazole (129)

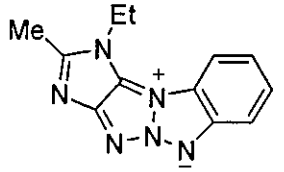


Benzotriazole (0.238 g, 2 mmol) in dry DMF (2 cm^3) was added to stirred NaH washed free from oil (0.1 g, 4.2 mmol) in dry DMF (2 cm^3) at 0 °C under nitrogen. After 5 min 5-chloro-1-methyl-4-nitro-1*H*-imidazole (0.379 g, 2mmol) in dry DMF (5 cm^3) was added dropwise. The reaction mixture was allowed to warm to room temperature. After 6 h the solvent was removed *in vacuo*. The residue was treated with water (10 cm^3) and acidified with concentrated hydrochloric acid until neutral to pH paper. The aqueous phase was extracted with dichloromethane (3 × 20 cm^3), the extracts combined, dried over $MgSO_4$, filtered and evaporated to dryness to yield a brown solid. Re-crystallisation from dichloromethane and petroleum ether gave a light brown solid (0.35 g, 64 %).

Brown solid, yield 64 %, m.p. 195-196°C; (Found: m/z, 272.1026, $C_{12}H_{12}N_6O_2$ requires: M, 272.1022); ν_{max} 2992, 1611, 1523, 1430, 1390, 1341, 1291, 1037, 852 and 748 cm^{-1}; δ_H (250MHz; $CDCl_3$) 1.25 (3H, t, *J* 7.2, CH_3), 2.58 (3H, s, CH_3), 3.69 (1H, br s, CH_2), 3.91 (1 H, br s, CH_2), 7.34 (1H, d, *J* 7.5, Ar-CH), 7.50 (1H, t, *J* 7.2, Ar-CH), 7.62 (1H, t, *J* 7.2, Ar-CH) and 8.19 (1H, d, *J* 7.95, Ar-CH); δ_H (400MHz; CD_3SOCD_3) at 30 °C, 1.18 (3H, t, *J* 7.2, CH_3), 2.59 (3H, s, CH_3), 3.75 (1H, br s, CH_2), 3.90 (1 H, br s, CH_2), 7.56-7.68 (3H, m, Ar-CH) and 8.19-8.25 (1H, m, Ar-CH); δ_H (400MHz; CD_3SOCD_3) at 100 °C, 1.08 (3H, t, *J*

7.2, CH_3), 2.48 (3H, s, CH_3), 3.73 (2H, q, *J* 7.2 CH_2), 7.42-7.45 (2H, m, Ar-CH), 7.56 (1H, t, *J* 7.6, Ar-CH) and 8.09-8.11 (H, m, Ar-CH); δ_C (100 MHz;$CDCl_3$) 14.0 (CH_3), 15.9 (CH_3), 40.7 (CH_2), 110.3 (Ar-CH), 121.1 (Ar-CH), 121.5 (Ar-C), 125.6 (Ar-CH), 130.2 (Ar-CH), 134.5 (Ar-C), 140.0 (Ar-C), 143.7 (Ar-C) and 145.7 (CO).

1-Ethyl-2-methyl-1*H*,4*H*-1,3,4,5,9b-pentaaza-4a-azoniapentaleno[1,2-*a*]indene (132)



Triethylphosphite (3 cm^3) was added to 1-(1-ethyl-4-methyl-4-nitro-1*H*-imidazol-5-yl)-1*H*-1,2,3-benzotriazole (0.129g, 0.49 mmol) and the reaction was heated under reflux. After 20 h TLC showed the reaction complete. Dry flash column chromatography on silica eluting with petroleum ether and ethyl acetate (2:1 to 1:4) and followed by dichloromethane/ethyl acetate (1:1) in methanol (5-30 %) gave a yellow solid (0.076g, 67 %).

Yellow solid, yield 67 %; m/z, 240 (15 %); δ_H (250MHz; $CDCl_3$) 1.07 (3H, t, *J* 7.4, CH_3), 2.44 (3H, s, CH_3), 3.50 (2H, q, *J* 7.3, CH_2), 7.41-7.47 (2H, m, Ar-CH), 7.53-7.59 (1H, m, Ar-CH) and 8.12-8.16 (1H, m, Ar-CH).

2.5 References

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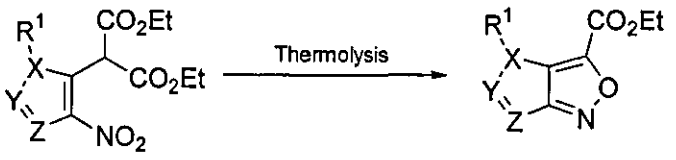
Chapter 3

Studies on the Synthesis of Other [5,5] Fused Isoxazole Derivatives

3.1 Introduction

The successful synthesis of imidazo[4,5-*c*]isoxazoles described in the previous chapter prompted an investigation into the possible extension of this reaction to generate other [5,5] hetero fused isoxazoles from nitroheteroaryl substituted malonate derivatives by thermolysis. It was planned to see if isoxazoles fused to isothiazole, pyrazole and thiophene heterocycles could be produced by this method, **Scheme 57**.



135 **136**

X, Y, Z = CH, N, S

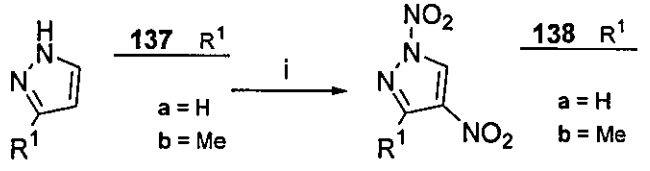
Scheme 57

3.2 Discussion

3.2.1 Attempted synthesis of pyrazole fused isoxazoles

Pyrazole and several of its derivatives are commercially available and it was planned to use literature methods to prepare the nitro substituted precursors required for the possible cyclisation to pyrazolo fused isoxazoles. One method employed was the synthesis of 1,4-dinitropyrazole and then *cine*-substitution at the 5-position to give nitropyrazole malonate ester **140b**. This had been reported by Buchanan and Wightman.[1]

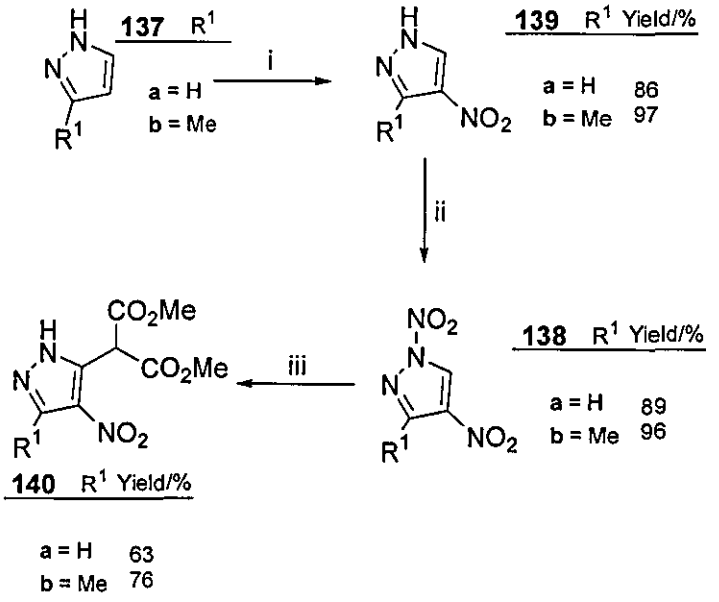
Using this methodology 1,4-dinitropyrazole **138a** was prepared by a one pot procedure from commercially available pyrazole. Initial studies lead to the formation of 1,4-dinitropyrazole in only poor to moderate yield with undesired 4-nitropyrazole, also produced, **Scheme 58**. We therefore switched to a sequential procedure[2], which consisted of two steps; the first classical nitration, followed by nitrogen atom nitration with nitric acid and acetic anhydride. This gave 1,4 dinitropyrazoles **138a** and **138b** in good yield and none of the 4-nitro pyrazoles were detected.



Reagents and conditions: i, TFAA, NH_4NO_2, TFA, 0 °C.

Scheme 58

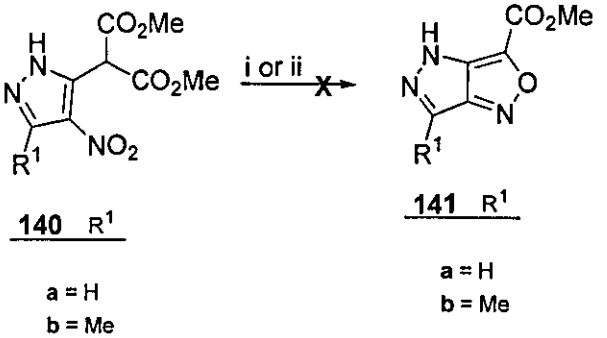
On treating di-nitropyrazoles **138a** and **138b** with the anion of dimethyl malonate generated by sodium in methanol at 0 °C to room temperature, 4-nitropyrazole malonate derivatives were obtained in good yields, **Scheme 59**.



Reagents and conditions: i, HNO_3, H_2SO_4, 100 °C. ii, Ac_2O, HNO_3, Glacial Acetic Acid, 0 °C. iii, Na, MeOH, dimethyl malonate, 0 °C - R.T.

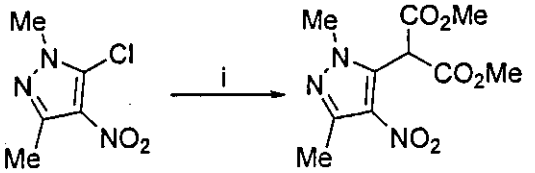
Scheme 59

Their behaviour towards thermolysis was then investigated to prepare pyrazolo fused isoxazoles. Disappointingly this was unsuccessful and heating **140a** or **140b** in refluxing toluene or xylene failed to produce either of pyrazolo[4,3-*c*]isoxazoles **141a** and **141b**. Only starting material was recovered unchanged, **Scheme 60**.



Conditions: i, Toluene, Reflux, or ii, Xylene, Reflux.

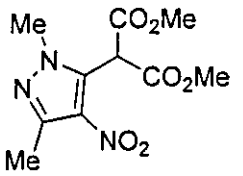
Scheme 60



142 143

Reagents and conditions: i, 2.2 NaH, dimethyl malonate, DMF, O °C - R.T.

Scheme 61



143

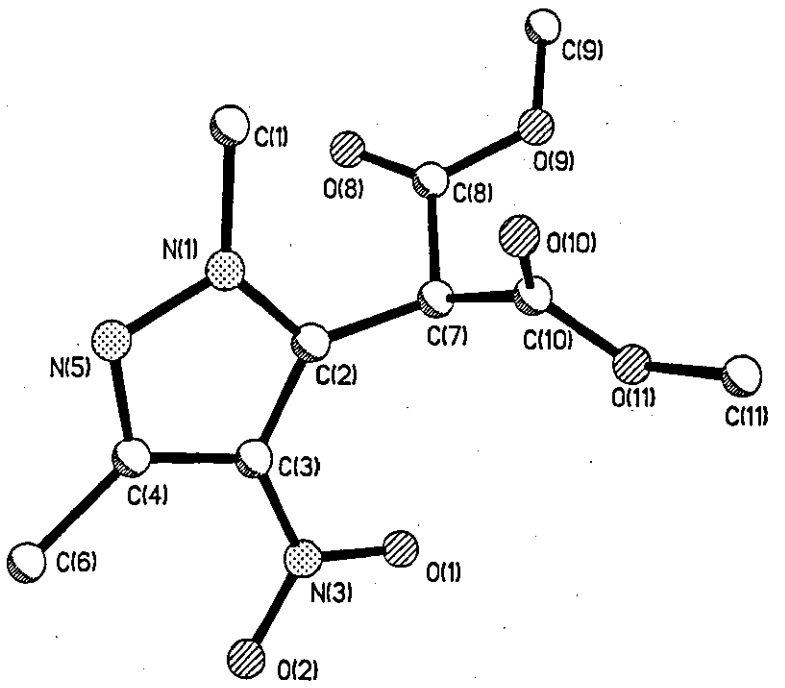
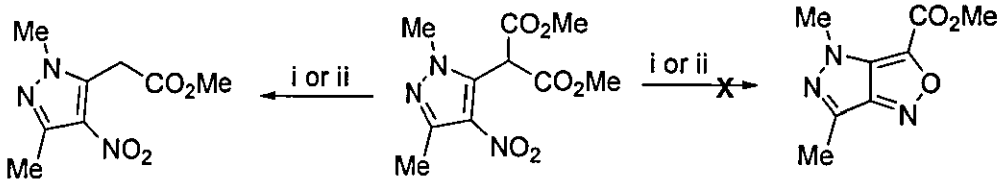


Figure 3.1, X-ray structure of dimethyl 2-(2,5-dimethyl-4-nitro-2*H*-pyrazol-3-yl)propanedioate (143).

Next commercially available[3] 5-chloro-1,3-dimethyl-4-nitro-pyrazole **142**, was investigated as a starting material. On treating **142** with the anion of malonate generated with sodium hydride in DMF, **Scheme 61**, the pyrazole malonate ester derivative **143** was formed in 74 % yield. Crystals of this compound were grown and X-ray crystallography, **Figure 3.1** and **Appendix 8**, showed it to be the desired nitropyrazolyl malonate **143**. On heating **143**, in toluene or xylene the cyclised product **144** was not isolated. Instead the decarboxylated product **145**, was obtained. Ester hydrolysis and decarboxylation may have occurred due to acid present or by a thermal process, **Scheme 62**. It is not clear why cyclisation to the fused isoxazole had not occurred, but it may have been due to a conformational effect which prevented the nitro group from attacking the adjacent substituent (believed to be a ketene) at *C*-5 of the pyrazole ring. The X-ray crystal structure of **143** had shown the nitro group to be twisted out of the plane of the pyrazole. This twist may have been caused by the methyl group at the C-3 position.

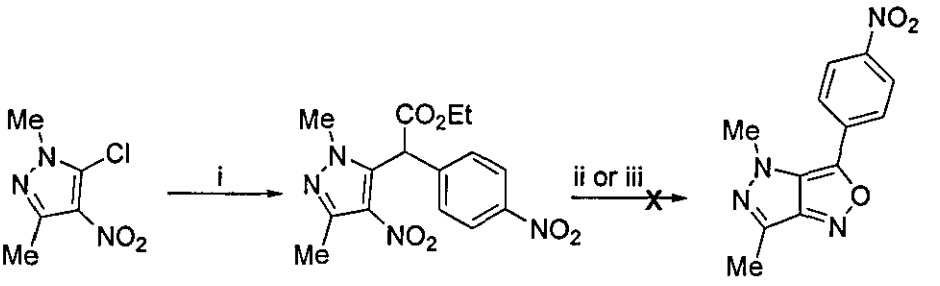


145 **143** **144**

Conditions: i, Toluene, Reflux, or ii, Xylene, Reflux.

Scheme 62

Ethyl nitrophenylacetate was next investigated as an active methylene compound as shown in **Scheme 63**. We had thought that exploiting this compound for thermolysis may prevent the unwanted decarboxylation and may stabilise the intermediate formed in the thermolysis process. The adduct **146** was readily prepared by displacement of chloride in the chloro-nitroimidazole **142** by 4-nitrophenylacetate anion to give **146**. Thermolysis of this compound in toluene and xylene was then studied. However, this was also unsuccessful and cyclisation did not occur under these conditions, and most of the starting material **146** was re-isolated.

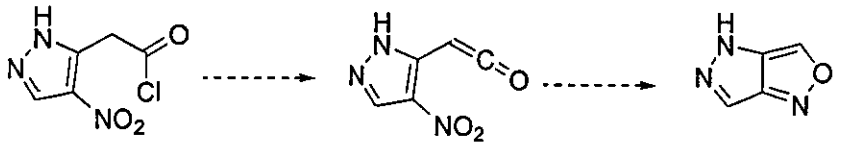


142 146 147

Reagents and conditions: i, 2.2 NaH, Ethyl 4-nitro phenylacetate, DMF, O °C - R.T. ii, Toluene, Reflux, or iii, Xylene, Reflux.

Scheme 63

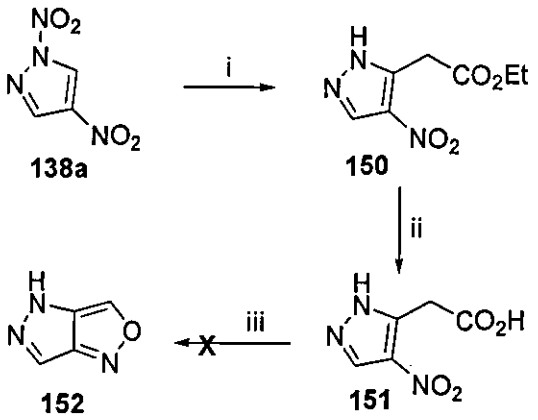
As an alternative to thermolysis another strategy was undertaken in which it was planned to activate the carboxyl group of a suitable nitropyrazolyl acetate derivative, and to introduce a better leaving group which might allow easier generation of the ketene thought to be required for cyclisation. Initially it was decided to investigate an acid chloride **148** as a possible ketene precursor, **Scheme 64**. In the presence of triethylamine the α protons adjacent to the carbonyl chloride may be removed, thus forming a ketene intermediate **149**, this may be trapped by the neighbouring nitro group cyclising to develop the 3-unsubstituted isoxazole ring, **150**.



148 149 150

Scheme 64

1,4-Dinitropyrazole **138a**, was treated with the anion of ethyl acetoacetate generated by sodium ethoxide in ethanol. This gave 4-(nitro-2*H*-pyrazol-3-yl)acetic acid ethyl ester in 63 % yield. Conversion to the carboxylic acid compound **151**, in 95 % yield was achieved using lithium hydroxide in water and tetrahydrofuran. Treatment of the acid derivative **151**, with thionyl chloride was expected to give the acid chloride. However under these conditions **Scheme 65**, only decomposed material was obtained after heating. This reaction may have needed to be carried out at a lower temperature.

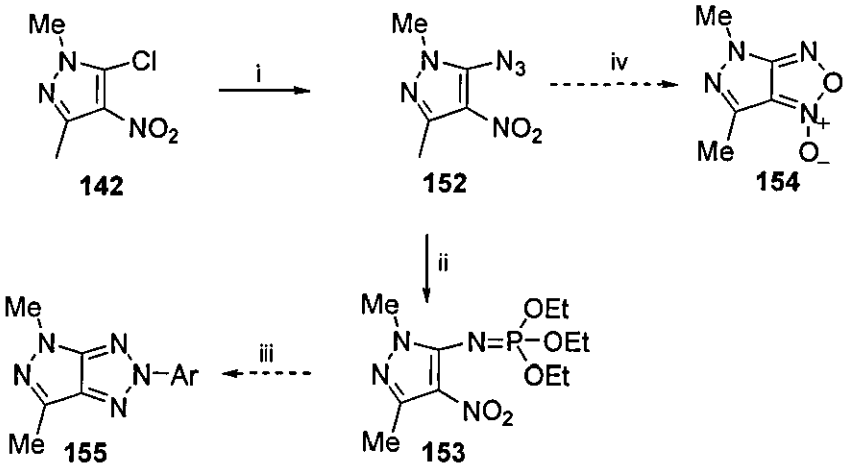


Reagents and conditions: i, Na, ethanol, ethyl acetoacetate 10 °C - R.T. ii, LiOH, THF, Reflux. iii, $SOCl_2$, Et_3N, Reflux.

Scheme 65

3.2.2 Further Chemistry of 5-chloro-1,3-dimethyl-4-nitro-pyrazole

As part of an investigation into the synthesis of [5,5] fused heterocycles, the displacement of the chloride in **142** with other nucleophiles was studied. Sodium azide was found to give a synthetically useful pyrazole derivative **152** in 64 % yield. This compound may be a precursor to the interesting fused furazan-N-oxide **153**, **Scheme 66**. A Staudinger reaction of the azide compound with triethyl phosphite was also successfully carried out to give synthetically useful iminophosphorane pyrazole derivative **153** in 99 % yield. Reaction with reactive heterocumulenes such as isocyanates in an aza-Wittig reaction may lead to pyrazolo[4,3-*d*]triazoles analogous to those described in chapter 5, **Scheme 66**. Due to time constraints this chemistry was not investigated.

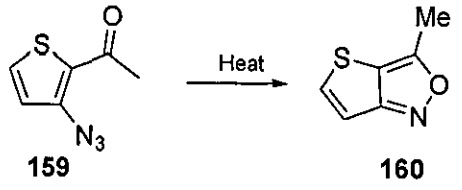


Reagents and conditions: i, NaN_3, DMF, room temperature; ii, $P(OEt)_3$, CH_2Cl_2, Reflux; iii, ArN=C=O, iv, thermolysis.

Scheme 66

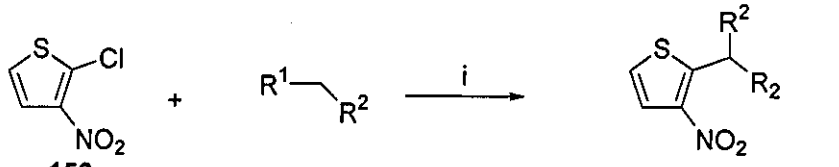
3.2.3 Synthesis of thiophene fused isoxazoles

Investigations then turned to the 2-chloro-3-nitrothiophene[3] **156** (**Scheme 68**), and the displacement of chloride by substituted carbanions derived from active methylene compounds **157a-c** to create synthetically useful thiophene derivatives **158**. There has been a report[4] that heating 1-(3-azido-thiophen-2-yl)-ethanone **159**, gave 3-methyl-thieno[3,2-*c*]isoxazole **160**, **Scheme 67**. This report was only limited to one example and no other examples of derivatives of this ring system are known. Therefore it was of interest to see if the methodology employing the nitro group cyclisation would be effective for forming new examples of this heterocycle.



Scheme 67

On reaction of **156** with the anion of dimethyl malonate, generated with sodium hydride in DMF at 0 °C, a bright orange solution was formed, from which the dimethyl 2-(3-nitro-thiophen-2-yl)-propanedioate **158a**, was isolated in 92 % yield after evaporation of the solvent and acidification in the work up. This reaction was extended to two more active methylene compounds shown in **Scheme 68** and the phenyl and 4-nitrophenyl acetate derivatives were successfully prepared.

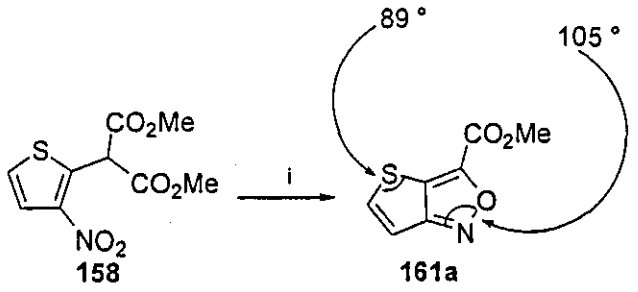


157	R^1	R^2	158	R^1	R^2	Yield/%
a = CO_2Me	CO_2Me		a = CO_2Me	CO_2Me	92	
b = Ph	CO_2Et		b = Ph	CO_2Et	73	
c =4-$O_2NC_6H_4$	CO_2Et		c =4-$O_2NC_6H_4$	CO_2Et	80	

Reagents and conditions: i, 2.2 NaH, DMF, O °C - R.T.

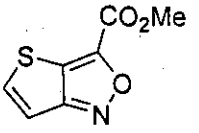
Scheme 68

As part of our continued effort for the synthesis of [5,5] fused isoxazole derivatives, we studied the chemical outcome of their thermolysis. Heating malonate derivative **158a** in refluxing toluene led to consumption of starting material and formation of thieno[3,2-*c*]isoxazole **161a** in 91 % yield after heating for 20 h, **Scheme 69**. Crystals of **161a** were grown and an X-ray structure, the first for this heterocyclic ring system, was obtained, **Figure 3.2** and **Appendix 8**. The X-ray shows the [5,5] fused ring system is strained. Key bond angles include a C-S-C bond angle of 89 ° and a C-N-O angle of 105 °.



Conditions: i, Toluene, Reflux.

Scheme 69



161a

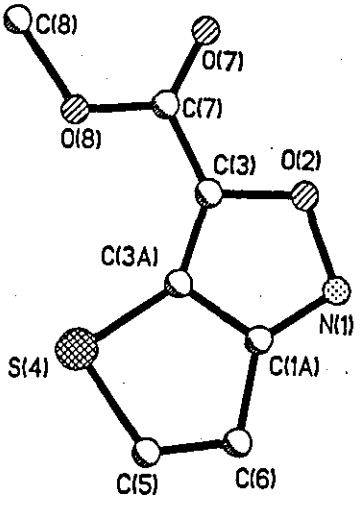
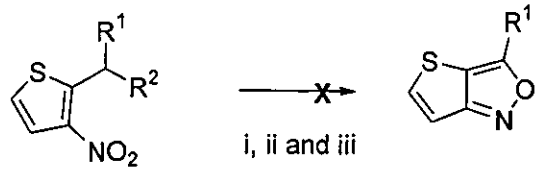


Figure 3.2, an X-ray structure of methyl thieno[3,2-*c*]isoxazole-3-carboxylate (161a).

The other substituted thiophenes were heated similarly. No cyclised material was obtained in refluxing toluene or xylene for 20 h or longer. We turned to higher boiling diglyme and starting material was then consumed after 6 h. Solids were obtained after evaporation of the solvents, however the materials could not be identified, **Scheme 70**.



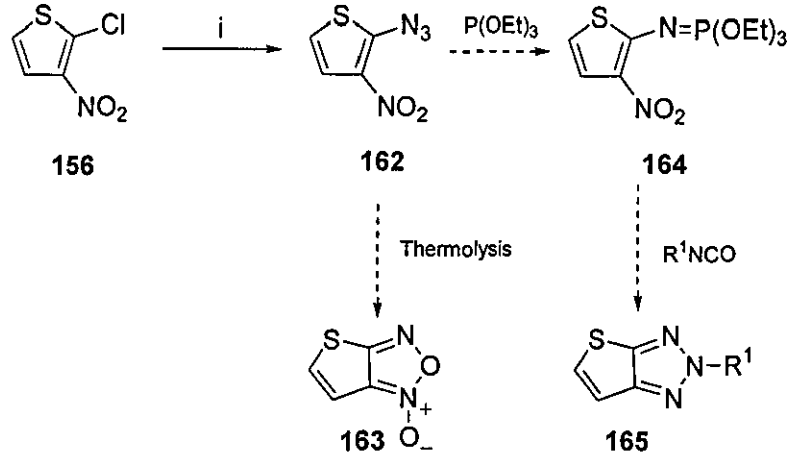
158	R^1	R^2
b	Ph	CO_2Et
c	4-$O_2NC_6H_4$	CO_2Et

161	R^1
b	Ph
c	4-$O_2NC_6H_4$

Conditions: i, Toluene, Reflux, ii, Xylene, Reflux, iii, Diglyme, Reflux.

Scheme 70

Substitution reaction between sodium azide and 2-chloro-3-nitrothiophene **156**, in the absence of light gave nitrothiophene azide[5] derivative **162** in 52 % yield. This compound is of interest for the annelation of triazole **165** or furazan-N-oxide **163** rings, but this could not be pursued in the time available, **Scheme 71**.



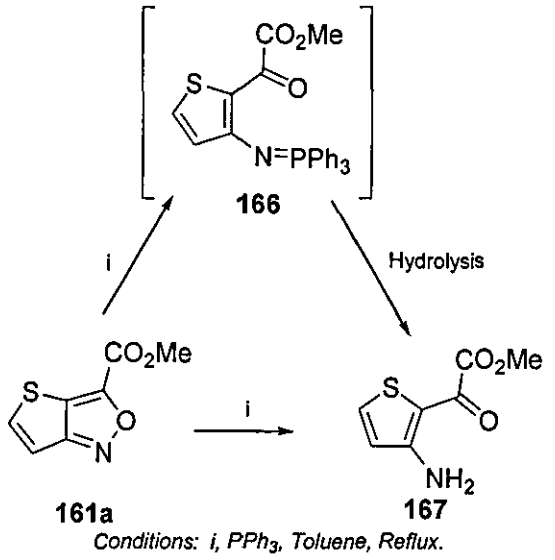
Reagents and conditions: i, NaN_3, DMF, R.T.

Scheme 71

3.2.4 Reactions of a methyl thieno[3,2-*c*]isoxazole-3-carboxylate (161a)

It was of interest to explore the reactivity of this strained heterocycle, as little is known about the chemistry of this class of compound. The reaction with soft nucleophiles such as triphenylphosphine was first studied. When this reagent was employed in refluxing toluene with methyl thieno[3,2-*c*]isoxazole-3-carboxylate **161a** a reaction was observed to

take place. The isoxazole ring had been cleaved to give the amino carbonyl ester compound **167** in 65 % yield, **Scheme 72**. That this compound had been formed, and not the expected iminophosphorane **166**, was indicated by a band at 3394 cm^{-1} in the infra-red spectrum showing the presence of an amino group. The ^1H NMR spectrum also lacked signals in the aromatic region for three phenyl groups and showed only two doublet signals consistent with the thiophene *H*-4 and *H*-5 protons at δ 6.54 and 7.52. This result demonstrates the labile bond between the atoms of nitrogen and oxygen, which had been severed by attack of the phosphine on the nitrogen forming the iminophosphorane **166**. This compound must have later hydrolysed by water present in the reaction mixture or during purification by chromatography.

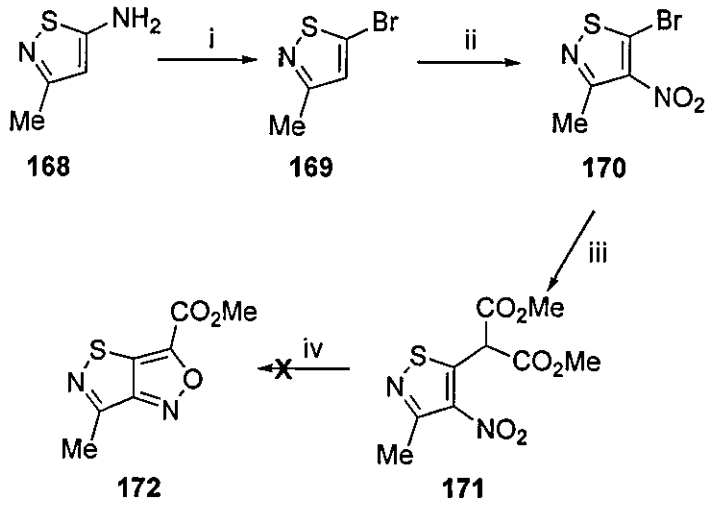


Scheme 72

3.2.5 Attempted synthesis of isothiazole fused isoxazoles

In order to try and extend the synthesis of [5,5] fused isoxazoles, it was envisioned that the isothiazolo[4,5-*c*]isoxazole ring system should possess similar geometry to the other [5,5] fused isoxazoles synthesised, but may have different electronic characteristics, possibly leading to interesting chemistry and biological properties. A literature search disclosed little information about derivatives of this ring system. Our approach started with 5-amino-3-methyl isothiazole hydrochloride[6] **168**, which was converted in a one pot procedure to 5-bromo-3-methyl isothiazole hydrochloride **169** using the method of Adams and Slack.[6] Diazotisation with sodium nitrite and aqueous hydrobromic acid, followed by

a Sandmeyer reaction using copper (II) bromide and aqueous hydrobromic acid, gave **169** in 72 % yield, **Scheme 73**. Under classical nitration conditions the nitro compound **170** was obtained in 70 % yield. The bromo substituent is activated for displacement by nucleophiles and reaction with the anion of dimethyl malonate formed by sodium methoxide in methanol gave dimethyl 2-(3-methyl-4-nitroisothiazol-5-yl)propanediote **171** in very good yield. Thermolysis of this compound was studied by heating it in refluxing toluene for 18 h. However, only starting material was recovered and not the hoped for isothiazolo[4,5-*c*]isoxazole **172**. The reaction may need to be carried out for longer periods of time or a higher boiling solvent employed. Due to limited time further thermolysis studies were not carried out.



Reagents and conditions: i, $NaNO_2$, 48 % HBr, H_2O, CuBr, 0 °C - R.T. ii, HNO_3, H_2SO_4, 115 °C. iii, NaOMe, MeOH, dimethyl malonate, Reflux; iv, Toluene, Reflux.

Scheme 73

3.3 Conclusion

Our studies on the thermolysis of pyrazolyl malonate derivatives to pyrazolo [5,5] fused isoxazoles proved unsuccessful after a continued effort in trying to attain this novel heterocycle. The imidazo malonate derivatives described in chapter 2 underwent readily conversion to imidazo[4,5-*c*]isoxazole derivatives by heating in toluene. Although, the pyrazole malonate derivatives are isomeric and, by analogy, should easily be transformed. However, this may have not been possible due to the different electronic nature of the pyrazole ring.

Further substitution reactions of 5-chloro-1,3-dimethyl-4-nitro-pyrazole **142**, with azide was carried out which led to a synthetically useful iminophosphorane compound.

Thermolysis of thiophene malonate derivatives to thieno[3,2-*c*]isoxazole derivatives proved successful as a new method has been established for the preparation of these compounds. The first example of an X-ray crystal structure for this compound has been obtained, showing its strained nature. The thermolysis of other thiophene malonate derivatives have been examined but so far the identity of the products has not been established. Reaction between thieno[3,2-*c*]isoxazole derivative **161a** and triphenylphosphine was found to ring open the isoxazole to give an aminothiophene derivative.

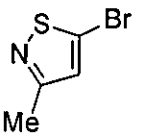
Substitution reactions with sodium azide and 1-chloro-2-nitrothiophene were carried out.

The synthesis of an isothiazolyl substituted malonate derivative proved easy from known chemistry. Endeavours to prepare an isothiazole fused isoxazole ring by thermolysis proved unsuccessful.

3.4 Experimental

For general experimental procedures see Chapter 1, section 1.8.1.

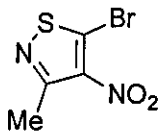
5-Bromo-3-methyl-isothiazole[6] (168)



A cold solution of sodium nitrite (1.05 g, 15 mmol) in water (5 cm^3) was added dropwise to stirred 5-amino-3-methyl-isothiazole hydrochloride salt in 48 % hydrobromic acid solution (40 cm^3) at 0 °C. The mixture turned red with evolution of brown fumes and formation of a red precipitate. After 0.5 h at 0 °C, a cold solution of CuBr (1.43 g, 10mmol) in 48 % hydrobromic acid solution (20 cm^3) was added dropwise to the reaction mixture. Effervescence occurred and the reaction mixture turned purple with precipitate formation. After 1 h the reaction was allowed to warm to room temperature. Neutralisation with 2M sodium hydroxide to pH 6-7 gave a black mixture containing solid. The solid was filtered. Extraction of the solid and the aqueous phase with dichloromethane (5 × 10 cm^3) gave an orange solution. This was combined, dried over $MgSO_4$, filtered and evaporated to yield an orange liquid (1.28 g, 72 %).

Orange liquid, yield 72 %, m/z, 113.0226 (50 %); ν_{max} 3091, 2956, 2923, 1608, 1499, 1472, 1396, 1366, 1331, 1061, 940, 806, 777 and 646 cm^{-1}; δ_H (250MHz; $CDCl_3$) 2.48 (3H, s, CH_3) and 7.03 (1H, s, Ar-CH); δ_C (62.9 MHz; $CDCl_3$) 19.2 (CH_3), 114.0 (Ar-C), 145.7 (Ar-CH) and 168.0 (Ar-C).

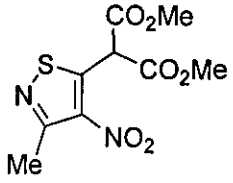
5-Bromo-3-methyl-4-nitro-isothiazole (169)



Fuming nitric acid (1.22 g, 19.4 mmol) was added dropwise to 5-bromo-3-methyl-isothiazole **168** (1.15 g, 6.5 mmol) in concentrated sulphuric acid (1.9 g, 19.4 mmol) at 0 °C. The mixture was heated at 115 °C for 2 h. The reaction was cooled and poured over ice. The solid and the aqueous phase was extracted with dichloromethane (20 cm^3) and the organic layer washed with saturated sodium hydrogen carbonate (3 × 10 cm^3). The organic layer was separated. The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to yield a white solid, which was dried under vacuum (1.0 g, 70 %).

White solid, yield 70 %, m.p. 76-77 °C (lit.,[6] 77-78 °C); m/z, 224 (M^+, ^{81}Br, 10 %) and 222 (M^+, ^{79}Br, 10 %); ν_{max} 3004, 2958, 2924, 1605, 1539, 1495, 1430, 1395, 1366, 1335, 1062, 941, 806, 776, 757 and 645 cm^{-1}; δ_H (250MHz; $CDCl_3$) 2.55 (3H, s, CH_3); δ_C (62.9 MHz; $CDCl_3$) 19.7 (CH_3), 114.0 (Ar-C), 134.5 (Ar-C) and 166.1 (Ar-C).

Dimethyl 2-(3-methyl-4-nitroisothiazol-5-yl)propanediote (170)

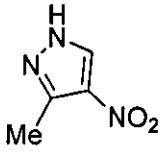


Dimethyl malonate (1.57 g, 11.8 mmol) was added dropwise to a stirred solution of sodium methoxide (0.53 g, 9.9 mmol) in dry methanol (50 cm^3). A Soxhlet extractor, containing 5-bromo-3-methyl-4-nitro-isothiazole (0.88 g, 4 mmol) in its thimble was attached to the

reaction flask and reaction mixture was heated under reflux for 12 h. The solvent was removed *in vacuo*. The residue was treated with water (10 cm^3) and the aqueous phase was acidified with glacial acetic acid. The aqueous phase was extracted with dichloromethane (3 × 20 cm^3). The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to dryness to yield a yellow solid. Re-crystallisation from ethanol gave a white solid (1.0 g, 94 %).

White solid, yield 94 %, m.p. 59-60 °C; Found: m/z, 276 (M^+, ^{81}Br, 5 %) and 274 (M^+, ^{79}Br, 5 %); ν_{max} 3003, 2957, 2849, 1738, 1548, 1495, 1437, 1335, 1277, 1205, 1153, 1061, 1026, 941, 806, 776 and 645 cm^{-1}; δ_H (250MHz; $CDCl_3$) 2.55 (3H, s, CH_3), 3.4 (H, s, CH) and 3.75 (6H, s CH_3); δ_C (62.9 MHz; $CDCl_3$) 19.6 (CH_3), 40.9 (CH_3), 52.4 (Ar-CH), 113.9 (Ar-C), 134.4 (Ar-C), 166.01 (Ar-C) and 166.7 (Ar-CO).

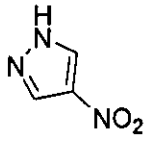
3-Methyl-4-nitro-pyrazole (139b)



Concentrated sulphuric acid (3.6 g, 0.037 mol) was added dropwise to 3-methyl-pyrazole (1.0 g, 0.012 mol) at 0 °C. Fuming nitric acid (2.3 g, 0.037 mol) was added dropwise to the reaction mixture. The mixture was heated at 100 °C for 3 h. The reaction was cooled to room temperature and poured over ice. The solid and the aqueous phase was extracted with ethyl acetate (30 cm^3) and the organic layer washed with saturated sodium hydrogen carbonate (3 × 20 cm^3). The organic layer was separated. The aqueous phase was further extracted with ethyl acetate (4 × 20 cm^3). The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to dryness to yield a white solid. Re-crystallisation from hot dichloromethane and petroleum ether gave white crystals (1.5 g, 97 %).

White crystals, yield 97 %, m.p. 129-131 °C (lit.,[7] 134 °C); (Found: m/z, 127.0384, $C_4H_5N_3O_2$ requires: M, 127.0382); ν_{max}(nujol) 3213, 3124, 2853, 1605, 1503, 1407, 1322, 1195, 945, 831 and 762 cm^{-1}; δ_H (250 MHz; CD_3COCD_3) 2.59 (3H, s, CH_3), 8.28 (1H, s, Ar-CH) and 11.4 (1H, s, N-H); δ_C (62.9 MHz; CD_3COCD_3), 16.2 (CH_3) and 139.4 (C).

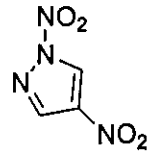
4-Nitro-pyrazole (139a)



Concentrated. sulphuric acid (21.6 g, 0.22 mol) was added dropwise to pyrazole (5.0 g, 0.073 mol) at 0 °C. Fuming nitric acid (13.8 cm^3, 0.22 mol) was added dropwise to the reaction mixture. The mixture was heated at 100 °C for 3 h. The reaction was cooled to room temperature and poured over ice. The solid and the aqueous phase was extracted with dichloromethane (30 cm^3) and the extract washed with saturated sodium hydrogen carbonate (3 × 20 cm^3). The organic layer was separated. The aqueous phase was further extracted with dichlromethane (4 × 20 cm^3). The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to dryness. This gave a white solid, re-crystallisation of which from hot ethanol gave white crystals (7.1 g, 86 %).

White solid, yield 86 %, m.p. 166-167 °C (lit.,[8] 163-164 °C); (Found: m/z, 113.0226 $C_3H_3N_3O_2$ requires: M, 113.0225); ν_{max} 3131, 2852, 1504 and 1357 cm^{-1}; δ_H (250MHz; CD_3COCD_3) 8.13 (1H, s, Ar-CH) and 8.66 (1H, s, Ar-CH); δ_C (62.89 MHz; CD_3COCD_3) 130.7 (Ar-CH), 137.0 (Ar-C) and 140.0 (Ar-CH).

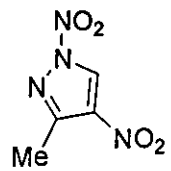
1,4-Dinitropyrazole (138a)



To a solution of 4-nitropyrazole (2.00 g, 17.6 mmol) in glacial acetic acid (6.25 cm^3) maintained at 17 °C was added dropwise (30 min) with stirring fuming nitric acid (2 cm^3). After 5 min acetic anyhydride was added (10 cm^3). The temperature was held at 17 °C for 2 h. After 2.5 h the solids dissolved and the mixture was allowed to warm to room temperature. TLC showed reaction complete after 8 h. The solution was diluted with dichloromethane (30 cm^3) and washed rapidly with ice water and ice-cold saturated sodium hydrogen carbonate solution. The organic layer was separated and the aqueous layer was re-extracted with dichloromethane (4 × 20 cm^3). The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to dryness. Flash column chromatography by eluting with petroleum ether and ethyl acetate (3:1) gave a white solid (2.15 g, 89 %).

White solid, yield 89 %, m.p. 52-53 °C (lit.,[2] 54 °C); m/z, 158.0732 (50 %); ν_{max} 1645, 1523, 1323 and 1278 cm^{-1}; δ_H (250MHz; $CDCl_3$) 8.20 (1H, d, *J* 0.81, Ar-CH) and 9.04 (1H, d, *J* 0.82, Ar-CH); δ_C (62.89 MHz; $CDCl_3$) 123.0 (Ar-CH), 134.5 (Ar-CH) and 137.0 (Ar-C).

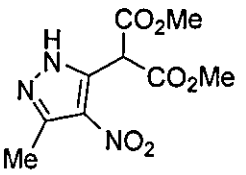
3-Methyl-1,4-dinitropyrazole (138b)



To a solution of 3-methyl-4-nitropyrazole (1.10 g, 87mmol) in glacial acetic acid (6.3 cm^3) maintained at 17 °C was added dropwise (30 min) with stirring fuming nitric acid (2 cm^3). After 5 min acetic anyhydride (5 cm^3) was added. The temperature was held at 17 °C for 2 h. After 2.5 h the solids dissolved and the mixture was allowed to warm to room temperature. TLC showed reaction complete after 8 h. The solution was diluted with dichloromethane (30 cm^3) and washed rapidly with ice water and ice-cold saturated sodium hydrogen carbonate solution. The organic layer was separated and the aqueous layer was re-extracted with dichloromethane (4 × 20 cm^3). The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to dryness. Flash column chromatography by eluting with petroleum ether and ethyl acetate (3:1) gave a white solid. Re-crystallisation from hot hexane gave a white solid (1.4 g, 96 %).

White solid, yield 96 %, m.p. 47-48 °C (lit.,[9] 47 °C); (Found: m/z, 172.0233, $C_4H_4N_4O_4$ requires: M, 172.0233); ν_{max} (nujol) 2854, 1648, 1564, 1348, 1223, 1141, 1601, 1007, 838, 812, 751 and 711 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 2.67 (3H, s, CH_3) and 9.04 (1H, s, Ar-CH); δ_C (62.9 MHz; $CDCl_3$) 13.5 (CH_3), 124.2 (Ar-CH), 134.1 (C) and 145.8 (C).

Dimethyl[3(5)-Methyl-4-nitropyrazol-5(3)-yl]propanedioate (140a)

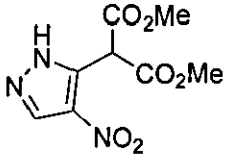


Sodium (0.23 g, 8.7 mmol) was added to dry methanol (20 cm) stirred at 10 °C under a nitrogen atmosphere. After the sodium had dissolved, dimethyl malonate (2.30 g, 17.4 mmol) was added. After 5 min 3-methyl-1,4-dinitropyrazole (1.0 g, 5.80 mmol) in dry diethyl ether (5 cm^3) was added slowly. The reaction turned from a colourless to a dark orange colour. The temperature was maintained at 10 °C at 0.5 h and then allowed to warm to room temperature. The solvent was removed *in vacuo*. The residue was treated

with water (15 cm^3). The aqueous phase was extracted with dichloromethane (4 × 10 cm^3), the organic extracts combined, dried over $MgSO_4$, filtered and evaporated to dryness to yield an orange liquid. The excess dimethyl malonate was removed under high vacuum to leave a cream coloured solid. Re-crystallisation from hot ethanol/hexane gave a cream coloured solid (1.14 g, 76 %).

Cream solid, yield 76 %, m.p. 191-192 °C (lit.,[1] 198 °C); m/z, 257.0648 (100 %); ν_{max} 3253, 2854, 1754, 1508 and 1313 cm^{-1}; δ_H (250MHz; CD_3COCD_3) 2.64 (3H, s, CH_3) and 3.74 (6H, s, CO_2Me); δ_C (62.89 MHz; CD_3COCD_3) 16.0 (CH_3), 56.8(CH), 57.4 (OCH_3), 148 (Ar-C) and 172.0 (CO).

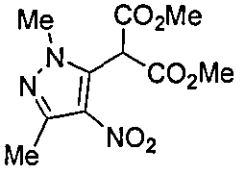
Dimethyl 2-[4-nitro-1*H*-pyrazol-5-yl] propanedioate (140b)



Sodium (0.22 g, 9.5 mmol) was added to dry methanol (20 cm^3) stirred at 10 °C under nitrogen atmosphere. After the sodium had dissolved, dimethyl malonate (2.5 g, 19 mmol) was added. After 5 min 1,4-dinitropyrazole (1.0 g, 6.30 mmol) in dry diethyl ether (5 cm^3) was added slowly. The reaction turned from colourless to a bright orange colour. The reaction mixture was maintained at 10 °C at 0.5 h and then allowed to warm to room temperature. The solvent was removed *in vacuo*. The residue was treated with water (10 cm^3) and acidified to neutral pH by addition of hydrochloric acid. The organic phase was extracted with dichloromethane (3 × 10 cm^3), the extracts combined, dried over $MgSO_4$, filtered and evaporated to yield a viscous orange liquid. Flash column chromatography on silica eluting with petroleum ether and ethyl actetate (2:1) gave a white coloured solid (0.96 g, 63 %).

White solid, yield 63 %, m.p. 131-132 °C; (Found : m/z, 243.04945, $C_8H_9N_3O_6$ requires: M, 243.04914); ν_{max} 3306, 2854, 1754 and 1509 cm^{-1}; δ_H (250MHz; $CDCl_3$) 3.84 (6H, s, CH_3), 5.58 (H, s, CH) and 8.34 (H, s, Ar-CH); δ_C (62.89 MHz; CD_3COCD_3) 56.1 (CH), 57.4 (OCH_3), 132.5 (Ar-CH), 136.1 (Ar-C) and 171.3 (CO).

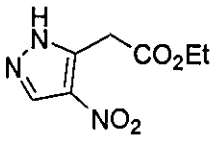
Dimethyl 2-(2,5-dimethyl-4-nitro-2*H*-pyrazol-3-yl)propanedioate (143)



Dimethyl malonate (3.96 g, 30 mmol) was added to stirred NaH washed free from oil (0.72 g, 30 mmol) in dry DMF (5 cm^3) at 0 °C under nitrogen. After 5 min 5-chloro-1,3-dimethyl-4-nitro-pyrazole (2.68 g, 15 mmol) in dry DMF (5 cm^3) was added dropwise. After 1 h the reaction mixture was allowed to warm to room temperature. The solvent was removed *in vacuo* after 6 h. The residue was treated with water (10 cm^3) and acidified with concentrated hydrochloric acid until neutral to pH paper. The aqueous phase was extracted with dichloromethane (3 × 20 cm^3), the extracts combined, dried over $MgSO_4$, filtered and evaporated to dryness. Re-crystallisation from dichloromethane and petroleum ether gave a cream coloured solid (3.0 g, 74 %).

Cream powder, yield 74 %, m.p. 94.5-95.5 °C; (Found : m/z, 271.0809, $C_{10}H_{13}N_3O_6$ requires: M, 271.0804); ν_{max} 2957, 1743, 1562, 1499, 1361, 1161 and 1028 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 2.53 (3H, s, CH_3), 3.83 (6H, s, CO_2CH_3), 3.85 (3H, s, CH_3) and 6.05 (H, s, C-H); δ_C (100 MHz; $CDCl_3$) 14.1 (CH_3), 38.8 (CH_3), 48.1 (CH), 53.66 (CH_3), 131.4 (C), 133.7 (C), 146.3 (C) and 165.4 (CO).

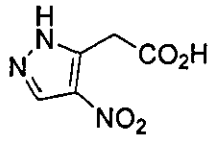
4-(Nitro-2*H*-pyrazol-3-yl)-acetic acid ethyl ester (150)



Sodium (0.33 g, 14.2 mmol) was added to dry ethanol (20 cm^3) stirred at 10 °C under a nitrogen atmosphere. After the sodium had dissolved, ethyl acetoacetate (3.7 g, 28 mmol) was added. After 5 min 1,4-dinitropyrazole (1.5 g, 95 mmol) in dry diethyl ether (5 cm^3) was added slowly. The mixture was maintained at 10 °C at 0.5 h and then allowed to warm to room temperature. The solvent was removed *in vacuo*. The residue was treated with water (10 cm^3) and acidified to neutral pH by addition of hydrochloric acid. The aqueous phase was extracted with dichloromethane (3 × 10 cm^3), the extracts combined, dried over $MgSO_4$, filtered and evaporated to dryness. Re-crystallisation from hot ethyl acetate gave a white solid (1.2 g, 63 %).

White solid, yield 63 %, m.p. 153-154 °C; (Found : m/z, 199.0595, $C_7H_9N_3O_4$ requires: M, 199.0593); ν_{max} (nujol) 3923, 3138, 1730, 1558, 1335, 1215, 1169, 1099, 1030, 791, 756 and 608 cm^{-1}; δ_H (400 MHz; CD_3COCD_3) 1.22 (3H, t, *J* 7.2, CH_3), 4.04 (3H, s, CH_2), 4.15 (2H, q, *J* 7.2, CH_2) and 8.49 (1H, s, Ar-H); δ_C (100 MHz; CD_3COCD_3) 14.45 (CH_3), 33.2 (CH_2), 61.6 (CH_3), 133.1 (Ar-CH), 134.4 (C), 141.4 (C) and 169.4 (CO).

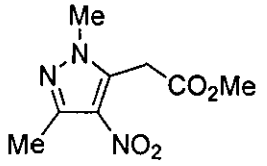
2-(4-Nitro-1*H*-pyrazol-5-yl) ethanoic acid (151)



Lithium hydroxide (0.12 g, 5 mmol) was added to 4-(nitro-2*H*-pyrazol-3-yl)-acetic acid ethyl ester **150** in tetrahydrofuran (30 cm^3) and water (2 cm^3) and the reaction mixture was heated under reflux. After 3 h the reaction was allowed to cool to room temperature. The solvent was removed *in vacuo* to reveal a white residue. The residue was treated with water (10 cm^3) and extracted with ethyl acetate (3 × 20 cm^3), the extracts combined, dried over $MgSO_4$, filtered and evaporated to dryness. Re-crystallisation from acetone and petroleum ether gave a white solid (0.41 g, 95 %).

White solid, yield 95 %, m.p. 193-194 °C, (Found : m/z, 171.0279, $C_5H_5N_3O_4$ requires: M, 171.0280); ν_{max} (nujol) 3478, 3320, 3142, 2850, 1721, 1572, 1343, 1223, 1177, 1120, 1068, 948, 837 and 783 cm^{-1}; δ_H (400 MHz; CD_3COCD_3) 4.01 (2H, s, CH_2) and 8.39 (1H, s, Ar-CH); δ_C (100 MHz; CD_3COCD_3) 39.3 (CH_2), 139.8 (Ar-C), 141.0 (Ar-CH), 148.0 (C) and 178.6 (CO).

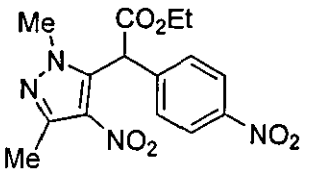
(2,5-Dimethyl-4-nitro-2*H*-pyrazol-3-yl)-acetic acid methyl ester (145)



Dimethyl 2-(2,5-dimethyl-4-nitro-2*H*-pyrazol-3-yl)propanedioate (0.60 g, 2.20 mmol) was dissolved in dry toluene (150 cm^3). A Soxhlet extractor, containing molecular sieves in its thimble was attached to the reaction flask and reaction mixture was refluxed for 28 h. The reaction mixture was cooled and the solvent was evaporated to give a viscous liquid. Flash column chromatography eluting with petroleum ether and ethyl acetate (2:1) gave a colourless oil (0.41 g, 88 %).

Colourless liquid, yield 88 %; (Found : m/z, 213.0749, $C_8H_{11}N_3O_4$ requires: M, 213.0745); ν_{max} 2956, 1743, 1570, 1498, 1468, 1361, 1173 and 826 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 2.51 (3H, s, CH_3), 3.75 (3H, s, CH_3), 3.82 (3H, s, CH_3) and 4.13 (2H, s, CH_2); δ_C (100 MHz; $CDCl_3$) 14.2 (CH_3), 31.4 (CH_2), 37.4 (CH_3), 53.1 (CH_3), 131.7 (C), 136.7 (C), 146.3 (C) and 168.1 (CO).

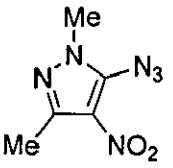
2,5-Dimethyl-4-nitro-2*H*-pyrazol-3-yl)-(4-nitro-phenyl)-acetic acid ethyl ester (146)



Ethyl 4-nitrophenylacetate (0.418 g, 2 mmol) in dry DMF (5 cm^3) was added to stirred NaH (0.119 g, 5 mmol) in dry DMF (5 cm^3) at 0 °C under Nitrogen. After 10 min 5-chloro-1,3-dimethyl-4-nitro-pyrazole (0.351 g, 2 mmol) in dry DMF (5 cm^3) was added dropwise. The reaction mixture was allowed to warm to room temperature. After 12 h the solvent was removed *in vacuo*. The residue was treated with water (10 cm^3) and acidified with concentrated hydrochloric acid until neutral to pH paper. The aqueous phase was extracted with dichloromethane (3 × 15 cm^3), the extracts combined, dried over $MgSO_4$, filtered and evaporated to yield a viscous orange oil (0.763 g). Purification by flash chromatography using petroleum ether/ethyl acetate (4:1) gave a yellow oil (0.434 g, 62 %).

Yellow oil, yield 62 %, (Found : m/z, 348.1070, $C_{15}H_{16}N_4O_6$ requires: M, 348.1070); ν_{max} (CH_2Cl_2) 3080, 2982, 1735, 1605, 1560, 1522, 1508, 1458, 1353, 1205, 1111, 1024, 857 and 734 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.23-1.29 (3H, m, CH_3), 2.54 (3H, s, CH_3), 3.71 (3H, s, CH_3), 4.26-4.32 (2H, m, CH_2), 6.02 (1H, s, CH), 7.48 (2H, d, *J* 8.8, Ar-H) and 8.18-8.21 (2H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 14.37 (CH_3), 14.50 (CH_3), 38.7 (CH_3), 47.3 (CH), 63.1 (CH_2), 124.3 (ArCH), 130.0 (ArCH), 131.6 (C), 138.4 (C), 140.9 (C), 146.7 (C), 147.9 (C) and 167.8 (CO).

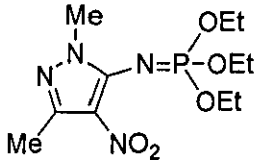
5-Azido-1,3-dimethyl-4-nitro-1*H*-pyrazole (152)



A solution of the 5-chloro-1,3-dimethyl-4-nitro-pyrazole (1.05 g, 6 mmol) in anhydrous DMF (5 cm^3) was treated with sodium azide (0.39 g, 6 mmol) and the mixture stirred at room temperature, with exclusion of light, for 16 h. The solvent was evaporated under vacuum and the residue treated with water (10 cm^3). The aqueous phase was extracted with dichloromethane (3 × 15 cm^3), the extracts combined, dried over $MgSO_4$, filtered and evaporated to dryness to yield a brown solid (0.7 g, 64 %).

Brown solid, yield 64 %, m.p. 82-83 °C; (Found : m/z, 182.0555, $C_5H_6N_6O_2$ requires: M, 182.0552); ν_{max} 2163 (N_3), 1547, 1467, 1364, 1261 and 1154 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 2.49 (3H, s, CH_3) and 3.67 (3H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 14.5 (CH_3), 35.7 (CH_3), 123.8 (C), 136.9 (C) and 145.0 (C).

2,5-Dimethyl-4-nitro-2*H*-pyrazol-3-yl-phosphorimidic acid triethyl ester (153)

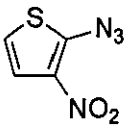


Triethyl phosphite (0.46 g, 2.8 mmol) was added dropwise to 5-azido-1,3-dimethyl-4-nitro-1*H*-pyrazole (0.5 g, 2.75 mmol) in dry dichloromethane (5 cm^3). The solution was stirred under nitrogen at room temperature for 30 min, and then heated under reflux for 1 h. The solution was evaporated and the residual yellow oil, dry flash chromatographed over silica.

Elution with dichloromethane/ethyl acetate (1:1) gave the phosphoramidate as a bright yellow oil (0.86 g, 99 %).

Yellow oil, yield 99 %; (Found : m/z, 320.1245, $C_{11}H_{21}N_4O_5P$ requires: M, 320.1250); ν_{max} 1596, 1516, 1420, 1275, 1147, 1036, 981 and 819 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.25 (9H, tt, *J* 1.1, 7.2, CH_3), 2.34 (3H, s, CH_3), 3.46 (3H, s, CH_3) and 4.08 (6H, p, *J* 0.93, C-H); δ_C (62.9 MHz; $CDCl_3$) 15.9 (CH_3), 16.2 (C, d, *J* 7.4, P-CH_3), 34.2 (CH_3), 64.9 (C, d, *J* 7.9, P-CH_2), 121.3 (C), 144.2 (C, d, *J* 18.7, P-C) and 144.6 (C); δ_P (101.2 MHz; $CDCl_3$) - 5.1.

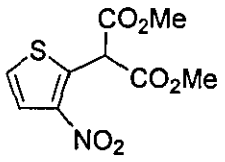
2-Azido-3-nitro-thiophene (162)



A solution of 2-chloro-3-nitro-thiophene (0.33 g, 2 mmol) in anhydrous DMF (3 cm^3) was treated with sodium azide (0.13 g, 2 mmol) and the mixture stirred at room temperature, with exclusion of light, for 16 h. The solvent was evaporated under vacuum and the residue treated with water (10 cm^3). The aqueous phase was extracted with dichloromethane (3 × 15 cm^3), the extracts combined, dried over $MgSO_4$, filtered and evaporated to dryness to yield a yellow solid (0.18 g, 52 %).

Yellow solid, yield 52 %, m.p. 78-79 °C (lit.,[5] 79-81 °C); ν_{max} 3107, 2152 (N_3), 1536, 1379, 1324 and 1189 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 6.87 (1H, d, *J* 6, CH_3) and 7.45 (1H, d, *J* 6.2, C-H).

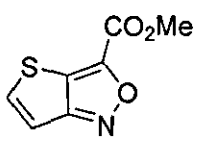
Dimethyl 2-(3-nitro-thiophen-2-yl)-propanedioate (158a)



2-Chloro-3-nitro thiophene (0.654 g, 4 mmol) in dry DMF (4 cm^3) was added to stirred NaH washed free from oil (0.191 g, 8 mmol) and dimethyl malonate (1.057 g, 8 mmol) in dry DMF (4 cm^3) at 0 °C under nitrogen. The reaction mixture was allowed to warm to room temperature. After 12 h the solvent was removed *in vacuo*. The residue was treated with water (10 cm^3) and acidified with concentrated hydrochloric acid until neutral to pH paper. The aqueous phase was extracted with dichloromethane (3 × 15 cm^3), the extracts combined, dried over $MgSO_4$, filtered and evaporated to dryness to yield a viscous orange oil (1.378g). Flash column chromatography eluting with petroleum ether and ethyl acetate (3:1) gave a white solid (0.949 g, 92 %).

White solid, yield 92 %, m.p. 65-66 °C; (Found : m/z, 259.0151, $C_9H_9NO_6S$ requires: M, 259.0151); ν_{max} 3121, 2957, 1741, 1543, 1508, 1436, 1385, 1336, 1221, 1152 and 1021 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 3.83 (6H, s, CO_2CH_3), 5.92 (1H, s, CH), 7.32 (1H, d, *J* 5.7, Ar-H) and 7.64 (1H, d, *J* 5.7, Ar-H); δ_C (62.9 MHz; $CDCl_3$) 51.6 (CH_3), 53.9 (CH), 124.4 (CH), 125.5 (CH), 136.6 (C), 145.9 (C) and 166.8 (CO).

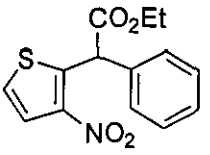
Methyl thieno[3,2-*c*]isoxazole-3-carboxylate (161a)



Dimethyl 2-(3-nitro-thiophen-2-yl)-propanedioate (0.578 g, 2.23 mmol) was added to dry toluene (150 cm^3). The reaction mixture was heated under reflux for 16 h. The reaction mixture was cooled and the solvent was evaporated to dryness to reveal a pale orange solid. The solid was re-crystallised from hot ethanol to afford a yellow solid (0.371 g, 91 %).

Yellow solid, yield 91 %, m.p. 119-120 °C; (Found: m/z, 182.9972, $C_7H_5NO_3S$ requires: M, 182.9990); ν_{max} 1735, 1478, 1437, 1386, 1308, 1198, 1160, 1074 and 760 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 4.03 (3H, s, CO_2CH_3), 7.09 (H, d, *J* 5.6, Ar-H) and 7.63 (H, d, *J* 5.6, Ar-H); δ_C (100 MHz; $CDCl_3$) 53.1 (CH_3), 112.2 (CH), 125.1 (C), 142.3 (CH), 150.4 (C), 156.7 (C) and 171.0 (CO).

(3-Nitro-thiophen-2-yl)-phenyl-acetic acid methyl ester (158b)

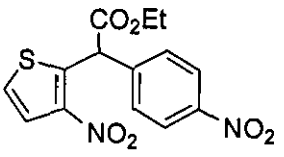


2-Chloro-3-nitro thiophene (0.409 g, 2.5 mmol) in dry DMF (4 cm^3) was added to stirred NaH washed free from oil (0.126 g, 5.25 mmol) and ethyl phenyl acetate (0.41 g, 2.5 mmol) in dry DMF (4 cm^3) at 0 °C under Nitrogen. The reaction mixture was allowed to warm to room temperature. After 12 h the solvent was removed *in vacuo*. The residue was treated with water (10 cm^3) and acidified with concentrated hydrochloric acid until neutral to pH paper. The aqueous phase was extracted with dichloromethane (3 × 15 cm^3), the extracts combined, dried over $MgSO_4$, filtered and evaporated to dryness to yield a viscous orange oil (0.763 g). Purification by flash chromatography eluting with petroleum ether/ethyl acetate (3:1) gave a yellow oil (0.532 g, 73 %).

Yellow oil, yield 73 %; (Found : m/z, 291.0561, $C_{14}H_{13}NO_4S$ requires: M, 291.0565); ν_{max} 3122, 2977, 1734, 1534, 1491, 1452, 1378, 1326, 1194, 1168, 1027 and 719 cm^{-1}; δ_H (400

MHz; $CDCl_3$) 1.25 (3H, t, *J* 7.2, CH_3), 4.13-4.02 (2H, m, CH_2), 5.86 (1H, s, CH), 7.15 (1H, d, *J* 6, Ar-H), 7.37-7.41 (5H, m, Ar-H) and 7.63 (H, d, *J* 5.6, Ar-H); δ_C (100 MHz; $CDCl_3$) 14.1 (CH_3), 51.6 (CH), 62.0 (CH_2), 123.9 (CH), 124.5 (CH), 128.7 (CH), 128.7 (CH), 129.0 (CH), 136.3 (C), 144.3 (C), 146.7 (C) and 170.3 (CO).

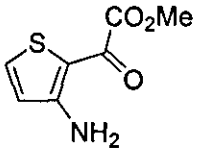
(4-Nitro-phenyl)-(3-nitro-thiophen-2-yl)-acetic acid ethyl ester (158c)



2-Chloro-3-nitro thiophene (0.409 g, 2.5 mmol) in dry DMF (4 cm^3) was added to stirred NaH washed free from oil (0.126 g, 5.3 mmol) and ethyl 4-nitrophenyl acetate (0.523 g, 2.5 mmol) in dry DMF (4 cm^3) at 0 °C under nitrogen. The reaction mixture was allowed to warm to room temperature. After 12 h the solvent was removed *in vacuo*. The residue was treated with water (10 cm^3) and acidified with concentrated hydrochloric acid until neutral to pH paper. The aqueous phase was extracted with dichloromethane (3 × 15 cm^3), the extracts combined, dried over $MgSO_4$, filtered and evaporated to yield a viscous orange oil (0.856 g). Purification by flash chromatography eluting with petroleum ether/ethyl acetate (3:1) gave a yellow solid (0. 675 g, 80 %).

Yellow solid, yield 80 %, m.p. 143.5-144.5 °C; (Found : m/z, 336.0421, $C_{14}H_{12}N_2O_6S$ requires: M, 336.0416); ν_{max} 3120, 2983, 1735, 1606, 1540, 1523, 1502, 1454, 1383, 1348, 1338, 1199, 1176 and 1023 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.26 (3H, m, CH_3), 4.13-4.36 (2H, m, CH_2), 6.06(1H, s, CH), 7.26 (1H, d, *J* 5.7, Ar-H), 7.59-8.24 (3H, m, Ar-H) and 8.26 (2H, d, *J* 7, Ar-H); δ_C (62.9 MHz; $CDCl_3$) 14.3 (CH_3), 51.2 (CH_2), 62.9 (CH), 124.5 (CH), 124.9 (CH), 130.0 (CH), 143.3 (CH), 143.4 (C), 145.0 (C), 148.2 (C) and 169.7 (CO).

(3-Amino-thiophen-2-yl)-oxo-acetic acid methyl ester (167)



Triphenylphosphine (0.143 g, 0.55 mmol) was added to methyl thieno[3,2-*c*]isoxazole-3-carboxylate (0.1 g, 0.5 mmol) in toluene (5 cm^3). The reaction mixture was heated under reflux. After 6 h the reaction was complete. The solvent was removed *in vacuo* to give a yellow liquid. Flash column chromatography eluting with petroleum ether/ethyl acetate (2:1), gave a yellow solid (0.065 g, 65 %)

Yellow solid, yield 65%, m.p. 143.5-144.5 °C; (Found: m/z, 185.0147, $C_7H_7NO_3S$ requires: M, 185.0147); ν_{max} 3394, 3266, 3172, 1726, 1665, 1498, 1420, 1347, 1220 and 763 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 3.92 (3H, s, CH_3), 6.54 (1H, d, *J* 5.5, Ar-CH), 6.82 (2H, br s, N-H) and 7.52 (1H, d, *J* 5.3, Ar-H); δ_C (100 MHz; $CDCl_3$) 53.46 (CH_3), 108.3 (C), 118.4 (CH), 140.1 (CH), 160.4 (C), 163.5 (CO) and 173.9 (CO).

3.5 References

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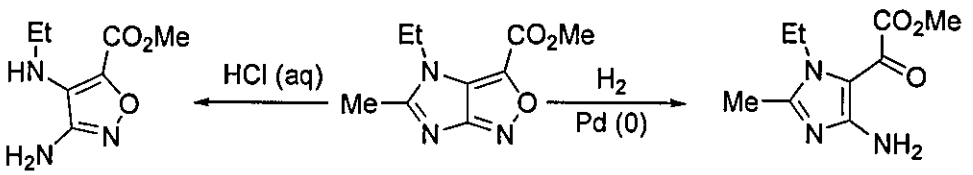
Chapter 4

Chemistry of Imidazo[4,5-*c*]isoxazole Derivatives

4.1 Introduction

We have been interested in the chemistry of fused [5,5] ring heterocycles since the strain in such molecules frequently leads to interesting ring opening and rearrangement reactions. Many [5,5] fused ring compounds[1] have been used in the construction of larger, ring expanded heterocycles.

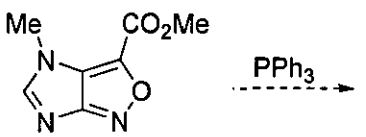
Tennant and co-workers[2] have demonstrated the strain inherent in the imidazo[4,5-*c*]isoxazole ring system e.g. the 3-carboxylate derivative **94b, Scheme 74** by the easy reductive cleavage of the N-O bond in the isoxazole ring by catalytic palladium hydrogenation and the easy hydrolytic opening of the imidazole ring with heating aqueous hydrochloric acid.



175 **94b** **174**

Scheme 74

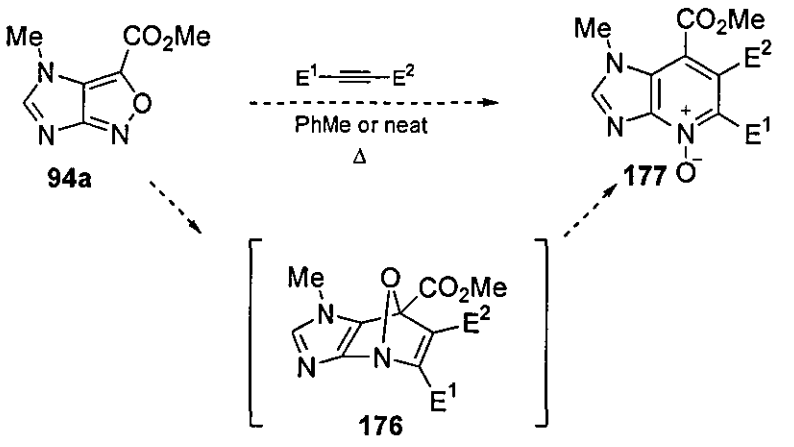
Little chemistry is known for this heterocycle, therefore it was decided to undertake an investigation into the reactivity of imidazo[4,5-*c*]isoxazole derivatives towards a range of reagents. A first study was on their behaviour towards soft nucleophiles such as triphenylphosphine, which may lead to interesting ring opened products suitable for further elaboration into other interesting heterocycles with potential biological activity, **Scheme 75.**



94a

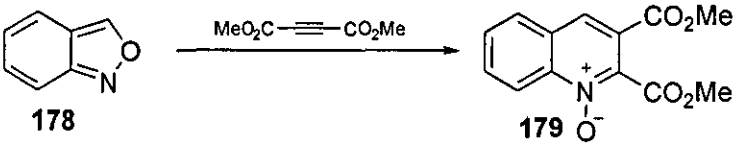
Scheme 75

We also anticipated that the strain existent in the fused isoxazole ring would make compounds of this class reactive towards dienophiles, and it was considered that the imidazo[4,5-*c*]isoxazole ring potentially could undergo hetero-Diels-Alder reaction with alkynes to create imidazo-fused bicyclic compounds such as **176**, or more likely, imidazo[4,5-*b*]pyridine-*N*-oxides such as **177**, which would arise through ring opening of the oxygen bridged structure **176**, **Scheme 76**.

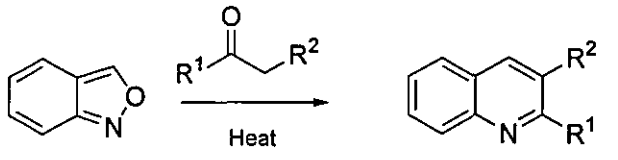


Scheme 76

Comparable processes are well known[3] for benzofurans, but few examples have been reported for 2,1-benzisoxazoles (anthranils). The quinoline-*N*-oxide **179** has been constructed[4] by reaction of 2,1-benzisoxazole **178** with dimethyl acetylenedicarboxylate (DMAD), **Scheme 77**. Quinolines **180** have been been prepared[5] by heating anthranils, **178** with ketones; the reaction is thought to proceed by cycloaddition of the enol form of the ketone to the isoxazole ring, **Scheme 78**. Subsequent ring opening and dehydration then leads to formation of a pyridine ring.



Scheme 77

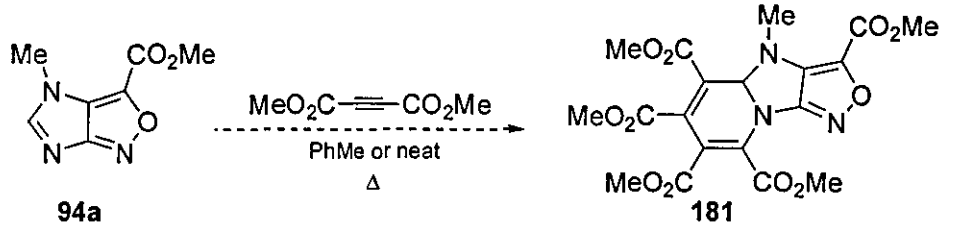


178 180

Scheme 78

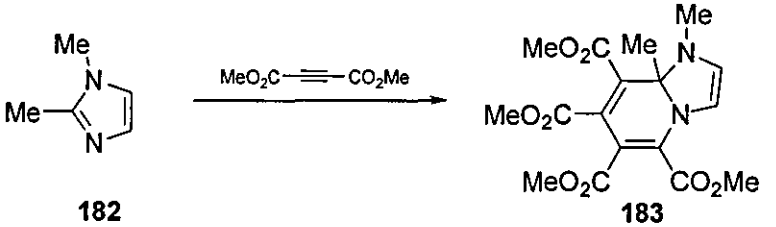
We considered that a similar type of reaction might occur with imidazo[4,5-*c*]isoxazoles which would provide a useful route to biologically[6] interesting imidazo[4,5-*b*]pyridine derivatives, which are an important class of heterocycles[7] that can be considered as 1-deazapurines. These heterocycles can be incorporated into modified nucleosides to act as anti-viral and anti-cancer agents. There are many routes[7] to imidazo[4,5-*b*]pyridine derivatives in the literature, but most have employed substituted pyridines as a starting point in synthesis and used various strategies to build up the imidazole nucleus of the bicycle. This has prompted us to consider an approach of starting from a imidazo[4,5-*c*]isoxazole derivative and constructing the pyridine ring directly with acetylenes.

Alternatively, it was thought that reaction may occur at the imidazole ring, since the isoxazole ring bears an electron withdrawing ester substituent, which would hinder reaction with an electron deficient dienophile. The fused pyridine **181** was considered to be a possible product from this proposed reaction, **Scheme 79**. It is documented that simple imidazoles such as **182** are transformed[8] into imidazo[1,2-*a*]pyridines, **183** on treatment with DMAD in ether at room temperature, **Scheme 80**.



94a 181

Scheme 79

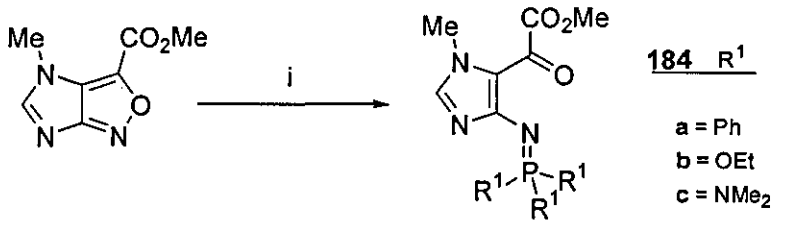


182 183

Scheme 80

4.2.1 Reactions with soft nucleophiles

The investigation of the reactivity of imidazo[4,5-*c*] isoxazole first started with reaction with various soft nucleophiles such as phosphine derivatives. When the fused isoxazole **94a** was reacted with triphenylphosphine in refluxing toluene, we obtained a cream coloured solid product in 98 % yield.

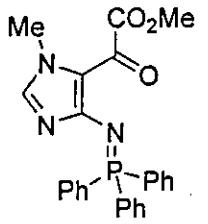


94a

*Reagents and Conditions: i, **185-187**, Toluene, Reflux.*

Scheme 81

Analytical and spectroscopic properties showed the compound to be the iminophosphorane **184a**. To confirm which atom the phosphorus was attached to crystals suitable for X-ray crystallographic analysis were prepared. The structure shown in **Figure 4.1** and **Appendix 8** provide evidence that the phosphorus nucleophile has attacked the nitrogen atom of the isoxazole ring, cleaving the bond between the nitrogen and oxygen to give keto-ester imidazole substituted iminophosphorane **184a**.



184a

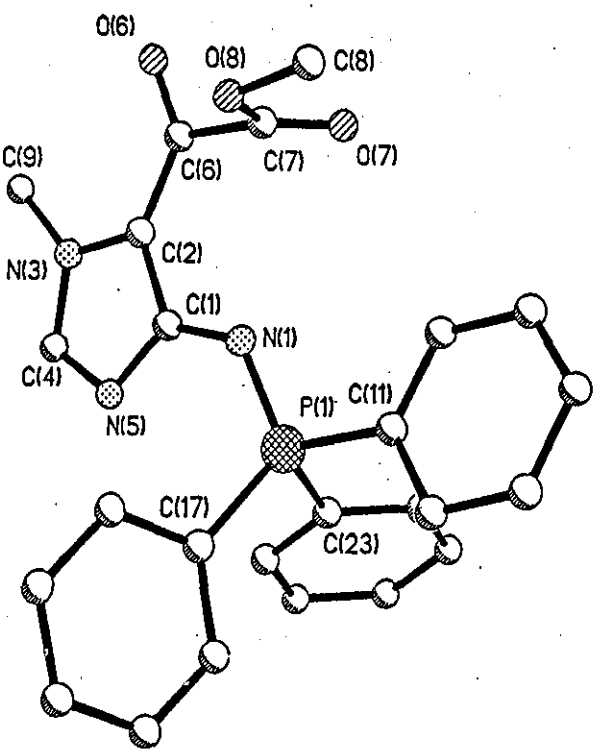


Figure 4.1, X-ray structure of methyl 2-1-methyl-4-[(1,1,1-triphenyl-λ^5-phosphanylidene)amino]-1*H*-imidazol-5-yl-2-oxoethanoate (184a).

We have extended this reaction and shown that other nucleophiles, such as triethyl phosphite and hexamethyl phosphrous triamide react in a similar fashion as shown in **Table 4.1**. The products were formed in very good yields.

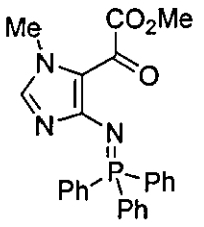
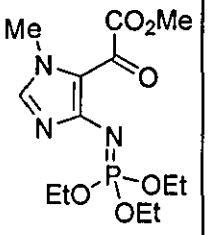
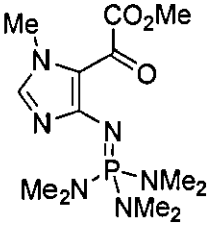
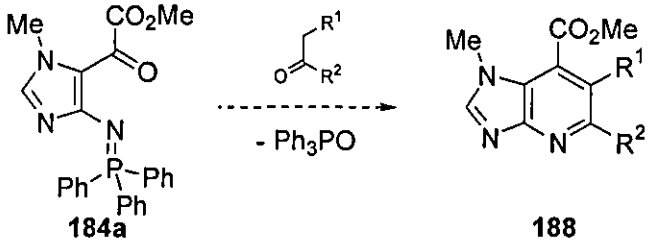
Substrates	Products	Yield (%)
PPh_3 **185**	 **184a**	98
$P(OEt)_3$ **186**	 **184b**	90
$P(NMe_2)_3$ **187**	 **184c**	92

Table 4.1

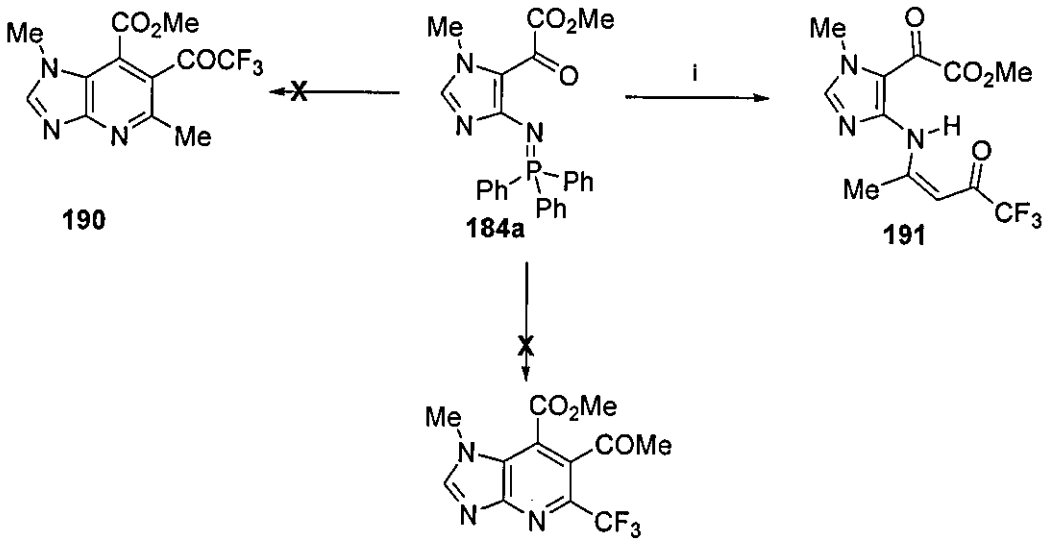
4.2.2 Studies on the possible ring closure of an imidazole substituted iminophosphorane derivative

It was predicted that the iminophosphorane **184a** would be reactive towards activated carbonyl compounds, and may undergo a combination of an aza-Wittig reaction and an aldol condensation to generate imidazo-fused bicyclic compounds such as the imidazo[4,5-*b*]pyridines **188**, with a loss of triphenylphosphine oxide, **Scheme 82.**



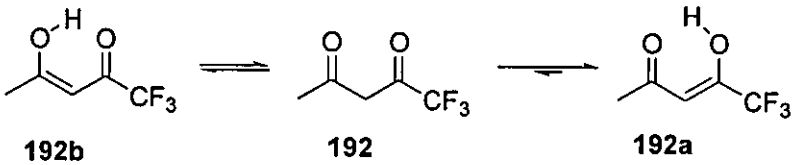
Scheme 82

This hypothesis was examined by a small-scale reaction using excess acetyl acetone with iminophosphorane **184a** under reflux. The reaction proved unsuccessful and starting material was recovered unchanged. When 1,1,1 trifluoroacetylacetone (1,1,1 trifluoropentandione) was employed with the iminophosphorane **184a** under reflux a reaction seemed to occur. After 28 h the solvent was removed to give a yellow oil, purification by flash column chromatography gave a yellow solid in 62 % yield. The solid analysed to give a molecular formula $C_{12}H_{12}F_3N_3O_4$ inconsistent with either of the expected imidazopyridines **189** or **190** with molecular formula $C_{12}H_{10}F_3N_3O_3$. The presence of an alkenyl proton signal at δ 5.63 also indicated the expected product **189** had not formed, and that the vinylogous amide **191** had been produced. This was verified carrying out an X-ray crystallographic analysis. **Figure 4.2** and **Appendix 8** show the structure to the *cis* configured alkene **189**, shown in **Scheme 83**. This result demonstrates the intial aza-Wittig reaction had occurred followed by tautomerisation of an imine to the stable enamine product. Cyclisation could then not occur easily to close the pyridine ring. The reaction may have proceeded further by a cyclocondensation reaction if catalytical amount of base was used, but this was not explored. It is interesting to note that the iminophosphorane **184a** nitrogen atom had attacked the seemingly less electrophilic methyl carbonyl group rather than the trifluoromethyl substituted carbonyl. This is most likely due to the trifluoroacetylacetone exisited largely in the enol tautomer **192a** shown in **Scheme 84.**

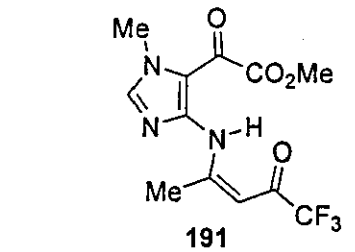


Reagents and Conditions: i, 1,1,1-trifluoropentandione, Reflux.

Scheme 83



Scheme 84



191

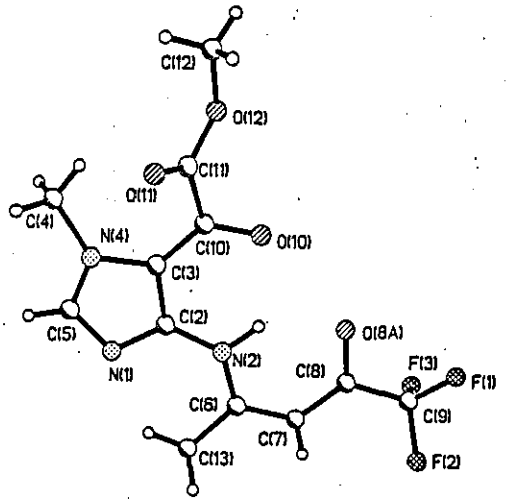
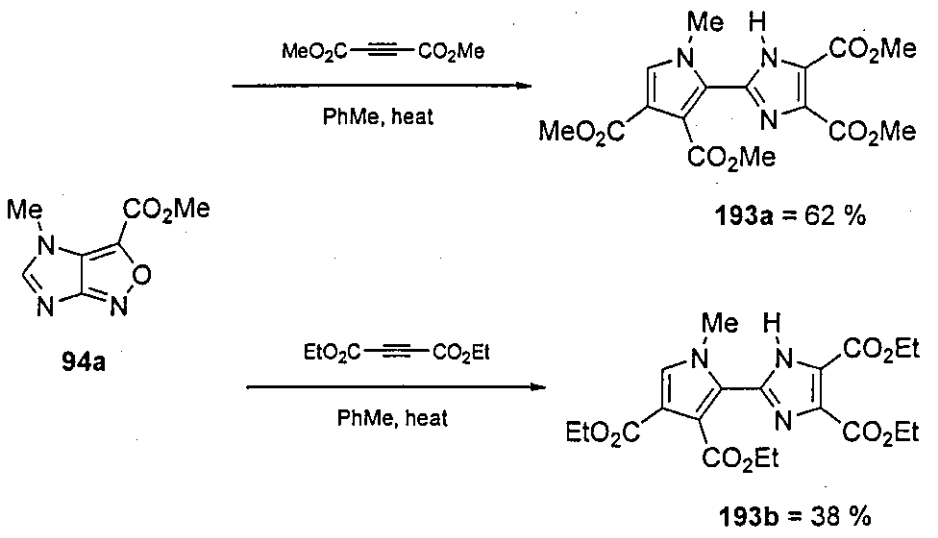


Figure 4.2, X-ray structure of [3-methyl-5-(4,4,4-trifluoro-1-methyl-3-oxo-but-1-enylamino)-3*H*-imidazol-4-yl]-oxo-acetic acid methyl ester (191).

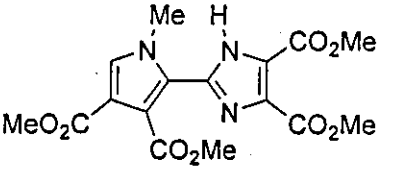
4.2.3 Investigation into the reactions of an imidazo[4,5-*c*]isoxazole carboxylate derivative with alkynes; synthesis of 2-pyrrol-2-yl imidazole derivatives

When the imidazo[4,5-*c*]isoxazole **94a, Scheme 85** was treated with DMAD in boiling toluene, a crystalline compound analysing for $C_{16}H_{17}N_3O_8$ was obtained in a moderate yield of 62 %. The ^{1}H n.m.r. spectrum of this compound displayed four methyl ester signals, a single aromatic proton at δ 7.25 and a three hydrogen singlet corresponding to a methyl attached to nitrogen. A broad peak at δ 12.9 suggested the presence of a NH group in the molecule. When the reaction was repeated using diethyl acetylene dicarboxylate, a similar compound was obtained in 38 % yield, which exhibited signals owing to four ethyl esters, but no methyl ester, suggesting that both the methyl ester at *C*-6 and the ring oxygen of the imidazoisoxazole had been lost during the reaction, and that two molecules of the acetylenic ester had been incorporated into the product, **Scheme 85**. The N.M.R and the

I.R spectra alone did not allow conclusive identification of the product, so crystals of the dimethyl acetylenedicarboxylate adduct were prepared; X-ray diffraction analysis of the compound showed it to be the 2-pyrrol-2-yl imidazole **193, Figure 4.3** and **Appendix 8**.



Scheme 85



193a

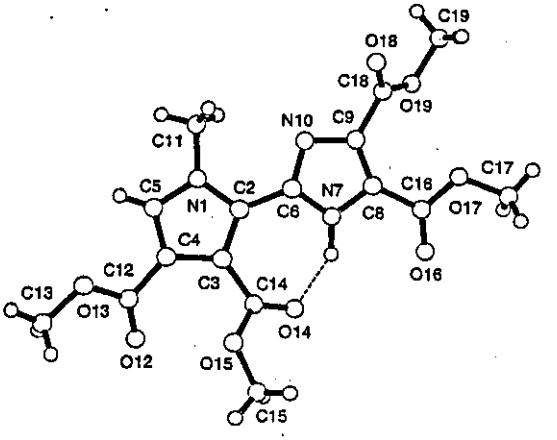
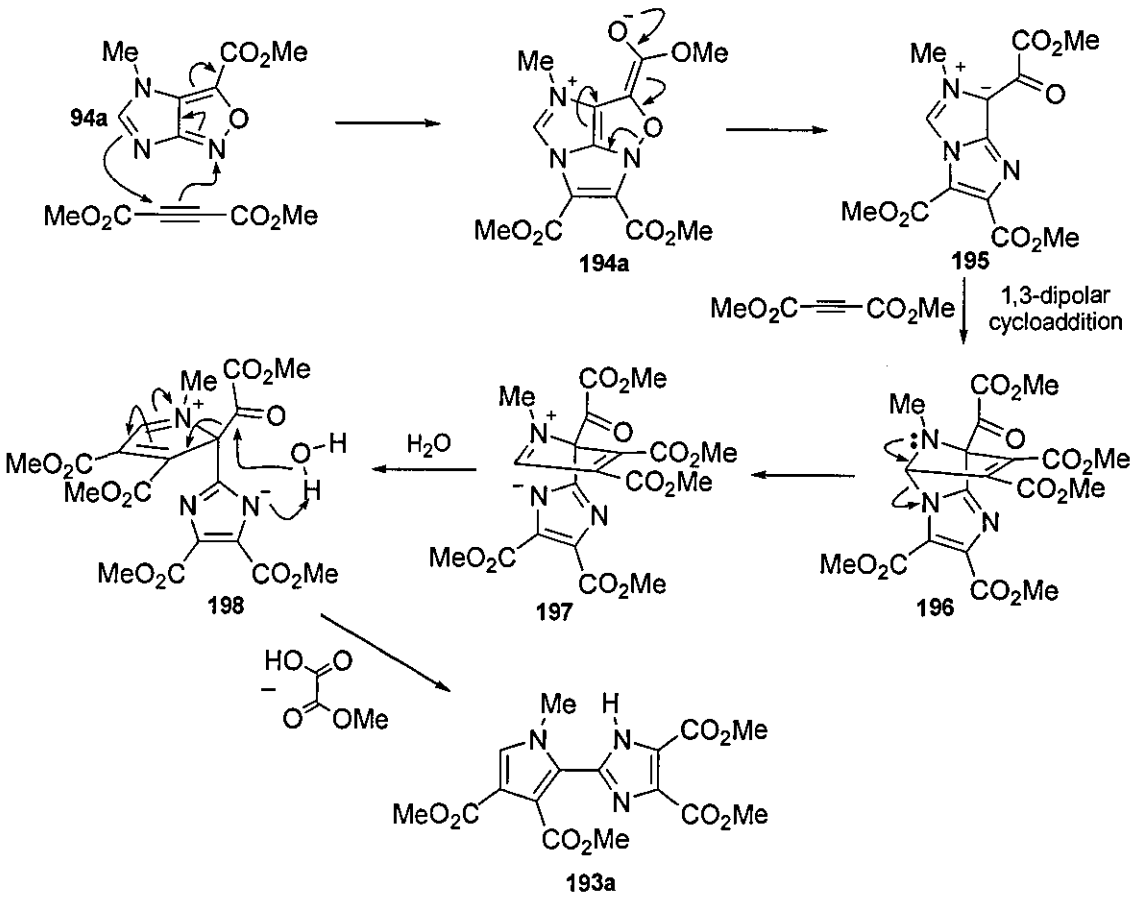


Figure 4.3, X-ray structure of dimethyl 2-1-methyl-3,4-di[(methoxy)carbonyl]-1*H*-pyrrol-2-yl-1*H*-imidazole-4,5-dicarboxylate (193a).

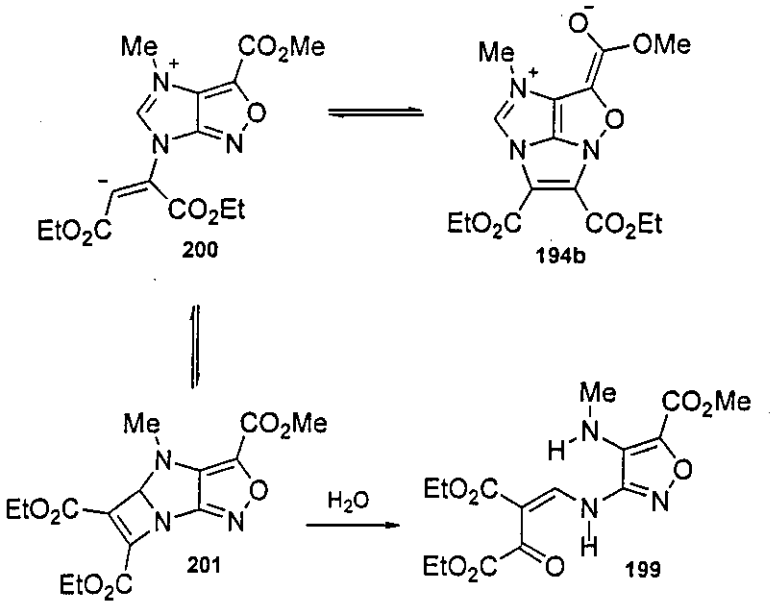
4.2.4 Proposed mechanism of pyrrolyl imidazole formation

A mechanism has been proposed to account for the formation of ester **193a** and this is outlined in **Scheme 86**. It is thought that nucleophilic addition of the imidazoisoxazole to the acetylenic ester occurs through *N*-3 and subsequent attack of the vinyl anion at *N*-4 of the imidazo-isoxazole leads to the tricyclic intermediate **194a**. Ring opening of the isoxazole by cleavage of the N-O bond would then form **195** setting up a 1,3-dipole across atoms 1,2 and 6a of the original bicycle. Cycloaddition of a second molecule of the acetylenic ester would generate the bridged intermediate **196**, which can fragment by elimination of an imidazolyl anion. Aromatisation of the pyrrole ring may then occur by loss of the keto-ester side chain. This most likely occurs through a retro-Claisen reaction mediated by traces of water in the reaction mixture or present during isolation. Water is also required to protonate the newly formed imidazole ring. We have not been able to determine the fate of the keto ester group. No mono-methyl oxalate was isolated during chromatographic separation of the products. Hydrolysis of the ester and decarboxylation and decarbonylation could also account for side chain loss and aromatisation of the pyrrole ring.

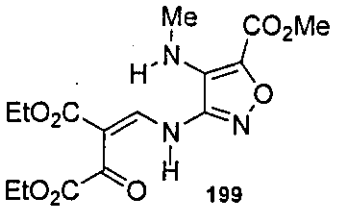


Scheme 86

Some evidence has been obtained which supports the proposed mechanism. This has been obtained from the reaction involving diethyl acetylenedicarboxylate. An orange crystalline compound analysing for $C_{15}H_{17}N_3O_7$ believed intially to be betaine **194b, Scheme 87** was also obtained in 47 % yield and corresponds to the adduct derived from addition of a single molecule of diethyl acetylenedicarboxylate. In an attempt to prepare crystals suitable for X-ray diffraction analysis, the substance was allowed to crystallise slowly from light petroleum and ethanol. The diffraction analysis however showed the compound to be the substituted isoxazole **199, Figure 4.4** and **Appendix 8.**



Scheme 87



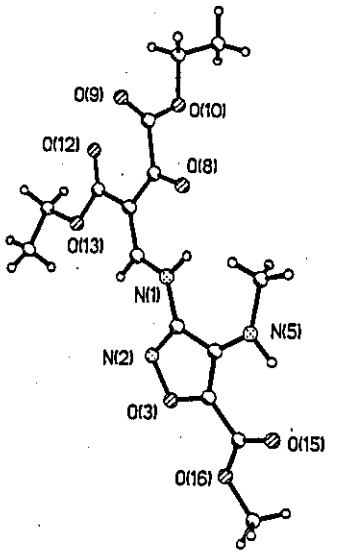
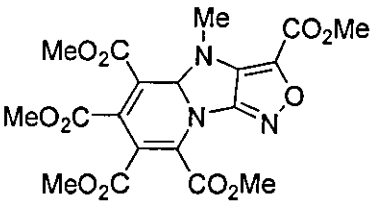


Figure 4.4, X-ray crystal structure of diethyl 2-[(*E*)-1-(4-(methylamino)-5-[(methoxy)carbonyl]isoxazol-3-ylamino)methylidene]-3-oxobutanedioate (199).

This has the molecular formula $C_{15}H_{19}N_3O_8$, denoting that hydration of the molecule had taken place during crystallisation. The presence of the intact isoxazole ring in this compound indicates that the substance initially isolated, cannot be **196**, and is either **194b**. If the addition of the vinyl anion **200** to the isoxazole ring is reversible, addition of the anion could also occur onto the iminium ion of the imidazole ring, to form **201**, albeit *via* a 4-*exo*-trig cyclisation (assuming a resonance structure involving the lone pair of the imidazole *N*-1 is important otherwise the reaction would correspond to 4-*endo*-trig). Addition of water to the unsaturated azetine ring, and subsequent hydrolytic opening of the four-membered ring and the aminal of the imidazole ring, then account for formation of the vinylogous amide side chain in the product isoxazole **199**.

No compounds of the type **181**, **Figure 4.4** were isolated, in which two molecules of the acetylenic ester had added consecutively to form a six membered ring fused across the 2,3 bond of the imidazole ring. This is a common pathway for reaction of imidazoles, pyridines and other heterocycles[9] with DMAD and it is not clear why cyclisation of the intermediate **200** occurs to form the four-membered ring required to account for production of the vinylogous amide **199**.



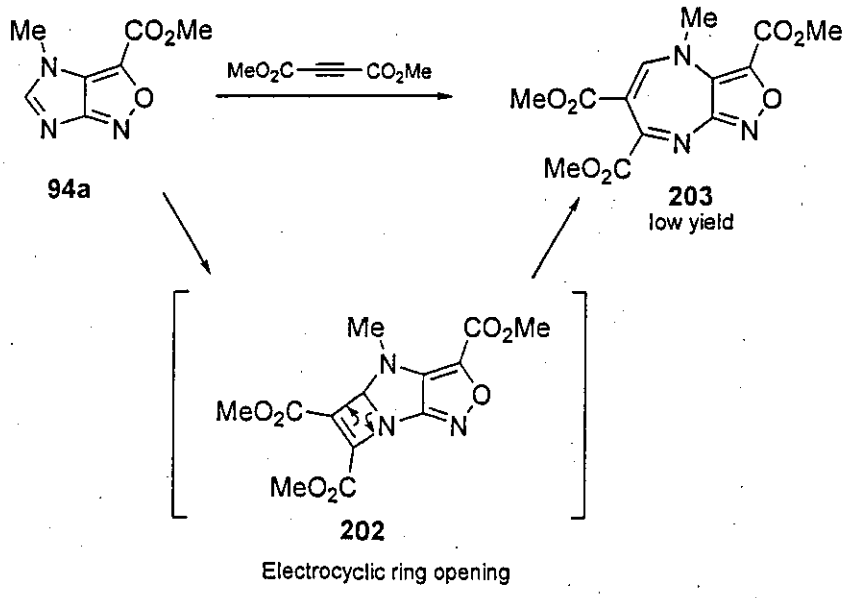
181

Figure 4.4

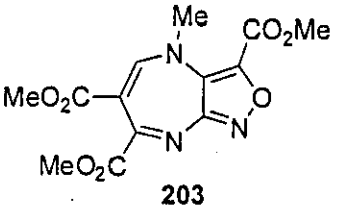
Several reactions of this type were repeated in order to isolate any intermediates in the reaction in order to verify the mechanism of this intriguing reaction. In another reaction with DMAD, a low yield of an orange red crystalline compound was obtained. From its analytical, spectroscopic and mass spectrometric data, this compound was also corresponded to the addition product of a single molecule of dimethyl acetylenedicarboxylate. This compound was also initially thought to be an intermediate in the reaction, possibly the imidazo[3,4-*a*]imidazolium betaine **194a**, **Scheme 86**.

The structure of the compound was again determined by X-ray crystallography and shown (**Figure 4.5** and **Appendix 8**) to be the first example of a derivative of the [1,4]diazepino[2,3-*c*]isoxazole ring system **203**. The isolation of this compound confirmed

the existence of the alternative route for the reaction between dimethyl acetylenedicarboxylate and the imidazo[4,5-*c*]isoxazole derivative **94a, Scheme 88.**



Scheme 88



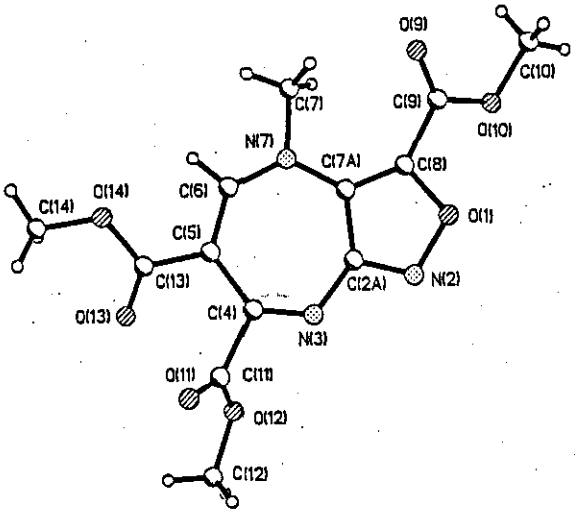
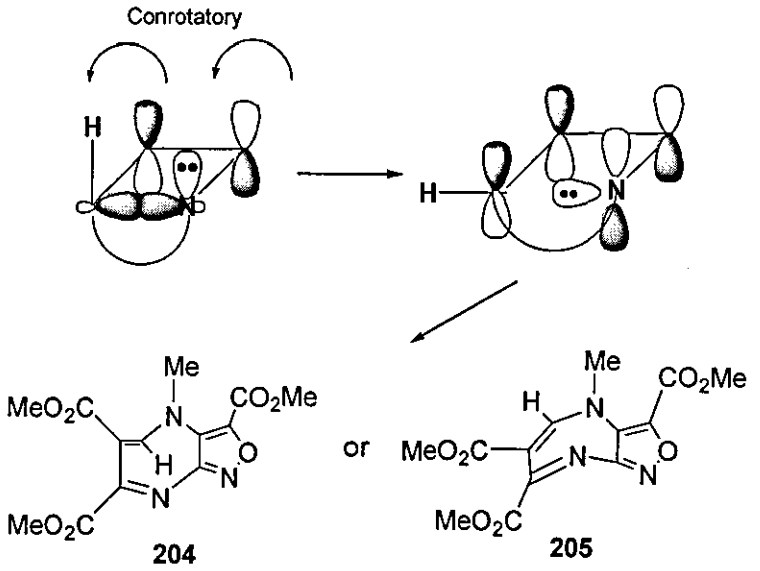


Figure 4.5. X-ray crystal structure of trimethyl 4-methyl-4*H*-[1-4]diazepino[2,3-*c*]isoxazole-3,6,7-tricarboxylate (203).

It is believed that this compound is formed by electrocyclic ring opening of the strained azetine[10] ring, the formation of which was indicated in **Scheme 88** would then produce the [1,4]diazepine ring in the product **203**.

The ring opening of **202** should be a conrotatory process, and unfavourable as thermal reaction for a fused azetine unless permitted by inversion at nitrogen. This is illustrated in **Scheme 89**, showing conrotatory ring opening of the azetine in this reaction would lead to products **204** and **205**, however this was not observed and we obtained product **203** by a disrotatory process that is not permitted according to Woodward-Hoffmann rules. Ring opening of a 1,2-diazabicyclo[3.2.0]hept-2-en-6-one, and its reversion to the starting 1,2-diazepin-6-one after photochemical cyclisation has been reported,[11] as have other disrotatory ring opening reactions of fused 2-azetines.[12] The different stereochemical outcome of azadiene-azetine interconversion has been attributed to a shift in the nodal position in the HOMO of the azadiene system.[13]

Alternatively, the fused azetine **202** may, be formed in a 2+2 cycloaddition between the acetylenic ester and the 2,3 C=N bond of the imidazoisoxazole **94a**.



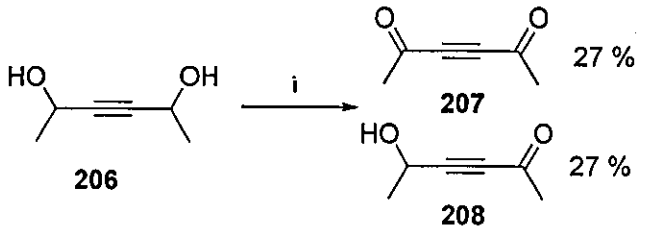
Scheme 89

Diazepine heterocycles are important pharmacologically active compounds,[14] and the isoxazole fused ring system **203** represents a useful building block for the synthesis of potentially biologically active diazepine molecules. The isoxazole ring in this molecule is a useful group for further manipulation, such as reductive ring opening to give adjacent amino and keto-ester substituents.

In an attempt to extend the scope of this we have investigated the use of other electron rich and deficient alkynes and alkenes.

4.2.5 Preparation of substituted alkynes required for experiments with imidazo-isoxazole carboxylate derivatives

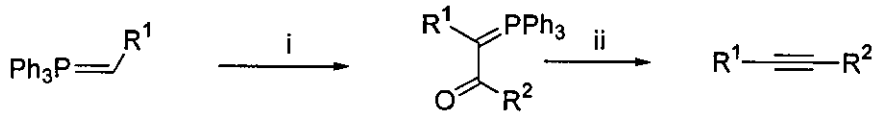
Alkynes that were required for reaction with imidazo[4,5-*c*]isoxazoles were prepared from known methods. Hex-3-yne-2,5-diol, **206** was oxidised by chromic acid[15] to prepare hex-3-yne-2,5-dione, **207** in 27 % yield. The partially oxidised product, 5-hydroxy-hex-3-yn-2-one, **208** was also obtained in the same yield, **Scheme 90**.



Reagents and Conditions: i, CrO_3/H_2SO_4, H_2O, Acetone.

Scheme 90

Another method[16] was utilised in a general preparation of various substituted acetylenes. This procedure made use of the phosphonium ylides **209a-c**, generated by treatment of the phosphonium salts with triethylamine. These were reacted with trifluoroacetic anhydride **210** or ethyl oxalychloride **211** to give substituted phosphonium ylides **212a-212e**. Pyrolysis of these at high temperature and under reduced pressure gave alkynes **213a - 213e** in moderate to very good yields, **Scheme 91**.

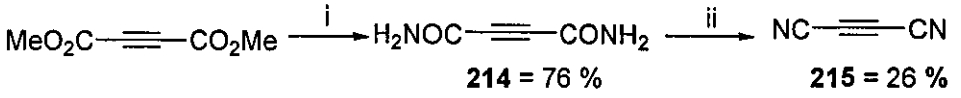


209 R^1	Reagent	212 R^1	R^2	Yield/%	213 R^1	R^2	Yield/%
a = CO_2Et	**210**	a = CO_2Et	CF_3	100	a = CO_2Et	CF_3	81
b = COMe	**210**	b = COMe	CF_3	92	b = COMe	CF_3	16
c = CN	**211**	c = CN	CO_2Et	92	c = CN	CO_2Et	41
	211	d = COMe	CO_2Et	90	d = COMe	CO_2Et	70
	210	e = CN	CF_3	74	e = CN	CF_3	–

*Reagents and Conditions: i, Et_3N, Substrates $(CF_3CO)_2O$ **210**, or ethyl oxalylchloride **211**, THF, 0 °C - R.T. ii, Heat 160-200 °C, reduced pressure.*

Scheme 91

Dicyano-acetylene **215** was prepared in 26 % yield[15b,17] by thermal dehydration of but-2-ynedoic-diamide **214** under reduced pressure with phosphorus pentoxide. But-2-ynedioic-diamide **214**, was in turn prepared by reaction of DMAD with concentrated ammonia solution.



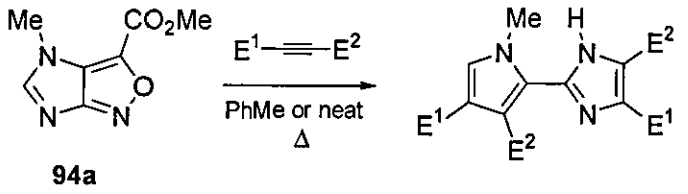
214 = 76 % **215** = 26 %

Reagents and Conditions: i, 35 % aqeous NH_3, -10 °C. ii, P_2O_5, Heat 160-200 °C, reduced pressure.

Scheme 92

4.2.6 Further reactions of imidazo[4,5-*c*]isoxazole deivatives with substituted alkynes

Most of the substituted alkynes prepared and the mono-substituted alkynes appear not to be effective in preparing pyrrolyl imidazoles. The imidazo-isoxazole **94a** was recovered unchanged in high yield after heating with acetylenes **216-223** shown on **Table 4.2**. The reactions with the highly electron deficient, and normally highly reactive, dicyano acetylene and cyanotrifluromethyl acetylene were surprisingly not successful, and the imidazo-isoxazole was retrieved unchanged. This may be accounted for rapid decompositon of the former, and the high volatility of the latter, impeding them from reacting with the substrate compound.



193	E^1	E^2	Yield/%
a = CO_2Me	CO_2Me		62
b = CO_2Et	CO_2Et		37
c = CF_3	CO_2Et		51
d = COMe	COMe		40

Scheme 93

Success was only obtained with ethyl 4,4,4-trifluorobut-2-ynoate **213a** and 2,5-dioxohex-3-yne **207** and the corresponding pyrrolyl imidazoles **193c** and **193d** were obtained in moderate yields of 51 % and 40 %, respectively, **Scheme 93**. The regio chemistry of the former compound was determined by ^{13}C NMR spectroscopy. Although no fluorine coupling could be seen to the pyrrole *H*-5 hydrogen atom in the ^1H NMR spectrum, the signal for the carbon atom at *C*-5, δ 128.3, was split into a quartet, with a three bond coupling constant, $^3J_{CF}$, of 6 Hz. The *C*-5 carbon was identified by proton-carbon correlation; the opposite α-carbon of the pyrrole ring resonating at a similar chemical shift of 127.8 ppm. The signal for the *C*-4 carbon of the pyrrole ring also showed a quartet splitting (q, $^2J_{CF}$, 40 Hz) at δ 115, not very far down field from a typical pyrrole β-carbon signal at δ 108. The *C*-4(5) carbon of the imidazole ring was also easily identified by the signal at δ 135.2 by fluorine coupling (q, $^2J_{CF}$, 40 Hz), **Figure 4.6** shows the key signals that determine the regioisomer. None of the alternative regioisomer was isolated.

	Alkynes	Outcome
216	NC—≡—CF_3	No Reaction
217	NC—≡—CN	Decomposition
218	Ph—≡—Ph	No Reaction
219	Me_3Si—≡—$SiMe_3$	No Reaction
220	≡—CO_2Me	No Reaction
221	≡—CO_2Et	No Reaction
222	≡—Ph	No Reaction
223	≡—COMe	No Reaction

Table 4.2

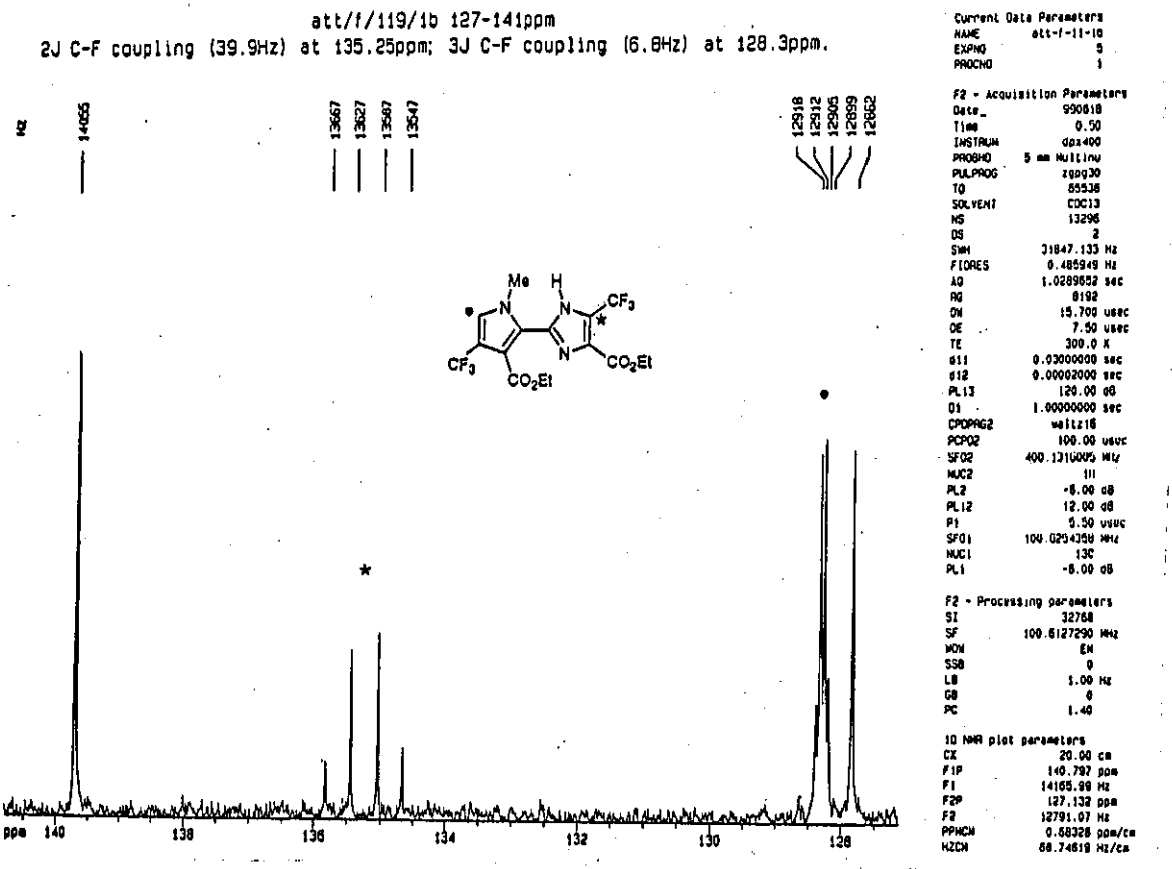


Figure 4.6, ^{13}C NMR spectroscopy of showing fundamental signals for determination of regioisomer ethyl 2-[3-[(ethoxy)carbonyl]-1-methyl-4-(trifluoromethyl)1*H*-pyrrol-2-yl]-1*H*-imidazole-5-carboxylate (193c).

4.2.7 Studies on the reaction of imidazo[4,5-*c*]isoxazole derivatives with alkenes

Reaction with electron deficient alkenes was expected to lead to saturated imidazo[1,2-*c*]imidazoles, while electron rich alkenes such as enol ethers, may be expected to form imidazopyridine-*N*-oxides if the coventional Diels-Alder mode of addition functions with electron rich dienophiles. Studies with electron rich and deficient alkenes **224-232** with imidazo-isoxazole were carried out by heating the substrate compound **94a** in refluxing toluene or in the neat alkene, **Table 4.3.** However, dissappointingly this investigation proved unsuccessful. The imidazo-isoxazole **94a** was unreactive towards the alkenes and the substrate was recovered unchanged in all cases. Even the highly reactive 4-phenyl-[1,2,4]triazole-3,5-dione **232** failed to react.[18]

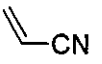
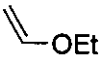
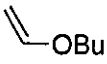
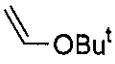
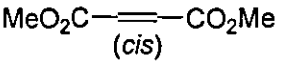
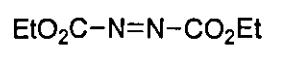
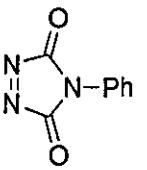
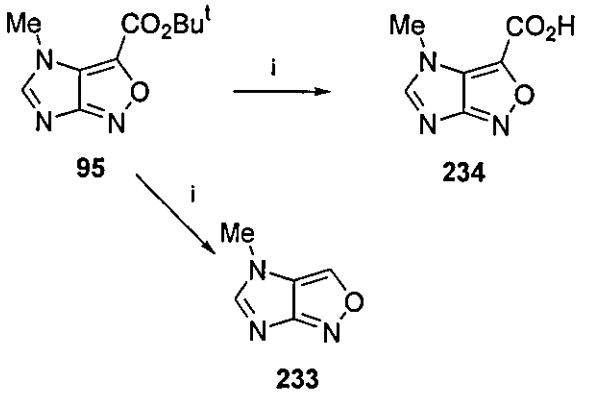
	Alkenes	Outcome
224		No Reaction
225		No Reaction
226		No Reaction
227		No Reaction
228		No Reaction
229		No Reaction
230		No Reaction
231		No Reaction
232		No Reaction

Table 4.3

4.2.8 Studies on the decarboxylation of imidazo[4,5-*c*]isoxazole-3-carboxylate derivatives

Another strategy was considered to modify the reactivity of the imidazo-isoxazole by removing the ester group from the *C*-3 position. This should alter the electronic nature of the ring system and allow alternative modes of reaction with unsaturated compounds. This could lead to synthesis of imidazo[4,5-*b*]pyridines. This may then allow dienophiles such as alkynes to undergo the conventional hetero-Diels-Alder reaction to create imidazo-fused bicyclic compounds such imidazo[4,5-*c*]pyridine-*N*-oxides such as **177** *via* ring opening of the oxygen bridged structure **176, Scheme 76.** Several methods for decarboxylation are reported.[19] It was decided to investigate first the use of *t*-butyl-4*H*-imidazo[4,5-*c*]isoxazole-3-carboxylate **95** with refluxing trifluoroacetic acid in chloroform.[20] This procedure expected to give the decarboxylated product, **233.** However we have only obtained 1-methyl-4*H*-imidazo[4,5-*c*]isoxazole-3-carboxylic acid, **234** in 89 % yield, **Scheme 94.** This may be due to the inability of TFA to protonate the *C*-3 of the ring to allow decarboxylation. Protonation is most likely to occur at *N*1 or *N*6. Time has not permitted us to continue further with this strategy.

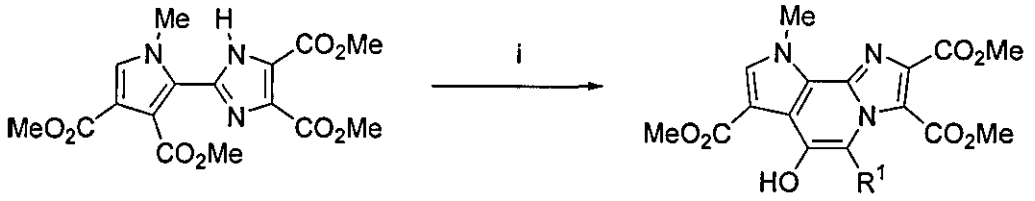


Reagents and Conditions: i, TFA,CHCl3, Reflux.

Scheme 94

4.2.9 Reactions of pyrrol-2-yl imidazoles; Synthesis of a novel heterocycle

With the 2-pyrrol-2-yl imidazole derivative **193a** in hand, it was decided to investigate its chemistry, and to see if a tricyclic molecule could be formed by bridging the pyrrole and imidazole rings. Thus it was decided to study alkylation of an imidazole nitrogen atom with a bromoacetate. Conversion of the pyrrol-2-yl imidazoles **193a** into the novel 9*H*-imidazo[1,2-*a*]pyrrolo[2,3-*c*]pyridine-2,3,7-tricarboxylate derivatives **235a** and **235b** was successful, **Table 4.4** and was achieved on treatment with sodium hydride and methyl or ethyl bromoacetate in DMF; the tricycle being formed in very good yields and existing as the fully aromatic tautomer with a hydroxyl group at *C*-6, **Scheme 95**. The reaction presumably involved deprotonation of the imidazole ring to generate a nucleophile which displaced the activated alkyl bromide to give *N* alkylated product. In the presence of excess sodium hydride the methylene group can also be deprotonated. Subsequent Dieckmann type cyclisation could then have occurred with an adjacent ester group on the pyrrole ring, rendering the tricyclic nucleus. When benzyl bromide was employed as a substrate, only the benzylated imidazole product **236** was obtained, **Scheme 96**. This may be due to sodium hydride not being strong enough to deprotonate the benzylic group to allow the Dieckmann cyclisation to occur to afford the tricyclic product.



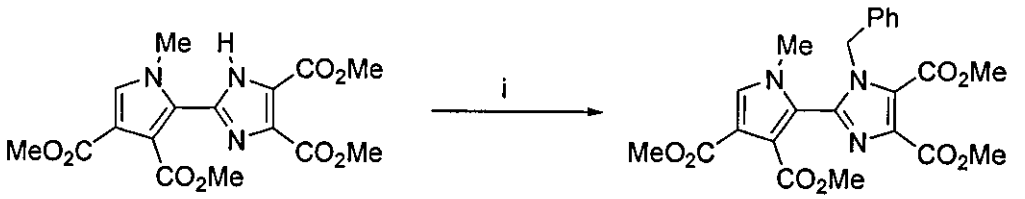
193a **235a-b**

Reagents and Conditions: i, 2.5 NaH, Substrates: methyl/ethyl bromoacetate, DMF, 0 °C - R.T.

Scheme 95

Substrates	R^1	Product	Yield (%)
Ethyl bromoacetate	CO_2Et	**235a**	90
Methyl bromoacetate	CO_2Me	**235b**	70

Table 4.4



193a **236** = 93 %

Reagents and Conditions: i, 2.5 NaH, benzyl bromide, DMF, 0 °C - R.T.

Scheme 96

4.3 Conclusion

The imidazo[4,5-*c*]isoxazole derivative **94a** proved to be a reactive molecule due to strain. It was shown to react readily with phosphine derivatives, to give highly functionalised iminophosphorane substituted imidazole derivatives. Two attempts were made to use these in a ring closure reaction to afford biologically interesting imidazo[4,5-*b*]pyridines (deazapurines). However, a vinylgous amide was only obtained in this case.

The reaction of imidazo[4,5-*c*]isoxazole with acetylenic esters, ketones and nitriles was studied and demonstrated an intriguing reaction. Two pathways were operating in this reaction. One reaction pathway gave us unique pyrrolyl substituted imidazoles in moderate to good yield. The other pathway led to novel diazepino-isoxazoles in low yield. The postulated mechanisms for these reactions were supported by isolation of some of the intermediates. The reactions with other electron rich, and deficient acetylenes and electron rich and deficient alkenes, proved not to be effective.

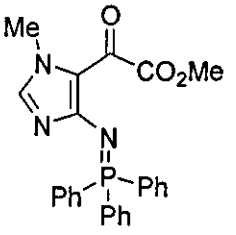
Further elaboration of pyrrolyl imidazoles were carried out by reaction with base and activated alkyl bromides. This afforded novel imidazo[1,2-*a*]pyrrolo[2,3-*c*]pyridine derivatives in very good yields.

An alternative strategy was considered in preparing imidazo[4,5-*b*]pyridines. This involved ester hydrolysis of the imidazo fused isoxazole, followed by reacting the unsubstituted imidazo isoxazole with alkynes. However, decarboxylation could not be effected and the 3-unsubstituted imidazo-isoxazole was not obtained.

4.4 Experimental

For general experimental procedures see Chapter 1; section 1.8.1.

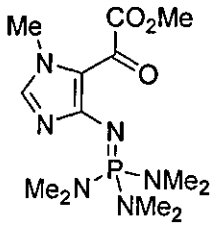
Methyl 2-1-methyl-4-[(1,1,1-triphenyl-λ^5-phosphanylidene)amino]-1*H*-imidazol-5-yl-2-oxoethanoate (184a)



Triphenyl phosphine (0.26 g, 1 mmol) was added to methyl 4-methyl-4*H*-imidazo[4,5-*c*]isoxazole-3-carboxylate (**94a**) (0.181 g, 1 mmol) in toluene (10 cm^3). The reaction mixture was heated under reflux. After 15 h the reaction was shown to be complete by TLC. The solvent was removed *in vacuo* to give a brown solid. Re-crystallisation from hot ethanol afforded a cream solid (0.4 g, 98 %).

Cream solid, yield 98 %, m.p. 222-223 °C; (Found : m/z, 443.1398, $C_{25}H_{22}N_3O_3P$ requires: M, 443.1390; ν_{max} 3009, 2950, 1738, 1599, 1504, 1437 and 1129 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.63 (3H, s, CH_3), 3.75 (3H, s, CH_3), 7.06 (1H, s, Ar-H), 7.43-7.52 (9H, m, Ar-H) and 7.74-7.78 (6H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 35.3 (CH_3), 52.3 (CH_3), 115.8 (CH, d, *J* 24, P-C), 128.9 (CH, d, *J* 12, P-C), 129.8 (C, d, *J* 102, P-C), 132.5 (CH, d, *J* 2, P-C), 133.5 (CH, d, *J* 10, P-C), 143.7 (C), 163.7 (CH, d, *J* 5, P-C), 167.1 (CO) and 174.5 (CO); δ_P (101.2 MHz; $CDCl_3$) 13.7.

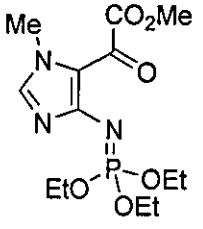
Methyl 2-(1-methyl-4-[(1,1,1-tri(dimethylamino)-λ^5-phosphanylidene]amino-1*H* imidazol-5-yl)-2-oxoethanoate (184c)



Hexamethyl phosphorous triamide (0.163 g, 1 mmol) was added to methyl 4-methyl-4*H*-imidazo[4,5-*c*]isoxazole-3-carboxylate (**94a**) (0.181 g, 1 mmol) in toluene (10 cm^3). The reaction mixture was heated under reflux. After 6 h the reaction was complete. The solvent was removed *in vacuo* to give a brown solid. Re-crystallisation from dichloromethane/petroleum ether afforded a brown solid (0.28 g, 94 %).

Brown powder, yield 94 %, m.p. 98-100 °C; (Found : m/z, 344.1726, $C_{13}H_{25}N_6O_3P$ requires: M, 344.1729); ν_{max} 3009, 2943, 1633, 1556, 1308 and 1002 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 2.60 (18H, d, *J* 9.8, N-CH_3), 3.71 (3H, s, CH_3), 3.77 (3H, s, CH_3) and 7.12 (1H, s, Ar-H); δ_C (62.9 MHz; $CDCl_3$) 36.9 (CH_3, d, *J* 116, P-NCH_3), 36.4 (CH_3), 37.3 (CH_3), 117.0 (CH, d, *J* 14.8, P-C), 141.1 (CH), 147.9 (C), 166.8 (CO) and 180.6 (CO); δ_P (101.2 MHz; $CDCl_3$) 35.9.

Methyl 2-(1-methyl-4-[(1,1,1-tri(ethyloxy)-λ^5-phosphanylidene]amino-1*H* imidazol-5-yl)-2-oxoethanoate (184b)

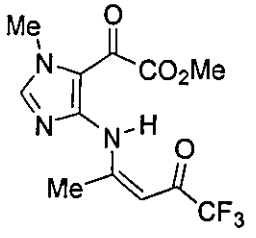


Triethyl phosphite (0.166 g, 1 mmol) was added to methyl 4-methyl-4*H*-imidazo[4,5-*c*]isoxazole-3-carboxylate (**94a**) (0.181 g, 1 mmol) in toluene (10 cm^3). The reaction mixture was heated under reflux. After 18 h the reaction was complete. The solvent was

removed *in vacuo* to give a viscous liquid. Flash column chromatography eluting with dichloromethane:ethyl acetate (2:1) gave a yellow oil, (0.313 g, 90 %).

Yellow oil, yield 90 %; (Found : m/z, 347.1241, $C_{13}H_{22}N_3O_6P$ requires: M, 347.1246; ν_{max} 2385, 2952, 2910, 1743, 1611, 1528, 1444, 1277, 1169, 1026 and 973 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.33-1.37 (9H, m, CH_3), 3.81-3.83 (3H, m, CH_3), 3.86-3.87 (3H, m, CH_3), 4.15-4.23 (6H, m, CH_2) and 7.28 (1H, s, Ar-H); δ_C (100 MHz; $CDCl_3$) 16.3 (CH_3, d, *J* 7, P-CH_3), 35.3 (CH_3), 52.2 (CH_3), 64.8 (CH_2, d, *J* 6.5, P-CH_2), 114.7 (C, d, *J* 29, P-C), 143.5 (CH), 160.3 (C, d, *J* 3, P-C) and 174.9 (CO); δ_P (101.2 MHz; $CDCl_3$) 6.3.

[3-Methyl-5-(4,4,4-trifluoro-1-methyl-3-oxo-but-1-enylamino)-3*H*-imidazol-4-yl]-oxo-acetic acid methyl ester (191)

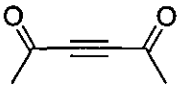


Methyl 2-1-methyl-4-[(1,1,1-triphenyl-λ^5-phosphanylidene)amino]-1*H*-imidazol-5-yl-2-oxoethanoate (0.1 g, 0.25 mmol) was added to 1,1,1 trifluoropentandione (1.5 cm^3). The reaction mixture was heated under reflux. After 28 h the mixture was cooled to room temperature. The solvent was removed *in vacuo* to yield a viscous yellow liquid. Flash column chromatography using the eluting solvents petroleum ether:ethyl acetate (2:1) gave a yellow solid (0.046 g, 62 %).

Yellow solid, yield 62 %, m.p 152-153 °C; (Found: m/z, 319.1242, $C_{12}H_{12}F_3N_3O_4$ requires: M, 319.1246); ν_{max} 3112, 2925, 1763, 1625, 1616, 1593, 1548, 1239, 1113, 861 and 723 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 2.37 (3H, s, CH_3), 3.89 (3H, s, CH_3), 3.93 (3H, s, CH_3), 5.63 (1H, s, CH), 7.51 (1H, s, Ar-H) and 12.45 (1H, br s, N-H); δ_C (100 MHz; $CDCl_3$) 22.33

(CH_3), 35.8 (CH_3), 53.8 (CH_3), 94.3 (CH), 115.9 (C), 118.5 (C), 142.2 (C), 142.0 (C), 163.8 (CO), 167.2 (CO), 175.2 (CO) and 178.3 (CF_3, q, *J* 33, C-F).

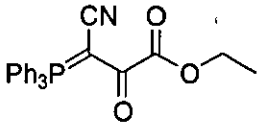
Hex-3-yne-2,5-dione (207)



A solution of chromium trioxide (63.4 g, 634 mmol) in water (320 cm^3) and concentrated sulphuric acid (56 cm^3) was added dropwise to a solution of Hex-3-yne-2, 5-diol (35.5 g, 310 mmol) in acetone (250 cm^3) maintaining the temperature between 40–45 °C over 1.5 h and stirred at this temperature for 1.25 h. The reaction mixture turned from a yellow solution to a dark green solution. The solvent was removed *in vacuo*. The dark green solution was extracted with diethyl ether (4 × 75 cm^3). The ether extracts were combined, washed with saturated sodium bicarbonate solution (20 cm^3) and saturated brine solution (20 cm^3), dried over $MgSO_4$, filtered and evaporated to dryness to yield a viscous yellow oil (25.46 g). Fractional distillation (receivers at -78 °C) in high *vacuo* gave the title compound as a colourless oil (9.3g, 27 %), b.p 25-49 °C/0.1 mbar, (lit.,[15] 26-38 °C at 0.1 Torr).

Yellow liquid, yield 27 %, ν_{max} 2221, 1686, 1596, 1362, 1229 and 988 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 2.44 (6H, s, CH_3); δ_C (62.9 MHz; $CDCl_3$) 32.2 (CH_3), 83.9 (C) and 182.7 (CO).

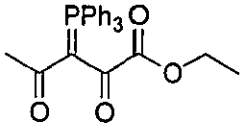
3-Cyano-2-oxo-3-(triphenyl-λ^5-phosphanylidene)-propionic acid ethyl ester (212c)



Triethylamine (11.14 g, 3.1 eq., 0.11 mol) was added dropwise over 5 min to a stirred suspension of cyanomethyltriphenylphosphonium chloride (12.0 g, 35.5 mmol) in anhydrous tetrahydrofuran (100 cm^3) at 0 °C under nitrogen atmosphere. After 30 min ethyl oxalyl chloride (4.85 g, 35.5 mmol) was added dropwise maintaining the temperature between 5-10 °C. The reaction mixture was stirred for 2 h, the solid product was filtered, washed with cold tetrahydrofuran (3 × 20 cm^3). The filtrate was concentrated under reduced pressure to afford a white solid. Re-crystallisation from hot ethanol gave a white solid (11.98 g, 92 %).

White solid, yield 92 %, m.p. 180-181°C (lit.,[21] 215-216 °C); (Found: m/z, 401.1179, $C_{24}H_{20}NO_3P$ requires: M, 401.1181; ν_{max} 3061, 2984, 2185, 1732, 1584, 1439, 1228, 1153 and 1109 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.37 (3H, t, *J* 7.0, CH_3), 4.37 (2H, q, *J* 7.2, CH_2) and 7.49-7.69 (15H, m, Ar-CH); δ_C (62.9 MHz; $CDCl_3$) 14.0 (CH_3), 61.8 (CH_2), 98.2 (C), 119.5 (C, d, *J* 12.8, P-C), 120.8 (C), 122.3 (C), 129.3 (C, d, *J* 13.3, P-C), 133.5 (C), 133.7 (C, d, *J* 10.4, P-C), 180.4 (CO) and 180.5 (CO).

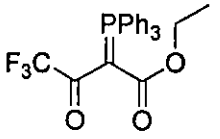
2,4-dioxo-3-(triphenyl-λ^5-phosphanylidene)-pentanoic acid ethyl ester (212d)



Triethylamine (10.6 g, 3.1 eq., 0.105 mol) was added dropwise over 5 min to a stirred suspension of acetonyltriphenylphosphonium chloride (12.0 g, 33.8 mmol) in anhydrous tetrahydrofuran (100 cm^3) at 0 °C under nitrogen atmosphere. After 30 min ethyl oxalyl chloride (4.62 g, 33.8 mmol) was added dropwise maintaining the temperature between 5-10 °C. The reaction mixture was stirred for 2 h, the solid product was filtered, washed with cold tetrahydrofuran (3 × 20 cm^3). The filtrate was concentrated under reduced pressure which solidified into a yellow solid. Re-crystallisation from hot ethanol gave a yellow solid, (12.76 g, 90 %).

Yellow solid, yield 90 %, m.p. 128.5-129.5 °C (lit.,[22] 138-140 °C); (Found: C, 71.56; H, 5.43 %; m/z, 418.1326, $C_{25}H_{23}O_4P$ calculated for: C, 71.76; H, 5.54 %; M, 418.1334); ν_{max} 3060, 2984, 2242, 1725, 1561, 1438, 1362, 1206, 1106, 1045, 917, 726 and 692 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.19 (3H, t, *J* 7.0, CH_3), 2.29 (3H, d, *J* 0.48, CH_2) 3.83 (2H, q, *J* 7.05, CH_2), 7.42-7.58 (6H, m, Ar-CH) and 7.64-7.75 (9H, m, Ar-CH); δ_C (62.9 MHz; $CDCl_3$) 13.6 (CH_3), 29.3 (CH_3, d, *J* 4.9, P-C), 61.0 (CH_2), 83.4 (C), 123.8 (C), 125.3 (C), 128.5 (CH, d, *J* 12.3, P-CH), 132.0 (CH, d, *J* 3, P-CH), 133.2 (CH, d, *J* 9.8, P-CH), 166.6 (CO, d, *J* 6.9, P-CO), 182.4 (CO, d, *J* 13.3, P-CO) and 194.8 (CO, d, *J* 5.4, P-CO).

Ethyl 4,4,4-trifluoro-2-(triphenylphosphoranylidene)acetoacetate (212a)

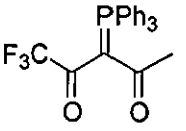


Triethylamine (7.3 g, 1.1 eq., 72 mmol) was added dropwise over 5 min to a stirred suspension of (carboethoxymethyl)triphenylphosphorane (22.64 g, 65 mmol) in anhydrous tetrahydrofuran (100 cm^3) at 0 °C under nitrogen atmosphere. After 30 min trifluoroacetic anhydride (15.1 g, 72 mmol) was added dropwise maintaining the temperature between 5-10 °C. The mixture was stirred for 2 hr and the solvent was evaporated under reduced pressure to afford an oily residue. Trituration with water (100 cm^3) gave a solid product which was collected, washed with water (3 × 50 cm^3) and dried under reduced pressure to afford a cream solid. Re-crystallisation in hot methanol (150 cm^3) and water (100 cm^3) gave a cream solid (30.49 g, 100 %).

Cream solid, yield 100 %, m.p. 126-127 °C (lit.,[16] 125-127 °C); ν_{max} 2924, 2854, 1688, 1580, 1570, 1460, 1377, 1261, 1175, 1140, 1084, 751 and 691 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 0.87 (3H, t, *J* 7.1, CH_3), 3.82 (2H, q, *J* 7.2, CH_2) and 7.43-7.71 (15H, m, Ar-CH); δ_C (62.9 MHz; $CDCl_3$) 13.5 (CH_3), 59.8 (CH_2), 115.7 (CF_3, d, *J* 14.7, C-F), 120.3 (C, d, *J* 14.7, P-

C), 123.3 (C), 124.8 (C), 128.8 (CH, d, *J* 12.8, P-CH), 132.4 (CH, d, *J* 3, P-CH) and 133.2 (CH, d, *J* 9.8, P-CH).

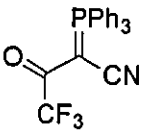
1,1,1-Trifluoro-3-(triphenyl-λ^5-phosphanylidene)-pentane-2,4-dione (212b)



Triethylamine (6.8 g, 2.0 eq., 67.6 mmol) was added dropwise over 5 min to a stirred suspension of acetonyltriphenylphosphonium chloride (12.0 g, 33.8 mmol) in anhydrous tetrahydrofuran (50 cm^3) at 0 °C under nitrogen atmosphere. After 30 min trifluoroacetic anhydride (7.1 g, 33.8 mmol) was added dropwise maintaining the temperature between 5-10 °C. The reaction mixture turned orange. The reaction mixture was stirred for 2 h and allowed to warm to room temperature, the solid product was filtered, washed with cold tetrahydrofuran (3 × 20 cm^3). The filtrate was concentrated under reduced pressure to afford a viscous orange liquid, trituration with water (50 cm^3) and cooling in the freezer gave an orange solid. The solid was filtered, re-crystallisation from hot methanol gave a yellow solid (11.93 g, 92 %).

Orange solid, yield 92 %, m.p. 121-122 °C, (Found: m/z, 414.0999, $C_{23}H_{18}F_3O_2P$ requires M, 414.0996); ν_{max} 3060, 1627, 1563, 1439, 1376, 1267, 1186, 1135, 1107, 998, 749 and 691 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 2.33 (3H, s, CH_3) and 7.43-7.73 (15H, m, Ar-CH); δ_C (62.9 MHz; $CDCl_3$) 30.0 (C, t, *J* 4.9, CH_3), 59.8 (CH_2), 115.7 (CF_3, d, *J* 14.7, C-F), 120.3 (C, d, *J* 14.7, P-C), 123.3 (C), 98.25 (C), 117.6 (CF_3, dd, *J* 13.8, 277, C-CF_3), 123.8 (C), 125.3 (C), 129 .2 (CH, d, *J* 12.6, P-CH), 132.2 (CH, d, *J* 2.8, P-CH), 133.0 (C, d, *J* 10.1, P-CH), 171.6 (CO, d, *J* 5.8, P-CO) and 194.2 (CO, d, *J* 4.9, F-CO).

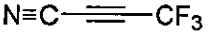
4,4,4-Trifluoro-3-oxo-2-(triphenyl-λ^5-phosphanylidene)-butyronitrile (212e)



Triethylamine (13.8 g, 2.1 eq., 0.137 mol) was added dropwise over 5 min to a stirred suspension of cyanomethyltriphenylphosphonium chloride (21.96 g, 65 mmol) in anhydrous tetrahydrofuran (100 cm^3) at 0 °C under nitrogen atmosphere. After 30 min trifluoroacetic anhydride (15.0 g, 71.5 mmol) was added dropwise maintaining the temperature between 5-10 °C. The reaction mixture was stirred for 2 h, the solid product was filtered, washed with cold tetrahydrofuran (3 × 20 cm^3). The filtrate was concentrated under reduced pressure to afford a dark red/brown liquid, which solidified into a yellow solid. Re-crystallisation from hot ethanol and washing with cold water gave a cream solid (18.4 g, 74 %).

Cream solid, yield 74 %, m.p. 190-193 °C (lit.,[16, 23] 187-188 °C); (Found: m/z, 397.0840, $C_{22}H_{15}F_3NOP$ requires: M, 397.0843); ν_{max} 2193, 1611, 1572, 1439, 1312, 1232, 1201, 1126, 1109, 998, 753, 719 and 690 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.48-7.73 (15H, m, Ar-CH); δ_C (62.9 MHz; $CDCl_3$) 116.3 (CF_3, dd, *J* 11.8, 159, C-CF_3), 119.4 (C), 120.2 (C), 121.7 (C), 129.5 (CH, d, *J* 13.1, P-CH), 133.6 (CH, d, *J* 10.1, P-CH) and 133.9 (CH, d, *J* 2.8, P-CH).

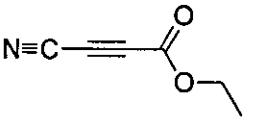
4,4,4-Trifluoro-but-2-ynenitrile[12b] (213e)



To a 250 cm^3 round bottom flask was added 4,4,4-trifluoro-3-oxo-2-(triphenyl-λ^5-phosphanylidene)-butyronitrile (5.0 g, 13.0 mmol) and potassium carbonate (1.16 g, 3.4

mmol). The mixture was gradually stirred and heated under vacuum to 150 °C using a distillation apparatus. The molten phosphorane was stirred and heated to 190-210 °C over 3.5 h. From the round bottom flask in the cold trap, an orange oil was obtained, which was used directly without analysis for a following reaction.

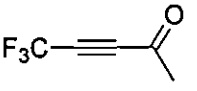
Cyano-propynoic acid ethyl ester (213c)



To a 250 cm^3 round bottom flask was added 3-Cyano-2-oxo-3-(triphenyl-λ^5-phosphanylidene)-propionic acid ethyl ester (10.0 g, 30 mmol) and potassium carbonate (2.68 g, 19.3 mmol). The mixture was gradually stirred and heated under vacuum to 150 °C using a distillation apparatus. The molten phosphorane was stirred and heated to 200-220 °C over 2.5 h. From the round bottom flask in the cold trap, a clear yellow oil was obtained, (1.5 g, 41 %).

Colourless liquid, yield 41 %; ν_{max} 2976, 2160, 1729, 1448, 1369, 1259, 1077, 1084, 855 and 743 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.35 (3H, t, *J* 7.1, CH_3), 4.34 (2H, q, *J* 7.13, CH_2) and 7.49-7.69 (15H, m, Ar-CH); δ_C (62.9 MHz; $CDCl_3$) 13.6 (CH_3), 57.2 (C), 63.9 (CH_2), 71.3 (C), 103.5 (C) and 149.9 (CO).

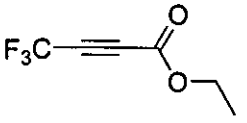
5,5,5-Trifluoro-pent-3-yn-2-one (213b)



To a 250 cm^3 round bottom flask was added 1,1,1-Trifluoro-3-(triphenyl-λ^5-phosphanylidene)-pentane-2,4-dione (8.0 g, 20.9 mmol) and potassium carbonate (1.86 g, 13.4 mmol). The mixture was gradually stirred and heated under vacuum to 150 °C using a distillation apparatus. The molten phosphorane was stirred and heated to 160-200 °C over 3 h. From the round bottom flask in the cold trap, an orange oil was obtained, (0.45 g, 16 %).

Orange liquid, yield 16 %; ν_{max} 2221, 1679, 1364, 1283, 1246, 1187, 1142 and 717 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.69 (15H, m, Ar-CH); δ_C (62.9 MHz; $CDCl_3$) 30.3 (CH_3), 71.9 (C), 72.0 (C), 116.3 (CF_3, dd, *J* 3, 398, C-CF_3) and 196.6 (CO).

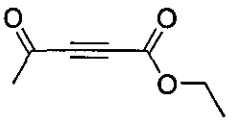
4,4,4-Trifluoro-but-2-ynoic acid ethyl ester[16] (213a)



To a 250 cm^3 round bottom flask was added ethyl 4,4,4-trifluoro-2-(triphenylphosphoranylidene)acetoacetate (28.0 g, 63 mmol) and potassium carbonate (5.6g, 40.5 mmol). The mixture was gradually stirred and heated under vacuum to 150 °C using the special apparatus. The molten phosphorane was stirred and heated to 160-200 °C over 3.5 h. From the round bottom flask in the cold trap a clear yellow oil was obtained, (8.45 g, 81 %).

Yellow liquid, yield 81 %; ν_{max} 2991, 1734, 1370, 1276, 1157, 1021, 858 and 748 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.35 (3H, t, *J* 7, CH_3), 4.33 (2H, q, *J* 7.2, CH_2); δ_H (62.9 MHz; $CDCl_3$) 13.5 (CH_3), 63.3 (CH_3), 70.0 (C), 75.5 (C), 113.3 (CF_3, q, *J* 260, C-CF_3) and 150.6 (CO).

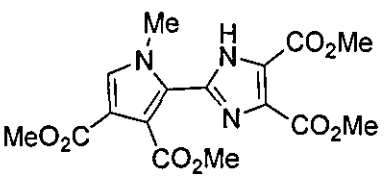
4-Oxo-pent-2-ynoic acid ethyl ester[22] (213d)



To a 250 cm^3 round bottom flask was added 2,4-dioxo-3-(triphenyl-λ^5-phosphanylidene)-pentanoic acid ethyl ester (10.0 g, 23.9 mmol) and potassium carbonate (2.13 g, 15.4 mmol). The mixture was gradually stirred and heated under vacuum to 150 °C using a distillation apparatus. The molten phosphorane was stirred and heated to 170-180 °C over 2.5 h. From the round bottom flask in the cold trap, a clear yellow oil was obtained, (2.33 g, 70 %).

Yellow liquid, yield 70 %; (Found: m/z, 140.0476, $C_7H_8O_3$ requires: M, 140.0474); ν_{max} 2988, 2221, 1720, 1686, 1368, 1246, 1022, 988, 858 and 748 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.34 (3H, t, *J* 7.2, CH_3), 2.43 (3H, s, CH_3) and 4.31 (2H, q, *J* 7.2, CH_2); δ_C (100 MHz; $CDCl_3$) 14.2 (CH_3), 32.6 (CH_3), 63.3 (CH_2), 78.2 (C), 81.0 (C), 152.5 (CO) and 182.8 (CO).

Dimethyl 2-1-methyl-3,4-di[(methoxy)carbonyl]-1*H*-pyrrol-2-yl-1*H*-imidazole-4,5-dicarboxylate (193a)

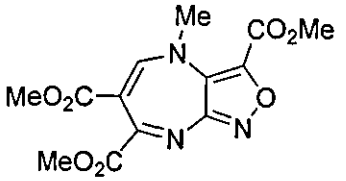


Dimethyl acetylenedicarboxylate (99 %), (3.46 g, 24mmol) was added to imidazo-isoxazole **94a** (0.181 g, 1 mmol). The mixture was stirred and heated to 110 °C. After 18

h the reaction was allowed to cool to room temperature. The crude mixture was purified by chromatography over silica eluting with petroleum ether and ethyl acetate (2:1). Collection and evaporation of the required fractions gave a light brown liquid. Crystallisation from dichloromethane and petroleum ether gave a white powder (0.234g, 62 %).

White solid, yield 62 %, m.p. 176-178 °C; (Found: C, 50.25; H, 4.46; N, 10.7 %; m/z, 379.0703, $C_{16}H_{17}N_3O_8$ requires: C, 50.66; H, 4.51; N, 11.1%; M, 379.1017); ν_{max} 3266, 2955, 1732, 1543, 1295 and 1213 cm^{-1}; δ_H (250MHz; $CDCl_3$) 3.83 (3H, s, CH_3), 3.91 (3H, s, CH_3), 3.96 (3H, s, CH_3), 3.98 (3H, s, CH_3), 4.12 (3H, s, N-CH_3), 7.25 (H, s, Ar-CH) and 12.9 (H, br s, NH); δ_C (62.89 MHz; $CDCl_3$) 38.6 (N-CH_3), 51.6 (CH_3), 52.3 (CH_3), 52.5 (CH_3), 52.8 (CH_3), 116.3 (Ar-C), 123.3 (Ar-C), 126.0 (Ar-C), 130.6 (Ar-CH), 137.0 (Ar-CH), 139.5 (Ar-CH), 159.0 (CO), 163.5 (CO) and 167.5 (CO).

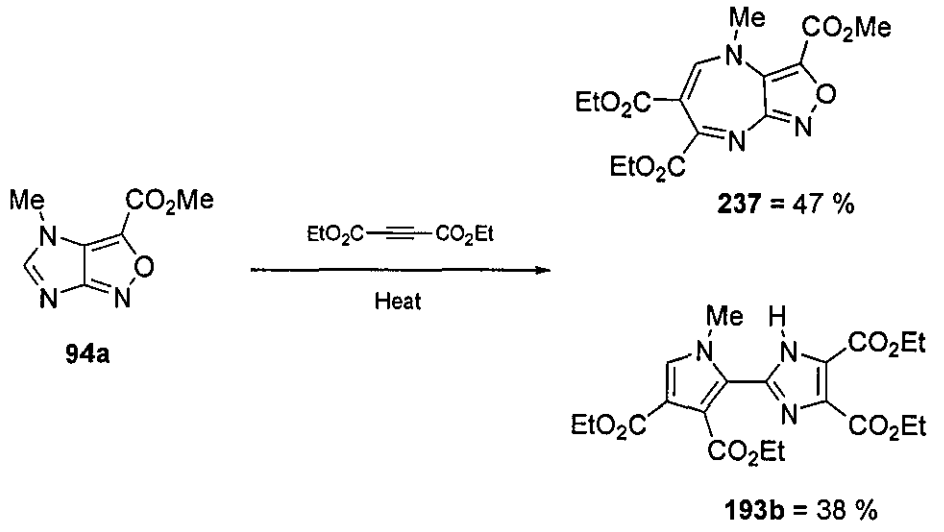
Trimethyl 4-methyl-4*H*-[1,4]diazepino[2,3-*c*]isoxazole-3,6,7-tricarboxylate (203)



Dimethyl acetylenedicarboxylate (96 %), (3.46 g, 24 mmol) was added to imidazo-isoxazole **94a** (0.181 g, 1mmol). The mixture was stirred and heated to 110 °C. After 8 h the reaction was allowed to cool to room temperature. The crude mixture was separated and purified by chromatography over silica eluting with petroleum ether and ethyl acetate (2:1). Collection and evaporation of the required fractions gave a red liquid. Crystallisation of the red liquid from dichloromethane/petroleum ether gave a bright red solid (0.078 g, 24 %).

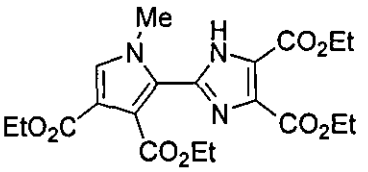
Red crystalline solid, yield 24 %, m.p 137-138 °C; (Found: m/z, 323.0754, $C_{13}H_{13}N_3O_7$ requires M, 323.0754); ν_{max} 2955, 1735, 1703, 1642, 1552, 1475, 1434, 1269, 1100, 1064, 956 and 733 cm^{-1}; δ_H (400MHz; $CDCl_3$) 3.37 (3H, s, CH_3), 3.69 (3H, s, CH_3), 3.85 (3H, s, CH_3), 3.93 (3H, s, CH_3) and 7.13 (1H, s, Ar-CH); δ_C (100 MHz; $CDCl_3$) 45.2 (N-CH_3), 52.4 (CH_3), 53.2 (CH_3), 53.7 (CH_3), 102.9 (Ar-C), 128.2 (Ar-C), 146.4 (Ar-C), 157.1 (Ar-C), 161.9 (Ar-CH), 162.7 (C), 164.9 (CO), 165.4 (CO) and 166.3 (CO).

Reaction of imidazo[4,5-*c*]isoxazole-3-carboxylate (94a) with diethyl acetylenedicarboxylate



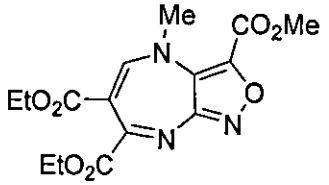
Diethyl acetylenedicarboxylate (96 %), (3 cm^3, 19 mmol) was added to imidazo-isoxazole **94a** (0.181 g, 1mmol). The mixture was stirred and heated under reflux. After 8 h the reaction was allowed to cool to room temperature. The crude mixture was separated and purified by chromatography over silica eluting with petroleum ether and ethyl acetate (2:1). Collection and evaporation of the required fraction gave two products a brown liquid and a red liquid. The brown liquid was found to be pyrrole substituted imidazole **193b** (0.166 g, 38 %). Crystallisation of the red liquid in dichloromethane/petroleum ether gave an orange solid **237** (0.1655 g, 47 %).

Diethyl 2-3,4-di[(ethoxy)carbonyl]-1methyl-1*H*-pyrrol-2-yl-1*H*-imidazole-4,5-dicarboxylate (193b)



Red oil, yield 38 %; (Found: m/z, 435.1644, $C_{20}H_{25}N_3O_8$ requires M, 435.1642); ν_{max} 3135, 2983, 1728 and 1542 cm^{-1}; δ_H (250MHz; $CDCl_3$) 1.34 (6H, t, *J* 7.2, CH_3), 1.14 (6H, t, *J* 7.2, CH_3), 4.12 (3H, s, N-CH_3), 4.24-4.47 (8H, q, *J* 7.15, CH_2), 7.23 (H, s, Ar-CH) and 12.88 (1H, br s, NH); δ_C (62.89 MHz; $CDCl_3$) 13.7 (CH_3), 14.15 (CH_3), 14.2 (CH_3), 38.5 (CH_3), 60.5 (CH_2), 61.5 (CH_2), 61.9 (CH_2), 62.4 (CH_2), 115.3 (Ar-C), 116.8 (Ar-C), 123.2 (Ar-C), 125.3 (Ar-C), 130.2 (Ar-CH), 136.5 (Ar-C), 139.6 (Ar-C), 158.4 (CO), 162.5 (CO), 163.3 (CO) and 166.7 (CO).

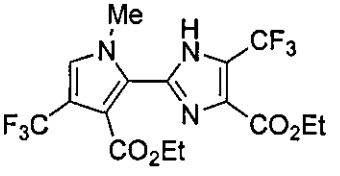
6,7-Diethyl 3-methyl 4-methyl-4*H*-[1,4]diazepino[2,3-*c*]isoxazole-3,6,7-tricarboxylate (237)



Orange solid, yield 47 %, m.p. 140-141 °C; (Found: C, 51.12; H, 4.83; N, 11.46 %; m/z, 351.3174, $C_{15}H_{17}N_3O_7$ requires C, 51.28; H, 4.87; N, 11.96 %; M, 351.3181); ν_{max} 2983,

1732, 1701, 1639, 1553 and 1098 cm^{-1}; δ_H (250MHz; $CDCl_3$) 1.24 (3H, t, *J* 7.18, CH_3), 1.35 (3H, t, *J* 7.18, CH_3), 3.36 (3H, s, CH_3), 3.93 (3H, s, N-CH_3), 4.15 (2H, q, *J* 7.15, CH_2), 4.29 (2H, q, *J* 7.15, CH_2) and 7.14 (H, s, Ar-CH); δ_C (100.62 MHz; $CDCl_3$) 14.3 (CH_3), 14.5 (CH_3), 45.0 (N-CH_3), 53.6 (OCH_3), 61.5 (CH_2), 62.6 (CH_2), 103.6 (Ar-C), 128.6 (Ar-C), 146.1 (Ar-C), 157.1 (Ar-C), 161.9 (Ar-CH), 162.9 (Ar-C), 165.0 (CO), 165.3 (CO) and 165.9 (CO).

Ethyl 2-[3-[(ethoxy)carbonyl]-1-methyl-4-(trifluoromethyl)1*H*-pyrrol-2-yl]-1*H*-imidazole-5-carboxylate (193c)

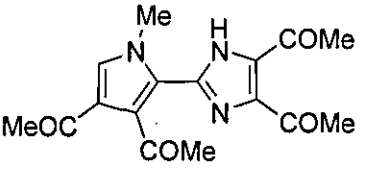


4,4,4-Trifluoro-but-2-ynoic acid ethyl ester (1.79g, 4.2 mmol) was added to imidazo-isoxazole (0.36 g, 2 mmol) in toluene (15 cm^3). The mixture was stirred under reflux. After 12 h the reaction was allowed to cool to room temperature. The crude mixture was separated and purified on silica eluting with petroleum ether and ethyl acetate (2:1) collection and evaporation of the required fractions gave a brown liquid. The brown liquid gave the pyrrole substituted imidazole **193c** on trituration with diethyl ether as colourless plates (0.436 g, 51 %).

Colourless plates, yield 51 %, m.p. 128-130 °C; (Found: m/z, 427.0971, $C_{16}H_{15}F_6N_3O_4$ requires M, 427.0967); ν_{max} 3151, 2999, 1703, 1669, 1449, 1296, 1214, 1185, 1136, 1050, 1027, 857 and 784 cm^{-1}; δ_H (400MHz; $CDCl_3$) 1.39 (3H, t, *J* 7.2, CH_3), 1.42 (3H, t, *J* 7.2, CH_3), 4.17 (3H, s, NCH_3), 4.41 (2H, q, *J* 7.2, CH_2), 4.43 (2H, q, *J* 7.2, CH_2), 7.13 (1H, s, Ar-CH) and 13.98 (1H, br s, NH); δ_C (100 MHz; $CDCl_3$) 13.9 (CH_3), 14.4 (CH_3), 40.1 (CH_3), 62.3 (CH_2), 62.6 (CH_2), 112.8 (C, d, $^3J_{CF}$ 2, Ar-C-4)), 115.5 (C, q, $^2J_{CF}$ 37, Ar-C-3), 121.2 (C, q, $^1J_{CF}$ 268, Ar-C-2), 121.3 (C, d, $^3J_{CF}$ 2, Ar-C-4), 122.9 (C, q, $^1J_{CF}$ 264, Ar-C-2),

127.8 (Ar-CH), 128.3 (C, q, $^3J_{CF}$ 6,Ar-C-5), 135.2 (C, q, $^2J_{CF}$ 40, Ar-C-4(5)), 139.7 (Ar-C), 158.5 (CO) and 165.8 (CO).

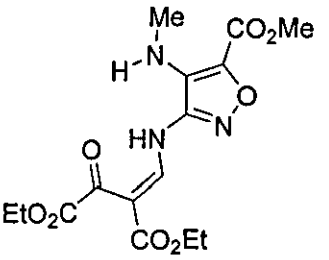
1-[4-Acetyl-2-(4,5-diacetyl-1*H*-imidazole-2-yl)-1-methyl-1*H*-pyrrol-3-yl]ethan-1-one (193d)



Hex-3-yne-2,5-dione (0.44g, 4 mmol) was added to imidazo-isoxazole (0.181g, 1mmol) in toluene (5 cm^3). The mixture was stirred under reflux. After 3 h the reaction was allowed to cool to room temperature. The crude mixture was separated and purified on silica eluting with petroleum ether and ethyl acetate (2:1). Collection and evaporation of the required fractions gave a brown liquid. The brown liquid was triturated with diethyl ether and light petroleum ether. Which on standing gave the pyrrole substituted imidazole **193d** as colourless crystals (0.127 g, 40 %).

Colourless crystals, yield 40 %, m.p. 113-114 °C; (Found : m/z, 315.1644, $C_{16}H_{17}N_3O_4$ requires M, 315.1642); ν_{max} 3284, 1692, 1603, 1554, 1434, 1358, 1221, 1076 and 786 cm^{-1}; δ_H (250MHz; $CDCl_3$) 2.15 (3H, s, CH_3), 2.23 (3H, s, CH_3), 2.41 (3H, s, CH_3), 2.52 (3H, s, CH_3), 2.61 (3H, s, CH_3) and 6.03 (1H, s, Ar-H); δ_C (100 MHz; $CDCl_3$) 13.2 (CH_3), 20.9 (CH_3), 26.8 (CH_3), 27.2 (CH_3), 31.6 (CH_3), 71.9 (Ar-CH), 116.5 (Ar-C), 126.0 (Ar-C), 131.2 (Ar-C), 148.3 (Ar-C), 156.2 (Ar-C), 170.1 (Ar-C), 188.0 (CO), 198.8 (CO) and 201.5 (CO).

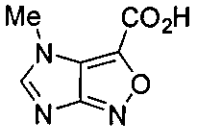
Diethyl 2-[(*E*)-1-(4-(methylamino)-5-[(methoxy)carbonyl]isoxazol-3-ylamino)methylidene]-3-oxobutanedioate (199)



Diethyl acetylenedicarboxylate (96 %), (2.0 g, 11.8 mmol) was added to imidazo-isoxazole **94a** (0.26 g, 1.42 mmol). The mixture was stirred and heated under reflux. After 8 h the reaction was allowed to cool to room temperature. The crude mixture was separated and purified by chromatography over silica eluting with petroleum ether and ethyl acetate (2:1). Collection and evaporation of the required fraction gave two products a brown liquid and a red liquid. The brown liquid was found to be pyrrole substituted imidazole **193b** (0.188 g, 43 %). Crystallisation of the red liquid in dichloromethane and petroleum ether gave an orange azetine solid **201** (0.088 g, 18 %). Re-crystallisation of the orange azetine intermediate **201** in ethanol and light petroleum ether for X-ray crystallography studies gave colourless cubes (0.074 g, 14 %).

Orange crystals, yield 14 %; (Found: m/z, 369.11806, $C_{15}H_{19}N_3O_8$ requires M, 369.1172).

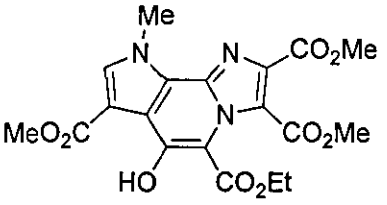
1-Methyl-4*H*-imidazo[4, 5-c]isoxazole-3-carboxylic acid (234)



Trifluoroacetic acid (20 cm^3) was added dropwise to a stirred solution of *t*-butyl-4-methyl-4*H*-imidazo[4,5-*c*]isoxazole-3-carboxylate (**95**) (1.3 g, 5.82 mmol) in chloroform (20 cm^3). The reaction mixture was heated under reflux conditions for 4 h. TLC showed consumption of starting material. The solvent was removed *in vacuo* to give a brown solid. Re-crystallisation from dichloromethane and petroleum ether gave a white solid (0.7 g, 72 %).

White solid, yield 72 %, m.p. 189-191 °C, m/z, 167.0332, $C_6H_5N_3O_3$ requires: M, 167.0332); ν_{max} (nujol) 3152, 3142, 3094, 2852, 1705, 1504, 1359, 1250, 1098, 1041, 812, 749 and 720 cm^{-1}; δ_H (400 MHz; CD_3SOCD_3), 3.81 (3H, s, CH_3) and 8.42 (1H, s, Ar-CH); δ_C (100 MHz; CD_3SOCD_3), 33.1 (CH_3), 125.2 (Ar-C), 129.1 (Ar-C), 139.2 (Ar-C), 144.5 (Ar-C), 157.1 (Ar-CH) and 174.5 (CO).

5-Ethyl-2,3,7-trimethyl 6-hydroxy-9methyl-9*H*-imidazo[1,2-*a*]pyrrolo[2,3,-*c*]pyridine-2,3,5,7-tetra carboxylate (235a)

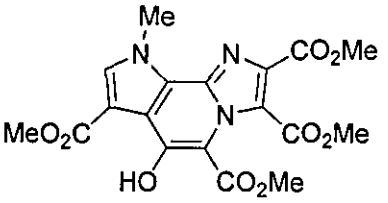


Ethyl bromoacetate (0.045g, 0.27 mmol) was added dropwise to a stirred mixture of NaH washed free from oil (0.015g, 0.7 mmol) and dimethyl 2-1-methyl-3,4-di[methoxy)carbonyl]-1*H*-pyrrol-2-yl-1*H*-imidazole-4,5-dicarboxylate (**193a**) (0.103 g, 0.27 mmol) in anhydrous DMF (5 cm^3) at 0 °C under nitrogen. The reaction was stirred overnight for 12 h and allowed to warm to room temperature. TLC showed the reaction to be complete. The solvent was removed under high vacuum. The solid was treated with water (2 cm^3) and was neutralised to pH 7 by dropwise addition of concentrated hydrochloric acid. The mixture was extracted with dichloromethane (4 × 15 cm^3), the organic extracts combined, dried over $MgSO_4$, filtered and evaporated to dryness, to give a

white solid. Re-crystallisation from dichloromethane and petroleum ether gave a white solid, (0.105g, 90 %).

White solid, yield 90 %, m.p. 229-230 °C; (Found: C, 52.06; H, 4.11; N, 9.39 %; m/z, 433.1130, $C_{19}H_{19}N_3O_9$ requires: C, 52.65; H, 4.41; N, 9.69 %; M, 433.1121); ν_{max} ($CHCl_3$) 3425, 2956, 1716, 1656, 1465, 1294, 1221 and 1120 cm^{-1}; δ_H (400MHz; $CDCl_3$) 1.41 (3H, t, *J* 8, CH_3), 3.93 (3H, s, CH_3), 3.96 (3H, s, CH_3), 3.96 (3H, s, CH_3), 4.32 (3H, s, N-CH_3), 4.42 (2H, q, *J* 8, CH_3), 7.64 (1H, s, Ar-CH) and 11.72 (1H, br s, OH); δ_C (100 MHz; $CDCl_3$) 14.5 (CH_3), 37.5 (CH_3), 52.8 (CH_2), 53.3 (CH_3), 61.9 (CH_3), 109.6 (Ar-C), 109.8 (Ar-C), 116.9 (Ar-C), 122.4 (Ar-C), 125.3 (Ar-C), 134.7 (Ar-C), 135.4 (Ar-CH), 146.5 (Ar-CH), 146.5 (CO), 161.7 (CO), 162.6 (CO), 163.5 (Ar-C), 167.8 (CO) and 209.1 (C-OH).

2,3,5,7-Tetramethyl 6-hydroxy-9methyl-9*H*-imidazo[1,2-*a*]pyrrolo[2,3,-*c*]pyridine-2,3,5,7-tetra carboxylate (235b)

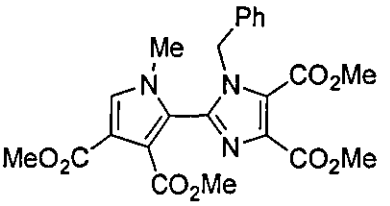


Methyl bromoacetate (0.046g, 0.3 mmol) was added dropwise to a stirred mixture of NaH washed free from oil (0.015g, 0.63 mmol) and dimethyl 2-1-methyl-3, 4-di[methoxy)carbonyl]-1*H*-pyrrol-2-yl-1*H*-imidazole-4,5-dicarboxylate (**193a**) (0.114 g, 0.3 mmol) in anhydrous DMF (2 cm^3) at 0 °C under nitrogen. The reaction was stirred overnight for 12 h and allowed to warm to room temperature. TLC showed the reaction to be complete. The solvent was removed under high vacuum. The solid was treated with water (2 cm^3) and was neutralised to pH 7 by dropwise addition of concentrated hydrochloric acid. The residue was extracted with ethyl acetate (4 × 15 cm^3), the organic layers combined, dried over $MgSO_4$, filtered and evaporated to dryness, to give a white

solid. Re-crystallisation from dichloromethane and petroleum ether gave a white solid, (0.086g, 71 %).

White solid, yield 71 %, m.p. 218-219 °C; (m/z, 419.0964, $C_{18}H_{17}N_3O_9$ requires: M, 419.0965); ν_{max} ($CHCl_3$) 3136, 2953, 1734, 1543, 1488, 1451, 1362, 1294, 1213, 1082 and 768 cm^{-1}; δ_H (400MHz; $CDCl_3$) 3.95 (3H, s, CH_3), 3.96 (3H, s, CH_3), 3.97 (6H, s, CH_3), 4.35 (3H, s, N-CH_3), 7.68 (1H, s, Ar-CH) and 11.84 (1H, br s, OH); δ_C (100 MHz; $CDCl_3$) 37.5 (CH_3), 52.6 (CH_3), 52.8 (CH_3), 52.8 (CH_3), 53.4 (CH_3), 109.4 (Ar-C), 109.9 (Ar-C), 116.9 (Ar-C), 122.5 (Ar-C), 125.5 (Ar-C), 134.8 (Ar-C), 135.4 (Ar-CH), 136.5 (Ar-C), 146.8 (Ar-C), 167.7 (CO), 162.9 (CO), 163.5 (CO) and 167.9 (CO).

1-Benzyl-dimethyl 2-1-methyl-3, 4-di[methoxy)carbonyl]-1*H*-pyrrol-2-yl-1*H*-imidazole-4,5-dicarboxylate (236)



Benzyl bromide (0.045 g, 0.26 mmol) was added dropwise to a stirred mixture of NaH (0.013g, 0.55 mmol) and dimethyl 2-1-methyl-3, 4-di[methyloxy)carbonyl]-1*H*-pyrrol-2-yl-1*H*-imidazole-4,5-dicarboxylate (**193a**) (0.10 g, 0.26 mmol) in anhydrous DMF (2 cm^3) at 0 °C under nitrogen. The reaction was stirred for 1 h and allowed to warm to room temperature. TLC showed the reaction to be complete. The solvent was removed under high vacuum. The solid was treated with water (5 cm^3) and was neutralised to pH 7 by dropwise addition of concentrated hydrochloric acid. The mixture was extracted with dichloromethane (3 × 20 cm^3), the organic layers combined, dried over $MgSO_4$, filtered and evaporated to dryness, to give a colourless liquid. Flash column chromatography on silica eluting with petroleum ether and ethyl acetate (1:2) gave the title compound as a colourless liquid (0.11 g, 89 %).

Colourless liquid, yield 89 %; (Found: m/z, 469.1476, $C_{23}H_{23}N_3O_8$ requires: M, 469.1485); ν_{max} (CH_2Cl_2) 3004, 2952, 1720, 1535, 1458, 1282, 1214 and 1166 cm^{-1}; δ_H (400MHz; $CDCl_3$) 2.76 (3H, s, N-CH_3), 3.76 (3H, s, CH_3), 3.85 (3H, s, CH_3), 3.92 (3H, s, CH_3), 3.97 (3H, s, CH_3), 6.88-6.90 (2H, m, CH_2), 7.15 (1H, s, Ar-CH) and 7.19-7.3 (5H, m, Ar-CH); δ_C (100 MHz; $CDCl_3$) 34.8 (CH_3), 50.1 (CH_2), 52.0 (CH_3), 52.37 (CH_3), 52.7 (CH_3), 53.3 (CH_3), 115.85 (C), 118.4 (Ar-C), 126.0 (Ar-C), 127.8 (Ar-C), 128.3 (Ar-CH), 128.6 (Ar-CH), 129.0 (Ar-CH), 129.7 (Ar-CH), 135.5 (Ar-C), 136.0 (Ar-C), 140.3 (Ar-C), 161.3 (CO), 162.3 (Ar-CO), 163.8 (CO) and 164.2 (CO).

4.5 References

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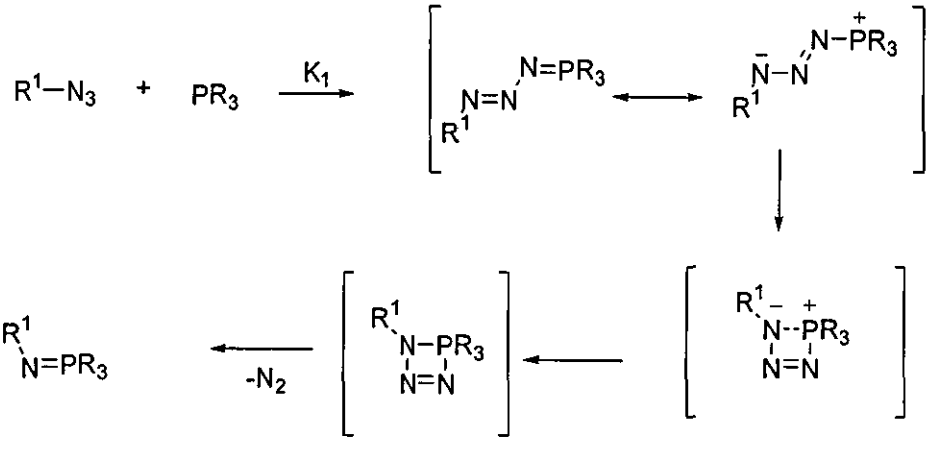
Chapter 5

Synthesis and Mechanistic Studies of Imidazo[4,5-*d*][1,2,3]triazole Derivatives

5.1 Introduction

5.1.1 Iminophosphoranes : versatile reagents for strategic organic synthesis

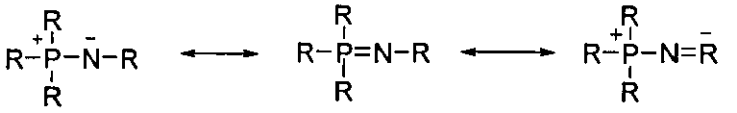
Iminophosphoranes and the Aza-Wittig reaction are an important implement in organic synthetic strategies. Iminophosphoranes were discovered as early as 1919. Staudinger and Meyer first reported the synthesis of an iminophosphorane from triphenylphosphine and an organic azide.[1] The area has been the subject of a recent review.[2] **Scheme 97** shows the mechanistic steps involved in the synthesis. The rate determining step is the formation of the trans phosphazide followed by isomerisation and extrusion of nitrogen. The presence of an electron withdrawing substituent on the phosphorus atom decreases the rate of the *trans* phosphazide formation.



Scheme 97

The iminophosphoranes and related phosphoramidate compounds have a phosphorus-nitrogen bond that is depicted as having a double bond which is involved in the reactivity. Experimental investigations (spectroscopic, X-ray analysis and dipole measurements)[3] and theoretical calculations[3] have shown a wide variability in the character of this bond. Substitution is the primary factor affecting the strength of this bond. The molecular orbital description of this bond shows pπ-dπ character. An electron withdrawing substituent on the nitrogen atom can amplify the positive charge on the phosphorus atom and subsequently the d orbital contracts and influences superior p orbital overlap on the

nitrogen atom. The bonding behaviour of this iminophosphorane group is shown by dipolar canonical formulas, **Scheme 98**.

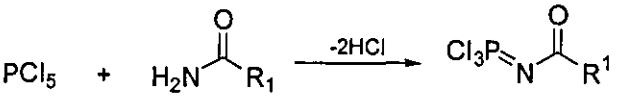


Scheme 98

5.1.2 Some examples of iminophosphorane synthesis

An asymmetric version[4] of iminophosphorane synthesis is known in which a chiral phosphane was reacted with a racemic azide to produce diastereoisomeric iminophosphoranes in different yields. After hydrolysis it is possible to isolate one of the two amines in slight enantiomeric excess.

The Kirsanov reaction[5] is a complement to the Staudinger reaction in which phosphorus pentachloride and amine or amide derivatives are reacted to give access to phosphorus halogenated iminophosphoranes, **Scheme 99**.



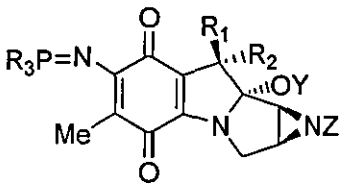
Scheme 99

Other methods of preparing iminophosphoranes include nucleophilic substitution of nitrogen silylated iminophosphoranes.[6] The synthesis of acyliminophosphoranes[7] and N-vinyliminophosphoranes[8] has been also studied.

Iminophosphoranes have also been used as protecting groups.[9] The stability under basic conditions allows increased yields in many reactions that involve alkaline labile groups. Staudinger studied the hydrolysis of iminophosphoranes and discovered the nature of the nitrogen substituent is the major factor involved. The protonation of nitrogen is the first

step involved in this process. Base hydrolysis is possible and occurs firstly by nucleophilic addition to the phosphorus atom, followed by protonation on the nitrogen atom.

There is little known about the biological activity of iminophosphoranes. However, some compounds containing triorganyl phosphoranylidene amino structural elements such as mitomycin (**238**), **figure 5.1** have proved to be interesting anti-tumor agents.[10] However, the biological profile of this compound is unlikely to be due to the iminophosphorane group.

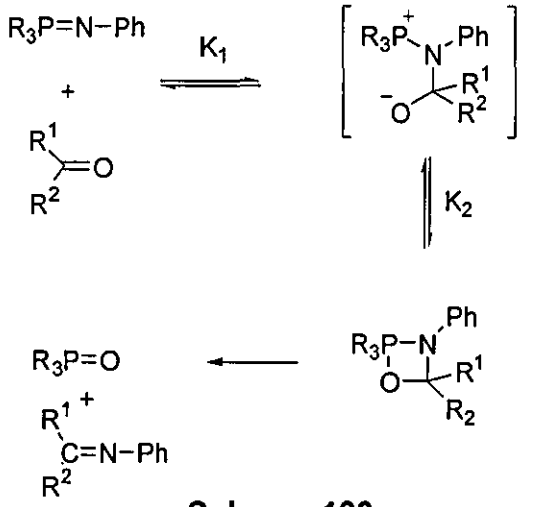


238

Figure 5.1

5.1.3 Aza-Wittig reaction

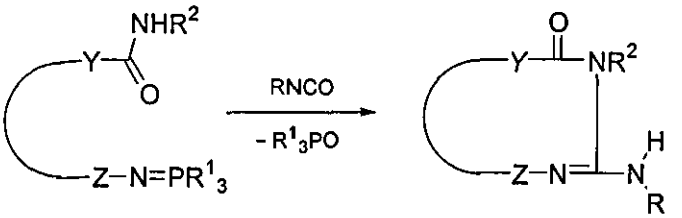
Staudinger investigated[10] this fundamental reaction type for several carbonyl and heteroanalog examples. The aza-Wittig reaction has become a very important synthetic procedure for construction of C=N, N=N and S=N bonds in novel heterocyclic synthesis. The reaction between a carbonyl group and an iminophosphorane and its mechanistic detail is shown in **Scheme 100.**



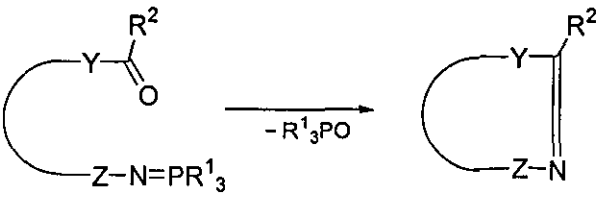
Scheme 100

The first step involves the rate determining nucleophilic attack of the iminophosphorane nitrogen on the carbonyl carbon to give the intermediate betaine. Conversion of the betaine by bond formation between phosphorus and oxygen gives the oxazaphosphetane. This compound then decomposes and results in the formation of a new C=N bond and phosphane oxide. The driving force of this reaction is the formation of low energy stable phosphane oxide compound. The reaction is thought to proceed faster in polar protic solvents and the reaction rates are not influenced by phosphorus substituents.

The aza-Wittig reaction is an important tool in building heterocyclic compounds by several strategies, including intermolecular and intramolecular reactions. The intermolecular example is a reaction between a heterocumulene component and an iminophosphorane, resulting in the formation of a reactive carbodiimide intermediate, thus generation of a new electrophilic centre within the molecule, which can be intercepted intramolecularly by another nucleophilic site of the intermediate, **Scheme 101**. The intramolecular example, starts with a molecule which contains both an iminophosphorane moiety and a carbonyl functionality in a geometrical favourable orientation, **Scheme 102**.



Scheme 101

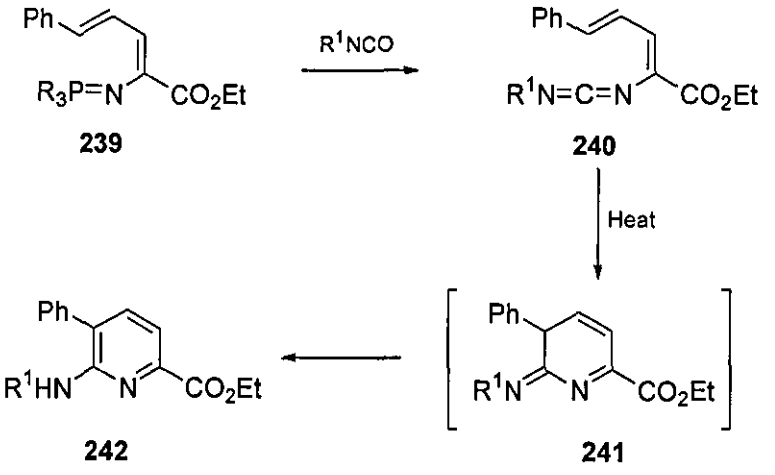


Scheme 102

Many chemists have continued the work of the Staudinger reaction adding a plethora of information and widening the scope of the reaction. The reaction has developed to be a useful tool in the synthesis of heterocyclic compounds.[11] Reaction with isocyanates has been used to synthesise carbodiimides[12] with the resulting heterocumulene frequently being designed to react further in a tandem cyclisation process to generate a new heterocyclic ring. A great effort in the area of using iminophosphoranes in synthesis has been achieved by Molina and his group, who have carried out extensive work in this area in producing heterocyclic compounds and utilising the tool in natural product synthesis.

5.1.4 Applications of the aza-Wittig reaction in synthesis

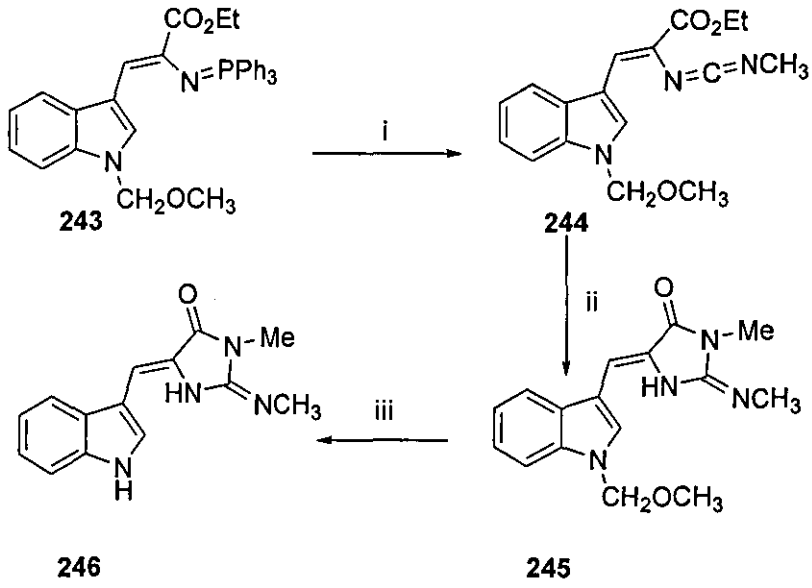
One interesting example[12] of a heterocyclisation reaction involves an aza-Wittig reaction is with an isocyanate to form a conjugate carbodimide, followed by subsequent 6π electrocyclic ring closure, and 1,3 hydride shift to give 2-aminopyridine derivatives in 68-86 % yields, **Scheme 103**.



Scheme 103

One application of iminophosphorane methodology is in natural product synthesis of Aplysinopsin-type alkaloids of marine origin.[13] These compounds exhibit interesting biological activities which have specific cytotoxicity for cancer cells. Treatment of

iminophosphorane **243** with methyl isocyanate gave the heterocumulene **244,** which undergo cyclisation by addition of methylamine completing the aplysinopsin molecular architecture. Deprotection of the cyclised product gave the naturally occurring aplysinopsin analogue **246, Scheme 104.**



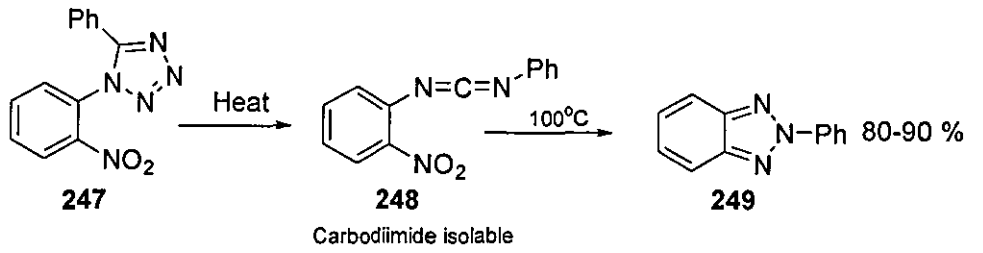
Reagents and conditions: i, CH_3NCO, Toluene, R.T.; ii, CH_3NH_2, Toluene, 45 °C; iii, HCO_2H, Reflux.

Scheme 104

5.1.5 Synthesis of fused triazole compounds

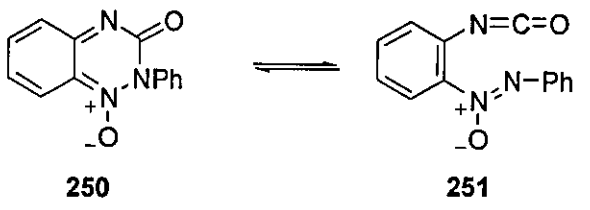
We have been investigating reactions of iminophosphorane and phosphoramidate compounds for the construction of nitrogen containing rings. We were interested in synthesising heterocyclic carbodiimides with an adjacent nitro substituent to investigate the possibility of intramolecular cyclisation between the carbodiimide and nitro group. Such a cyclisation could be employed to generate triazole or triazene rings. Nitro compounds are known to react with carbodiimides and other heterocumulenes.[14] Rees has demonstrated[15] that in the thermolysis of *N*-nitrophenyl tetrazole derivative **247**, phenyl 2-nitrophenylcarbodiimide **248** is generated, which is rapidly transformed to phenyl

benzotriazole, **249**, with loss of carbon dioxide, by a *ortho*-nitro group interaction, **Scheme 105.**



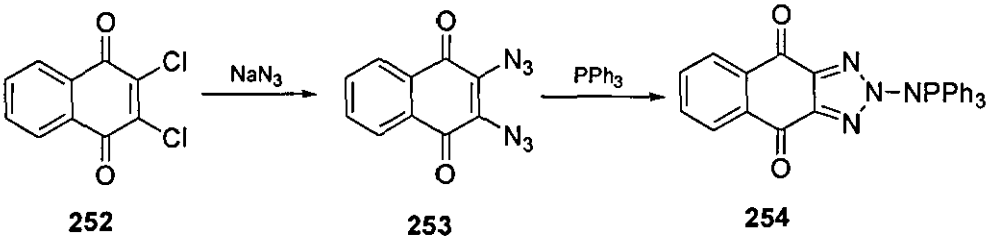
Scheme 105

This interesting reaction was carried out in various solvents and with variation of temperature. Nitrogen and carbon dioxide gases were detected by chemical tests and mass spectrometry measurements. The intermediacy of the carbodiimide was demonstrated by carrying out the same reaction with the *para*-nitrophenyl substituted tetrazole, which resulted in an intermediate unable to cyclise. The resulting carbodiimide was isolated. A mechanism of this reaction was proposed and involves a series of electrocyclic ring opening and ring closure steps. The mechanism is supported by infra-red spectroscopic evidence for one of the intermediates **250** or **251** isolated from the reaction, **Scheme 106.**



Scheme 106

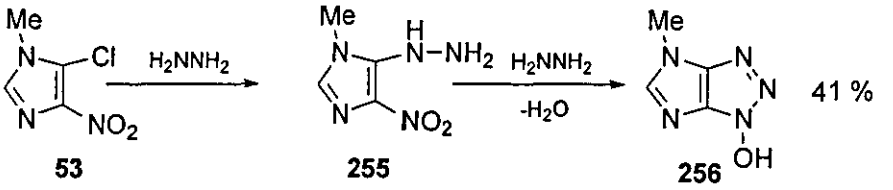
An interesting example of 1,2,3 triazole synthesis was reported by Sun and Watson.[16] The chlorines in the dichloronaphthoquinone compound **252** are readily displaced by azide to give the di-azidonaphthoquinone compound **253**, addition of triphenylphosphine gave the 1,2,3 triazole substituted compound, **254, Scheme 107.** No mechanism was discussed, however it may intially involve formation of an iminophosphorane by the Staudinger reaction followed by electrocyclisation.



252 253 254

Scheme 107

There appears to be only two examples of imidazo triazole derivatives reported in the literature. The first, a 1,4-dihydro compound, unsubstituted on the triazole ring, has been described as a photographic fog inhibitor.[17] The second example[18] is the reaction between 5-chloro-4-nitro-1-methylimidazole, **53** and hydrazine forming the expected intermediate 5-hydrazino-4-nitro-1-methylimidazole, **255**. This reacts further to form a deeply purple coloured compound found to be 1-hydroxy-4-methylimidazole[4,5-*d*]-*v*-triazole **256**, formed in 41 % yield. This may have formed due to alkaline action of hydrazine, **Scheme 108.** The mechanism of this reaction was not discussed and was limited to one example of the hydroxy imidazo triazole.



53 255 256

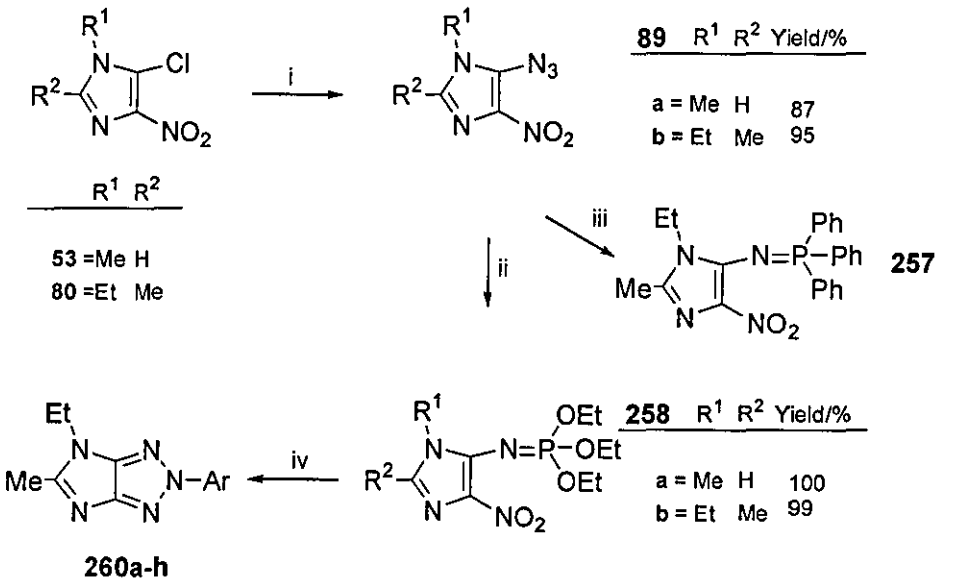
Scheme 108

There has been little synthetic work[17,18] on the construction of imidazo[4,5-*d*][1,2,3]triazole derivatives, and there are no general methods available for the synthesis of this ring system. This chapter demonstrates a general route for the preparation of imidazo triazole compounds with aryl substituents at the 2-position of the ring.

5.2 Results and Discussion

5.2.1 Synthesis of fused imidazo[4,5-*d*][1,2,3]triazole derivatives

The required 4-nitroimidazol-5-yl phosphoramidates **258a** and **b** were easily prepared by reaction with the corresponding azides **89a** and **b** with triethyl phosphite (**Scheme 109**). The reaction proceeded smoothly in dichloromethane at room temperature to form the phosphoramidates **258a** and **b** in high yield. The iminophosphorane **257** was also similarly prepared. The azides[19] **89a** and **b** was in turn readily prepared in high yield by treatment of the corresponding chloro compounds[20] **53** and **80** with sodium azide in dimethylformamide. The nitro compounds **258a** and **b** were obtained as yellow oils and had analytical and spectroscopic properties fully in accord with the phosphoramidate structure. The ^{1}H NMR of spectra of the phosphoramidates **258a** and **b** showed signals for three ethyl groups attached to oxygen and signals consistent with the methyl substituted, or ethyl-2-methyl substituted nitroimidazole rings. The ^{31}P NMR spectrum of **258b** showed a

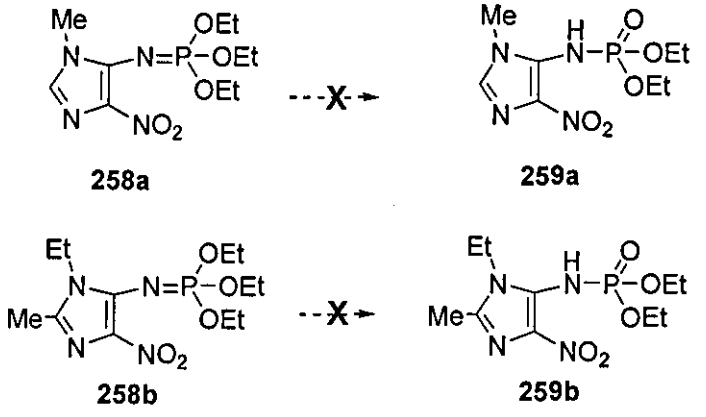


Reagents and conditions: i, NaN_3, DMF, room temperature; ii, $P(OEt)_3$, CH_2Cl_2, Reflux; iii, $P(Ph)_3$, CH_2Cl_2, Reflux; iv, ArN=C=O, CH_3CN, 60 °C or Reflux.

Scheme 109

singlet at δ -5, consistent with a trialkyl N-aryl phosphoramidate. The structure of **258a** has been confirmed by single crystal X-ray diffraction analysis.[21]

The phosphoramidate compounds **258a** and **258b** were stable and showed no tendency to undergo rearrangement, or undergo dealkylation in an Arbuzov type process to the corresponding diethyl phosphoramidates **259a**and **259b**, **Scheme 110**.



Scheme 110

On heating the phosphoramidate **258b** with phenylisocyanate in acetonitrile at 60°C rapid consumption of the phosphoramidate occurred, and the fused imidazo[4,5-*d*][1,2,3]triazole **260a**, **Scheme 111** was isolated as a crystalline solid in good yield, simply by evaporating the solvent, and triturating with ethanol to remove the triethyl phosphate formed. Acetonitrile was found to be the most effective solvent for carrying out the reaction and the yield was not improved by the use of other solvents. Carrying out the reaction in hot toluene gave a reduced yield of imidazotriazole and effecting the reaction at room temperature in dichloromethane gave only the fused triazole in low yield. A large range of other aryl isocyanates were used and the 5-aryl imidazotriazoles **260b-h** being formed in moderate to good yield as the only identifiable product in each case, **Table 5.1**. Work-up again simply involved trituration and chromatography was not required. The triethyl phosphoramidate reagent thus has the advantage over the corresponding triphenyl iminophosphoranes often used in aza-Wittig reactions, where the triphenylphosphine oxide by-product formed usually requires removal by chromatography. The structures of the

triazole products were supported by NMR spectroscopy, mass spectrometric and analytical data. X-ray crystallography of the 4-trifluoromethylphenyl derivative **260d** as shown in **Figure 5.2** gave the ultimate structural proof of a flat planar bicyclic hetero aromatic compound and showed the product to be the 5-aryl isomer.

258b **260a-h**

Reagents and conditions: i, ArN=C=O, CH_3CN, 60 °C or reflux.

Scheme 111

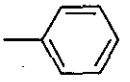
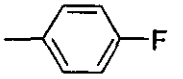
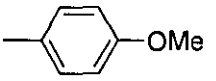
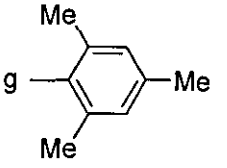
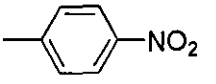
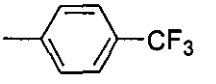
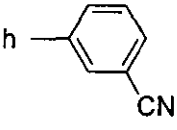
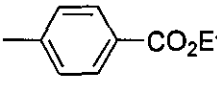
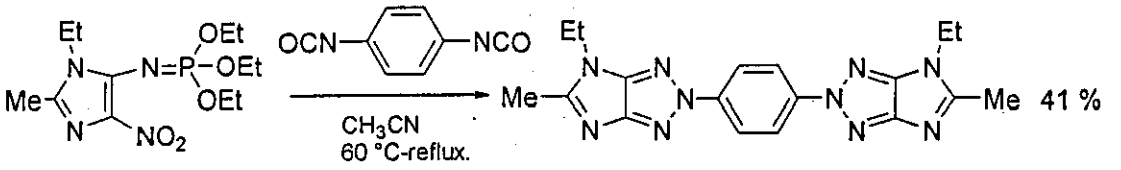
260	Ar	Yield/%	260	Ar	Yield/%
a		63	f		62
b		64	g		57
c		79			
d		66	h		61
e		62			

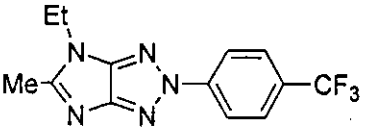
Table 5.1, Imidazo[4,5-*d*][1,2,3]triazoles **260a-h** prepared from **258b**.

Phosphoramidate **258b**, was also reacted with 1,4 diisocyanatobenzene under the same reaction conditions. After separation and purification by flash chromatography the *bis*-triazole compound **261** was obtained in 41 % yield, **Scheme 112**.



258b **261**

Scheme 112



260d

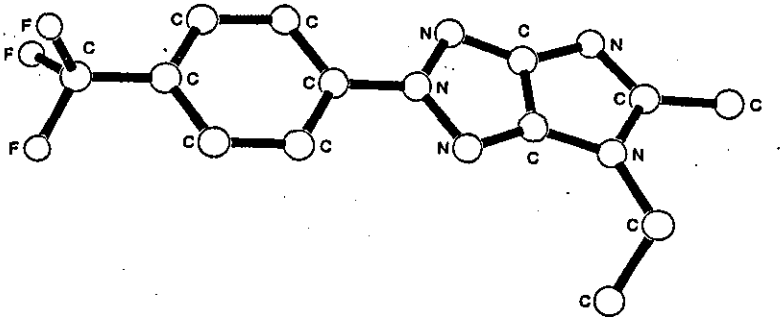


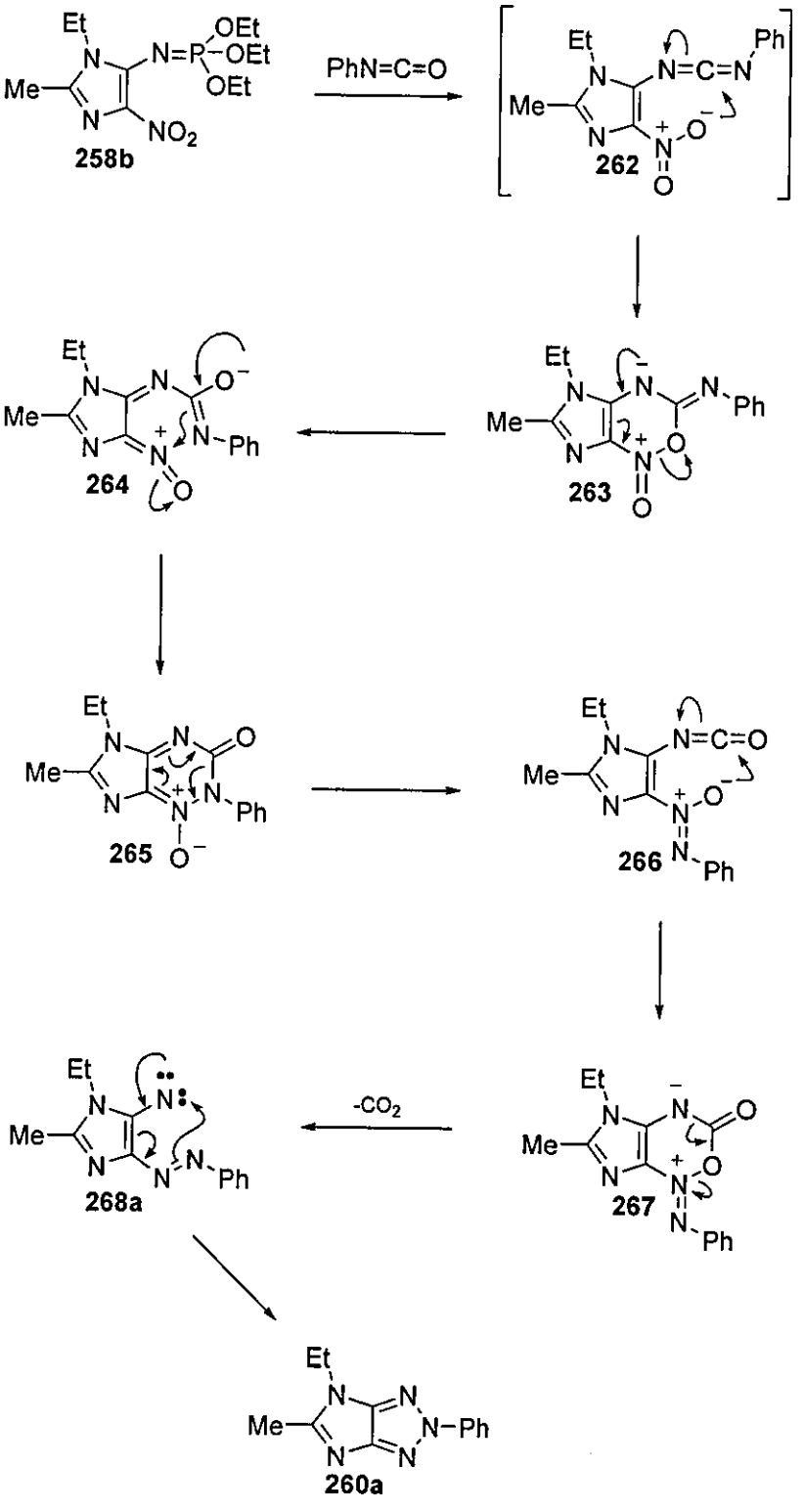
Figure 5.2, The X-ray crystal structure of 2-trifluoromethylphenyl substituted 2*H*, 4*H*-imidazo[4,5-*d*][1,2,3]triazole, (260d).

5.2.2 Proposed Mechanisms for Imidazo-triazole formation

The formation of the fused triazole ring in this reaction suggests a complicated reaction pathway in which both oxygen atoms are ultimately lost from the nitro group. The isocyanate nitrogen becomes bonded to both the nitro group nitrogen atom and the nitrogen of the phosphoramidate group. Two possible mechanisms can be considered for the reaction leading to production of the fused [1,2,3]triazole ring.

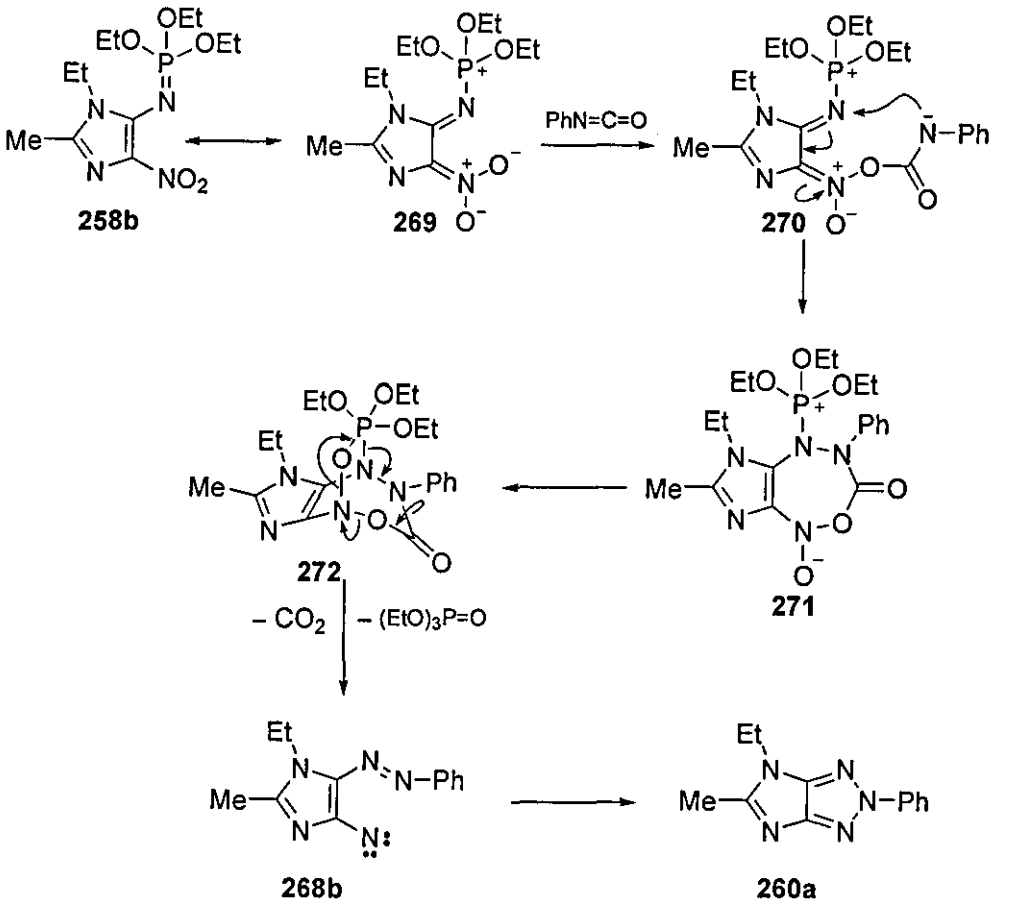
The first mechanism involves an initial aza-Wittig type reaction between the phosphoramidate group and the isocyanate leading to formation of a carbodiimide substituted nitro imidazole such as **262, Scheme 113.**

Attack on the carbodiimide by an oxygen atom of the neighbouring nitro group would then initiate a sequence of ring opening and ring closure reactions, **Scheme 113** paralleling the reaction pathway suggested by Rees and co-workers in their report on the cyclisation of 2-nitrophenyl carbodiimides,[15] **Scheme 105, 247→249.** Ring opening of the intermediate **263** would generate the nitrosonium ion **264** which could recyclise through the nitrogen of the urea anion to form the imidazo[4,5-*e*][1,2,4]triazene-*N*-oxide **265.** Electrocyclic ring opening of this molecule would generate the imidazol-5-yl isocyanate **266** in which the azoxy substituent at the 4-position is ideally placed to add to the isocycanate by attack through oxygen. The resulting intermediate **267** can then eliminate carbon dioxide to form the nitrene **268a** which would be expected to rapidly cyclise to the imidazo[4,5-*d*][1,2,3]triazole ring.


Et
N
N=P
OEt
OEt
OEt
Me
N
NO2
258b
PhN=C=O
Et
N
N=C=N
Ph
Me
N
O
262
Et
N
N
N
Ph
Me
N
O
N
263
Et
N
N
O
Me
N
N
Ph
N
O
264
Et
N
N
O
Me
N
N
Ph
O
265
Et
N
N=C=O
Me
N
O
N
Ph
266
Et
N
N
O
Me
N
O
N
Ph
267
-CO2
Et
N
N
Me
N
N
Ph
268a
Et
N
N
Me
N
N-Ph
N
260a

Scheme 113

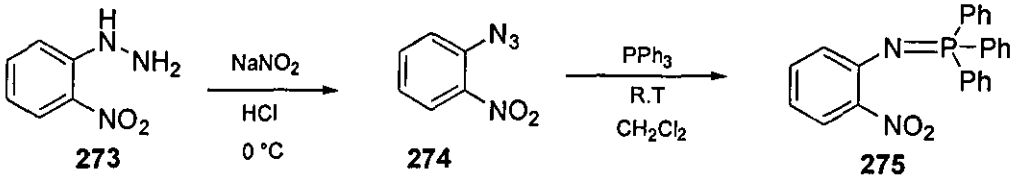
An alternative reaction pathway in which initial attack on the aryl isocyanate occurs through a nitro group oxygen atom as illustrated in **Scheme 114**. This would form the carbamoyl nitronate **270**. This intermediate could then follow several different pathways leading to the formation of the triazole ring and elimination of both carbon dioxide and triethyl phosphate. One possible fate for the nitronate **270** is that it could undergo cyclisation to form an imidazo fused seven membered ring **271**. The nitrogen atom at the 5-position of the imidazole ring would be expected to be electrophilic in character as shown by resonance structure **269**. One mechanism to convert the carbamoyl nitronate to the imidazotriazole would involve simultaneous loss of carbon dioxide and triethyl phophate. The acylated nitronate **270** could cyclise to **271**. If the seven membered ring was flexible enough to allow formation of the bridged pentacoordinate phosphorane **272**, this could eliminate both carbon dioxide and triethyl phosphate to generate the azo nitrene **268b**. Electrocyclic ring closure would finally produce the bicyclic triazole product **260a**.



Scheme 114

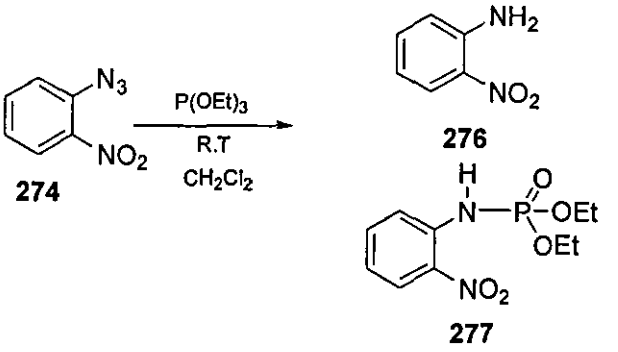
5.2.3 Mechanistic studies on the synthesis of imidazotriazoles

Studies were undertaken in attempt to determine the reaction pathway for the imidazotriazole synthesis. One approach was to produce a model *ortho*-nitro substituted iminophosphorane group on benzene. Commercially available *ortho*-nitro phenylhydrazine **273** was reacted under nitrosation conditions to form 1-azido-2-nitro benzene,[22] **274** in good yield. This was reacted with triphenyl phosphine to give the corresponding iminophosphorane[23] **275** in good yield, **Scheme 115.**

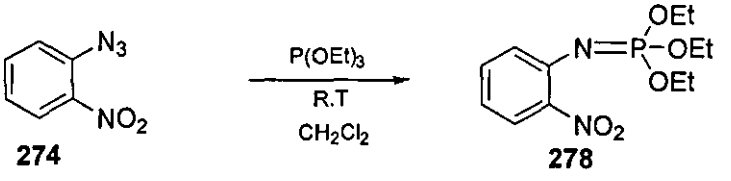


Scheme 115

When triethylphosphite was employed in the reaction, hydrolysis occurred and we obtained aniline **276** and the Arbuzov product **277**, Scheme **116**. This reaction in producing the iminophosphorane was carried out several times and finally the phosphoramidate[23] was prepared in good yield by carrying out the reaction under anhydrous conditions and involving no purification as this may have led to the hydrolysis of the phosphoramidate compound **278, Scheme 117**.

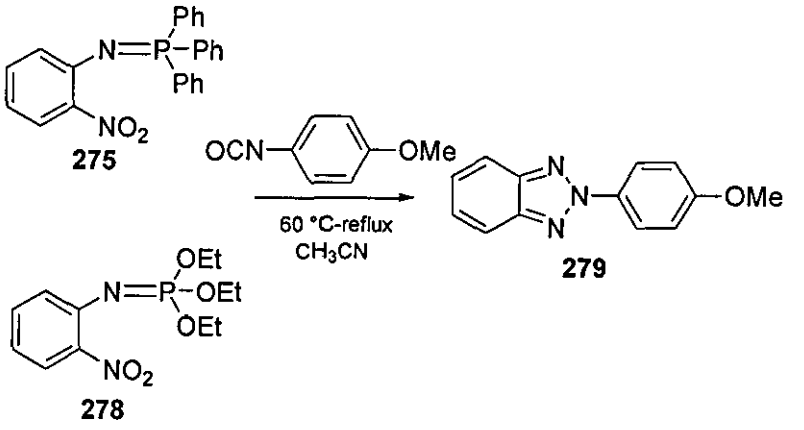


Scheme 116



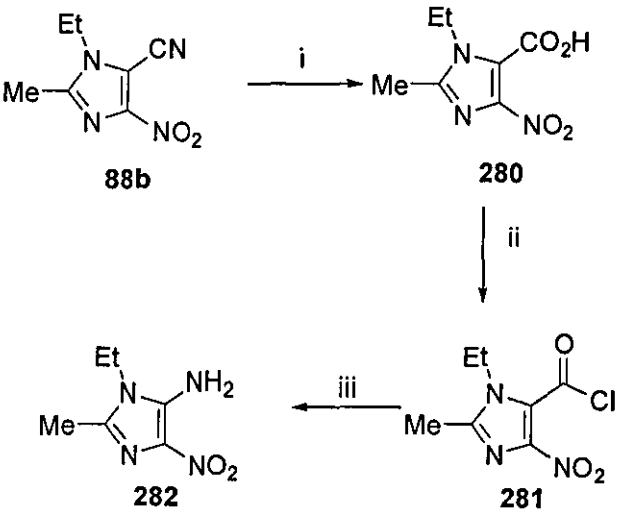
Scheme 117

Both the iminophosphorane **275** and the phosphoramidate **278** were utilised in the reaction with *para*-methoxyphenyl isocyanate to investigate whether the benzotriazole **279**, or the carbodiimide, would be formed under the reaction conditions employed to form the imidazo-triazoles. The reaction gave in all cases the benzotriazole **279** and the carbodiimides could not be isolated, **Scheme 118**.



Scheme 118

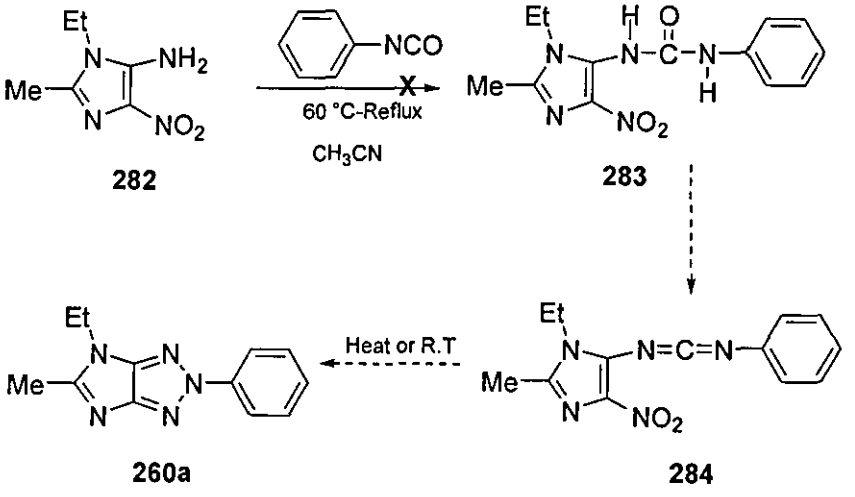
Another mechanistic challenge was to prepare the imidazol-5-yl carbodiimide, which cannot be isolated in the normal reaction condtions. Imidazol-5-yl carbodiimide could be heated and it may convert to the imidazotriazole. This would then demonstrate the reaction pathway goes *via* the carbodiimide. This challenge first started by hydrochloric acid hydrolysis of 4-nitroimidazol-5-yl phosphoramidate, **278** in order to obtain the amino imidazole. The reaction appeared to go to completion by TLC but isolation of this compound proved quite difficult due to its water solubility. Another strategy was employed to prepare high yields of the amino imidazole. The cyano compound[20] **88b** was readily prepared in high yield by treatment of the corresponding chloro compound[20] **80b** with sodium cyanide in dimethylformamide. Deaminative acid hydrolysis of the nitrile compound **80b**, under known conditions[24] gave a quantitative yield of the carboxylic acid **280**, in good yield. The carboxylic acid was readily converted to the acid chloride by treatment with thionyl chloride. The acid chloride **281** was carried forward to the next stage without purification and analysis. The primary amine **282** was eventually prepared[25] in good yield by reaction with sodium azide in aqueous acetone in a Curtius rearrangement, **Scheme 119**.



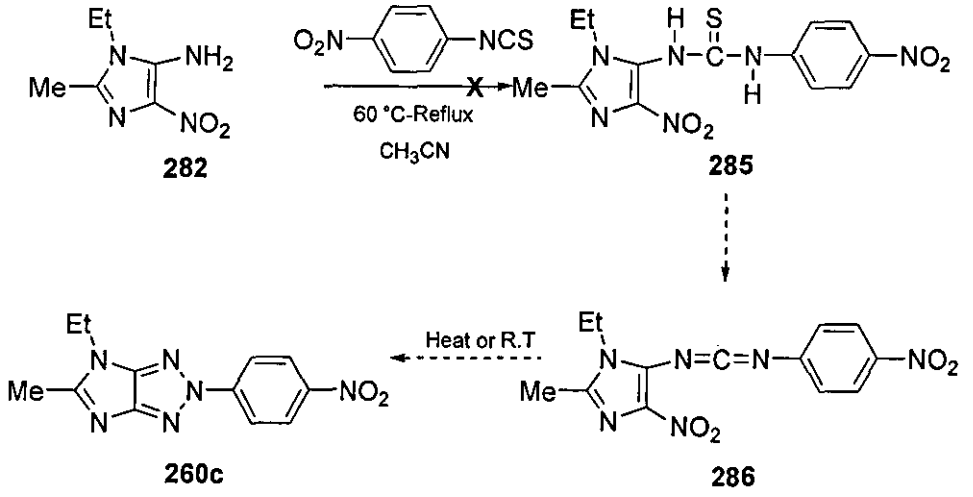
Reagents and conditions: i, H_2SO_4, $NaNO_2$ 100 °C; ii, $SOCl_2$,, Reflux; iii, NaN_3, CH_3COCH_3, H_2O, Reflux.

Scheme 119

The amine compound **282**, was treated with phenyl isocyanate or 4-nitrophenyl isothiocyanate, in two similar experiments in order to prepare the urea **283** and the thiourea **285** which could be converted into the carbodiimide **284** and **286**. Nevertheless, the reaction did not proceed to the required imidazo phenyl urea **283** or imidazo nitrophenyl thiourea **285**, **Scheme 120** and **121**. After several experiments and varying the solvents and reaction times these proved impossible to prepare. This may be due to nucleophilicity of the amine functionality, which is considerably reduced due to the inductive effect of the nitro group.

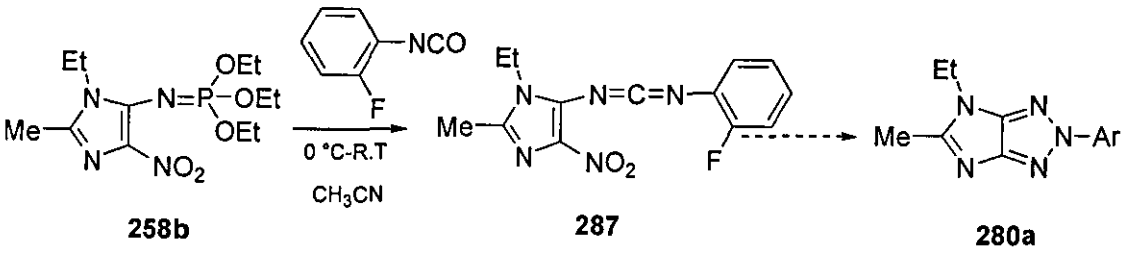


Scheme 120



Scheme 121

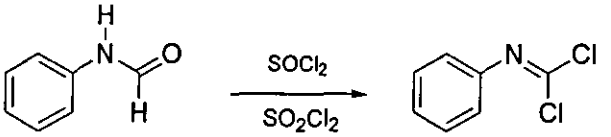
One final mechanistic study was undertaken which involved a series of reactions to try to determine the reaction pathway of this novel imidazo triazole synthesis. These reactions were monitored by infra-red spectroscopy. These involved removing a small aliquot of the reaction mixture for analysis at timed intervals using an infra-red spectrometer. This proved very successful in determining the reaction pathway to proceed *via* the carbodiimide route. One experiment that was performed was the reaction of 4-nitroimidazol-5-yl phosphoramidate **258b**, with 2 fluorophenyl isocyanate at 0 °C. The I.R spectrum showed strong isocyanate signals at 2271 and 2245 cm^{-1} and weak bands at 2157 and 2120 cm^{-1} corresponding to a carbodiimide intermediate **287**, **Scheme 122** (see **Appendix 8** showing a selection of I.R spectras). As the reaction progressed the isocyanate signals became relatively weaker and the carbodiimide signals intensified. This strongly supports the reaction proceeding *via* the carbodiimide rather than by acylation of the nitro group. An attempt was made to isolate the carbodiimide formed in this reaction.



Scheme 122

However, this proved unsuccessful and two other products were isolated. The urea compound of **287** was isolated as proven by mass spectrometry measurement of 306, indicative of the urea substituted compound.

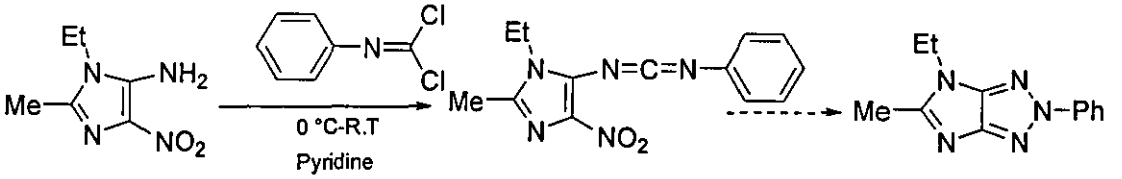
An alternatively approach to synthesising the carbodiimide **284**, involved using commercially available phenyl formamide **288** which was reacted with sulphuryl chloride and thionyl chloride to afford the reactive phenyl carboimidoyl dichloride **289** in good yield[26], **Scheme 123**.



288 **289**

Scheme 123

When amino nitro imidazole **282** was treated with phenyl carboimidoyl dichloride at 0 °C in pyridine, **Scheme 124**, a procession of changes were observed by infra-red spectroscopy. As time progressed in the reaction, the spectra showed intense isocyanate peaks at 2271 and 2245 cm^{-1}, and weak peaks at 2134 and 2107 cm^{-1} corresponding to the formation of small concentrations of the carbodiimide **284**. As time elapsed the intensity of the carbodiimide peaks increased. Attempts were made to isolate the carbodiimde created, however this was unsuccessful as only unidentified material was obtained.

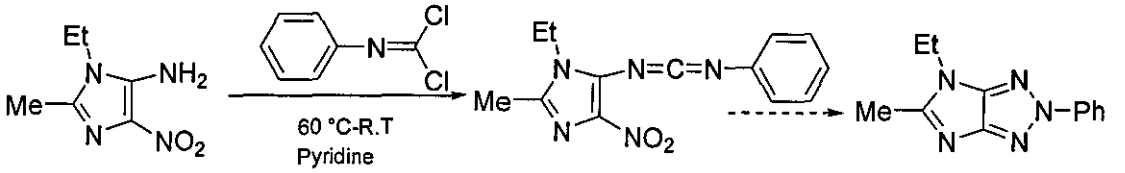


282 **284** **260a**

Scheme 124

The same experiment was repeated except it was commenced at 60 °C, **Scheme 125**, in an endeavor to produce the imidazo triazole **260a**. The reaction was also monitored by infra-

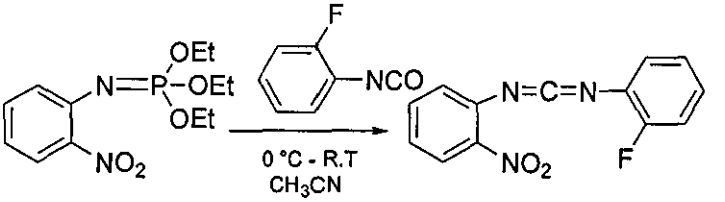
red spectroscopy. The spectra showed no isocyanate peaks, indicative of its rapid consumption in the production of the imidazo triazole **260a**. Intially the spectra showed intense peaks of the carbodiimide **284** at 2135 and 2108 cm^{-1}, which weakened with time. Dissapointingly neither the carbodiimide **284** or the triazole product **260a** could be isolated.



282 **284** **260a**

Scheme 125

Another experiment involved the reaction of the model compound **278** with 2-fluorophenyl isocyanate at 0 °C, **Scheme 126**. The I.R spectra had shown strong isocyanate signals of the substrate at 2270 and 2244 cm^{-1} and a strong doublet band at 2122 cm^{-1} corresponding to a carbodiimide intermediate **290**. As time progressed the isocyanate signals diminished and the carbodiimide signals intensified. An effort was made to isolate the carbodiimide at the end of the reaction. Two solid materials were isolated but were unidentifiable.



278 **290**

Scheme 126

Studies to determine the precise mechanistic steps involved in this transformation have been carried out. Some evidence for the preference of the proposed mechanism involving the carbodiimide has been obtained.

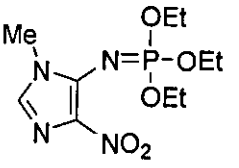
5.3 Conclusion

The application of iminophosphoranes in synthetic heterocyclic chemistry stands as an important synthetic appliance in constructing novel heterocyclic rings in the past and in today's modern heterocyclic chemistry. This methodology has proved very successful in the synthesis of imidazo[4,5-*d*][1,2,3]triazole derivatives in good yield. An X-ray crystal structure was determined to prove the correct substitution on the imidazo-triazole ring system. Evidence to support the mechanism of this reaction has now been established. This primarily indicates initial reaction at the iminophosphorane substituent, proceeding to the carbodiimide generated by the aza-Wittig reaction mechanism. A sequence of electrocyclic ring opening and closure occurs analogous to that postulated by Rees[15] account for the imidazo[4,5-*d*][1,2,3]triazole derivatives formed. Other possible mechanisms that involve acylation of the nitro group may occur in parallel, but at the moment cannot be supported by the experimental evidence.

5.4 Experimental

For general experimental procedures see Chapter 1, section 1.8.1.

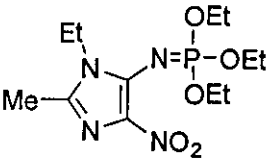
Triethyl *N*-(1-methyl-4-nitro-1*H*-imidazol-5-yl)phosphoramidate[21] (258a)



A solution of the azide **89a** (0.34 g, 0.002 mol) in dichloromethane (5.0 cm^3) was treated dropwise with triethyl phosphite (0.33 g, 0.002 mol) and the solution heated under reflux under nitrogen until consumption of the azide was complete (TLC). The mixture was evaporated under reduced pressure to give a yellow oil (0.61 g, quantitative). Flash chromatography on silica eluting with dichloromethane/light petroleum ether (2:1) gave the phosphoramidate as a bright yellow oil in quantitative yield.

Bright yellow liquid, yield 100 %; (Found: m/z, 306.1094 $C_{10}H_{19}N_4O_5P$ requires M, 306.1093); ν_{max} 1599, 1378, 1299, 1262 and 1031 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.28 (9H, t, *J* 7, CH_3CH_2), 3.34 (3H, s, 1-CH_3), 4.12 (6H, quin, *J* 7, CH_3CH_2) and 7.26 (1H, s, H-2); δ_C (100 MHz; $(CD_3)_2SO$) 16.4 (CH_3CH_2), 30.5 (CH_3), 65.2 (CH_2), 128.6 (C-4), 130.7 (C-2) and 139.5 (d, $^2J_{CP}$ 20, C-5); δ_P (101.3 MHz; $(CD_3)_2SO$) 1.93.

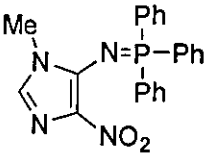
Triethyl *N*-(1-ethyl-2-methyl-4-nitro-1*H*-imidazol-5-yl)phosphoramidate (258b)



A solution of the azide **89b** (0.75 g, 0.0038 mol) in dichloromethane (10 cm^3) was treated dropwise with triethyl phosphite (0.63 g, 0.0038mol). The solution was stirred under nitrogen at room temperature for 30 min, and then heated under reflux for 1 h. The solution was evaporated and the residual yellow oil flash chromatographed over silica. Elution with light petroleum (bp 40-60°C)/ethyl acetate (2:1) gave the phosphoramidate as a bright yellow oil, (1.27 g, 99 %).

Bright yellow oil, yield 99 %; (Found: m/z, 334.1410, $C_{12}H_{23}N_4O_5P$ requires: M, 334.1406); ν_{max} 1600, 1303, 1245 and 1039 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.28 (3H, t, *J* 7, CH_3CH_2N), 1.35-1.40 (9H, m, CH_3CH_2O), 2.34 (3H, s, CH_3-2), 3.85 (2H, q, *J* 7, CH_3CH_2 N) and 4.09-4.24 (6H, m, CH_3CH_2 O); δ_C (100 MHz; $CDCl_3$) 13.9 (CH_3), 14.6 (CH_3), 16.1 (d, $^3J_{CP}$ 7, CH_3CH_2OP), 37.5 (CH_2), 64.9 (d, $^2J_{CP}$ 8, CH_3CH_2OP), 132.2 (C-4), 138.2 (C-2) and 139.2 (d, $^2J_{CP}$, 21, C-5); δ_P (101.3 MHz; $CDCl_3$) –5.2.

***N*-(1-methyl-4-nitro-1*H*-imidazol-5-yl)-*N*-(1,1,1-triphenyl-λ^5-phosphanylidene)amine (257)**



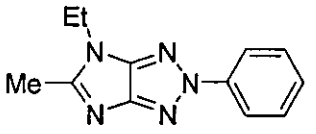
A solution of the azide **89a** (0.75 g, 0.0038 mol) in dichloromethane (10 cm^3) was treated dropwise with triphenyl phosphine (0.63 g, 0.0038mol). The solution was stirred under nitrogen at room temperature for 30 min, and then heated under reflux for 1 h. The solution was evaporated to give a yellow solid. Re-crystallisation from dichloromethane and light petroleum ether gave the iminophosphorane as a bright yellow solid, (1.27 g, 94 %).

Yellow solid, yield 94%, m.p. 276-277 °C; (Found: C, 65.67; H, 4.69; N, 13.84 %; m/z, 402.1251, $C_{22}H_{19}N_4O_2P$ requires: C, 65.67; H, 4.76 %; N; 13.92 M, 402.1246); ν_{max} 3058, 1634, 1582, 1567, 1438, 1366, 1290, 1248, 1110, 1040, 998, 820 and 693 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 3.52 (3H, s, CH_3), 7.05 (H, d, *J* 2.2, Ar-CH), 7.38-7.53 (10H, m, Ar-CH) and 7.63-7.72 (5H, m, Ar-CH); δ_C (62.9 MHz; $CDCl_3$) 30.3 (CH_3), 128.4 (CH, d, *J* 12.8, P-CH), 130.8 (C), 131.1 (Ar-CH), 131.7 (CH, d, *J* 3, P-CH), 132.0 (CH, d, *J* 10.8, P-CH) and 132.5 (C); δ_P (101.2 MHz; $CDCl_3$) 12.9.

General procedure for synthesis of imidazo[4,5-*d*][1,2,3]triazoles

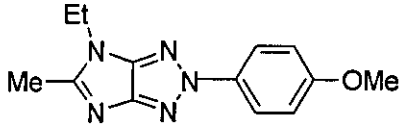
A solution of the phosphoramidate **258b** (0.334 g, 0.001 mol) in anhydrous acetonitrile (5.0 cm^3) was stirred and treated dropwise at room temperature with the appropriate aryl isocyanate (0.001 mol) neat, or in acetonitrile (2.0 cm^3) (for solid compounds). The resulting solution was heated at 60 °C or under reflux for 6 h then cooled and evaporated under reduced pressure. The residue was triturated with diethyl ether or ethanol to afford the imidazotriazole as an insoluble solid, which was collected by suction filtration, dried and re-crystallised to give the following compounds.

4-Ethyl-5-methyl-2-phenyl-2*H*,4*H*-imidazo[4,5-*d*][1,2,3]triazole (260a)



Colourless cubes, yield 63 %, m.p. 143-144 °C (from ethyl acetate); (Found: C, 63.2; H, 5.7; N, 30.8 %; m/z, 227.1171. $C_{12}H_{13}N_5$ requires: C, 63.4; H, 5.8; N, 30.8 %; M, 227.1171); ν_{max} 1599, 1502, 1395 and 1355 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.57 (3H, t, *J* 7, CH_3CH_2), 2.60 (3H, s, 5-CH_3), 4.12 (2H, q, *J* 7, CH_3CH_2), 7.25-7.31 (1H, m, PhH), 7.42-7.49 (2H, m, PhH), and 8.07-8.11 (2H, m, PhH); δ_C (100 MHz; $CDCl_3$) 14.9 (CH_3), 15.3 (CH_3), 40.3 (CH_2), 119.0 (PhC), 126.9 (PhC), 129.5 (PhC), 141.7 (C), 147.2 (C), 155.3 (C) and 159.5 (C).

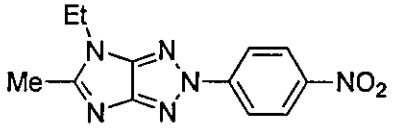
4-Ethyl-5-methyl-2-(4-methoxyphenyl)-2*H*,4*H*-imidazo[4,5-*d*][1,2,3]triazole (260b)



Pale brown needles, yield 64 %, m.p. 141-142 °C (from ethanol); (Found: C, 60.4; H, 5.86; N, 27.1 %; m/z, 257.1279. $C_{13}H_{15}N_5O$ requires: C, 63.7; H, 5.90; N, 27.2 %; M, 257.1279); ν_{max} 1605, 1507, 1258 and 842 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.57 (3H, t, *J* 7, CH_3CH_2), 2.60 (3H, s, 5-CH_3), 3.85 (3H, s, CH_3O), 4.12 (2H, q, *J* 7, CH_3CH_2), 6.96-7.00 (2H, m, ArH) and 7.97-8.01 (2H, m, ArH); δ_C (100 MHz; $CDCl_3$) 14.9 (CH_3), 15.2

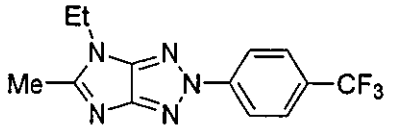
(CH_3), 40.3 (CH_2), 55.9 (CH_3O), 114.7 (ArC), 120.5 (ArC), 135.5 (C), 146.9 (C), 154.9 (C), 158.6 (C) and 158.7 (C).

4-Ethyl-5-methyl-2-(4-nitrophenyl)-2*H*,4*H*-imidazo[4,5-*d*][1,2,3]triazole (260c)



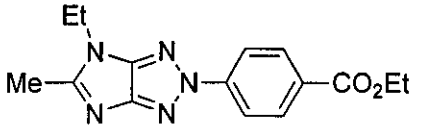
Cream powder, yield 79 %, m.p. 215-216 °C (from chloroform/light petroleum b.p. 40-60 °C); (Found: C, 52.7; H, 4.4; N, 30.5 %; m/z, 272.1019, $C_{12}H_{12}N_6O_2$ requires: C, 52.9; H, 4.4; N, 30.9 %; M, 272.1022); ν_{max} 1615, 1598, 1503 (NO_2), 1337 (NO_2), 1113 and 854 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.57 (3H, t, *J* 7, CH_3CH_2), 2.60 (3H, s, 5-CH_3), 4.10 (2H, q, *J* 7, CH_3CH_2) and 8.14-8.26 (4H, ABq, ArH); δ_C (100 MHz; $CDCl_3$) 14.9 (CH_3), 15.5 (CH_3), 40.5 (CH_2), 118.6 (ArCH), 125.4 (ArCH), 145.7 (C), 145.8 (C), 148.5 (C), 156.6 (C) and 162.2 (C).

4-Ethyl-5-methyl-2-(4-trifluoromethylphenyl)-2*H*,4*H*-imidazo[4,5-*d*][1,2,3]triazole (260d)



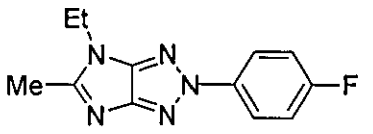
Pale green cubes, yield 66 %, m.p. 151-152 °C (from chloroform/light petroleum b.p. 40-60 °C); (Found: C, 52.9; H, 4.1; N, 23.7 %; m/z, 295.1045, $C_{13}H_{12}F_3N_5$ requires: C, 52.9; H, 4.1; N, 23.6 %; M, 295.1046); ν_{max} 1614, 1500, 1318, 1163, 1125 and 1104 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.57 (3H, t, *J* 7, CH_3CH_2), 2.59 (3H, s, 5-CH_3), 4.11 (2H, q, *J* 7, CH_3CH_2), 7.68 (2H, d, *J* 9, ArH), and 8.17 (2H, d, *J* 9, ArH); δ_C (62.9 MHz; $CDCl_3$) 14.3 (CH_3), 14.9 (CH_3), 39.9 (CH_2), 118.3 (ArC-2), 124.0 (q, $^1J_{CF}$ 274, CF_3), 126.3 (q, $^3J_{CF}$ 4, ArC-3), 128.0 (q, $^2J_{CF}$ 33, ArC-4), 143.6 (C), 147.4 (C), 155.5 (C) and 160.5 (C).

Ethyl 4-(4-Ethyl-5-methyl-2*H*, 4*H*-imidazo[4,5-*d*][1,2,3]triazol-5-yl)benzoate (260e)



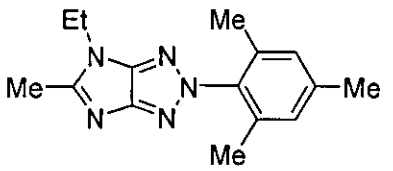
Cream powder, yield 62 %, m.p. 119-121 °C (from dichloromethane/light petroleum b.p. 40-60 °C); (Found: C, 60.3; H, 5.7; N, 23.3 %; m/z, 299.1385. $C_{15}H_{17}N_5O_2$ requires: C, 60.2; H, 5.7; N, 23.4 %; M, 299.1382); ν_{max} 1713 (C=O), 1606, 1506, 1349 and 1274 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.41 (3H, t, *J* 7, CH_3CH_2O), 1.61 (3H, t, *J* 7, CH_3CH_2N), 2.62 (3H, s, 5-CH_3), 4.13 (2H, q, *J* 7, CH_3CH_2N), 4.40 (2H, q, *J* 7, CH_3CH_2O) and 8.12-8.17 (4H, ABq, ArH); δ_C (100 MHz; $CDCl_3$) 14.4 (CH_3), 14.5 (CH_3), 15.1 (CH_3), 40.0 (CH_2), 61.1 (CH_2O), 118.0 (ArCH), 128.2 (C), 130.9 (ArCH), 144.4 (C), 147.5 (C), 155.6 (C), 160.4 (C) and 166.0 (C).

4-Ethyl-2-(4-fluorophenyl)-5-methyl-2*H*,4*H*-imidazo[4,5-*d*][1,2,3]triazole (260f)



Cream coloured powder, yield 62 %, m.p. 122-123 °C (from dichloromethane/light petroleum b.p. 40-60 °C); (Found: C, 58.5; H, 4.8; N, 28.4 %; m/z, 245.1078, $C_{12}H_{12}FN_5$ requires: C, 58.8; H, 4.9; N, 28.6 %; M, 245.1077); ν_{max} 1601, 1535, 1507, 1384, 1230 and 829 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.56 (3H, t, *J* 7, CH_3CH_2), 2.59 (3H, s, 5-CH_3), 4.12 (2H, q, *J* 7, CH_3CH_2), 7.11-7.15 (2H, m, ArH) and 8.01-8.05 (2H, m, ArH); δ_C (62.9 MHz; $CDCl_3$) 14.7 (CH_3), 15.2 (CH_3), 40.3 (CH_2), 116.2 (d, $^2J_{CF}$ 23, ArC-3), 120.6 (d, $^3J_{CF}$ 8, ArC-2), 137.9 (d, $^4J_{CF}$ 3, ArC-1), 147.2 (C), 155.2 (C), 159.5 (C) and 161.5 (d, $^1J_{CF}$ 244, ArC-4).

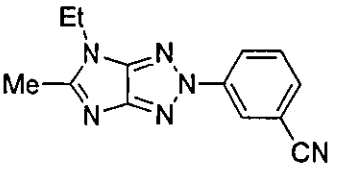
4-Ethyl-5-methyl-2-(2,4,6-trimethylphenyl)-2*H*,4*H*-imidazo[4,5-*d*][1,2,3]triazole (260g)



White powder, yield 57 %, m.p. 174-175 °C (from dichloromethane/diethyl ether); (Found: C, 66.7; H, 7.1; N, 25.8 %; m/z, 269.1641, $C_{15}H_{19}N_5$ requires: C, 66.9; H, 7.1; N, 26.0 %; M, 269.1641); ν_{max} 1589, 1502, 1387, 1352 and 1124 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.55 (3H, t, *J* 7, CH_3CH_2), 1.96 (6H, s, 2-ArCH_3), 2.31 (3H, s, 4-ArCH_3), 2.60 (3H, s, 5-CH_3),

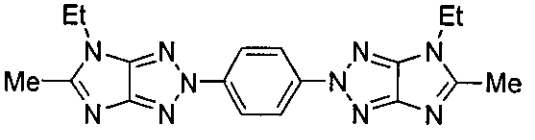
4.11 (2H, q, *J* 7, CH_3CH_2) and 6.93 (2H, s, 3-ArH); δ_C (62.9 MHz; $CDCl_3$) 14.3 (CH_3), 14.7 (CH_3), 17.3 (CH_3), 21.0 (CH_3), 39.9 (CH_2), 128.6 (C), 135.9 (C), 137.8 (C), 139.3 (C), 145.8 (C), 153.9 (C) and 157.5 (C).

3-(4-Ethyl-5-methyl-2*H*,4*H*-imidazo[4,5-*d*][1,2,3]triazol-2-yl)benzonitrile (260h)



Off white powder, yield 61 %, m.p. 151-153 °C (from dichloromethane/diethyl ether); (Found: C, 61.7; H, 4.7; N, 33.1 %; m/z, 252.1121, $C_{13}H_{12}N_6$ requires: C, 61.9; H, 4.7; N, 33.3 %; M, 252.1123); ν_{max} 2231 (C≡N), 1606, 1583, 1503, 1351 and 903 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.57 (3H, t, *J* 7, CH_3CH_2), 2.60 (3H, s, 5-CH_3), 4.11 (2H, q, *J* 7, CH_3CH_2), 7.50-7.53 (2H, m, Ar-H) and 8.26-8.34 (2H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 14.3 (CH_3), 15.0 (CH_3), 40.0 (CH_2), 113.2 (C), 118.1 (C), 121.5 (C), 122.3 (C), 129.4 (C), 130.1 (C), 141.6 (C), 147.4 (C), 155.4 (C) and 160.7 (C).

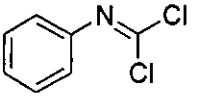
4-Ethyl-2-[4-(4-ethyl-5-methyl-2,4-dihydroimidazo[4,5-*d*][1,2,3]triazo(-2-yl)phenyl]-5-methyl-2,4-dihydroimidazo[4,5-*d*][1,2,3]triazole (261)



A solution of the phosphoramidate **258b** (2 eq.) in anhydrous acetonitrile (5.0 cm^3) was stirred and treated dropwise at room temperature with the 1,4-phenyl diisocyanate (1 eq.) in acetonitrile (2.0 cm^3). The resulting solution was heated at 60 °C or under reflux for 6 h then cooled and evaporated under reduced pressure. Flash column chromatography on silica eluting with petroleum ether and ethyl acetate (2:1) gave the title compound as a white solid.

White solid, yield 41 %, m.p. 340 °C (dec), (m/z, 376.1879, $C_{18}H_{20}N_{10}$ requires: M, 376.1872); ν_{max} 2924, 1685 and 1545 cm^{-1}; δ_H (400 MHz; CF_3CO_2D) 1.88 (6H, br t, *J* 8, CH_3CH_2), 3.07 (6H, br s, CH_3), 4.56 (4H, br q, *J* 8, CH_3CH_2) and 8.43 (4H, br s, PhH); δ_C (100 MHz; CF_3CO_2D) 13.5 (CH_3), 13.9 (CH_3), 45.0 (CH_2), 122.9 (Ar-CH), 142.3 (PhC), 143.9 (PhC), 146.3 (C) and 160.2 (C).

Phenyl carbodiimidoyl dichloride (289)

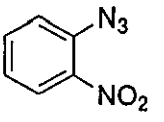


Sulfuryl chloride (5.39 g, 40 mmol) in thionyl chloride (35 cm^3) was added portionwise to formanilide (4.84 g, 40 mmol) at 15-20 °C over 2 h and further continued for 2 h at room temperature. The reaction was heated to 100 °C under reflux conditions and hydrogen chloride and sulphur dioxide gases were liberated. After 2 h the solvent was removed *in vacuo* to reveal a viscous orange oil. Vacuum distillation of the viscous oil at 101-105 °C at 0.1 mbar (lit.[26], 94-99 °C at 14 mm Hg) gave phenyl isocyanide dichloride as a viscous colourless oil (3.41 g, 49 %).

Colourless liquid, yield 49 %; (Found: m/z, 172.9801, $C_7H_5Cl_2N$ requires: M, 172.9799); ν_{max} 3064, 3035, 2262, 2057, 1720, 1656, 1595, 1485, 1208, 1089, 913, 885 and 826 cm^{-1};

δ_H (250 MHz; $CDCl_3$) 6.88-6.97 (2H, m, Ar-CH), 7.09-7.27 (1H, m, Ar-CH) and 7.29-7.43 (2H, m, Ar-CH); δ_C (100 MHz; $CDCl_3$) 120.6 (C), 121.1 (C), 126.4 (C), 129.4 (C) and 129.6.

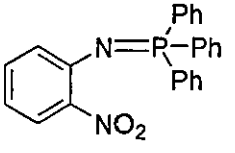
1-Azido-2-nitrobenzene (274)



Concentrated hydrochloric acid (40 cm^3) was added dropwise to 2-nitrophenylhydrazine (4.00 g, 26.1 mmol) and sodium nitrite (3.60 g, 52.1 mmol) in water (20 cm^3) at 0 °C in the absence of light. The reaction mixture was allowed to stand at room temperature after 3 h and then stirred for a further 3 h. The brown solid was filtered and washed with saturated sodium hydrogen carbonate solution and then water. The solid was left to dry under vacuum to give a brown solid (3.0 g, 70 %).

Brown solid, yield 70 %; m.p. 53-54 °C (lit.,[22] 53-55 °C); (Found: m/z,164.0336, $C_6H_4N_4O_2$ requires: M, 164.0334); ν_{max} 2123 (N_3), 1624, 1603, 1573, 1525, 1346, 1292, 1259, 1168, 856, 779 and 742 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.26-7.28 (1H, m, Ar-H), 7.33-7.35 (1H, m, Ar-CH), 7.60-7.63 (1H, m, Ar-CH) and 7.92-7.94 (1H, m, Ar-CH); δ_C (100 MHz; $CDCl_3$) 120.8 (CH), 124.9 (CH), 126.1 (CH), 134.0 (CH), 134.8 (C) and 141.0 (C).

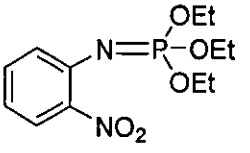
2-Nitro-N-triphenylphosphoranyliden-aniline (275)



A solution of 1-azido-2-nitrobenzene **274** (1.5 g, 0.0091 mol) in dichloromethane (10.0 ml) was treated portionwise with triphenyl phosphine (1.6 g, 0.0091 mol) and the solution heated under reflux under nitrogen until consumption of the azide was complete (TLC). The mixture was evaporated under reduced pressure to give a brown solid (3.6 g, quantitative). Re-crystallisation from dichloromethane/light petroleum ether gave the iminophosphorane as a brown solid.

Brown solid, yield 100 %, m.p. 151-152 °C (lit.,[23] 153-154 °C); (Found : m/z, 398.1183, $C_{24}H_{19}O_2N_2P$ requires: M, 398.1184); δ_H (250MHz; $CDCl_3$) 7.23-7.36 (11H, m, Ar-H), 7.59-7.66 (4H, m, Ar-H) and 7.91-7.95 (4H, m, Ar-H).

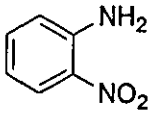
2-Nitro-phenyl-phosphorimidic acid triethyl ester[23] (278)



A solution of the azide **274** (1.0 g, 0.0061 mol) in dichloromethane (5.0 ml) was treated dropwise with triethyl phosphite (1.01 g, 0.0061 mol) and the solution heated under reflux under nitrogen until consumption of the azide was complete (TLC). The mixture was evaporated under reduced pressure to give a brown residue. Attempts were made to purify the brown residue on silica by flash column chromatography eluting with 4:1 light petroleum ether and ethyl acetate. However, this always led to hydrolysis to 2-nitroaniline **276** and product **277**. Therefore the phosphoramidate, compound **278** was used in the next step without purification and analysis was carried out only on the crude material (2.781 g 100 %).

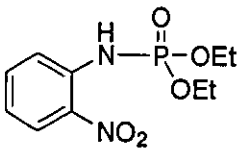
Viscous brown liquid, yield 100 %; (Found : m/z, 302.1039, $C_{12}H_{19}N_2O_5P$ requires: M, 302.1031); δ_H (250 MHz; $CDCl_3$) 1.28-1.35 (9H, m, CH_3), 4.06-4.20 (6H, m, CH_2), 6.61-6.85 (1H, m, Ar-H), 7.15-7.35 (1H, m, Ar-H) and 7.48-7.65 (1H, m, Ar-H).

2-Nitro-phenyl aniline (276)



Yellow liquid, yield 18 %; (Found : m/z, 138.0431, $C_6H_6N_2O_2$ requires: M, 138.0429); ν_{max} (nujol) 3474, 3323, 2985, 2989, 1615, 1579, 1529, 1494, 1338, 1264, 1164, 1023 and 745 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 6.09 (2H, br s, NH_2), 6.66-6.72 (1H, m, CH), 6.81 (1H, dd, *J*, 0.9, 8.3, Ar-H), 7.31-7.38 (1H, m, Ar-H) and 8.10 (1H, dd, *J* 1.4, 8.6, Ar-H).

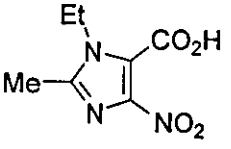
(2-Nitro-phenyl)-phosphoramidic acid diethyl ester (277)



Viscous yellow liquid, yield 66 %; (Found : m/z, 274.0739, $C_{10}H_{15}N_2O_5P$ requires: M, 274.0736); ν_{max} (nujol) 3483, 3356, 2923, 2986, 1619, 1570, 1500, 1426, 1343, 1245, 1156, 1097 and 740 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.38 (6H, t, *J* 8, CH_3), 4.15-4.25 (4H, m, CH_2), 7.04 (1H, tt, *J* 1.6, 7.2, Ar-H), 7.55-7.64 (2H, m, Ar-H), 8.19-8.22 (1H, m, Ar-H) and 7.04 (1H, d, *J* 9.2, N-H); δ_C (100 MHz; $CDCl_3$) 16.3 (CH_3), 63.7 (CH_2), 119.7 (CH),

121.0 (CH), 126.1 (CH), 135.5 (C, d *J* 10, P-C), 135.9 (CH) and 137.9 (C, d *J* 4, P-C); δ_P (101.2 MHz; $CDCl_3$) 0.48.

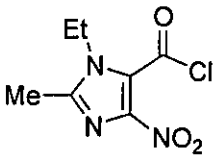
3-Ethyl-2-methyl-5-nitro-3*H*-imidazole-4-carboxylic acid (280)



1-Ethyl-2-methyl-4-nitro-1*H*-imidazol-5-yl cyanide (2.0 g, 12mmol) in concentrated sulphuric acid (22 g) was heated to 100 °C for 2 h. The reaction mixture was cooled in ice-water and sodium nitrite (0.91 g, 13.2 mmol) in water (10 cm^3) was added slowly. The reaction mixture was heated 100 °C for 4 h until effervescence ceased. The reaction contents were poured on to ice. The precipitated product was collected and washed with water and purified by dissolving in cold 5 % aqueous sodium carbonate solution, filtering from a trace of insoluble impurity and re-precipitating with dilute hydrochloric acid. This gave a white solid (1.9 g, 79 %).

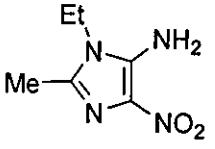
White solid, yield 79 %, m.p. 149-151 °C (lit.,[24] 139-141 °C); (Found : m/z, 199.0593, $C_7H_9N_3O_4$ requires: M, 199.0593); ν_{max} (nujol) 3423, 2726, 1736, 1654, 1527, 1345, 1231, 1181, 1130, 1061, 969 and 801 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.42 (3H, t, *J* 7.4, CH_3), 2.39 (3H, s, CH_3) and 3.94 (2H, q, *J* 7.2 CH_2); δ_C (100 MHz; $CDCl_3$) 13.2 (CH_3), 15.8 (CH_3), 42.5 (CH_2), 121.6 (Ar-C), 145.0 (Ar-C), 145.6 (Ar-C) and 159.6 (CO).

3-Ethyl-2-methyl-5-nitro-3*H*-imidazole-4-carbonyl chloride[25] (281)



Thionyl chloride (32.6g, 0.274 mol) was added to 3-ethyl-2-methyl-5-nitro-3*H*-imidazole-4-carboxylic acid (1.9g, 9.54 mmol) the reaction mixture was heated under reflux for 4 h. The solvent was removed *in vacuo* and the brown viscous liquid was used in the next step without purification or analysis.

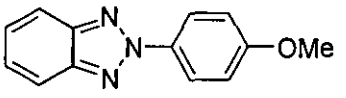
3-Ethyl-2-methyl-5-nitro-3*H*-imidazole-4-yl amine (282)



Sodium azide (0.682 g, 0.0105 mol) was added to 3-ethyl-2-methyl-5-nitro-3*H*-imidazole-4-carbonyl chloride (**281**), (2.076 g, 9.5 mmol) in acetone (30 cm^3) and water (5 cm^3). The reaction mixture was stirred at room temperature for 1 h during which time gas was evolved. The mixture was evaporated and the yellow solid residue was extracted with boiling acetone in a soxhlet apparatus for 24 h. Evaporation of the organic extract gave a yellow solid. Re-crystallisation from ethanol gave yellow spars (1.3 g, 82 %).

Yellow solid, yield 82%, m.p. 218-219 °C (lit.,[25] 214-215 °C); (Found : m/z, 170.0804, $C_6H_{10}N_4O_2$ requires: M, 170.0804); ν_{max} (nujol) 3425, 3227, 3161, 2854, 1654, 1576, 1654, 1378, 1258, 1221, 1160, 1032, 969 and 867 cm^{-1}; δ_H (400 MHz; CD_3SOCD_3) 1.17 (3H, t, *J* 7.2, CH_3), 2.23 (3H, s, CH_3), 3.88 (2H, q, *J* 7.2 CH_2) and 7.64 (2H, br s, N-H_2); δ_C (100 MHz; CD_3SOCD_3) 13.1 (CH_3), 14.1 (CH_3), 37.8 (CH_2), 127.2 (Ar-C), 139.5 (Ar-CH), and 144.3 (Ar-C).

2-[4-(Methoxy)phenyl)]-2*H*-1,2,3-benzotriazole (279)

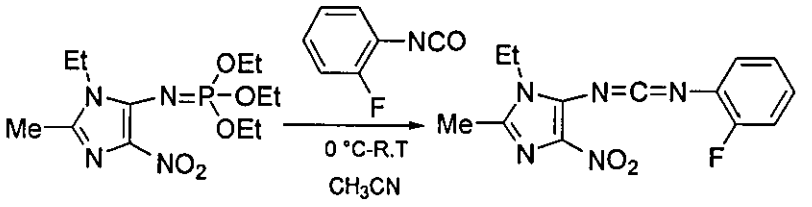


Neat 4-methoxyphenyl isocyanate (0.298g, 0.002 mol) was added dropwise at room temperature to a solution of the iminophosphorane **275** (0.604 g, 0.002 mol) in acetonitrile (5.0 cm^3). The resulting solution was stirred and heated at 60 °C for 6 h then cooled and evaporated under reduced pressure. The residue was triturated with diethyl ether to afford the 4-methoxyphenyltriazole as an insoluble solid which was collected by suction filtration, dried and recrystallised from dichloromethane and light petroleum ether to give a white solid (0.332 g, 55 %).

The method above was repeated using iminophosphorane **278** (0.796 g, 0.002 mol) the brown viscous oil was purified by flash column chromatography eluting with 4:1 light petroleum ether and ethyl acetate to afford a white solid (0.405g, 67 %).

White solid, m.p. 110-112 °C (lit.,[27] 111-113 °C); (Found : m/z, 225.0902, $C_{13}H_{11}N_3O$ requires; M, 225.0902); ν_{max} 2978, 1601, 1566, 1512, 1250, 1024, 966, 828 and 735 cm^{-1}; δ_H (250 MHz; $CDCl_3$ 3.86 (3H, s, CH_3), 7.02 (2H, d, *J* 8.8, Ar-CH), 7.37-7.41 (2H, m, Ar-CH), 7.89-7.93 (2H, m, Ar-CH) and 8.26 (2H, d, *J* 9, Ar-CH); δ_C (100 MHz; $CDCl_3$) 55.6 CH_3), 114.5 (Ar-CH), 118.2 (Ar-CH), 122.0 (Ar-CH), 126.8 (Ar-CH), 133.9 (Ar-C), 144.9 (Ar-C) and 160.2 (Ar-C).

Attempted preparation of carbodiimide 287 at 0 °C



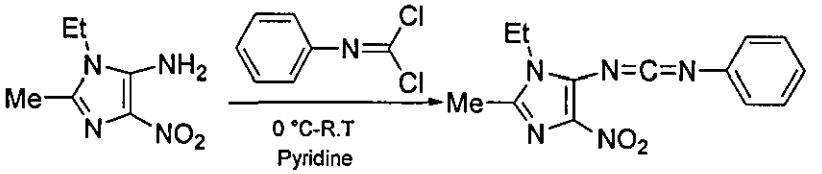
258b **287**

A solution of the triethyl *N*-(1-ethyl-2-methyl-4-nitro-1*H*-imidazol-5-yl)phosphoramidate (0.5 g, 0.0015 mol) in anhydrous acetonitrile (5.0 cm^3) was stirred and treated dropwise at 0 °C with the 2-fluorophenyl isocyanate (0.0015 mol) in acetonitrile (2.0 cm^3) under nitrogen. The resulting solution was stirred at 0 °C and the reaction was monitored by infra-red spectroscopy at regular timed intervals as shown in **Table 5.2 (Appendix 8** showing a selection of I.R spectras). After 1.5 hours the solvent was removed *in vacuo* after showing starting materials were consumed. An attempt was made to isolate the carbodiimde formed in the reaction. The residue was separated and purified by flash column chromatography eluting with 8:1 light petroleum ether and ethyl acetate to give two coloured products. One a yellow liquid (0.046 g) which solidified partially and having characteristic functional group stretches at 2151 and 2118 cm^{-1} in dichloromethane. The ^1H NMR spectrum showed unidentifiable signals. Further purification by preparative TLC eluting with 4:1 light petroleum ether and ethyl acetate showed no characteristic functional group stretches except at 3300 and 1734 cm^{-1} in dichloromethane. Mass spectrometry measurements showed an m/z value of 306. The other product, a blue liquid (0.071 g) had a characteristic functional group signals at 3418 and 1732 cm^{-1} in dichloromethane. Mass spectrometry measurements showed a m/z value of 290. The two products could not be identified.

Time of Reaction	I.R characteristic peaks (cm^{-1})	Inference
5 min	2271, 2245 strong bands and 2157, 2120 weak bands.	Isocyanate groups present in high concentration and carbodiimide beginning to form.
1 h	2271, 2245 strong bands and 2153, 2120 strong bands.	Concentration of isocyanate falling. Concentration of carbodiimide rising.
1.5 h	2153, 2120 strong bands.	Carbodiimide group present in high concentrations.

Table 5.2

Attempted preparation of carbodiimide (284) using phenyl carboimidoyl dichloride at 0 °C



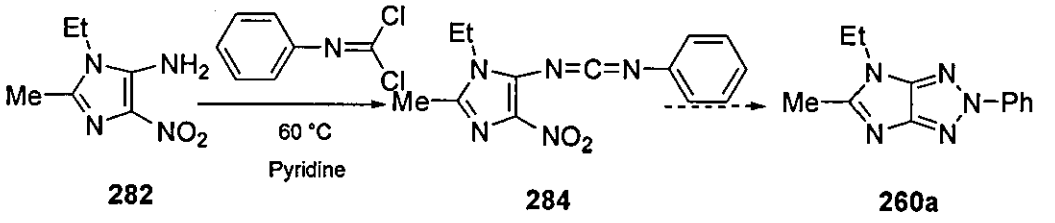
282 **284**

A solution of the amino imidazole (0.166 g, 0.001 mol) in anhydrous pyridine (3.0 cm^3) was stirred and treated dropwise at 0 °C with the phenyl carboimidoyl dichloride (0.174g, 0.001 mol) in pyridine (2.0 cm^3) under nitrogen. The resulting solution was stirred at 0 °C and the reaction was monitored by infra-red spectroscopic measurement at regular timed intervals as shown in **Table 5.3**. After 26 hours the solvent was removed *in vacuo* after showing starting materials were consumed. The residue was separated and purified by flash column chromatography eluting with 4:1 light petroleum ether and ethyl acetate to try and isolate the carbodiimide. This gave only unidentifiable products.

Time of Reaction	**I.R characteristic peaks (cm^{-1})**	**Inferences**
3 h	2271, 2245 strong bands and 2134, 2107 weak bands.	Isocyanate groups present in high concentration and carbodiimide beginning to form.
15 h	2271, 2245 strong bands and 2135, 2107 strong bands.	Isocyanate groups and carbodiimide groups in near equal concentration.
18 h	2231 strong bands and 2135, 2107 strong bands.	Isocyanate groups and carbodiimide groups in high concentration.
26 h	2231 weak bands and 2135, 2107 strong bands.	Isocyanate groups and carbodiimide groups in high concentration.

Table 5.3

Reaction of amino-nitroimidazole 282 with phenyl carboimidoyl dichloride at 60 °C

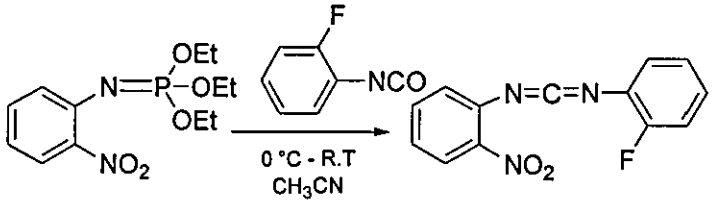


A solution of the amino imidazole (0.166 g, 0.001 mol) in anhydrous pyridine (3.0 cm^3) was stirred and treated dropwise at 60 °C with the phenyl carboimidoyl dichloride (0.174 g, 0.001 mol) in pyridine (2.0 cm^3) under nitrogen. The resulting solution was stirred at 60 °C and the reaction was monitored by infra-red spectroscopy at regular timed intervals as shown in **Table 5.4**. After 15 hours of infra-red measurements, the solvent was removed *in vacuo* after showing starting materials were consumed. The residue was separated and purified by flash column chromatography eluting with 4:1 light petroleum ether and ethyl acetate in an attempt to isolate the imidazo triazole **260a**. However this was unsuccessful as it gave unidentified products.

Time of Reaction	I.R characteristic peaks (cm^{-1})	Inferences
0.5 h	2132, 2108 strong bands.	Carbodiimide present.
1.5 h	2135, 2108 strong bands.	Carbodiimide present in high concentrations.
2 h	2135, 2108 weak bands.	Carbodiimide present in low concentrations.
12 h	2135, 2108 very weak bands.	Carbodiimide present in low concentrations.

Table 5.4

Attempted preparation of carbodiimide (290) at 0 °C



278 **290**

A solution of the 2-nitrophenyl phosphoramidate, **278** (0.334 g, 0.001 mol) in anhydrous acetonitrile (3.0 cm^3) was stirred and treated dropwise at 0 °C with the phenyl isocyanate (0.001 mol) in acetonitrile (2.0 cm^3) under nitrogen. The resulting solution was stirred at 0 °C and the reaction was monitored by infra-red spectroscopy at regular timed intervals as shown in **Table 5.5**. After retrieving sufficient infra-red spectra, the reaction was allowed to warm to room temperature and the solvent was removed *in vacuo*, after TLC showed

starting materials to be consumed. The residue was separated and purified by flash column chromatography eluting with 4:1 light petroleum ether and ethyl acetate in an attempt to isolate the carbodiimide. This afforded two unidentifiable yellow liquids; 0.042 g and 0.028 g.

Time of Reaction	I.R characteristic peaks (cm^{-1})	Inferences
0.5 h	2270, 2244 strong bands and 2122 doublet strong bands.	Isocyanate and carbodiimide present in high concentrations.
1.5 h	2122 doublet strong bands.	Carbodiimide groups present in high concentrations.
7 h	2121 strong bands.	Carbodiimide groups present in high concentrations.
24 h	2123 very strong bands.	Carbodiimide groups present in high concentrations.
25 h	2123 very strong bands.	Carbodiimide groups present in very high concentrations.

Table 5.5

5.5 References

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Chapter 6

Synthesis and Mechanistic Studies of 2-Aryl-2*H*- indazole Derivatives

6.1 Introduction

The indazoles[1] are a group of pharmaceutically important compounds that are constituents of broad range of pharmacologically active drugs. They include anti-inflammatory, anti-tumour,[2] anti-HIV,[3] antidepressant and contraceptive substances. Examples include granisetron,[4] **Figure 6.1** a 5-HT_3 receptor antagonist used as an anti-emetic in cancer chemotherapy and benzydamine[5] an anti-inflammatory agent.

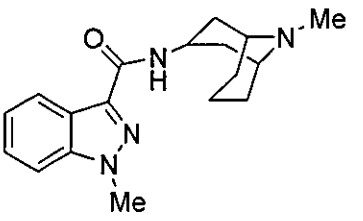
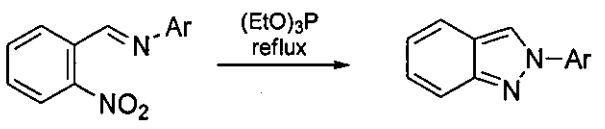


Figure 6.1

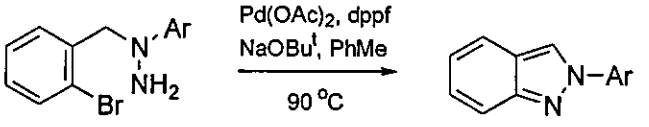
Indazoles can be synthesised by a number of methods, usually involving construction of the *N*(1)-*N*(2) bond as the key step. Examples in preparing N-substituted indazoles include; treating *o*-nitrobenzylamines with Sn, Zn, or Fe in acidic conditions[6] or $PdCl_2(PPh_3)_2/SnCl_2/CO(g)$.[7] One electrochemical procedure[8] involved the reduction of *o*-nitrobenzylamines and subsequent cyclisation to 2-substituted indazoles were achieved. One of the now classical methods[9] for the synthesis of indazole derivatives **292** in very good yields is the deoxygenation of 2-nitroanils **291** with triethyl phosphite developed by Cadogan and Mackie shown in **Scheme 127**.



291 **292**

Scheme 127

More recently Song and Yee[10] have described the use of a palladium catalysed intramolecular amination cyclisation of bromobenzyl aryl hydrazines **293**, **Scheme 128** to prepare several indazole derivatives **292** in good yields, in this case it represents the first general method in creating a *C*(1)-*N*(7a) bond as the key ring closing step followed by oxidation.

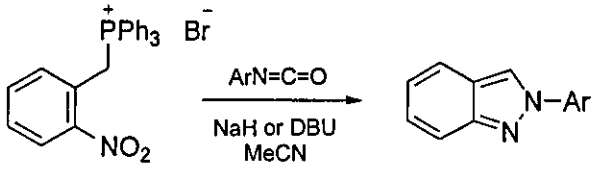


293 **292**

Scheme 128

6.2.1 Base catalysed synthesis of Indazole derivatives

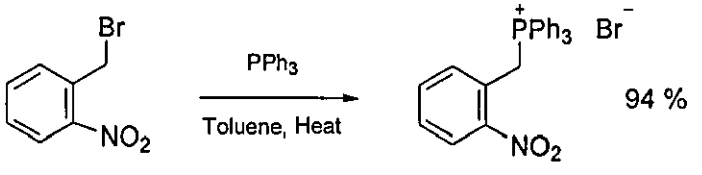
Our research is focussed on developing new hetero aromatic cyclisation reactions. We have been investigating reactions in which the nitrogen atom of a nitro substituent on an aromatic or heteroaromatic ring undergoes transformation into a new nitrogen containing heterocyclic ring. We have discovered that 2-nitrobenzyl triphenylphosphonium bromide[11] **294** reacts readily with aryl isocyanates in the presence of a base, such as sodium hydride or DBU, to form 2-aryl-2*H*-indazoles **292** in moderate to good yield; the nitro group nitrogen being transformed into the indazole *N*-1 atom, **Scheme 129**.



294 **292**

Scheme 129

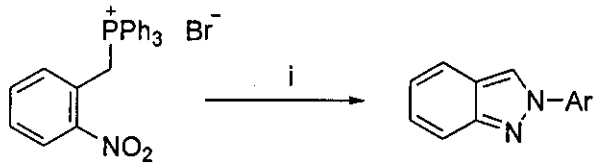
Our novel route to the syntheses of indazole derivatives employs a nitro compound with readily available nitrobenzyl triphenylphosphonium bromide **294** acting as the starting material. This is easily prepared by heating triphenylphosphine with *ortho*-nitro benzyl bromide **295** in toluene, in which the crystalline product is prepared in almost quantitative yield, **Scheme 130**.



295 **294**

Scheme 130

The salt, **294** can be deprotoned to form the purple ylide with a range of bases. We have used NaH and DBU and deduced DBU to be the better base to use in this reaction. The ylide of **294** can be treated with an aryl isocyanate, and we have found that heating the mixture at 60 °C or under reflux in acetonitrile affords the 2-aryl indazoles **292a-e** shown in **Scheme 131** and **Table 6.1**. The yields of the indazole derivatives range from 40 % to 62 %. The reaction works well for aryl isocyanates with either electron withdrawing, or electron donating substituents. Sodium hydride can also be used as the base, although in this case the indazoles were accompanied by small amounts of 2-nitrotoluene as a by-product. This may be created by the presence of sodium hydroxide traces in the hydride reagent which attack the phosphonium cation forming a penta-coordinate phosphorane. This can then sever to form triphenylphosphine oxide, and the nitrotoluene anion, which is later protonated during work-up.



294 **292a-g**

Reagents and conditions: i, DBU, Ar-N=C=O, CH_3CN, 60 °C or reflux.

Scheme 131

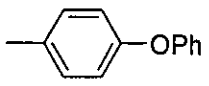
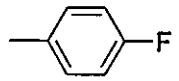
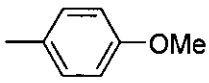
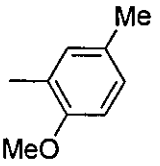
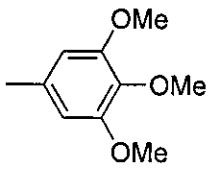
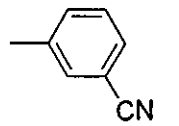
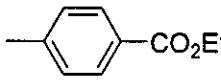
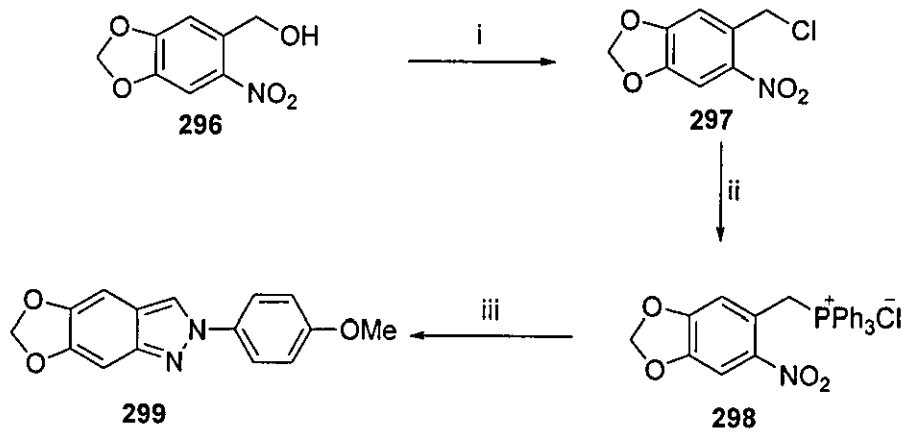
292	Ar	Yield/%	292	Ar	Yield/%
a		45	e		55[14,16]
b		57[9]	f		40
c		62	g		53[14]
d		60[15]			

Table 6.1, Indazoles 292a-g synthesised.

We have further extended these reactions by preparing substituted nitrobenzyl triphenylphosphonium chloride compounds. 6-Nitropiperonyl alcohol **296** was reacted with excess thionyl chloride to give 6-nitropiperonyl chloride in good yield. Heating the chloride compound **297** with triphenylphosphine gave a modest yield of the 6-nitropiperonylphosphonium chloride compound **298**. This may be due to the chlorine atom not being as a good leaving group as the bromine atom in the nitrobenzyl bromide. Compound **298** was then treated with DBU to give a purple ylide and the appropriate aryl isocyanate was administered to afford the piperonyl aryl indazole **299** in modest yield, **Scheme 132.**

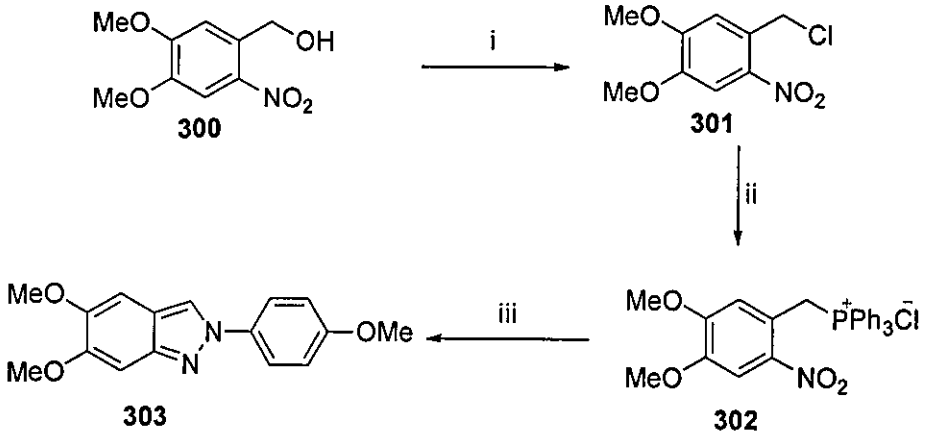


Reagents and conditions: i, $SOCl_2$, Reflux, 68 %; ii, PPh_3, Toluene Reflux, 54 %; iii, DBU, 4-MeO-Ph-NCO, CH_3CN, Reflux; 43 %.

Scheme 132

Another example to demonstrate the utility of this base catalysed indazole synthesis was using 6-nitroveratryl alcohol **300** which was treated with thionyl chloride to give 6-nitroveratryl chloride **301** in good yield. The phosphonium chloride salt **302** was prepared in modest yield by reaction with triphenylphosphine. Subsequent reaction with DBU gave the purple ylide and addition of the aryl isocyanate gave the substituted aryl indazole **303** in modest yield, **Scheme 133.** These further examples show that more substituted indazoles can be prepared in modest yield. Substitution on the indazole ring with groups such as dimethoxy and piperonyl groups, is found in many biological active natural

products and biologically active drugs. The indazole compounds **299** and **303** may be evaluated as potentially biological active substances.



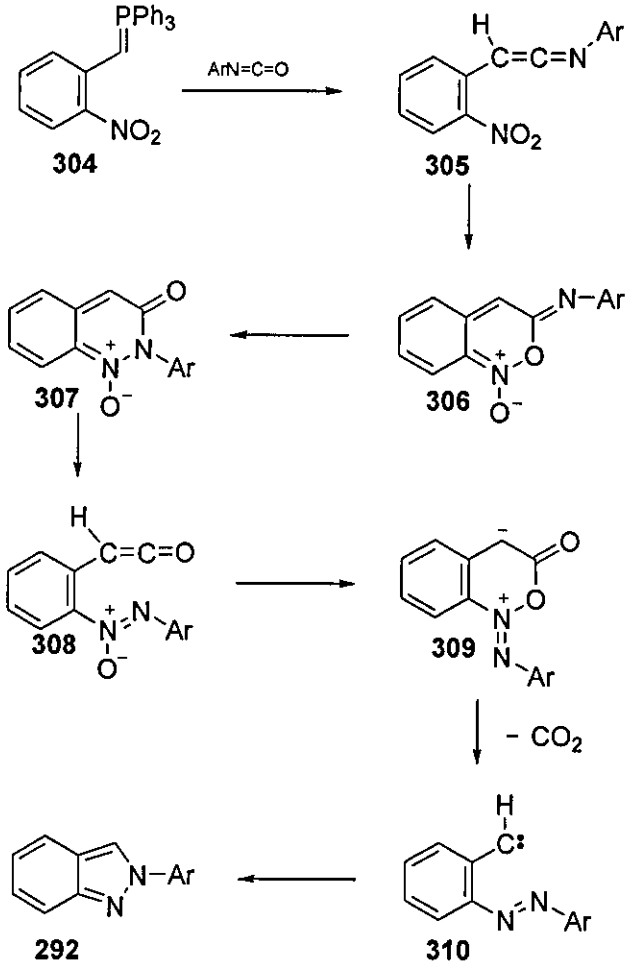
Reagents and conditions: i, $SOCl_2$, Reflux, 75 %; ii, PPh_3, Toluene, Reflux, 56 %; iii, DBU, 4-MeO-Ph-NCO, CH_3CN, Reflux; 38 %.

Scheme 133

6.2.2 Proposed mechanism for the base catalysed indazole synthesis

The reaction to form the indazole ring involves the formal loss of triphenylphosphine oxide and carbon dioxide, and several mechanisms can be envisaged to transform the nitro compound into the indazole nucleus. We have considered two possible reaction pathways as the most likely that could lead to closure of the pyrazole ring. The first and most likely parallels that described in Chapter 5 for the formation of imidazo fused triazole derivatives. This involves a Wittig reaction between the phosphonium ylide **304** and the aryl isocyanate to form a ketimine such as **305, Scheme 134.** This could undergo and intramolecular nucleophilic attack by an oxygen atom of the adjacent nitro group leading to intermediate **306.** Ring opening and reclosure through the aryl substituted nitrogen would generate the cinnoline-*N*-oxide **307.** A second ring opening would yield the ketene **308,** which may be intramolecularly nucleophilic attacked by the oxygen atom of the neighbouring azoxy group to form intermediate **309.** Loss of carbon dioxide would then generate the azo-carbene intermediate **310** which would readily undergo electrocyclic ring closure to produce the 2-indazole. This mechanism is closely related to that postulated by Rees[12] to

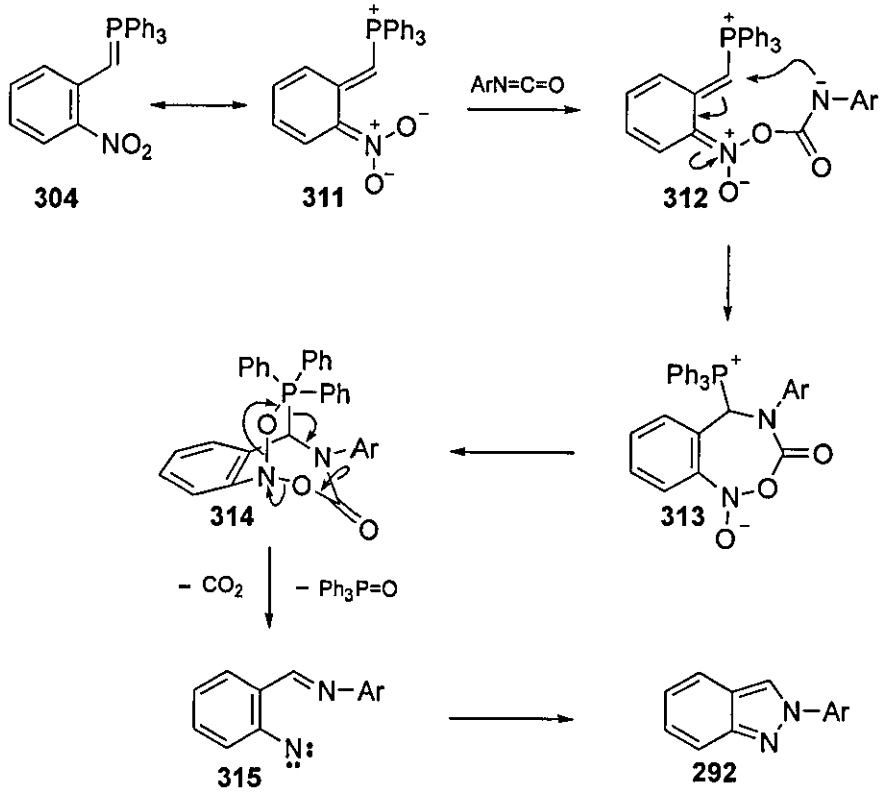
rationalise for the creation of phenyl benzotriazole in the thermolysis of 2-nitrophenyl carbodiimide, Chapter 5; **Scheme 105.**



Scheme 134

Alternatively a mechanism involving the acylation of a nitro group oxygen atom may proceed to form an acyl nitronate intermediate of the type **13, Scheme 135.** Aliphatic nitro compounds are known to undergo acylation by isocyanates in the dehydration reaction to form nitrile oxides.[13] There are no reports on the acylation of aromatic nitro compounds, and aryl isocyanates are inert to nitrobenzene and 2- nitrotoluene up to 150 °C. It is possible that the aryl nitro substituent is more nucleophilic due to delocalisation of the negative charge from the ylide carbon as shown by resonance structure **311.** Delocalisation evidence is supported by the intense purple colour of the ylide in the reaction mixture. The acyl nitronate could then be converted into the indazole as shown in **Scheme 135.** Cyclisation of the carbamate nitrogen onto the methine carbon would then

produce the seven membered ring intermediate **313**. Triphenylphosphine oxide and carbon dioxide could be simultaneously lost from the bridged structure **314**, loss of these two compounds may also be separate events to generate the nitrene imine intermediate **315**, which would rapidly undergo electrocyclic ring closure to produce the indazole ring.



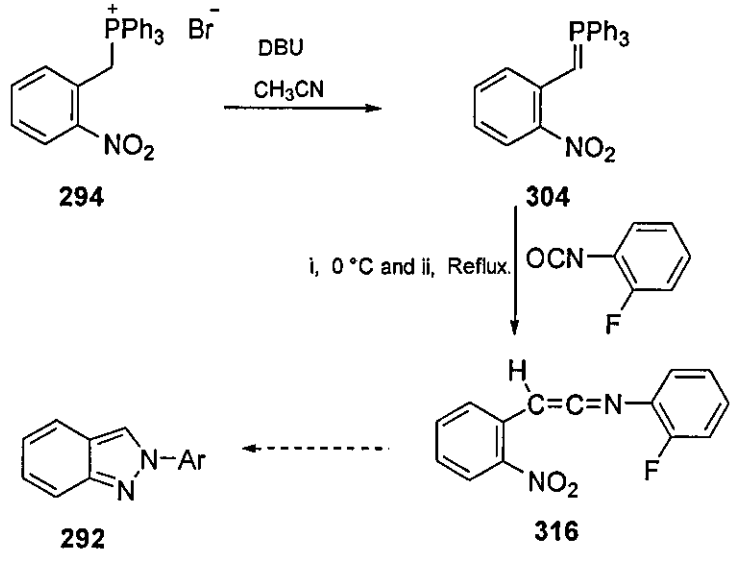
Scheme 135

6.2.3 Mechanistic studies on indazole synthesis

Some experimental evidence has been obtained to support the first of these two proposed pathways by use of infra-red spectroscopy to determine the changes of the functional groups during the course of the reactions both at 0 °C to room temperature, and under reflux.

The first mechanistic experiment involved the reaction of the phosphonium bromide salt **294** with DBU at 0 °C. After 5 minutes of adding DBU, the I.R spectrum of an aliquot of the reaction mixture showed signals consistent with the purple ylide **304**. After a total of

10 minutes at 0 °C after administering 2-fluorophenyl isocyanate the I.R spectrum was again recorded. A doublet signal of low intensity centered at 2255 cm^{-1} was seen correlating to the isocyanate functional group, and also a very weak doublet signal centered at 2134 cm^{-1} indicative of the ketimine intermediate **316, Scheme 136** (see also **Appendix 8** for selected I. R spectras). After 30 minutes this signal was more intense relative to the isocyanate band. The reaction mixture was allowed to warm to room temperature. After a series of recording further infra-spectrums the reaction was continued. An attempt to isolate the intermediate ketimine proved unsuccessful as the only products separated decomposed and were unidentifiable.



Scheme 136

A second mechanistic experiment was carried out under reflux conditions. After 5 minutes of addition of DBU at room temperature, the I.R spectra showed no unexpected peaks. The reaction was heated to reflux and after 10 minutes, 2-fluorophenyl isocyanate was administered and intense peaks were recorded. No peaks indicative of the isocyanate group were seen, however an intense doublet peak centred at 2134 cm^{-1}corresponding to ketimine intermediate **316** was seen. After 24 hours further measurement showed the doublet peak at 2134 cm^{-1} to have increased in intensity. The reaction was allowed to cool to room temperature, but no attempt was made to isolate the intermediates in the reaction. These results support the first mechanism proposed involving the ketimine formed by a Wittig reaction with the isocyanate.

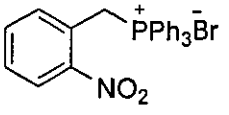
6.3 Conclusion

The base catalysed reaction of triphenylphosphonium salts with aryl isocyanates represents a convenient way to synthesise indazole derivatives in modest to good yield substituted at the 2-position with a variety of aromatic groups. The reaction was further extended by preparing phenyl substituted triphenylphosphonium salts, which proved successful in preparing more highly substituted indazole derivatives. The mechanism of the reaction sequence is thought to involve a Wittig reaction generating a ketimine intermediate which further proceeds by electrocyclic ring closing and ring opening reactions involving the *ortho*-nitro substituent ultimately generating the indazole.

6.4 Experimental

For general experimental procedures see Chapter 1, section 1.8.1.

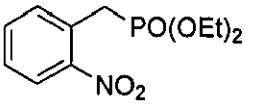
[(2-Nitrophenyl)methyl](triphenyl)phosphonium bromide (294)



Triphenylphosphine (4.86 g, 0.0185 mol) was added to a stirred solution of 2-nitrobenzyl bromide (4.00 g, 0.0185 mol) in toluene (20 cm^3). The reaction was heated to 100 °C. After 3 h the reaction mixture was cooled to room temperature and the solid was filtered under vacuum and washed with light petroleum ether (3 x 15 cm^3) and diethyl ether (3 x 15 cm^3). This afforded a white solid (8.35 g).

White powder, yield 94 %, m.p. 239-240 °C (lit.,[11] 233-235 °C); (Found: m/z, 398.1310 (M-Br), $C_{25}H_{21}NO_2P$ requires: M, 398.1310; ν_{max} 3007, 2861, 1608, 1587, 1576, 1525, 1438 and 1341 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 5.98 (2H, d, *J* 15, CH_2), 7.54-7.69 (15H, m, Ar-H), 7.79-7.83 (2H, m, Ar-H) and 7.92-7.95 (2H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 28.9 (d, *J* 49, CH_2), 117.4 (d, *J* 86, CH), 124.7 (d, *J* 9, C), 126.1 (d, *J* 2, C), 130.5 (d, *J* 4, CH), 130.7 (d, *J* 12, CH), 134.5 (d, *J* 10, CH), 135.2 (d, *J* 5, CH), 135.2 (d, *J* 3, CH), 135.7 (d, *J* 3, CH), and 148.6 (d, *J* 5, C).

Diethyl[(2-nitrophenyl)methyl]phosphonate[11] (317)



Triethyl phosphite (0.646 g, 3.88mmol) was added to a stirred solution of 2-nitrobenzyl bromide (0.84 g, 3.88 mmol) in dry acetonitrile (5 cm^3). The reaction was heated under reflux. After 18 h the reaction mixture was cooled to room temperature and the solvent removed *in vacuo* to give a viscous brown oil. Purification by flash column chromatography elution by petroleum ether then light petroleum ether/ethyl acetate (2:1) and dichloromethane/ethyl acetate (1:1) gave an orange oil (0.961 g, 91 %).

Orange oil, yield 91 %; (Found : m/z, 274.0841, $C_{11}H_{16}NO_5P$ requires: M, 274.0844; ν_{max} 2985, 1610, 1578, 1528, 1354, 1265, 1295 and 1025 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.23 (6H, t, *J* 7.2, CH_3), 3.70 (2H, d, *J* 23, CH_2), 4.03 (4H, p, *J* 7.2, OCH_2), 7.3-7.6 (3H, m, Ar-H) and 7.95 (1H, d, *J* 8.4, Ar-H); δ_C (100 MHz; $CDCl_3$) 16.6 (p, CH_3), 30.8 (d, *J* 137, CH_2), 62.7 (d, *J* 7, CH_2), 125.5 (d, *J* 3, CH), 127.7 (d, *J* 9, C), 128.4 (d, *J* 4, CH), 133.3 (d, *J* 3, CH), 133.5 (d, *J* 5, CH) and 149.8 (d, *J* 7, C).

General procedure for synthesis of 2-aryl-2*H*-indazoles

Using DBU as base

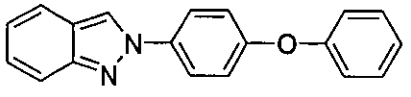
The aryl isocyanate (2 mmol) was added dropwise to a stirred bright purple solution of the aryl phosphonium ylide generated from the phosphonium bromide salt (0.957 g, 2 mmol) and DBU (0.335 g, 2.2 mmol) in dry acetonitrile (5 cm^3) under nitrogen at room temperature.

After 5 min the reaction was refluxed under nitrogen. The reaction mixture turned from purple to a brown colour. After 24 h the reaction mixture was cooled to room temperature and the solvent removed to yield a brown/black product. Purification by flash column chromatography, eluting with petroleum ether then light petroleum ether/ethyl acetate (20:1) gave the following products.

Using NaH as a base

The aryl isocyanate (2 mmol) in dry acetonitrile (5 cm^3) was added dropwise to a stirred bright purple solution of the aryl phosphonium ylide generated from the phosphonium bromide salt (0.957 g, 2 mmol) and NaH washed free of oil (0.053 g, 2.2 mmol) in dry acetonitrile under nitrogen at room temperature. After 5 min the reaction was refluxed under nitrogen. The reaction mixture turned from a bright purple colour to brown mixture. After 24 h the reaction mixture and the solvent removed to yield a brown/black product. Purification by flash column chromatography, eluting with petroleum ether then light petroleum ether/ethyl acetate (10:1) gave the following products.

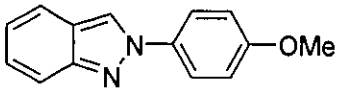
2-[4-(Phenoxy)phenyl]-2*H*-indazole (292a)



Cream coloured powder, yield 45 %, m.p. 94.5-95.5 °C; (Found: C, 77.19; H, 4.75; N, 9.57 %; m/z, 286.1105, $C_{19}H_{14}N_2O$ requires: C, 79.7; H, 4.93; N, 9.78 %; M, 286.1106); ν_{max} 1589, 1519, 1266, 1107 and 1046 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.04-7.11 (4H, m, Ar-H), 7.13 (2H, d, *J* 4.4, Ar-H), 7.30-7.39 (3H, m, Ar-H), 7.65 (H, d, *J* 8.4, Ar-H), 7.77 (H, d, *J* 8.8, Ar-H), 7.83 (2H, d, *J* 9.2, Ar-H) and 8.32 (H, d, *J* 0.8, Ar-H); δ_C (100 MHz; $CDCl_3$) 118.3 (CH), 119.6 (CH), 119.8 (CH), 120.7 (CH), 120.8 (CH), 122.8 (CH), 122.9 (CH),

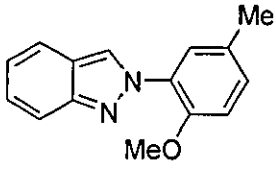
123.2 (C), 124.3 (CH), 127.2 (CH), 130.4 (CH), 136.4 (C), 150.1 (C), 157.1 (C) and 157.5 (C).

2-[4-(Methoxy)phenyl]-2*H*-indazole (292b)



White powder, yield 57 %, m.p. 130-131 °C (lit.,[9] 130-131 °C); (Found: m/z, 224.0946, $C_{14}H_{12}N_2O$ requires: M, 224.0950); ν_{max} 2958, 2836, 1626, 1609, 1248, 1108 and 1129 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.84 (3H, s, OCH_3), 7.00 (2H, d, *J* 4.8 Ar-H), 7.09 (H, t, *J* 7.2, Ar-H), 7.30 (1H, t, *J* 6.4, Ar-H), 7.67 (1H, d, *J* 8.4, Ar-H), 7.77 (2H, d, *J* 6.4 Ar-H) and 8.28 (1H, s, Ar-H); δ_C (100 MHz; $CDCl_3$) 55.9 (OCH_3), 115.0 (CH), 118.1 (CH), 120.6 (CH), 120.7 (CH), 122.6 (CH), 122.8 (CH), 123.1 (C), 126.9 (CH), 134.5 (C), 149.9 (C) and 159.7 (C).

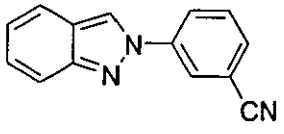
2-(2*H*-Indazol-2-yl)-4-methylphenylmethyl ether (292f)



Yellow oil, yield 40 %; (Found: m/z, 238.1104, $C_{15}H_{14}N_2O$ requires: M, 238.1106); ν_{max} 2850, 1616, 1521, 1284, 1250, 1140 and 1024 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 2.37 (3H, s, CH_3), 3.85 (3H, s, OCH_3), 6.98 (1H, d, *J* 8.3 Ar-H), 7.06-7.21 (2H, m, Ar-H), 7.27-7.34 (1H, m, Ar-H), 7.69-7.72 (2H, m, Ar-H), 7.76-7.81 (1H, m, Ar-H) and 8.51 (1H, d, *J* 0.92,

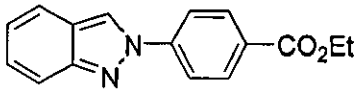
Ar-H); δ_C (62.9 MHz; $CDCl_3$) 20.7 (CH_3), 56.4 (OCH_3), 112.7 (CH), 118.0 (CH), 119.0 (C), 120.8 (CH), 122.1 (CH), 122.3 (C), 125.8 (CH), 126.8 (CH), 127.2 (CH) 129.8 (CH), 131.2 (C), 149.0 (C) and 149.9 (C).

3-(2*H*-Indazol-2-yl)phenyl cyanide (292g)



White powder, yield 53 %, m.p. 114-115 °C (lit.,[14] 110-112 °C); (Found: C, 76.23; H, 4.09; N, 19.18 %; m/z, 219.0800, $C_{14}H_9N_3$ requires: C, 76.7; H, 4.14; N, 19.17 %; M, 219.0797); ν_{max} 2231, 1630, 1585 and 1521 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.09-7.15 (1H, m, Ar-H), 7.29-7.36 (1H, m, Ar-H), 7.66-7.76 (4H, m, Ar-H), 8.10-8.14 (H, m, Ar-H), 8.22-8.23 (H, m, Ar-H) and 8.38 (1H, s, Ar-H); δ_C (62.9 MHz; $CDCl_3$) 114.1 (CN), 118.0 (C), 118.3 (CH), 120.5 (CH), 120.8 (CH), 123.3 (C), 123.4 (CH), 124.7 (CH), 124.8 (CH), 127.9 (CH), 130.8 (CH), 131.2 (CH), 141.2 (C) and 150.4 (C).

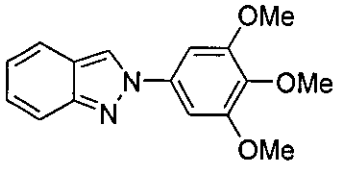
Ethyl-4-(2*H*-indazol-2-yl)-benzene-1-carboxylate (292d)



White crystals, yield 60 %, m.p. 132-133 °C (lit.,[15] 126-127 °C); (Found: m/z, 266.1057, $C_{16}H_{14}N_2O_2$ requires M, 266.1055); ν_{max} 2979, 1709, 1608, 1630, 1279 and 1105 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.41 (3H, t, *J* 7, CH_3), 4.40 (2H, q, *J* 7, CH_2), 7.07-7.13 (1H, m, Ar-H), 7.29-7.32 (1H, m, Ar-H), 7.65-7.66 (2H, m, Ar-H), 7.75-7.79 (2H, m, Ar-H), 7.96-8.00

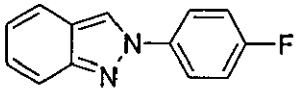
(2H, m, Ar-H), 8.16-8.20 (2H, m, Ar-H) and 8.44 (1H, d, *J* 0.9, Ar-H); δ_C (100 MHz; $CDCl_3$) 14.3 (CH_3), 61.2 (CH_2), 118.1 (CH), 120.2 (CH), 120.5 (CH), 122.9 (CH), 123.0 (CH), 127.4 (CH), 129.6 (C), 131.1 (CH), 133.5 (C), 143.5 (C), 150.1 (C) and 165.7 (CO).

2-[3,4,5-Tri-(methoxy)phenyl]-2*H*-indazole (292c)



Yellow/brown oil, yield 62 %; (Found: m/z, 284.1161, $C_{16}H_{16}N_2O_3$ requires M, 284.1161); ν_{max} 2850, 1629, 1603, 1520 and 1507 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.89 (3H, s, OCH_3), 3.95 (6H, s, OCH_3), 7.10-7.12 (3H, m, Ar-H), 7.29-7.32 (1H, m, Ar-H), 7.67-7.70 (1H, m, Ar-H), 7.76-7.78 (1H, m, Ar-H) and 8.36 (1H, d, *J* 0.8, Ar-H); δ_C (100 MHz; $CDCl_3$) 56.8 (OCH_3), 61.4 (OCH_3), 99.4 (CH), 118.1 (CH), 120.7 (CH), 121.1 (CH), 122.8 (CH), 123.0 (C), 127.3 (CH), 136.9 (C), 138.3 (C), 150.0 (C) and 154.2 (C).

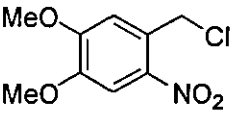
2-(4-Fluorophenyl)-2*H*-indazole (292f)



White crystals, yield 55 %, m.p. 108-109 °C (from dichloromethane/light petroleum b.p. 40-60 °C), (lit.,[14,16] 110-112 °C), (Found: C, 72.54; H, 4.22; N, 12.93 %; m/z, 212.0750, $C_{13}H_9FN_2$ requires: C, 73.57; H, 4.27; N, 13.2 %; M, 212.0750); ν_{max} 3009, 1638, 1629, 1523, 1509, 1098, 779 and 752 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.08-7.28 (3H, m, ArH), 7.29-

7.36 (1H, m, ArH), 7.67-7.71 (1H, m, ArH), 7.76-7.87 (3H, m, ArH) and 8.31 (1H, d, *J* 0.8, ArH); δ_C (62.9 MHz; $CDCl_3$) 116.9 (d, $^2J_{CF}$ 23, ArC-3), 118.2 (Ar-CH) 120.8 (d, $^3J_{CF}$ 7.8, ArC-2), 122.6 (d, $^4J_{CF}$ 3.9, ArC-1), 122.7 (Ar-CH), 124.7 (Ar-C), 126.8 (Ar-CH), 133.5 (Ar-C), 136.9 (Ar-C), 149.7 (Ar-C) and 161.9 (d, $^1J_{CF}$ 247, ArC-4).

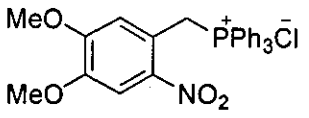
1-(Chloromethyl)-4,5-di(methoxy)-2-nitrobenzene (301)



Thionyl chloride (50 cm^3) was added to stirred 6-nitro veratryl alcohol (4.90 g, 23 mmol) at room temperature. After 5 min the reaction mixture was heated under reflux for 2 h. The excess thionyl chloride was removed *in vacuo*. The remaining crude product was dissolved in dichloromethane and washed with water (15 cm^3) and saturated sodium bicarbonate (3 x 15 cm^3). The aqueous phases were extracted with dichloromethane (3 x 30 cm^3). The organic fractions were combined and dried over $MgSO_4$. The solvent was filtered and removed *in vacuo* to afford a yellow powder (4.02 g).

Yellow powder, yield 75 %, m.p. 92-93 °C (lit.,[17] 89-90 °C); (Found: m/z, 231.0300, $C_9H_{10}ClNO_4$ requires M, 231.0298); ν_{max} 2926, 1617, 1508, 1363, 1270, 1111, 878 and 755 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.97 (3H, s, OCH_3), 4.01 (3H, s, OCH_3), 5.01 (2H, s, CH_2), 7.11 (1H, s, Ar-H) and 7.05 (1H, s, Ar-H); δ_C (100 MHz; $CDCl_3$) 43.6 (CH_2), 56.5 (OCH_3), 56.6 (OCH_3), 108.4 (CH), 112.8 (CH), 127.2 (C), 140.3 (C), 148.7 (C) and 153.4 (C).

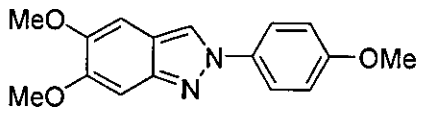
[4,5-Di(methoxy)-2-nitrophenyl]methyl(triphenyl)phosphonium chloride (302)



Triphenylphosphine (4.86 g, 0.0185 mol) was added to a stirred solution of 1-(chloromethyl)-4,5-di(methoxy)-2-nitrobenzene (4.00 g, 18.5 mmol) in toluene (20 cm^3). The reaction mixture was heated under reflux. After 3 h the reaction mixture was cooled to room temperature and the solid was filtered under vacuum and washed with light petroleum ether (3 x 15 cm^3) and diethyl ether (3 x 15 cm^3). This afforded a white solid (8.35 g).

White powder, yield 56 %, m.p. 225-226 °C; (Found: m/z, 459.1596, $C_{27}H_{25}NO_4P$ requires: M+H, 459.1599); ν_{max} 2939, 1612, 1579, 1524, 1439, 1327, 1278 and 1234 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.87 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 6.02 (2H, d, *J* 14.4, CH_2), 7.49 (1H, s, Ar-H) and 7.62-7.87 (16H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 28.5 (CH_2), 56.4 (OCH_3), 57.6 (OCH_3), 108.1 (d, *J* 2, CH), 117.3 (d, *J* 5, C), 117.9 (CH), 119.0 (d, *J* 9, C), 130.2 (d, *J* 13, CH), 134.4 (d, *J* 10, CH), 135.2 (d, *J* 3, CH), 140.7 (d, *J* 5, C), 148.9 (d, *J* 3, C) and 154.0 (d, *J* 3, C).

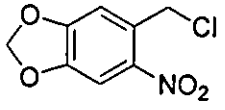
5,6-Di(methyloxy)-2-[4-(methyloxy)phenyl]-2*H*-indazole (303)



Colourless solid, yield 38 %, m.p. 143-145 °C; (Found: m/z, 284.1164, $C_{16}H_{16}N_2O_3$ requires: M, 284.1164); ν_{max} 2925, 2850, 1641, 1514 and 1228 cm^{-1}; δ_H (400 MHz;

$CDCl_3$) 3.86 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 6.79 (1H, s, Ar-H), 7.00 (1H, dd, *J* 2, 4.8, Ar-H), 7.05 (1H, s, Ar-H), 7.73 (1H, dd, *J* 2, 4.8, Ar-H) and 8.12 (H, d, *J* 0.8, Ar-H); δ_C (100 MHz; $CDCl_3$) 55.5 (OCH_3), 56.0 (OCH_3), 56.1 (OCH_3), 96.4 (CH), 97.4 (CH), 114.7 (C), 115.2 (CH), 119.2 (C), 119.9 (CH), 121.5 (CH), 122.5 (C), 138.9 (C), 146.6 (C) and 156.0 (C).

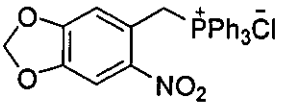
5-(Chloromethyl)-6-nitro-1, 3-benzodioxole (297)



Thionyl chloride (50 cm^3) was added to 6-nitropiperonyl alcohol (4.93 g, 25 mmol) at room temperature. After 5 min the reaction mixture was heated under reflux for 2 h. The excess thionyl chloride was removed *in vacuo*. The remaining crude product was dissolved in dichloromethane washed with water (15 cm^3) and saturated sodium bicarbonate (3 x 15 cm^3). The mixture was further extracted with dichloromethane (3 x 30 cm^3). The solvent extracts were combined and dried over $MgSO_4$. The solvent was filtered and removed *in vacuo* to afford a green powder (3.68 g).

Green powder, yield 68 %, m.p. 75-76 °C (lit.,[18] 78-80 °C); (Found: m/z, 214.9990, $C_8H_6ClNO_4$ requires M, 214.9985); ν_{max} 2938, 2848, 1612, 1524, 1329, 1278 and 873 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 4.91 (2H, s, CH_2), 6.14 (2H, s, OCH_2O), 7.08 (1H, s, Ar-H) and 7.56 (1H, s, Ar-H); δ_C (100 MHz; $CDCl_3$) 43.4 (CH_2), 101.3 (OCH_2O), 106.0 (CH), 110.3 (CH), 122.0 (C), 142.2 (C), 148.0 (C) and 152.1 (C).

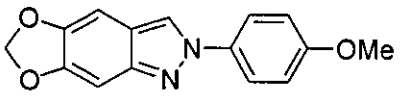
[(6-Nitro-1, 3-benzodioxol-5-yl)-methyl](triphenyl)phosphonium chloride (298)



Triphenylphosphine (4.86 g, 0.0185mol) was added to a stirred solution of 5-(chloromethyl)-6-nitro-1,3-benzodioxole (4.00 g, 18.5 mmol) in toluene (20 cm^3). The reaction mixture was heated under reflux. After 3 h the reaction mixture was cooled to room temperature and the solid was filtered under vacuum and washed with light petroleum ether (3 x 15 cm^3) and diethyl ether (3 x 15 cm^3). This afforded a white solid (8.35 g).

White powder, yield 54 %, m.p. 265-266 °C, (Found: m/z, 442.1201 (M-Cl), $C_{26}H_{21}NO_4P$ requires: M, 442.1208; ν_{max} 2912, 1618, 1508, 1438, 1324, 1267 and 1110 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 6.02 (2H, s, CH_2), 6.07 (2H, s, OCH_2O), 7.90-7.27 (1H, m, Ar-H), 7.34 (1H, s, Ar-H), 7.45 (1H, s, Ar-H) and 7.62-7.74 (14H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 28.9 (d, *J* 48, CH_2), 103.8 (OCH_2), 105.9 (d, *J*, 2, CH), 113.3 (d, *J* 5, CH), 117.4 (d, *J* 9, C), 121.6 (d, *J* 10, C), 130.3 (d, *J* 13, CH), 134.3 (d, *J* 10, CH), 135.3 (d, *J* 3, CH), 142.7 (d, *J* 6, C), 148.7 (d, *J* 3, C) and 152.9 (d, *J* 3, C).

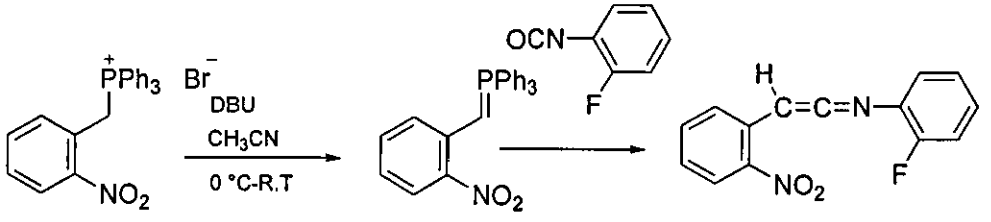
2-[4-(Methoxy)phenyl]-2*H*-[1,3]dioxolo[4,5-*f*]indazole (299)



Colourless crystals, yield 43 %, m.p. 213-214 °C; (Found: m/z, 268.0847, $C_{15}H_{12}N_2O_3$ requires: M, 268.0848); ν_{max} 2923, 2850, 1638, 1560, 1545 and 1109 cm^{-1}; δ_H (400 MHz;

$CDCl_3$) 3.86 (3H, s, OCH_3), 5.96 (2H, s, OCH_2O), 6.88 (1H, s, Ar-H), 7.00 (2H, dd, *J* 4.8, 2, Ar-H), 7.03 (1H, s, Ar-H), 7.71 (2H, dd, *J* 4.8, 2, Ar-H) and 8.09 (1H, d, *J* 0.8, Ar-H); δ_C (100 MHz; $CDCl_3$) 55.6 (OCH_3), 94.1 (CH), 94.8 (CH), 100.9 (OCH_2O), 114.6 (CH), 118.3 (C), 119.6 (CH), 121.6 (CH), 134.2 (C), 145.9 (C), 147.1 (C), 149.4 (C) and 158.7 (C).

Attempted preparation of Ketimine (316) at 0 °C



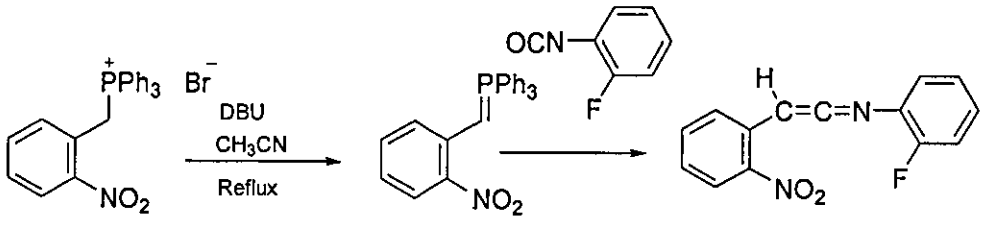
294 **304** **316**

A bright purple solution of the aryl phosphonium ylide generated from the phosphonium bromide salt (0.478 g, 1 mmol) and DBU (0.335 g, 2.2 mmol) in dry acetonitrile (5 cm^3) was stirred under nitrogen and treated dropwise at 0 °C with 2-fluorophenyl isocyanate (0.0011 mol). The resulting solution was stirred at 0 °C and the reaction was monitored by infra-red spectroscopy at regular timed intervals as shown in **Table 6.2** (see **Appendix 8** for selected I. R spectras). After 3 h the reaction was allowed to warm to room temperature After 24 h the solvent was removed *in vacuo* after showing starting materials were consumed. An attempt was made to isolate the ketimine formed in the reaction. The residue was separated and purified by flash column chromatography eluting with light petroleum ether and ethyl acetate (4:1) to give decomposed material.

Time of Reaction	I.R characteristic peaks (cm^{-1})	Inference
10 min	2268, 2246 strong bands and 2118 very weak bands.	Isocyanate groups present in high concentration and ketimine beginning to form.
30 min	2270, 2244 strong bands and 2134, 2118 weak bands.	Concentration of isocyanate falling. Concentration of ketiimine rising.
1.5 h	2267, 2244 strong bands, 2150 2117 weak bands.	Ketimine group of high concentration.
24 h	2249, doublet of 2150 and 2117 strong bands.	Ketimine group of high concentration.

Table 6.2

Attempted preparation of Ketimine (316) under reflux



294 **304** **316**

A bright purple solution solution of the aryl phosphonium ylide generated from the phosphonium bromide salt (0.478 g, 1 mmol) and DBU (0.335 g, 1.1 mmol) in dry acetonitrile (5 cm^3) was stirred under nitrogen and treated dropwise at room temperature with 2-fluorophenyl isocyanate (0.0011 mol). The resulting solution was stirred under reflux and the reaction was monitored by infra-red spectroscopy at regular timed intervals as shown in **Table 6.3**. After 24 hours the starting materials were consumed and no attempt was made to isolate the intermediates in this reaction.

Time of Reaction	**I.R characteristic peaks (cm^{-1})**	**Inference**
5 min	2151, 2118 strong bands.	Concentration of Ketimine rising.
10 min	2150, 2118 strong bands.	Ketimine in high concentration.
30 min	2150, 2118 very strong bands.	High concentration of Ketimine.
1.5 h	2150, 2117 very strong bands.	High concentration of Ketimine.
3 h	2150, 2117 very strong bands.	High concentration of Ketimine.
24 h	2150, 2117 very strong bands.	High concentration of Ketimine.

Table 6.3

6.5 References

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Chapter 7

Summary and Recommendation for further Studies

7.0 Summary

A series of novel oxamides has been successfully prepared in high yield. These were investigated as substrates for the Wallach imidazole synthesis. Modification of the conditions traditionally used for this reaction met with limited success. Simply substituted imidazoles were prepared in good yield, but we failed to achieve the more functionally substituted imidazoles in high yields. We have uncovered that there may be more than one mechanism operating in the Wallach reaction. Variation of the Wallach reaction using other reagents failed to prepare halogenated imidazole other than chloro derivatives.

5-Chloro-4-nitro-imidazole **53** and **80** was shown to be an important building block for heterocyclic synthesis. Displacement reactions with various nucleophiles including anions of malonate esters gave entry to imidazo fused isoxazoles. An X-ray structure, of the first example of an imidazo[4,5-*c*]isoxazole ring system was determined.
Other heteroaromatic methylene compounds were prepared by displacement reactions with 5-chloro-4-nitro-imidazole **53**. X-ray analysis confirmed their absolute structures. Thermolysis of one derivative was carried out but without success.

Thermolysis of other heterocyclic malonate derivatives to form [5,5] fused isoxazoles proved unsuccessful except for thiophene malonate derivative **158**. We have obtained a first example of an X-ray crystal structure for the fused thieno[3,2-*c*]isoxazole. The chemistry of this heterocycle has been briefly investigated.

An investigation into the chemistry of the imidazo[4,5-*c*]isoxazole ring system has been carried out. Ring opening occurred to give synthetically useful iminophosphorane substituted imidazole derivatives.
The reaction of imidazo[4,5-*c*]isoxazole with alkynes was successful and gave a number of addition and rearrangement products with acetylinic esters and ketones. Two pathways were operating in this reaction, one gave pyrrolyl imidazoles in moderate to good yield. The other route gave novel biologically interesting [1,4]diazepino[2,3-*c*] isoxazoles in low yield. The mechanisms proposed for these reactions were supported by isolation of some intermediate products.

Elaboration of pyrrolyl imidazoles were carried out and afforded novel imidazo[1,2-*a*]pyrrolo[2,3-*c*]pyridine derivatives in very good yields.

The application of nitro imidazole iminophosphoranes in constructing imidazo[4,5-*d*][1,2,3]triazole derivatives with various aryl isocyanates proved successful. An X-ray crystal structure to prove the position of substitution on the imidazo-triazole ring system was obtained. Evidence to support the mechanism of this reaction has now been established by infrared spectroscopy. This involves carbodiimide generation by aza-Wittig reaction, which occurs through the iminophosphorane substituent. A sequence of electrocyclic ring opening and closure occurs to form the imidazole[4,5-*d*][1,2,3]triazole derivatives.

Possible extension of this reaction was investigated and base catalysis of 2-nitrobenzyl triphenylphosphonium bromide salts with various aryl isocyanates was found to be a convenient way to synthesise 5-aryl-2*H* indazole derivatives in modest to good yields.

The application of nitro group compounds in preparing a number of novel heterocycles has proved successful and has led to some interesting mechanistic heterocyclic chemistry.[1,2,3,4] The biological activity of these compounds were not investigated due to limited time.

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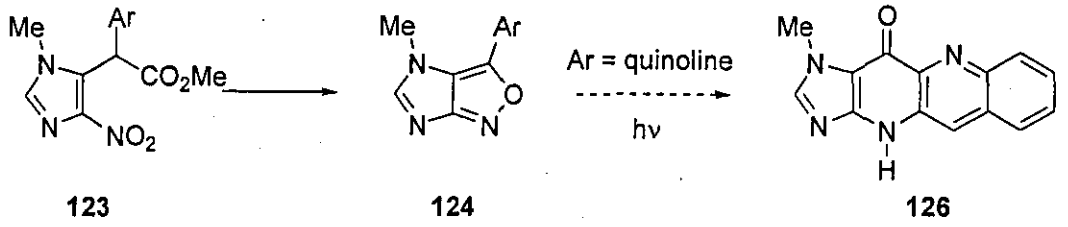
3)Taher, A., Eichenseher, S., and Weaver, G.W., *Tetrahedron Letters* **2000**, *41*, 9889-9891.
4)Taher, A., Ladwa, S., Rajan, S.T., and Weaver., G.W., *Tetrahedron Letters* **2000**, *41*, 9893-9897.

7.1 Recommendation for further studies

In chapter one, the use of reagents other than phosphorus pentachloride to prepare halogenated substituted imidazoles was studied. This could be continued by pursuing new reagents and conditions.

Chapter two described the preparation of various heteroaryl nitroimidazolyl acetates. Thermolysis of all these derivatives should be investigated, to give heteroaryl substituted imidazo[4,5-*c*]isoxazoles. Photochemical reaction of these should be studied and may result in formation of interesting tetracyclic compounds **126**, **Scheme 137**. Reduction of the nitro group on the benzotriazole substituted imidazole derivative, by triethyl phosphite should also be studied further for the possible synthesis of tetracyclic compounds.



123 **124** **126**

Scheme 137

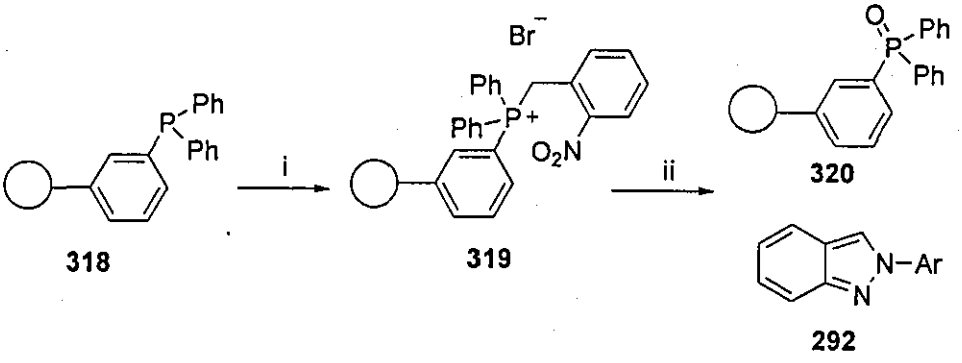
Chapter three described the synthesis of thieno[3,2-*c*]isoxazoles and possible routes to other [5,5] fused isoxazoles. Work in this area should continue and methods other than thermolysis investigated to effect cyclisation.

Chapter four described an approach to imidazo[4,5-*b*]pyridines (1-deazapurines) using acylimidazolyl iminophosphoranes as precursors, and reaction with 1,3 dicarbonyl compounds. Base catalysis should be studied to see if cyclisation can be effected as only the initial addition product was isolated. Reaction of the 3-unsubstituted imidazo[4,5-*c*]isoxazole with alkynes should be studied. Decarboxylation using a radical procedure may give the required precursor.

Further work on the preparation of novel imidazo[1,2-*a*]pyrrolo[2,3-*c*]pyridine derivatives could be pursued and their biological activity investigated.

Chapter five described the synthesis of imidazo[4,5-*d*]triazole derivatives. Further chemistry and biological activity of this fused heterocycle should be investigated. This procedure for preparing [5,5] fused triazoles could be applied in the pyrazole and thiophene series, as the necessary precursors can be conveniently prepared.

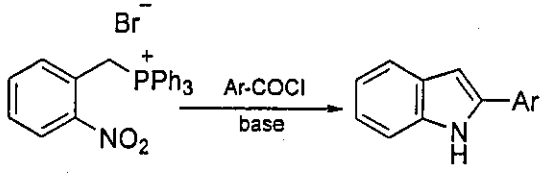
Chapter six revealed a new method for preparation of 2-aryl indazole derivatives. The yields may be improved, and the isolation of the products from the reaction may be made easier by carrying out the reaction on a polymer support, **Scheme 138**. The triphenyl phosphine polystyrene resin **318** could be alkylated with nitrobenzyl bromide to give the salt **319**. This may be reacted with aryl isocyanates to afford the aryl indazole **292** leaving the polymer bound triphenylphosphine oxide **320** as a by-product.



Reagents and conditions: i, 2-nitrobenzyl bromide; ii) Base, Ar-NCO.

Scheme 138

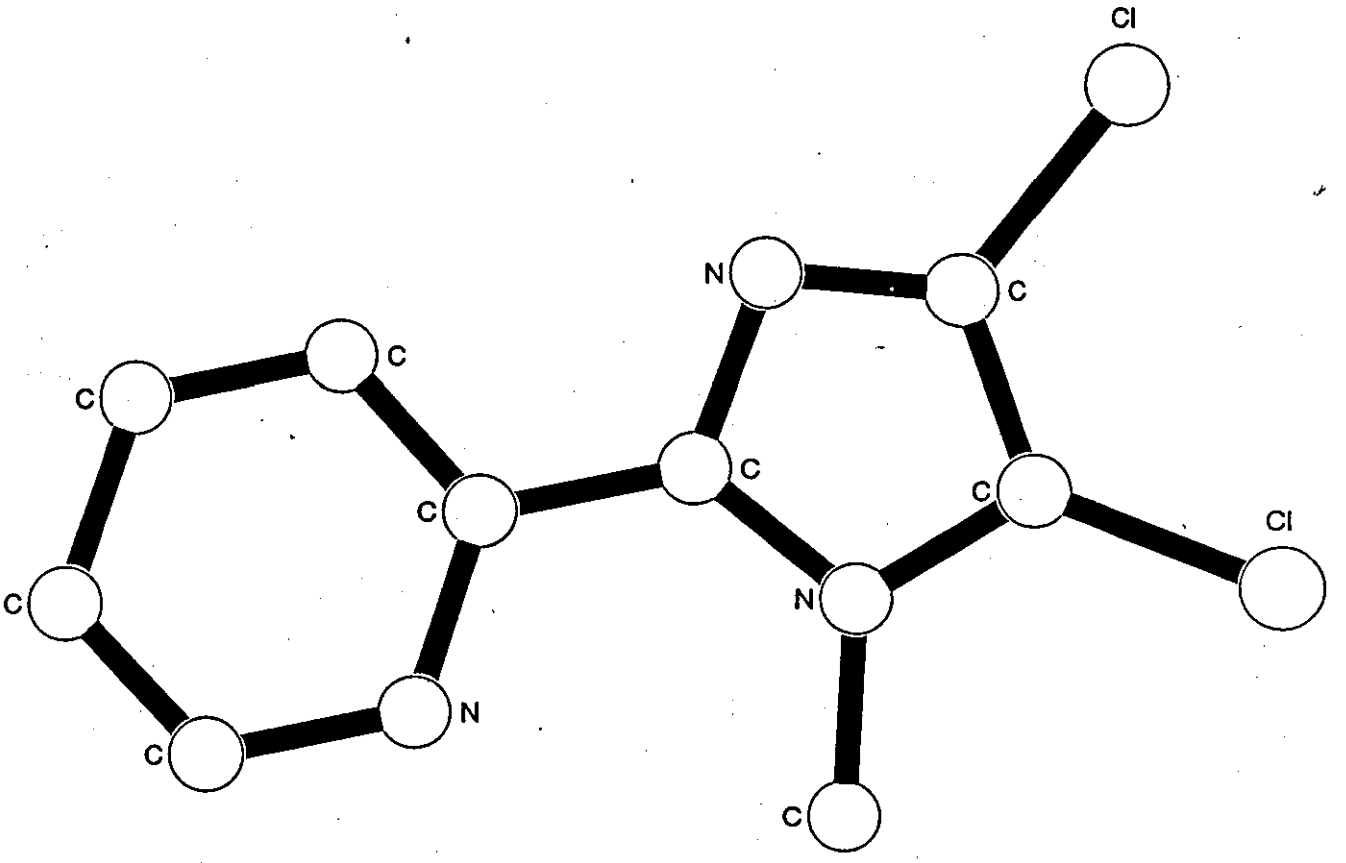
2-Aryl-1*H*-indoles such as **321** may be formed in an analogous manner using aryl acid chlorides in place of isocyanates and this reaction should be investigated, **Scheme 139**.



Scheme 139

Chapter 8

Appendix


Cl
N
C
C
C
C
C
C
Cl
C
N
N
C
C

Experimental

Data Collection

A colourlessblock block crystal of $C_9H_7N_3Cl_2$ having approximate dimensions of 0.20 x 0.20 x 0.20 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC7S diffractometer with graphite monochromated Cu-Kα radiation.

Cell constants and an orientation matrix for data collection , obtained from a least-squares refinement using the setting angles of 25 carefully centered reflections in the range $70.25 < 2\theta < 74.87°$ corresponded to a primitive monoclinic cell with dimensions:

$a = 7.065(5)\ \AA$

$b = 13.048(4)\ \AA \qquad \beta = 93.34(5)°$

$c = 10.781(5)\ \AA$

$V = 992.1(9)\ \AA^3$

For Z = 4 and F.W. = 228.08, the calculated density is 1.53 g/cm^3. The systematic absences of:

h0l: $h \neq 2n$

0k0: $k \neq 2n$

uniquely determine the space group to be:

$P2_1/a$ (#14)

The data were collected at a temperature of 20 $\pm$ 1°C using the ω scan technique to a maximum 2θ value of 120.4°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.31° with a take-off angle of 6.0°. Scans of $(1.26 + 0.35 \tan \theta)°$ were made at a speed of 16.0°/min (in omega). The weak reflections ($I < 12.0\sigma(I)$) were rescanned (maximum of 4 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 1.0 mm and the crystal to detector distance was 400 mm, The computer-controlled slits were set to 9.0 mm (horizontal) and 13.0 mm (vertical).

Data Reduction

Of the 1683 reflections which were collected, 1546 were unique ($R_{int} = 0.142$). The intensities of three representative reflection were measured after every 150 reflections. Over the course of data collection, the standards decreased by 0.3%. A linear correction factor was applied to the data to account for this phenomenon.

The linear absorption coefficient, μ, for Cu-Kα radiation is 56.9 cm^{-1}. An empirical absorption correction using the program DIFABS[1] was applied which resulted in transmission factors ranging from 0.31 to 1.00. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction

was applied (coefficient = 1.78308e-05).

Structure Solution and Refinement

The structure was solved by direct methods[2] and expanded using Fourier techniques[3]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement[4] was based on 843 observed reflections ($I > 3.00\sigma(I)$) and 128 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma||Fo| - |Fc||/\Sigma|Fo| = 0.071$$

$$R_w = \sqrt{(\Sigma w(|Fo| - |Fc|)^2/\Sigma wFo^2)} = 0.042$$

The standard deviation of an observation of unit weight[5] was 6.15. The weighting scheme was based on counting statistics and included a factor (p = 0.001) to downweight the intense reflections. Plots of $\Sigma w(|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, $\sin\theta/\lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.25 and -0.27 $e^-/\AA^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[6] . Anomalous dispersion effects were included in Fcalc[7]; the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley[8]. The values for the mass attenuation coefficients are those of Creagh and Hubbel[9]. All calculations were performed using the teXsan[10] crystallographic software package of Molecular Structure Corporation.

References

(1) DIFABS: Walker, N. & Stuart, Acta Cryst. A39, 158-166 (1983). An empirical absorption correction program.

(2) SIR92: Altomare, A., Cascarano, M., Giacovazzo, C., Guagliardi, A. (1993). J. Appl. Cryst., 26, 343.

(3) DIRDIF94: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., de Gelder, R., Israel, R. and Smits, J.M.M. (1994). The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(4) Least-Squares:

Function minimized: $\Sigma w(|Fo| - |Fc|)^2$

where w = $\frac{1}{\sigma^2(Fo)} = [\sigma_c^2(Fo) + \frac{p^2}{4}Fo^2]^{-1}$

$\sigma_c(Fo)$ = e.s.d. based on counting statistics

p = p-factor

(5) Standard deviation of an observation of unit weight:

$$\sqrt{\Sigma w(|Fo| - |Fc|)^2/(No - Nv)}$$

where: No = number of observations

Nv = number of variables

(6) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(7) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

(8) Creagh, D. C. & McAuley, W.J .; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

(9) Creagh, D. C. & Hubbell, J.H..; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

(10) teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992).

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_9H_7N_3Cl_2$
Formula Weight	228.08
Crystal Color, Habit	colourlessblock, block
Crystal Dimensions	0.20 X 0.20 X 0.20 mm
Crystal System	monoclinic
Lattice Type	Primitive
No. of Reflections Used for Unit Cell Determination (2θ range)	25 (70.2 - 74.9°)
Omega Scan Peak Width at Half-height	0.31°
Lattice Parameters	a = 7.065(5)Å b = 13.048(4) Å c = 10.781(5) Å β = 93.34(5)° V = 992.1(9) Å^3
Space Group	$P2_1/a$ (#14)
Z value	4
D_{calc}	1.527 g/cm^3
F_{000}	464.00
μ(CuKα)	56.91 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku AFC7S

Radiation	CuKα (λ = 1.54178 Å) graphite monochromated
Attenuator	Ni foil (factor = 9.42)
Take-off Angle	6.0°
Detector Aperture	9.0 mm horizontal 13.0 mm vertical
Crystal to Detector Distance	400 mm
Voltage, Current	0kV, 0mA
Temperature	20.0°C
Scan Type	ω
Scan Rate	16.0°/min (in ω) (up to 4 scans)
Scan Width	$(1.26 + 0.35 \tan \theta)°$
$2\theta_{max}$	120.4°
No. of Reflections Measured	Total: 1683 Unique: 1546 (R_{int} = 0.142)
Corrections	Lorentz-polarization Absorption (trans. factors: 0.3112 - 1.0000) Decay (0.35% decline) Secondary Extinction (coefficient: 1.78308e-05)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w(\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$w = \frac{1}{\sigma^2(Fo)} = [\sigma_c^2(Fo) + \frac{p^2}{4}Fo^2]^{-1}$
p-factor	0.0010
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	843
No. Variables	128

Reflection/Parameter Ratio	6.59
Residuals: R; Rw	0.071 ; 0.042
Goodness of Fit Indicator	6.15
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.25 $e^-/\AA^3$
Minimum peak in Final Diff. Map	-0.27 $e^-/\AA^3$

Table 1. Atomic coordinates and B_{iso}/B_{eq}

atom	x	y	z	B_{eq}
Cl(4)	0.6362(3)	0.4184(1)	0.0759(2)	10.35(7)
Cl(5)	0.6013(3)	0.1640(1)	-0.0089(2)	10.32(7)
N(1)	0.6856(7)	0.1576(4)	0.2387(7)	7.6(2)
N(3)	0.7157(8)	0.3211(5)	0.2926(7)	7.7(2)
N(7)	0.7882(9)	0.1011(5)	0.4958(7)	9.1(2)
C(2)	0.725(1)	0.2251(6)	0.3339(9)	7.3(2)
C(4)	0.668(1)	0.3124(6)	0.1708(9)	7.6(2)
C(5)	0.650(1)	0.2141(6)	0.1331(7)	7.5(2)
C(6)	0.7733(9)	0.2003(7)	0.4641(9)	7.6(3)
C(8)	0.833(1)	0.0827(6)	0.6160(9)	9.4(3)
C(9)	0.867(1)	0.1557(8)	0.7055(8)	9.5(3)
C(10)	0.850(1)	0.2561(7)	0.6706(9)	9.1(3)
C(11)	0.804(1)	0.2797(6)	0.548(1)	8.5(3)
C(12)	0.670(1)	0.0447(5)	0.2446(7)	9.9(3)
H(8)	0.8419	0.0130	0.6412	11.3188
H(9)	0.9005	0.1372	0.7891	11.3575
H(10)	0.8710	0.3092	0.7303	10.9736
H(11)	0.7927	0.3491	0.5222	10.2484
H(12b)	0.7548	0.0147	0.1895	11.8374
H(12c)	0.7025	0.0222	0.3270	11.8374
H(12a)	0.5442	0.0245	0.2211	11.8374

$$B_{eq} = \frac{8}{3}\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^*\cos\gamma + 2U_{13}aa^*cc^*\cos\beta + 2U_{23}bb^*cc^*\cos\alpha)$$

Table 2. Anisotropic Displacement Parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Cl(4)	0.136(2)	0.101(1)	0.157(2)	0.012(1)	0.019(1)	0.022(1)
Cl(5)	0.131(2)	0.123(2)	0.139(2)	0.005(1)	0.014(1)	-0.013(1)
N(1)	0.075(4)	0.080(4)	0.134(6)	0.005(4)	0.021(4)	0.000(5)
N(3)	0.079(4)	0.081(4)	0.136(6)	0.003(3)	0.023(4)	0.009(4)
N(7)	0.118(5)	0.082(5)	0.145(6)	0.000(4)	0.011(5)	0.013(4)
C(2)	0.067(5)	0.088(6)	0.126(7)	0.003(5)	0.028(5)	-0.008(6)
C(4)	0.069(5)	0.089(6)	0.134(7)	0.012(4)	0.028(5)	0.017(5)
C(5)	0.078(5)	0.093(6)	0.115(6)	0.011(5)	0.028(5)	0.004(5)
C(6)	0.061(5)	0.100(6)	0.129(8)	0.004(5)	0.021(5)	-0.007(6)
C(8)	0.126(7)	0.101(6)	0.133(8)	0.011(6)	0.028(7)	0.018(7)
C(9)	0.107(6)	0.114(7)	0.141(8)	0.015(6)	0.024(6)	0.009(6)
C(10)	0.101(6)	0.117(7)	0.131(8)	0.006(6)	0.019(6)	-0.009(6)
C(11)	0.100(6)	0.085(5)	0.141(8)	0.005(5)	0.017(6)	-0.004(6)
C(12)	0.123(6)	0.083(5)	0.169(8)	-0.001(5)	0.017(5)	-0.009(5)

The general temperature factor expression:

$$\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$$

Table 3. Bond Lengths($\AA$)

atom	atom	distance	atom	atom	distance
Cl(4)	C(4)	1.728(7)	Cl(5)	C(5)	1.682(7)
N(1)	C(2)	1.367(8)	N(1)	C(5)	1.367(7)
N(1)	C(12)	1.480(7)	N(3)	C(2)	1.330(8)
N(3)	C(4)	1.341(8)	N(7)	C(6)	1.341(8)
N(7)	C(8)	1.337(8)	C(2)	C(6)	1.462(9)
C(4)	C(5)	1.349(8)	C(6)	C(11)	1.387(8)
C(8)	C(9)	1.367(9)	C(8)	H(8)	0.95
C(9)	C(10)	1.367(9)	C(9)	H(9)	0.95
C(10)	C(11)	1.374(9)	C(10)	H(10)	0.95
C(11)	H(11)	0.95	C(12)	H(12b)	0.95
C(12)	H(12c)	0.95	C(12)	H(12a)	0.95

Table 4. Bond Angles(°)

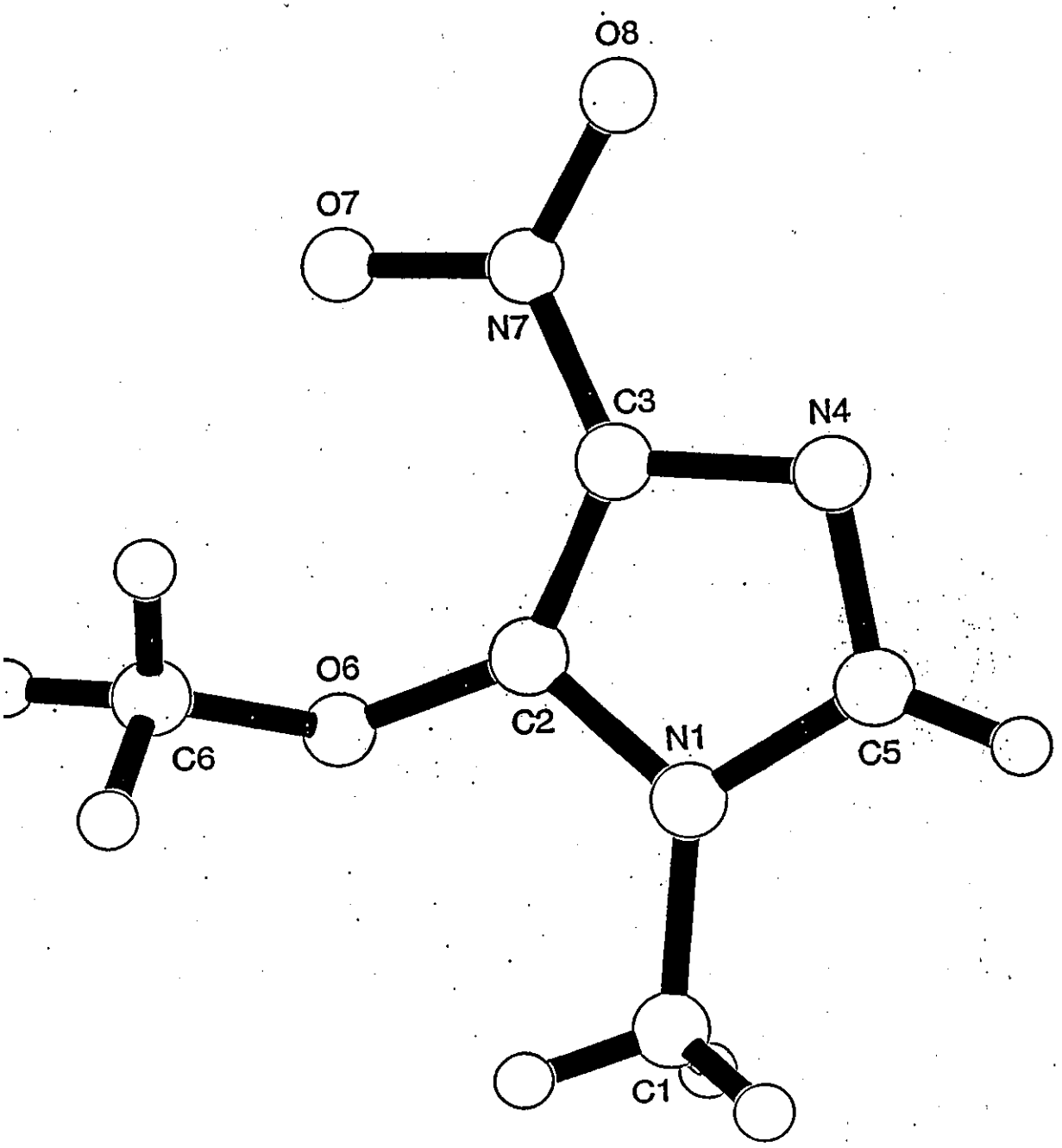
atom	atom	atom	angle	atom	atom	atom	angle
C(2)	N(1)	C(5)	107.3(6)	C(2)	N(1)	C(12)	128.4(7)
C(5)	N(1)	C(12)	124.2(8)	C(2)	N(3)	C(4)	104.6(7)
C(6)	N(7)	C(8)	115.5(8)	N(1)	C(2)	N(3)	110.6(8)
N(1)	C(2)	C(6)	127.2(8)	N(3)	C(2)	C(6)	122.3(8)
Cl(4)	C(4)	N(3)	121.9(7)	Cl(4)	C(4)	C(5)	125.2(8)
N(3)	C(4)	C(5)	112.9(7)	Cl(5)	C(5)	N(1)	124.5(7)
Cl(5)	C(5)	C(4)	130.9(8)	N(1)	C(5)	C(4)	104.6(7)
N(7)	C(6)	C(2)	118.0(8)	N(7)	C(6)	C(11)	123.1(8)
C(2)	C(6)	C(11)	118.9(8)	N(7)	C(8)	C(9)	125.5(8)
N(7)	C(8)	H(8)	117.3	C(9)	C(8)	H(8)	117.3
C(8)	C(9)	C(10)	117.7(9)	C(8)	C(9)	H(9)	121.1
C(10)	C(9)	H(9)	121.1	C(9)	C(10)	C(11)	119.4(8)
C(9)	C(10)	H(10)	120.3	C(11)	C(10)	H(10)	120.3
C(6)	C(11)	C(10)	118.7(8)	C(6)	C(11)	H(11)	120.6
C(10)	C(11)	H(11)	120.6	N(1)	C(12)	H(12b)	109.5
N(1)	C(12)	H(12c)	109.5	N(1)	C(12)	H(12a)	109.5
H(12b)	C(12)	H(12c)	109.5	H(12b)	C(12)	H(12a)	109.5
H(12c)	C(12)	H(12a)	109.5				

Table 5. Torsion Angles(°)

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
Cl(4)	C(4)	N(3)	C(2)	179.1(5)	Cl(4)	C(4)	C(5)	Cl(5)	2(1)
Cl(4)	C(4)	C(5)	N(1)	-179.1(5)	Cl(5)	C(5)	N(1)	C(2)	178.2(5)
Cl(5)	C(5)	N(1)	C(12)	-5(1)	Cl(5)	C(5)	C(4)	N(3)	-177.7(6)
N(1)	C(2)	N(3)	C(4)	0.6(8)	N(1)	C(2)	C(6)	N(7)	2(1)
N(1)	C(2)	C(6)	C(11)	-178.3(7)	N(1)	C(5)	C(4)	N(3)	1.1(9)
N(3)	C(2)	N(1)	C(5)	0.1(8)	N(3)	C(2)	N(1)	C(12)	-176.5(6)
N(3)	C(2)	C(6)	N(7)	-176.8(6)	N(3)	C(2)	C(6)	C(11)	3(1)
N(7)	C(6)	C(11)	C(10)	0(1)	N(7)	C(8)	C(9)	C(10)	1(2)
C(2)	N(1)	C(5)	C(4)	-0.7(8)	C(2)	N(3)	C(4)	C(5)	-1.0(9)
C(2)	C(6)	N(7)	C(8)	180.0(7)	C(2)	C(6)	C(11)	C(10)	-179.7(7)
C(4)	N(3)	C(2)	C(6)	179.9(7)	C(4)	C(5)	N(1)	C(12)	176.1(6)
C(5)	N(1)	C(2)	C(6)	-179.2(7)	C(6)	N(7)	C(8)	C(9)	-1(1)
C(6)	C(2)	N(1)	C(12)	4(1)	C(6)	C(11)	C(10)	C(9)	0(1)
C(8)	N(7)	C(6)	C(11)	1(1)	C(8)	C(9)	C(10)	C(11)	-1(1)

Table 6. Non-bonded Contacts out to 3.60 Å

atom	atom	distance	ADC	atom	atom	distance	ADC
Cl(4)	H(12b)	3.15	45504	Cl(4)	H(9)	3.22	65602
Cl(4)	Cl(4)	3.247(4)	66503	Cl(4)	H(12b)	3.26	65502
Cl(4)	H(12a)	3.28	4	Cl(4)	H(8)	3.29	65602
Cl(4)	H(9)	3.50	45404	Cl(5)	H(9)	3.14	55401
Cl(5)	H(10)	3.19	45404	Cl(5)	H(12a)	3.47	65503
N(1)	N(3)	3.415(8)	45504	N(1)	C(4)	3.553(9)	4
N(3)	H(8)	2.64	65602	N(3)	H(12a)	3.20	4
N(3)	C(2)	3.573(9)	45504	N(3)	C(8)	3.57(1)	65602
N(7)	H(11)	3.34	64602	N(7)	H(8)	3.42	75603
N(7)	H(11)	3.59	45504	C(2)	C(2)	3.592(4)	4
C(2)	C(2)	3.592(4)	45504	C(4)	H(8)	3.31	65602
C(4)	H(12a)	3.42	4	C(4)	C(5)	3.47(1)	4
C(6)	C(11)	3.50(1)	45504	C(6)	H(11)	3.55	45504
C(8)	H(11)	3.48	64602	C(8)	H(12a)	3.56	65603
C(8)	H(11)	3.57	4	C(8)	H(12c)	3.58	75603
C(9)	H(10)	3.56	45504	C(9)	H(10)	3.59	4
C(10)	H(12c)	3.49	65602	C(10)	C(10)	3.536(3)	4
C(10)	C(10)	3.536(3)	45504	C(10)	C(11)	3.56(1)	4
C(10)	H(10)	3.59	45504	C(11)	H(12c)	3.44	65602
C(12)	H(10)	3.10	64602	C(12)	H(11)	3.58	64602
H(8)	H(11)	2.90	64602	H(8)	H(12a)	3.22	65603
H(8)	H(12c)	3.25	75603	H(8)	H(12b)	3.31	75603
H(9)	H(12b)	3.14	75603	H(9)	H(10)	3.49	4
H(10)	H(12c)	2.89	65602	H(10)	H(12a)	2.91	65602
H(10)	H(12b)	2.97	65602	H(11)	H(12c)	2.78	65602


O8
O7
N7
C3
N4
O6
C2
N1
C5
C6
C1

Experimental

Data Collection

A yellow prism crystal of $C_5H_7N_3O_3$ having approximate dimensions of 0.12 x 0.13 x 0.15 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC7S diffractometer with graphite monochromated Cu-Kα radiation.

Cell constants and an orientation matrix for data collection , obtained from a least-squares refinement using the setting angles of 8 carefully centered reflections in the range $72.02 < 2\theta < 75.01°$ corresponded to a primitive monoclinic cell with dimensions:

a = 7.27(2) $\AA$
b = 8.89(1) $\AA$ $\beta = 93.0(1)°$
c = 10.919(7) $\AA$
V = 705(2) $\AA^3$

For Z = 4 and F.W. = 157.13, the calculated density is 1.48 g/cm^3. The systematic absences of:

h0l: h $\neq$ 2n
0k0: k $\neq$ 2n

uniquely determine the space group to be:

$P2_1/a$ (#14)

The data were collected at a temperature of 20 $\pm$ 1°C using the ω scan technique to a maximum 2θ value of 120.5°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.33° with a take-off angle of 6.0°. Scans of (1.37 + 0.35 tan θ)° were made at a speed of 16.0°/min (in omega). The weak reflections ($I < 12.0\sigma(I)$) were rescanned (maximum of 4 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 1.0 mm and the crystal to detector distance was 400 mm, The computer-controlled slits were set to 9.0 mm (horizontal) and 13.0 mm (vertical).

Data Reduction

Of the 1242 reflections which were collected, 1133 were unique (R_{int} = 0.086). The intensities of three representative reflection were measured after every 150 reflections. Over the course of data collection, the standards decreased by 0.1%. A linear correction factor was applied to the data to account for this phenomenon.

The linear absorption coefficient, μ, for Cu-Kα radiation is 10.7 cm^{-1}. An empirical absorption correction using the program DIFABS[1] was applied which resulted in transmission factors ranging from 0.49 to 1.00. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction

was applied (coefficient = 1.55112e-05).

Structure Solution and Refinement

The structure was solved by direct methods[2] and expanded using Fourier techniques[3]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement[4] was based on 597 observed reflections ($I > 3.00\sigma(I)$) and 101 variable parameters and converged (largest parameter shift was 0.02 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma||Fo| - |Fc||/\Sigma|Fo| = 0.072$$

$$R_w = \sqrt{(\Sigma w(|Fo| - |Fc|)^2/\Sigma wFo^2)} = 0.035$$

The standard deviation of an observation of unit weight[5] was 4.82. The weighting scheme was based on counting statistics and included a factor (p = 0.001) to downweight the intense reflections. Plots of $\Sigma w(|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, $\sin\theta/\lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.27 and -0.24 $e^-/\AA^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[6] . Anomalous dispersion effects were included in Fcalc[7]; the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley[8]. The values for the mass attenuation coefficients are those of Creagh and Hubbel[9]. All calculations were performed using the teXsan[10] crystallographic software package of Molecular Structure Corporation.

References

(1) DIFABS: Walker, N. & Stuart, Acta Cryst. A39, 158-166 (1983). An empirical absorption correction program.

(2) SIR92: Altomare, A., Cascarano, M., Giacovazzo, C., Guagliardi, A. (1993). J. Appl. Cryst., 26, 343.

(3) DIRDIF94: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., de Gelder, R., Israel, R. and Smits, J.M.M. (1994). The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(4) Least-Squares:

Function minimized: $\Sigma w(|Fo| - |Fc|)^2$

where $w = \frac{1}{\sigma^2(Fo)} = [\sigma_c^2(Fo) + \frac{p^2}{4}Fo^2]^{-1}$

$\sigma_c(Fo)$ = e.s.d. based on counting statistics

p = p-factor

(5) Standard deviation of an observation of unit weight:

$$\sqrt{\Sigma w(|Fo| - |Fc|)^2/(No - Nv)}$$

where: No = number of observations

Nv = number of variables

(6) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(7) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

(8) Creagh, D. C. & McAuley, W.J .; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

(9) Creagh, D. C. & Hubbell, J.H..; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

(10) teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992).

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_5H_7N_3O_3$
Formula Weight	157.13
Crystal Color, Habit	yellow, prism
Crystal Dimensions	0.12 X 0.13 X 0.15 mm
Crystal System	monoclinic
Lattice Type	Primitive
No. of Reflections Used for Unit Cell Determination (2θ range)	8 (72.0 - 75.0°)
Omega Scan Peak Width at Half-height	0.33°
Lattice Parameters	a = 7.27(2)Å b = 8.89(1) Å c = 10.919(7) Å β = 93.0(1)° V = 705(2) Å^3
Space Group	$P2_1/a$ (#14)
Z value	4
D_{calc}	1.481 g/cm^3
F_{000}	328.00
μ(CuKα)	10.73 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku AFC7S

Radiation	CuKα (λ = 1.54178 Å) graphite monochromated
Attenuator	Ni foil (factor = 9.42)
Take-off Angle	6.0°
Detector Aperture	9.0 mm horizontal 13.0 mm vertical
Crystal to Detector Distance	400 mm
Voltage, Current	0kV, 0mA
Temperature	20.0°C
Scan Type	ω
Scan Rate	16.0°/min (in ω) (up to 4 scans)
Scan Width	(1.37 + 0.35 tan θ)°
$2\theta_{max}$	120.5°
No. of Reflections Measured	Total: 1242 Unique: 1133 (R_{int} = 0.086)
Corrections	Lorentz-polarization Absorption (trans. factors: 0.4925 - 1.0000) Decay (0.10% decline) Secondary Extinction (coefficient: 1.55112e-05)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w(\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$w = \frac{1}{\sigma^2(Fo)} = [\sigma_c^2(Fo) + \frac{p^2}{4}Fo^2]^{-1}$
p-factor	0.0010
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	597
No. Variables	101

Reflection/Parameter Ratio	5.91
Residuals: R; Rw	0.072 ; 0.035
Goodness of Fit Indicator	4.82
Max Shift/Error in Final Cycle	0.02
Maximum peak in Final Diff. Map	0.27 $e^-/\AA^3$
Minimum peak in Final Diff. Map	-0.24 $e^-/\AA^3$

Table 1. Atomic coordinates and B_{iso}/B_{eq}

atom	x	y	z	B_{eq}
O(6)	0.9552(7)	0.1346(5)	0.6319(4)	4.8(1)
O(7)	0.9659(7)	0.4689(5)	0.6451(4)	5.8(2)
O(8)	0.8434(9)	0.5709(5)	0.8002(5)	8.1(2)
N(1)	0.8463(8)	0.0757(7)	0.8192(5)	4.3(2)
N(4)	0.7954(8)	0.2975(7)	0.9048(5)	4.9(2)
N(7)	0.8931(9)	0.4593(7)	0.7447(6)	5.2(2)
C(1)	0.853(1)	-0.0886(8)	0.8037(7)	6.0(3)
C(2)	0.8902(9)	0.1794(9)	0.7362(6)	4.0(2)
C(3)	0.8534(9)	0.3144(8)	0.7885(6)	3.8(2)
C(5)	0.793(1)	0.1509(9)	0.9205(7)	5.2(2)
C(6)	0.8567(9)	0.1734(9)	0.5206(6)	5.3(2)
H(1a)	0.7564	-0.1337	0.8461	7.1776
H(1b)	0.8391	-0.1127	0.7191	7.1776
H(1c)	0.9682	-0.1254	0.8363	7.1776
H(5)	0.7577	0.1031	0.9934	6.2171
H(6b)	0.7937	0.2658	0.5310	6.4297
H(6c)	0.7704	0.0965	0.4992	6.4297
H(6a)	0.9407	0.1841	0.4574	6.4297

$$B_{eq} = \frac{8}{3}\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^*\cos\gamma + 2U_{13}aa^*cc^*\cos\beta + 2U_{23}bb^*cc^*\cos\alpha)$$

Table 2. Anisotropic Displacement Parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(6)	0.081(4)	0.054(3)	0.051(3)	0.008(3)	0.038(3)	0.001(3)
O(7)	0.092(5)	0.054(3)	0.077(4)	0.001(3)	0.047(4)	0.012(3)
O(8)	0.133(6)	0.042(4)	0.140(6)	0.002(4)	0.081(5)	-0.018(4)
N(1)	0.066(5)	0.042(4)	0.058(4)	0.001(3)	0.034(4)	0.002(4)
N(4)	0.069(4)	0.057(4)	0.064(4)	0.000(4)	0.038(3)	-0.005(4)
N(7)	0.067(5)	0.049(5)	0.086(6)	0.003(4)	0.039(4)	-0.001(4)
C(1)	0.080(7)	0.049(6)	0.103(7)	0.005(5)	0.041(5)	0.017(5)
C(2)	0.061(5)	0.046(5)	0.050(4)	-0.008(4)	0.038(4)	0.001(4)
C(3)	0.054(5)	0.034(4)	0.059(5)	-0.003(5)	0.029(4)	0.001(5)
C(5)	0.074(6)	0.061(6)	0.066(6)	-0.012(4)	0.044(5)	-0.002(5)
C(6)	0.059(5)	0.077(6)	0.070(5)	-0.009(5)	0.031(4)	-0.012(5)

The general temperature factor expression:

$$\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$$

Table 3. Bond Lengths($\AA$)

atom	atom	distance	atom	atom	distance
O(6)	C(2)	1.316(6)	O(6)	C(6)	1.421(7)
O(7)	N(7)	1.238(6)	O(8)	N(7)	1.227(6)
N(1)	C(1)	1.471(8)	N(1)	C(2)	1.343(7)
N(1)	C(5)	1.366(7)	N(4)	C(3)	1.366(7)
N(4)	C(5)	1.314(8)	N(7)	C(3)	1.409(8)
C(2)	C(3)	1.362(9)			

Table 4. Bond Lengths(Å)

atom	atom	distance	atom	atom	distance
C(1)	H(1a)	0.95	C(1)	H(1b)	0.95
C(1)	H(1c)	0.95	C(5)	H(5)	0.95
C(6)	H(6b)	0.95	C(6)	H(6c)	0.95
C(6)	H(6a)	0.95			

Table 5. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
C(2)	O(6)	C(6)	118.6(6)	C(1)	N(1)	C(2)	126.4(6)
C(1)	N(1)	C(5)	126.3(6)	C(2)	N(1)	C(5)	107.3(6)
C(3)	N(4)	C(5)	103.7(6)	O(7)	N(7)	O(8)	122.0(6)
O(7)	N(7)	C(3)	117.8(6)	O(8)	N(7)	C(3)	120.0(6)
O(6)	C(2)	N(1)	119.0(6)	O(6)	C(2)	C(3)	135.8(7)
N(1)	C(2)	C(3)	105.2(5)	N(4)	C(3)	N(7)	119.7(6)
N(4)	C(3)	C(2)	111.7(6)	N(7)	C(3)	C(2)	127.9(5)
N(1)	C(5)	N(4)	111.9(6)				

Table 6. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
N(1)	C(1)	H(1a)	109.4	N(1)	C(1)	H(1b)	109.5
N(1)	C(1)	H(1c)	109.4	H(1a)	C(1)	H(1b)	109.5
H(1a)	C(1)	H(1c)	109.4	H(1b)	C(1)	H(1c)	109.6
N(1)	C(5)	H(5)	124.1	N(4)	C(5)	H(5)	124.0
O(6)	C(6)	H(6b)	109.4	O(6)	C(6)	H(6c)	109.5
O(6)	C(6)	H(6a)	109.4	H(6b)	C(6)	H(6c)	109.6
H(6b)	C(6)	H(6a)	109.4	H(6c)	C(6)	H(6a)	109.6

Table 7. Non-bonded Contacts out to 3.60 $\AA$

atom	atom	distance	ADC	atom	atom	distance	ADC
O(6)	C(3)	3.32(1)	4	O(6)	N(7)	3.46(1)	4
O(6)	C(6)	3.518(8)	75603	O(7)	O(7)	3.279(9)	76603
O(7)	N(1)	3.30(1)	4	O(7)	C(1)	3.40(1)	4
O(7)	C(6)	3.41(1)	65602	O(7)	C(6)	3.45(1)	4
O(7)	C(2)	3.45(1)	4	O(8)	C(1)	3.027(9)	56501
O(8)	C(5)	3.333(8)	65702	O(8)	C(1)	3.57(1)	45504
N(1)	N(7)	3.37(1)	45504	N(1)	N(4)	3.53(1)	4
N(4)	C(2)	3.40(1)	45504	N(4)	C(3)	3.54(1)	45504
N(4)	C(1)	3.562(8)	65702	N(7)	C(5)	3.54(1)	4
N(7)	C(1)	3.56(1)	4	C(2)	C(3)	3.39(1)	4
C(3)	C(5)	3.45(1)	4				

The ADC (atom designator code) specifies the position of an atom in a crystal. The 5-digit number shown in the table is a composite of three one-digit numbers and one two-digit number: TA (first digit) + TB (second digit) + TC (third digit) + SN (last two digits). TA, TB and TC are the crystal lattice translation digits along cell edges a, b and c. A translation digit of 5 indicates the origin unit cell. If TA = 4, this indicates a translation of one unit cell length along the a-axis in the negative direction. Each translation digit can range in value from 1 to 9 and thus ± 4 lattice translations from the origin (TA=5, TB=5, TC=5) can be represented.

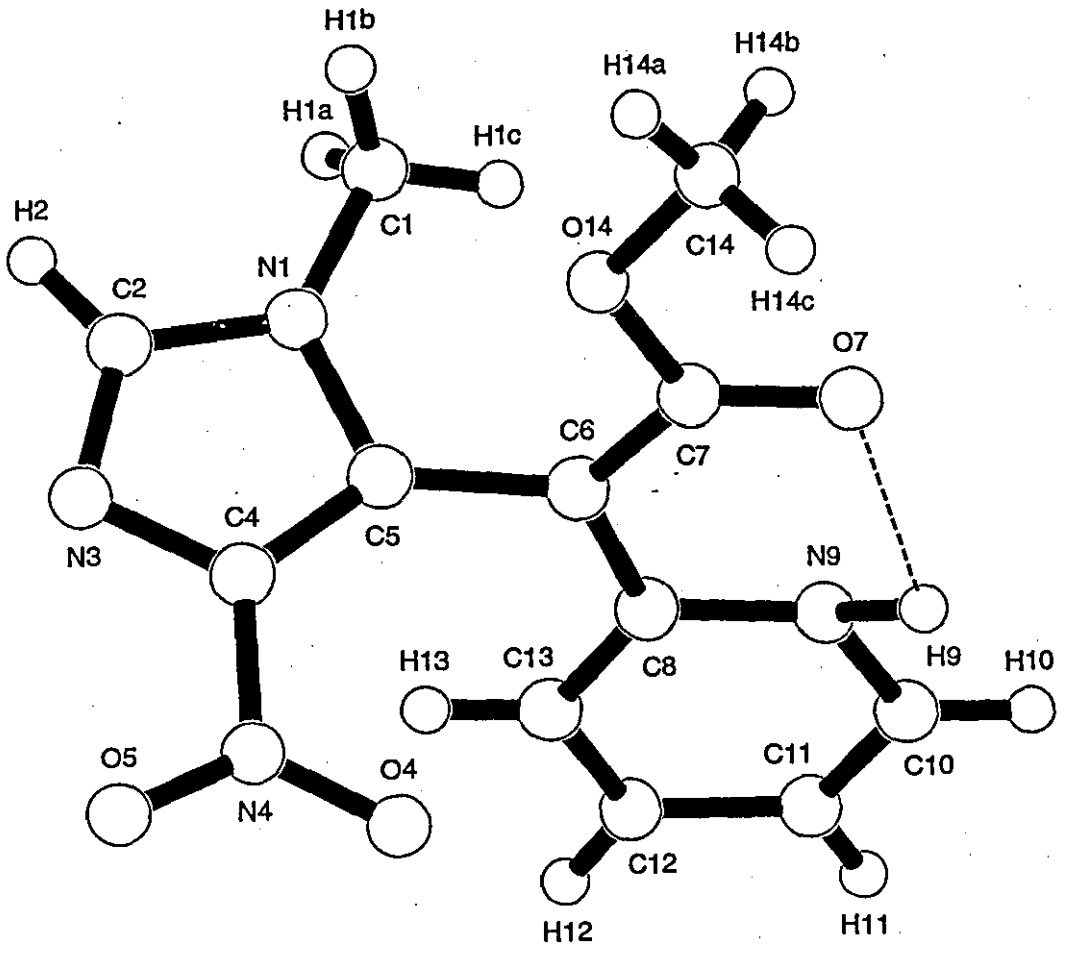
The SN, or symmetry operator number, refers to the number of the symmetry operator used to generate the coordinates of the target atom. A list of symmetry operators relevant to this structure are given below.

For a given intermolecular contact, the first atom (origin atom) is located in the origin unit cell and its position can be generated using the identity operator (SN=1). Thus, the ADC for an origin atom is always 55501. The position of the second atom (target atom) can be generated using the ADC and the coordinates of the atom in the parameter table. For example, an ADC of 47502 refers to the target atom moved through symmetry operator two, then translated -1 cell translations along the a axis, +2 cell translations along the b axis, and 0 cell translations along the c axis.

An ADC of 1 indicates an intermolecular contact between two fragments (eg. cation and anion) that reside in the same asymmetric unit.

Symmetry Operators:

(1)	X,	Y,	Z	(2)	1/2-X,	1/2+Y,	-Z
(3)	-X,	-Y,	-Z	(4)	1/2+X,	1/2-Y,	Z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C4
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C8
H9
H10
O5
O4
C11
C10
N4
C12
H12
H11

The structure was solved by direct methods[2] and expanded using Fourier techniques[3]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement[4] was based on 967 observed reflections ($I > 3.00\sigma(I)$) and 182 variable parameters and converged (largest parameter shift was 0.04 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma||Fo| - |Fc||/\Sigma|Fo| = 0.062$$

$$R_w = \sqrt{(\Sigma w(|Fo| - |Fc|)^2/\Sigma wFo^2)} = 0.041$$

The standard deviation of an observation of unit weight[5] was 3.35. The weighting scheme was based on counting statistics. Plots of $\Sigma w(|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, $\sin\theta/\lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.19 and -0.26 $e^-/\AA^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[6] . Anomalous dispersion effects were included in Fcalc[7]; the values for Δf' and Δf" were those of Creagh and McAuley[8]. The values for the mass attenuation coefficients are those of Creagh and Hubbel[9]. All calculations were performed using the teXsan[10] crystallographic software package of Molecular Structure Corporation.

References

(1) DIFABS: Walker, N. & Stuart, Acta Cryst. A39, 158-166 (1983). An empirical absorption correction program.

(2) SHELXS86: Sheldrick, G.M. (1985). In: "Crystallographic Computing 3" (Eds G.M. Sheldrick, C. Kruger and R. Goddard) Oxford University Press, pp. 175-189.

(3) DIRDIF94: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., de Gelder, R., Israel, R. and Smits, J.M.M. (1994). The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(4) Least-Squares:

Function minimized: $\Sigma w(|Fo| - |Fc|)^2$

where w = $\frac{1}{\sigma^2(Fo)} = [\sigma_c^2(Fo) + \frac{p^2}{4}Fo^2]^{-1}$

$\sigma_c(Fo)$ = e.s.d. based on counting statistics

p = p-factor

(5) Standard deviation of an observation of unit weight:

$$\sqrt{\Sigma w(|Fo| - |Fc|)^2/(No - Nv)}$$

where: No = number of observations

Nv = number of variables

Experimental

Data Collection

An orange prism crystal of $C_{12}H_{12}N_4O_4$ having approximate dimensions of 0.10 x 0.10 x 0.10 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC7S diffractometer with graphite monochromated Cu-Kα radiation.

Cell constants and an orientation matrix for data collection , obtained from a least-squares refinement using the setting angles of 25 carefully centered reflections in the range $61.74 < 2\theta < 73.69°$ corresponded to a primitive triclinic cell with dimensions:

a = 8.103(2) Å	α = 106.80(4)°
b = 11.687(4) Å	β = 106.02(3)°
c = 7.240(3) Å	γ = 73.05(2)
V = 614.0(4) Å^3	

For Z = 2 and F.W. = 276.25, the calculated density is 1.49 g/cm^3. Based on a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be:

$P\bar{1}$ (#2)

The data were collected at a temperature of 20 $\pm$ 1°C using the ω scan technique to a maximum 2θ value of 120.2°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.14° with a take-off angle of 6.0°. Scans of (1.26 + 0.35 tan θ)° were made at a speed of 16.0°/min (in omega). The weak reflections ($I < 12.0\sigma(I)$) were rescanned (maximum of 4 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 1.0 mm and the crystal to detector distance was 400 mm, The computer-controlled slits were set to 9.0 mm (horizontal) and 13.0 mm (vertical).

Data Reduction

Of the 1972 reflections which were collected, 1822 were unique (R_{int} = 0.387). The intensities of three representative reflection were measured after every 150 reflections. Over the course of data collection, the standards increased by 0.6%. A linear correction factor was applied to the data to account for this phenomenon.

The linear absorption coefficient, μ, for Cu-Kα radiation is 9.3 cm^{-1}. An empirical absorption correction using the program DIFABS[1] was applied which resulted in transmission factors ranging from 0.47 to 1.00. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = 3.40496e-05).

Structure Solution and Refinement

(6) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(7) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

(8) Creagh, D. C. & McAuley, W.J .; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

(9) Creagh, D. C. & Hubbell, J.H..; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

(10) teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992).

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{12}H_{12}N_4O_4$
Formula Weight	276.25
Crystal Color, Habit	orange, prism
Crystal Dimensions	0.10 X 0.10 X 0.10 mm
Crystal System	triclinic
Lattice Type	Primitive
No. of Reflections Used for Unit Cell Determination (2θ range)	25 (61.7 - 73.7°)
Omega Scan Peak Width at Half-height	0.14°
Lattice Parameters	a = 8.103(2)Å b = 11.687(4) Å c = 7.240(3) Å α = 106.80(4)° β = 106.02(3)° γ = 73.05(2)°
	V = 614.0(4) Å^3
Space Group	$P\bar{1}$ (#2)
Z value	2
D_{calc}	1.494 g/cm^3
F_{000}	288.00
μ(CuKα)	9.30 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku AFC7S
Radiation	CuKα (λ = 1.54178 Å) graphite monochromated
Attenuator	Ni foil (factor = 9.42)
Take-off Angle	6.0°
Detector Aperture	9.0 mm horizontal 13.0 mm vertical
Crystal to Detector Distance	400 mm
Voltage, Current	0kV, 0mA
Temperature	20.0°C
Scan Type	ω
Scan Rate	16.0°/min (in ω) (up to 4 scans)
Scan Width	(1.26 + 0.35 tan θ)°
$2\theta_{max}$	120.2°
No. of Reflections Measured	Total: 1972 Unique: 1822 (R_{int} = 0.387)
Corrections	Lorentz-polarization Absorption (trans. factors: 0.4734 - 1.0000) Decay (0.64% increase) Secondary Extinction (coefficient: 3.40496e-05)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SHELXS86)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w(\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$w = \frac{1}{\sigma^2(Fo)} = [\sigma_c^2(Fo) + \frac{p^2}{4}Fo^2]^{-1}$
p-factor	0.0000
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	967

No. Variables	182
Reflection/Parameter Ratio	5.31
Residuals: R; Rw	0.062 ; 0.041
Goodness of Fit Indicator	3.35
Max Shift/Error in Final Cycle	0.04
Maximum peak in Final Diff. Map	0.19 $e^-/\AA^3$
Minimum peak in Final Diff. Map	-0.26 $e^-/\AA^3$

Table 1. Atomic coordinates and B_{iso}/B_{eq}

atom	x	y	z	B_{eq}
O(4)	0.7324(5)	0.3672(4)	0.0169(6)	6.3(1)
O(5)	0.5093(6)	0.3460(5)	-0.2249(7)	7.4(1)
O(7)	1.1094(5)	0.0998(3)	0.4133(6)	5.4(1)
O(14)	0.9067(5)	0.0070(3)	0.1839(5)	4.8(1)
N(1)	0.5346(6)	0.1470(4)	0.2164(7)	4.5(1)
N(3)	0.3915(6)	0.2234(5)	-0.0512(7)	5.6(1)
N(4)	0.5996(7)	0.3290(5)	-0.0659(8)	5.2(1)
N(9)	1.0042(5)	0.3271(4)	0.5880(6)	4.1(1)
C(1)	0.5638(8)	0.0844(6)	0.3709(9)	5.6(2)
C(2)	0.3900(7)	0.1581(6)	0.065(1)	5.3(2)
C(4)	0.5484(7)	0.2556(5)	0.0292(8)	4.5(2)
C(5)	0.6421(7)	0.2133(5)	0.1928(8)	3.9(1)
C(6)	0.8167(7)	0.2155(5)	0.3251(8)	4.0(2)
C(7)	0.9571(8)	0.1090(5)	0.3152(9)	4.4(2)
C(8)	0.8460(7)	0.3268(6)	0.4561(8)	3.9(2)
C(10)	1.0401(7)	0.4306(6)	0.7257(8)	4.6(2)
C(11)	0.9187(8)	0.5366(5)	0.7399(9)	4.8(2)
C(12)	0.7553(7)	0.5418(5)	0.6066(9)	4.6(2)
C(13)	0.7192(7)	0.4383(6)	0.4702(9)	4.4(2)
C(14)	1.0424(8)	-0.1034(6)	0.1739(9)	5.2(2)
H(1a)	0.4739	0.1213	0.4445	6.7633
H(1b)	0.5618	0.0004	0.3142	6.7633
H(1c)	0.6756	0.0896	0.4553	6.7633
H(2)	0.2955	0.1205	0.0457	6.2923

Table 1. Atomic coordinates and B_{iso}/B_{eq} (continued)

atom	x	y	z	B_{eq}
H(9)	1.1369	0.2737	0.5462	6.1843
H(10)	1.1526	0.4267	0.8121	5.5280
H(11)	0.9427	0.6073	0.8380	5.7572
H(12)	0.6691	0.6172	0.6114	5.5457
H(13)	0.6066	0.4422	0.3839	5.2786
H(14b)	1.0685	-0.1303	0.2927	6.2329
H(14c)	1.1455	-0.0881	0.1565	6.2329
H(14a)	1.0036	-0.1651	0.0655	6.2329

$$B_{eq} = \frac{8}{3}\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^*\cos\gamma + 2U_{13}aa^*cc^*\cos\beta + 2U_{23}bb^*cc^*\cos\alpha)$$

Table 2. Anisotropic Displacement Parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(4)	0.079(3)	0.077(3)	0.089(3)	-0.037(3)	-0.002(3)	0.027(3)
O(5)	0.095(4)	0.106(4)	0.076(3)	-0.026(3)	-0.012(3)	0.041(3)
O(7)	0.046(2)	0.054(3)	0.085(3)	-0.017(2)	-0.014(2)	0.006(2)
O(14)	0.054(3)	0.043(3)	0.071(3)	-0.014(2)	-0.002(2)	-0.003(2)
N(1)	0.056(3)	0.046(3)	0.072(3)	-0.026(3)	0.000(3)	0.017(3)
N(3)	0.066(4)	0.055(4)	0.081(4)	-0.030(3)	-0.017(3)	0.015(3)
N(4)	0.062(4)	0.062(4)	0.067(4)	-0.019(3)	-0.001(3)	0.012(3)
N(9)	0.042(3)	0.054(3)	0.058(3)	-0.023(3)	0.001(3)	0.010(3)
C(1)	0.072(4)	0.068(5)	0.079(5)	-0.034(4)	0.012(4)	0.009(4)
C(2)	0.047(4)	0.056(5)	0.082(5)	-0.024(4)	-0.006(4)	0.000(4)
C(4)	0.055(4)	0.048(4)	0.065(4)	-0.024(3)	-0.001(4)	0.009(4)
C(5)	0.050(4)	0.037(4)	0.059(4)	-0.017(3)	0.000(3)	0.010(3)
C(6)	0.049(4)	0.044(4)	0.053(4)	-0.020(3)	0.003(3)	0.003(3)
C(7)	0.066(4)	0.041(4)	0.060(4)	-0.022(4)	0.010(4)	0.009(3)
C(8)	0.052(4)	0.051(4)	0.051(4)	-0.028(3)	0.002(3)	0.009(3)
C(10)	0.053(4)	0.060(4)	0.058(4)	-0.032(4)	-0.003(3)	0.001(4)
C(11)	0.067(4)	0.049(4)	0.061(4)	-0.029(4)	-0.002(4)	0.001(4)
C(12)	0.057(4)	0.052(4)	0.065(4)	-0.017(3)	0.016(3)	0.002(3)
C(13)	0.047(4)	0.049(4)	0.067(4)	-0.026(4)	-0.001(3)	0.003(3)
C(14)	0.066(4)	0.048(4)	0.072(5)	-0.015(4)	0.003(4)	0.005(4)

The general temperature factor expression:

$$\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$$

Table 3. Bond Lengths($\AA$)

atom	atom	distance	atom	atom	distance
O(4)	N(4)	1.219(4)	O(5)	N(4)	1.217(5)
O(7)	C(7)	1.234(5)	O(14)	C(7)	1.381(6)
O(14)	C(14)	1.429(7)	N(1)	C(1)	1.439(7)
N(1)	C(2)	1.372(6)	N(1)	C(5)	1.393(6)
N(3)	C(2)	1.291(7)	N(3)	C(4)	1.356(5)
N(4)	C(4)	1.445(7)	N(9)	C(8)	1.371(5)
N(9)	C(10)	1.374(6)	C(4)	C(5)	1.359(7)
C(5)	C(6)	1.476(6)	C(6)	C(7)	1.419(8)
C(6)	C(8)	1.411(7)	C(8)	C(13)	1.401(8)
C(10)	C(11)	1.336(8)	C(11)	C(12)	1.404(6)
C(12)	C(13)	1.372(7)			

Table 4. Bond Lengths($\AA$)

atom	atom	distance	atom	atom	distance
N(9)	H(9)	1.15	C(1)	H(1a)	0.95
C(1)	H(1b)	0.95	C(1)	H(1c)	0.95
C(2)	H(2)	0.95	C(10)	H(10)	0.95
C(11)	H(11)	0.95	C(12)	H(12)	0.95
C(13)	H(13)	0.95	C(14)	H(14b)	0.95
C(14)	H(14c)	0.95	C(14)	H(14a)	0.95

Table 5. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
C(7)	O(14)	C(14)	114.9(4)	C(1)	N(1)	C(2)	126.9(5)
C(1)	N(1)	C(5)	127.8(4)	C(2)	N(1)	C(5)	105.2(5)
C(2)	N(3)	C(4)	101.7(5)	O(4)	N(4)	O(5)	124.7(5)
O(4)	N(4)	C(4)	117.6(5)	O(5)	N(4)	C(4)	117.7(5)
C(8)	N(9)	C(10)	122.7(5)	N(1)	C(2)	N(3)	115.1(5)
N(3)	C(4)	N(4)	117.9(5)	N(3)	C(4)	C(5)	115.2(5)
N(4)	C(4)	C(5)	126.9(5)	N(1)	C(5)	C(4)	102.7(4)
N(1)	C(5)	C(6)	120.3(5)	C(4)	C(5)	C(6)	136.8(5)
C(5)	C(6)	C(7)	120.9(5)	C(5)	C(6)	C(8)	119.2(5)
C(7)	C(6)	C(8)	119.8(5)	O(7)	C(7)	O(14)	119.8(6)
O(7)	C(7)	C(6)	127.2(5)	O(14)	C(7)	C(6)	112.9(5)
N(9)	C(8)	C(6)	119.2(6)	N(9)	C(8)	C(13)	116.3(5)
C(6)	C(8)	C(13)	124.4(5)	N(9)	C(10)	C(11)	120.9(5)
C(10)	C(11)	C(12)	118.7(5)	C(11)	C(12)	C(13)	120.3(6)
C(8)	C(13)	C(12)	121.0(5)				

Table 6. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
C(8)	N(9)	H(9)	122.8	C(10)	N(9)	H(9)	104.8
N(1)	C(1)	H(1a)	109.6	N(1)	C(1)	H(1b)	109.3
N(1)	C(1)	H(1c)	109.4	H(1a)	C(1)	H(1b)	109.6
H(1a)	C(1)	H(1c)	109.7	H(1b)	C(1)	H(1c)	109.3
N(1)	C(2)	H(2)	122.5	N(3)	C(2)	H(2)	122.3
N(9)	C(10)	H(10)	119.6	C(11)	C(10)	H(10)	119.5
C(10)	C(11)	H(11)	120.7	C(12)	C(11)	H(11)	120.6
C(11)	C(12)	H(12)	119.9	C(13)	C(12)	H(12)	119.9
C(8)	C(13)	H(13)	119.5	C(12)	C(13)	H(13)	119.5
O(14)	C(14)	H(14b)	109.5	O(14)	C(14)	H(14c)	109.4
O(14)	C(14)	H(14a)	109.5	H(14b)	C(14)	H(14c)	109.5
H(14b)	C(14)	H(14a)	109.5	H(14c)	C(14)	H(14a)	109.4

Table 7. Non-bonded Contacts out to 3.60 Å

atom	atom	distance	ADC	atom	atom	distance	ADC
O(4)	C(11)	3.212(6)	76602	O(4)	C(14)	3.224(8)	75502
O(4)	C(10)	3.249(6)	76602	O(4)	O(5)	3.495(7)	66502
O(5)	C(13)	3.315(7)	66502	O(5)	C(12)	3.338(7)	66502
O(5)	C(10)	3.581(8)	45401	O(5)	C(1)	3.586(8)	55401
O(7)	C(1)	3.228(8)	75602	O(7)	C(14)	3.517(7)	75602
O(7)	O(14)	3.534(6)	75602	O(14)	C(14)	3.271(7)	75502
O(14)	C(2)	3.324(6)	65502	O(14)	O(14)	3.351(8)	75502
N(1)	C(2)	3.528(8)	65502	N(3)	C(10)	3.505(8)	45401
N(4)	C(14)	3.403(8)	75502	N(9)	C(11)	3.484(7)	76602
N(9)	C(12)	3.555(7)	76602	C(1)	C(1)	3.58(1)	65602
C(2)	C(2)	3.58(1)	65502	C(7)	C(14)	3.524(8)	75502
C(8)	C(11)	3.574(8)	76602	C(10)	C(12)	3.407(8)	76602
C(10)	C(13)	3.563(8)	76602	C(13)	C(13)	3.52(1)	66602

The ADC (atom designator code) specifies the position of an atom in a crystal. The 5-digit number shown in the table is a composite of three one-digit numbers and one two-digit number: TA (first digit) + TB (second digit) + TC (third digit) + SN (last two digits). TA, TB and TC are the crystal lattice translation digits along cell edges a, b and c. A translation digit of 5 indicates the origin unit cell. If TA = 4, this indicates a translation of one unit cell length along the a-axis in the negative direction. Each translation digit can range in value from 1 to 9 and thus ± 4 lattice translations from the origin (TA=5, TB=5, TC=5) can be represented.

The SN, or symmetry operator number, refers to the number of the symmetry operator used to generate the coordinates of the target atom. A list of symmetry operators relevant to this structure are given below.

For a given intermolecular contact, the first atom (origin atom) is located in the origin unit cell and its position can be generated using the identity operator (SN=1). Thus, the ADC for an origin atom is always 55501. The position of the second atom (target atom) can be generated using the ADC and the coordinates of the atom in the parameter table. For example, an ADC of 47502 refers to the target atom moved through symmetry operator two, then translated -1 cell translations along the a axis, +2 cell translations along the b axis, and 0 cell translations along the c axis.

An ADC of 1 indicates an intermolecular contact between two fragments (eg. cation and anion) that reside in the same asymmetric unit.

Symmetry Operators:

(1)	X,	Y,	Z	(2)	-X,	-Y,	-Z

Table 8. Least Squares Planes

Plane number 1

Atoms defining plane	Distance
C(5)	0.0
C(7)	0.0
C(8)	0.0

Additional Atoms	Distance
C(6)	-0.023

Summary

plane	mean deviation	χ^2
1	0.0000	0.0

Hydrogen bonds

A	H	B	B-adc	A...B	A-H	H...B	A-H...B
N(9)	H(9)	O(7)	1	2.592(6)	1.15	2.03	105.9

The ADC (atom designator code) specifies the position of an atom in a crystal. The 5-digit number shown in the table is a composite of three one-digit numbers and one two-digit number: TA (first digit) + TB (second digit) + TC (third digit) + SN (last two digits). TA, TB and TC are the crystal lattice translation digits along cell edges a, b and c. A translation digit of 5 indicates the origin unit cell. If TA = 4, this indicates a translation of one unit cell length along the a-axis in the negative direction. Each translation digit can range in value from 1 to 9 and thus ± 4 lattice translations from the origin (TA=5, TB=5, TC=5) can be represented.

The SN, or symmetry operator number, refers to the number of the symmetry operator used to generate the coordinates of the target atom. A list of symmetry operators relevant to this structure are given below.

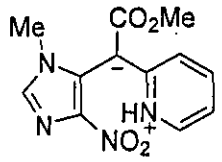
For a given intermolecular contact, the first atom (origin atom) is located in the origin unit cell and its position can be generated using the identity operator (SN=1). Thus, the ADC for an origin atom is always 55501. The position of the second atom (target atom) can be generated using the ADC and the coordinates of the atom in the parameter table. For example, an ADC of 47502 refers to the target atom moved through symmetry operator two, then translated -1 cell translations along the a axis, +2 cell translations along the b axis, and 0 cell translations along the c axis.

An ADC of 1 indicates an intermolecular contact between two fragments (eg. cation and anion) that reside in the same asymmetric unit.

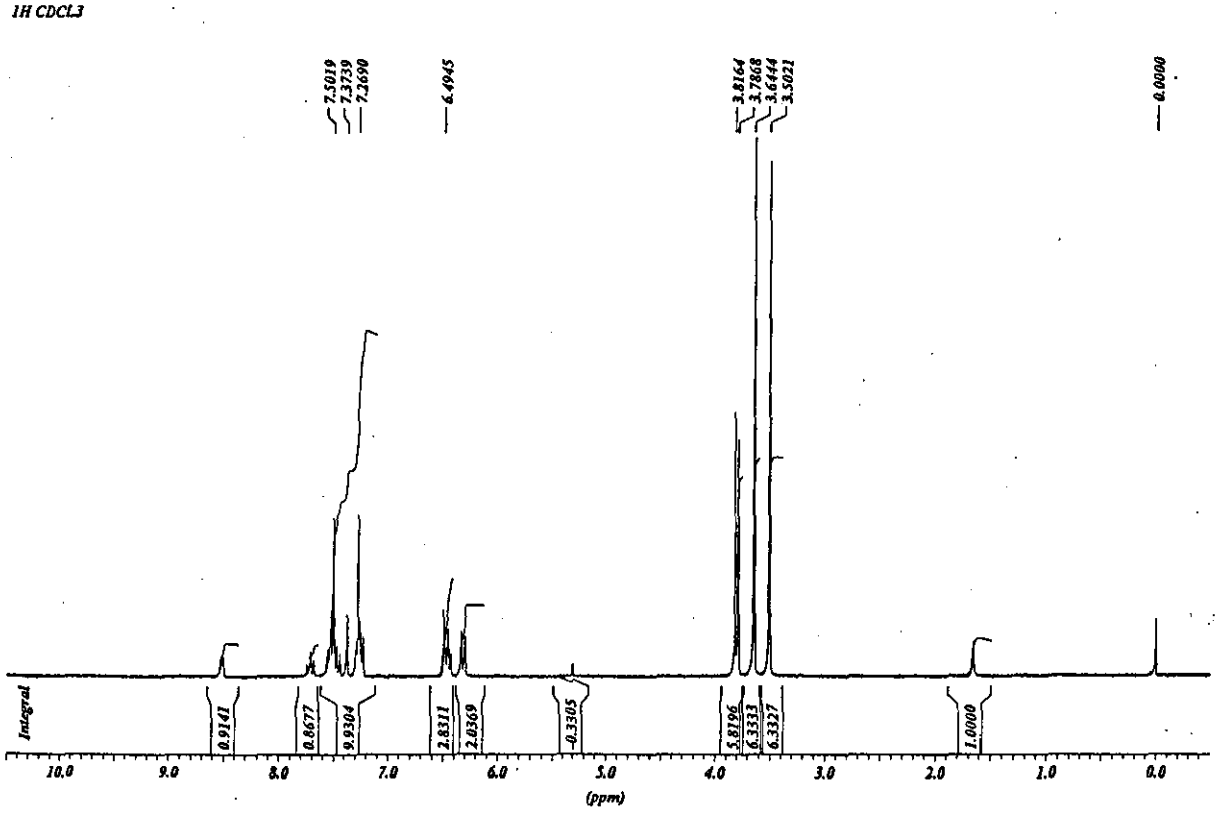
Symmetry Operators:

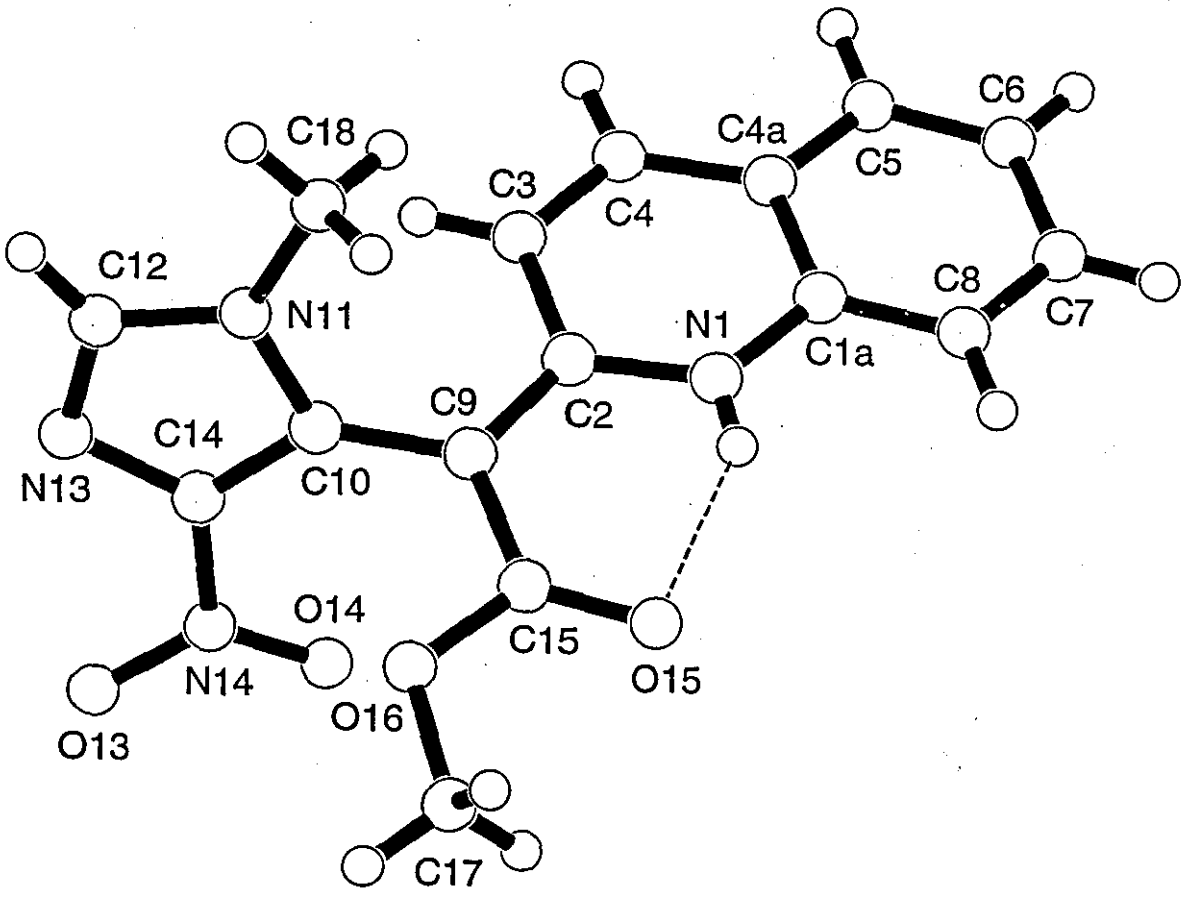
(1)	X,	Y,	Z	(2)	1/2-X,	1/2+Y,	-Z
(3)	-X,	-Y,	-Z	(4)	1/2+X,	1/2-Y,	Z

^{1}H NMR spectrum at 250 MHz, showing methyl 2-(1-methyl-4-nitro-1*H*-imidazol-5-yl)-2-pyridin-2-yl ethanoate (109), showing duplicate signals.



109




C18
C3
C4
C4a
C5
C6
C12
N11
N1
C1a
C8
C7
C9
C2
C14
C10
N13
O14
C15
N14
O15
O16
O13
C17

Experimental

Data Collection

An orange plate crystal of $C_{16}H_{14}N_4O_4$ having approximate dimensions of 0.10 x 0.10 x 0.02 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC7S diffractometer with graphite monochromated Cu-Kα radiation.

Cell constants and an orientation matrix for data collection , obtained from a least-squares refinement using the setting angles of 25 carefully centered reflections in the range $45.74 < 2\theta < 65.62°$ corresponded to a primitive orthorhombic cell with dimensions:

a = 12.053(8) $\AA$

b = 29.350(7) $\AA$

c = 8.597(6) $\AA$

V = 3041(3) $\AA^3$

For Z = 8 and F.W. = 326.31, the calculated density is 1.42 g/cm^3. The systematic absences of:

0kl: $k \neq 2n$

h0l: $l \neq 2n$

hk0: $h \neq 2n$

uniquely determine the space group to be:

Pbca (#61)

The data were collected at a temperature of 20 $\pm$ 1°C using the ω scan technique to a maximum 2θ value of 120.2°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.26° with a take-off angle of 6.0°. Scans of (1.15 + 0.35 tan θ)° were made at a speed of 16.0°/min (in omega). The weak reflections ($I < 12.0\sigma(I)$) were rescanned (maximum of 4 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 1.0 mm and the crystal to detector distance was 400 mm, The computer-controlled slits were set to 9.0 mm (horizontal) and 13.0 mm (vertical).

Data Reduction

A total of 2626 reflections was collected. The intensities of three representative reflection were measured after every 150 reflections. Over the course of data collection, the standards increased by 0.8%. A linear correction factor was applied to the data to account for this phenomenon.

The linear absorption coefficient, μ, for Cu-Kα radiation is 8.4 cm^{-1}. An empirical absorption correction using the program DIFABS[1] was applied which resulted in transmission factors ranging from 0.51 to 1.00.

The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = 1.20577e-06).

Structure Solution and Refinement

The structure was solved by direct methods[2] and expanded using Fourier techniques[3]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement[4] was based on 803 observed reflections ($I > 3.00\sigma(I)$) and 218 variable parameters and converged (largest parameter shift was 0.02 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma||Fo| - |Fc||/\Sigma|Fo| = 0.048$$

$$R_w = \sqrt{(\Sigma w(|Fo| - |Fc|)^2/\Sigma wFo^2)} = 0.027$$

The standard deviation of an observation of unit weight[5] was 2.50. The weighting scheme was based on counting statistics and included a factor (p = 0.001) to downweight the intense reflections. Plots of $\Sigma w(|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, $\sin\theta/\lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.16 and -0.15 $e^-/\AA^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[6] . Anomalous dispersion effects were included in Fcalc[7]; the values for Δf' and Δf" were those of Creagh and McAuley[8]. The values for the mass attenuation coefficients are those of Creagh and Hubbel[9]. All calculations were performed using the teXsan[10] crystallographic software package of Molecular Structure Corporation.

References

(1) DIFABS: Walker, N. & Stuart, Acta Cryst. A39, 158-166 (1983). An empirical absorption correction program.

(2) SIR92: Altomare, A., Cascarano, M., Giacovazzo, C., Guagliardi, A. (1993). J. Appl. Cryst., 26, 343.

(3) DIRDIF94: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., de Gelder, R., Israel, R. and Smits, J.M.M. (1994). The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(4) Least-Squares:

Function minimized: $\Sigma w(|Fo| - |Fc|)^2$

where w = $\frac{1}{\sigma^2(Fo)} = [\sigma_c^2(Fo) + \frac{p^2}{4}Fo^2]^{-1}$

$\sigma_c(Fo)$ = e.s.d. based on counting statistics

p = p-factor

(5) Standard deviation of an observation of unit weight:

$$\sqrt{\Sigma w(|Fo| - |Fc|)^2/(No - Nv)}$$

where: No = number of observations

Nv = number of variables

(6) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(7) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

(8) Creagh, D. C. & McAuley, W.J .; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

(9) Creagh, D. C. & Hubbell, J.H..; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

(10) teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992).

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{16}H_{14}N_4O_4$
Formula Weight	326.31
Crystal Color, Habit	orange, plate
Crystal Dimensions	0.10 X 0.10 X 0.02 mm
Crystal System	orthorhombic
Lattice Type	Primitive
No. of Reflections Used for Unit	
Cell Determination (2θ range)	25 (45.7 - 65.6°)
Omega Scan Peak Width	
at Half-height	0.26°
Lattice Parameters	a = 12.053(8)Å b = 29.350(7) Å c = 8.597(6) Å
	V = 3041(3) Å^3
Space Group	Pbca (#61)
Z value	8
D_{calc}	1.425 g/cm^3
F_{000}	1360.00
μ(CuKα)	8.40 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku AFC7S
Radiation	CuKα (λ = 1.54178 Å)

	graphite monochromated
Attenuator	Ni foil (factor = 9.42)
Take-off Angle	6.0°
Detector Aperture	9.0 mm horizontal 13.0 mm vertical
Crystal to Detector Distance	400 mm
Voltage, Current	0kV, 0mA
Temperature	20.0°C
Scan Type	ω
Scan Rate	16.0°/min (in ω) (up to 4 scans)
Scan Width	$(1.15 + 0.35 \tan \theta)°$
$2\theta_{max}$	120.2°
No. of Reflections Measured	Total: 2626
Corrections	Lorentz-polarization Absorption (trans. factors: 0.5093 - 1.0000) Decay (0.84% increase) Secondary Extinction (coefficient: 1.20577e-06)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w(\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$w = \frac{1}{\sigma^2(Fo)} = [\sigma_c^2(Fo) + \frac{p^2}{4}Fo^2]^{-1}$
p-factor	0.0010
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	803
No. Variables	218
Reflection/Parameter Ratio	3.68

Residuals: R; Rw	0.048 ; 0.027
Goodness of Fit Indicator	2.50
Max Shift/Error in Final Cycle	0.02
Maximum peak in Final Diff. Map	0.16 $e^-/\AA^3$
Minimum peak in Final Diff. Map	-0.15 $e^-/\AA^3$

Table 1. Atomic coordinates and B_{iso}/B_{eq}

atom	x	y	z	B_{eq}
O(13)	1.2857(4)	0.1612(2)	-0.0695(5)	7.9(2)
O(14)	1.1789(4)	0.1092(2)	0.0290(6)	7.0(2)
O(15)	0.8621(4)	0.1078(2)	0.1493(5)	6.8(2)
O(16)	0.9621(4)	0.1635(2)	0.0312(6)	6.9(2)
N(1)	0.9321(4)	0.0819(2)	0.4312(6)	5.8(2)
N(11)	1.1205(5)	0.2107(2)	0.3513(6)	5.6(2)
N(13)	1.2590(5)	0.2151(2)	0.1831(7)	6.4(2)
N(14)	1.2194(5)	0.1469(2)	0.0304(8)	6.0(2)
C(1a)	0.9240(7)	0.0506(3)	0.5522(9)	5.6(2)
C(2)	1.0143(6)	0.1123(3)	0.4075(9)	5.2(2)
C(3)	1.0985(6)	0.1137(3)	0.528(1)	6.1(2)
C(4a)	1.0065(7)	0.0518(3)	0.669(1)	6.0(3)
C(4)	1.0923(7)	0.0840(3)	0.6496(8)	6.6(3)
C(5)	1.0012(7)	0.0199(3)	0.7858(9)	7.5(3)
C(6)	0.9194(8)	-0.0122(3)	0.7880(9)	7.6(3)
C(7)	0.8365(7)	-0.0123(3)	0.674(1)	6.9(3)
C(8)	0.8390(6)	0.0195(3)	0.5576(8)	6.1(2)
C(9)	1.0202(6)	0.1402(3)	0.2764(9)	5.2(2)
C(10)	1.1076(7)	0.1722(3)	0.2599(9)	5.0(2)
C(12)	1.2113(7)	0.2349(3)	0.303(1)	6.7(3)
C(14)	1.1964(7)	0.1775(3)	0.1567(9)	5.2(2)
C(15)	0.9395(6)	0.1344(3)	0.1508(9)	5.9(3)
C(17)	0.8906(6)	0.1599(3)	-0.1015(8)	8.6(3)
C(18)	1.0424(6)	0.2249(3)	0.4753(8)	7.9(3)

Table 1. Atomic coordinates and B_{iso}/B_{eq} (continued)

atom	x	y	z	B_{eq}
H(1)	0.8956	0.0802	0.3632	8.1015
H(3)	1.1569	0.1354	0.5210	7.4856
H(4)	1.1494	0.0851	0.7254	7.8229
H(5)	1.0555	0.0205	0.8657	9.2774
H(6)	0.9183	-0.0345	0.8682	9.1856
H(7)	0.7789	-0.0340	0.6759	8.3346
H(8)	0.7825	0.0202	0.4808	7.3366
H(12)	1.2364	0.2621	0.3500	8.1788
H(17a)	0.8791	0.1285	-0.1253	10.4135
H(17b)	0.8214	0.1738	-0.0790	10.4135
H(17c)	0.9238	0.1745	-0.1882	10.4135
H(18a)	0.9694	0.2269	0.4338	9.4954
H(18b)	1.0640	0.2539	0.5143	9.4954
H(18c)	1.0435	0.2032	0.5572	9.4954

$$B_{eq} = \frac{8}{3}\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^*\cos\gamma + 2U_{13}aa^*cc^*\cos\beta + 2U_{23}bb^*cc^*\cos\alpha)$$

Table 2. Anisotropic Displacement Parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(13)	0.100(4)	0.114(5)	0.085(4)	0.000(4)	0.028(3)	0.008(3)
O(14)	0.090(4)	0.075(4)	0.100(4)	-0.013(4)	0.006(3)	-0.011(4)
O(15)	0.073(4)	0.106(5)	0.079(4)	-0.027(4)	-0.011(3)	0.009(3)
O(16)	0.069(4)	0.119(5)	0.074(4)	-0.007(3)	-0.011(3)	0.013(4)
N(1)	0.056(4)	0.088(5)	0.074(5)	-0.007(4)	-0.006(4)	0.007(4)
N(11)	0.061(5)	0.075(5)	0.076(5)	-0.003(4)	-0.004(4)	-0.006(4)
N(13)	0.076(5)	0.087(6)	0.081(5)	-0.009(5)	0.002(4)	-0.002(4)
N(14)	0.070(5)	0.083(6)	0.077(5)	0.006(5)	0.003(4)	0.004(6)
C(1a)	0.070(6)	0.075(6)	0.067(6)	-0.002(5)	0.012(6)	0.007(5)
C(2)	0.046(5)	0.068(5)	0.084(6)	-0.009(5)	0.005(5)	-0.005(5)
C(3)	0.053(5)	0.084(6)	0.093(6)	-0.011(5)	-0.011(5)	-0.002(5)
C(4a)	0.062(6)	0.099(7)	0.065(6)	-0.010(6)	-0.003(6)	-0.001(6)
C(4)	0.074(6)	0.099(7)	0.075(6)	-0.001(6)	-0.012(5)	0.001(5)
C(5)	0.100(8)	0.118(8)	0.067(6)	-0.005(7)	0.003(6)	0.012(6)
C(6)	0.101(8)	0.119(9)	0.069(7)	0.006(7)	0.013(6)	0.014(6)
C(7)	0.076(6)	0.099(8)	0.088(6)	-0.005(6)	0.018(5)	0.004(6)
C(8)	0.069(6)	0.087(7)	0.077(6)	-0.012(5)	0.002(5)	0.007(5)
C(9)	0.049(5)	0.080(6)	0.069(6)	-0.011(5)	0.004(5)	0.012(5)
C(10)	0.060(5)	0.062(6)	0.066(6)	-0.002(5)	-0.003(5)	0.001(5)
C(12)	0.067(6)	0.094(7)	0.096(7)	-0.024(6)	-0.014(5)	0.002(6)
C(14)	0.060(6)	0.056(5)	0.081(6)	0.003(5)	-0.010(6)	0.009(5)
C(15)	0.059(6)	0.091(8)	0.074(6)	-0.005(5)	0.001(6)	0.007(6)
C(17)	0.078(6)	0.172(9)	0.078(6)	-0.021(6)	-0.018(5)	0.022(6)
C(18)	0.079(6)	0.124(8)	0.095(6)	-0.004(6)	0.009(5)	-0.023(5)

Table 2. Anisotropic Displacement Parameters (continued)

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}

The general temperature factor expression:

$$\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$$

Table 3. Bond Lengths($\AA$)

atom	atom	distance	atom	atom	distance
O(13)	N(14)	1.245(7)	O(14)	N(14)	1.210(7)
O(15)	C(15)	1.217(7)	O(16)	C(15)	1.365(7)
O(16)	C(17)	1.434(7)	N(1)	C(1a)	1.391(7)
N(1)	C(2)	1.348(7)	N(11)	C(10)	1.384(8)
N(11)	C(12)	1.369(8)	N(11)	C(18)	1.482(7)
N(13)	C(12)	1.313(8)	N(13)	C(14)	1.355(8)
N(14)	C(14)	1.436(9)	C(1a)	C(4a)	1.412(9)
C(1a)	C(8)	1.373(9)	C(2)	C(3)	1.452(8)
C(2)	C(9)	1.395(8)	C(3)	C(4)	1.363(8)
C(4a)	C(4)	1.410(9)	C(4a)	C(5)	1.376(9)
C(5)	C(6)	1.36(1)	C(6)	C(7)	1.399(9)
C(7)	C(8)	1.369(9)	C(9)	C(10)	1.418(8)
C(9)	C(15)	1.463(9)	C(10)	C(14)	1.399(9)

Table 4. Bond Lengths($\mathring{A}$)

atom	atom	distance	atom	atom	distance
N(1)	H(1)	0.73	C(3)	H(3)	0.95
C(4)	H(4)	0.95	C(5)	H(5)	0.95
C(6)	H(6)	0.95	C(7)	H(7)	0.94
C(8)	H(8)	0.95	C(12)	H(12)	0.95
C(17)	H(17a)	0.95	C(17)	H(17b)	0.95
C(17)	H(17c)	0.95	C(18)	H(18a)	0.95
C(18)	H(18b)	0.95	C(18)	H(18c)	0.95

Table 5. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
C(15)	O(16)	C(17)	115.6(6)	C(1a)	N(1)	C(2)	127.0(6)
C(10)	N(11)	C(12)	109.8(6)	C(10)	N(11)	C(18)	124.5(7)
C(12)	N(11)	C(18)	125.6(8)	C(12)	N(13)	C(14)	104.3(7)
O(13)	N(14)	O(14)	124.0(8)	O(13)	N(14)	C(14)	115.8(7)
O(14)	N(14)	C(14)	120.1(8)	N(1)	C(1a)	C(4a)	117.7(8)
N(1)	C(1a)	C(8)	121.1(8)	C(4a)	C(1a)	C(8)	121.2(8)
N(1)	C(2)	C(3)	115.1(7)	N(1)	C(2)	C(9)	123.3(7)
C(3)	C(2)	C(9)	121.6(7)	C(2)	C(3)	C(4)	119.4(7)
C(1a)	C(4a)	C(4)	116.8(8)	C(1a)	C(4a)	C(5)	118.0(8)
C(4)	C(4a)	C(5)	125.1(9)	C(3)	C(4)	C(4a)	123.9(7)
C(4a)	C(5)	C(6)	120.9(9)	C(5)	C(6)	C(7)	120.5(9)
C(6)	C(7)	C(8)	119.7(8)	C(1a)	C(8)	C(7)	119.6(7)
C(2)	C(9)	C(10)	120.5(7)	C(2)	C(9)	C(15)	119.6(7)
C(10)	C(9)	C(15)	119.8(7)	N(11)	C(10)	C(9)	124.6(8)
N(11)	C(10)	C(14)	100.6(7)	C(9)	C(10)	C(14)	134.8(8)
N(11)	C(12)	N(13)	111.1(7)	N(13)	C(14)	N(14)	121.8(8)
N(13)	C(14)	C(10)	114.2(7)	N(14)	C(14)	C(10)	123.9(8)
O(15)	C(15)	O(16)	123.2(8)	O(15)	C(15)	C(9)	126.3(8)
O(16)	C(15)	C(9)	110.5(7)				

Table 6. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
C(1a)	N(1)	H(1)	120.6	C(2)	N(1)	H(1)	111.4
C(2)	C(3)	H(3)	119.4	C(4)	C(3)	H(3)	121.2
C(3)	C(4)	H(4)	117.6	C(4a)	C(4)	H(4)	118.5
C(4a)	C(5)	H(5)	119.0	C(6)	C(5)	H(5)	120.1
C(5)	C(6)	H(6)	119.7	C(7)	C(6)	H(6)	119.8
C(6)	C(7)	H(7)	121.0	C(8)	C(7)	H(7)	119.3
C(1a)	C(8)	H(8)	119.8	C(7)	C(8)	H(8)	120.6
N(11)	C(12)	H(12)	124.1	N(13)	C(12)	H(12)	124.7
O(16)	C(17)	H(17a)	109.3	O(16)	C(17)	H(17b)	109.5
O(16)	C(17)	H(17c)	109.7	H(17a)	C(17)	H(17b)	109.4
H(17a)	C(17)	H(17c)	109.3	H(17b)	C(17)	H(17c)	109.7
N(11)	C(18)	H(18a)	109.5	N(11)	C(18)	H(18b)	109.3
N(11)	C(18)	H(18c)	109.6	H(18a)	C(18)	H(18b)	109.3
H(18a)	C(18)	H(18c)	109.5	H(18b)	C(18)	H(18c)	109.5

Table 7. Non-bonded Contacts out to 3.60 $\AA$

atom	atom	distance	ADC	atom	atom	distance	ADC
O(13)	C(17)	3.098(9)	55408	O(13)	N(1)	3.154(7)	8
O(13)	C(12)	3.364(9)	55407	O(13)	C(2)	3.405(8)	8
O(14)	N(1)	3.174(7)	8	O(14)	C(8)	3.35(1)	8
O(14)	C(6)	3.46(1)	75605	O(14)	C(1a)	3.489(9)	8
O(14)	C(4)	3.504(9)	55401	O(14)	O(15)	3.539(7)	8
O(15)	C(14)	3.311(8)	45508	O(15)	N(14)	3.444(8)	45508
O(15)	C(3)	3.529(8)	45508	O(16)	C(18)	3.448(9)	55407
N(1)	N(14)	3.213(8)	45508	N(1)	C(6)	3.307(9)	75605
N(1)	C(7)	3.573(9)	75605	N(13)	C(15)	3.517(9)	8
C(2)	C(6)	3.48(1)	75605	C(2)	C(7)	3.51(1)	75605
C(3)	C(7)	3.53(1)	75605	C(4a)	C(8)	3.410(9)	75605
C(4)	C(7)	3.59(1)	75605	C(14)	C(15)	3.60(1)	8

The ADC (atom designator code) specifies the position of an atom in a crystal. The 5-digit number shown in the table is a composite of three one-digit numbers and one two-digit number: TA (first digit) + TB (second digit) + TC (third digit) + SN (last two digits). TA, TB and TC are the crystal lattice translation digits along cell edges a, b and c. A translation digit of 5 indicates the origin unit cell. If TA = 4, this indicates a translation of one unit cell length along the a-axis in the negative direction. Each translation digit can range in value from 1 to 9 and thus ± 4 lattice translations from the origin (TA=5, TB=5, TC=5) can be represented.

The SN, or symmetry operator number, refers to the number of the symmetry operator used to generate the coordinates of the target atom. A list of symmetry operators relevant to this structure are given below.

For a given intermolecular contact, the first atom (origin atom) is located in the origin unit cell and its position can be generated using the identity operator (SN=1). Thus, the ADC for an origin atom is always 55501. The position of the second atom (target atom) can be generated using the ADC and the coordinates of the atom in the parameter table. For example, an ADC of 47502 refers to the target atom moved through symmetry operator two, then translated -1 cell translations along the a axis, +2 cell translations along the b axis, and 0 cell translations along the c axis.

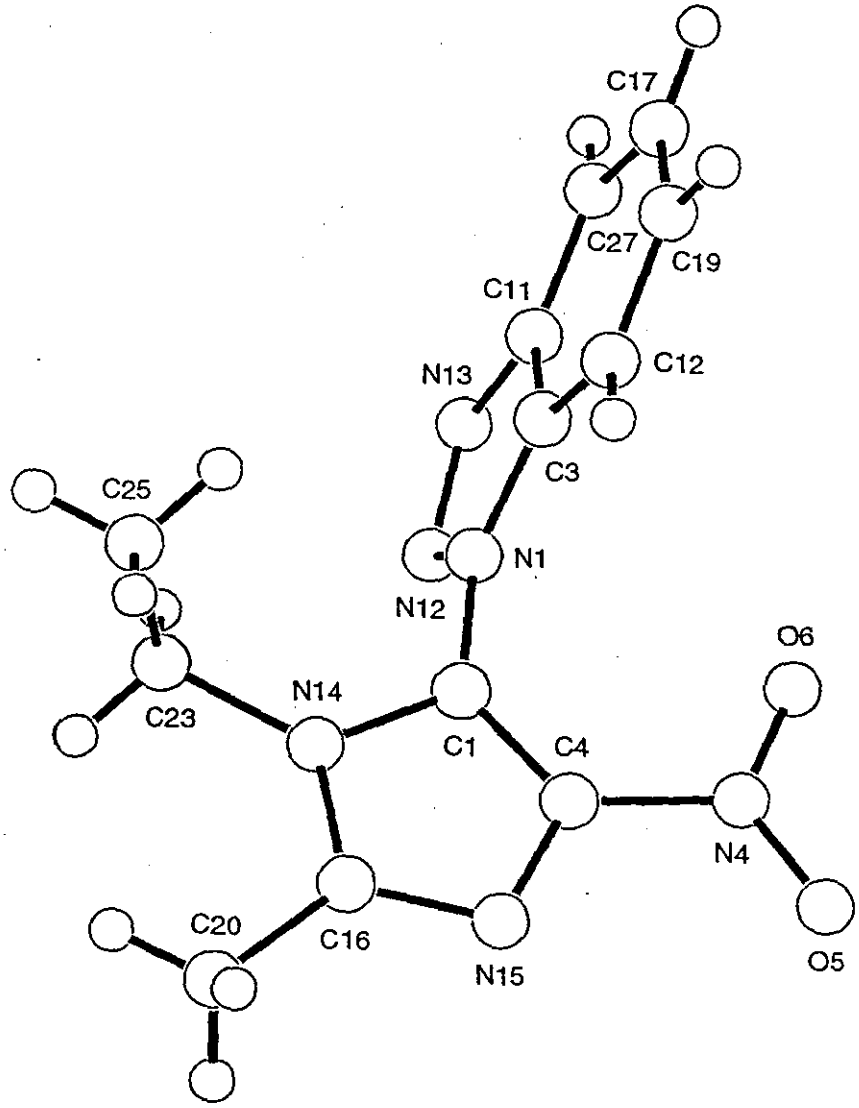
An ADC of 1 indicates an intermolecular contact between two fragments (eg. cation and anion) that reside in the same asymmetric unit.

Symmetry Operators:

(1)	X,	Y,	Z	(2)	1/2+X,	1/2-Y,	-Z
(3)	-X,	1/2+Y,	1/2-Z	(4)	1/2-X,	-Y,	1/2+Z
(5)	-X,	-Y,	-Z	(6)	1/2-X,	1/2+Y,	Z
(7)	X,	1/2-Y,	1/2+Z	(8)	1/2+X,	Y,	1/2-Z

Hydrogen bonds

A	H	B	B-adc	A...B	A-H	H...B	A-H...B
N(1)	H(1)	O(15)	1	2.676(7)	0.73	2.05	143.8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C27
C19
C11
C12
N13
C3
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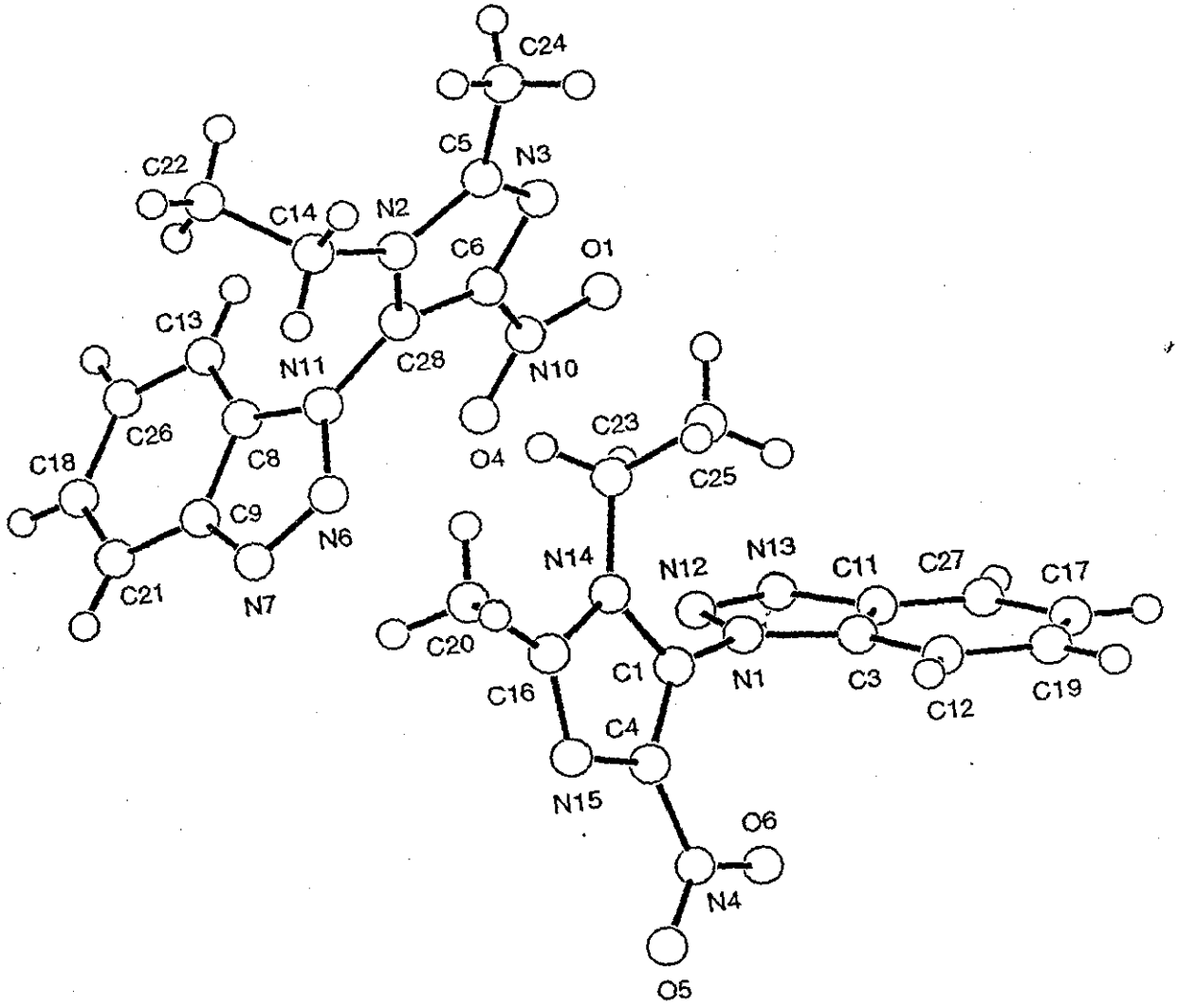
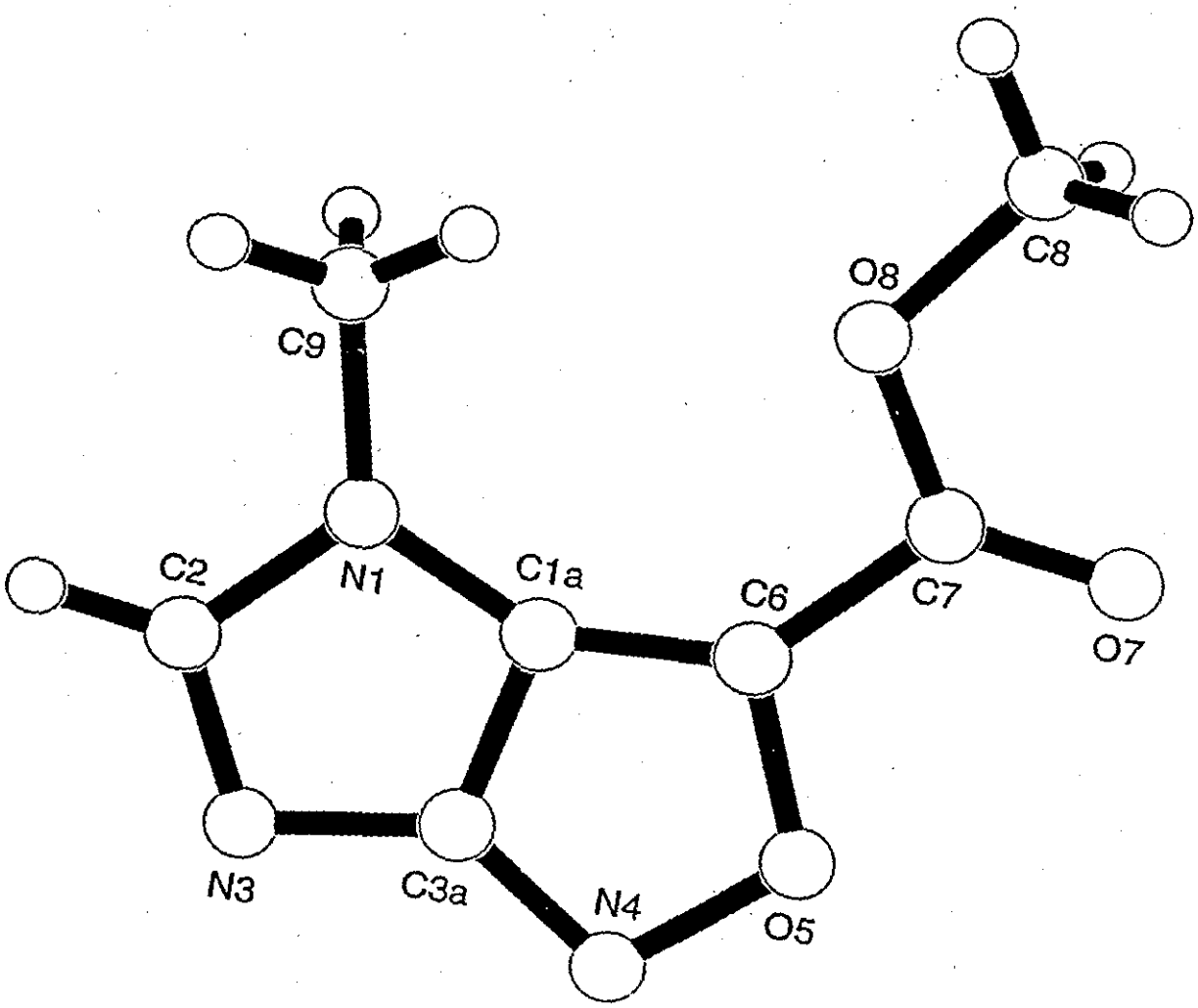
N12
O6
N14
C23
C1
C4
N4
C20
C16
N15
O5


C24
C5
N3
C22
C14
N2
C6
O1
C13
N11
C28
N10
C26
C8
O4
C23
C18
C25
C9
N6
N14
N12
N13
C11
C27
C17
C21
N7
C20
C1
N1
C3
C12
C19
C16
C4
N15
O6
N4
O5

Preliminary structure, which requires further refinement.


C9
C8
O8
C2
N1
C1a
C6
C7
O7
N3
C3a
N4
O5

Experimental

Data Collection

A colorless plate crystal of $C_7H_7N_3O_3$ having approximate dimensions of 0.10 x 0.10 x 0.02 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC7S diffractometer with graphite monochromated Cu-Kα radiation.

Cell constants and an orientation matrix for data collection , obtained from a least-squares refinement using the setting angles of 25 carefully centered reflections in the range $61.29 < 2\theta < 74.23°$ corresponded to a primitive monoclinic cell with dimensions:

$a = 7.784(4)\ \AA$

$b = 14.272(2)\ \AA \qquad \beta = 114.04(3)°$

$c = 7.871(3)\ \AA$

$V = 798.6(5)\ \AA^3$

For Z = 4 and F.W. = 181.15, the calculated density is 1.51 g/cm^3. The systematic absences of:

h0l: h $\neq$ 2n

0k0: k $\neq$ 2n

uniquely determine the space group to be:

$P2_1/a$ (#14)

The data were collected at a temperature of 20 $\pm$ 1°C using the ω scan technique to a maximum 2θ value of 120.2°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.32° with a take-off angle of 6.0°. Scans of $(1.21 + 0.35 \tan \theta)°$ were made at a speed of 16.0°/min (in omega). The weak reflections ($I < 12.0\sigma(I)$) were rescanned (maximum of 4 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 1.0 mm and the crystal to detector distance was 400 mm, The computer-controlled slits were set to 9.0 mm (horizontal) and 13.0 mm (vertical).

Data Reduction

Of the 1346 reflections which were collected, 1249 were unique ($R_{int} = 0.061$). The intensities of three representative reflection were measured after every 150 reflections. Over the course of data collection, the standards increased by 1.1%. A linear correction factor was applied to the data to account for this phenomenon.

The linear absorption coefficient, μ, for Cu-Kα radiation is 10.4 cm^{-1}. An empirical absorption correction using the program DIFABS[1] was applied which resulted in transmission factors ranging from 0.46 to 1.00. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction

was applied (coefficient = 7.90791e-06).

Structure Solution and Refinement

The structure was solved by direct methods[2] and expanded using Fourier techniques[3]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement[4] was based on 747 observed reflections ($I > 3.00\sigma(I)$) and 119 variable parameters and converged (largest parameter shift was 0.01 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma||Fo| - |Fc||/\Sigma|Fo| = 0.065$$

$$R_w = \sqrt{(\Sigma w(|Fo| - |Fc|)^2/\Sigma wFo^2)}] = 0.045$$

The standard deviation of an observation of unit weight[5] was 5.09. The weighting scheme was based on counting statistics and included a factor (p = 0.001) to downweight the intense reflections. Plots of $\Sigma w(|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, sin θ/λ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.19 and -0.21 $e^-/\AA^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[6] . Anomalous dispersion effects were included in Fcalc[7]; the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley[8]. The values for the mass attenuation coefficients are those of Creagh and Hubbel[9]. All calculations were performed using the teXsan[10] crystallographic software package of Molecular Structure Corporation.

References

(1) DIFABS: Walker, N. & Stuart, Acta Cryst. A39, 158-166 (1983). An empirical absorption correction program.

(2) SHELXS86: Sheldrick, G.M. (1985). In: "Crystallographic Computing 3" (Eds G.M. Sheldrick, C. Kruger and R. Goddard) Oxford University Press, pp. 175-189.

(3) DIRDIF94: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., de Gelder, R., Israel, R. and Smits, J.M.M. (1994). The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(4) Least-Squares:

Function minimized: $\Sigma w(|Fo| - |Fc|)^2$

where w = $\frac{1}{\sigma^2(Fo)} = [\sigma_c^2(Fo) + \frac{p^2}{4}Fo^2]^{-1}$

$\sigma_c(Fo)$ = e.s.d. based on counting statistics

p = p-factor

(5) Standard deviation of an observation of unit weight:

$$\sqrt{\Sigma w(|Fo| - |Fc|)^2/(No - Nv)}$$

where: No = number of observations

Nv = number of variables

(6) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(7) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

(8) Creagh, D. C. & McAuley, W.J .; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

(9) Creagh, D. C. & Hubbell, J.H..; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

(10) teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992).

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_7H_7N_3O_3$
Formula Weight	181.15
Crystal Color, Habit	colorless, plate
Crystal Dimensions	0.10 X 0.10 X 0.02 mm
Crystal System	monoclinic
Lattice Type	Primitive
No. of Reflections Used for Unit Cell Determination (2θ range)	25 (61.3 - 74.2°)
Omega Scan Peak Width at Half-height	0.32°
Lattice Parameters	a = 7.784(4)Å b = 14.272(2) Å c = 7.871(3) Å β = 114.04(3)° V = 798.6(5) Å^3
Space Group	$P2_1/a$ (#14)
Z value	4
D_{calc}	1.507 g/cm^3
F_{000}	376.00
μ(CuKα)	10.37 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku AFC7S

Radiation	CuKα ($\lambda = 1.54178$ Å) graphite monochromated
Attenuator	Ni foil (factor = 9.42)
Take-off Angle	6.0°
Detector Aperture	9.0 mm horizontal 13.0 mm vertical
Crystal to Detector Distance	400 mm
Voltage, Current	0kV, 0mA
Temperature	20.0°C
Scan Type	ω
Scan Rate	16.0°/min (in ω) (up to 4 scans)
Scan Width	$(1.21 + 0.35 \tan \theta)°$
$2\theta_{max}$	120.2°
No. of Reflections Measured	Total: 1346 Unique: 1249 ($R_{int} = 0.061$)
Corrections	Lorentz-polarization Absorption (trans. factors: 0.4635 - 1.0000) Decay (1.07% increase) Secondary Extinction (coefficient: 7.90791e-06)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SHELXS86)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w(\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$w = \frac{1}{\sigma^2(Fo)} = [\sigma_c^2(Fo) + \frac{p^2}{4}Fo^2]^{-1}$
p-factor	0.0010
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	747
No. Variables	119

Reflection/Parameter Ratio	6.28
Residuals: R; Rw	0.065 ; 0.045
Goodness of Fit Indicator	5.09
Max Shift/Error in Final Cycle	0.01
Maximum peak in Final Diff. Map	0.19 $e^-/\AA^3$
Minimum peak in Final Diff. Map	-0.21 $e^-/\AA^3$

Table 1. Atomic coordinates and B_{iso}/B_{eq}

atom	x	y	z	B_{eq}
O(5)	0.0864(5)	0.9360(2)	0.3429(4)	6.08(9)
O(7)	0.2862(5)	1.0899(2)	0.5322(4)	6.9(1)
O(8)	0.0582(4)	1.1832(2)	0.3359(4)	5.59(9)
N(1)	-0.2744(5)	1.0620(3)	-0.0192(5)	5.3(1)
N(3)	-0.3150(6)	0.9035(3)	-0.0748(5)	5.9(1)
N(4)	-0.0332(6)	0.8699(3)	0.2154(5)	5.9(1)
C(1A)	-0.1323(7)	1.0197(3)	0.1268(6)	4.9(1)
C(2)	-0.3775(7)	0.9890(4)	-0.1329(6)	5.8(1)
C(3A)	-0.1610(7)	0.9217(3)	0.0884(6)	5.4(1)
C(6)	0.0227(7)	1.0257(3)	0.2839(6)	5.2(1)
C(7)	0.1404(7)	1.1005(4)	0.3993(6)	5.6(1)
C(8)	0.1591(8)	1.2655(3)	0.4381(7)	6.6(1)
C(9)	-0.3177(7)	1.1629(3)	-0.0505(6)	6.1(1)
H(2)	-0.4853	1.0004	-0.2443	7.0073
H(8a)	0.2011	1.2546	0.5681	7.9201
H(8b)	0.2642	1.2772	0.4094	7.9201
H(8c)	0.0773	1.3181	0.4038	7.9201
H(9a)	-0.2491	1.1889	-0.1159	7.3466
H(9b)	-0.2822	1.1937	0.0654	7.3466
H(9c)	-0.4483	1.1710	-0.1226	7.3466

$$B_{eq} = \frac{8}{3}\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^*\cos\gamma + 2U_{13}aa^*cc^*\cos\beta + 2U_{23}bb^*cc^*\cos\alpha)$$

Table 2. Anisotropic Displacement Parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(5)	0.093(3)	0.057(2)	0.051(2)	0.010(2)	0.000(2)	0.009(2)
O(7)	0.082(3)	0.082(3)	0.058(2)	0.008(2)	-0.011(2)	0.002(2)
O(8)	0.081(2)	0.054(2)	0.051(2)	-0.002(2)	0.000(2)	-0.007(2)
N(1)	0.078(3)	0.051(3)	0.043(2)	0.001(2)	-0.005(2)	0.005(2)
N(3)	0.087(3)	0.052(3)	0.064(3)	-0.006(3)	0.007(2)	0.001(2)
N(4)	0.089(3)	0.057(3)	0.058(3)	0.002(2)	0.008(2)	0.004(2)
C(1A)	0.083(4)	0.042(3)	0.044(3)	-0.002(3)	0.007(3)	0.005(2)
C(2)	0.078(4)	0.073(4)	0.047(3)	-0.006(3)	0.003(3)	0.000(3)
C(3A)	0.080(4)	0.053(4)	0.055(3)	0.000(3)	0.010(3)	0.006(3)
C(6)	0.081(4)	0.049(3)	0.044(3)	0.003(3)	0.001(3)	0.001(3)
C(7)	0.076(4)	0.071(4)	0.044(3)	0.009(3)	0.003(3)	0.005(3)
C(8)	0.092(4)	0.064(4)	0.072(4)	-0.006(3)	0.009(3)	-0.011(3)
C(9)	0.095(4)	0.049(3)	0.060(3)	0.012(3)	0.001(3)	0.011(3)

The general temperature factor expression:

$$\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$$

Table 3. Bond Lengths($\AA$)

atom	atom	distance	atom	atom	distance
O(5)	N(4)	1.415(4)	O(5)	C(6)	1.384(4)
O(7)	C(7)	1.199(4)	O(8)	C(7)	1.338(5)
O(8)	C(8)	1.459(5)	N(1)	C(1A)	1.368(5)
N(1)	C(2)	1.394(5)	N(1)	C(9)	1.477(5)
N(3)	C(2)	1.324(5)	N(3)	C(3A)	1.378(5)
N(4)	C(3A)	1.314(5)	C(1A)	C(3A)	1.429(5)
C(1A)	C(6)	1.332(5)	C(6)	C(7)	1.458(6)

Table 4. Bond Lengths($\AA$)

atom	atom	distance	atom	atom	distance
C(2)	H(2)	0.95	C(8)	H(8a)	0.95
C(8)	H(8b)	0.95	C(8)	H(8c)	0.95
C(9)	H(9a)	0.95	C(9)	H(9b)	0.95
C(9)	H(9c)	0.95			

Table 5. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
N(4)	O(5)	C(6)	109.7(3)	C(7)	O(8)	C(8)	115.8(3)
C(1A)	N(1)	C(2)	105.5(4)	C(1A)	N(1)	C(9)	128.4(4)
C(2)	N(1)	C(9)	126.1(4)	C(2)	N(3)	C(3A)	101.9(4)
O(5)	N(4)	C(3A)	103.9(3)	N(1)	C(1A)	C(3A)	104.5(4)
N(1)	C(1A)	C(6)	150.2(5)	C(3A)	C(1A)	C(6)	105.3(4)
N(1)	C(2)	N(3)	115.6(4)	N(3)	C(3A)	N(4)	134.8(5)
N(3)	C(3A)	C(1A)	112.5(4)	N(4)	C(3A)	C(1A)	112.7(4)
O(5)	C(6)	C(1A)	108.5(4)	O(5)	C(6)	C(7)	114.9(4)
C(1A)	C(6)	C(7)	136.6(5)	O(7)	C(7)	O(8)	125.2(5)
O(7)	C(7)	C(6)	125.6(5)	O(8)	C(7)	C(6)	109.2(4)

Table 6. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
N(1)	C(2)	H(2)	121.8	N(3)	C(2)	H(2)	122.6
O(8)	C(8)	H(8a)	109.5	O(8)	C(8)	H(8b)	109.5
O(8)	C(8)	H(8c)	109.3	H(8a)	C(8)	H(8b)	109.5
H(8a)	C(8)	H(8c)	109.3	H(8b)	C(8)	H(8c)	109.6
N(1)	C(9)	H(9a)	109.3	N(1)	C(9)	H(9b)	109.6
N(1)	C(9)	H(9c)	109.5	H(9a)	C(9)	H(9b)	109.3
H(9a)	C(9)	H(9c)	109.2	H(9b)	C(9)	H(9c)	109.9

Table 7. Non-bonded Contacts out to 3.60 Å

atom	atom	distance	ADC	atom	atom	distance	ADC
O(5)	C(8)	3.168(6)	54602	O(5)	C(7)	3.229(7)	57603
O(5)	N(1)	3.417(5)	57503	O(5)	C(6)	3.418(6)	57603
O(5)	O(7)	3.441(5)	57603	O(5)	C(2)	3.473(7)	57503
O(5)	O(8)	3.588(5)	57603	O(7)	C(2)	3.202(5)	65601
O(7)	N(4)	3.368(6)	57603	O(7)	C(3A)	3.503(6)	57603
O(8)	C(8)	3.587(7)	47504	N(1)	C(2)	3.457(7)	47503
N(1)	N(4)	3.475(6)	57503	N(1)	N(3)	3.595(7)	47503
N(3)	C(7)	3.348(7)	57503	N(3)	C(6)	3.459(7)	57503
N(3)	C(9)	3.513(7)	47503	N(4)	C(9)	3.245(6)	44502
N(4)	C(8)	3.415(6)	54602	N(4)	C(7)	3.484(7)	57603
N(4)	C(9)	3.500(7)	57503	C(1A)	C(1A)	3.45(1)	57503
C(1A)	C(3A)	3.455(8)	57503	C(2)	C(2)	3.37(1)	47503
C(2)	C(6)	3.429(8)	57503	C(2)	C(7)	3.548(8)	57503
C(3A)	C(6)	3.589(7)	57503				

The ADC (atom designator code) specifies the position of an atom in a crystal. The 5-digit number shown in the table is a composite of three one-digit numbers and one two-digit number: TA (first digit) + TB (second digit) + TC (third digit) + SN (last two digits). TA, TB and TC are the crystal lattice translation digits along cell edges a, b and c. A translation digit of 5 indicates the origin unit cell. If TA = 4, this indicates a translation of one unit cell length along the a-axis in the negative direction. Each translation digit can range in value from 1 to 9 and thus ± 4 lattice translations from the origin (TA=5, TB=5, TC=5) can be represented.

The SN, or symmetry operator number, refers to the number of the symmetry operator used to generate the coordinates of the target atom. A list of symmetry operators relevant to this structure are given below.

For a given intermolecular contact, the first atom (origin atom) is located in the origin unit cell and its position can be generated using the identity operator (SN=1). Thus, the ADC for an origin atom is always 55501. The position of the second atom (target atom) can be generated using the ADC and the coordinates of the atom in the parameter table. For example, an ADC of 47502 refers to the target atom moved through symmetry operator two, then translated -1 cell translations along the a axis, +2 cell translations along the b axis, and 0 cell translations along the c axis.

An ADC of 1 indicates an intermolecular contact between two fragments (eg. cation and anion) that reside in the same asymmetric unit.

Symmetry Operators:

(1)	X,	Y,	Z	(2)	1/2-X,	1/2+Y,	-Z
(3)	-X,	-Y,	-Z	(4)	1/2+X,	1/2-Y,	Z

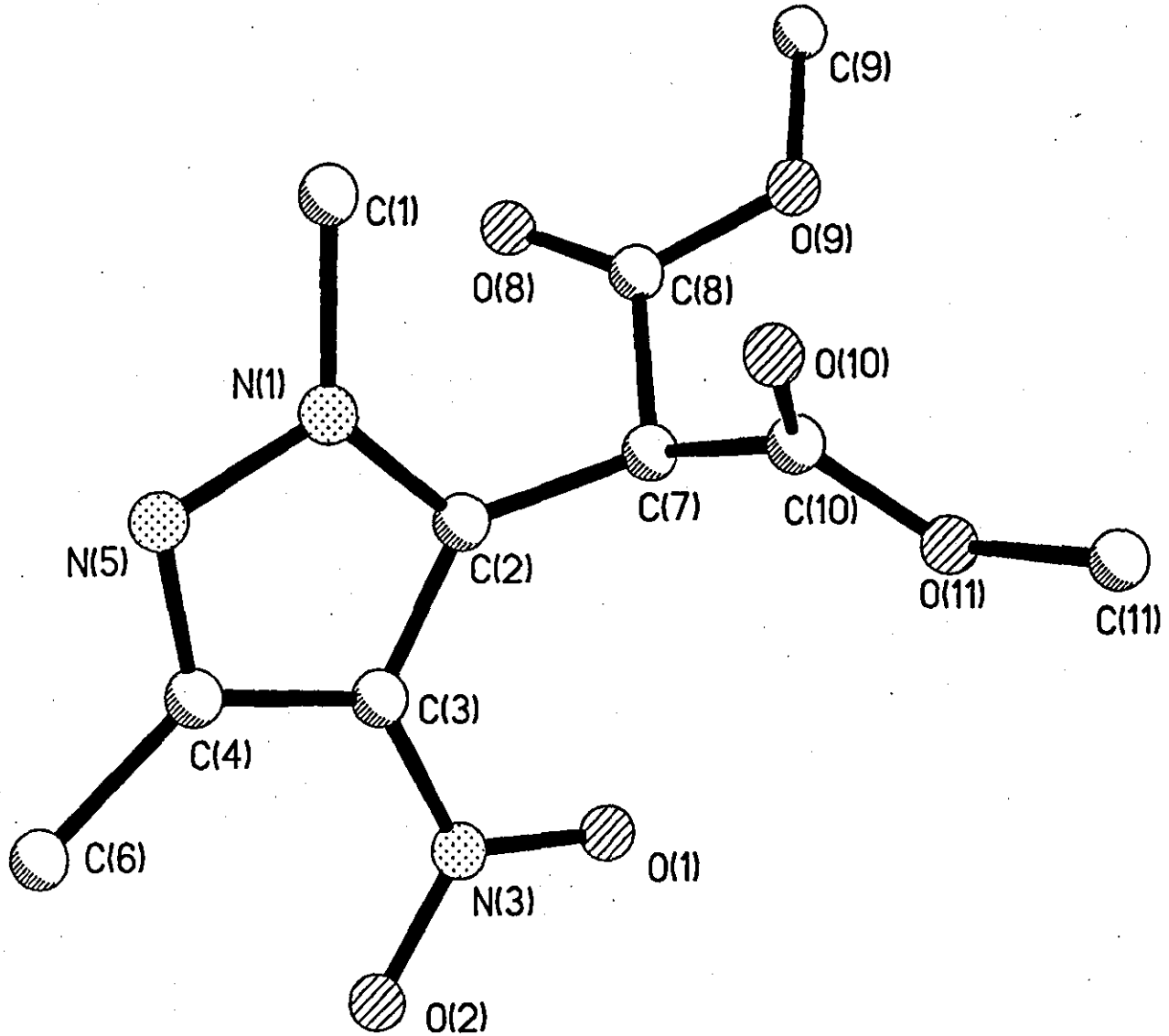

C(9)
C(1)
O(9)
O(8)
C(8)
O(10)
N(1)
C(7)
C(10)
N(5)
C(2)
O(11)
C(11)
C(3)
C(4)
C(6)
O(1)
N(3)
O(2)

Table 1. Crystal data and structure refinement for 1.

Identification code	atgw13
Empirical formula	$C_{10}H_{13}N_3O_6$
Formula weight	271.23
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	$P\bar{1}$
Unit cell dimensions	a = 7.8410(5) Å alpha = 89.6080(10)° b = 7.9420(6) Å beta = 71.3280(10)° c = 11.2213(8) Å gamma = 77.824(2)°
Volume, Z	645.72(8) $Å^3$, 2
Density (calculated)	1.395 Mg/m^3
Absorption coefficient	0.117 mm^{-1}
F(000)	284
Crystal size	.12 x .1 x .04 mm
θ range for data collection	1.92 to 23.27°
Limiting indices	$-8 \le h \le 8$, $-7 \le k \le 8$, $-12 \le l \le 12$
Reflections collected	3955
Independent reflections	1860 (R_{int} = 0.0118)
Absorption correction	Sadabs
Max. and min. transmission	1.00000 and 0.968636
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1855 / 0 / 173
Goodness-of-fit on F^2	1.009
Final R indices [I>2σ(I)]	R1 = 0.0486, wR2 = 0.1163
R indices (all data)	R1 = 0.0695, wR2 = 0.1350
Extinction coefficient	0.009(5)
Largest diff. peak and hole	0.202 and -0.194 $eÅ^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 1. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
N(1)	342(3)	7978(3)	1595(2)	53(1)
C(1)	1364(5)	7245(5)	307(3)	75(1)
C(2)	469(4)	7406(3)	2699(2)	44(1)
C(3)	-827(4)	8620(3)	3604(2)	45(1)
N(3)	-1243(3)	8586(3)	4930(2)	55(1)
O(1)	-464(4)	7352(3)	5370(2)	83(1)
O(2)	-2356(4)	9800(3)	5600(2)	85(1)
C(4)	-1674(4)	9886(4)	2964(3)	54(1)
N(5)	-962(4)	9473(3)	1743(3)	62(1)
C(6)	-3140(5)	11484(4)	3451(4)	80(1)
C(7)	1817(4)	5835(3)	2828(2)	44(1)
C(8)	1795(4)	4237(4)	2109(3)	49(1)
O(8)	509(3)	4021(3)	1833(2)	71(1)
O(9)	3375(3)	3086(3)	1888(2)	63(1)
C(9)	3475(6)	1436(4)	1307(4)	87(1)
C(10)	3736(4)	6206(4)	2535(3)	54(1)
O(10)	4508(4)	6812(4)	1601(3)	98(1)
O(11)	4381(3)	5817(3)	3477(2)	64(1)
C(11)	6164(5)	6210(5)	3320(4)	95(1)

Table 3. Bond lengths [Å] and angles [°] for 1.

N(1)-C(2)	1.343(3)	N(1)-N(5)	1.366(3)
N(1)-C(1)	1.464(4)	C(2)-C(3)	1.390(4)
C(2)-C(7)	1.495(4)	C(3)-C(4)	1.407(4)
C(3)-N(3)	1.419(4)	N(3)-O(2)	1.221(3)
N(3)-O(1)	1.229(3)	C(4)-N(5)	1.318(4)
C(4)-C(6)	1.491(4)	C(7)-C(8)	1.515(4)
C(7)-C(10)	1.525(4)	C(8)-O(8)	1.190(3)
C(8)-O(9)	1.327(3)	O(9)-C(9)	1.444(4)
C(10)-O(10)	1.186(4)	C(10)-O(11)	1.320(4)
O(11)-C(11)	1.452(4)		

C(2)-N(1)-N(5)	112.6(2)	C(2)-N(1)-C(1)	130.0(2)
N(5)-N(1)-C(1)	117.4(2)	N(1)-C(2)-C(3)	104.6(2)
N(1)-C(2)-C(7)	124.5(2)	C(3)-C(2)-C(7)	130.9(2)
C(2)-C(3)-C(4)	107.4(2)	C(2)-C(3)-N(3)	126.5(2)
C(4)-C(3)-N(3)	126.0(3)	O(2)-N(3)-O(1)	121.9(3)
O(2)-N(3)-C(3)	118.7(2)	O(1)-N(3)-C(3)	119.4(2)
N(5)-C(4)-C(3)	108.9(2)	N(5)-C(4)-C(6)	120.2(3)
C(3)-C(4)-C(6)	130.9(3)	C(4)-N(5)-N(1)	106.5(2)
C(2)-C(7)-C(8)	113.5(2)	C(2)-C(7)-C(10)	110.7(2)
C(8)-C(7)-C(10)	113.6(2)	O(8)-C(8)-O(9)	125.0(3)
O(8)-C(8)-C(7)	124.5(3)	O(9)-C(8)-C(7)	110.3(2)
C(8)-O(9)-C(9)	116.1(3)	O(10)-C(10)-O(11)	125.0(3)
O(10)-C(10)-C(7)	124.2(3)	O(11)-C(10)-C(7)	110.8(3)
C(10)-O(11)-C(11)	115.1(3)		

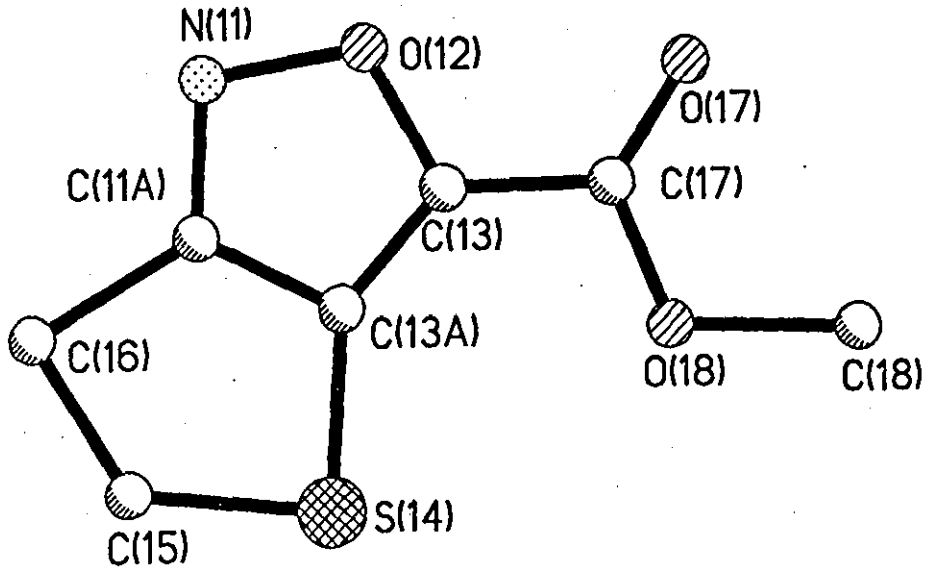
Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$] for 1. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [(ha^*)^2 U_{11} + ... + 2hka^*b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
N(1)	67(2)	47(1)	47(1)	9(1)	-23(1)	-8(1)
C(1)	104(3)	73(2)	42(2)	7(2)	-22(2)	-7(2)
C(2)	49(2)	44(2)	45(2)	9(1)	-18(1)	-17(1)
C(3)	44(2)	45(2)	47(2)	6(1)	-16(1)	-13(1)
N(3)	56(2)	53(2)	52(2)	3(1)	-12(1)	-16(1)
O(1)	104(2)	81(2)	50(1)	13(1)	-19(1)	1(1)
O(2)	93(2)	78(2)	60(1)	-13(1)	-5(1)	2(1)
C(4)	54(2)	43(2)	66(2)	5(1)	-22(2)	-8(1)
N(5)	75(2)	45(2)	68(2)	11(1)	-32(1)	-3(1)
C(6)	76(2)	59(2)	99(3)	1(2)	-30(2)	4(2)
C(7)	47(2)	43(2)	42(2)	8(1)	-16(1)	-10(1)
C(8)	51(2)	46(2)	47(2)	9(1)	-15(1)	-10(1)
O(8)	73(2)	62(1)	90(2)	-2(1)	-44(1)	-16(1)
O(9)	59(1)	51(1)	68(1)	-8(1)	-15(1)	0(1)
C(9)	106(3)	55(2)	86(3)	-16(2)	-21(2)	-2(2)
C(10)	53(2)	49(2)	63(2)	5(2)	-20(2)	-13(1)
O(10)	78(2)	141(2)	90(2)	48(2)	-26(1)	-56(2)
O(11)	53(1)	68(1)	82(2)	6(1)	-34(1)	-16(1)
C(11)	62(2)	100(3)	141(4)	9(3)	-52(2)	-29(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2 \times 10^3$) for 1.

	x	y	z	U(eq)
H(1A)	948(5)	7969(5)	-278(3)	113
H(1B)	1157(5)	6111(5)	216(3)	113
H(1C)	2659(5)	7173(5)	139(3)	113
H(6A)	-3408(5)	12062(4)	2756(4)	121
H(6B)	-2719(5)	12235(4)	3907(4)	121
H(6C)	-4235(5)	11184(4)	4002(4)	121
H(7A)	1420(4)	5598(3)	3722(2)	53
H(9A)	4666(6)	702(4)	1188(4)	131
H(9B)	3291(6)	1599(4)	505(4)	131
H(9C)	2535(6)	909(4)	1841(4)	131
H(11A)	6524(5)	5887(5)	4046(4)	142
H(11B)	6081(5)	7425(5)	3231(4)	142
H(11C)	7067(5)	5578(5)	2581(4)	142


N(11)
O(12)
O(17)
C(11A)
C(17)
C(13)
C(13A)
C(16)
O(18)
C(18)
S(14)
C(15)

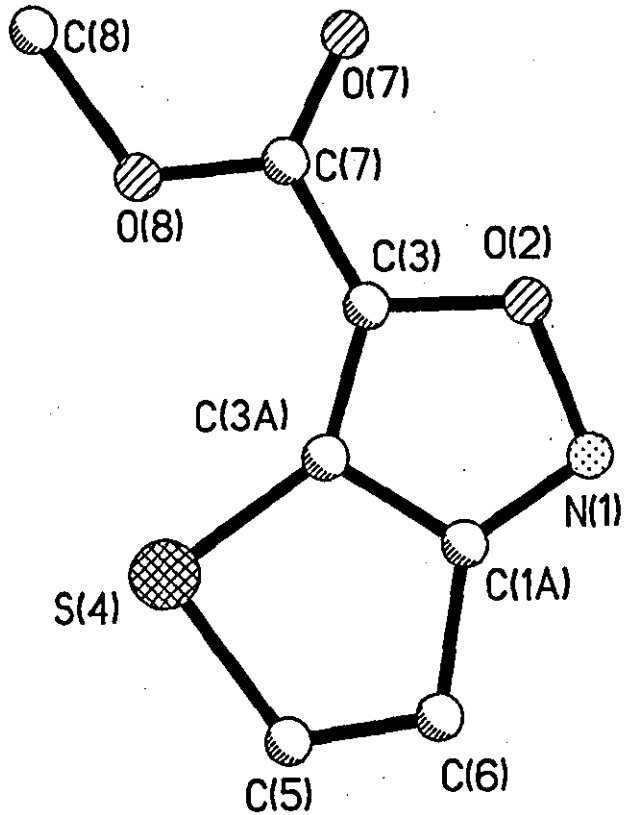

C(8)
O(7)
C(7)
O(8)
C(3)
O(2)
C(3A)
N(1)
C(1A)
S(4)
C(5)
C(6)

Table 1. Crystal data and structure refinement for 1.

Identification code	atgw14
Empirical formula	$C_7H_5NO_3S$
Formula weight	183.18
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 7.8607(11) Å alpha = 90° b = 15.255(2) Å beta = 97.860(5)° c = 13.551(2) Å gamma = 90°
Volume, Z	1609.6(4) $Å^3$, 8
Density (calculated)	1.512 Mg/m^3
Absorption coefficient	0.364 mm^{-1}
F(000)	752
Crystal size	.14 x .1 x .01 mm
θ range for data collection	2.02 to 23.50°
Limiting indices	$-8 \le h \le 8$, $-17 \le k \le 16$, $-9 \le l \le 15$
Reflections collected	5777
Independent reflections	2380 (R_{int} = 0.0622)
Absorption correction	Sadabs
Max. and min. transmission	1.00000 and 0.432728
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2342 / 0 / 218
Goodness-of-fit on F^2	0.916
Final R indices [$I>2\sigma(I)$]	R1 = 0.0726, wR2 = 0.1689
R indices (all data)	R1 = 0.1469, wR2 = 0.2358
Extinction coefficient	0.002(2)
Largest diff. peak and hole	0.700 and -0.408 $eÅ^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 1. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
N(1)	-2900(7)	9489(3)	8774(4)	59(2)
C(1A)	-1366(9)	9117(4)	8803(5)	48(2)
O(2)	-4083(5)	8776(3)	8689(3)	55(1)
C(3)	-3174(8)	7997(4)	8700(4)	44(2)
C(3A)	-1476(8)	8177(4)	8759(4)	38(2)
S(4)	517(2)	7687(1)	8804(1)	45(1)
C(5)	1465(9)	8743(4)	8890(5)	55(2)
C(6)	396(8)	9430(4)	8874(5)	50(2)
C(7)	-4174(8)	7166(5)	8639(4)	41(2)
O(7)	-5720(6)	7136(3)	8603(3)	61(1)
O(8)	-3123(6)	6489(3)	8626(4)	57(1)
C(8)	-3938(10)	5610(5)	8570(6)	76(2)
N(11)	2094(7)	1536(4)	8768(4)	56(2)
C(11A)	3647(9)	1898(4)	8796(4)	43(2)
O(12)	939(6)	2258(3)	8730(3)	51(1)
C(13)	1853(8)	3030(4)	8742(4)	39(2)
C(13A)	3534(8)	2839(4)	8767(4)	39(2)
S(14)	5545(2)	3325(1)	8809(1)	45(1)
C(15)	6469(9)	2264(5)	8846(5)	52(2)
C(16)	5394(7)	1554(4)	8827(4)	37(2)
C(17)	851(8)	3846(4)	8726(5)	45(2)
O(17)	-680(6)	3901(3)	8742(4)	70(2)
O(18)	1914(5)	4526(3)	8685(3)	62(1)
C(18)	1127(10)	5429(5)	8658(6)	71(2)

Table 3. Bond lengths [Å] and angles [°] for 1.

N(1)-C(1A)	1.328(8)	N(1)-O(2)	1.426(7)
C(1A)-C(3A)	1.436(8)	C(1A)-C(6)	1.457(8)
O(2)-C(3)	1.385(8)	C(3)-C(3A)	1.354(8)
C(3)-C(7)	1.487(9)	C(3A)-S(4)	1.730(6)
S(4)-C(5)	1.773(7)	C(5)-C(6)	1.341(9)
C(7)-O(7)	1.210(7)	C(7)-O(8)	1.324(8)
O(8)-C(8)	1.484(8)	N(11)-C(11A)	1.336(8)
N(11)-O(12)	1.424(7)	C(11A)-C(13A)	1.438(8)
C(11A)-C(16)	1.465(8)	O(12)-C(13)	1.378(7)
C(13)-C(13A)	1.350(8)	C(13)-C(17)	1.471(9)
C(13A)-S(14)	1.740(6)	S(14)-C(15)	1.772(7)
C(15)-C(16)	1.371(9)	C(17)-O(17)	1.209(7)
C(17)-O(18)	1.338(7)	O(18)-C(18)	1.508(8)

C(1A)-N(1)-O(2)	104.8(5)	N(1)-C(1A)-C(3A)	112.1(6)
N(1)-C(1A)-C(6)	135.5(6)	C(3A)-C(1A)-C(6)	112.4(6)
C(3)-O(2)-N(1)	108.9(5)	C(3A)-C(3)-O(2)	109.2(6)
C(3A)-C(3)-C(7)	133.3(6)	O(2)-C(3)-C(7)	117.5(6)
C(3)-C(3A)-C(1A)	105.0(6)	C(3)-C(3A)-S(4)	142.6(5)
C(1A)-C(3A)-S(4)	112.4(5)	C(3A)-S(4)-C(5)	88.8(3)
C(6)-C(5)-S(4)	116.9(6)	C(5)-C(6)-C(1A)	109.4(6)
O(7)-C(7)-O(8)	126.4(6)	O(7)-C(7)-C(3)	123.7(7)
O(8)-C(7)-C(3)	109.9(6)	C(7)-O(8)-C(8)	116.1(5)
C(11A)-N(11)-O(12)	104.9(5)	N(11)-C(11A)-C(13A)	111.0(6)
N(11)-C(11A)-C(16)	134.6(6)	C(13A)-C(11A)-C(16)	114.3(6)
C(13)-O(12)-N(11)	109.4(5)	C(13A)-C(13)-O(12)	108.8(5)
C(13A)-C(13)-C(17)	134.8(6)	O(12)-C(13)-C(17)	116.5(6)
C(13)-C(13A)-C(11A)	105.9(5)	C(13)-C(13A)-S(14)	142.2(5)
C(11A)-C(13A)-S(14)	111.9(4)	C(13A)-S(14)-C(15)	88.7(3)
C(16)-C(15)-S(14)	118.2(5)	C(15)-C(16)-C(11A)	106.9(6)
O(17)-C(17)-O(18)	125.1(6)	O(17)-C(17)-C(13)	126.2(6)
O(18)-C(17)-C(13)	108.7(5)	C(17)-O(18)-C(18)	116.9(5)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2$ x 10^3] for 1.
The anisotropic displacement factor exponent takes the form:
$-2\pi^2$ [$(ha^*)^2U_{11}$ + ... + $2hka^*b^*U_{12}$]

	U11	U22	U33	U23	U13	U12
N(1)	47(4)	33(3)	98(4)	7(3)	16(3)	11(3)
C(1A)	53(5)	22(4)	70(5)	4(3)	11(3)	-1(3)
O(2)	27(3)	42(3)	96(4)	4(2)	15(2)	7(2)
C(3)	27(4)	45(4)	58(4)	1(3)	2(3)	-3(4)
C(3A)	28(4)	25(3)	61(4)	-4(3)	5(3)	1(3)
S(4)	28(1)	36(1)	70(1)	-2(1)	4(1)	6(1)
C(5)	40(4)	51(5)	73(5)	-4(4)	-2(3)	-13(4)
C(6)	38(4)	27(4)	84(5)	-5(3)	5(3)	-16(4)
C(7)	17(4)	59(5)	48(4)	-9(3)	6(3)	-5(4)
O(7)	36(3)	51(3)	96(4)	-5(3)	6(3)	0(3)
O(8)	29(3)	37(3)	107(4)	-8(3)	11(2)	-3(2)
C(8)	56(6)	45(5)	128(7)	-25(5)	14(5)	2(4)
N(11)	44(4)	35(3)	91(4)	5(3)	16(3)	-6(3)
C(11A)	45(4)	26(4)	59(4)	-2(3)	13(3)	1(3)
O(12)	34(3)	46(3)	73(3)	2(2)	11(2)	-5(2)
C(13)	31(4)	35(4)	53(4)	1(3)	10(3)	-5(3)
C(13A)	22(4)	38(4)	58(4)	0(3)	8(3)	-2(3)
S(14)	28(1)	37(1)	70(1)	-1(1)	5(1)	-5(1)
C(15)	24(4)	60(5)	73(5)	2(4)	9(3)	23(4)
C(16)	20(4)	37(4)	53(4)	0(3)	3(3)	-5(3)
C(17)	24(4)	43(4)	68(4)	-1(3)	6(3)	-5(3)
O(17)	28(3)	56(3)	129(4)	9(3)	19(3)	4(2)
O(18)	27(3)	35(3)	124(4)	0(3)	11(2)	8(2)
C(18)	48(5)	46(5)	117(6)	18(4)	6(4)	-11(4)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

	x	y	z	U(eq)
H(5A)	2648(9)	8818(4)	8943(5)	67
H(6A)	729(8)	10016(4)	8903(5)	60
H(8A)	-3070(10)	5168(5)	8565(6)	114
H(8B)	-4741(10)	5568(5)	7971(6)	114
H(8C)	-4530(10)	5525(5)	9137(6)	114
H(15A)	7649(9)	2191(5)	8878(5)	63
H(16A)	5714(7)	967(4)	8832(4)	44
H(18A)	2006(10)	5861(5)	8631(6)	106
H(18B)	594(10)	5518(5)	9247(6)	106
H(18C)	280(10)	5482(5)	8080(6)	106

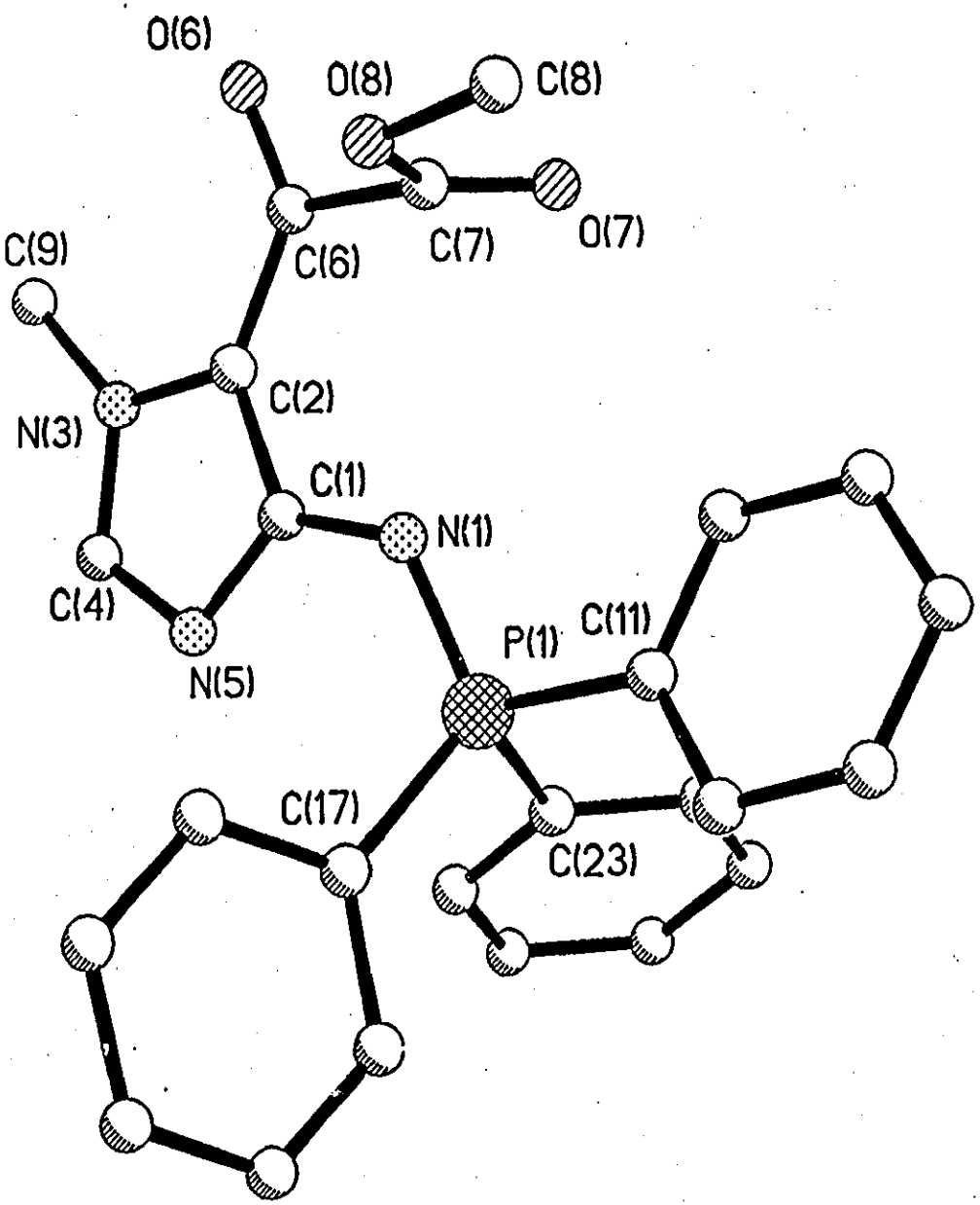

O(6)
O(8)
C(8)
C(9)
C(6)
C(7)
O(7)
C(2)
N(3)
C(1)
N(1)
C(4)
P(1)
C(11)
N(5)
C(17)
C(23)

Table 1. Crystal data and structure refinement for 1.

Identification code	atgw9
Empirical formula	$C_{22}H_{22}N_3O_3P$
Formula weight	407.40
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$Pna2_1$
Unit cell dimensions	a = 21.4954(7) Å alpha = 90° b = 8.2004(3) Å beta = 90° c = 12.9522(5) Å gamma = 90°
Volume, Z	2283.10(14) $Å^3$, 4
Density (calculated)	1.185 Mg/m^3
Absorption coefficient	0.146 mm^{-1}
F(000)	856
Crystal size	.05 x .1 x .2 mm
θ range for data collection	1.89 to 23.26°
Limiting indices	$-23 \le h \le 23$, $-9 \le k \le 8$, $-14 \le l \le 9$
Reflections collected	9433
Independent reflections	2497 (R_{int} = 0.0460)
Absorption correction	Sadabs
Max. and min. transmission	1.000000 and 0.820125
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2447 / 1 / 290
Goodness-of-fit on F^2	0.983
Final R indices [I>2σ(I)]	R1 = 0.0340, wR2 = 0.0781
R indices (all data)	R1 = 0.0503, wR2 = 0.0946
Absolute structure parameter	0.29(12)
Extinction coefficient	0.0059(10)
Largest diff. peak and hole	0.155 and -0.113 $eÅ^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 1. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
P(1)	1340(1)	7355(1)	5159(1)	42(1)
N(1)	1928(1)	8405(3)	5475(2)	48(1)
C(1)	1890(1)	9890(4)	5947(3)	45(1)
C(2)	2391(1)	10974(4)	6084(3)	48(1)
N(3)	2143(1)	12308(3)	6615(2)	53(1)
C(4)	1549(2)	11953(5)	6769(3)	59(1)
N(5)	1368(1)	10537(3)	6389(2)	53(1)
C(6)	3021(2)	10822(4)	5764(3)	61(1)
O(6)	3436(1)	11823(4)	5886(3)	104(1)
C(7)	3215(2)	9234(5)	5234(5)	69(1)
O(7)	3223(2)	9069(4)	4324(3)	95(1)
O(8)	3424(1)	8171(4)	5933(3)	96(1)
C(8)	3705(2)	6678(7)	5505(6)	146(3)
C(9)	2460(2)	13792(4)	6937(4)	75(1)
C(11)	1650(1)	5575(4)	4517(3)	44(1)
C(12)	2233(2)	5670(4)	4066(3)	58(1)
C(13)	2481(2)	4330(5)	3574(3)	73(1)
C(14)	2160(2)	2896(5)	3518(4)	73(1)
C(15)	1593(2)	2786(5)	3968(3)	75(1)
C(16)	1330(2)	4109(4)	4473(3)	58(1)
C(17)	862(1)	6640(4)	6212(3)	43(1)
C(18)	1106(2)	6640(4)	7207(3)	52(1)
C(19)	763(2)	6064(5)	8021(3)	68(1)
C(20)	170(2)	5480(6)	7851(4)	77(1)
C(21)	-77(2)	5477(5)	6894(4)	71(1)
C(22)	260(1)	6058(4)	6069(3)	54(1)
C(23)	805(1)	8301(4)	4264(3)	45(1)
C(24)	366(1)	9419(5)	4619(3)	58(1)
C(25)	-31(2)	10179(5)	3935(4)	75(1)
C(26)	6(2)	9852(6)	2886(4)	82(1)
C(27)	448(2)	8772(5)	2525(3)	82(1)
C(28)	845(2)	8009(5)	3212(3)	61(1)

Table 3. Bond lengths [Å] and angles [°] for 1.

P(1)-N(1)	1.582(3)	P(1)-C(17)	1.805(3)
P(1)-C(11)	1.807(3)	P(1)-C(23)	1.808(3)
N(1)-C(1)	1.365(4)	C(1)-N(5)	1.366(4)
C(1)-C(2)	1.407(4)	C(2)-N(3)	1.398(4)
C(2)-C(6)	1.422(5)	N(3)-C(4)	1.324(4)
N(3)-C(9)	1.457(5)	C(4)-N(5)	1.320(5)
C(6)-O(6)	1.222(4)	C(6)-C(7)	1.530(5)
C(7)-O(7)	1.187(6)	C(7)-O(8)	1.334(6)
O(8)-C(8)	1.472(6)	C(11)-C(12)	1.385(4)
C(11)-C(16)	1.385(4)	C(12)-C(13)	1.377(5)
C(13)-C(14)	1.366(5)	C(14)-C(15)	1.352(6)
C(15)-C(16)	1.388(5)	C(17)-C(18)	1.392(5)
C(17)-C(22)	1.393(4)	C(18)-C(19)	1.369(5)
C(19)-C(20)	1.380(5)	C(20)-C(21)	1.348(6)
C(21)-C(22)	1.376(5)	C(23)-C(28)	1.387(5)
C(23)-C(24)	1.394(5)	C(24)-C(25)	1.378(5)
C(25)-C(26)	1.387(6)	C(26)-C(27)	1.380(6)
C(27)-C(28)	1.382(5)		

N(1)-P(1)-C(17)	115.8(2)	N(1)-P(1)-C(11)	105.38(14)
C(17)-P(1)-C(11)	107.1(2)	N(1)-P(1)-C(23)	116.1(2)
C(17)-P(1)-C(23)	105.13(13)	C(11)-P(1)-C(23)	106.6(2)
C(1)-N(1)-P(1)	123.6(2)	N(5)-C(1)-N(1)	125.6(3)
N(5)-C(1)-C(2)	109.3(3)	N(1)-C(1)-C(2)	125.1(3)
N(3)-C(2)-C(1)	105.3(3)	N(3)-C(2)-C(6)	125.1(3)
C(1)-C(2)-C(6)	129.5(3)	C(4)-N(3)-C(2)	105.6(3)
C(4)-N(3)-C(9)	126.3(3)	C(2)-N(3)-C(9)	128.0(3)
N(5)-C(4)-N(3)	114.9(3)	C(4)-N(5)-C(1)	104.9(3)
O(6)-C(6)-C(2)	126.7(3)	O(6)-C(6)-C(7)	115.5(3)
C(2)-C(6)-C(7)	117.7(3)	O(7)-C(7)-O(8)	126.5(4)
O(7)-C(7)-C(6)	123.1(5)	O(8)-C(7)-C(6)	110.1(5)
C(7)-O(8)-C(8)	115.2(5)	C(12)-C(11)-C(16)	118.7(3)
C(12)-C(11)-P(1)	118.8(3)	C(16)-C(11)-P(1)	122.5(3)
C(13)-C(12)-C(11)	120.1(3)	C(14)-C(13)-C(12)	121.0(4)
C(15)-C(14)-C(13)	119.3(4)	C(14)-C(15)-C(16)	121.1(4)
C(11)-C(16)-C(15)	119.7(3)	C(18)-C(17)-C(22)	118.2(3)
C(18)-C(17)-P(1)	119.0(2)	C(22)-C(17)-P(1)	122.7(3)
C(19)-C(18)-C(17)	120.7(3)	C(18)-C(19)-C(20)	119.6(4)
C(21)-C(20)-C(19)	120.8(4)	C(20)-C(21)-C(22)	120.4(4)
C(21)-C(22)-C(17)	120.3(3)	C(28)-C(23)-C(24)	118.6(3)
C(28)-C(23)-P(1)	121.1(3)	C(24)-C(23)-P(1)	120.2(3)
C(25)-C(24)-C(23)	120.3(4)	C(24)-C(25)-C(26)	120.4(4)
C(27)-C(26)-C(25)	119.7(4)	C(26)-C(27)-C(28)	119.8(4)
C(27)-C(28)-C(23)	121.1(4)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2$ x 10^3] for 1.
The anisotropic displacement factor exponent takes the form:
$-2\pi^2$ [$(ha^*)^2U_{11}$ + ... + $2hka^*b^*U_{12}$]

	U11	U22	U33	U23	U13	U12
P(1)	36(1)	44(1)	46(1)	-2(1)	1(1)	0(1)
N(1)	36(1)	50(2)	59(2)	-10(1)	2(1)	-2(1)
C(1)	40(2)	50(2)	45(2)	-5(2)	1(2)	-1(2)
C(2)	42(2)	50(2)	53(2)	-9(2)	-4(2)	-2(2)
N(3)	53(2)	45(2)	61(2)	-9(2)	-2(2)	-1(1)
C(4)	53(2)	55(2)	68(3)	-15(2)	8(2)	10(2)
N(5)	43(2)	51(2)	66(2)	-9(2)	8(1)	3(1)
C(6)	45(2)	64(3)	74(3)	-19(2)	3(2)	-13(2)
O(6)	53(1)	97(2)	163(3)	-48(2)	12(2)	-28(2)
C(7)	41(2)	74(3)	91(4)	-13(3)	14(2)	-15(2)
O(7)	100(2)	97(2)	88(3)	-23(2)	45(2)	-31(2)
O(8)	67(2)	94(2)	127(3)	-11(2)	-17(2)	15(2)
C(8)	78(3)	100(4)	258(11)	-35(5)	-6(4)	24(3)
C(9)	80(3)	53(2)	91(3)	-21(2)	-15(2)	-4(2)
C(11)	49(2)	40(2)	43(2)	2(2)	-1(2)	0(2)
C(12)	62(2)	49(2)	62(2)	-7(2)	14(2)	-3(2)
C(13)	78(3)	61(3)	79(3)	-8(2)	32(2)	9(2)
C(14)	92(3)	53(3)	74(3)	-8(2)	22(3)	14(2)
C(15)	96(3)	44(2)	86(4)	-14(2)	3(3)	-8(2)
C(16)	51(2)	54(2)	67(3)	-7(2)	2(2)	-7(2)
C(17)	36(2)	43(2)	49(2)	3(2)	0(2)	6(1)
C(18)	51(2)	51(2)	53(2)	-3(2)	-6(2)	14(2)
C(19)	93(3)	65(3)	47(2)	9(2)	0(2)	23(2)
C(20)	76(3)	83(3)	73(3)	27(2)	20(3)	10(3)
C(21)	50(2)	76(3)	88(3)	21(2)	6(2)	-4(2)
C(22)	43(2)	64(2)	55(2)	9(2)	-4(2)	-7(2)
C(23)	45(2)	42(2)	50(2)	4(2)	-1(2)	-9(2)
C(24)	52(2)	64(2)	59(2)	7(2)	2(2)	7(2)
C(25)	62(2)	71(3)	90(4)	18(3)	-8(2)	14(2)
C(26)	85(3)	74(3)	88(4)	18(3)	-32(3)	7(2)
C(27)	117(4)	71(3)	58(3)	3(2)	-30(3)	10(3)
C(28)	70(3)	51(2)	62(3)	0(2)	-8(2)	6(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

	x	y	z	U(eq)
H(4A)	1280(2)	12648(5)	7118(3)	71
H(8A)	3841(2)	5989(7)	6060(6)	218
H(8B)	4054(2)	6963(7)	5080(6)	218
H(8C)	3402(2)	6109(7)	5097(6)	218
H(9A)	2889(2)	13741(4)	6730(4)	112
H(9B)	2436(2)	13897(4)	7674(4)	112
H(9C)	2265(2)	14718(4)	6618(4)	112
H(12A)	2457(2)	6639(4)	4095(3)	69
H(13A)	2873(2)	4403(5)	3276(3)	87
H(14A)	2329(2)	2004(5)	3175(4)	88
H(15A)	1376(2)	1806(5)	3937(3)	90
H(16A)	941(2)	4013(4)	4781(3)	69
H(18A)	1505(2)	7037(4)	7322(3)	62
H(19A)	930(2)	6065(5)	8683(3)	82
H(20A)	-62(2)	5085(6)	8402(4)	93
H(21A)	-478(2)	5079(5)	6791(4)	86
H(22A)	84(1)	6063(4)	5413(3)	65
H(24A)	340(1)	9654(5)	5320(3)	70
H(25A)	-326(2)	10915(5)	4178(4)	90
H(26A)	-265(2)	10359(6)	2428(4)	99
H(27A)	479(2)	8558(5)	1822(3)	99
H(28A)	1143(2)	7288(5)	2964(3)	73

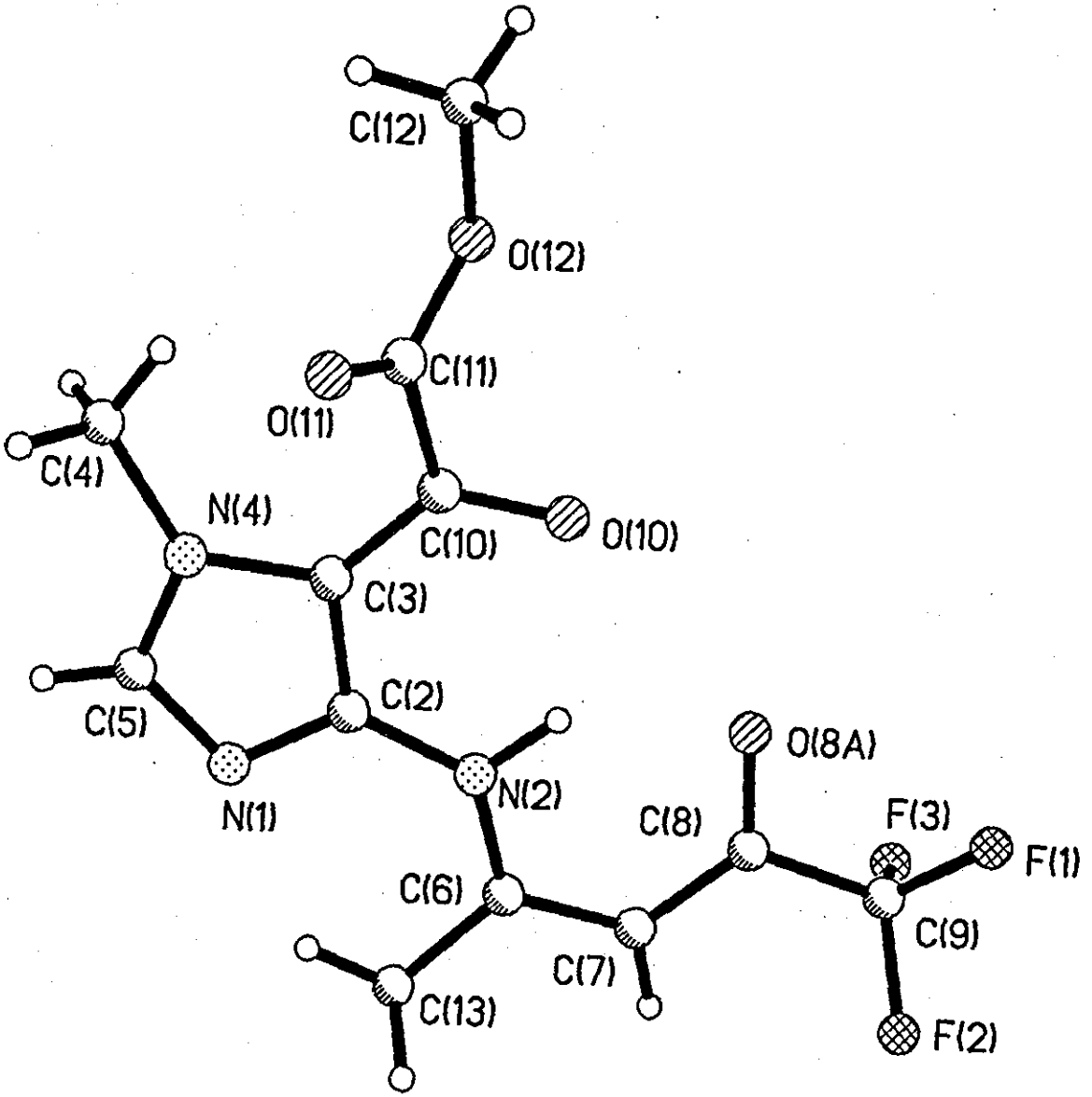

C(12)
O(12)
C(11)
O(11)
C(4)
N(4)
C(10)
O(10)
C(3)
C(5)
C(2)
O(8A)
N(1)
N(2)
C(8)
F(3)
F(1)
C(6)
C(9)
C(7)
C(13)
F(2)

Table 1. Crystal data and structure refinement for 1.

Identification code	atgw12
Empirical formula	$C_{12}H_{12}F_3N_3O_4$
Formula weight	319.25
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 9.8188(2) Å alpha = 90° b = 15.1030(3) Å beta = 95.229(2)° c = 9.6292(3) Å gamma = 90°
Volume, Z	1422.00(6) $Å^3$, 4
Density (calculated)	1.491 Mg/m^3
Absorption coefficient	0.137 mm^{-1}
F(000)	656
Crystal size	.15 x .1 x .01 mm
θ range for data collection	2.08 to 23.24°
Limiting indices	$-10 \le h \le 10$, $-16 \le k \le 16$, $-7 \le l \le 10$
Reflections collected	6069
Independent reflections	2031 (R_{int} = 0.0500)
Absorption correction	Sadaabs
Max. and min. transmission	1.00000 and 0.665211
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1997 / 1 / 213
Goodness-of-fit on F^2	0.901
Final R indices [I>2σ(I)]	R1 = 0.0558, wR2 = 0.1449
R indices (all data)	R1 = 0.1182, wR2 = 0.2117
Extinction coefficient	0.002(2)
Largest diff. peak and hole	0.212 and -0.177 $eÅ^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 1. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
N(1)	8692(4)	751(2)	759(4)	71(1)
C(2)	8885(4)	1622(2)	868(5)	54(1)
N(2)	8173(3)	2250(2)	35(4)	59(1)
C(3)	9889(4)	1840(2)	1947(4)	54(1)
N(4)	10308(3)	1011(2)	2486(4)	63(1)
C(4)	11220(5)	822(3)	3736(5)	85(2)
C(5)	9558(5)	414(3)	1747(5)	75(1)
C(6)	7190(4)	2140(3)	-1032(5)	61(1)
C(7)	6538(4)	2864(3)	-1631(5)	68(1)
C(8)	6803(4)	3741(3)	-1220(5)	63(1)
O(8A)	7592(22)	3997(16)	-215(22)	72(4)
O(8B)	7881(52)	3972(36)	-559(55)	54(7)
C(9)	5898(5)	4466(3)	-1934(6)	73(1)
F(1)	6452(3)	5247(2)	-1818(4)	115(1)
F(2)	5576(3)	4316(2)	-3272(3)	110(1)
F(3)	4712(3)	4509(2)	-1389(4)	120(1)
C(10)	10401(4)	2692(3)	2311(4)	56(1)
O(10)	9833(3)	3367(2)	1837(3)	79(1)
C(11)	11771(5)	2822(3)	3164(5)	63(1)
O(11)	12813(4)	2503(3)	2861(5)	125(2)
O(12)	11687(3)	3375(2)	4176(3)	74(1)
C(12)	12956(5)	3649(3)	4963(5)	88(2)
C(13)	6811(6)	1231(3)	-1552(5)	92(2)

Table 3. Bond lengths [Å] and angles [°] for 1.

N(1)-C(5)	1.319(5)	N(1)-C(2)	1.331(5)
C(2)-N(2)	1.389(5)	C(2)-C(3)	1.405(6)
N(2)-C(6)	1.354(5)	C(3)-N(4)	1.404(5)
C(3)-C(10)	1.413(5)	N(4)-C(5)	1.328(5)
N(4)-C(4)	1.461(5)	C(6)-C(7)	1.368(5)
C(6)-C(13)	1.497(6)	C(7)-C(8)	1.399(6)
C(8)-O(8A)	1.24(3)	C(8)-O(8B)	1.24(6)
C(8)-C(9)	1.533(6)	C(9)-F(1)	1.300(5)
C(9)-F(3)	1.322(6)	C(9)-F(2)	1.317(5)
C(10)-O(10)	1.230(4)	C(10)-C(11)	1.524(6)
C(11)-O(11)	1.191(5)	C(11)-O(12)	1.293(5)
O(12)-C(12)	1.458(5)		

C(5)-N(1)-C(2)	104.3(4)	N(1)-C(2)-N(2)	124.6(4)
N(1)-C(2)-C(3)	112.1(4)	N(2)-C(2)-C(3)	123.3(3)
C(6)-N(2)-C(2)	129.9(3)	N(4)-C(3)-C(2)	103.0(3)
N(4)-C(3)-C(10)	129.4(4)	C(2)-C(3)-C(10)	127.4(4)
C(5)-N(4)-C(3)	106.2(3)	C(5)-N(4)-C(4)	125.2(4)
C(3)-N(4)-C(4)	128.0(4)	N(4)-C(5)-N(1)	114.4(4)
N(2)-C(6)-C(7)	119.7(4)	N(2)-C(6)-C(13)	120.3(4)
C(7)-C(6)-C(13)	120.0(4)	C(6)-C(7)-C(8)	124.7(4)
O(8A)-C(8)-O(8B)	21(2)	O(8A)-C(8)-C(7)	126.9(12)
O(8B)-C(8)-C(7)	123(3)	O(8A)-C(8)-C(9)	114.9(12)
O(8B)-C(8)-C(9)	118(3)	C(7)-C(8)-C(9)	117.6(4)
F(1)-C(9)-F(3)	107.4(5)	F(1)-C(9)-F(2)	107.5(4)
F(3)-C(9)-F(2)	104.8(4)	F(1)-C(9)-C(8)	112.9(4)
F(3)-C(9)-C(8)	110.7(4)	F(2)-C(9)-C(8)	113.1(4)
O(10)-C(10)-C(3)	121.6(3)	O(10)-C(10)-C(11)	116.2(4)
C(3)-C(10)-C(11)	121.8(4)	O(11)-C(11)-O(12)	124.2(4)
O(11)-C(11)-C(10)	123.5(5)	O(12)-C(11)-C(10)	112.1(4)
C(11)-O(12)-C(12)	117.7(4)		

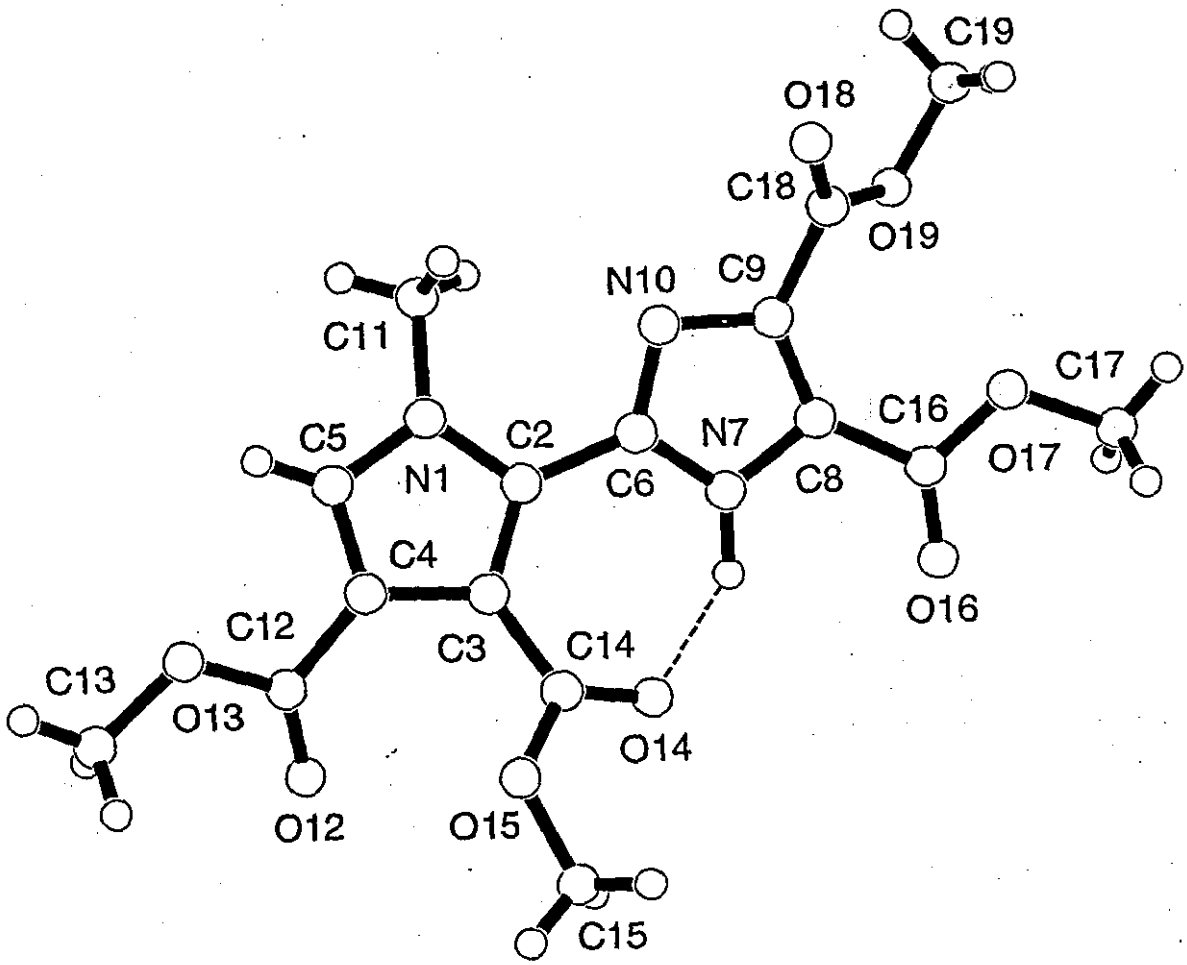
Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2$ x 10^3] for 1.
The anisotropic displacement factor exponent takes the form:
$-2\pi^2$ [$(ha^*)^2U_{11}$ + ... + $2hka^*b^*U_{12}$]

	U11	U22	U33	U23	U13	U12
N(1)	68(2)	42(2)	99(3)	-2(2)	-8(2)	-2(2)
C(2)	51(2)	42(2)	68(3)	-2(2)	7(2)	1(2)
N(2)	58(2)	42(2)	74(3)	-3(2)	-12(2)	-3(2)
C(3)	50(2)	40(2)	69(3)	2(2)	-5(2)	5(2)
N(4)	63(2)	43(2)	81(3)	7(2)	0(2)	8(2)
C(4)	81(3)	72(3)	99(4)	21(3)	-12(3)	20(3)
C(5)	70(3)	44(3)	110(4)	-1(3)	10(3)	-2(2)
C(6)	59(3)	56(3)	66(3)	-4(2)	-6(2)	-10(2)
C(7)	61(3)	70(3)	70(3)	0(3)	-15(2)	-9(2)
C(8)	49(3)	60(3)	75(3)	1(2)	-18(2)	-4(2)
O(8A)	78(11)	58(4)	75(11)	-10(6)	-23(7)	5(7)
O(8B)	54(12)	44(9)	65(18)	-6(10)	9(9)	-5(8)
C(9)	56(3)	69(3)	91(4)	8(3)	-16(3)	-2(3)
F(1)	117(3)	67(2)	149(3)	23(2)	-50(2)	-4(2)
F(2)	119(2)	117(2)	86(2)	11(2)	-43(2)	12(2)
F(3)	78(2)	125(3)	157(3)	31(2)	16(2)	31(2)
C(10)	60(3)	49(3)	57(3)	1(2)	-2(2)	2(2)
O(10)	86(2)	45(2)	97(3)	-1(2)	-38(2)	6(2)
C(11)	62(3)	50(3)	75(3)	-3(2)	-7(2)	7(2)
O(11)	70(2)	130(3)	171(4)	-71(3)	-15(3)	20(2)
O(12)	62(2)	88(2)	70(2)	-11(2)	-10(2)	-5(2)
C(12)	86(4)	100(4)	74(4)	-3(3)	-23(3)	-24(3)
C(13)	108(4)	62(3)	96(4)	-11(3)	-37(3)	-25(3)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

	x	Y	z	U(eq)
H(2N)	8261(39)	2865(9)	347(38)	70(13)
H(4A)	11643(5)	1361(3)	4082(5)	127
H(4B)	11913(5)	411(3)	3510(5)	127
H(4C)	10703(5)	569(3)	4437(5)	127
H(5A)	9638(5)	-192(3)	1913(5)	90
H(7A)	5869(4)	2767(3)	-2363(5)	82
H(12A)	12754(5)	4056(3)	5682(5)	133
H(12B)	13537(5)	3932(3)	4348(5)	133
H(12C)	13413(5)	3138(3)	5378(5)	133
H(13A)	7362(6)	801(3)	-1026(5)	137
H(13B)	6964(6)	1186(3)	-2520(5)	137
H(13C)	5863(6)	1123(3)	-1443(5)	137


C19
O18
C18
O19
N10
C9
C11
C17
C5
C2
N7
C16
N1
C6
C8
O17
C4
O16
C12
C3
C14
C13
O13
O14
O12
O15
C15

Experimental

Data Collection

A colourlessprism prism crystal of $C_{16}H_{17}N_3O_8$ having approximate dimensions of 0.15 x 0.15 x 0.15 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC7S diffractometer with graphite monochromated Cu-Kα radiation.

Cell constants and an orientation matrix for data collection , obtained from a least-squares refinement using the setting angles of 25 carefully centered reflections in the range $60.46 < 2\theta < 72.75°$ corresponded to a C-centered monoclinic cell with dimensions:

$a = 25.358(5)\ \AA$

$b = 7.331(9)\ \AA \qquad \beta = 94.08(2)°$

$c = 18.771(3)\ \AA$

$V = 3481(4)\ \AA^3$

For Z = 8 and F.W. = 379.33, the calculated density is 1.45 g/cm^3. Based on the systematic absences of:

hkl: $h+k \neq 2n$

h0l: $l \neq 2n$

packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be:

C2/c (#15)

The data were collected at a temperature of 20 $\pm$ 1°C using the ω scan technique to a maximum 2θ value of 120.4°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.27° with a take-off angle of 6.0°. Scans of $(1.05 + 0.35 \tan \theta)°$ were made at a speed of 16.0°/min (in omega). The weak reflections ($I < 12.0\sigma(I)$) were rescanned (maximum of 4 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 1.0 mm and the crystal to detector distance was 400 mm, The computer-controlled slits were set to 9.0 mm (horizontal) and 13.0 mm (vertical).

Data Reduction

Of the 2904 reflections which were collected, 2827 were unique ($R_{int} = 0.025$). The intensities of three representative reflection were measured after every 150 reflections. Over the course of data collection, the standards decreased by 1.9%. A linear correction factor was applied to the data to account for this phenomenon.

The linear absorption coefficient, μ, for Cu-Kα radiation is 10.1 cm^{-1}. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted in transmission factors

ranging from 0.93 to 1.00. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = 7.74564e-07).

Structure Solution and Refinement

The structure was solved by direct methods[1] and expanded using Fourier techniques[2]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement[3] was based on 1431 observed reflections ($I > 3.00\sigma(I)$) and 245 variable parameters and converged (largest parameter shift was 0.01 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma||Fo| - |Fc||/\Sigma|Fo| = 0.051$$

$$R_w = \sqrt{(\Sigma w(|Fo| - |Fc|)^2/\Sigma wFo^2)} = 0.040$$

The standard deviation of an observation of unit weight[4] was 3.30. The weighting scheme was based on counting statistics and included a factor (p = 0.002) to downweight the intense reflections. Plots of $\Sigma w(|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, $\sin\theta/\lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.17 and -0.21 $e^-/\AA^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[5] . Anomalous dispersion effects were included in Fcalc[6]; the values for Δf' and Δf" were those of Creagh and McAuley[7]. The values for the mass attenuation coefficients are those of Creagh and Hubbel[8]. All calculations were performed using the teXsan[9] crystallographic software package of Molecular Structure Corporation.

References

(1) SIR92: Altomare, A., Cascarano, M., Giacovazzo, C., Guagliardi, A. (1993). J. Appl. Cryst., 26, 343.

(2) DIRDIF94: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., de Gelder, R., Israel, R. and Smits, J.M.M. (1994). The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(3) Least-Squares:

Function minimized: $\Sigma w(|Fo| - |Fc|)^2$

where w = $\frac{1}{\sigma^2(Fo)} = [\sigma_c^2(Fo) + \frac{p^2}{4}Fo^2]^{-1}$

$\sigma_c(Fo)$ = e.s.d. based on counting statistics

p = p-factor

(4) Standard deviation of an observation of unit weight:

$$\sqrt{\Sigma w(|Fo| - |Fc|)^2/(No - Nv)}$$

where: No = number of observations

Nv = number of variables

(5) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(6) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

(7) Creagh, D. C. & McAuley, W.J .; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

(8) Creagh, D. C. & Hubbell, J.H..; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

(9) teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992).

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{16}H_{17}N_3O_8$
Formula Weight	379.33
Crystal Color, Habit	colourlessprism, prism
Crystal Dimensions	0.15 X 0.15 X 0.15 mm
Crystal System	monoclinic
Lattice Type	C-centered
No. of Reflections Used for Unit	
Cell Determination (2θ range)	25 (60.5 - 72.8°)
Omega Scan Peak Width	
at Half-height	0.27°
Lattice Parameters	a = 25.358(5)Å b = 7.331(9) Å c = 18.771(3) Å β = 94.08(2)°
	V = 3481(4) Å^3
Space Group	C2/c (#15)
Z value	8
D_{calc}	1.448 g/cm^3
F_{000}	1584.00
μ(CuKα)	10.14 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku AFC7S

Radiation	CuKα ($\lambda = 1.54178$ Å) graphite monochromated
Attenuator	Ni foil (factor = 9.42)
Take-off Angle	6.0°
Detector Aperture	9.0 mm horizontal 13.0 mm vertical
Crystal to Detector Distance	400 mm
Voltage, Current	0kV, 0mA
Temperature	20.0°C
Scan Type	ω
Scan Rate	16.0°/min (in ω) (up to 4 scans)
Scan Width	$(1.05 + 0.35 \tan\theta)°$
$2\theta_{max}$	120.4°
No. of Reflections Measured	Total: 2904 Unique: 2827 ($R_{int} = 0.025$)
Corrections	Lorentz-polarization Absorption (trans. factors: 0.9256 - 1.0000) Decay (1.87% decline) Secondary Extinction (coefficient: 7.74564e-07)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w(\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$w = \frac{1}{\sigma^2(Fo)} = [\sigma_c^2(Fo) + \frac{p^2}{4}Fo^2]^{-1}$
p-factor	0.0020
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	1431
No. Variables	245

Reflection/Parameter Ratio	5.84
Residuals: R; Rw	0.051 ; 0.040
Goodness of Fit Indicator	3.30
Max Shift/Error in Final Cycle	0.01
Maximum peak in Final Diff. Map	0.17 $e^-/\AA^3$
Minimum peak in Final Diff. Map	-0.21 $e^-/\AA^3$

Table 1. Atomic coordinates and B_{iso}/B_{eq}

atom	x	y	z	B_{eq}
O(12)	0.5584(1)	0.2299(5)	-0.1414(2)	6.5(1)
O(13)	0.6139(1)	0.3725(5)	-0.0615(2)	6.1(1)
O(14)	0.4010(1)	0.1541(6)	-0.0929(2)	6.5(1)
O(15)	0.4553(1)	0.3594(5)	-0.1352(2)	6.1(1)
O(16)	0.2733(1)	0.0070(6)	-0.0067(2)	7.6(1)
O(17)	0.2471(1)	0.0346(6)	0.1047(2)	6.6(1)
O(18)	0.3445(2)	0.2664(6)	0.2664(2)	7.9(1)
O(19)	0.3081(2)	-0.0028(6)	0.2366(2)	7.1(1)
N(1)	0.5143(2)	0.2198(6)	0.0894(2)	5.1(1)
N(7)	0.3739(2)	0.1180(6)	0.0408(2)	5.2(1)
N(10)	0.4093(2)	0.1966(6)	0.1487(2)	5.0(1)
C(2)	0.4678(2)	0.2095(7)	0.0474(2)	4.9(1)
C(3)	0.4787(2)	0.2420(7)	-0.0228(2)	4.9(1)
C(4)	0.5344(2)	0.2743(7)	-0.0215(2)	5.0(1)
C(5)	0.5539(2)	0.2588(8)	0.0474(3)	5.5(2)
C(6)	0.4170(2)	0.1777(8)	0.0796(3)	5.0(2)
C(8)	0.3347(2)	0.0954(8)	0.0874(3)	5.0(2)
C(9)	0.3575(2)	0.1416(7)	0.1528(2)	4.9(1)
C(11)	0.5227(2)	0.1891(9)	0.1663(2)	6.6(2)
C(12)	0.5683(2)	0.2883(8)	-0.0824(3)	5.3(2)
C(13)	0.6519(2)	0.3871(8)	-0.1158(3)	6.6(2)
C(14)	0.4412(2)	0.2470(8)	-0.0851(3)	5.2(2)
C(15)	0.4256(2)	0.3489(9)	-0.2040(3)	7.4(2)
C(16)	0.2823(2)	0.0397(8)	0.0548(3)	5.6(2)

Table 1. Atomic coordinates and B_{iso}/B_{eq} (continued)

atom	x	y	z	B_{eq}
C(17)	0.1947(2)	-0.0253(9)	0.0784(3)	7.8(2)
C(18)	0.3355(2)	0.146(1)	0.2250(3)	5.4(2)
C(19)	0.2845(2)	-0.007(1)	0.3049(3)	9.1(2)
H(5)	0.5900	0.2734	0.0637	6.6174
H(7)	0.3700	0.0994	-0.0142	8.6970
H(11b)	0.5047	0.0812	0.1788	7.8787
H(11c)	0.5094	0.2899	0.1912	7.8787
H(11a)	0.5594	0.1756	0.1789	7.8787
H(13a)	0.6369	0.4553	-0.1552	7.9765
H(13b)	0.6609	0.2686	-0.1314	7.9765
H(13c)	0.6829	0.4471	-0.0962	7.9765
H(15a)	0.4212	0.2248	-0.2176	8.9207
H(15b)	0.3920	0.4041	-0.2009	8.9207
H(15c)	0.4444	0.4113	-0.2387	8.9207
H(17a)	0.1796	0.0617	0.0454	9.3926
H(17b)	0.1729	-0.0366	0.1174	9.3926
H(17c)	0.1971	-0.1400	0.0554	9.3926
H(19a)	0.2622	0.0960	0.3086	10.9609
H(19b)	0.2644	-0.1155	0.3082	10.9609
H(19c)	0.3117	-0.0043	0.3425	10.9609

$$B_{eq} = \frac{8}{3}\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^*\cos\gamma + 2U_{13}aa^*cc^*\cos\beta + 2U_{23}bb^*cc^*\cos\alpha)$$

Table 2. Anisotropic Displacement Parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(12)	0.081(3)	0.112(4)	0.053(2)	-0.012(3)	0.009(2)	-0.011(2)
O(13)	0.074(3)	0.098(3)	0.059(2)	-0.014(2)	0.013(2)	-0.003(2)
O(14)	0.074(3)	0.123(4)	0.051(2)	-0.015(3)	-0.002(2)	0.003(2)
O(15)	0.087(3)	0.091(3)	0.053(2)	0.000(2)	-0.001(2)	0.013(2)
O(16)	0.080(3)	0.154(4)	0.055(2)	-0.023(3)	0.003(2)	-0.012(3)
O(17)	0.062(3)	0.121(4)	0.065(2)	-0.010(3)	0.000(2)	-0.002(2)
O(18)	0.107(3)	0.124(4)	0.073(3)	-0.027(3)	0.030(2)	-0.031(3)
O(19)	0.100(3)	0.108(4)	0.062(3)	-0.031(3)	0.015(2)	0.001(2)
N(1)	0.064(3)	0.086(4)	0.043(2)	-0.008(3)	-0.002(2)	-0.003(2)
N(7)	0.063(3)	0.086(4)	0.047(2)	-0.004(3)	-0.004(2)	-0.001(2)
N(10)	0.061(3)	0.077(3)	0.053(3)	-0.004(3)	0.003(2)	-0.004(2)
C(2)	0.065(4)	0.071(4)	0.049(3)	-0.002(3)	-0.002(3)	-0.003(3)
C(3)	0.065(4)	0.076(4)	0.043(3)	-0.004(3)	-0.004(3)	0.002(3)
C(4)	0.066(4)	0.076(4)	0.045(3)	-0.010(3)	0.001(3)	-0.001(3)
C(5)	0.061(4)	0.094(5)	0.054(3)	-0.015(4)	0.005(3)	-0.007(3)
C(6)	0.066(4)	0.079(5)	0.047(3)	-0.003(3)	0.003(3)	-0.002(3)
C(8)	0.060(4)	0.075(4)	0.055(3)	-0.002(3)	0.005(3)	0.000(3)
C(9)	0.066(4)	0.071(4)	0.051(3)	0.002(3)	0.003(3)	-0.002(3)
C(11)	0.076(4)	0.125(6)	0.047(3)	-0.010(4)	-0.004(3)	0.001(3)
C(12)	0.078(4)	0.067(4)	0.054(3)	-0.001(4)	-0.002(3)	-0.001(3)
C(13)	0.075(4)	0.102(5)	0.078(4)	-0.005(4)	0.023(3)	0.007(4)
C(14)	0.077(4)	0.072(5)	0.050(3)	0.007(4)	0.006(3)	-0.004(3)
C(15)	0.106(5)	0.127(6)	0.048(3)	0.008(4)	-0.008(3)	0.012(4)
C(16)	0.065(4)	0.091(5)	0.058(3)	-0.005(4)	0.005(3)	0.005(4)

Table 2. Anisotropic Displacement Parameters (continued)

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(17)	0.063(4)	0.149(7)	0.085(4)	-0.017(4)	0.000(3)	0.007(4)
C(18)	0.059(4)	0.093(5)	0.055(4)	0.005(4)	0.000(3)	-0.002(4)
C(19)	0.121(6)	0.161(7)	0.068(4)	-0.035(5)	0.025(4)	0.016(4)

The general temperature factor expression:

$$\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$$

Table 3. Bond Lengths($\AA$)

atom	atom	distance	atom	atom	distance
O(12)	C(12)	1.196(5)	O(13)	C(12)	1.344(6)
O(13)	C(13)	1.457(5)	O(14)	C(14)	1.225(6)
O(15)	C(14)	1.318(6)	O(15)	C(15)	1.450(5)
O(16)	C(16)	1.187(5)	O(17)	C(16)	1.338(5)
O(17)	C(17)	1.453(6)	O(18)	C(18)	1.191(6)
O(19)	C(18)	1.316(6)	O(19)	C(19)	1.454(5)
N(1)	C(2)	1.373(5)	N(1)	C(5)	1.350(5)
N(1)	C(11)	1.461(5)	N(7)	C(6)	1.342(5)
N(7)	C(8)	1.380(5)	N(10)	C(6)	1.333(5)
N(10)	C(9)	1.380(5)	C(2)	C(3)	1.386(6)
C(2)	C(6)	1.479(6)	C(3)	C(4)	1.431(6)
C(3)	C(14)	1.454(6)	C(4)	C(5)	1.356(6)
C(4)	C(12)	1.483(6)	C(8)	C(9)	1.362(6)
C(8)	C(16)	1.480(6)	C(9)	C(18)	1.502(6)

Table 4. Bond Lengths($\AA$)

atom	atom	distance	atom	atom	distance
N(7)	H(7)	1.04	C(5)	H(5)	0.95
C(11)	H(11b)	0.95	C(11)	H(11c)	0.95
C(11)	H(11a)	0.95	C(13)	H(13a)	0.95
C(13)	H(13b)	0.95	C(13)	H(13c)	0.95
C(15)	H(15a)	0.95	C(15)	H(15b)	0.95
C(15)	H(15c)	0.95	C(17)	H(17a)	0.95
C(17)	H(17b)	0.95	C(17)	H(17c)	0.95
C(19)	H(19a)	0.95	C(19)	H(19b)	0.95
C(19)	H(19c)	0.95			

Table 5. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
C(12)	O(13)	C(13)	115.3(4)	C(14)	O(15)	C(15)	116.9(4)
C(16)	O(17)	C(17)	114.3(4)	C(18)	O(19)	C(19)	114.8(5)
C(2)	N(1)	C(5)	108.6(4)	C(2)	N(1)	C(11)	128.2(4)
C(5)	N(1)	C(11)	123.2(4)	C(6)	N(7)	C(8)	107.0(4)
C(6)	N(10)	C(9)	103.3(4)	N(1)	C(2)	C(3)	108.4(4)
N(1)	C(2)	C(6)	120.7(4)	C(3)	C(2)	C(6)	130.8(5)
C(2)	C(3)	C(4)	106.0(4)	C(2)	C(3)	C(14)	127.3(5)
C(4)	C(3)	C(14)	126.7(5)	C(3)	C(4)	C(5)	107.1(4)
C(3)	C(4)	C(12)	128.6(4)	C(5)	C(4)	C(12)	123.3(5)
N(1)	C(5)	C(4)	109.9(4)	N(7)	C(6)	N(10)	113.0(5)
N(7)	C(6)	C(2)	121.9(4)	N(10)	C(6)	C(2)	125.0(5)
N(7)	C(8)	C(9)	105.1(4)	N(7)	C(8)	C(16)	116.0(4)
C(9)	C(8)	C(16)	138.8(5)	N(10)	C(9)	C(8)	111.5(4)
N(10)	C(9)	C(18)	117.4(4)	C(8)	C(9)	C(18)	131.0(5)
O(12)	C(12)	O(13)	123.7(5)	O(12)	C(12)	C(4)	126.4(5)
O(13)	C(12)	C(4)	109.9(4)	O(14)	C(14)	O(15)	121.9(5)
O(14)	C(14)	C(3)	124.9(5)	O(15)	C(14)	C(3)	113.2(5)
O(16)	C(16)	O(17)	125.7(5)	O(16)	C(16)	C(8)	124.3(5)
O(17)	C(16)	C(8)	110.1(5)	O(18)	C(18)	O(19)	125.8(5)
O(18)	C(18)	C(9)	122.5(6)	O(19)	C(18)	C(9)	111.6(5)

Table 6. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
C(6)	N(7)	H(7)	126.7	C(8)	N(7)	H(7)	126.2
N(1)	C(5)	H(5)	125.1	C(4)	C(5)	H(5)	125.1
N(1)	C(11)	H(11b)	109.4	N(1)	C(11)	H(11c)	109.5
N(1)	C(11)	H(11a)	109.5	H(11b)	C(11)	H(11c)	109.5
H(11b)	C(11)	H(11a)	109.4	H(11c)	C(11)	H(11a)	109.5
O(13)	C(13)	H(13a)	109.5	O(13)	C(13)	H(13b)	109.5
O(13)	C(13)	H(13c)	109.5	H(13a)	C(13)	H(13b)	109.4
H(13a)	C(13)	H(13c)	109.4	H(13b)	C(13)	H(13c)	109.5
O(15)	C(15)	H(15a)	109.5	O(15)	C(15)	H(15b)	109.5
O(15)	C(15)	H(15c)	109.4	H(15a)	C(15)	H(15b)	109.5
H(15a)	C(15)	H(15c)	109.5	H(15b)	C(15)	H(15c)	109.4
O(17)	C(17)	H(17a)	109.4	O(17)	C(17)	H(17b)	109.5
O(17)	C(17)	H(17c)	109.5	H(17a)	C(17)	H(17b)	109.4
H(17a)	C(17)	H(17c)	109.5	H(17b)	C(17)	H(17c)	109.5
O(19)	C(19)	H(19a)	109.4	O(19)	C(19)	H(19b)	109.5
O(19)	C(19)	H(19c)	109.4	H(19a)	C(19)	H(19b)	109.6
H(19a)	C(19)	H(19c)	109.4	H(19b)	C(19)	H(19c)	109.6

Table 7. Non-bonded Contacts out to 3.60 Å

atom	atom	distance	ADC	atom	atom	distance	ADC
O(12)	C(15)	3.085(6)	65402	O(12)	N(10)	3.238(6)	65503
O(12)	C(6)	3.250(7)	65503	O(12)	C(9)	3.475(7)	65503
O(12)	N(7)	3.543(6)	65503	O(13)	C(17)	3.300(7)	5
O(13)	C(6)	3.401(7)	66503	O(13)	N(10)	3.587(6)	66503
O(14)	C(5)	3.325(7)	65503	O(14)	N(1)	3.479(6)	65503
O(14)	C(11)	3.514(7)	65503	O(14)	C(19)	3.573(7)	55404
O(15)	C(5)	3.265(6)	66503	O(15)	N(1)	3.280(6)	66503
O(15)	C(11)	3.415(7)	66503	O(16)	C(19)	3.567(6)	55404
O(18)	C(17)	3.493(7)	6	O(18)	C(15)	3.512(7)	56504
O(18)	C(11)	3.558(7)	65502	N(7)	C(12)	3.386(7)	65503
N(10)	C(13)	3.460(7)	66503	C(2)	C(4)	3.579(8)	65503
C(6)	C(12)	3.437(8)	65503	C(8)	C(13)	3.590(8)	65503
C(9)	C(13)	3.529(8)	66503	C(11)	C(11)	3.422(9)	65502

The ADC (atom designator code) specifies the position of an atom in a crystal. The 5-digit number shown in the table is a composite of three one-digit numbers and one two-digit number: TA (first digit) + TB (second digit) + TC (third digit) + SN (last two digits). TA, TB and TC are the crystal lattice translation digits along cell edges a, b and c. A translation digit of 5 indicates the origin unit cell. If TA = 4, this indicates a translation of one unit cell length along the a-axis in the negative direction. Each translation digit can range in value from 1 to 9 and thus ± 4 lattice translations from the origin (TA=5, TB=5, TC=5) can be represented.

The SN, or symmetry operator number, refers to the number of the symmetry operator used to generate the coordinates of the target atom. A list of symmetry operators relevant to this structure are given below.

For a given intermolecular contact, the first atom (origin atom) is located in the origin unit cell and its position can be generated using the identity operator (SN=1). Thus, the ADC for an origin atom is always 55501. The position of the second atom (target atom) can be generated using the ADC and the coordinates of the atom in the parameter table. For example, an ADC of 47502 refers to the target atom moved through symmetry operator two, then translated -1 cell translations along the a axis, +2 cell translations along the b axis, and 0 cell translations along the c axis.

An ADC of 1 indicates an intermolecular contact between two fragments (eg. cation and anion) that reside in the same asymmetric unit.

Symmetry Operators:

(1)	X,	Y,	Z	(2)	-X,	Y,	1/2-Z
(3)	-X,	-Y,	-Z	(4)	X,	-Y,	1/2+Z

Hydrogen bonds

A	H	B	B-adc	A...B	A-H	H...B	A-H...B
N(7)	H(7)	O(14)	1	2.662(5)	1.04	1.77	141.5

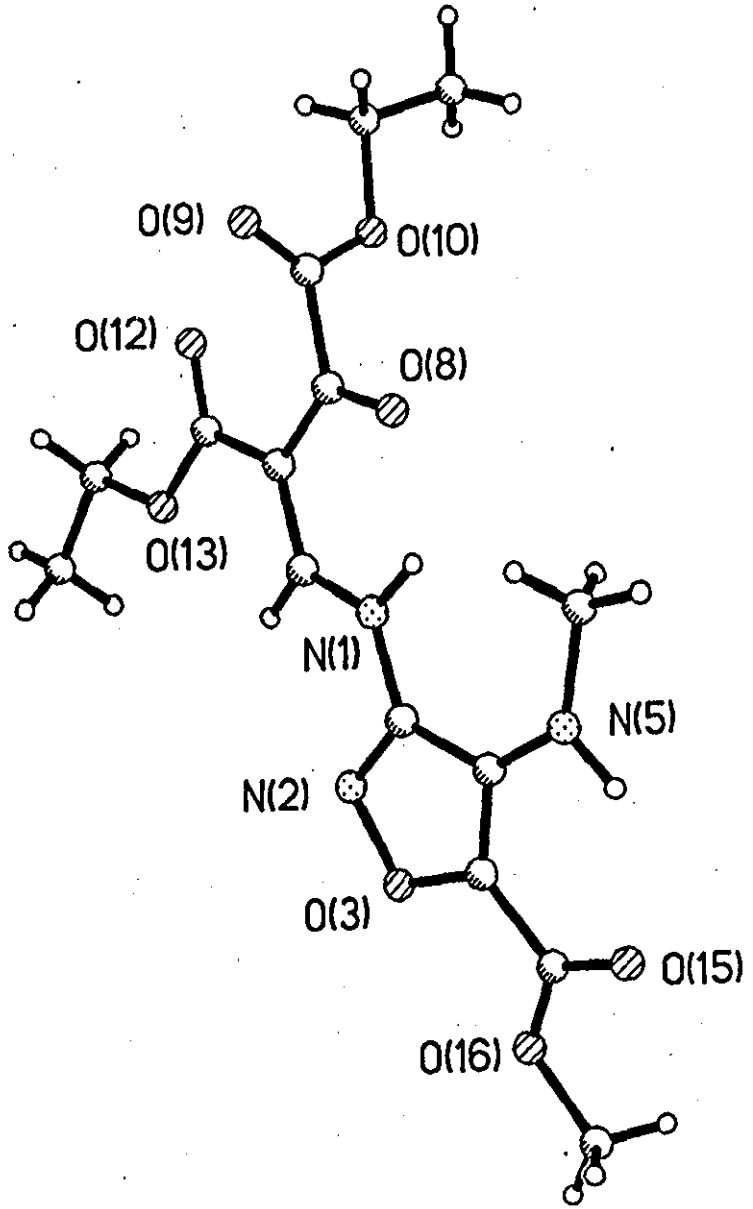

O(9)
O(10)
O(12)
O(8)
O(13)
N(1)
N(5)
N(2)
O(3)
O(15)
O(16)

Table 1. Crystal data and structure refinement for 1.

Identification code	atgw8
Empirical formula	$C_{15}H_{19}N_3O_8$
Formula weight	369.33
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	$P\bar{1}$
Unit cell dimensions	a = 8.0448(6) Å alpha = 100.3570(10)° b = 10.7261(8) Å beta = 102.31° c = 11.0069(8) Å gamma = 102.571(2)°
Volume, Z	879.83(11) $Å^3$, 2
Density (calculated)	1.394 Mg/m^3
Absorption coefficient	0.114 mm^{-1}
F(000)	388
Crystal size	.18 x .18 x .03 mm
θ range for data collection	1.95 to 23.26°
Limiting indices	$-8 \le h \le 8$, $-11 \le k \le 9$, $-12 \le l \le 12$
Reflections collected	4478
Independent reflections	2499 (R_{int} = 0.0245)
Absorption correction	SADABS
Max. and min. transmission	1.000000 and 0.498566
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2449 / 2 / 244
Goodness-of-fit on F^2	1.018
Final R indices [I>2σ(I)]	R1 = 0.0475, wR2 = 0.1248
R indices (all data)	R1 = 0.0676, wR2 = 0.1591
Extinction coefficient	0.007(4)
Largest diff. peak and hole	0.263 and -0.171 $eÅ^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 1. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
N(1)	-2040(2)	2857(2)	-1(2)	47(1)
C(1)	-436(3)	3478(2)	904(2)	42(1)
N(2)	-374(2)	3718(2)	2119(2)	57(1)
O(3)	1387(2)	4326(2)	2769(1)	58(1)
C(4)	2334(3)	4433(2)	1884(2)	48(1)
C(5)	1265(3)	3923(2)	667(2)	42(1)
C(6)	-3527(3)	2307(2)	274(2)	46(1)
C(7)	-5074(3)	1635(2)	-634(2)	49(1)
C(8)	-5161(3)	1454(3)	-1978(2)	56(1)
O(8)	-3925(2)	1955(2)	-2387(2)	76(1)
C(9)	-6840(3)	648(3)	-3010(3)	62(1)
O(9)	-7913(3)	1128(2)	-3516(2)	83(1)
O(10)	-6798(2)	-588(2)	-3335(2)	80(1)
C(10)	-8245(5)	-1451(4)	-4404(4)	111(1)
C(11)	-7853(6)	-2647(4)	-4801(4)	119(2)
C(12)	-6630(3)	1033(2)	-236(3)	53(1)
O(12)	-7966(2)	310(2)	-978(2)	84(1)
O(13)	-6427(2)	1371(2)	1020(2)	61(1)
C(13)	-7914(3)	794(3)	1480(3)	69(1)
C(14)	-7415(4)	1227(4)	2897(3)	87(1)
C(15)	4244(3)	4975(2)	2287(2)	49(1)
O(15)	5104(2)	5145(2)	1531(2)	63(1)
O(16)	4884(2)	5210(2)	3544(2)	64(1)
C(16)	6777(3)	5745(3)	4031(3)	74(1)
N(5)	1717(3)	3862(2)	-444(2)	56(1)
C(17)	607(3)	3109(3)	-1677(2)	59(1)

Table 3. Bond lengths [Å] and angles [°] for 1.

N(1)-C(6)	1.335(3)	N(1)-C(1)	1.393(3)
C(1)-N(2)	1.303(3)	C(1)-C(5)	1.443(3)
N(2)-O(3)	1.394(2)	O(3)-C(4)	1.365(3)
C(4)-C(5)	1.369(3)	C(4)-C(15)	1.457(3)
C(5)-N(5)	1.343(3)	C(6)-C(7)	1.374(3)
C(7)-C(8)	1.441(3)	C(7)-C(12)	1.469(3)
C(8)-O(8)	1.235(3)	C(8)-C(9)	1.532(3)
C(9)-O(9)	1.188(3)	C(9)-O(10)	1.319(3)
O(10)-C(10)	1.467(3)	C(10)-C(11)	1.403(5)
C(12)-O(12)	1.208(3)	C(12)-O(13)	1.330(3)
O(13)-C(13)	1.456(3)	C(13)-C(14)	1.483(4)
C(15)-O(15)	1.205(3)	C(15)-O(16)	1.326(3)
O(16)-C(16)	1.448(3)	N(5)-C(17)	1.437(3)
C(6)-N(1)-C(1)	124.6(2)	N(2)-C(1)-N(1)	119.9(2)
N(2)-C(1)-C(5)	112.9(2)	N(1)-C(1)-C(5)	127.3(2)
C(1)-N(2)-O(3)	106.2(2)	C(4)-O(3)-N(2)	108.1(2)
O(3)-C(4)-C(5)	111.0(2)	O(3)-C(4)-C(15)	120.5(2)
C(5)-C(4)-C(15)	128.4(2)	N(5)-C(5)-C(4)	128.2(2)
N(5)-C(5)-C(1)	130.1(2)	C(4)-C(5)-C(1)	101.8(2)
N(1)-C(6)-C(7)	123.9(2)	C(6)-C(7)-C(8)	120.6(2)
C(6)-C(7)-C(12)	119.8(2)	C(8)-C(7)-C(12)	119.5(2)
O(8)-C(8)-C(7)	123.2(2)	O(8)-C(8)-C(9)	115.0(2)
C(7)-C(8)-C(9)	121.7(2)	O(9)-C(9)-O(10)	126.2(2)
O(9)-C(9)-C(8)	123.0(3)	O(10)-C(9)-C(8)	110.3(2)
C(9)-O(10)-C(10)	116.4(2)	C(11)-C(10)-O(10)	109.9(3)
O(12)-C(12)-O(13)	123.3(2)	O(12)-C(12)-C(7)	123.4(2)
O(13)-C(12)-C(7)	113.4(2)	C(12)-O(13)-C(13)	116.1(2)
O(13)-C(13)-C(14)	108.4(2)	O(15)-C(15)-O(16)	125.5(2)
O(15)-C(15)-C(4)	122.0(2)	O(16)-C(15)-C(4)	112.4(2)
C(15)-O(16)-C(16)	116.2(2)	C(5)-N(5)-C(17)	125.4(2)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2$ x 10^3] for 1. The anisotropic displacement factor exponent takes the form: $-2\pi^2$ [$(ha^*)^2U_{11}$ + ... + $2hka^*b^*U_{12}$]

	U11	U22	U33	U23	U13	U12
N(1)	34(1)	52(1)	47(1)	6(1)	11(1)	0(1)
C(1)	31(1)	42(1)	48(1)	8(1)	9(1)	3(1)
N(2)	38(1)	72(2)	51(1)	9(1)	11(1)	-1(1)
O(3)	38(1)	81(1)	45(1)	12(1)	9(1)	-3(1)
C(4)	38(1)	56(2)	46(1)	14(1)	11(1)	3(1)
C(5)	35(1)	38(1)	46(1)	10(1)	9(1)	3(1)
C(6)	34(1)	44(1)	55(1)	7(1)	12(1)	4(1)
C(7)	34(1)	48(2)	58(2)	9(1)	9(1)	4(1)
C(8)	43(1)	55(2)	63(2)	6(1)	9(1)	8(1)
O(8)	56(1)	97(2)	58(1)	8(1)	15(1)	-6(1)
C(9)	46(2)	64(2)	62(2)	-1(1)	2(1)	13(1)
O(9)	67(1)	79(2)	86(2)	3(1)	-10(1)	28(1)
O(10)	51(1)	64(1)	97(2)	-13(1)	-13(1)	15(1)
C(10)	77(2)	85(3)	115(3)	-37(2)	-28(2)	12(2)
C(11)	131(4)	94(3)	97(3)	-22(2)	2(2)	18(3)
C(12)	33(1)	54(2)	68(2)	15(1)	10(1)	5(1)
O(12)	40(1)	100(2)	82(1)	7(1)	4(1)	-21(1)
O(13)	36(1)	69(1)	71(1)	16(1)	17(1)	-3(1)
C(13)	43(1)	73(2)	97(2)	31(2)	30(1)	7(1)
C(14)	72(2)	108(3)	95(3)	36(2)	45(2)	22(2)
C(15)	39(1)	52(2)	46(1)	11(1)	7(1)	1(1)
O(15)	41(1)	90(1)	47(1)	13(1)	12(1)	-6(1)
O(16)	39(1)	93(1)	45(1)	19(1)	4(1)	-7(1)
C(16)	42(2)	106(2)	54(2)	22(2)	-2(1)	-8(2)
N(5)	38(1)	75(2)	45(1)	8(1)	11(1)	-4(1)
C(17)	51(2)	69(2)	49(2)	2(1)	18(1)	5(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

	x	y	z	U(eq)
H(1N)	-2130(33)	2728(24)	-917(7)	65(8)
H(6A)	-3515(3)	2382(2)	1131(2)	55
H(10A)	-9331(5)	-1614(4)	-4138(4)	133
H(10B)	-8412(5)	-1027(4)	-5112(4)	133
H(11A)	-8805(6)	-3207(4)	-5501(4)	179
H(11B)	-7702(6)	-3069(4)	-4102(4)	179
H(11C)	-6785(6)	-2483(4)	-5073(4)	179
H(13A)	-8207(3)	-158(3)	1218(3)	83
H(13B)	-8939(3)	1076(3)	1121(3)	83
H(14A)	-8383(4)	854(4)	3216(3)	130
H(14B)	-7134(4)	2169(4)	3147(3)	130
H(14C)	-6404(4)	939(4)	3243(3)	130
H(16A)	7101(3)	5878(3)	4946(3)	111
H(16B)	7127(3)	6570(3)	3808(3)	111
H(16C)	7360(3)	5142(3)	3663(3)	111
H(5N)	2967(11)	4214(25)	-383(26)	76(8)
H(17A)	1230(3)	3227(3)	-2318(2)	88
H(17B)	-444(3)	3401(3)	-1867(2)	88
H(17C)	295(3)	2195(3)	-1668(2)	88

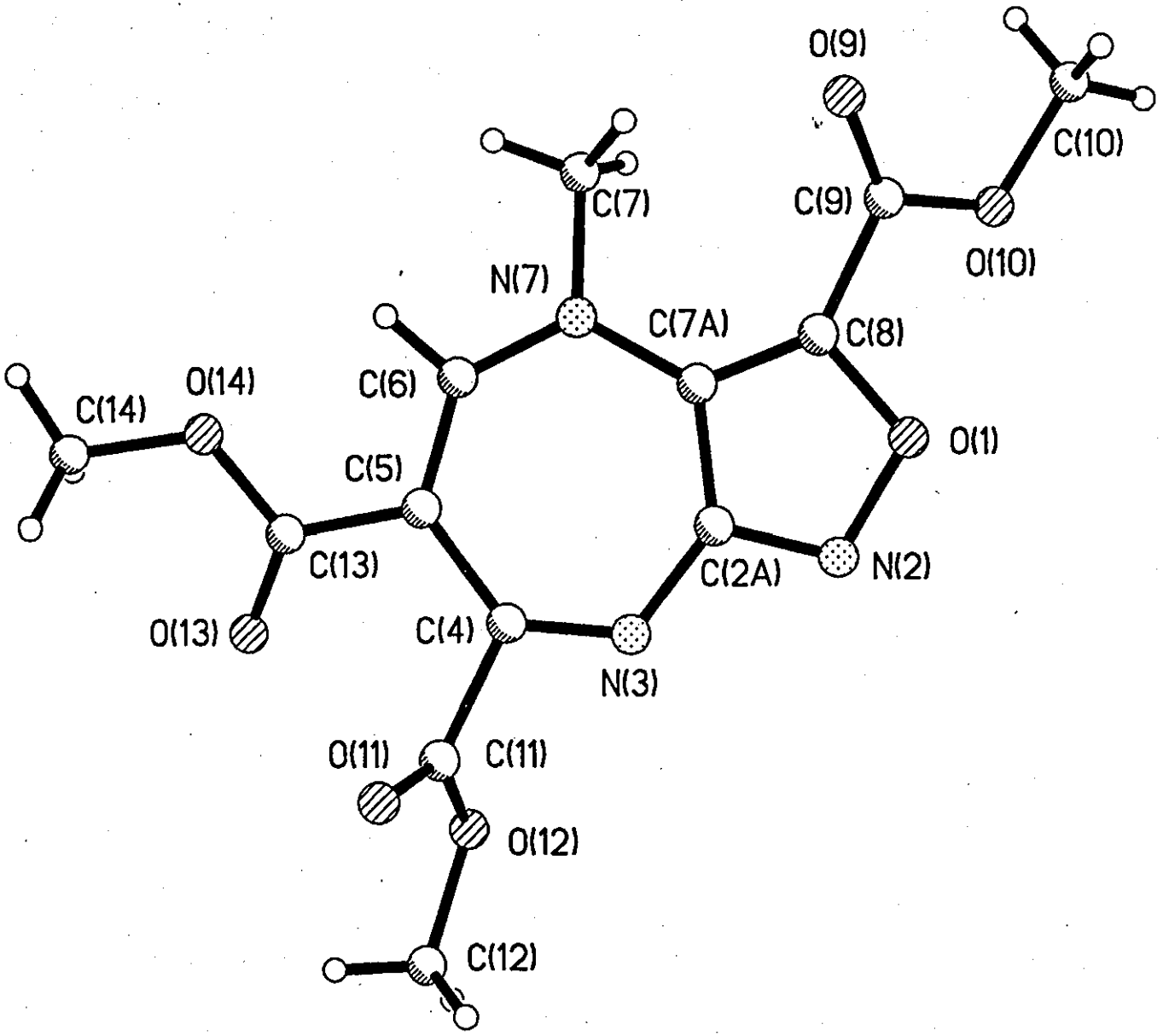

O(9)
C(10)
C(7)
C(9)
O(10)
N(7)
C(7A)
C(8)
C(6)
O(14)
C(14)
O(1)
C(5)
C(13)
C(2A)
N(2)
O(13)
C(4)
N(3)
O(11)
C(11)
O(12)
C(12)

Table 1. Crystal data and structure refinement for 1.

Identification code	atgw10
Empirical formula	$C_{13}H_{13}N_3O_7$
Formula weight	323.26
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 9.2044(8) Å alpha = 90° b = 14.8350(12) Å beta = 98.614(2)° c = 10.6332(9) Å gamma = 90°
Volume, Z	1435.6(2) $Å^3$, 4
Density (calculated)	1.496 Mg/m^3
Absorption coefficient	0.124 mm^{-1}
F(000)	672
Crystal size	.12 x .12 x .03 mm
θ range for data collection	2.24 to 23.28°
Limiting indices	$-10 \le h \le 9$, $-15 \le k \le 16$, $-11 \le l \le 11$
Reflections collected	6250
Independent reflections	2067 (R_{int} = 0.0431)
Absorption correction	Sadabs
Max. and min. transmission	1.00000 and 0.817096
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2017 / 0 / 209
Goodness-of-fit on F^2	1.168
Final R indices [$I>2\sigma(I)$]	R1 = 0.0448, wR2 = 0.1049
R indices (all data)	R1 = 0.0859, wR2 = 0.1350
Extinction coefficient	0.0012(7)
Largest diff. peak and hole	0.323 and -0.255 $eÅ^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 1. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	3534(2)	6037(1)	-4515(2)	62(1)
N(2)	4498(3)	5686(2)	-3488(3)	62(1)
C(2A)	5084(3)	6367(2)	-2835(3)	44(1)
N(3)	6111(3)	6128(2)	-1792(2)	46(1)
C(4)	6806(3)	6706(2)	-1040(3)	40(1)
C(5)	6731(3)	7690(2)	-1017(3)	39(1)
C(6)	5887(3)	8238(2)	-1866(3)	42(1)
N(7)	4891(3)	8071(1)	-2898(2)	43(1)
C(7)	4037(3)	8845(2)	-3514(3)	60(1)
C(7A)	4543(3)	7206(2)	-3406(3)	39(1)
C(8)	3604(3)	6966(2)	-4443(3)	44(1)
C(9)	2694(4)	7402(2)	-5537(3)	46(1)
O(9)	3032(3)	8081(2)	-6029(2)	62(1)
O(10)	1510(3)	6923(1)	-5940(2)	64(1)
C(10)	557(4)	7274(2)	-7045(3)	72(1)
C(11)	7967(4)	6241(2)	-95(3)	47(1)
O(11)	9250(3)	6273(2)	-160(2)	70(1)
O(12)	7360(2)	5733(1)	712(2)	55(1)
C(12)	8347(4)	5164(2)	1562(3)	69(1)
C(13)	7583(3)	8128(2)	88(3)	44(1)
O(13)	7967(3)	7756(1)	1093(2)	62(1)
O(14)	7884(2)	8998(1)	-96(2)	60(1)
C(14)	8658(4)	9468(2)	997(3)	69(1)

Table 3. Bond lengths [Å] and angles [°] for 1.

O(1)-C(8)	1.381(3)	O(1)-N(2)	1.401(3)
N(2)-C(2A)	1.297(3)	C(2A)-N(3)	1.391(3)
C(2A)-C(7A)	1.442(4)	N(3)-C(4)	1.277(3)
C(4)-C(5)	1.462(4)	C(4)-C(11)	1.517(4)
C(5)-C(6)	1.367(4)	C(5)-C(13)	1.464(4)
C(6)-N(7)	1.344(3)	N(7)-C(7A)	1.410(3)
N(7)-C(7)	1.487(3)	C(7A)-C(8)	1.343(4)
C(8)-C(9)	1.477(4)	C(9)-O(9)	1.197(3)
C(9)-O(10)	1.318(4)	O(10)-C(10)	1.453(3)
C(11)-O(11)	1.194(4)	C(11)-O(12)	1.327(4)
O(12)-C(12)	1.453(3)	C(13)-O(13)	1.208(3)
C(13)-O(14)	1.340(3)	O(14)-C(14)	1.447(4)

C(8)-O(1)-N(2)	108.0(2)	C(2A)-N(2)-O(1)	106.9(2)
N(2)-C(2A)-N(3)	114.0(2)	N(2)-C(2A)-C(7A)	111.0(2)
N(3)-C(2A)-C(7A)	135.0(2)	C(4)-N(3)-C(2A)	123.1(2)
N(3)-C(4)-C(5)	131.3(3)	N(3)-C(4)-C(11)	110.3(2)
C(5)-C(4)-C(11)	118.2(3)	C(6)-C(5)-C(4)	127.4(3)
C(6)-C(5)-C(13)	116.6(3)	C(4)-C(5)-C(13)	115.8(2)
N(7)-C(6)-C(5)	132.8(3)	C(6)-N(7)-C(7A)	124.7(2)
C(6)-N(7)-C(7)	117.9(2)	C(7A)-N(7)-C(7)	117.3(2)
C(8)-C(7A)-N(7)	129.6(3)	C(8)-C(7A)-C(2A)	104.8(2)
N(7)-C(7A)-C(2A)	125.5(3)	C(7A)-C(8)-O(1)	109.2(2)
C(7A)-C(8)-C(9)	138.6(3)	O(1)-C(8)-C(9)	112.1(2)
O(9)-C(9)-O(10)	124.6(3)	O(9)-C(9)-C(8)	124.0(3)
O(10)-C(9)-C(8)	111.3(3)	C(9)-O(10)-C(10)	116.1(3)
O(11)-C(11)-O(12)	125.1(3)	O(11)-C(11)-C(4)	123.3(3)
O(12)-C(11)-C(4)	111.3(3)	C(11)-O(12)-C(12)	116.6(3)
O(13)-C(13)-O(14)	122.0(3)	O(13)-C(13)-C(5)	123.9(3)
O(14)-C(13)-C(5)	114.1(3)	C(13)-O(14)-C(14)	115.7(2)

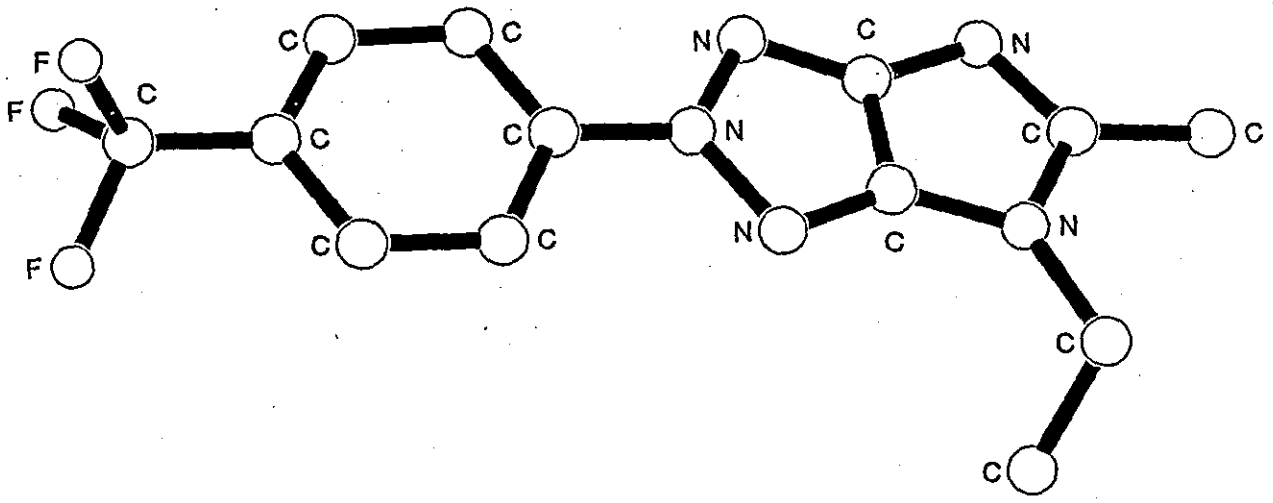
Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2$ x 10^3] for 1.
The anisotropic displacement factor exponent takes the form:
$-2\pi^2$ [$(ha^*)^2U_{11}$ + ... + $2hka^*b^*U_{12}$]

	U11	U22	U33	U23	U13	U12
O(1)	79(2)	31(1)	64(2)	-3(1)	-24(1)	1(1)
N(2)	85(2)	29(2)	62(2)	-2(1)	-25(2)	5(1)
C(2A)	53(2)	27(2)	49(2)	2(2)	-3(2)	0(1)
N(3)	57(2)	27(1)	51(2)	2(1)	-5(1)	2(1)
C(4)	47(2)	32(2)	42(2)	5(2)	4(2)	3(1)
C(5)	48(2)	25(2)	43(2)	4(1)	1(2)	0(1)
C(6)	46(2)	27(2)	48(2)	-3(2)	-1(2)	-1(1)
N(7)	53(2)	21(1)	49(2)	1(1)	-9(1)	1(1)
C(7)	70(2)	26(2)	72(3)	2(2)	-23(2)	4(2)
C(7A)	48(2)	26(2)	43(2)	-1(1)	2(2)	-1(1)
C(8)	54(2)	25(2)	49(2)	1(1)	-1(2)	-1(1)
C(9)	53(2)	37(2)	45(2)	-5(2)	1(2)	2(2)
O(9)	73(2)	52(2)	57(2)	14(1)	-2(1)	-6(1)
O(10)	65(2)	44(1)	74(2)	3(1)	-25(1)	-4(1)
C(10)	73(3)	67(2)	66(3)	-4(2)	-29(2)	11(2)
C(11)	54(2)	34(2)	50(2)	0(2)	-4(2)	4(2)
O(11)	52(2)	71(2)	85(2)	23(1)	5(2)	14(1)
O(12)	61(2)	43(1)	59(2)	18(1)	0(1)	5(1)
C(12)	95(3)	40(2)	64(3)	19(2)	-13(2)	6(2)
C(13)	49(2)	33(2)	47(2)	2(2)	-3(2)	3(2)
O(13)	87(2)	40(1)	52(2)	6(1)	-16(1)	-3(1)
O(14)	83(2)	36(1)	52(2)	2(1)	-19(1)	-11(1)
C(14)	86(3)	48(2)	64(3)	-8(2)	-16(2)	-14(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

	x	y	z	U(eq)
H(6A)	6032(3)	8849(2)	-1694(3)	50
H(7A)	3370(3)	8635(2)	-4236(3)	89
H(7B)	4698(3)	9278(2)	-3789(3)	89
H(7C)	3491(3)	9122(2)	-2916(3)	89
H(10A)	-268(4)	6878(2)	-7259(3)	109
H(10B)	1096(4)	7312(2)	-7750(3)	109
H(10C)	215(4)	7862(2)	-6856(3)	109
H(12A)	7793(4)	4830(2)	2102(3)	104
H(12B)	9060(4)	5533(2)	2076(3)	104
H(12C)	8840(4)	4753(2)	1072(3)	104
H(14A)	8821(4)	10082(2)	772(3)	103
H(14B)	9585(4)	9178(2)	1267(3)	103
H(14C)	8081(4)	9454(2)	1678(3)	103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Experimental

Data Collection

A colourlessprism prism crystal of $C_{13}H_{12}N_5F_3$ having approximate dimensions of 0.10 x 0.10 x 0.22 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC7S diffractometer with graphite monochromated Cu-Kα radiation.

Cell constants and an orientation matrix for data collection , obtained from a least-squares refinement using the setting angles of 11 carefully centered reflections in the range $12.96 < 2\theta < 26.10°$ corresponded to a primitive triclinic cell with dimensions:

a = 7.188(2) Å	α = 88.99(2)°
b = 9.088(2) Å	β = 100.84(2)°
c = 10.682(2) Å	γ = 91.56(1)
V = 685.0(3) Å^3	

For Z = 2 and F.W. = 295.27, the calculated density is 1.43 g/cm^3. Based on a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be:

$P\bar{1}$ (#2)

The data were collected at a temperature of 25 $\pm$ 1°C using the ω scan technique to a maximum 2θ value of 120.0°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.27° with a take-off angle of 6.0°. Scans of (1.37 + 0.35 tan θ)° were made at a speed of 16.0°/min (in omega). The weak reflections ($I < 12.0\sigma(I)$) were rescanned (maximum of 4 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 1.0 mm and the crystal to detector distance was 400 mm, The computer-controlled slits were set to 9.0 mm (horizontal) and 13.0 mm (vertical).

Data Reduction

Of the 2231 reflections which were collected, 2023 were unique (R_{int} = 0.003). The intensities of three representative reflection were measured after every 150 reflections. Over the course of data collection, the standards decreased by 0.2%. A linear correction factor was applied to the data to account for this phenomenon.

The linear absorption coefficient, μ, for Cu-Kα radiation is 10.3 cm^{-1}. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted in transmission factors ranging from 0.91 to 1.00. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = 1.28083e-05).

Structure Solution and Refinement

The structure was solved by direct methods[1] and expanded using Fourier techniques[2]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement[3] was based on 1439 observed reflections ($I > 3.00\sigma(I)$) and 191 variable parameters and converged (largest parameter shift was 0.01 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma||Fo| - |Fc||/\Sigma|Fo| = 0.051$$

$$R_w = \sqrt{(\Sigma w(|Fo| - |Fc|)^2/\Sigma wFo^2)} = 0.035$$

The standard deviation of an observation of unit weight[4] was 4.44. The weighting scheme was based on counting statistics and included a factor (p = 0.002) to downweight the intense reflections. Plots of $\Sigma w(|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, $\sin\theta/\lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.31 and -0.25 $e^-/\AA^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[5] . Anomalous dispersion effects were included in Fcalc[6]; the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley[7]. The values for the mass attenuation coefficients are those of Creagh and Hubbel[8]. All calculations were performed using the teXsan[9] crystallographic software package of Molecular Structure Corporation.

References

(1) SHELXS86: Sheldrick, G.M. (1985). In: "Crystallographic Computing 3" (Eds G.M. Sheldrick, C. Kruger and R. Goddard) Oxford University Press, pp. 175-189.

(2) DIRDIF94: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., de Gelder, R., Israel, R. and Smits, J.M.M. (1994). The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(3) Least-Squares:

Function minimized: $\Sigma w(|Fo| - |Fc|)^2$

where w = $\frac{1}{\sigma^2(Fo)} = [\sigma_c^2(Fo) + \frac{p^2}{4}Fo^2]^{-1}$

$\sigma_c(Fo)$ = e.s.d. based on counting statistics

p = p-factor

(4) Standard deviation of an observation of unit weight:

$$\sqrt{\Sigma w(|Fo| - |Fc|)^2/(No - Nv)}$$

where: No = number of observations

Nv = number of variables

(5) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(6) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

(7) Creagh, D. C. & McAuley, W.J .; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

(8) Creagh, D. C. & Hubbell, J.H..; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

(9) teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992).

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{13}H_{12}N_5F_3$
Formula Weight	295.27
Crystal Color, Habit	colourlessprism, prism
Crystal Dimensions	0.10 X 0.10 X 0.22 mm
Crystal System	triclinic
Lattice Type	Primitive
No. of Reflections Used for Unit Cell Determination (2θ range)	11 (13.0 - 26.1°)
Omega Scan Peak Width at Half-height	0.27°
Lattice Parameters	a = 7.188(2)Å b = 9.088(2) Å c = 10.682(2) Å α = 88.99(2)° β = 100.84(2)° γ = 91.56(1)° V = 685.0(3) Å^3
Space Group	$P\bar{1}$ (#2)
Z value	2
D_{calc}	1.432 g/cm^3
F_{000}	304.00
μ(CuKα)	10.33 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku AFC7S
Radiation	CuKα (λ = 1.54178 Å) graphite monochromated
Attenuator	Ni foil (factor = 9.06)
Take-off Angle	6.0°
Detector Aperture	9.0 mm horizontal 13.0 mm vertical
Crystal to Detector Distance	400 mm
Voltage, Current	0kV, 0mA
Temperature	25.0°C
Scan Type	ω
Scan Rate	16.0°/min (in ω) (up to 4 scans)
Scan Width	(1.37 + 0.35 tan θ)°
$2\theta_{max}$	120.0°
No. of Reflections Measured	Total: 2231 Unique: 2023 (R_{int} = 0.003)
Corrections	Lorentz-polarization Absorption (trans. factors: 0.9140 - 1.0000) Decay (0.16% decline) Secondary Extinction (coefficient: 1.28083e-05)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SHELXS86)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w(\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$w = \frac{1}{\sigma^2(Fo)} = [\sigma_c^2(Fo) + \frac{p^2}{4}Fo^2]^{-1}$
p-factor	0.0020
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	1439

No. Variables	191
Reflection/Parameter Ratio	7.53
Residuals: R; Rw	0.051 ; 0.035
Goodness of Fit Indicator	4.44
Max Shift/Error in Final Cycle	0.01
Maximum peak in Final Diff. Map	0.31 $e^-/\AA^3$
Minimum peak in Final Diff. Map	-0.25 $e^-/\AA^3$

Table 1. Atomic coordinates and B_{iso}/B_{eq}

atom	x	y	z	B_{eq}
F(1)	-0.3922(4)	0.2242(4)	-0.0256(3)	12.7(1)
F(2)	-0.2176(5)	0.0461(3)	0.0240(3)	14.3(1)
F(3)	-0.1809(4)	0.1877(3)	-0.1257(2)	9.77(9)
N(1)	0.6448(4)	0.7719(3)	0.4714(3)	4.42(8)
N(3)	0.4145(4)	0.7800(3)	0.5912(3)	4.96(8)
N(5)	0.2162(4)	0.5990(3)	0.4413(3)	4.54(8)
N(6)	0.2760(4)	0.5432(3)	0.3389(2)	3.99(7)
N(7)	0.4502(4)	0.5899(3)	0.3182(2)	4.27(8)
C(2)	0.5837(5)	0.8277(4)	0.5757(3)	4.5(1)
C(4)	0.3626(5)	0.6861(3)	0.4895(3)	3.94(9)
C(8)	0.4999(5)	0.6795(3)	0.4161(3)	3.75(9)
C(9)	0.1557(5)	0.4517(3)	0.2515(3)	3.98(9)
C(10)	-0.0197(5)	0.4098(4)	0.2764(3)	4.7(1)
C(11)	-0.1388(5)	0.3220(4)	0.1901(3)	5.1(1)
C(12)	-0.0836(5)	0.2772(4)	0.0810(3)	4.9(1)
C(13)	0.0920(6)	0.3179(4)	0.0583(3)	5.3(1)
C(14)	0.2140(5)	0.4059(4)	0.1436(3)	4.9(1)
C(15)	0.7024(5)	0.9352(4)	0.6630(3)	5.7(1)
C(16)	0.8229(5)	0.8036(5)	0.4270(4)	6.5(1)
C(17)	0.7960(6)	0.8611(6)	0.2974(5)	10.4(2)
C(18)	-0.2142(8)	0.1827(6)	-0.0091(4)	7.2(1)
H(10)	-0.0584	0.4414	0.3518	5.5577
H(11)	-0.2595	0.2921	0.2068	6.1541
H(13)	0.1307	0.2856	-0.0169	6.4250

Table 1. Atomic coordinates and B_{iso}/B_{eq} (continued)

atom	x	y	z	B_{eq}
H(14)	0.3355	0.4344	0.1278	5.9008
H(15a)	0.7264	1.0207	0.6159	6.8618
H(15b)	0.8182	0.8914	0.7001	6.8618
H(15c)	0.6358	0.9610	0.7281	6.8618
H(16b)	0.8911	0.7153	0.4312	7.7899
H(16a)	0.8943	0.8743	0.4822	7.7899
H(17a)	0.9161	0.8797	0.2744	12.5939
H(17b)	0.7258	0.7916	0.2410	12.5939
H(17c)	0.7289	0.9506	0.2920	12.5939

$$B_{eq} = \frac{8}{3}\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^*\cos\gamma + 2U_{13}aa^*cc^*\cos\beta + 2U_{23}bb^*cc^*\cos\alpha)$$

Table 2. Anisotropic Displacement Parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
F(1)	0.093(2)	0.235(4)	0.143(3)	-0.038(3)	-0.015(2)	-0.085(3)
F(2)	0.281(4)	0.081(2)	0.131(3)	-0.086(3)	-0.075(2)	0.013(2)
F(3)	0.155(3)	0.138(2)	0.068(2)	-0.051(2)	0.000(2)	-0.037(2)
N(1)	0.050(2)	0.054(2)	0.060(2)	-0.007(2)	0.003(2)	-0.009(2)
N(3)	0.068(2)	0.060(2)	0.059(2)	-0.011(2)	0.010(2)	-0.017(2)
N(5)	0.062(2)	0.058(2)	0.052(2)	-0.009(2)	0.010(2)	-0.013(2)
N(6)	0.055(2)	0.049(2)	0.046(2)	-0.007(2)	0.004(1)	-0.008(1)
N(7)	0.049(2)	0.057(2)	0.055(2)	-0.004(2)	0.006(1)	-0.007(2)
C(2)	0.065(3)	0.045(2)	0.054(2)	0.001(2)	-0.003(2)	-0.006(2)
C(4)	0.055(2)	0.044(2)	0.048(2)	-0.005(2)	0.005(2)	-0.006(2)
C(8)	0.048(2)	0.042(2)	0.049(2)	0.000(2)	0.003(2)	-0.002(2)
C(9)	0.056(2)	0.044(2)	0.047(2)	-0.005(2)	0.000(2)	-0.003(2)
C(10)	0.065(3)	0.060(2)	0.050(2)	-0.013(2)	0.008(2)	-0.010(2)
C(11)	0.063(3)	0.066(3)	0.063(3)	-0.017(2)	0.004(2)	-0.003(2)
C(12)	0.076(3)	0.058(3)	0.048(2)	-0.016(2)	-0.001(2)	-0.004(2)
C(13)	0.083(3)	0.069(3)	0.048(2)	-0.011(2)	0.009(2)	-0.013(2)
C(14)	0.065(3)	0.065(3)	0.055(2)	-0.013(2)	0.012(2)	-0.011(2)
C(15)	0.075(3)	0.056(3)	0.077(3)	-0.009(2)	-0.011(2)	-0.015(2)
C(16)	0.054(3)	0.098(3)	0.096(3)	-0.014(2)	0.013(3)	-0.024(3)
C(17)	0.088(4)	0.216(6)	0.096(4)	-0.031(4)	0.032(3)	0.023(4)
C(18)	0.102(4)	0.095(4)	0.065(3)	-0.031(3)	-0.008(3)	-0.013(3)

The general temperature factor expression:

$$\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$$

Table 3. Bond Lengths($\AA$)

atom	atom	distance	atom	atom	distance
F(1)	C(18)	1.323(5)	F(2)	C(18)	1.286(5)
F(3)	C(18)	1.312(5)	N(1)	C(2)	1.381(4)
N(1)	C(8)	1.370(4)	N(1)	C(16)	1.466(4)
N(3)	C(2)	1.319(4)	N(3)	C(4)	1.383(4)
N(5)	N(6)	1.359(3)	N(5)	C(4)	1.328(4)
N(6)	N(7)	1.367(3)	N(6)	C(9)	1.412(3)
N(7)	C(8)	1.326(4)	C(2)	C(15)	1.496(4)
C(4)	C(8)	1.374(4)	C(9)	C(10)	1.379(4)
C(9)	C(14)	1.374(4)	C(10)	C(11)	1.383(4)
C(11)	C(12)	1.371(4)	C(12)	C(13)	1.370(4)
C(12)	C(18)	1.480(5)	C(13)	C(14)	1.388(4)
C(16)	C(17)	1.452(5)			

Table 4. Bond Lengths($\AA$)

atom	atom	distance	atom	atom	distance
C(10)	H(10)	0.95	C(11)	H(11)	0.95
C(13)	H(13)	0.95	C(14)	H(14)	0.95
C(15)	H(15a)	0.95	C(15)	H(15b)	0.95
C(15)	H(15c)	0.95	C(16)	H(16b)	0.95
C(16)	H(16a)	0.95	C(17)	H(17a)	0.95
C(17)	H(17b)	0.95	C(17)	H(17c)	0.95

Table 5. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
C(2)	N(1)	C(8)	104.5(3)	C(2)	N(1)	C(16)	128.6(3)
C(8)	N(1)	C(16)	126.8(3)	C(2)	N(3)	C(4)	102.0(3)
N(6)	N(5)	C(4)	101.2(3)	N(5)	N(6)	N(7)	117.1(2)
N(5)	N(6)	C(9)	121.0(3)	N(7)	N(6)	C(9)	121.6(3)
N(6)	N(7)	C(8)	99.6(3)	N(1)	C(2)	N(3)	115.1(3)
N(1)	C(2)	C(15)	121.7(3)	N(3)	C(2)	C(15)	123.2(3)
N(3)	C(4)	N(5)	138.1(3)	N(3)	C(4)	C(8)	112.2(3)
N(5)	C(4)	C(8)	109.7(3)	N(1)	C(8)	N(7)	141.4(3)
N(1)	C(8)	C(4)	106.2(3)	N(7)	C(8)	C(4)	112.3(3)
N(6)	C(9)	C(10)	119.1(3)	N(6)	C(9)	C(14)	120.0(3)
C(10)	C(9)	C(14)	121.0(3)	C(9)	C(10)	C(11)	119.1(3)
C(10)	C(11)	C(12)	120.5(3)	C(11)	C(12)	C(13)	119.8(3)
C(11)	C(12)	C(18)	119.1(4)	C(13)	C(12)	C(18)	121.1(4)
C(12)	C(13)	C(14)	120.7(3)	C(9)	C(14)	C(13)	118.9(3)
N(1)	C(16)	C(17)	113.5(4)	F(1)	C(18)	F(2)	105.4(4)
F(1)	C(18)	F(3)	102.3(4)	F(1)	C(18)	C(12)	112.9(4)
F(2)	C(18)	F(3)	106.9(4)	F(2)	C(18)	C(12)	114.5(4)
F(3)	C(18)	C(12)	113.8(4)				

Table 6. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
C(9)	C(10)	H(10)	120.4	C(11)	C(10)	H(10)	120.5
C(10)	C(11)	H(11)	119.7	C(12)	C(11)	H(11)	119.8
C(12)	C(13)	H(13)	119.7	C(14)	C(13)	H(13)	119.6
C(9)	C(14)	H(14)	120.4	C(13)	C(14)	H(14)	120.8
C(2)	C(15)	H(15a)	109.3	C(2)	C(15)	H(15b)	109.3
C(2)	C(15)	H(15c)	109.0	H(15a)	C(15)	H(15b)	109.9
H(15a)	C(15)	H(15c)	109.6	H(15b)	C(15)	H(15c)	109.6
N(1)	C(16)	H(16b)	108.5	N(1)	C(16)	H(16a)	108.3
C(17)	C(16)	H(16b)	108.5	C(17)	C(16)	H(16a)	108.5
H(16b)	C(16)	H(16a)	109.6	C(16)	C(17)	H(17a)	109.4
C(16)	C(17)	H(17b)	109.6	C(16)	C(17)	H(17c)	109.5
H(17a)	C(17)	H(17b)	109.6	H(17a)	C(17)	H(17c)	109.2
H(17b)	C(17)	H(17c)	109.5				

Table 7. Non-bonded Contacts out to 3.60 $\AA$

atom	atom	distance	ADC	atom	atom	distance	ADC
F(1)	N(7)	3.486(4)	56502	F(2)	C(17)	3.330(6)	44501
F(2)	F(2)	3.393(8)	2	F(3)	C(15)	3.229(4)	44401
F(3)	N(7)	3.260(4)	56502	F(3)	N(6)	3.307(4)	56502
F(3)	C(9)	3.533(4)	56502	N(1)	N(6)	3.476(4)	66602
N(1)	N(5)	3.599(4)	66602	N(3)	C(11)	3.436(4)	56602
N(3)	N(7)	3.591(4)	66602	N(5)	C(16)	3.404(5)	45501
N(5)	C(8)	3.445(4)	66602	N(5)	C(10)	3.560(4)	56602
N(6)	C(8)	3.456(4)	66602	N(6)	C(4)	3.581(4)	66602
N(6)	C(2)	3.597(4)	66602	N(7)	C(4)	3.359(4)	66602
C(2)	C(9)	3.486(4)	66602	C(4)	C(8)	3.566(4)	66602

The ADC (atom designator code) specifies the position of an atom in a crystal. The 5-digit number shown in the table is a composite of three one-digit numbers and one two-digit number: TA (first digit) + TB (second digit) + TC (third digit) + SN (last two digits). TA, TB and TC are the crystal lattice translation digits along cell edges a, b and c. A translation digit of 5 indicates the origin unit cell. If TA = 4, this indicates a translation of one unit cell length along the a-axis in the negative direction. Each translation digit can range in value from 1 to 9 and thus ± 4 lattice translations from the origin (TA=5, TB=5, TC=5) can be represented.

The SN, or symmetry operator number, refers to the number of the symmetry operator used to generate the coordinates of the target atom. A list of symmetry operators relevant to this structure are given below.

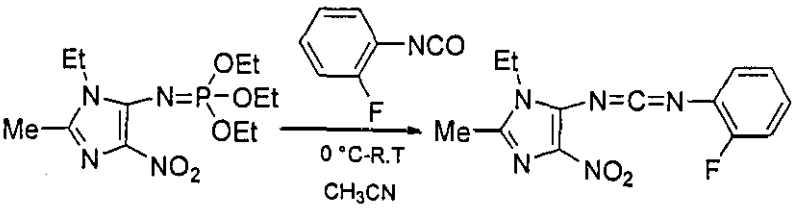
For a given intermolecular contact, the first atom (origin atom) is located in the origin unit cell and its position can be generated using the identity operator (SN=1). Thus, the ADC for an origin atom is always 55501. The position of the second atom (target atom) can be generated using the ADC and the coordinates of the atom in the parameter table. For example, an ADC of 47502 refers to the target atom moved through symmetry operator two, then translated -1 cell translations along the a axis, +2 cell translations along the b axis, and 0 cell translations along the c axis.

An ADC of 1 indicates an intermolecular contact between two fragments (eg. cation and anion) that reside in the same asymmetric unit.

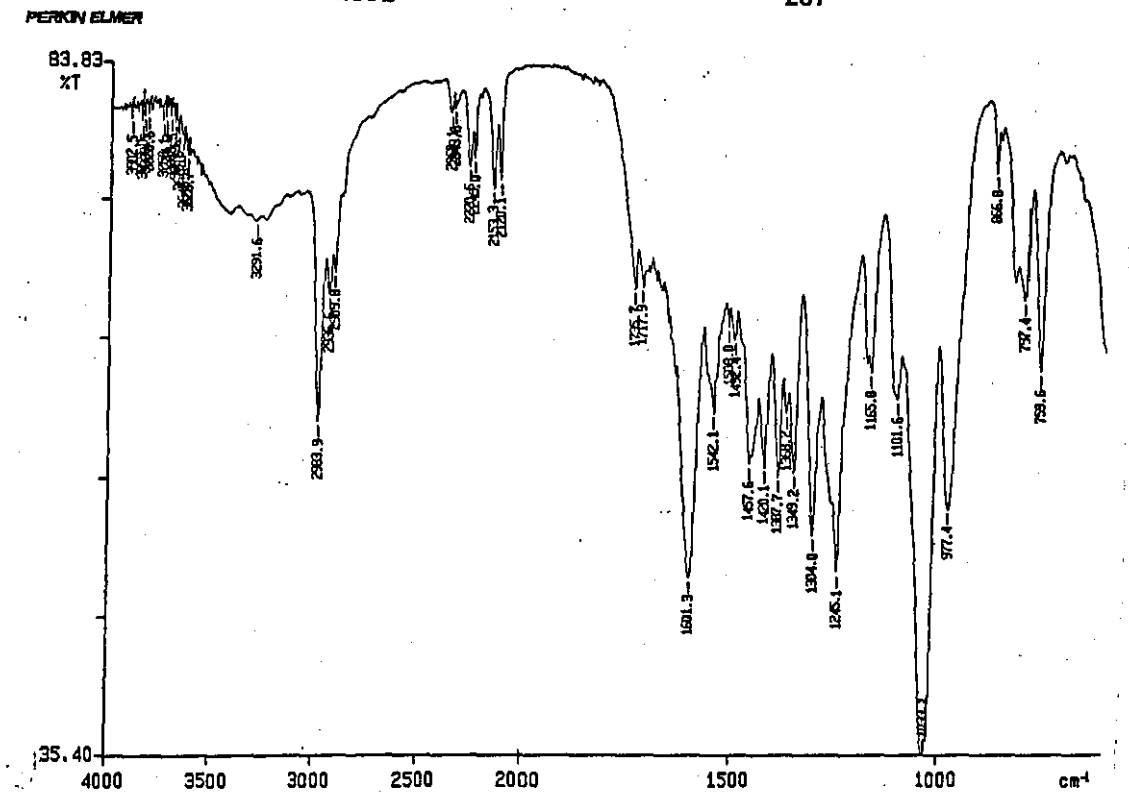
Symmetry Operators:

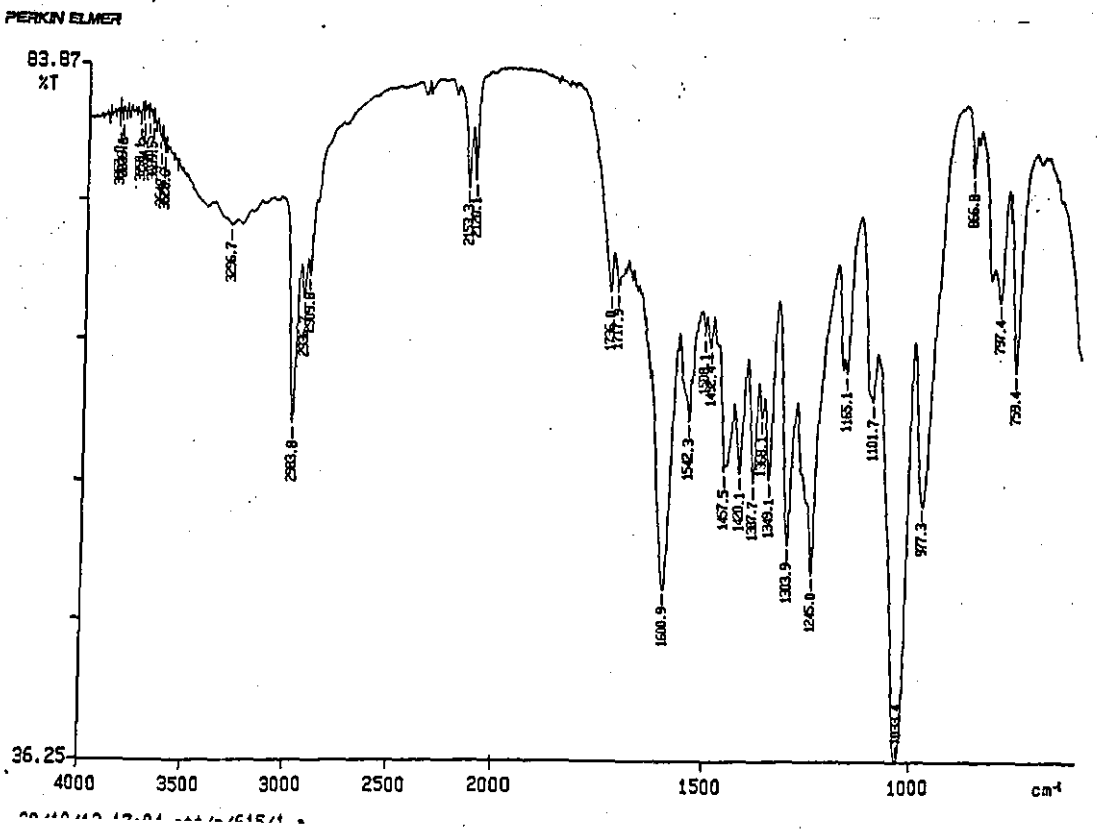
(1)	X,	Y,	Z		(2)	-X,	-Y,	-Z

Selected I. R Spectras showing key signals in identifying intermediate 287

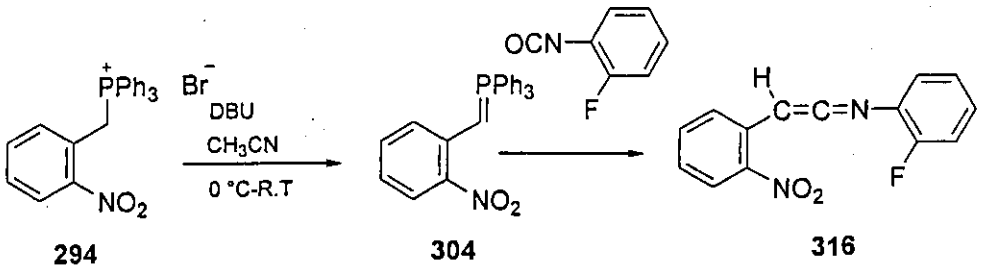


258b 287





Selected I. R Spectras showing key signals in identifying intermediate 316



294 304 316