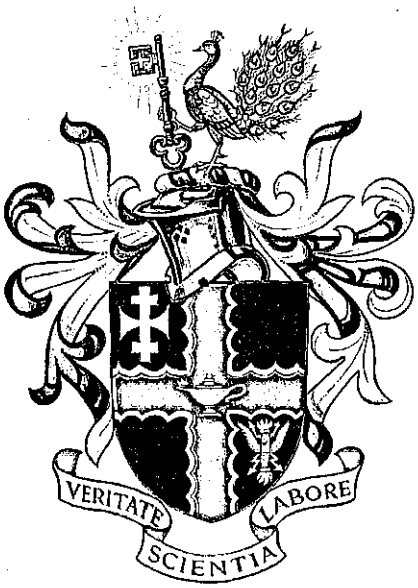
Rhodium Carbenoid Route To Oxazoles

by

Keyin James Doyle



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Abstract

This thesis describes investigations by the author into the preparation of the oxazole heterocyclic system, by the use of rhodium carbenoid methodology.

Chapter 1 is a review of the literature on the formation of oxazoles, by the reaction between diazocarbonyl compounds and nitriles. The various conditions that have been employed in the reaction are detailed, as well as developments into the understanding of its mechanism.

Chapter 2 reports the study into the preparation of 4-functionalised oxazoles. A series of 4-benzenesulfonyloxazoles, oxazole-4-phosphates and oxazole-4-carbonitriles were prepared by a rhodium(II)-catalysed reaction. The effect of varying the rhodium(II) catalyst on oxazole formation is detailed. The oxazole-4-carbonitrile methodology was extended to form bis-oxazoles. Attempts to extend this chemistry towards tris-oxazoles is discussed.

Chapter 3 describes the synthesis of the oxazolylindole alkaloids pimprinine, pimprinethine and WS-30581A. This was achieved by the reaction of *tert*-butyl 3-diazoacetylindole-1-carboxylate with the appropriate nitrile, under rhodium(II) catalysis, followed by deprotection. Studies into varying the substituents at the 2- and 4-positions of the oxazole ring is described.

Chapter 4 relates investigations into the synthesis of the cytotoxic cyclic peptides, diazonamide A and B, isolated from the ascidian, *Diazona chinesis*. These investigations were centred on key skeletal features: an oxazolylindole moiety, an oxazole based around (*S*)-valine and a functionalised benzofuranol. Model studies towards the oxazolylindole and the valine oxazole sections were undertaken, utilising rhodium carbenoid methodology to prepare the azole heterocycle. Formation of the benzofuranol model involved a one step deprotection and cyclisation, the precursor being prepared *via* a Claisen rearrangement and an ozonolysis.

Chapter 5 contains the experimental data, whilst Chapter 6 contains the references.

Acknowledgements

It has been my pleasure to have had the friendship and enthusiasm of my supervisor Chris Moody over the past few years. I think we've both survived the encounter intact.

A big thank you goes to the slaves chained within the department who provide excellent technical support. The labs were kept running smoothly by Messrs Alistair Daley and Paul Hartopp. A special thanks goes to Paul for his preparation of certain starting materials. The other slaves to the machines were Messrs John Greenfield (mass spectra.) and John Kershaw (nmr and associated services).

If Dr. McCoy had ever beamed down from the starship 'Enterprise' into the labs, he would have walked into F0113 and stated those immortal words "It's life Jim, but not as we know it !" For taking me on that galactic journey of discovery that is organic chemistry, I would like to thank my compadré's on that adventure. They were Cpt. Lizzie, Dr Frostie, Science Officer Davie, Lt. Josie and Mr. Martin. Liz and Dave also took on a most dangerous of missions, that of proof reading this tome. For this I would like to thank them kindly.

To all the other people I have met on my way, names of whom are too many to mention, I am warmly appreciative of the help and friendship offered to me.

They say patience is a virtue granted to few. One of those few is Hayley Jayne, without who's warmth, love and companionship none of this you see before you would have been possible. To you I send my deepest thanks.

They also say that it isn't over 'till the fat lad sings, or something like that. Hopefully I'll be able to croon soon.

TO MY PARENTS, RUBY AND JIM,
IN APPRECIATION OF THEIR
KIND LOVE, PATIENCE AND SUPPORT.

Contents

Abbreviations

Ac	=	acetyl ≡ CH_3CO
acac	=	acetylacetonyl ≡ 2,4-pentanedione
^{n}Bu	=	*n*-butyl ≡ $CH_3(CH_2)_3$
^{i}Bu	=	*i*-butyl ≡ $(CH_3)_2CHCH_2$
^{t}Bu	=	*t*-butyl ≡ $(CH_3)_3C$
DCM	=	dichloromethane
DMAP	=	4-dimethylaminopyridine
DME	=	1,2-dimethoxyethane
DMF	=	*N*,*N*-dimethylformamide
DMPU	=	1,1-dimethyl-3,4,5,6-tetrahydro-2-(1*H*)-pyrimidone
Et	=	ethyl ≡ CH_3CH_2
h	=	hour
hv	=	light
nOe	=	nuclear Overhauser enhancement
nmr	=	nuclear magnetic resonance
Me	=	methyl ≡ CH_3
min	=	minute
Ms	=	methanesulfonyl
Ph	=	phenyl ≡ C_6H_5
phth	=	phthaloyl
^{n}Pr	=	*n*-propyl ≡ $CH_3(CH_2)_2$
py	=	pyridine
Tf	=	trifluoromethanesulfonyl
THF	=	tetrahydrofuran
tlc	=	thin layer chromatography
Ts	=	4-methylbenzenesulfonyl
Δ	=	heat

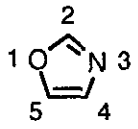
Chapter 1

Oxazoles From Nitriles and Diazocarbonyls

A Review

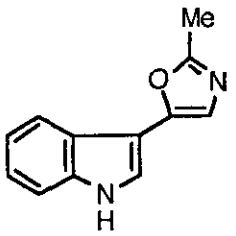
1.1 Overview

Oxazoles, which have been known for over one hundred years, have been of considerable interest to organic chemists. The intensive work on penicillin by Cornforth *et al.* in the 1940's allowed development of new routes to the heterocycle.[1] Also, the subsequent discoveries during the 1950's by Kondrat'eva that oxazoles can function as 2-azadienes in the Diels-Alder reaction[2] paved the foundations of modern oxazole chemistry.

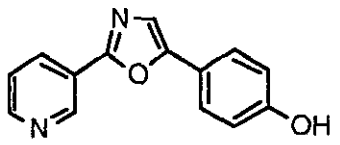


Oxazole

The oxazole heterocycle belongs to the 1,3-azole ring-system and has been the subject of various extensive reviews.[3,4] They have been found to occur in a variety of natural products, from the simply substituted oxazole alkaloids such as pimprinine[5] **1a**, halfordinol[6] **2** and annuloline[7] **3** (Figure 1) to complex marine natural products, for example hennoxazole[8] **4**, calyculin A[9,10] **5** and diazonamide B **6**.[11] It is the occurrence of these complex oxazole natural products that has inspired chemists to develop new routes to the ring system. (Figure 2).



1a



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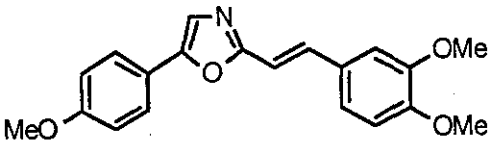

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Figure 1

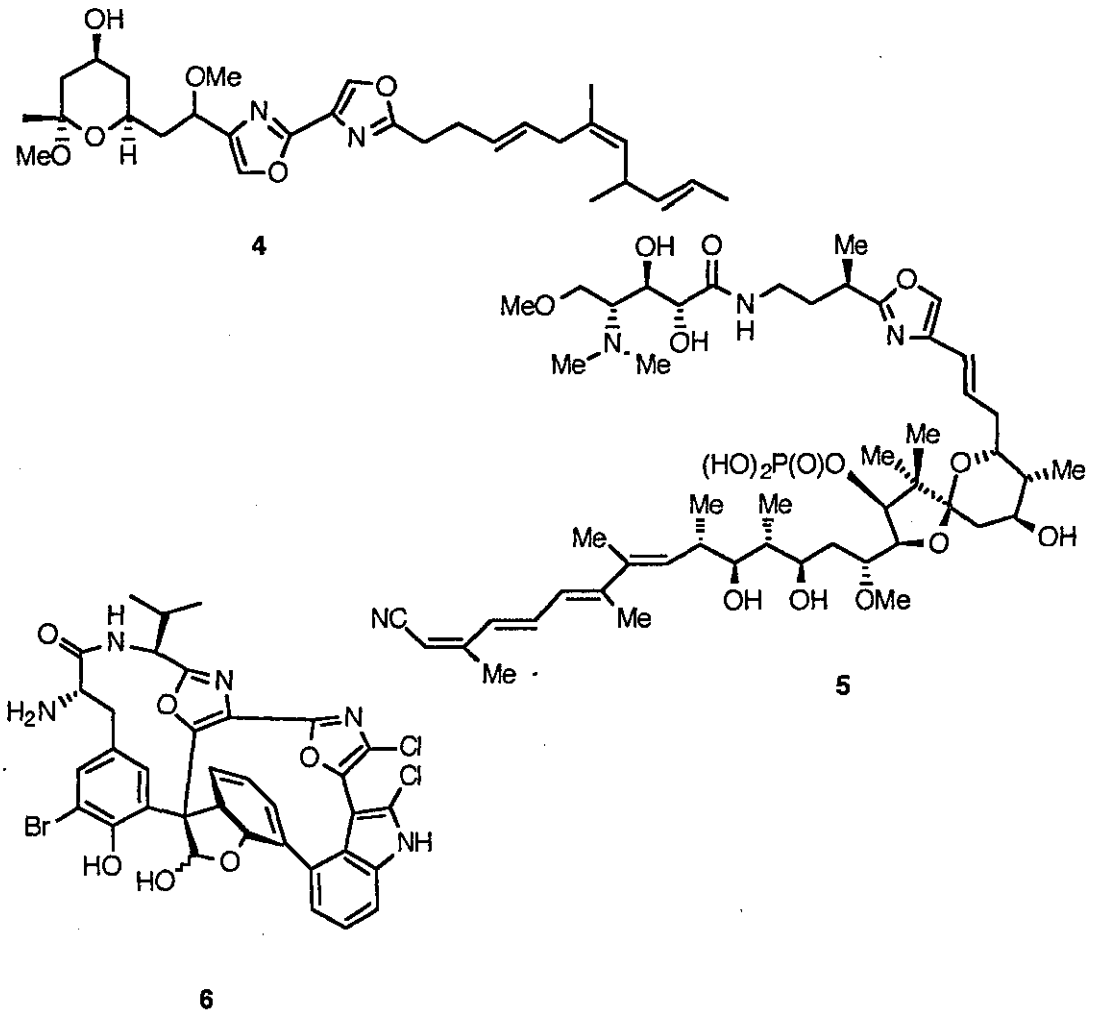


Figure 2

There are four main classical routes to the oxazole ring system, and many of the recently reported preparations of the oxazole ring are variations of them, although some novel routes have been developed.[12-15] (Figure 3).

Route (1) is the Robinson-Gabriel preparation, which occurs *via* the cyclodehydration of the intermediate 2-acylaminoketone **7**.[16,17]

Route (2) is the Cornforth preparation.[18-20]

Route (3) is the oxidative dehydrogenation of a 2-oxazoline **8** to yield an oxazole.[21-27]

Route (4) shows the reaction between a nitrile and a diazocarbonyl compound.

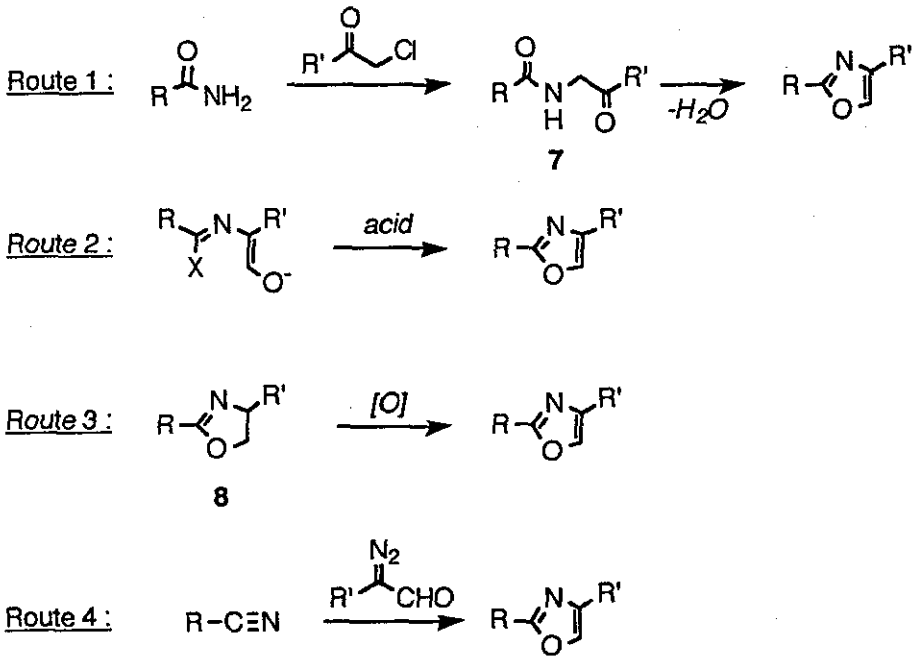


Figure 3

It is this final method, that is the reaction between a diazocarbonyl compound and a nitrile, that this review will encompass.

1.2 Introduction

An analysis of the oxazole ring **9** could lead to a nitrile **10** and a diazocarbonyl compound **12.** This would happen by cleavage between the oxygen and the 2-position carbon, and the nitrogen and the 4-position carbon, yielding the nitrile and a 1,3-dipolar species. This 1,3-dipolar species is an isomer of the ketocarbene **11**, which in turn could be formed by decomposition of the 1-diazocarbonyl compound **12.** However, there is the possibility of the ketocarbene **11** undergoing a Wolff Rearrangement leading to a ketene, and hence to unwanted secondary products. So, for the oxazole formation to be successful, the possibility of a Wolff rearrangement would have to be suppressed. (Figure 4).

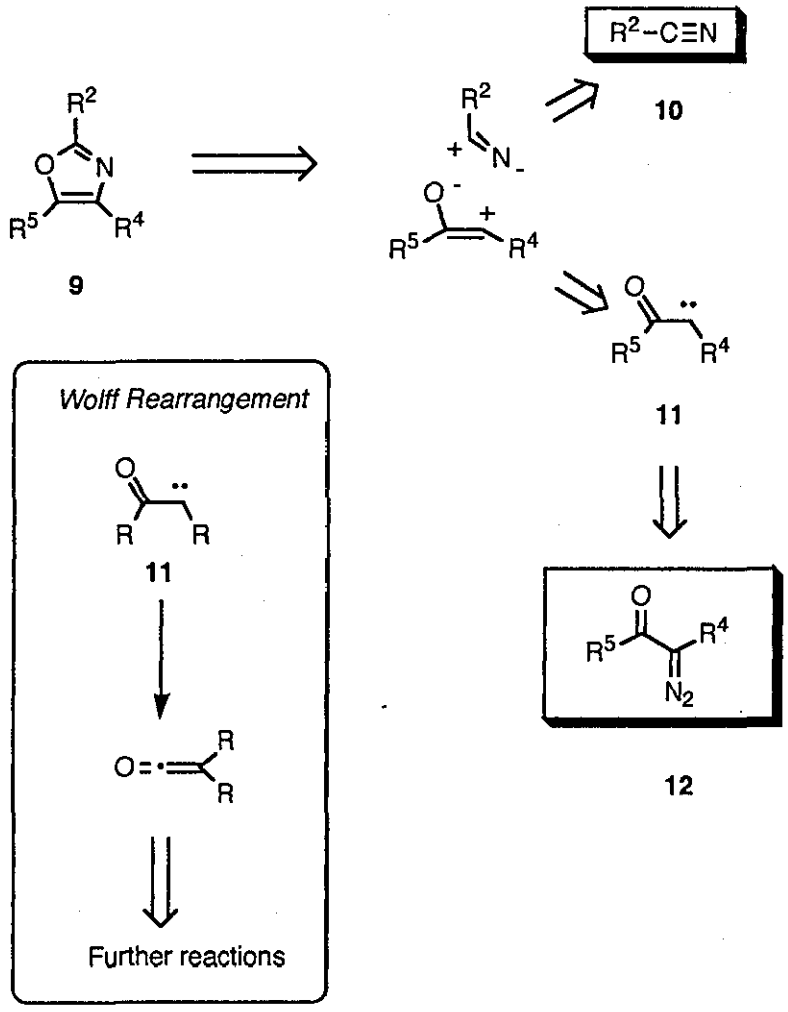


Figure 4

There are three main pathways for the formation of ketocarbenes from diazocarbonyls,[28,29] each of which has been successfully used to form oxazoles in the presence of nitriles. They are,

(i) Thermal decomposition

(ii) Photochemical decomposition

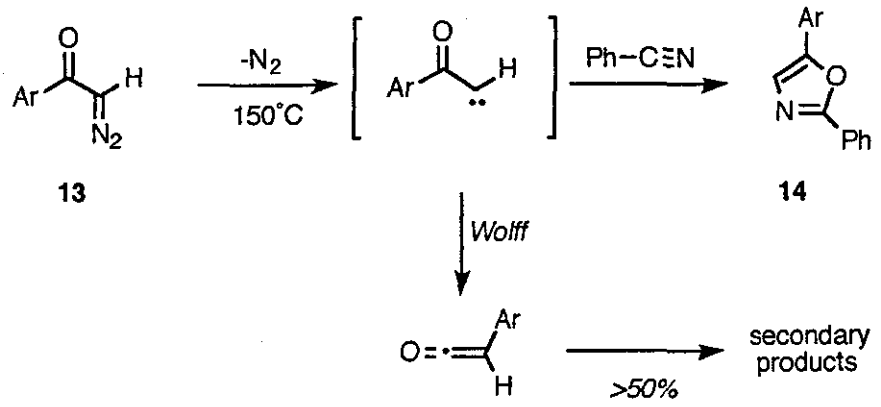
(iii) Catalytic decomposition, by use of either Lewis acids or transition metal salts.

1.3 Thermal and Photochemical Decomposition

1.3.1 Thermal Decomposition

The formation of oxazoles from nitriles and diazocarbonyl compounds, can be firstly attributed to Huisgen.[30] He and co-workers found, in the early 1960's, that the ketocarbene, derived from diazoacetophenone **13a** by thermolysis at 150°C, could be trapped with

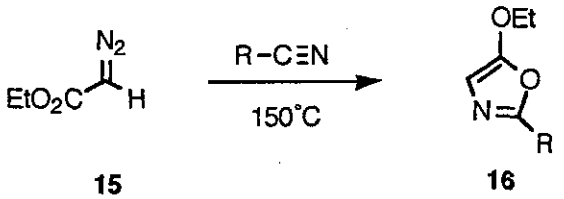
benzonitrile giving 0.4% yield of 2,5-diphenyloxazole **14a** and greater than 50% of secondary products, derived from a Wolff rearrangement. The presence of electron withdrawing groups at the 2-position on the aromatic ring allowed the isolation of the oxazole product in greater yield. (Scheme 1).



Diazo	*Ar*	*Oxazole*	*Yield (%)*
13a	Ph	**14a**	0.4
13b	2-Cl-C_6H_4	**14b**	38
13c	2-NO_2-C_6H_4	**14c**	45

Scheme 1

Huisgen *et al.*[31] also studied the thermal decomposition of ethyl diazoacetate **15**, in the presence of benzonitrile and phenylacetonitrile, to give the requisite 2-substituted-5-ethoxy oxazoles **16** in variable yields. (Table 1).

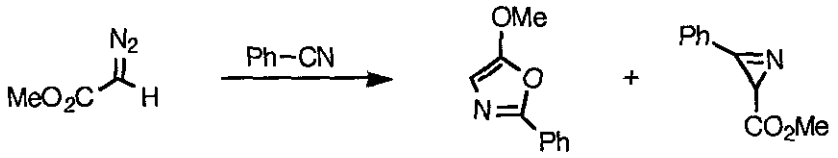


R	*Oxazole*	*Yield (%)*
Ph	**16a**	42
$PhCH_2$	**16b**	11

Table 1

The authors found that the solvent had an effect on the rate of decomposition of ethyl diazoacetate **15**. In the polar solvent, nitrobenzene, the rate was found to be twice than that in the hydrocarbon solvent, decalin.

Komendantov *et al.* found that thermal decomposition of methyl diazoacetate **17** in the presence of benzonitrile, yielded two products.[32] One is the expected 2-phenyl-5-methoxy oxazole **18** in about 35% and the other product, the unexpected methyl 3-phenyl-2*H*-azirine-2-carboxylate **19** in around 1%. (Table 2).

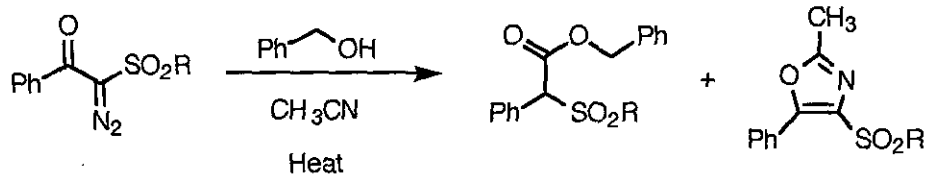


17 **18** **19**

Temp. °C	*Yield (%)*	*Ratio* **18 : 19**
145 - 150	35	97 : 3
175 - 180	33	96 : 4

Table 2

In studies on the Wolff rearrangement of 1-diazo-2-ketosulfones, Shoiri *et al.*[33] found that the thermal decomposition of 1-benzoylsulfonyldiazomethanes **20** with benzyl alcohol in acetonitrile, gave two products. One is the expected 1-sulfonyl acetate **21**, whilst the other is the 4-sulfonyl oxazole **22**. (Table 3).

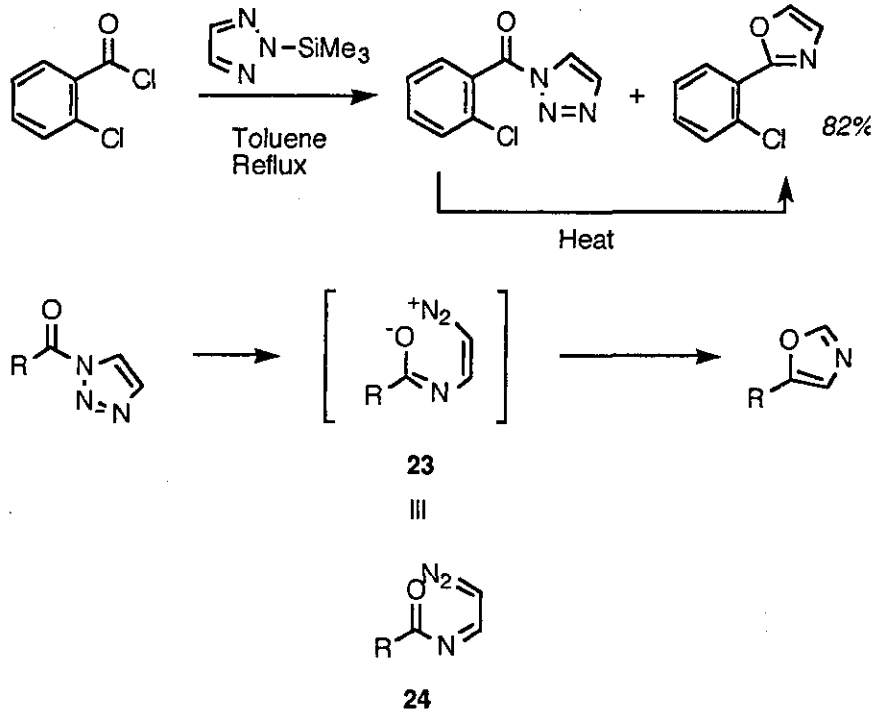


20 **21** **22**

R	*Yield (%)*
	21 : 22
$PhCH_2$	41 : 59
^tBu	62 : 24
4-Me-C_6H_4	33 : 24
4-MeO-C_6H_4	37 : 0

Table 3

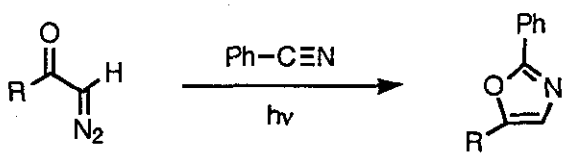
In a recent paper, Williams describes the one pot synthesis of 2-substituted oxazoles, *via* the thermolysis of triazole amides, the reaction not proceeding photochemically.[34] He describes the reaction as going through the zwitterionic intermediate **23**, which is an isomeric form of the diazo imine **24**. So there is the possibility that this reaction may be thought of as a thermal decomposition of a diazo imine, although this is yet to be proved. (Scheme 2).



Scheme 2

1.3.2 Photochemical Decomposition

The photochemical decomposition in benzonitrile of ethyl diazoacetate **15**, methyl diazoacetate **17** and diazoacetophones **13** have been studied by Huisgen and Komendantov.[31,32] The reaction using ethyl diazoacetate **15** failed to undergo oxazole formation, whilst methyl diazoacetate **17** gave a 20% yield of the oxazole **18**. As in the thermal decomposition of **17**, the 2*H*-azirine was isolated in ~2% yield. The photolytic decomposition of diazoacetophenone **13a**, was found to be low yielding. An electron withdrawing group at the 2-position on the aromatic ring **13b** allowed isolation of the oxazole in slightly higher yield. (Table 4).



Diazo	*R*	*Oxazole*	*Yield (%)*
15	OEt	**16a**	0
17	OMe	**18**	20 (2)[a]
13a	Ph	**14a**	0.1
13b	2-Cl-C_6H_4	**14b**	0.5

[a] = Yield of **19**

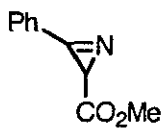


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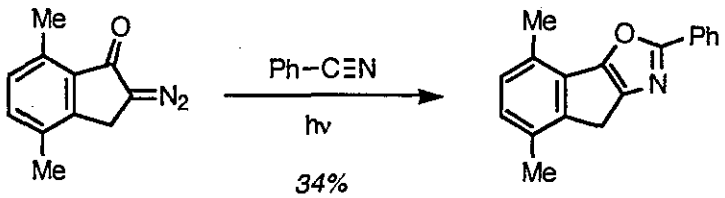
Table 4

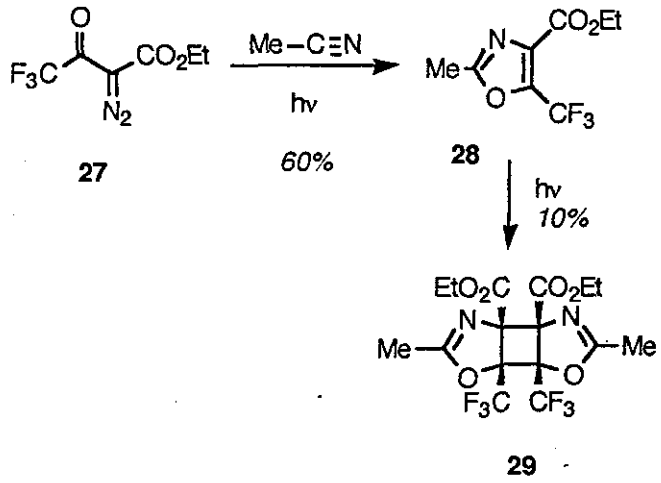
Huisgen found that the cyclic diazo ketone, 4,7-dimethyl-2-diazoindan-1-one **25**, undergoes photolysis in benzonitrile to give the oxazole **26** in 34% yield.[30] (Scheme 3).



25 **26**

Scheme 3

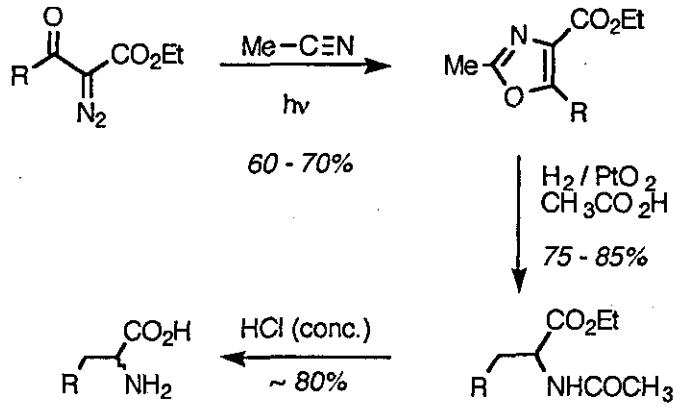
The reaction of trifluoroacetyl diazoacetic ester **27** in acetonitrile, has been studied by Weygand *et al.*[35] who found that ethyl 2-methyl-5-trifluoromethyloxazole-4-carboxylate **28** could be formed photochemically in 60% yield. Further photolysis of the oxazole led to the formation of the dimeric species **29**, derived from a [2 + 2] cycloaddition reaction, in around 10% yield. (Scheme 4).



27 **28** **29**

Scheme 4

Weygand and co-workers have exploited this reaction to give a general approach for the preparation of 2-perfluoroalkylalanines **30**.[36] The oxazole ring is formed from the photolysis of the appropriate perfluoroacyl diazo esters in acetonitrile, which are then degraded under acid hydrogenolysis conditions to give the *N*-acetyl esters **31**, which are then transformed to the racemic 2-perfluoroalkylalanines **30**. (Scheme 5).



30 **31**

R = CF_3, C_2F_5 or C_3F_7

Scheme 5

1.3.3 Mechanistic Aspects

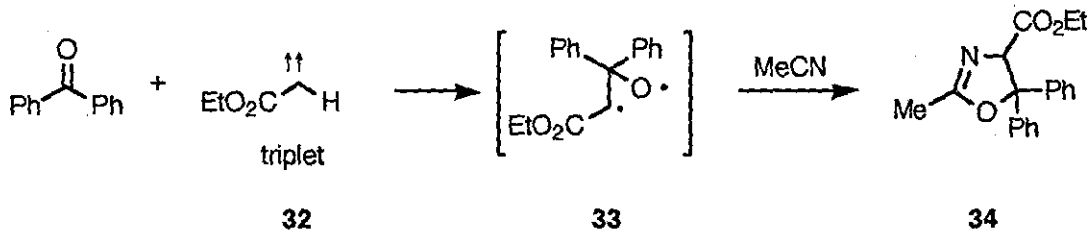
The mechanism of the thermal and photochemical formation of oxazoles from diazocarbonyls is thought to involve the intermediary of a 'naked' ketocarbene.

In the thermal and photochemical decomposition of methyl diazoacetate **17** in benzonitrile, the 2*H*-azirine **19** was found to have been prepared along with the expected oxazole **18**. However, when the photolysis was conducted in a 10 : 1 mixture of hexafluorobenzene and benzonitrile, the sole product was the oxazole in 20% yield.

It was assumed that the formation of the 2*H*-azirine **19** and oxazole **18** was due to the reaction of methoxycarbonylcarbene in either its singlet or triplet state. The workers thought that decomposition of the excited σ^2-singlet state led to the formation of the 2*H*-azirine, whilst the ground triplet state gave the oxazole. They rationalised the observed product ratio as being due to the presence of the inert solvent, hexafluorobenzene, and assumed it caused enhancement of the singlet-triplet transition, leading to more oxazole formation.

However, a thorough investigation into the photodecomposition of diazoesters in acetonitrile has been conducted by Buu and Edward.[37] Their results lead to a different conclusion for the reaction of ketocarbenes in their singlet and triplet states.

These investigators found that only singlet ethoxycarbonylcarbene reacts with nitriles to yield oxazoles. Upon benzophenone sensitisation of the reaction mixture, no oxazole formation takes place, instead an oxazoline **34** is formed. This was due to the triplet carbene **32**, formed due to reaction sensitisation, reacting with benzophenone to give the diradical **33**, which added to acetonitrile yielding the oxazoline **34**. (Scheme 6).

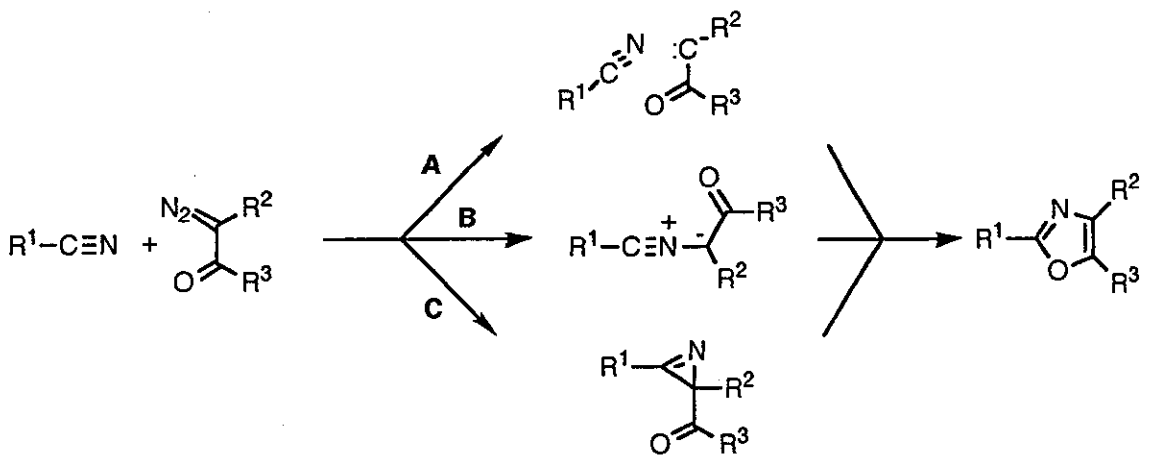


32 **33** **34**

Scheme 6

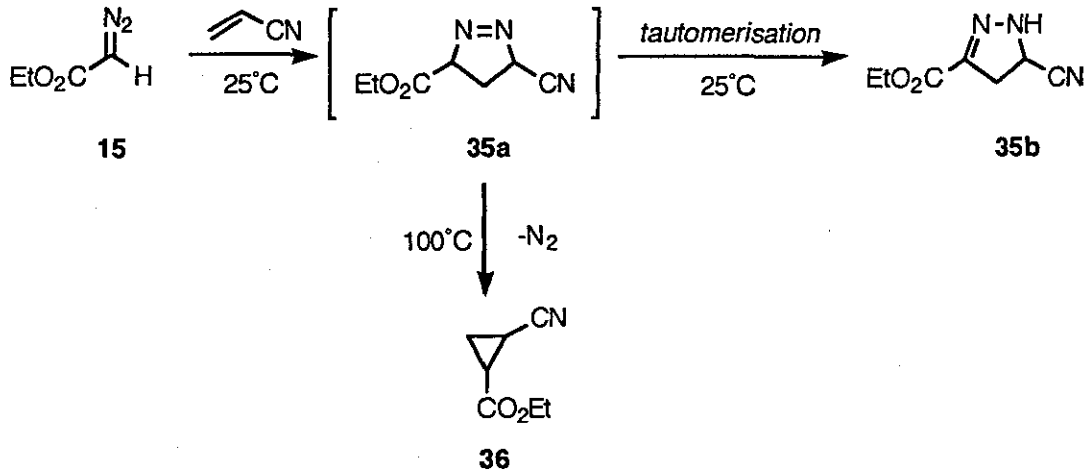
Oxazole formation can be envisaged working *via* any of three possible pathways; 1,3-dipolar cycloaddition of the ketocarbene to the nitrile (path A), the formation and subsequent 1,5-

cyclisation of a nitrile ylide (path B) or the formation and subsequent cyclisation of a 2-keto-2*H*-azirine (path C). (Scheme 7).



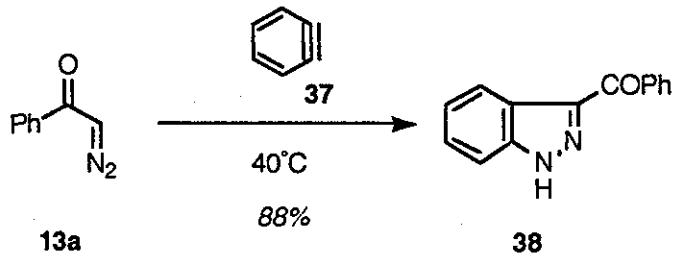
Scheme 7

The 1,3-dipolar cycloaddition of diazocarbonyl compounds with π-bonds has been investigated with olefins,[38-40] aldehydes[41-43] and nitriles.[38] Teyssié *et al.*[38] studying the cycloaddition of ethyl diazoacetate **15** to acrylonitrile, found that in the absence of any catalyst, at room temperature, the 2*H*-pyrazoline **35b** was obtained, whilst at 100°C the cyclopropane **36** was obtained. These observations were rationalised by the formation of the pyrazoline **35a**, which tautomerised to its 2*H*-isomer **35b** at room temperature, and which under went nitrogen gas extrusion, to give the cyclopropane at an elevated temperature. (Scheme 8).



Scheme 8

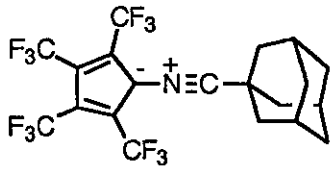
This tendency for the diazo group in diazocarbonyl compounds to act as the 1,3-dipole has been noted in other systems. For example, diazoacetophenone **13a** was found to undergo addition at 40°C with the dipolarphile, benzyne **37**, giving the heterocycle **38**, after tautomerisation of the initial 1,3-dipolar adduct.[44] (Scheme 9).



13a 38

Scheme 9

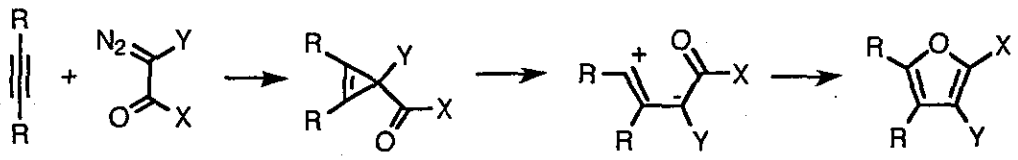
In path B we have the intermediacy of a nitrilium ylide. The formation of nitrilium ylides, from the interaction of nitriles with carbenes is well documented. For example, the ylide **39** is a stable compound, its structure being determined by a single crystal X-ray diffraction.[45] However, no stable compounds are known to exist from the interaction of nitriles and ketocarbenes. But this does not, necessarily, preclude them from being an intermediate species. (Figure 5).



39

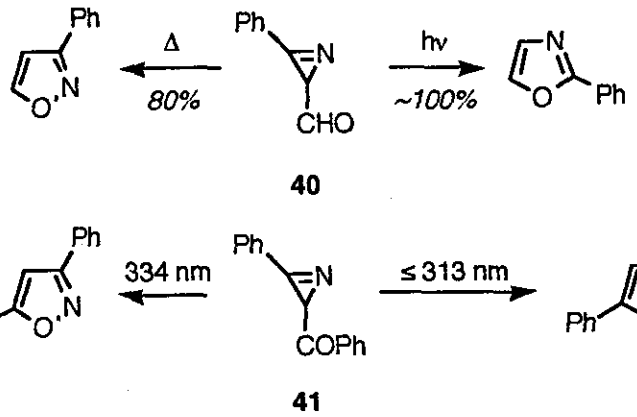
Figure 5

Path C, the formation of the 2-keto-2*H*-azirine, has mechanistic similarities with the formation of furans, from acetylenes and diazocarbonyls.[46,47] This reaction involves the intermediary of a 2-keto cyclopropene, which undergoes ring opening, forming a dipolar intermediate, which closes, yielding the heterocycle. In several examples, the cyclopropene is isolated along with the furan. (Scheme 10).



Scheme 10

The photochemical and thermal cyclisation of 2-keto-2*H*-azirines has been studied by Singh and Ullman,[48] and by Padwa *et al.*[49] The cyclisation reactions were found to be dependent upon the conditions employed. The thermal cyclisation of the 2*H*-azirine **40** led to the isolation of an isoxazole in 80% yield. Photochemical conditions gave, exclusively, oxazole formation. The photochemistry of 2-keto-2*H*-azirines was, found, however to be wavelength dependent. Photolysis at 313 nm on the 2*H*-azirine **41** gave oxazole formation in quantitative yield, whereas the longer wavelength of 334 nm resulted in the formation of isoxazoles. (Scheme 11).



Scheme 11

In the 1,3-dipolar cycloaddition reactions of diazocarbonyls, there is a preference for the diazo group to act as the dipole, giving, for example, 2*H*-pyrazolines upon reaction with olefins. But if the ketocarbene were able to be formed by decomposition of the diazocarbonyl, there is still the possiblity of it acting as 1,3-dipole, and hence give oxazole formation. In the thermal and photochemical decomposition of methyl diazoacetate **17** in acetonitrile, studied by Komendantov,[32] the oxazole **18** was isolated, along with the 2*H*-azirine **19** in small amounts (*ca.* 2%). This suggests the possible workings of path C, the 2-keto 2*H*-azirine formation and subsequent cyclisation. However, this is the only paper that cites isolation of a 2*H*-azirine side-product. Due to wavelength dependence of 2*H*-azirine in oxazole formation and their failure to form oxazoles under thermal conditions, it seems less likely that path C is in operation, with the Komendantov observation being a spurious result.

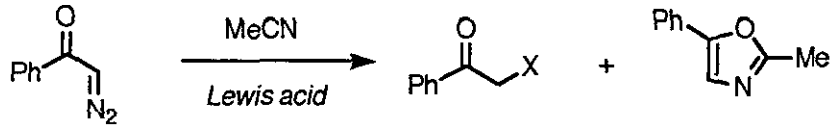
However it is still unclear if the reaction proceeds by a 1,3-dipolar mechanism (path A) or by formation of a nitrile ylide (path B).

1.4 Lewis Acid Catalysis

1.4.1 Oxazole Formation by Lewis Acid Catalysis

The role of Lewis acids in the formation of oxazoles, from diazocarbonyl compounds and nitriles, has primarily been studied independently by two groups.

Doyle *et al.* first reported the use of aluminium(III) chloride as a catalyst in the decomposition of 1-diazoketones.[50] In a more detailed study, a range of Lewis acids was screened for catalytic activity, using diazoacetophenone **13a** and acetonitrile.[51] Of these, boron trifluoride etherate was found to be the catalyst of choice, due to the low yield of the 1-halogenated side-product **42** compared to 2-methyl-5-phenyl oxazole **43**. Unfortunately, it was found that in the case of boron trifluoride etherate, the nitrile had to be used in a ten fold excess, however the use of antimony(V) fluoride allowed the use of the nitrile in only a three fold excess. (Table 5).



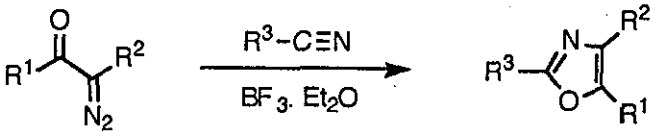
13a **42** **43**

X = Cl or F

Lewis Acid	*Relative Yield (%)* **42: 43**	*Isolated Yield (%)*
$AlCl_3$	36 : 64	91
$ZrCl_4$	31 : 69	99
$MoCl_5$	28 : 72	95
$SnCl_4$	24 : 76	41
TiF_4	5 : 95	99
$FeCl_3$	0 : 100	76
WCl_6	0 : 100	86
$TaCl_5$	0 : 100	84
$BF_3.Et_2O$	0 : 100	99
SbF_5	0 : 100	99

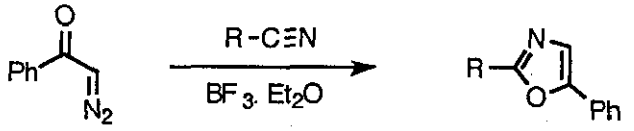
Table 5

The group of Ibata have also reported the effectiveness of boron trifluoride etherate in the catalytic formation of oxazoles.[52] They found that not only diazoketones, as reported by Doyle, but also diazoesters could be decomposed in the presence of nitriles (Table 6). They also studied the range of nitriles that could be employed, finding that substituted thiocyanates and cyanamides[53] along with chloroacetonitrile[54] could undergo ring formation. (Table 7).



R^1	R^2	R^3	Yield (%)
Ph	H	Me	94
Ph	H	MeO_2CCH_2	46
4-NO_2-C_6H_4	H	Me	84
Me	MeO_2C	Me	80

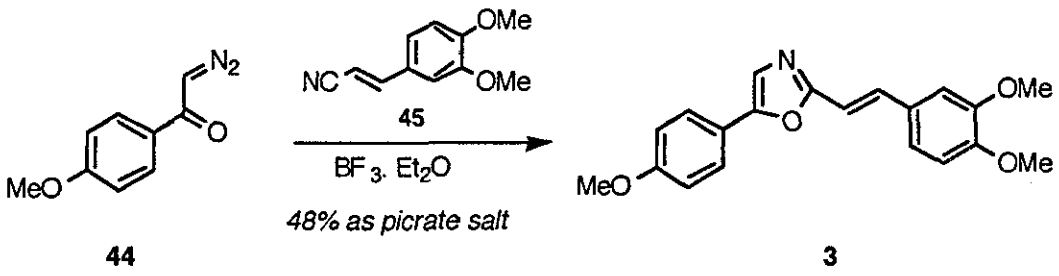
Table 6



R	Yield (%)
MeS	78
EtS	66
Me_2N	29
$ClCH_2$	84

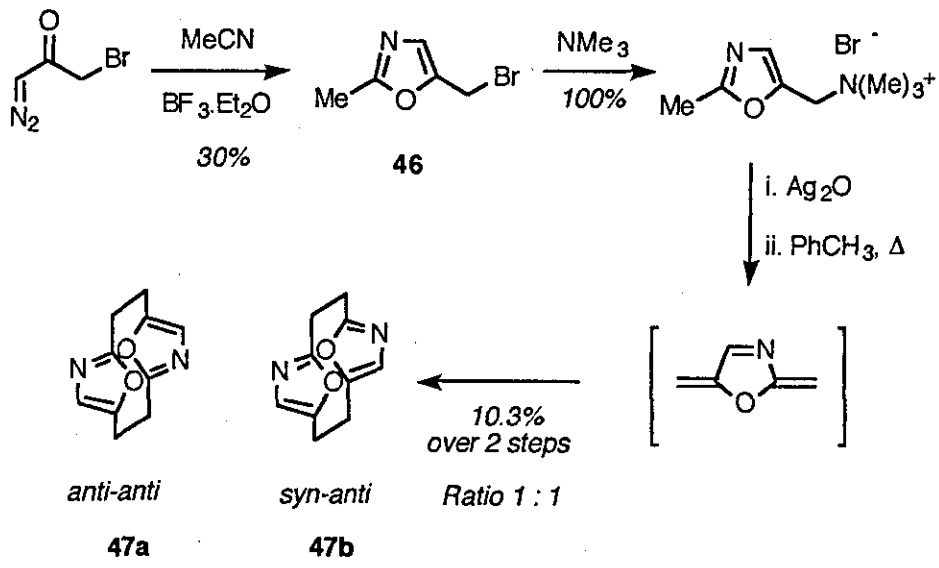
Table 7

Doyle has successfully employed this reaction in the synthesis of annuloline **3**, a 2,5-diaryl oxazole isolated from the roots of the annual rye grass, *Lolium multiflorum.*[7,55] So, 1-diazo-4'-methoxyacetophenone **44** was reacted with 3,4-dimethoxycinnamonitrile **45** in the presence of boron trifluoride etherate to yield the natural product, isolated as its picrate salt in 48%.[51] (Scheme 12).



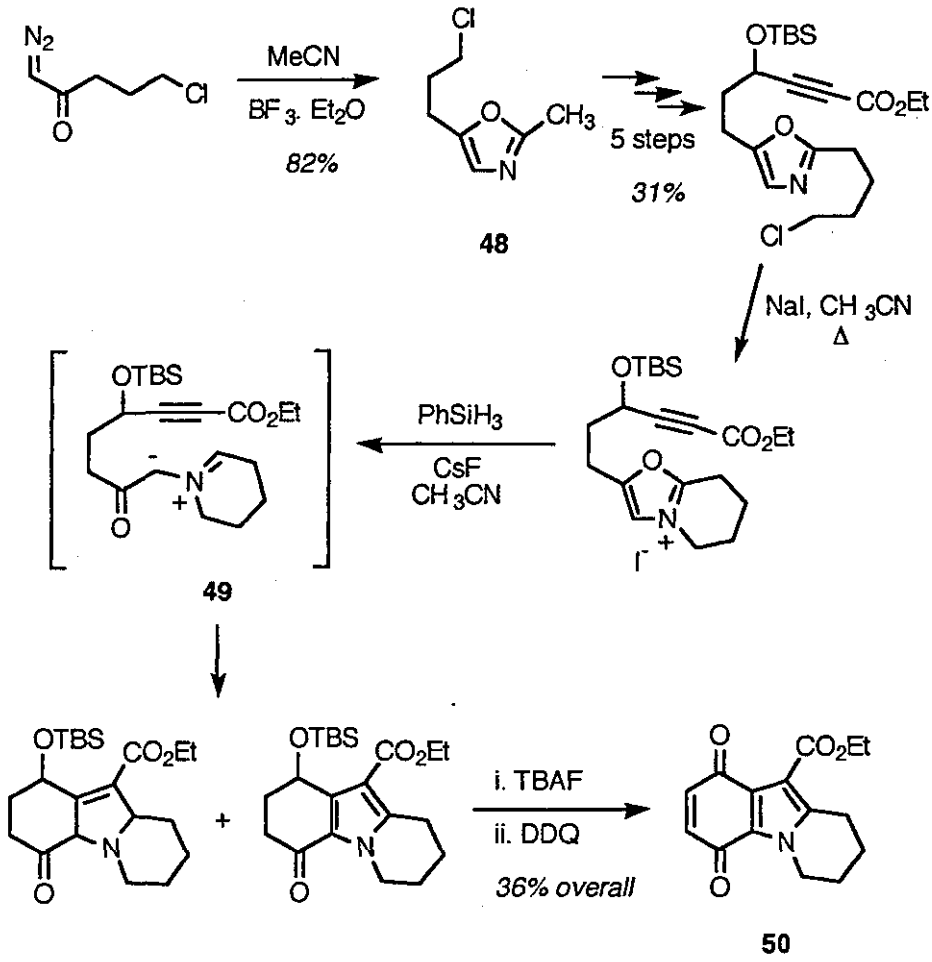
Scheme 12

The use of boron trifluoride etherate catalysed formation of oxazoles has been widely used for a variety of synthetic purposes. Keehn and Mashraqui, in their studies into cyclophanes,[56] used this ring-formation reaction to prepare the oxazole **46**, which was then elaborated to give the [2,2]-(2,5)oxazolophanes **47**, *via* a Hofmann pyrolytic condensation. (Scheme 13).



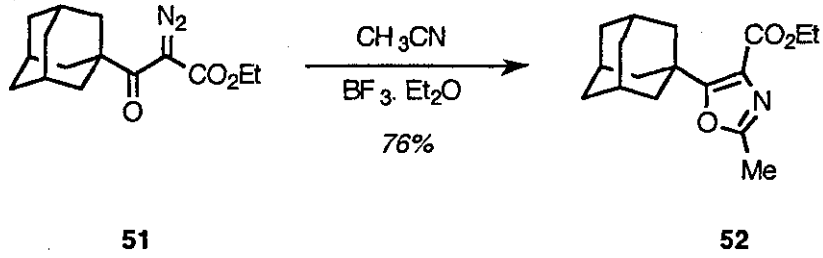
Scheme 13

Vedejs and Piotrowski,[57] in their studies of various indoloquinone derivatives, have started this study with oxazoles, prepared by Lewis acid catalysis. For example, the oxazole **48** was prepared *via* the use of boron trifluoride etherate in 82% yield. This oxazole was then transformed into the azomethine ylide **49**, which was then trapped *via* a [2 + 3] cycloaddition, and was subsequently taken to the indoloquinone derivative **50**. (Scheme 14).



Scheme 14

Even highly hindered diazo carbonyl compounds have been shown to give oxazoles, using boron trifluoride etherate catalysis, when other methods have failed. For example, ethyl 3-(1-adamantyl)-2-diazo-3-oxopropanoate **51** was shown to undergo oxazole formation to yield **52** in 76% yield using boron trifluoride etherate, whilst photochemical methods and rhodium(II) acetate catalysis (see Chapter 1.5.4) failed to give any desired product.[58] (Scheme 15).

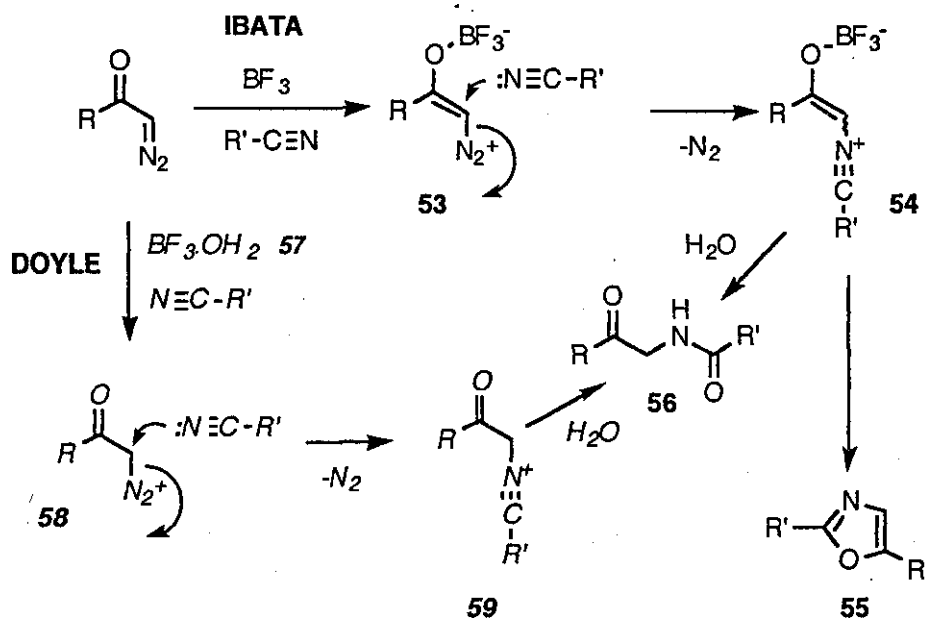


51 **52**

Scheme 15

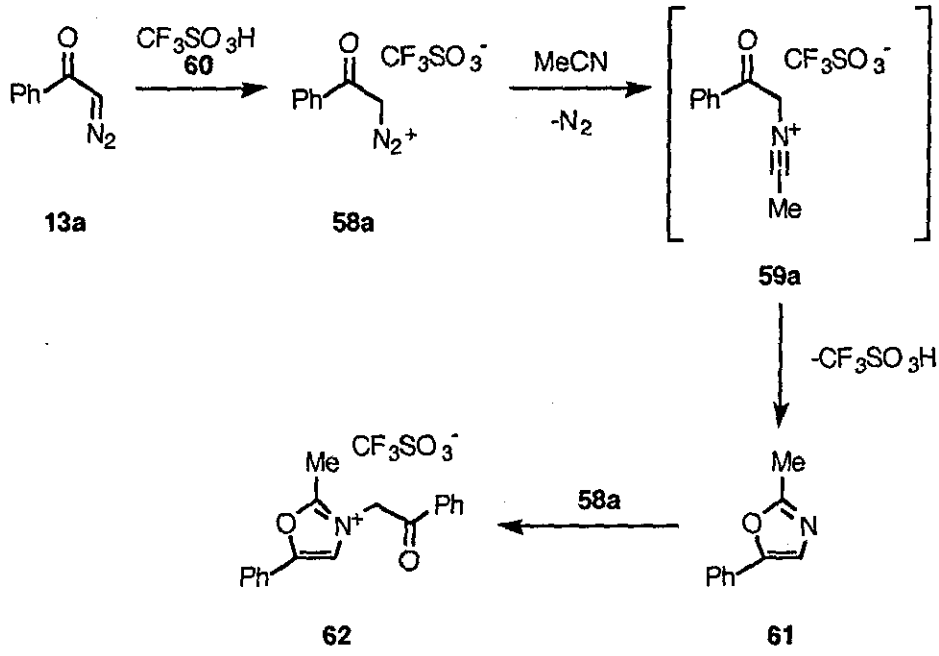
1.4.2 Mechanistic Aspects

Different mechanisms for the role of the Lewis acids, have been put forward by both the Ibata and Doyle groups, each explained by the side products formed. The Ibata mechanism involves the initial attack of the catalyst on the carbonyl oxygen to give a diazonium betaine intermediate **53**. The nitrile then undergoes nucleophilic attack, with extrusion of nitrogen gas to give the betaine **54**, cyclisation of which produces the oxazole **55**. Excess water in the reaction was thought to account for the amide **56**.[52] However, Doyle states that the presence of the amide **56**, does not necessarily demonstrate the presence of the intermediate vinyl nitrilium ion **54**. He says that the presence of water in the reaction will form the protic acid $BF_3.OH_2$ **57**. This will undergo proton addition at the 1-carbon of the diazo-compound, to yield **58**. Displacement by the nitrogen lone-pair on the nitrile would lead to the phenacylnitrilium ion **59** and ultimately to the amide **56**.[51] (Scheme 16).



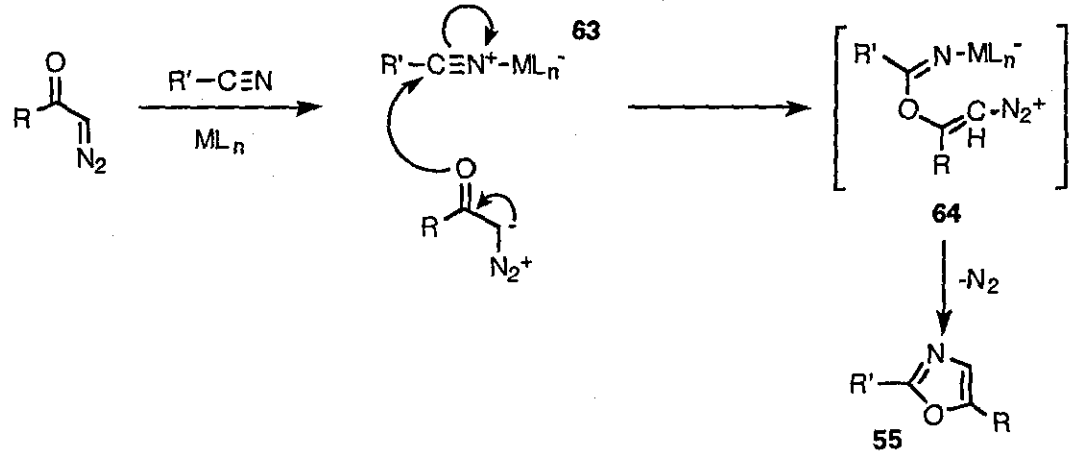
Scheme 16

The use of protic acids in oxazole formation, from diazoketones and nitriles, has been cited in the literature. Holt, and co-workers,[59] found that diazoacetophenone **13a** in the presence of the protic acid, trifluoromethanesulfonic acid **60**, and acetonitrile, gave 2-methyl-5-phenyl oxazole **61**. It was assumed that the protic acid caused proton addition at the 1-carbon of **13a**, leading to the phenacyldiazonium ion **58a**. This underwent nucleophilic displacement by acetonitrile to give the phenacylnitrilium ion **59a**, which cyclised to the oxazole. This oxazole was found to undergo reaction with the intermediate phenacyldiazonium ion **58a**, to give the oxonium salt **62**. (Scheme 17).



Scheme 17

If, as Doyle suggests, the protic acid $BF_3.OH_2$ **57** is formed leading to amide production, it may also account for the formation of oxazoles. For the observations of Holt *et al.*, **57** may cause cyclisation of the intermediate nitrilium species **59**, as in the case of trifluoromethanesulfonic acid **60**, leading to oxazole formation. A more detailed study by Doyle *et al.*[51] into the role of Lewis acid catalysis in oxazole formation, however, has led to the postulation of a mechanism different to that of Ibata's. This mechanism involves the initial formation of a Lewis acid-nitrile adduct **63**. This adduct then undergoes addition to the diazoketone to give a 2-imidatoalkenediazonium salt **64**, which cyclises, with extrusion of nitrogen gas, yielding the oxazole **55**. (Scheme 18).



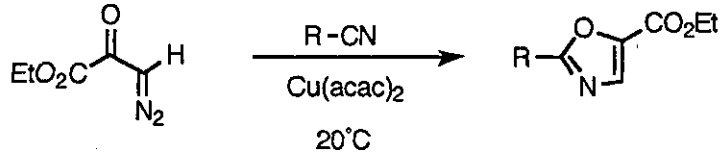
Scheme 18

1.5 Transition Metal Catalysis.

1.5.1 Copper

Many of the early workers who studied the thermal decomposition reactions found that the addition of copper, either as a powder or as a salt, allowed the reaction to be achieved at a lower temperature.[30-32] A rational explanation for these observations was never stated.

Alonso and Jano[60] studied the copper-salt reaction of ethyl diazopyruvate **65** with acetonitrile and benzonitrile. The corresponding oxazoles were found to be formed in 35% and 52% yield, respectively. (Table 8).

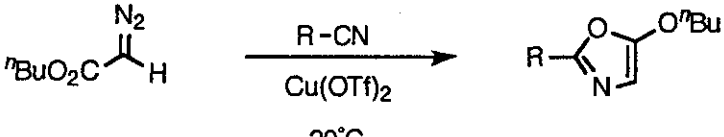


65

R	*Yield (%)*
Me	35
Ph	52

Table 8

The use of copper complexes in the selective formation of oxazoles from saturated nitriles and *n*-butyl diazoacetate **66** has been the subject of an intensive investigation by Teyssié *et al.*[61] (Table 9).



64

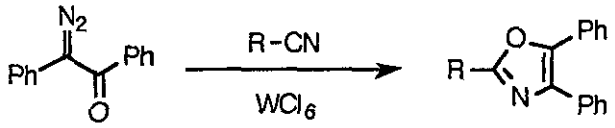
R	*Yield (%)*
$H_2C=C(CH_3)$	80
$H_2C=CH$	15
PhCH=CH	50 (30°C)

Table 9

Their studies pointed towards the copper undergoing two key changes in the catalytic process. The first being a reduction, within the reaction conditions, of copper(II) to copper(I), and the second was a change of ligands around the copper(I). The reactants, notably the nitrile and diazo compound, were found to play an important role in the formation of the most effective catalytic species.

1.5.2 Tungsten

Kitaytani *et al.* found that tungsten(VI) chloride would catalyse the formation of a range of oxazoles.[62,63] (Table 10).

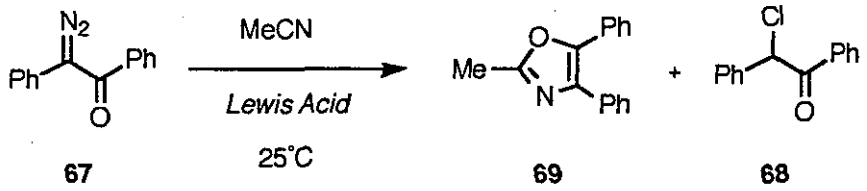


67

R	*Yield (%)*
Me	65
Et	45
$H_2C=CH$	50

Table 10

They studied the reaction of benzoylphenyldiazomethane **67** and acetonitrile with a range of other Lewis acids comparing them to tungsten(VI) chloride, but here the preferred product was 2-chloro-1,2-diphenylethanone **68** rather than the oxazole **69**. (Table 11).



67 69 68

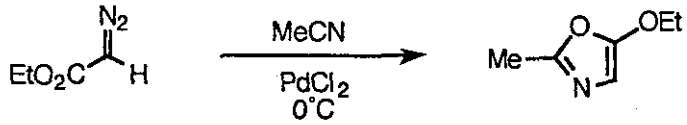
Lewis Acid	Yield (%) 69 : 68
$ZnCl_2$	12 : 33
$SnCl_4$	6 : 22
$TiCl_4$	16 : 48
$AlCl_3$	8 : 41

Table 11

They attributed the catalytic nature of tungsten(VI) chloride, to both its Lewis acidity and the affinity of tungsten for carbenes.

1.5.3 Palladium

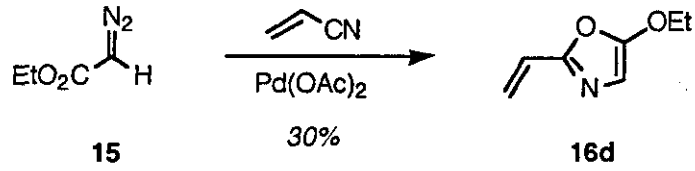
Early studies into the decomposition of ethyl diazoacetate **15** by palladium(II) chloride, in the presence of acetonitrile, led to the isolation of 2-methyl-5-ethoxyoxazole **16c** in 16% yield.[64] (Scheme 19).



15 *16%* **16c**

Scheme 19

Teyssié *et al.* studied the cycloaddition of ethyl diazoacetate **15** to acrylonitrile, finding that in the presence of palladium(II) acetate, the oxazole **16d** was prepared in 30% yield.[38] (Scheme 20).



15 **16d**

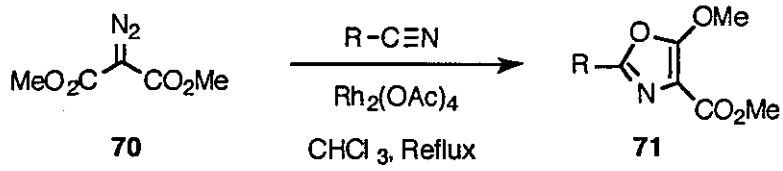
Scheme 20

They found, as described earlier, in the absence of any catalyst, at room temperature, the 2*H*-pyrazoline **35b** was obtained, whilst at 100°C the cyclopropane **36** was obtained. The authors claim that these observations fit with an oxazole formation mechanism involving the decomposition of the diazoester *via* co-ordination with the palladium. They assumed the nitrile formed an active complex with the catalyst, which decomposed the diazo compound.

1.5.4 Rhodium

It is, as with most studies into diazocarbonyl compounds, the rhodium catalysed reaction that has been the most investigated.[65]

Much of the early work into the rhodium(II)-catalysed formation of oxazoles has been pioneered by the group of Helquist. They first reported, in 1986, the rhodium(II) acetate catalysed reaction of dimethyl diazomalonate **70** with nitriles.[66,67] A range of nitriles were screened, including aromatic, alkenyl and vinylic species. In unsaturated nitriles, cyclopropanation, not surprisingly, was found to be a competitive reaction. (Table 12).



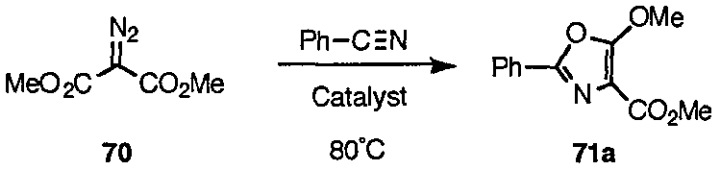
70 **71**

R	*Oxazole*	*Yield (%)*
Ph	**71a**	85
3-Cl-C6H4	**71b**	96
Me	**71c**	58
MeCH=CH	**71d**	64*E*, 10*Z*
H2C=CHCH2	**71e**	45 (21)[a]
EtOCH=CH	**71f**	97

[a] = cyclopropanation product

Table 12

A series of catalysts were also screened in the reaction of **70** with benzonitrile, forming methyl 2-phenyl-5-methoxyoxazole-4-carboxylate **71a**. Out of these, rhodium(II) acetate was found to be the most effective.[67] (Table 13).



70 **71a**

Catalyst	*Yield (%)*
$Rh_2(O_2CCH_3)_4$	99
$Rh_2(NHCOCH_3)_4$	83
$Cu(OTf)_2$	65
$Cu(Et\text{-}acac)_2$	44
$Rh_2(O_2CC_3F_7)_4$	35
$Rh_3(CO)_{16}$	23

Table 13

The work Helquist and co-workers is aimed towards the synthesis of certain members of the type A family of streptogramin antibiotics, such as virginiamycin M_1 and madumycin I. (Figure 6).

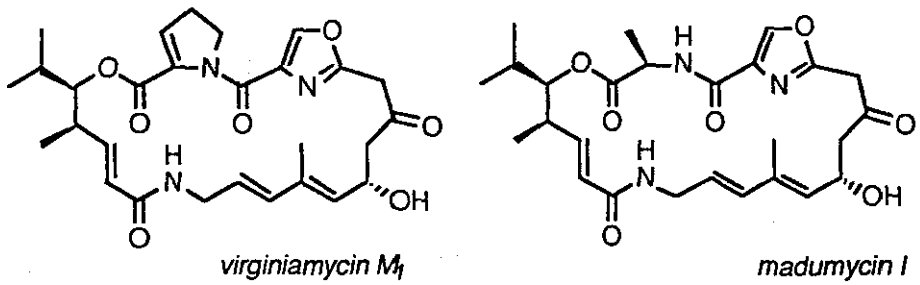
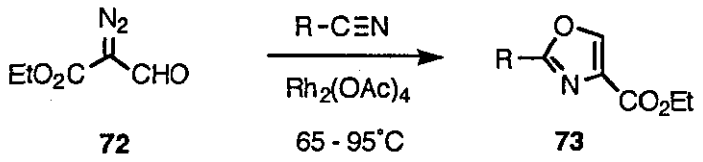


Figure 6

This has involved the study of the rhodium(II)-catalysed reactions of ethyl 1-formyldiazoacetate **72** with nitriles.[67,68] (Table 14).

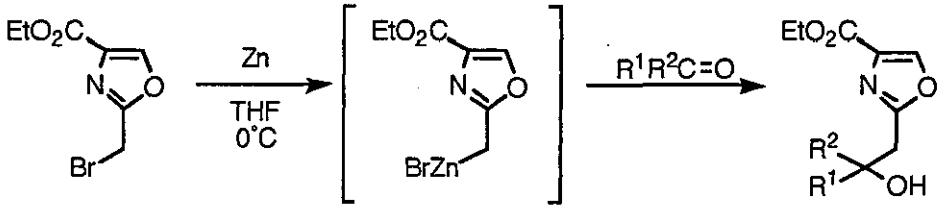


72 73

R	*Oxazole*	*Yield (%)*
Ph	**73a**	45
MeCH=CH	**73b**	30
EtOCH=CH	**73c**	36
Me	**73d**	18
$BrCH_2$	**73e**	65

Table 14

The oxazole obtained with bromoacetonitrile, ethyl 2-(bromomethyl)oxazole-4-carboxylate **73e** formed in 65% yield, was found to give a heteroaromatic benzylic organozinc derivative **74.** This underwent nucleophilic attack with aldehydes and ketones, leading a range of alcohols **75** in good yield.[69] (Table 15).



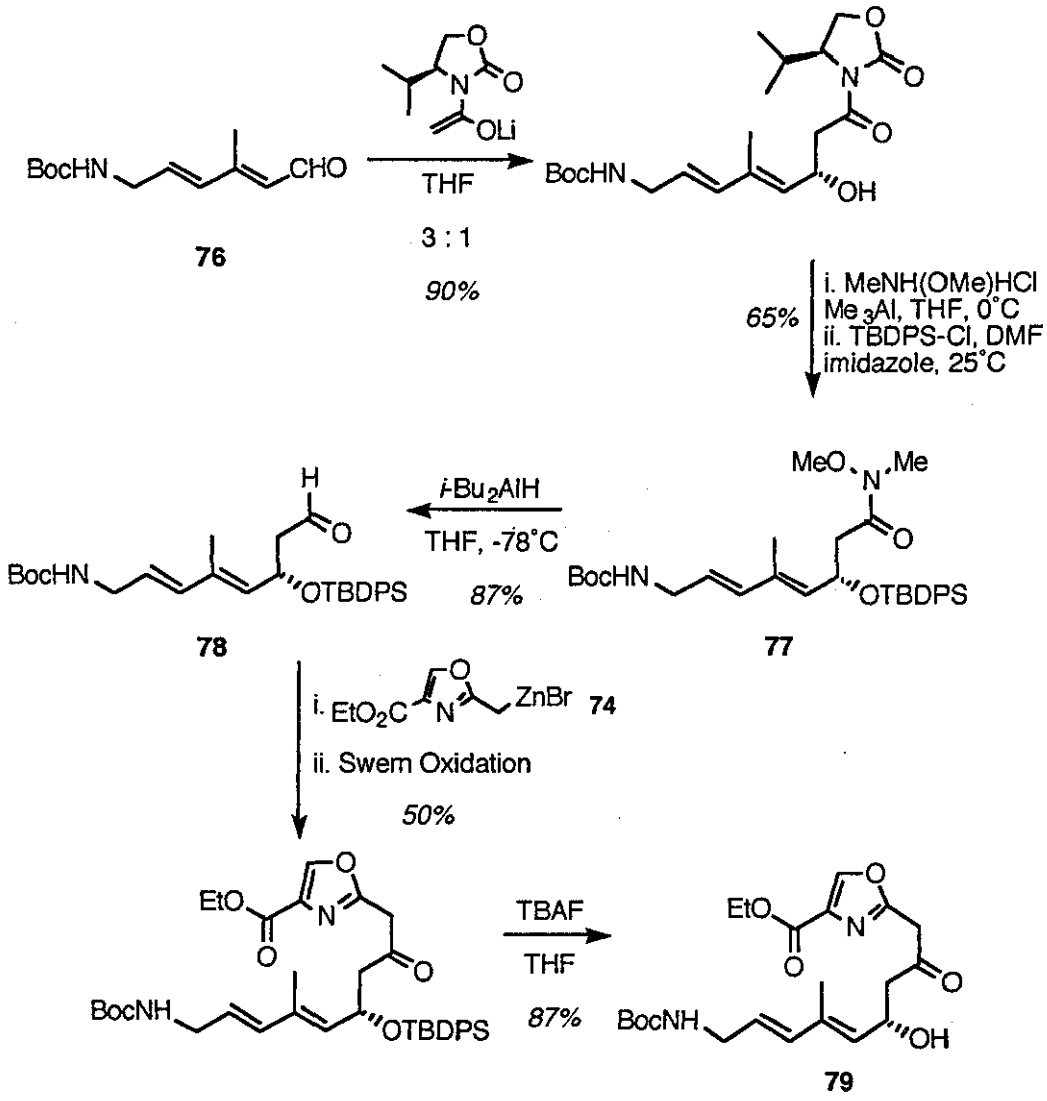
73e **74** **75**

$R^1R^2C=O$	*Yield (%)*
hexanal	92
$TBSO(CH_2)_3CHO$	62
cyclohexanone	49
cyclopentenone	90

Table 15

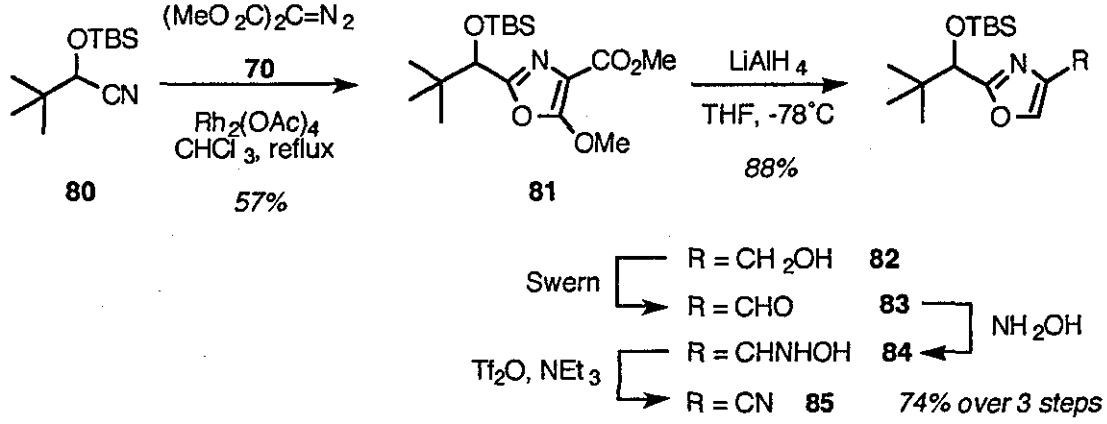
Utilising this reaction has led Helquist *et al.*[70] to a non-racemic route to a protected form of the right hand portion, **79**, of the type A streptogramin antibiotics. The required aldehyde **78** was prepared *via* an Evans asymmetric aldol condensation on the substrate **76**, followed by transformation to the Weinreb amide **77**, and then reduction to the aldehyde **78.** This underwent nucleophilic addition to the organozinc derivative **74** followed by Swern oxidation

then deprotection, to yield the required chiral protected right-hand portion **79**, in 44% yield, over the three steps. (Scheme 21)



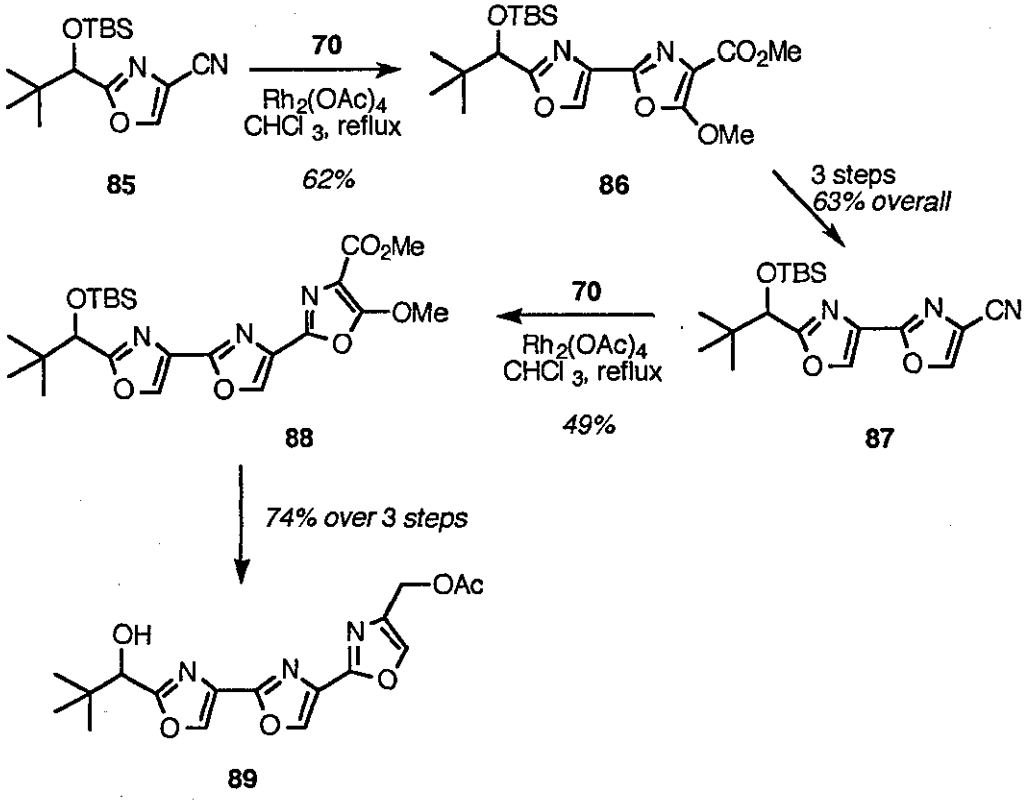
Scheme 21

Yoo has utilised the reaction of dimethyl diazomalonate **70** to give a route to tris-oxazoles.[71] The silyl-protected cyanohydrin **80** was reacted with dimethyl diazomalonate **70**, under rhodium(II) acetate catalysis, to yield the methyl 5-methoxyoxazole-4-carboxylate **81**, in 57%. This was then reduced to the alcohol **82**, with simultaneous removal of the 5-methoxy group, which was taken to the aldehyde **83**, *via* a Swern oxidation. The aldehyde **83** was then transformed to the aldoxime **84**, which underwent dehydration to the oxazole-4-carbonitrile **85**. (Scheme 22).



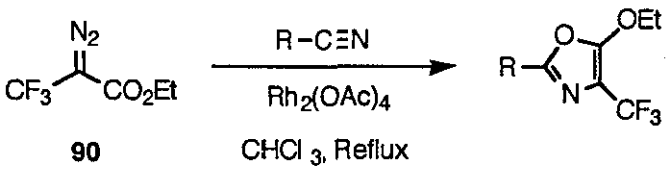
Scheme 22

The oxazole-4-carbonitrile **85** then underwent oxazole ring formation, again using dimethyl diazomalonate **70** and rhodium(II) acetate in 62%. This bis-oxazole-4-carboxylate **86** was transformed to the bis-oxazole-4-carbonitrile **87**, which under the same conditions was taken to the substituted tris-oxazole **88** in 49%, and then ultimately to the tris-oxazole **89**. (Scheme 23).



Scheme 23

Various other diazo carbonyl compounds have been shown to undergo oxazole formation, under rhodium(II)-catalysis. Shi and Xu have shown that ethyl 3-trifluoro-2-diazo propionate **90**, will undergo oxazole formation in the presence of rhodium(II) acetate and a range of nitriles.[72] (Table 16).

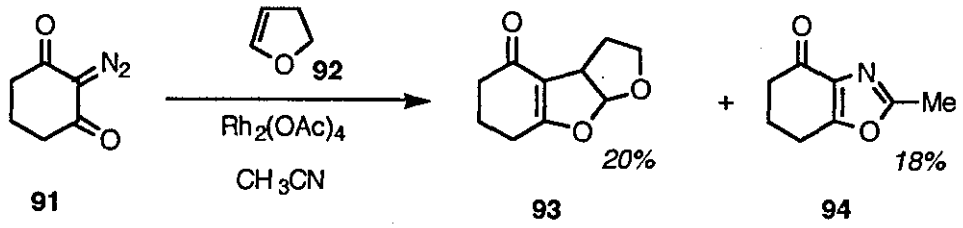


90

R	*Yield (%)*
Ph	89
$PhCH_2$	86
MeCH=CH	88
Me	80
EtO_2CCH_2	30

Table 16

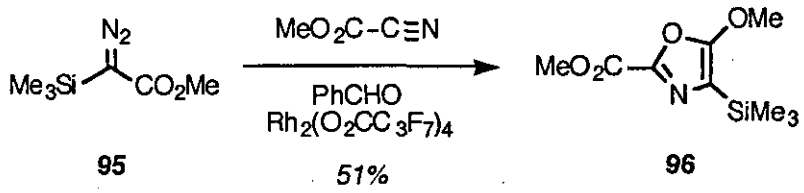
Pirrung *et al.*[73] studied the decomposition of 2-diazo-1,3-cyclohexandione **91** in the presence of dihydrofuran, **92**, forming the bistetrahydrofuran system **93**. Using rhodium(II) acetate catalysis and acetonitrile, as solvent, they found the expected heterocyclic system **93** was formed in 20% yield, along with the unexpected oxazole **94** in 18% yield. (Scheme 24).



91 **93** **94**

Scheme 24

Alt and Maas have studied the decomposition of methyl diazo(trimethylsilyl)acetate **95** in the presence of various aldehydes, forming intermediate carbonyl ylides, which could be trapped with a range of dienophiles.[74] However, in the presence of benzaldehyde and methyl cyanoformate, under rhodium(II) perfluorobutyrate catalysis, the only product isolated was the oxazole **96**, no product from carbonyl ylide formation was detected. (Scheme 25).



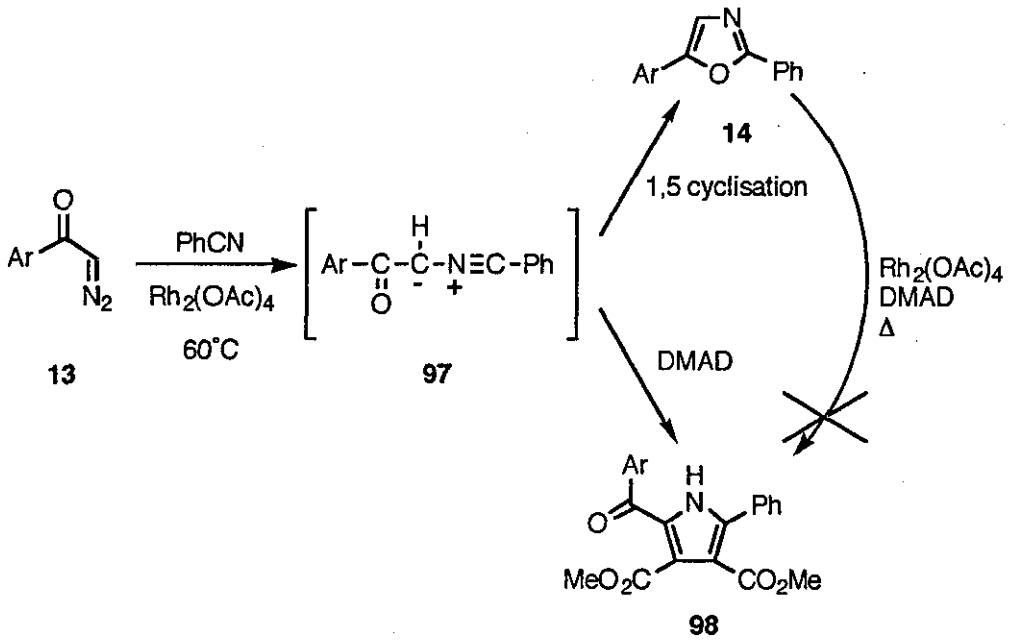
95 *51%* **96**

Scheme 25

1.5.5 Mechanistic Aspects

The catalytic nature of these metal catalysts can be attributed to both their Lewis acidity and their affinity for carbenes. In many catalysed reactions involving acrylonitrile (H_2C=CHCN) there was, often, a noted lack of cyclopropanation products, with only oxazole formation taking place. This led to the suggestion, by various authors, of an electrophilic nature for the carbenic centre. The formation of a carbenoid species, from the interaction of the carbene and the transition metal, could account for this 'electrophilic carbene'.

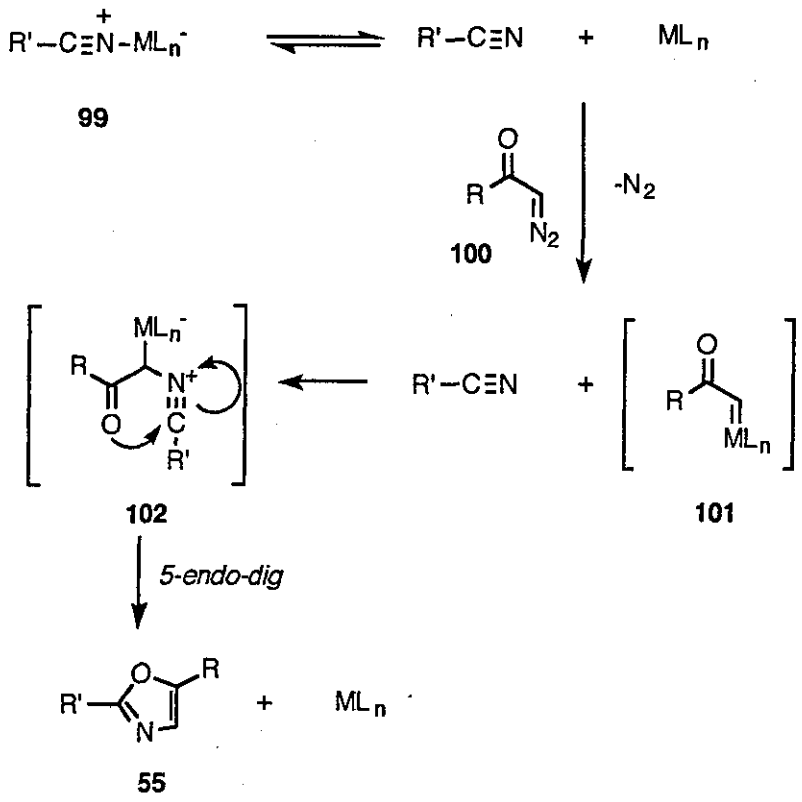
Apart from the Teyssié study on the role of copper in the catalytic process,[38] as described earlier, the only other mechanistic study has been undertaken by Ibata and Fukushima.[75] They studied the rhodium(II) acetate catalysed decomposition of various substituted diazoacetophenones **13** in benzonitrile in the presence of the dipolarphile dimethyl acetylenedicarboxylate (DMAD). They found that this reaction mixture gave two products. The first being the expected 2,5-diaryloxazole **14**, whilst the second being a dimethyl 2,5-substituted pyrrole-3,4-dicarboxylate **98**. These results were explained by the formation of the nitrile ylide **97**. This ylide arose from the interaction of the nitrile and the diazocarbonyl compound with loss of nitrogen gas. This nitrile ylide can then either undergo 1,5-cyclisation to give the oxazole **14**, or be trapped by DMAD leading to the pyrrole **98**. The oxazole alone, in the presence of rhodium(II) acetate and DMAD, under thermal conditions, was found not to yield the pyrrole. (Scheme 26).



Ar	*Yield (%)* **14 : 98**
Ph	50.6 : 11.0
4-MeO-C_6H_4	38.2 : 5.8
4-Cl-C_6H_4	63.0 : 11.0
4-CN-C_6H_4	60.9 : 9.0
4-NO_2-C_6H_4	61.2 : 18.3

Scheme 26

From these we can postulate a plausible mechanism for oxazole formation, involving transition metal catalysis. Initially, due to the Lewis acidity of the catalysts, there is the formation of a nitrile-catalyst adduct **99**. However, this adduct is in a rate determining equilibrium with the free nitrile and the catalyst. The catalyst reacts with the diazocarbonyl compound **100** to yield the carbenoid species **101**, with the nitrile remaining with in the ligand sphere. This transitional species reacts with the nitrile to give an intermediate nitrilium species **102**, which collapses, *via* a probable 5-*endo dig* ring closure, to yield the oxazole **55** with regeneration of the catalyst. (Scheme 27).



Scheme 27

1.6 Conclusion.

There is an ever increasing number of oxazole containing natural products being isolated. Many of these compounds are not only synthetically challenging, but are also, due to their potency, finding themselves as medicinal targets. The need for mild, chemoselective formation of these heterocycles is, therefore, becoming more important.

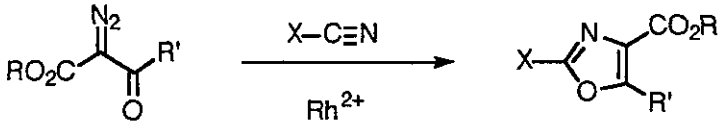
The preparation of oxazoles from diazocarbonyls and nitriles, has been shown to be an effective one-step reaction, using readily prepared reagents. The reaction has been shown to proceed under a variety of conditions, with high chemoselective control. However, apart from a few noteworthy examples, many of the reported studies to-date have been limited in their scope. Much work has been done using diazoesters or diazoketones, but with little else. As for the nitriles, the ones studied have mostly been simple aromatic, unsaturated or saturated systems. As yet an α-chiral nitrile is yet to be shown to undergo oxazole formation with retention of chirality.

Chapter 2

Preparation of 4-Functionalised Oxazoles

2.1 Introduction

At the outset of this project, much of the work on rhodium(II)-catalysed reactions of 1-diazocarbonyl compounds and nitriles, had been centred on methyl diazomalonate **70** and ethyl 1-formyldiazoacetate **72**.[67] These reactions yielded the oxazole-4-carboxylates **71** and **73**. (Figure 7).



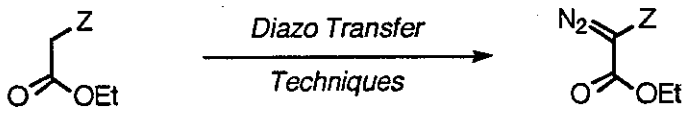
Diazo	*R*	*R'*	*Oxazole*
70	Me	OMe	**71**
72	Et	H	**73**

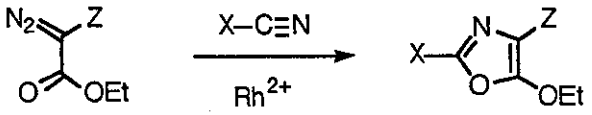
Figure 7

It was intended that this work should show that other readily prepared 1-diazocarbonyl compounds would undergo oxazole formation by the use of rhodium(II)-catalysis, and that these compounds would show synthetic potential, aimed towards natural product chemistry.

It was decided that the study would use functionalised diazoesters for three reasons. Firstly, the ester carbonyl oxygen could partake in ring formation, becoming the oxygen atom in the heterocycle. The ester group would, secondly, provide some form of stabilisation to the diazo group and, finally, it was the intention that they could be prepared by standard diazo transfer techniques on the corresponding methylene compounds.

The 1-diazoesters considered were ethyl diazo(benzenesulfonyl)acetate **103**, triethyl diazophosphonoacetate[76] **104** and ethyl diazocyanoacetate **105**.[77] These diazoesters would lead to the formation of 4-benzenesulfonyloxazoles **106**, oxazole-4-phosphonates **107** and oxazole-4-carbonitriles **108** respectively. Although 4-arylsulfonyloxazoles are known,[33] the present use of diazosulfones would represent a useful extension of the rhodium carbenoid methodology. (Figure 8).



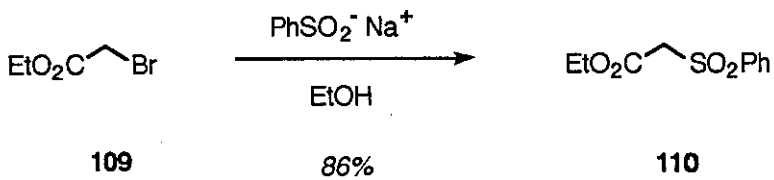


Diazo	*Z*	*Oxazole*
103	SO_2Ph	**106**
104	$PO(OEt)_2$	**107**
105	CN	**108**

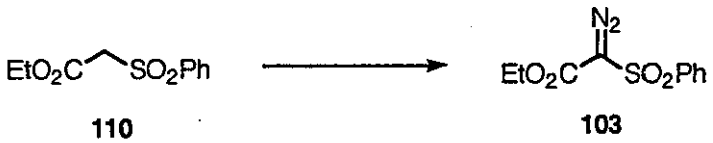
Figure 8

2.2 Preparation of Functionalised 1-Diazoesters

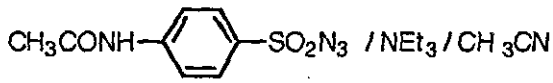
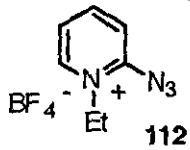
Ethyl diazo(benzenesulfonyl)acetate **103** was readily obtained in two steps from ethyl bromoacetate **109**. The first of these was a nucleophilic displacement, using the sodium salt of benzenesulfinic acid, to yield ethyl benzenesulfonylacetate **110**, in 86% yield. This methylene compound underwent diazo transfer to yield the diazosulfone **103** as a yellow solid. Using 4-acetamidobenzenesulfonyl azide[78] **111** as the diazo transfer reagent gave **103** in 74% yield, whilst use of 1-ethyl-2-azidopyridinium tetrafluoroborate **112** (Monteiro's Reagent, prepared *in situ* from 1-ethyl-2-chloropyridinium tetrafluoroborate **113** and sodium azide)[79,80] gave **103** in 65% yield. (Scheme 28).



109 *86%* **110**

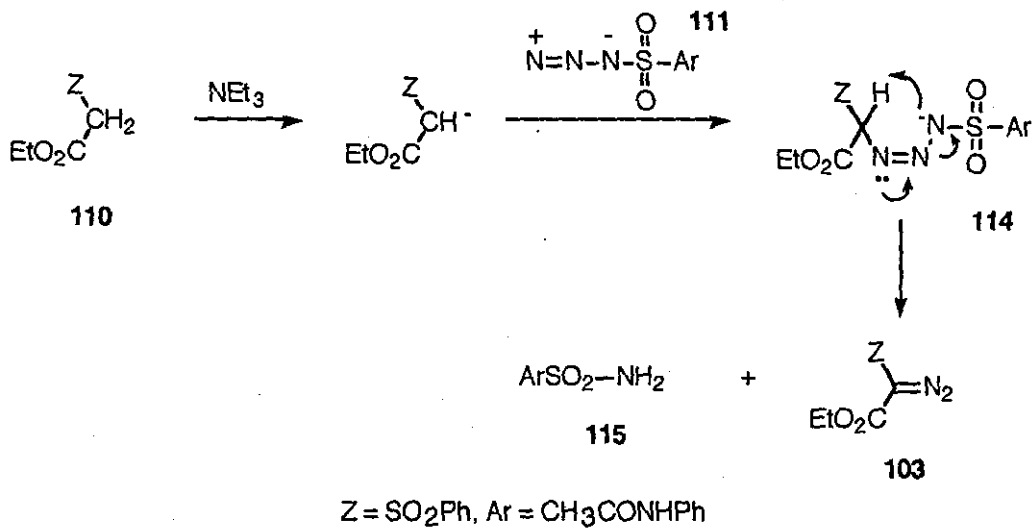


110 **103**

Reagents	Yield (%)
 **111**	74
 **112** / NaOAc / MeOH	65

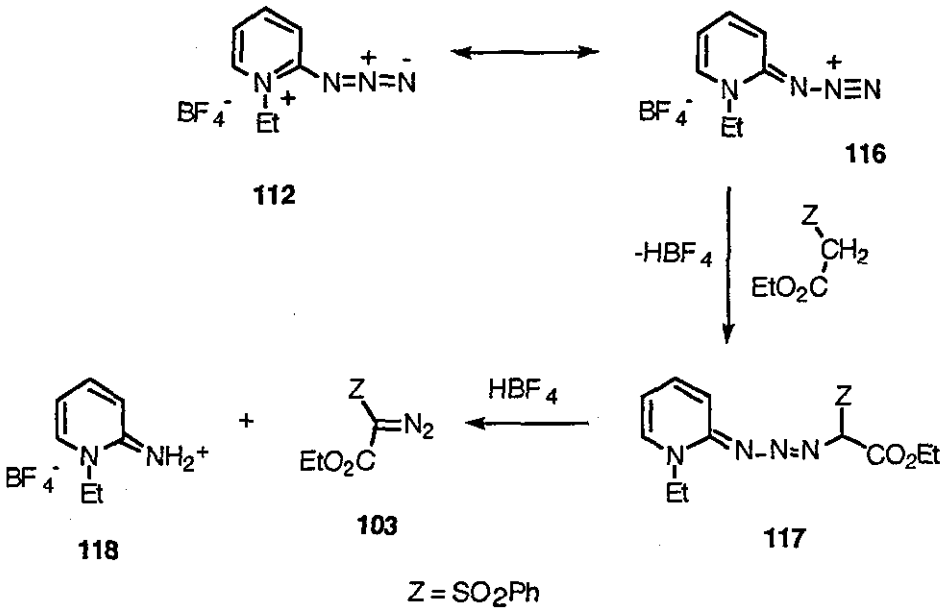
Scheme 28

Although the two diazo transfer reagents both gave the diazosulfone **103**, they work *via* different mechanisms. The sulfonyl azide **111** reacts, under basic conditions, with the methylene compound **110** to form the intermediate triazene **114**, which decomposes *via* proton transfer, yielding the diazosulfone **103** and the sulfonyl amide **115**. (Scheme 29).



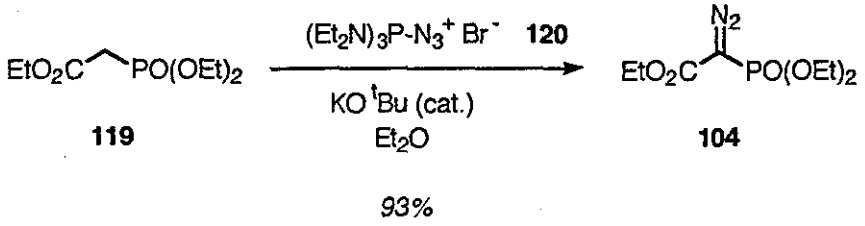
Scheme 29

The azidinium salt **112**, which may be considered more as the electrophilic *N*-diazonium salt **116**, reacts under near neutral conditions with the methylene compound, giving the triazene-like intermediate **117**. This collapses yielding the diazosulfone **103** and the amidium salt **118**. (Scheme 30).



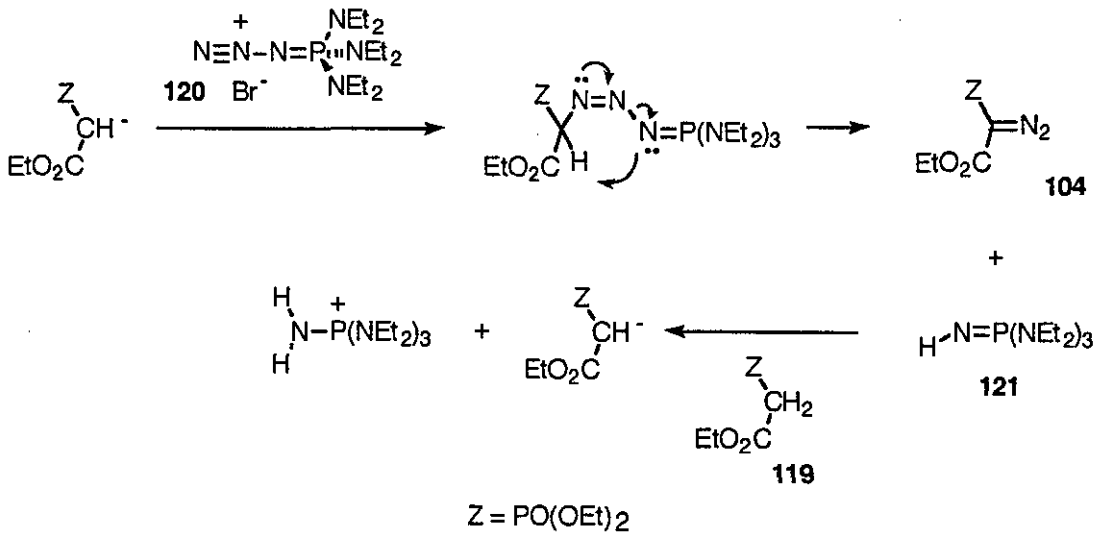
Scheme 30

Triethyl diazophosphonoacetate **104**, a well studied diazocompound,[76,81] was prepared by the literature procedure[82] from triethyl phosphonoacetate **119** and azidotris(diethylamino)phosphonium bromide **120**, in 93% yield. (Scheme 31).



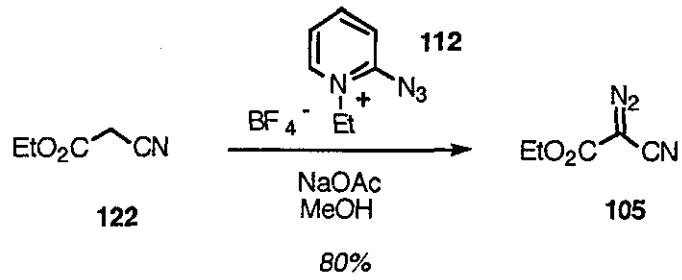
Scheme 31

This reagent can be thought of as a hybrid of the sulfonyl azide / azidinium salt classes of diazo transfer reagents. The reaction is thought to proceed *via* three steps The first is attack of the carbanion on the terminal nitrogen of **120**; second, proton transfer and finally elimination to give **121** and the required diazophosphonate **104**. The presence of **121** is enough to catalyse the reaction by deprotonation of the methylene compound, yielding the starting carbanion. (Scheme 32).



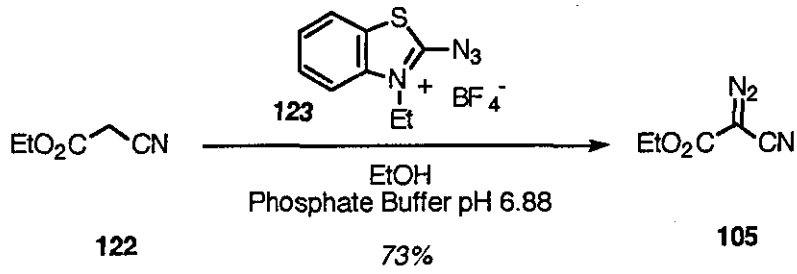
Scheme 32

Ethyl diazocyanoacetate **105** was prepared from ethyl cyanoacetate **122** and 1-ethyl-2-azidopyridinium tetrafluoroborate **112** in 80% yield. Changing the diazo transfer agent to either 4-acetamidobenzenesulfonyl azide **111** or azidotris(diethylamino)phosphonium bromide **120** failed to give any of the required 1-diazoester. (Scheme 33).



Scheme 33

The diazonitrile **105** had been previously been prepared by Balli *et al.*[77] by the reaction between the azidinium salt, 2-azido-3-ethylbenzo-1,3-benzothiazolium tetrafluoroborate (Balli's Reagent) **123** and ethyl cyanoacetate **122** in 73% yield. (Scheme 34).

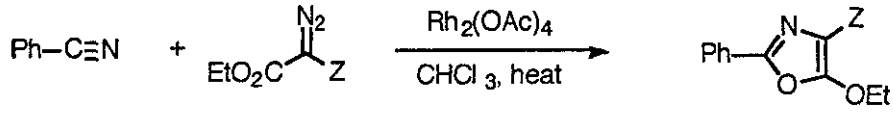


122 105

Scheme 34

2.3 Preparation of 4-Functionalised Oxazoles.

The functionalised 1-diazoesters, ethyl diazo(benzenesulfonyl)acetate **103**, triethyl diazophosphonoacetate **104** and ethyl diazoacetate **105**, each underwent slow addition to benzonitrile, in refluxing ethanol-free chloroform, using rhodium(II) acetate as catalyst. In each case oxazole formation took place to give, respectively, 4-benzenesulfonyl-5-ethoxy-2-phenyloxazole **106a** in 74%, diethyl 5-ethoxy-2-phenyloxazole-4-phosphonate **107a** in 16% and 5-ethoxy-2-phenyloxazole-4-carbonitrile **108a** in 25% yield. (Table 17).

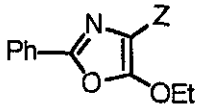


Diazo	*Z*	*Oxazole*	*Yield (%)*
103	SO_2Ph	**106a**	71
104	$PO(OEt)_2$	**107a**	16
105	CN	**108a**	25

Table 17

The increase in electronegativity of the substituents is reflected in the carbon nmr.[83] Moving from nitrile to phosphonate to sulfonyl, there is a shift downfield of the C-4 resonance, demonstrating the increase in the substituents ability to act as π-acceptors. Variation of the substituents have little effect, however, on the resonance's of the C-2 and C-5 atoms. In the

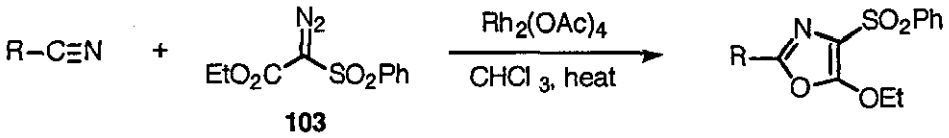
oxazole **107a**, due to carbon-phosphorous coupling, the C-2 and C-4 resonance's appear split. (Table 18).



		δC		
Oxazole	*Z*	*C-2*	*C-4*	*C-5*
106a	SO_2Ph	158.0	141.5	151.5
107a	$PO(OEt)_2$	163.1 / 163.6	131.8	152.6 / 153.0
108a	CN	164.0	125.8	152.3

Table 18

The diazosulfone **103** was then reacted with a range of nitriles, using the same conditions as before, to give the 4-benzenesulfonyloxazoles **106b - 106g**. (Table 19).



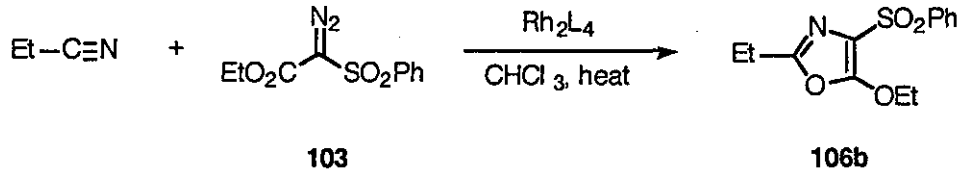
103

R	*Oxazole*	*Yield (%)*
Et	**106b**	52
2-Cl-C_6H_4	**106c**	56
4-Cl-C_6H_4	**106d**	46
3-MeO-C_6H_4	**106e**	24
4-MeO-C_6H_4	**106f**	28
2-thienyl	**106g**	22

Table 19

A range of other rhodium(II) catalysts were screened in the preparation of one of these 4-benzenesulfonyloxazoles, 4-benzenesulfonyl-5-ethoxy-2-ethyloxazole **106b**, which had a yield of 52% using rhodium(II) acetate. The catalysts studied were the carboxamide rhodium(II) trifluoroacetamide **124** and the modified carboxylates, rhodium(II) (*S*)-mandelate **125**, rhodium(II) 1-naphthoate **126** and rhodium(II) 1-benzenesulfonyl-(*S*)-prolinate **127**. All

except rhodium(II) 1-benzenesulfonyl-(*S*)-prolinate **127** were found to increase the yield of the oxazole, by an average of around 13%. (Table 20).

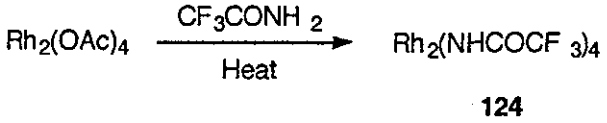


103 **106b**

L	*Catalyst*	*Yield (%)*
$MeCO_2$-	-	52
CF_3CONH-	**124**	64
$PhCH(OH)CO_2$-	**125**	68
1-$C_{10}H_7CO_2$-	**126**	65
1-benzenesulfonylprolinate	**127**	44

Table 20

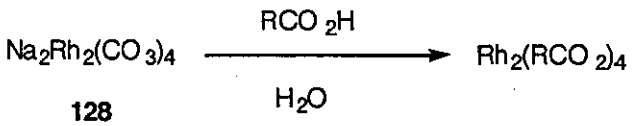
Of these, rhodium(II) trifluoroacetamide **124**, has previously been found useful for other carbenoid transformations.[84] It is readily prepared by the procedure of Bear *et al.*[85] from rhodium(II) acetate and trifluoroacetamide. (Scheme 35).



124

Scheme 35

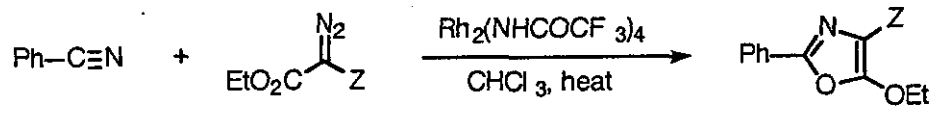
The catalysts, **125** - **127**, were previously prepared with in our group, by the method of McKervey and Roos.[86] Reaction of the appropriate carboxylic acid with the rhodium(II) carbonato species, **128**, yielded the required catalyst in good yield. (Scheme 36).



128

Scheme 36

Using rhodium(II) trifluoroacetamide **124**, the preparation of the oxazole-4-phosphonate **107a** and the oxazole-4-carbonitrile **108a** were reinvestigated, and compared with the reactions using rhodium(II) acetate. In the case of **107a**, the yield was increased from 16% to 53%, whilst for **108a**, the yield decreased to 12% from 25%. (Table 21).



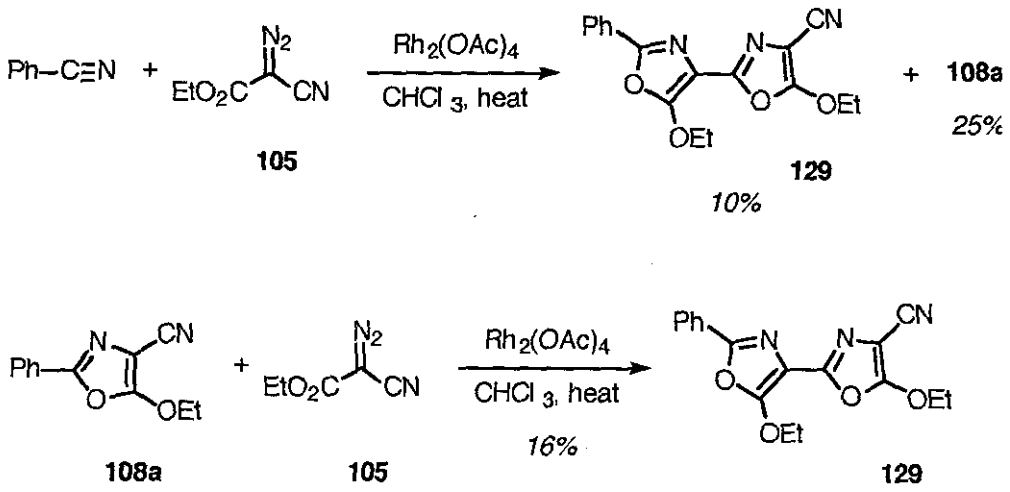
Diazo	*Z*	*Oxazole*	*Yield (%)*
104	$PO(OEt)_2$	**107a**	53 (16)[a]
105	CN	**108a**	12 (25)[a]

Note : [a] = yield obtained using rhodium(II) acetate

Table 21

2.4 Studies into Bis- and Tris-Oxazoles

Careful examination of the preparation of the oxazole-4-carbonitrile **108a**, showed that in addition to the oxazole **108a** (25%), the bis-oxazole **129** is also formed. Although the yield of **129** is low (10%), a simple nitrile is converted to a relatively complex bis-oxazole in a single step. The oxazole **108a** was readily taken to the bis-oxazole **129** in a 16% yield, by the reaction of benzonitrile and ethyl diazocyanoacetate **105**, using rhodium(II) acetate as catalyst. (Scheme 37).

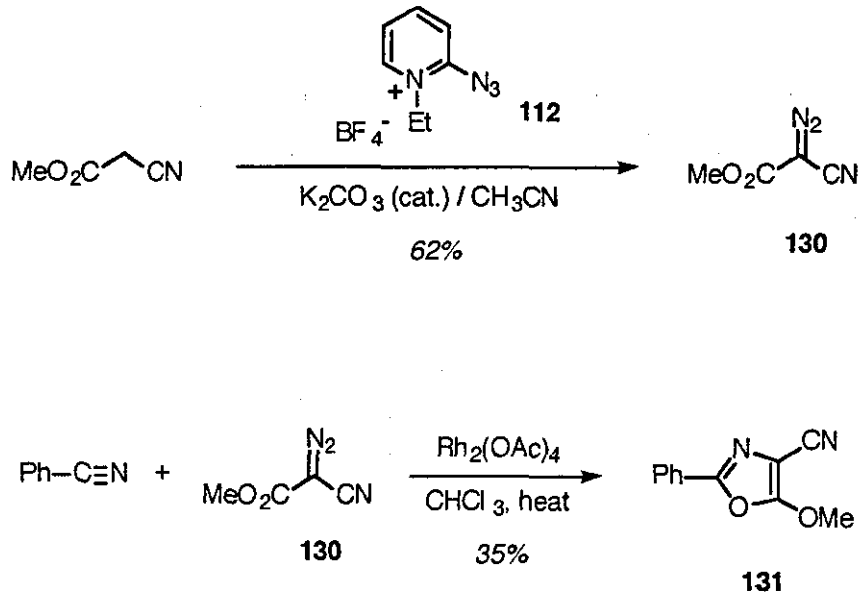


Scheme 37

Bis-oxazoles, in which the two heterocyclic rings are directly linked through their 4- and 2-positions, occur in a variety of oxazole natural products, for example hennoxazole A **4** and diazonamide B **6**. The oxazole-4-carbonitrile could act, in principle, as a direct precursor to bis-oxazoles. Bis- and tris-oxazoles have been prepared previously by iterative cyclisations,[21] double cyclisations,[24] or repetitive rhodium(II) acetate catalysed addition reactions of diazomalonates to nitriles.[71] The use of diazonitriles to give directly oxazole-4-carbonitriles circumvents the 4-step conversion of the oxazole-4-ester to the corresponding nitrile.[71]

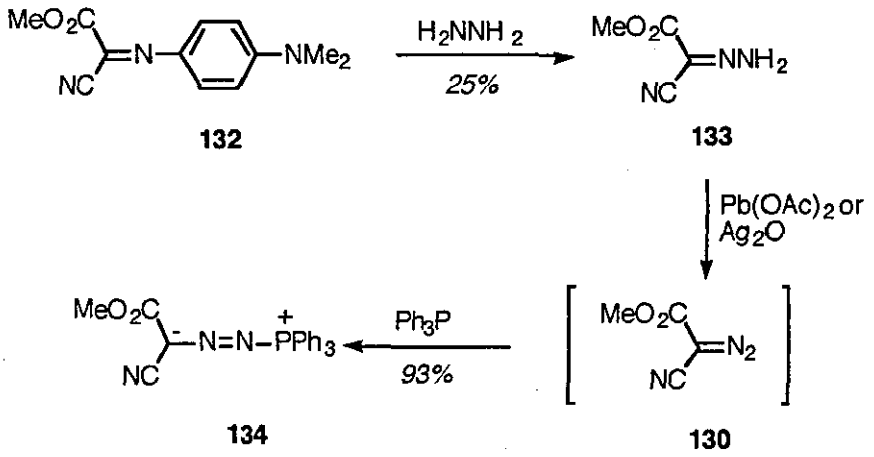
Thus, although ethyl diazocyanoacetate **105** only gave a poor yield of the oxazole-4-carbonitrile **108a**, the corresponding methyl ester, methyl diazocyanoacetate **130**, reacted with benzonitrile in the presence of rhodium(II) acetate to give the oxazole-4-carbonitrile **131** in an acceptable 35% yield.

The diazonitrile **130** was prepared in a similar manner to **105**, by use of 1-ethyl-2-azidopyridinium tetrafluoroborate **112**, in a 62% yield. In this case the base and solvent were changed to catalytic potassium carbonate and acetonitrile, respectively. (Scheme 38).



Scheme 38

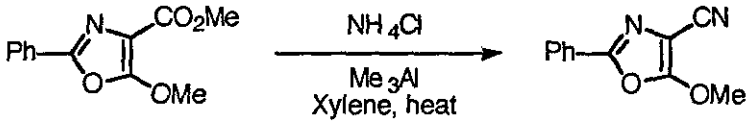
Methyl diazocyanoacetate **130** had previously been prepared by Ciganek[87] in two steps from methyl (4-dimethylaminophenylimino)cyanoacetate **132.** The first involved hydrazinolysis of **132** to the hydrazone **133** in 25% yield, which underwent oxidation to yield the diazonitrile, isolated as the triphenylphosphazine **134,** in 93% yield. Interestingly, the author considered methyl diazocyanoacetate **130** too much of an explosive hazard to be isolated in its pure form! (Scheme 39).



Scheme 39

The oxazole-4-carbonitrile **131** could also be prepared from methyl 5-methoxy-2-phenyloxazole-4-carboxylate **71a,** in 68% yield. This was achieved by the use of trimethyl

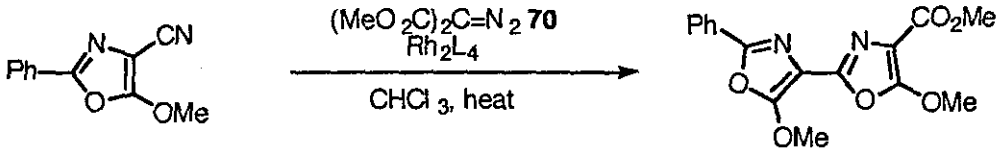
aluminium and aluminium chloride in refluxing xylene, as described by Weinreb.[88] (Scheme 40).



71a *68%* **131**

Scheme 40

The oxazole-4-carbonitrile **131** underwent reaction with dimethyl diazomalonate **70**, to give the bis-oxazole **135**, using rhodium(II) acetate in 48% yield. Changing to the carboxamide catalyst, rhodium(II) trifluoroacetamide, allowed the isolation of the bis-oxazole **135** in 53% yield. (Table 22).

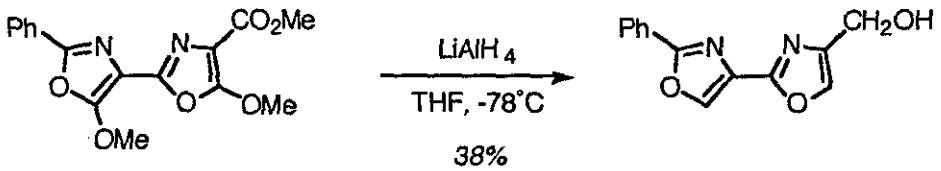


131 **135**

L	*Yield (%)*
$MeCO_2$-	48
CF_3CONH-	53

Table 22

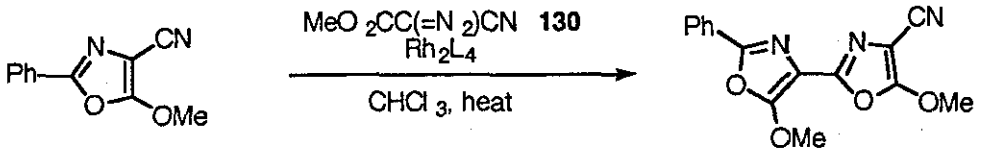
Both methoxy groups were cleaved from the bis-oxazole **135**, with concomitant reduction of the ester, by reaction with lithium aluminium hydride in THF at -78°C. This yielded the bis-oxazole **136** in 38%. (Scheme 41).



135 *38%* **136**

Scheme 41

The oxazole-4-carbonitrile **131** also underwent reaction with methyl diazocyanoacetate **130** and rhodium(II) acetate catalysis, to deliver the bis-oxazole nitrile **137** in 28% yield (62% based on recovered starting materials). The use of rhodium(II) trifluoroacetamide **124** as catalyst allowed the isolation of **137** in only a 5% yield. (Table 23).

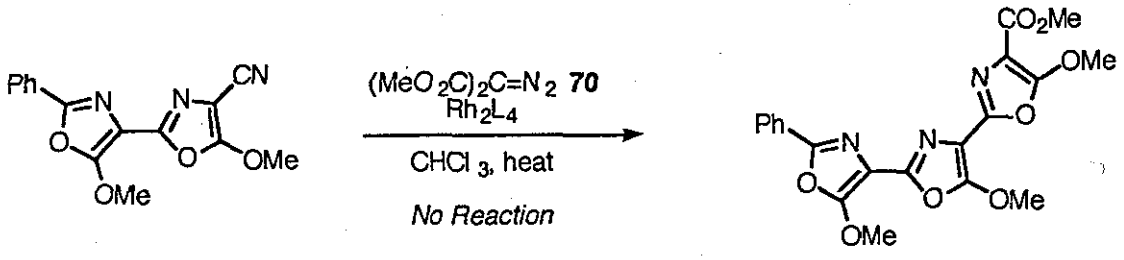


131 **137**

L	*Yield (%)*
$MeCO_2$-	28
CF_3CONH-	5

Table 23

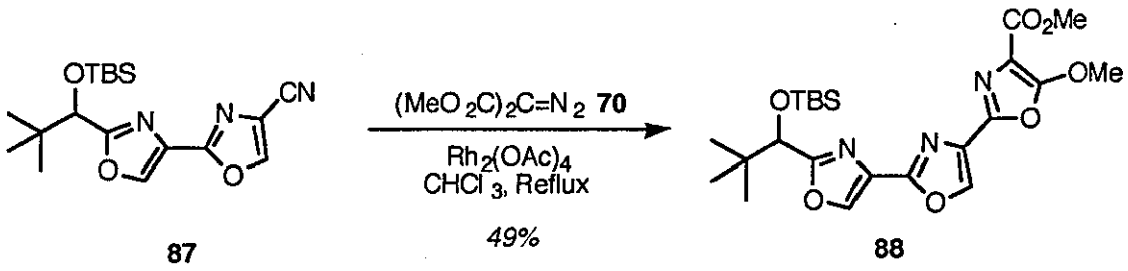
Attempts to take the bis-oxazole nitrile **137** to the tris-oxazole **138**, by use of dimethyl diazomalonate **70** and rhodium(II)-catalysis failed. In most cases, the starting nitrile could be recovered quantitatively from the reaction mixture. The catalysts screened were the carboxamide catalyst, rhodium(II) trifluoroacetamide (L=$NHCOCF_3$) **124** and the two carboxylate catalysts, rhodium(II) acetate (L=O_2CCH_3), and rhodium(II) (*S*)-mandelate (L=$O_2CCH(OH)Ph$) **125**. (Scheme 42).



137 **138**

Scheme 42

Yoo[71] had previously shown that the bis-oxazole **87** could be taken to the tris-oxazole **88**, using dimethyl diazomalonate **70** and rhodium(II) acetate catalysis, in 49% yield. (Scheme 43).



Scheme 43

There are only two differences between the Yoo bis-oxazole **87** and the bis-oxazole **137**. In the bis-oxazole **137** there is the presence of the phenyl group at 2', instead of an alkyl unit, and the methoxy groups at 5 and 5', which are not present in the Yoo system.

It seems unlikely that the electron-donating factor of the phenyl ring influences the reactivity of the 4-cyano group, over two heterocyclic rings. We can only assume that the electron-donating methoxy groups at 5 and 5' have an accumulative, detrimental effect on the ability of the 4-cyano group to undergo oxazole formation. (Figure 9).

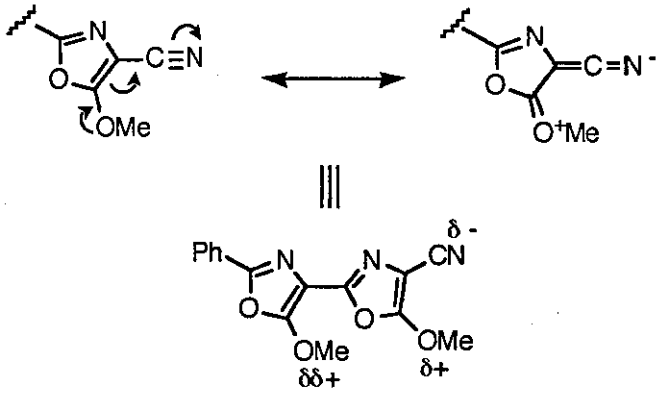


Figure 9

This effect would increase the nucleophilicity of the nitrile nitrogen. Binding to the rhodium catalyst would be preferential, with the formation of a more stable nitrile-catalyst adduct, the reverse reaction becoming unfavourable. With the catalytic sites on rhodium 'blocked', the reaction halts, and tris-oxazole formation does not occur.

2.5 Conclusion.

The use of diazosulfones, diazophosphonates and diazonitriles, under rhodium(II) catalysis, leads to the preparation of, respectively, 4-benzenesulfonyloxazoles, oxazole-4-phosphonates and oxazole-4-carbonitriles. Extension of the oxazole-4-carbonitrile methodology has allowed the preparation of bis-oxazoles systems, but extending this to the formation of tris-oxazole systems has, to-date, proved unattainable.

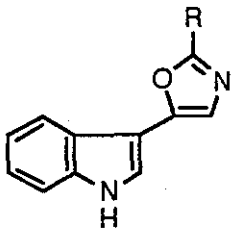
Many of the oxazole formation reactions were found to be dependent upon the rhodium(II) catalyst used. A qualitative explanation for this observation is not yet clear, but may lie with the catalysts ability to undergo co-ordination with the nitrile ligand, and the subsequent energy required to unbind the nitrile-catalyst adduct.

Chapter 3

Synthesis of and Studies into Oxazolylindole Alkaloids

3.1 Introduction

Pimprinine **1a** was the first of the oxazolylindole containing mould metabolites, isolated initially in 1960 from *Streptomyces pimprina*,[5] and consequently from *Streptoverticillium olivoreticuli*[89] and *S. waksmanii*.[90] It is often found co-occurring with other microbial oxazolylindole alkaloids.[91] (Table 24).



2-Substituted-5-(3-indolyl)oxazole

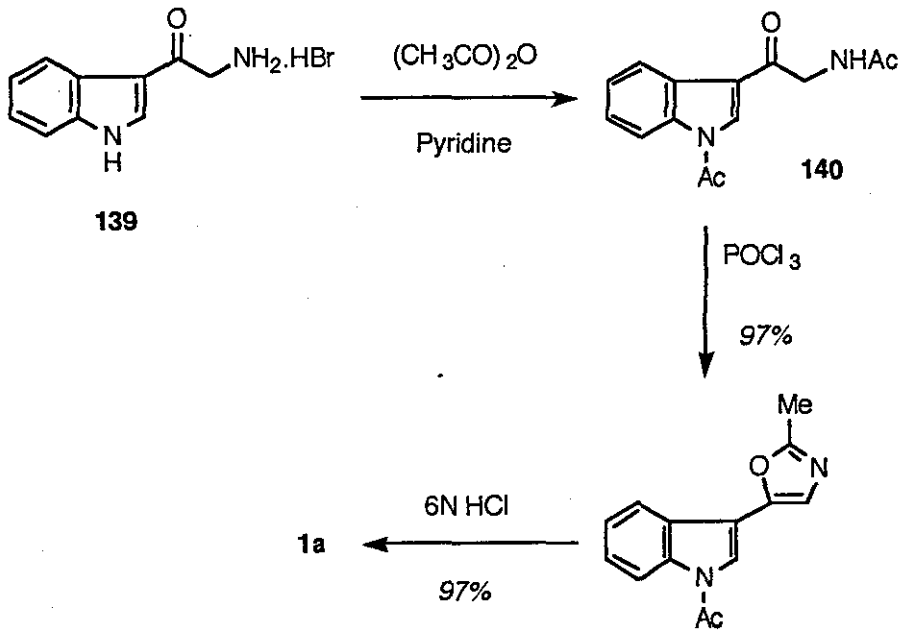
1

R	*Oxazole*	*Name*	*Source*
Me	**1a**	pimprinine	*Streptomyces pimprina* *Streptoverticillium olivereticuli* *S. waksmanii*
Et	**1b**	pimprinethine	*Streptoverticillium olivereticuli* *Streptomyces cinnamomeus*
^{n}Pr	**1c**	WS-30581A	*Strepoverticillium waksmanii*
^{n}Bu	**1d**	WS-30581B	*Strepoverticillium waksmanii*
$PhCH_2$	**1e**	pimprinaphine	*Strepoverticillium olivereticuli*

Table 24

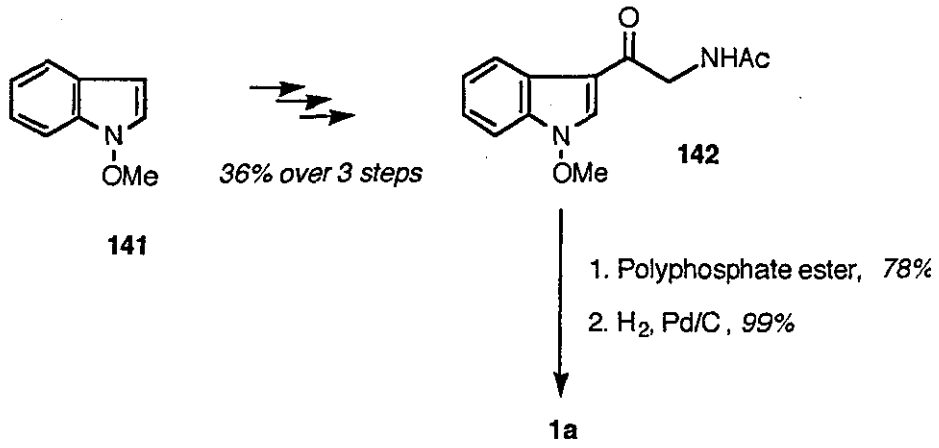
Pimprinine **1a** has been shown to exhibit antiepileptic and monoamine oxidase inhibitory effects. Also, along with WS-30581A **1c**, -B **1d**, it has a potent effect on platelet aggregation.[90]

Most of the synthesis towards the pimprinine series of alkaloids has been based around the Robinson-Gabriel preparation of oxazoles, or modified versions thereof. The first reported preparation, by Joshi *et al.* in 1963,[5] relied upon the cyclodehydration of the 2-ketoamide **140**, derived from 3-(2-aminoacetyl)indole **139**, using phosphorus oxychloride, to give pimprinine **1a** after acid-hydrolysis of the 1-acyl group. (Scheme 44).



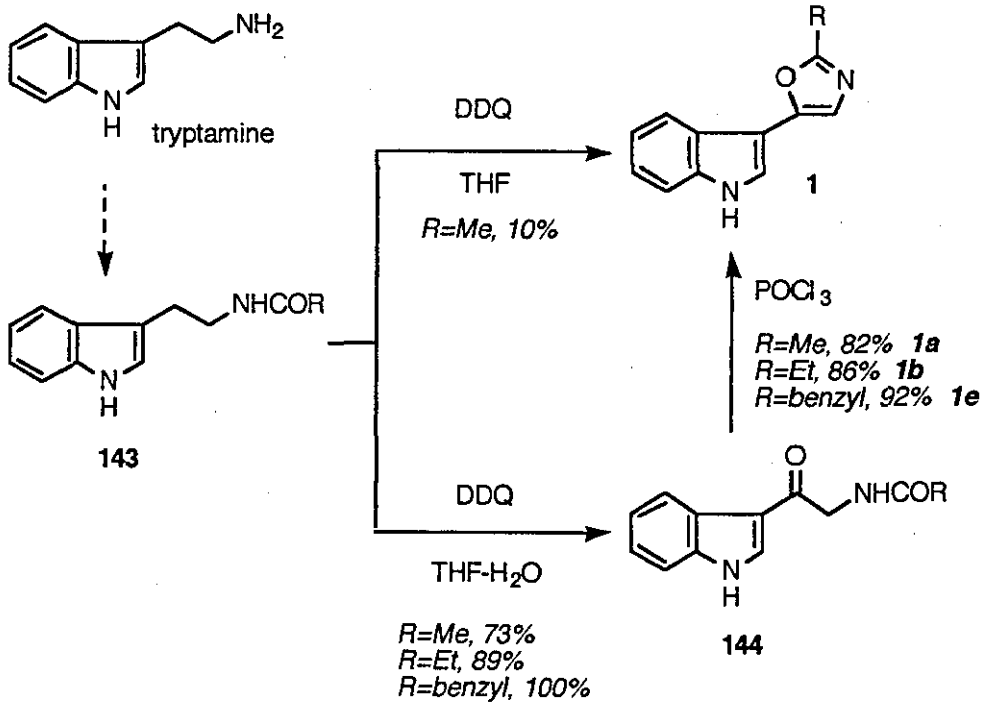
Scheme 44

In their synthetic studies of the chemistry of 1-methoxyindoles, Somie *et al.*[92] prepared pimprinine **1a**, again *via* a Robinson-Gabriel reaction, in a similar fashion to Joshi. Starting from 1-methoxyindole **141**, they prepared 3-(2-aminoacetyl)-1-methoxyindole **142** in 36% yield. This unstable compound underwent reaction with polyphosphate ester to give the oxazolylindole skeleton. Catalytic hydrogenation gave pimprinine **1a**, in 77% yield over both steps. (Scheme 45).



Scheme 45

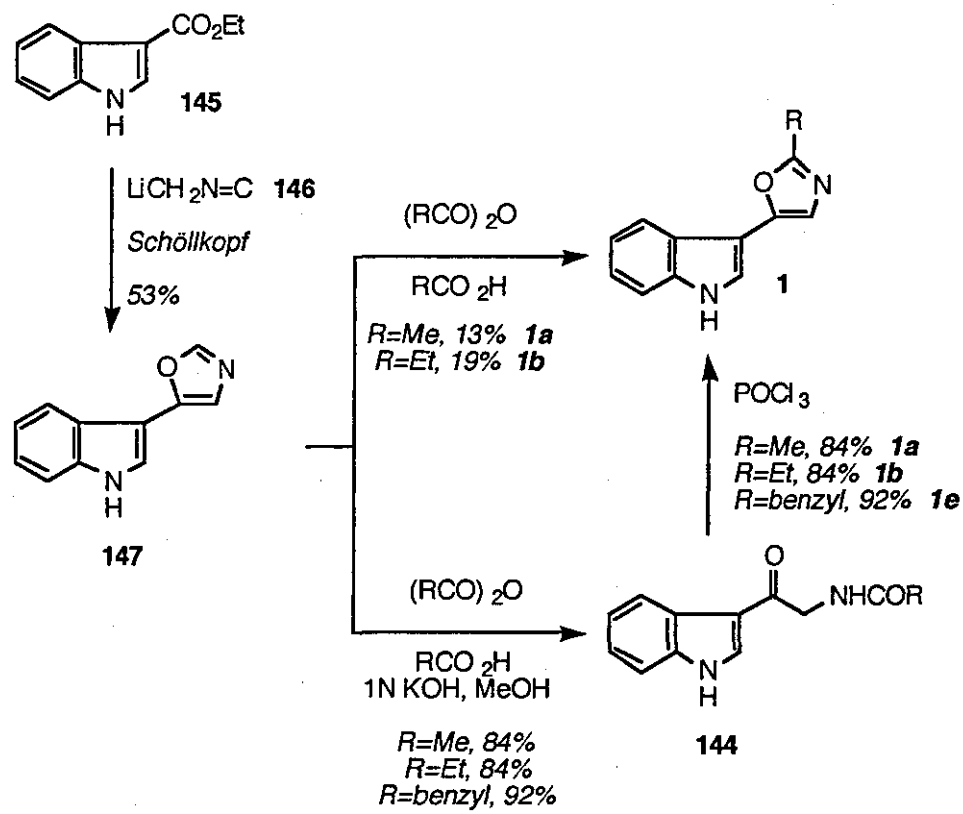
Although, 3-(2-aminoacetyl) indole **139** is a difficult starting material to synthesise, Oikawa and co-workers,[93,94] found that the selective oxidation of the C-3 side chain of indoles using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), proved an effective by-pass in the preparation of these intermediate 3-acylaminoacetylindoles. The readily available acyl derivatives of tryptamine **143** underwent DDQ oxidation to provide the appropriate 2-ketoamide **144**, which undergo cyclodehydration, using phosphorus oxychloride to give either **1a**, **1b** or **1e**. The use of dry THF in the oxidation of 1-acetyltryptamine, **143a** (**143**, R = Me), led directly to the isolation of **1a**, albeit in 10% yield. (Scheme 46).



Scheme 46

Along with the isolation and characterisation of pimprinine **1a**, pimprinethine **1b** and pimprinaphine **1e** from *Streptoverticillium olivoreticuli*, Dolby *et al.*[89] also published their synthesis utilising the Schöllkopf condensation[95] to form the oxazole ring. Thus ethyl indole-3-carboxylate **145** was reacted with isocyanomethyllithium **146** to give 5-(3-indolyl)oxazole **147** in 53% yield. Refluxing with acetic anhydride in acetic acid gave pimprinine **1a** in 13% yield. Similarly, reaction with propionic anhydride in propionic acid gave pimprinethine **1b** in 19% yield. Both these reactions probably work *via* a ring opening mechanism, giving the appropriate 2-ketoamide, which then undergo ring-closure to give the natural products.

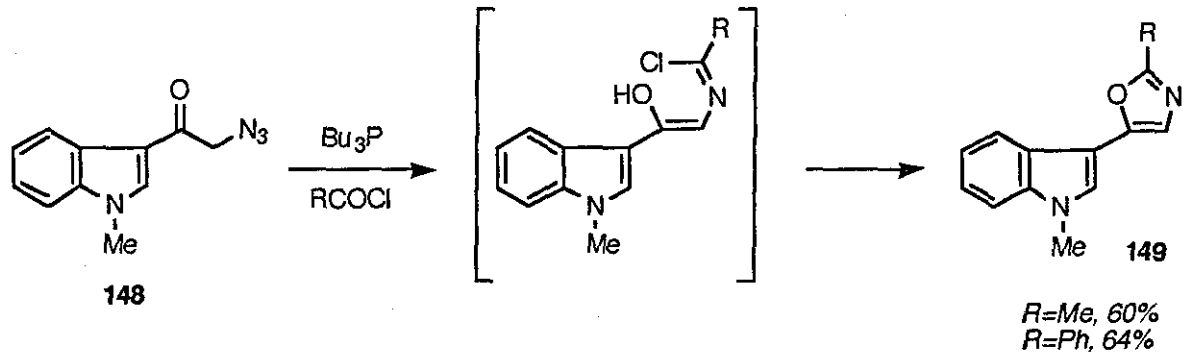
However, taking 5-(3-indolyl)oxazole **147** with the appropriate acid anhydride in the corresponding carboxylic acid and subjecting the mixture to hydrolysis with potassium hydroxide in refluxing methanol, gave the corresponding 3-acylaminoacetylindoles **144** These underwent the Robinson-Gabriel cyclodehydration, to give the corresponding alkaloids **1a**, **1b** and **1e**, in 84%, 84% and 92% yields respectively. (Scheme 47).



Scheme 47

Molina *et al.*[96] have used their one-pot iminophosphorane-mediated synthesis of oxazoles, to give access to the oxazolylindole skeleton. This reaction relies upon the aza-Wittig reaction

of iminophosphoranes derived from azidocarbonyl compounds with acid chlorides. Hence 3-azidoacetyl-1-methylindole **148** was reacted with tributylphosphine to give the intermediate iminophosphorane, which underwent reaction with acid chlorides to give a variety of 2-substituted-5-(3-(1-methylindolyl)) oxazoles **149**. (Scheme 48).



Scheme 48

3.2 Synthesis of Oxazolylindole Alkaloids.

If we look at these alkaloids from the view of a reaction involving rhodium carbenoid methodology, we can envisage that we would required an 1-protected 3-diazoacetylindole **150** and an appropriate nitrile. (Figure 10).

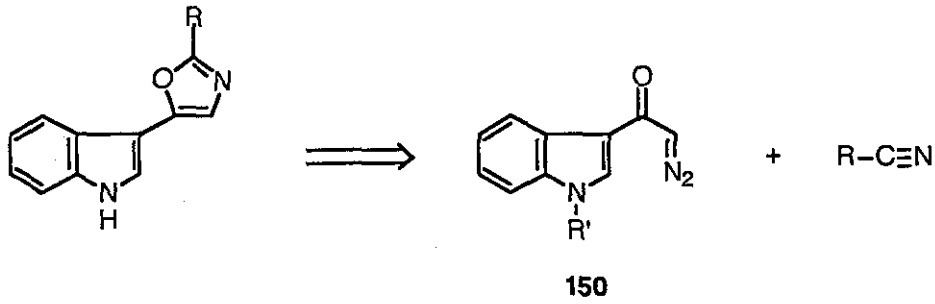
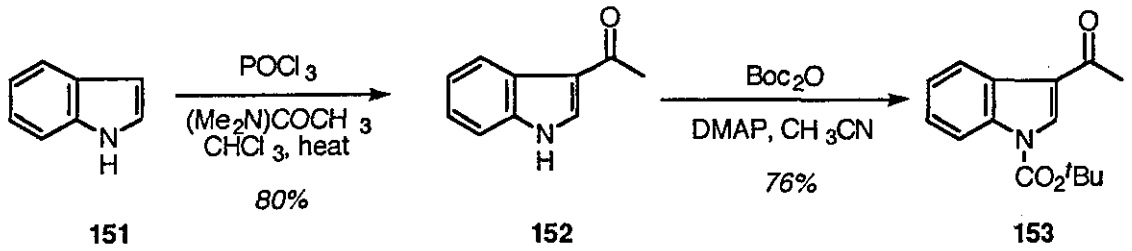


Figure 10

Danheiser reports the preparation of *tert*-butyl 3-diazoacetylindole-1-carboxylate **150a** (**150**, R'=$CO_2{}^tBu$) from *tert*-butyl 3-acetylindole-1-carboxylate **153**, by a diazotransfer procedure.[97] The indole **153** was prepared in two steps from indole **151** itself. The first being a Vilsmeier acetylation, using phosphorus oxychloride and dimethylacetamide, to yield

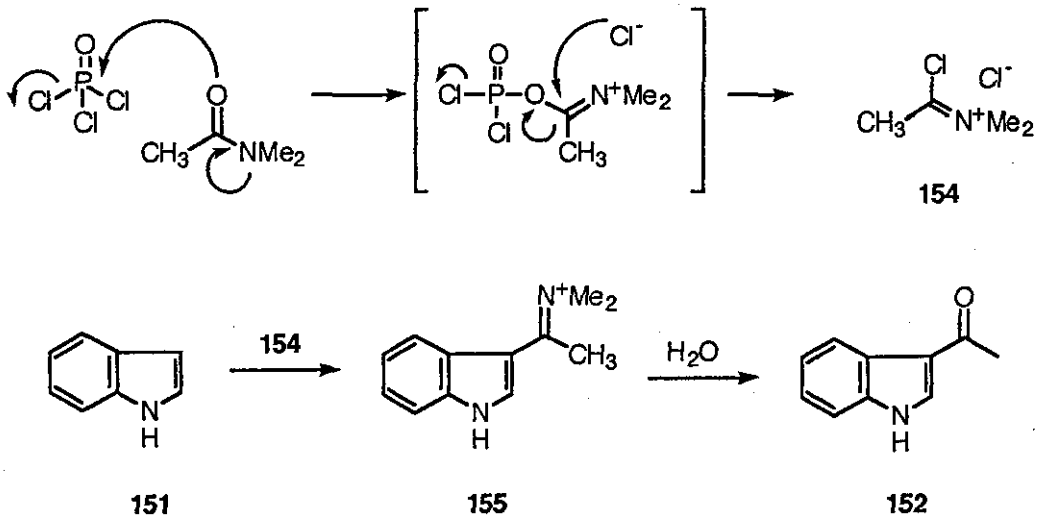
3-acetylindole **152** in 80% yield. The second being protection of the nitrogen of **152** as a *tert*-butyl carbamate, to yield **153** in 76% yield.[98] (Scheme 49).



151 **152** **153**

Scheme 49

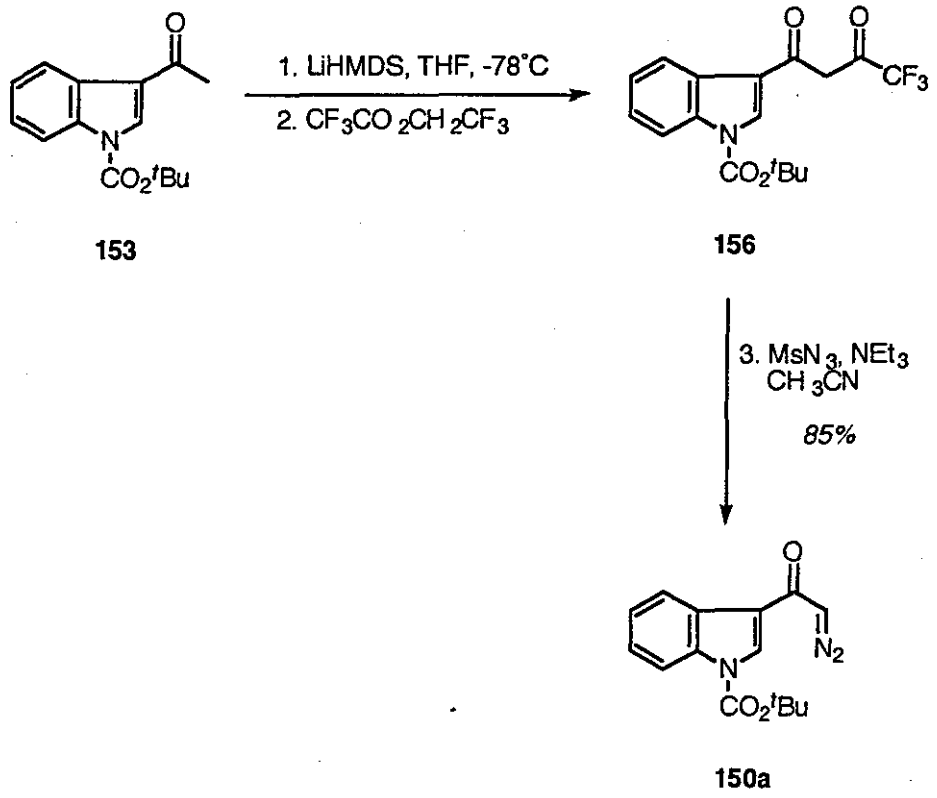
The acetylation works by the initial formation of the Vilsmeier complex **154**, by the reaction between phosphorus oxychloride and dimethyl acetamide. This complex undergoes selective addition to the C-3 position of indole **151**, to give the intermediate **155**. Hydrolytic work-up generates 3-acetylindole **152**. (Scheme 50).



151 **155** **152**

Scheme 50

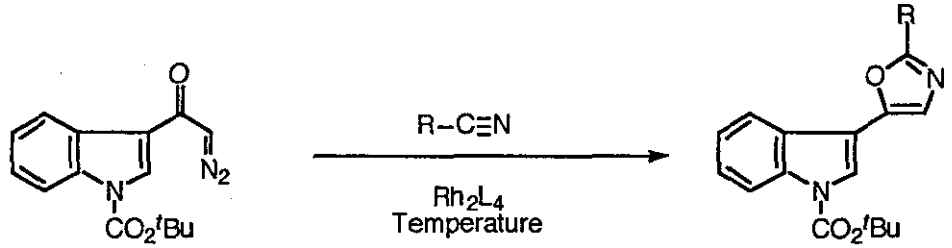
tert-Butyl 3-diazoacetylindole-1-carboxylate **150a** was then prepared from **153**, according to the procedure of Danheiser. The reaction works by activation of the acetyl group by conversion into the trifluoromethane-1,3-diketone **156**, which readily undergoes diazotransfer using mesyl azide, with loss of the activation group, to yield **150a** in 85%. (Scheme 51).



153 156 150a

Scheme 51

The diazoketone **150a** was then reacted with both acetonitrile and propionitrile, using either the carboxylate catalyst rhodium(II) acetate ($L=O_2CCH_3$) or the carboxamide catalyst, rhodium(II) trifluoroacetamide **124** ($L=NHCOCF_3$). The reactions were conducted at both room temperature and at 75°C, giving either 2-methyl-5-[3-(1-*tert*-butoxycarbonyl)indolyl]oxazole **157a** or 2-ethyl-5-[3-(1-*tert*-butoxycarbonyl)indolyl]oxazole **157b** respectively, as summarised. (Table 25).

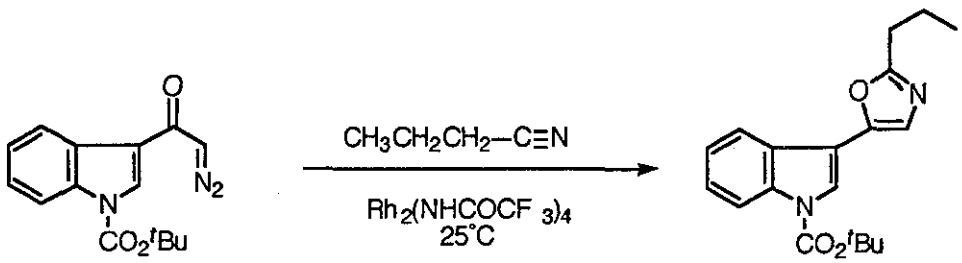


150a 157

L	R	Temp. °C	Oxazole	Yield (%)
CH_3CO_2-	Me	75	**157a**	37
	Et	75	**157b**	0
	Me	25	**157a**	0
	Et	25	**157b**	0
CF_3CONH-	Me	75	**157a**	36
	Et	75	**157b**	55
	Me	25	**157a**	46
	Et	25	**157b**	90

Table 25

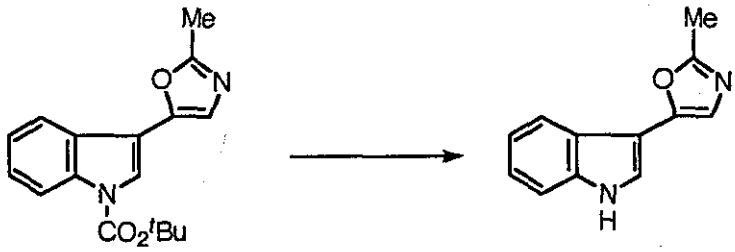
The best conditions were found to be a slow addition of the diazoketone, to the nitrile, at 25°C, using rhodium(II) trifluoroacetamide **124** catalyst. This was applied to the reaction with butyronitrile and the diazoketone **150a** to give 2-*n*-propyl-5-[3-(1-*tert*-butoxycarbonyl)indolyl]oxazole **157c** in 24% yield. (Scheme 52).



150a **157c**

Scheme 52

For isolation of the oxazolylindole alkaloids **1a** - **1c**, the *tert*-butoxy carbamate protecting group would need to be cleaved. Deprotection, using either trifluoroacetic acid in dichloromethane[99] or 30% sodium methoxide in methanolic THF[100] was attempted on 2-methyl-5-[3-(1-*tert*-butoxycarbonyl)indolyl]oxazole **157a**, yielding the alkaloid pimprinine **1a** in 12% and 78% respectively. (Table 26).

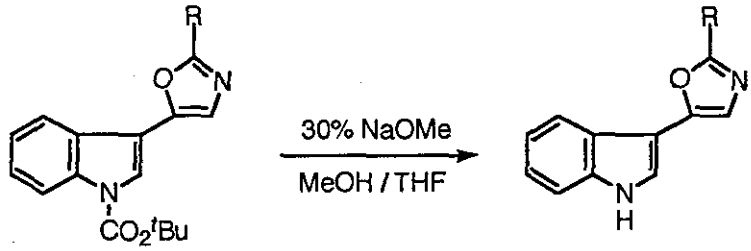


157a **1a**

Reagents	*Yield (%)*
CF_3CO_2H / DCM	12
30% NaOMe / MeOH / THF	78

Table 26

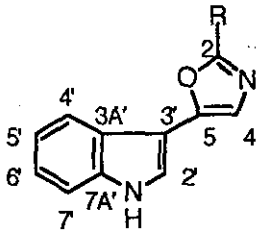
Deprotection, using 30% sodium methoxide in methanolic THF, of **157b** and **157c** took place, to give the alkaloids pimprinethine **1b** in 78% and WS-30581A **1c** in 47% yields, respectively. This is the first known synthesis of the antiplatelet agent, WS-30581A. (Table 27).



Oxazole	*R*	*Alkaloid*	*Yield (%)*
157b	Et	**1b**	78
157c	^{n}Pr	**1c**	47

Table 27

The carbon nmr data for the alkaloids is given. For both **1a** and **1b** these were recorded at 100 MHz, whilst for **1c** the lower frequency of 62.9 MHz was used. (Table 28).



Position	*Alkaloid*		
	1a	**1b**	**1c**
2	159.1	163.6 (164.4)[a]	162.7
4	123.0	122.9 (123.4)[a]	122.8
5	147.2	147.0 (149.5)[a]	147.2
2'	120.8	120.7 (123.1)[a]	120.7
3'	106.0	106.1 (105.0)[a]	105.8
3A'	124.0	124.0 (125.0)[a]	124.1
4'	120.0	119.9 (120.1)[a]	119.9
5'	119.9	119.8 (118.1)[a]	119.6
6'	121.3	121.3 (121.0)[a]	121.6
7'	111.4	111.4 (112.5)[a]	111.5
7A'	136.1	136.1 (137.8)[a]	136.2

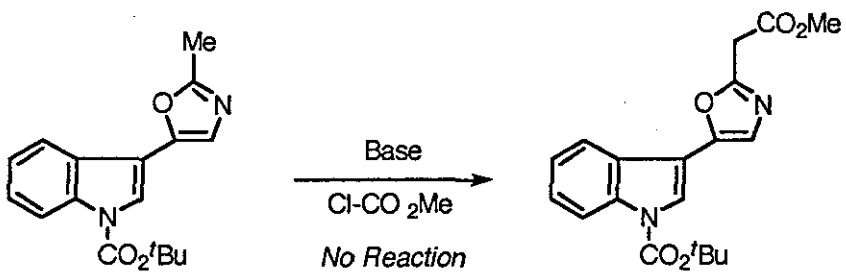
Note: [a] = literature values, reference 91.

Table 28

3.3 Modifications on the Oxazole Ring

After showing that rhodium carbenoid methodology could be successfully used to prepare the oxazolylindole skeleton, our attention turned to alteration of the oxazole sub-structure by studying a range of possible substituents. The modification of the substituent at the C2 position of the oxazole ring was the first study undertaken.

The study was initiated by reacting 2-methyl-5-[3-(1-*tert*-butoxycarbonyl)indolyl]oxazole **157a** with a range of bases, and quenching the intermediate anion with the electrophile, methyl cyanoformate, in the hope of introducing an methyl ester functionality. Unfortunately, the reaction could not be made to proceed. (Scheme 53).

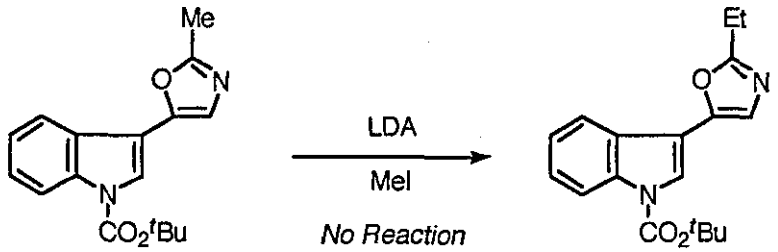


157a

Base : ^{n}BuLi / LDA / LiHMDS or NaHMDS

Scheme 53

To test whether the anion was being formed, **157a** was reacted with lithium diisopropylamide (LDA), and then quenched with methyl iodide, in the hope of forming 2-ethyl-5-[3-(1-*tert*-butoxycarbonyl)indolyl]oxazole **157b**. However, formation of **157b** could not be detected under the conditions employed. (Scheme 54).

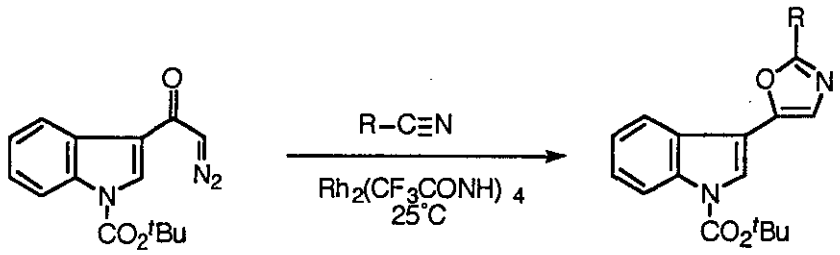


157a **157b**

Scheme 54

The lithiation of 2-methyl substituted oxazoles, followed by condensation with a range of electrophiles, is a well documented reaction.[101-104] The reason for the lack of reactivity of **157a** towards deprotonation and subsequent reaction is still unclear.

A range of functionalised nitriles was screened in the reaction with the diazoketone **150a**, under rhodium(II) trifluoroacetamide **124** catalysis. The nitriles studied were bromoacetonitrile **158**, 3-*tert* butyldimethylsiloxypropane-1-carbonitrile **159**, methyl cyanoacetate and 2-phenyl-5-methoxyoxazole-4-carbonitrile **131**. Of these, only the first two underwent oxazole formation to give the heterocycles **157d** and **157e**, in 19% and 20% yield, respectively. (Table 29).

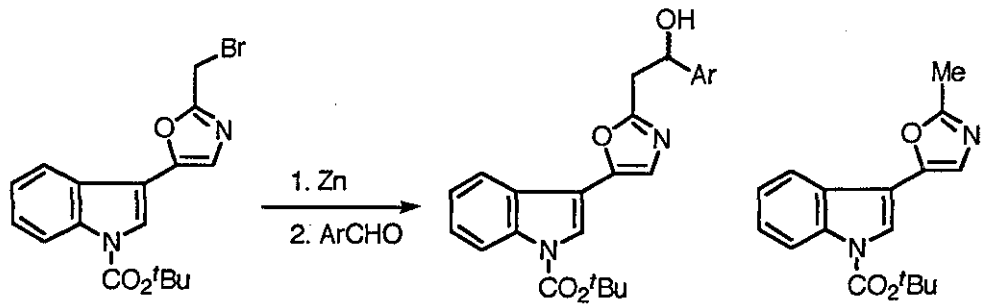


150a **157**

Nitrile	*R*	*Oxazole*	*Yield (%)*
158	$BrCH_2$-	**157d**	19
159	$TBSOCH_2CH_2$-	**157e**	20

Table 29

Subsequent reactions on the oxazoles **157d** and **157e** were attempted. The formation of the 2-(zinc bromomethyl)oxazole organometallic group is a known reaction of various 2-bromomethyl oxazoles.[69] In an analogous fashion, the oxazole **157d** was reacted with zinc, to form the intermediate zinc bromide **161**, which was then reacted with both benzaldehyde and 3-bromobenzaldehyde. Instead of the expected formation of the alcohol **160**, the only isolated product in each case was 2-methyl-5-[3-(1-*tert*-butoxycarbonyl)indolyl]oxazole **157a**. (Scheme 55).

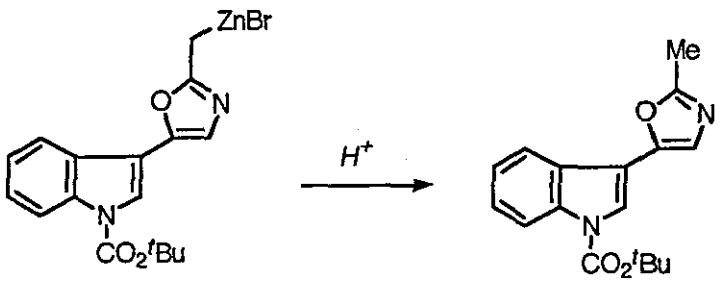


157d **160** **157a**

Ar	*Yield (%)*	
	160	**157a**
Ph	0	40
3-Br-C_6H_4-	0	54

Scheme 55

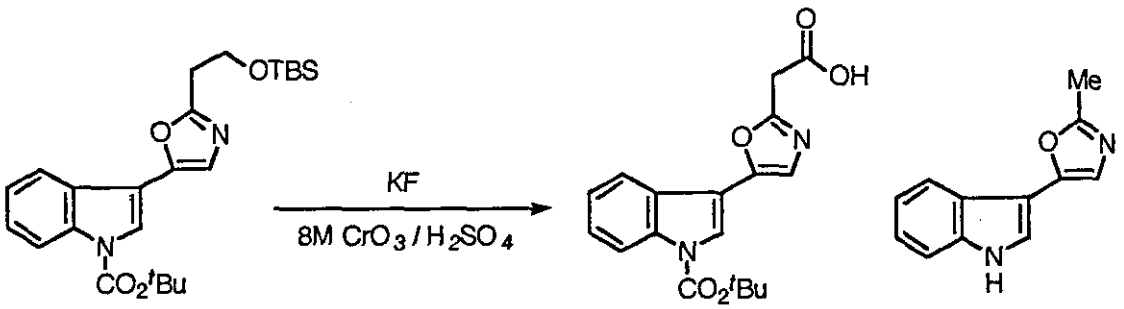
The oxazole **157a** probably arises from protonation of the intermediate zinc bromide **161**, after failure to react with the aryl aldehydes. (Scheme 56).



161 **157a**

Scheme 56

Deprotection of *tert*-butyldimethylsilyl protected heterocycle **157e**, was attempted under the oxidative conditions of Jones' Reagent, in the hope of yielding the carboxylic acid **162**.[105,106] Unfortunately, the only isolated product was the alkaloid pimprinine, i.e. 2-methyl-5-(3-indolyl)oxazole, **1a** in 46% yield. (Scheme 57).

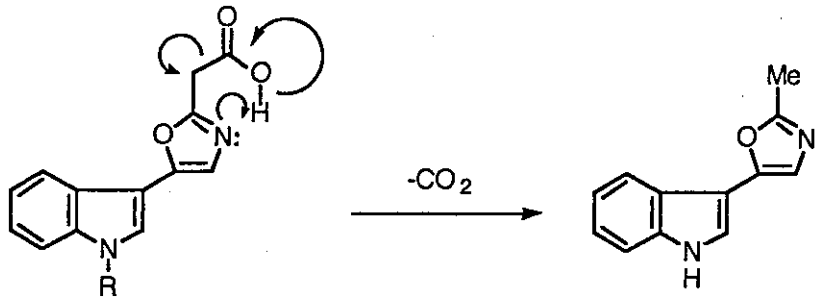


157e **162** **1a**

0% *46%*

Scheme 57

This can possibly be accounted for by the initial formation of **162**, which underwent internal proton abstraction followed by decarboxylation, then proton transfer to give **1a**. The acidic conditions causes removal of the *tert*-butyl carbamate group. (Scheme 58).



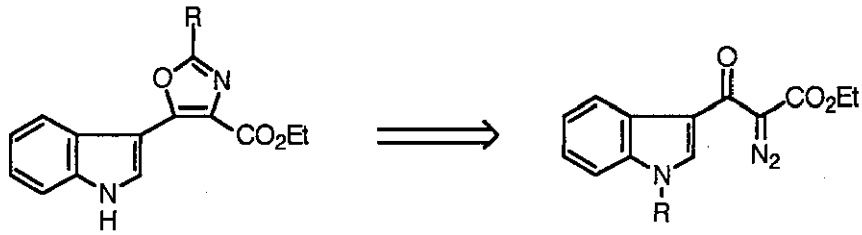
162

R = $CO_2{}^tBu$ or H

1a

Scheme 58

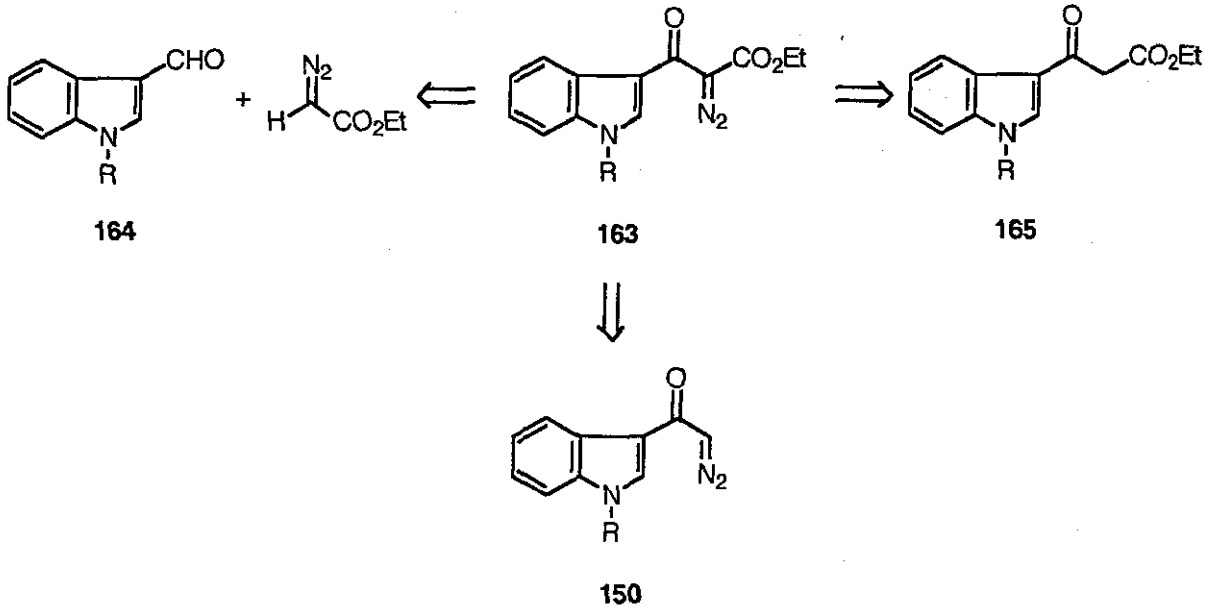
The second modification of the oxazole ring studied was the inclusion of functionality at the 4-position. This would arrive from the reaction of a functionalised diazoketone. It was decided to study the chemistry of the 2-keto-1-diazo ester **163**, which would hopefully introduce the ester functionality to the 4-position of the oxazole ring. (Figure 11).



163

Figure 11

Synthetically, there are various routes to the 2-keto-1-diazo ester **163**, one being the reaction between the aldehyde **164** and a derivative of ethyl diazoacetate; another, is the reaction between the diazoketone **150** and carboxylation reagents. Another is the formation of the 2-keto ester **165**, and subsequent diazotransfer. (Figure 12).



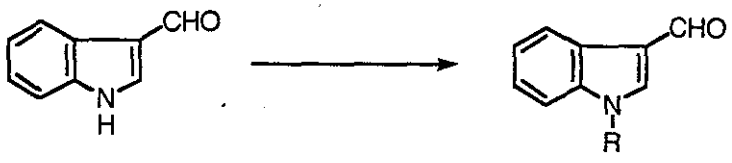
164 163 165

150

Figure 12

The preparation of 1-diazo-2-hydroxy esters, by the condensation of aldehydes with ethyl diazoacetate is a well documented reaction. The reaction may be conducted under various conditions. The preferred method is by the use of ethyl lithiodiazoacetate,[107] but tin(II) chloride[108,109] or methanolic potassium hydroxide[110] can be used to instigate the condensation.

The aldehydes **164a** - **165c** were prepared from indole-3-carboxaldehyde **166**, by conventional chemistry.[111,112] (Table 30).



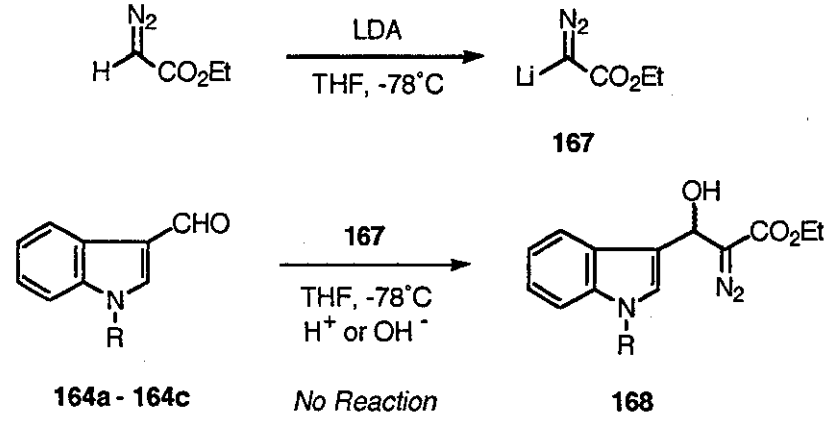
166 164

R	*Aldehyde*	*Yield (%)*
$^{t}BuCO_2$-	**164a**	64
CH_3OCH_2-	**164b**	52
$PhCH_2$-	**164c**	83

Table 30

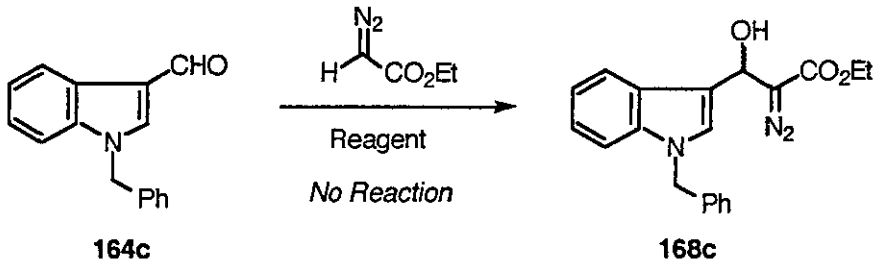
Each were reacted with ethyl lithiodiazoacetate **167**, prepared by reaction of lithium diisopropylamide and ethyl diazoacetate at -78°C,[113] and quenched under either basic or

acidic conditions. However, in each case only starting materials were obtained. (Scheme 59).



Scheme 59

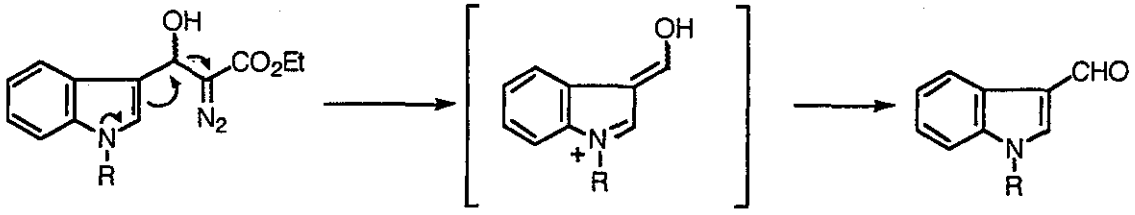
The 1-benzyl aldehyde **164c** was also reacted with both tin(II) chloride and methanolic potassium hydroxide to implement the condensation; but as before only the starting aldehyde was obtained. (Scheme 60).



Reagent : $SnCl_2$ or 10% KOH / MeOH

Scheme 60

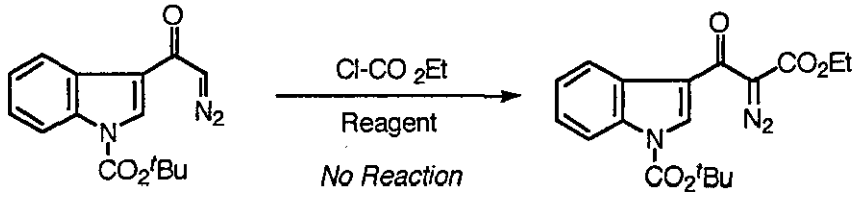
The failure of these reactions may due to several factors, the lack of reactivity of the aldehydes **164a - 164c** being one of these. However, it is plausible that the reaction to form the 1-diazo-2-hydroxy ester **168** takes place in some instances, but itself undergoes a favourable retro-pseudo aldol condensation to give back the starting aldehyde. The aldehyde **164a**, which has a carbamate protecting group, and hence may be considered as having some delocalisation of the indole nitrogen lone-pair into the π-system of the carbonyl, would be expected to undergo some form of reaction. Even in this instance, the retro-pseudo aldol reaction must prove to be more thermodynamically favourable. (Scheme 61).



168 164

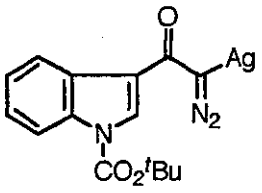
Scheme 61

The diazoketone **150a** was taken with a range of bases, in the hope to deprotonate the diazoproton, followed by quenching with ethyl chloroformate in an attempt to prepare the 2-keto-1-diazo ester **163a** (**163**, R=$CO_2{}^t$Bu). It was also reacted with silver(I) oxide,[114a] to prepare the silver derivative **169**, and then quenched with ethyl chloroformate. However, in each case, no products were obtained. (Scheme 62).



150a **163a**

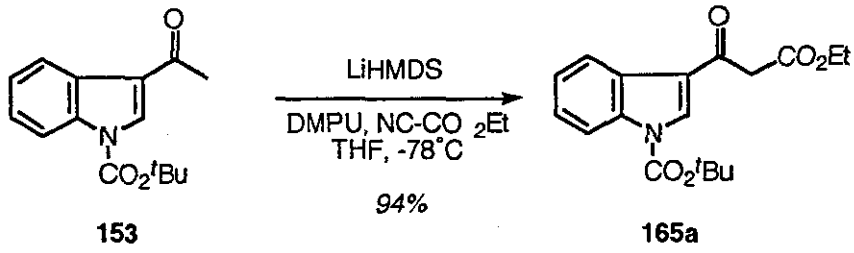
Reagents : NEt_3, LDA, LiHMDS, Ag_2O



169

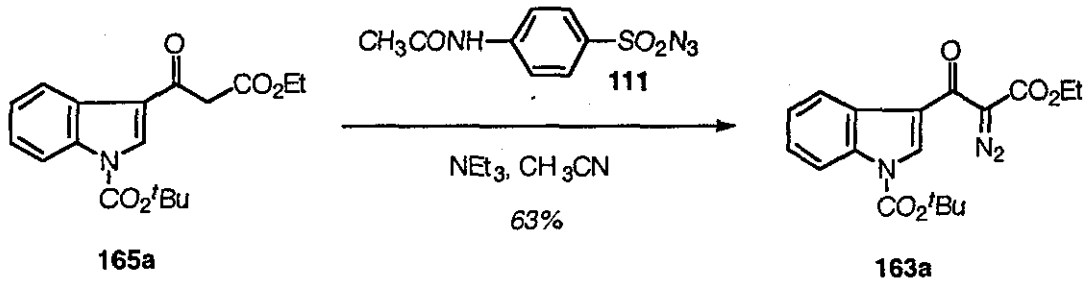
Scheme 62

It was shown by the preparation of the diazoketone **150a**, that *tert*-butyl 3-acetylindole-1-carboxylate **153** could be deprotonated on the methyl group using lithium 1,1,1,3,3,3-hexamethyldisilazide (LiHMDS). The intermediate anion was quenched with both ethyl chloroformate and ethyl cyanoformate.[114b] The use of ethyl chloroformate resulted in a complex, inseparable mixture of both *O*- and *C*-carboxylated product. However the reaction with ethyl cyanoformate allowed the isolation of the 2-keto ester **165a** (**165**, R=$CO_2{}^t$Bu) in 94% yield. (Scheme 63).



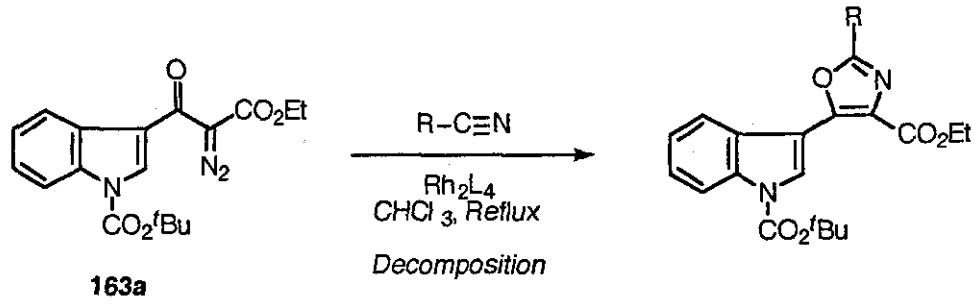
Scheme 63

This compound underwent diazotransfer using 4-acetamidobenzenesulfonyl azide **111** and triethylamine in acetonitrile, to yield the 2-keto-1-diazoketone **163a** (**163**, R=$CO_2{}^t$Bu) in 63% yield. (Scheme 64).



Scheme 64

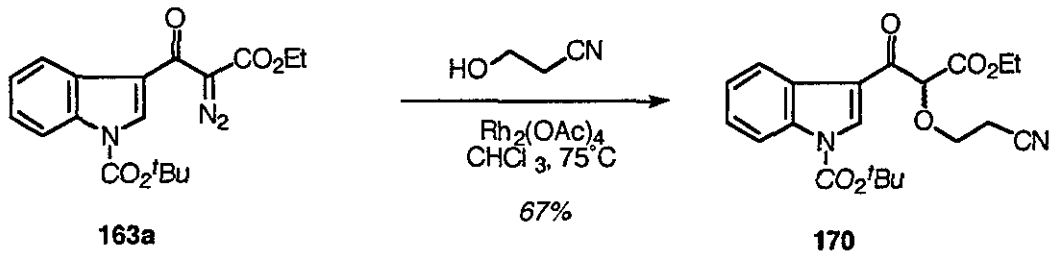
Unfortunately, the 2-keto-1-diazo ester **163a** did not undergo oxazole formation with either acetonitrile (R=CH_3) or bromoacetonitrile (R=$BrCH_2$) under rhodium(II) catalysis at 75°C. The reactions were conducted with both the carboxylate catalyst, rhodium(II) acetate (L=O_2CCH_3) and the carboxamide catalyst, rhodium(II) trifluoroacetamide (L=$NHCOCF_3$) **124**. The diazoester was found to decompose under the conditions employed. (Scheme 65).



Scheme 65

The OH-insertion of diazocarbonyl compounds is one of their better studied and understood reactions.[115,116] It often acts as a guide to their ability to undergo carbenoid formation, by

yielding a 1-alkoxy carbonyl. The diazoester **163a** was taken with 3-hydroxyproprionitrile, in the presence of rhodium(II) acetate. This yielded the OH-insertion product **170**, in 67%. (Scheme 66).



163a **170**

Scheme 66

This result suggests the formation of an intermediate rhodium carbenoid. The reason for this carbenoid to undergo OH-insertion, but not oxazole formation is unclear. The indole nitrogen affecting the nucleophilicity of the keto-carbonyl is a possibility, but, as yet this is uncertain.

3.4 Conclusion.

The use of rhodium carbenoid methodology has allowed the synthesis of the simple oxazolylindole alkaloids pimprinine **1a**, pimprinethine **1b** and WS-30581A **1c** in two steps from *tert*-butyl 3-diazoacetylindole-1-carboxylate **150a**. Their spectroscopic data being identical to that in the literature. The reactions were found, again, to be dependent on the rhodium(II) catalyst employed.

Modifications on the 2-position allowed the preparation of functionalised oxazoles, but further attempts to develop these heterocycles only led to the isolation of previously prepared compounds. Unfortunately, studies towards the synthesis of 4-substituted oxazoles did not succeed. The reason for this was unclear, as the prepared 2-keto diazoester readily succeeded in undergoing OH-insertion.

Chapter 4

Synthetic Studies Towards the Diazonamides

4.1 Introduction

The diazonamides, A **171** and B **6**, were isolated in 1991 from the ascidian, *Diazona chinesis*, by Lindquist and co-workers.[11] Their structures were elucidated by a single-crystal X-ray diffraction analysis of the 4-bromobenzamide derivative of diazonamide B; a representation of diazonamide B **6**, assigned from the X-ray crystal structure, is shown overleaf. (Figure 13).

Their skeletal structure contains derivatives of at least three amino acids: a 3,4,5,-trisubstituted (*S*)-tyrosine (C1 - C9), a tryptophan substituted at the 2- and 4-positions of the indole (C18 - C27) and a (*S*)-valine (C31 - C35). They were found to have potent *in vitro* activity against HCT-116 human colon carcinoma and B-16 murine melanoma cancer cell lines. Of the two natural products, diazonamide A **171** is the most active, with IC_{50} values less than 15 ng/mL. Interestingly, the UV spectra of **171** and **6** show little evidence of their high degree of unsaturation, probably due to the strict steric requirements of the bicyclic framework preventing appreciable overlap of the conjugated heterocycles. These compounds represent an new class of halogenated, highly unsaturated cyclic peptides. (Figure 14, showing crystal structure numbering).

Diazonamide A **171** : R^1 = H, R^2 =

Diazonamide B **6** : R^1 = Br, R^2 = H

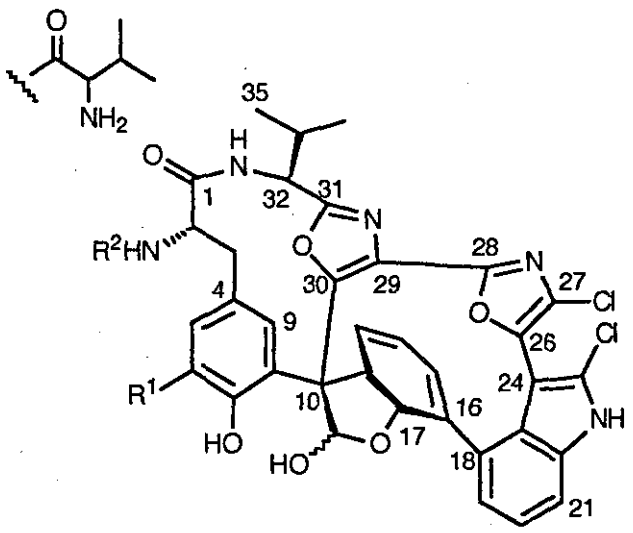
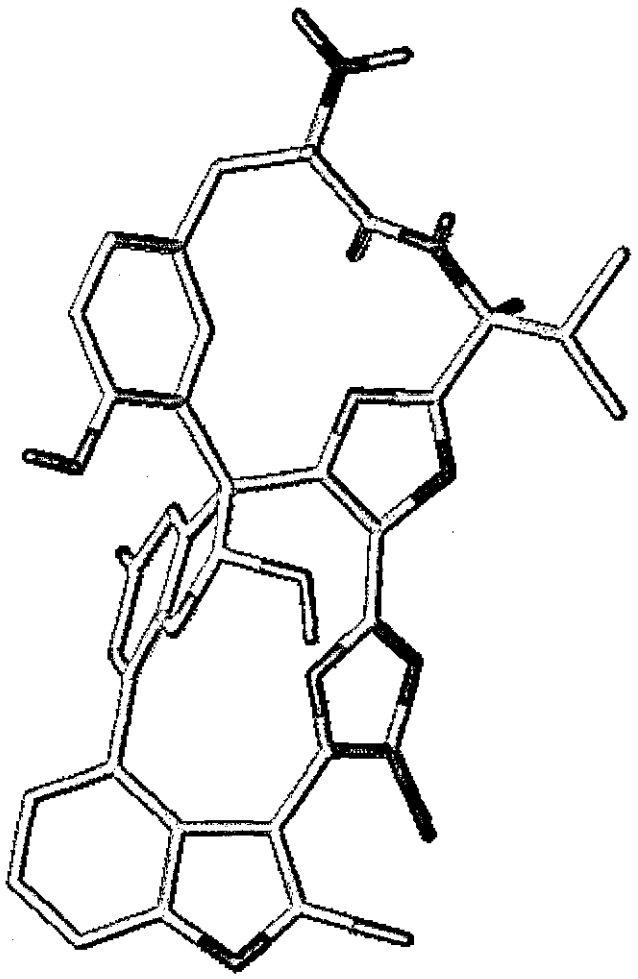


Figure 14

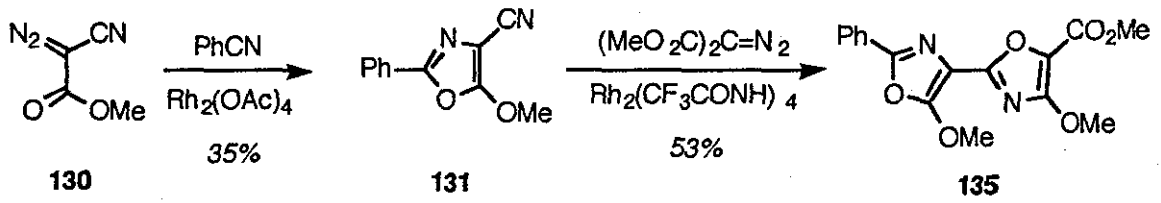
The diazonamides contain a bis-oxazole unit, directly linked through their 4- and 2-positions. Using rhodium carbenoid chemistry we have already shown an approach to this heterocyclic system (see Chapter 2.4). (Scheme 67).



Diazonamide B **6**

Derived from X-ray crystal structure of the 4-bromobenzamide derivative, obtained from the Cambridge Structural Database, (reference 11). This representation was visualised using the Sybyl Molecular Graphics package.

Figure 13



Scheme 67

There were three other areas into which synthetic studies were undertaken. The first being the oxazolylindole portion, C18 to C28, the next being the oxazole based around valine i.e. C29 to N5 and thirdly the benzofuranol, C10 to C17. These studies will be discussed in turn. (Figure 15).

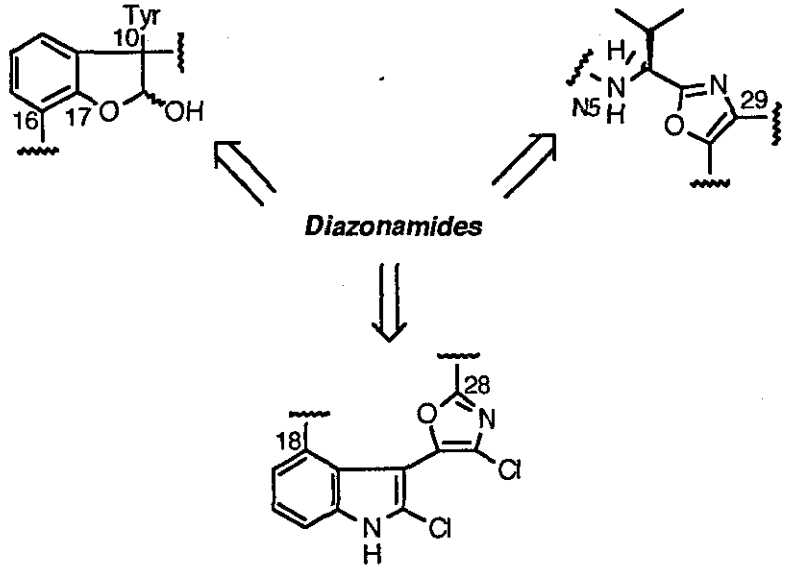


Figure 15

4.2 Oxazolylindole Section.

4.2.1 Introduction

In the synthesis of the alkaloids pimprinine **1a**, pimprinethine **1b** and WS-30581A **1c**, it has been shown that the oxazolylindole skeleton can be prepared by rhodium carbenoid methodology, as described in Chapter 3. In studies towards the diazonamides a more intricate system is required. This system has substitution at the 4-position and chlorination at the 2-position of the indole and chlorination at the 4-position of the oxazole. A simple model

system would involve aryl or halide substitution at the 4-position of the indole **172**, and chlorination at the 2-position of the indole **173**. (Figure 16).

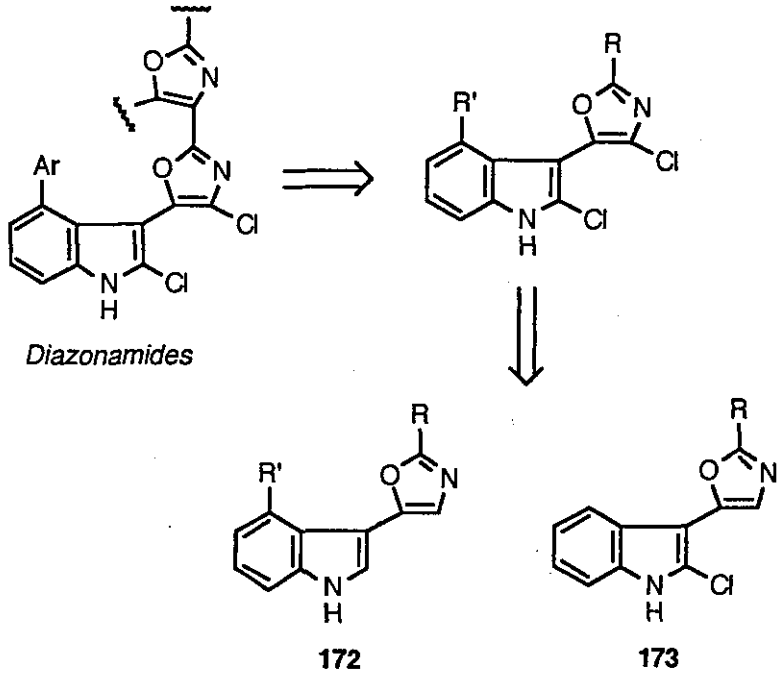
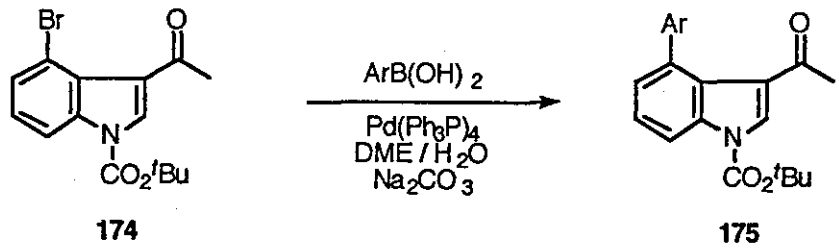


Figure 16

It was intended to prepare these oxazolylindole systems by rhodium carbenoid chemistry, the findings of which studies will now be discussed.

4.2.2 Studies into the 4-Substituted System.

Concerted work within the group has shown that *tert*-butyl 4-bromoindole-1-carboxylate **174** will undergo coupling with arylboronic acids under Suzuki conditions, yielding the 4-arylindole system **175** in good yield.[117] (Table 31).



174 **175**

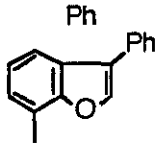
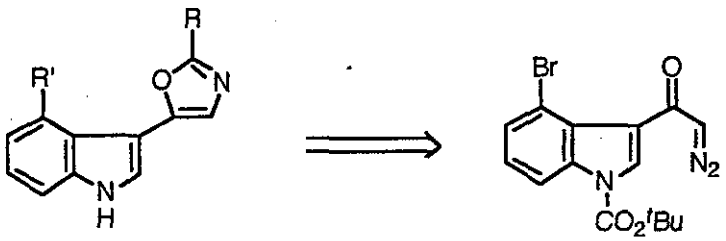
Ar	*Product*	*Yield (%)*
Ph	**175a**	66
	**175b**	80

Table 31

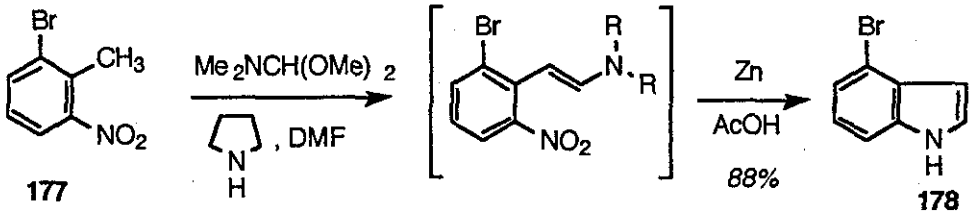
In conjunction with this work, it was thought that the 4-substituted system could be derived from a 4-bromo-3-oxazolylindole heterocycle. Preparation of this system *via* rhodium carbenoid chemistry would require the preparation of the brominated diazoketone **176a.** (Figure 17).



172 **176a**

Figure 17

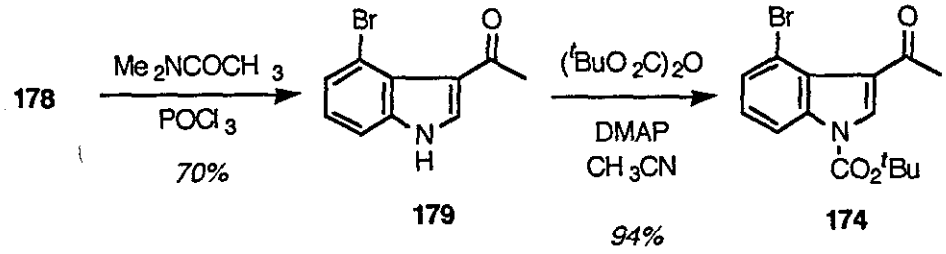
The diazoketone **176a** was synthesised in an analogous fashion to *tert*-butyl 3-diazoacetylindole-1-carboxylate **150a.** The starting indole, 4-bromoindole **178**, was prepared from 2-bromo-6-nitro toluene **177**, by a modified Batcho-Leimgruber process in 88% yield.[118] (Scheme 68).



177 **178**

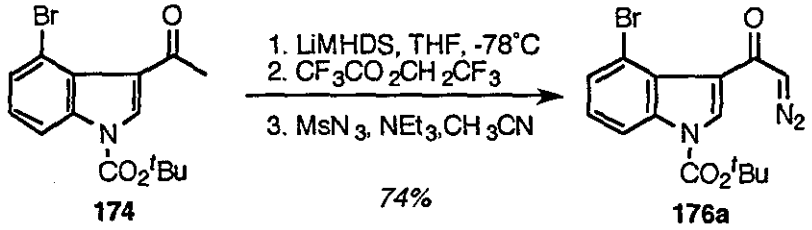
Scheme 68

This indole then underwent a Vilsmeier acetylation to yield 3-acetyl-4-bromoindole **179** in 70%. Protection of the indole nitrogen as its *tert*-butyl carbamate, gave *tert*-butyl 3-acetyl-4-bromoindole-1-carboxylate **174** in 94% yield. (Scheme 69).



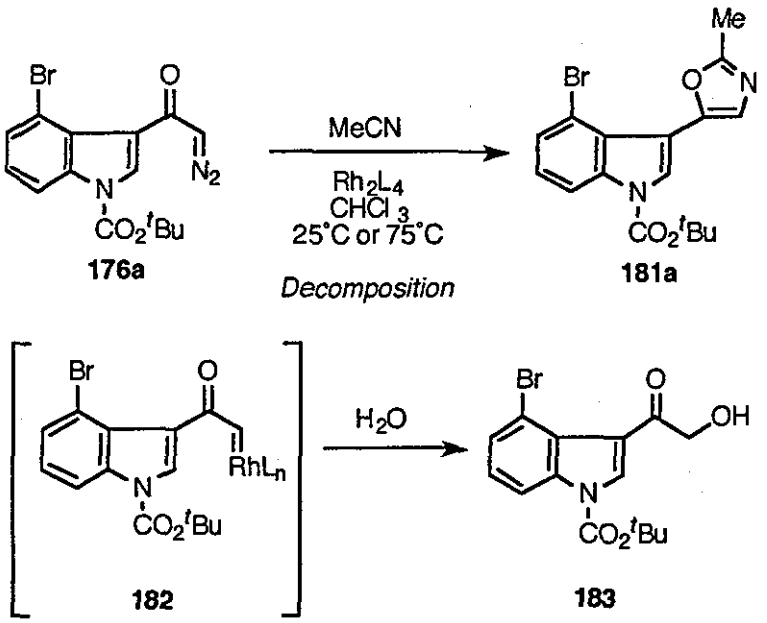
Scheme 69

tert-Butyl 3-acetyl-4-bromoindole-1-carboxylate **174** underwent diazo transfer, using the Danheiser conditions to give the expected diazoketone, *tert*-butyl 4-bromo-3-diazoacetylindole-1-carboxylate **176a** in 74% yield. (Scheme 70).



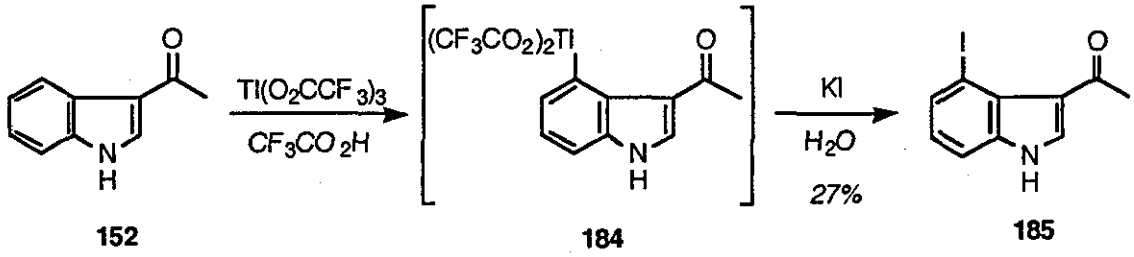
Scheme 70

The formation of oxazoles, using the diazoketone **176a** and acetonitrile, was investigated with a range of rhodium(II) catalysts. These reactions were conducted with the carboxylate catalysts, rhodium(II) acetate ($L=O_2CCH_3$) and rhodium(II) perfluorobutyrate ($L=O_2CC_3F_7$) **180** and the carboxamide rhodium(II) trifluoroacetamide ($L=CONHCF_3$) **124** . However, in each case the oxazole **181a** could not be isolated from the reaction mixture, with the diazoketone undergoing complete decomposition. Periodically the 1-hydroxy ketone **183** was isolated in low yield, probably derived from OH insertion into the intermediate carbenoid **182**, from adventitious water. (Scheme 71).

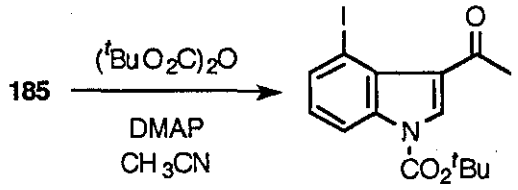


Scheme 71

It was thought that the presence of the bromine at the 4-position, was preventing oxazole formation. To test this hypothesis, the iodo equivalent of **176a** was prepared, starting from 3-acetylindole **152**. Iodination was achieved by initial formation of the 4-thallium(III) bis-trifluoroacetate **184**, by reaction with thallium(III) trifluoroacetate in trifluoroacetic acid.[119,120] This preference for thallation at the 4-position is rationalised by assuming first that thallium co-ordinates with the carbonyl group and secondly that the two-position is simply more deactivated. The crude intermediate **184**, was taken to the corresponding 4-iodo derivative **185** by treatment with aqueous potassium iodide, in 27% yield. (Scheme 72). Protection as the *tert*-butyl carbamate, gave *tert*-butyl 3-acetyl-4-iodoindole-1-carboxylate **186**, in 94% yield. (Scheme 73).

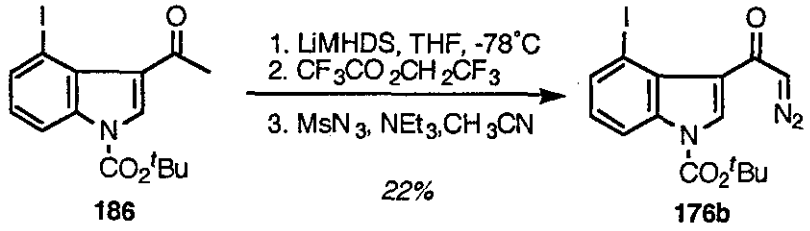


Scheme 72



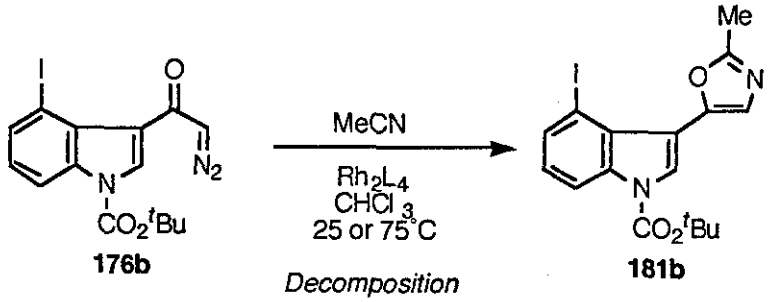
Scheme 73

The 4-iodo indole derivative **186** underwent diazo transfer, using the Danheiser conditions, to yield 3-diazoacetyl-4-iodoindole-1-carboxylate **176b**, in 22%. The diazoketone was found to be contaminated with traces of methanesulfonyl azide. (Scheme 74).



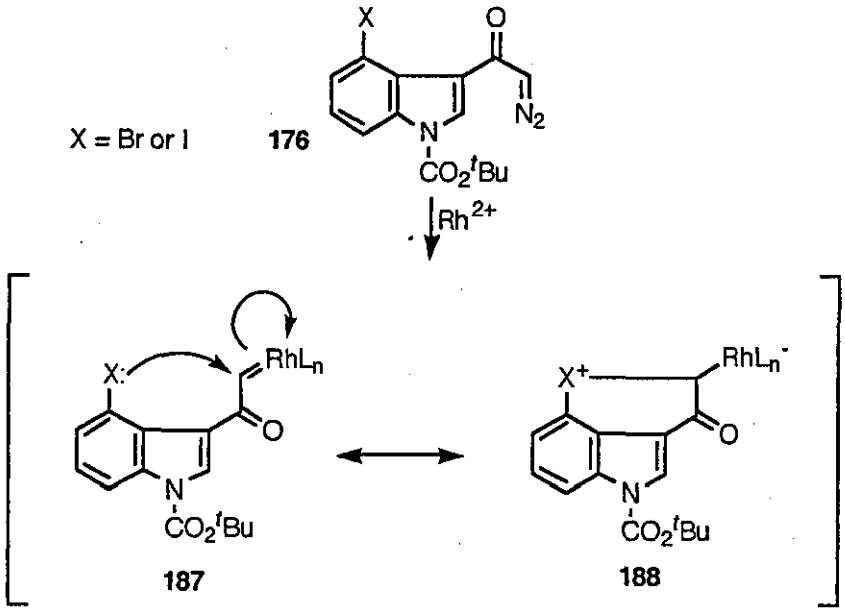
Scheme 74

However, as with the bromo diazoketone **176a**, the iodo diazoketone **176b** could not be made to undergo oxazole formation. In this case, unlike in the case of **176a**, no discernible products could be isolated. The reactions were conducted with acetonitrile, using either the carboxamide catalyst, rhodium(II) trifluoroacetamide (L=$CONHCF_3$) **124** or the modified carboxylate catalyst, rhodium(II) perfluorobutyrate (L=$O_2CC_3F_7$) **180**. (Scheme 75).



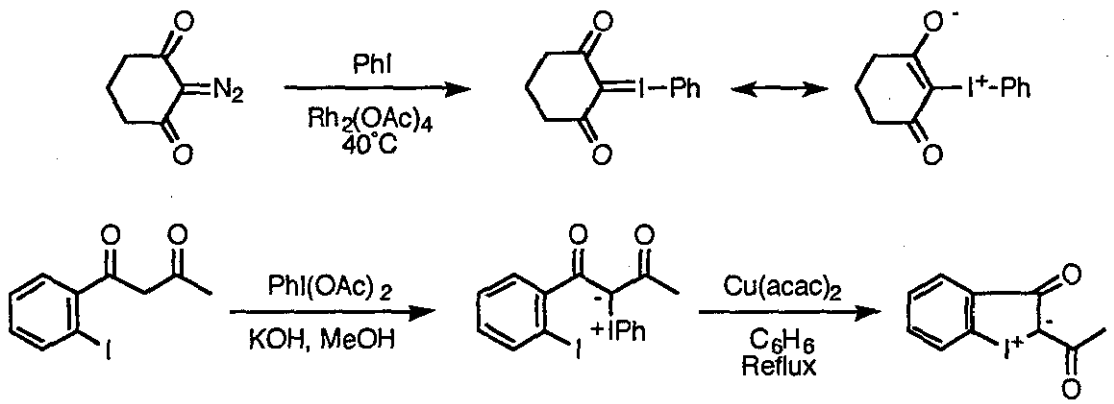
Scheme 75

The failure of the diazo ketones **176** to undergo oxazole formation, when the unsubstituted equivalent **150a**, reacts, may be due to several factors. The stereoelectronic effect arising from halide substitution on the 4-position, may be lowering the reactivity of the diazo ketone functionality. There is also the theoretical possibility of the intermediate rhodium carbenoid **187** undergoing ring closure, *via* the aryl halide, to give a 6-membered halonium ylide **188.** This may have some form of stabilisation *via* back-bonding into the vacant d-orbitals of the halide cation. This stabilisation may prevent oxazole formation, and in the case of **176a**, undergo OH insertion upon work-up, yielding the hydroxy ketone **183.** (Scheme 76).



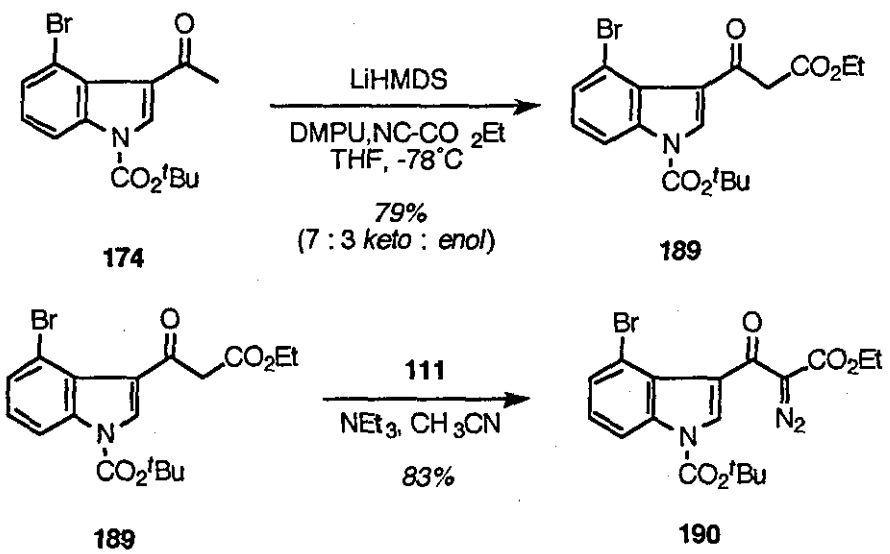
Scheme 76

There is precedence in the literature for the formation of halonium ylides by the interaction of halides and ketocarbenes. Intermolecular formation of an iodonium ylide, by the capture of aryl iodides by a ketocarbene, generated by rhodium(II) acetate, has been reported by Moriarty *et al.*[121] An example of intramolecular ylide formation is detailed by Dai *et al.*[122] In this system, the ketocarbene, generated by an unprecedented transylidation, is trapped to form the cyclic stable iodonium ylide. Representative examples are shown. (Scheme 77).



Scheme 77

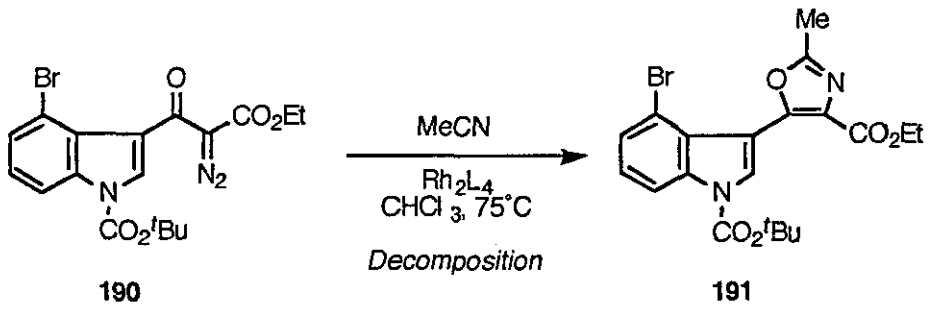
In an analogous fashion to the 2-keto-1-diazo ester, **163a** as outlined in Chapter 3.3, the 4-bromo derivative was prepared, in two steps, from *tert*-butyl 4-bromo-3-acetylindole-1-carboxylate **174**. The first step involved the formation of the 2-keto ester **189**, by deprotonation of **174** by LiHMDS, and quenching of the anion with ethyl cyanoformate, yielding **189** in 79%. This 2-keto ester was isolated as a 7:3 ratio of *keto* : *enol* forms, as determined by proton nmr. The second step involved diazo transfer, using 4-acetomidobenzenesulfonyl azide **111** and triethylamine, in acetonitrile, giving the required 2-keto diazoester **190** in 83% yield. (Scheme 78).



Scheme 78

But as was found previously, with the 2-keto-1-diazo ester **163a**, the 4-bromo equivalent **190** could not be made to undergo oxazole formation to yield **191**. The reactions were attempted using acetonitrile, under rhodium(II) acetate ($L=O_2CCH_3$) and rhodium(II)

trifluoroacetamide (L=$NHCOCF_3$) **124** catalysis, at 75°C. Under the reaction conditions employed, no desired products could be isolated. (Scheme 79).

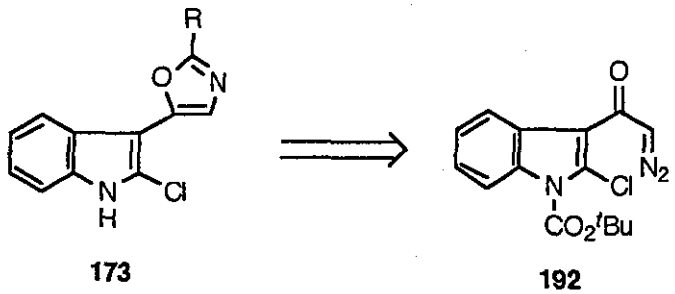


190 **191**

Scheme 79

4.2.2 Studies into the 2-Substituted System.

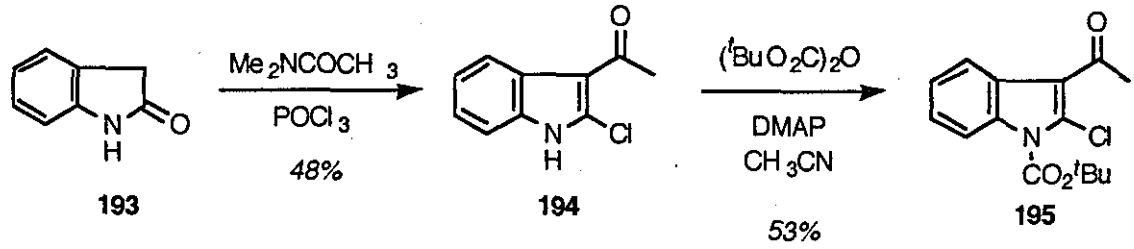
It was hoped to extend the chemistry of rhodium carbenoids into the preparation the model oxazolylindole compounds **173.** This study would involve the preparation of *tert*-butyl 2-chloro-3-diazoacetylindole-1-carboxylate **192**, and an investigation of its effectiveness in oxazole formation. (Figure 18).



173 **192**

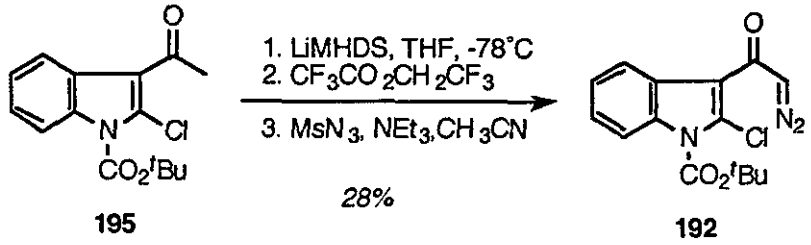
Figure 18

The intermediate, 3-acetyl-2-chloroindole **194**, was readily prepared by treating oxindole **193**, under Vilsmeier acetylation conditions, as outlined by Coppola and Hardtmann.[123] Treating oxindole with the reagent obtained from *N,N*-dimethyl acetamide and phosphorus oxychloride, yielded **194**, after work-up in 48% yield. Protection as the *tert*-butyl carbamate, gave **195** in 53% yield. (Scheme 80).



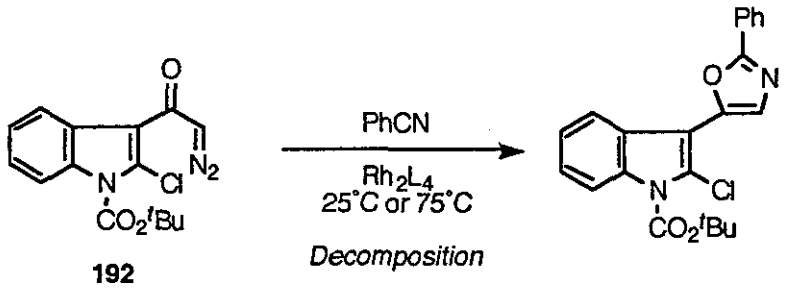
Scheme 80

tert-Butyl 3-acetyl-2-chloroindole-1-carboxylate **195** underwent diazo transfer, using the Danheiser conditions, to give *tert*-butyl 2-chloro-3-diazoacetylindole-1-carboxylate **192** in a low 28% yield. (Scheme 81).



Scheme 81

However, the diazo ketone **192** could not be made to undergo oxazole formation, but instead underwent decomposition under the conditions employed. For example, using benzonitrile, with either the carboxylate catalyst, rhodium(II) acetate ($L=O_2CCH_3$) or the carboxamide catalyst rhodium(II) trifluoroacetamide ($L=NHCOCF_3$) **124**, at 25°C and 75°C, resulted in no isolatable products. (Scheme 82).



Scheme 82

The failure for the diazoketone **192** to undergo oxazole formation may be influenced by several factors. Again there is the possibility of ylide formation, from the interaction of the diazoketone and the rhodium(II) catalyst. In this instance, the ylide would be the cyclic five membered chloronium ylide **196**. (Figure 19).

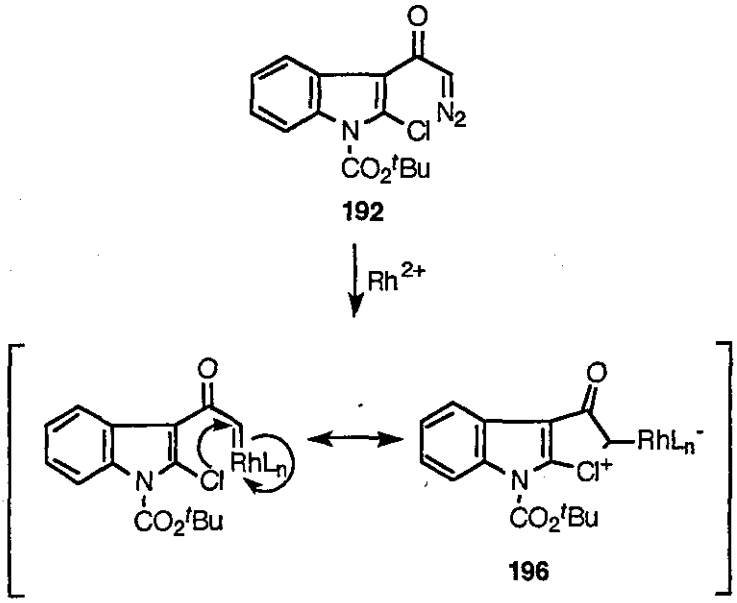


Figure 19

The intermediary of chloronium ylides in various processes has been shown by the use of spectroscopic techniques such as CIDNP,[124] and in the case of **197**, proven by an X-ray crystal structure.[125] (Figure 20).

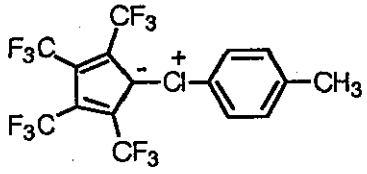


Figure 20

However, due to the size and polarisability of the postulated chloronium ylide and structural requirements of what is effectively a cyclopentene system, the intermediary of a chloronium ylide in the reactions of the diazoketone **192** would be hard to envisage.

4.2.3 Discussion

The diazoketone **150a** (R and R'=H) was found to undergo oxazole formation, under rhodium(II) catalysis, whilst the diazoketones **176a** (R=Br, R'=H), **176b** (R=I, R'=H) and **192** (R=H, R'=Cl) each failed to react under identical conditions. (Figure 21).

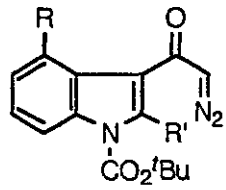
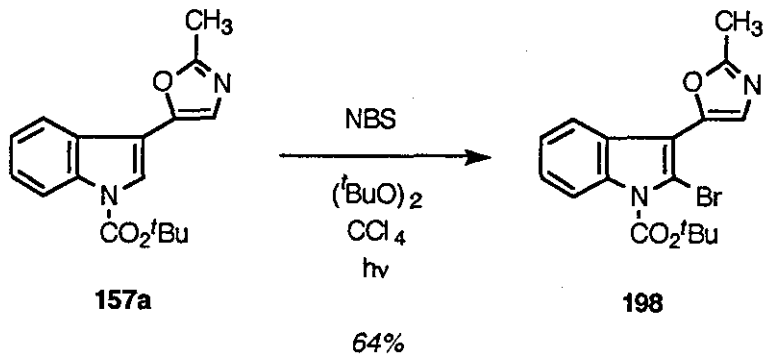


Figure 21

This failure was thought to arise from an interaction of the halide atom with the intermediate rhodium carbenoid. Due to lack of time, no other reaction conditions were investigated such as photolysis, Lewis acid catalysis or other transition metal salt catalysis. Use of one or more of these conditions may prove effective on the halogentated diazoketones.

A separate approach to the 2-chlorinated oxazole system **173** may come from the use of chlorination agents. Studies on 2-methyl-5-(3-(1-*tert* butoxycarbonylindolyl)oxazole **157a** showed that bromination could be achieved at the 2-position by use of *N*-bromosuccinimide (NBS), under photolytic conditions, yielding **198** in 64%. (Scheme 83).



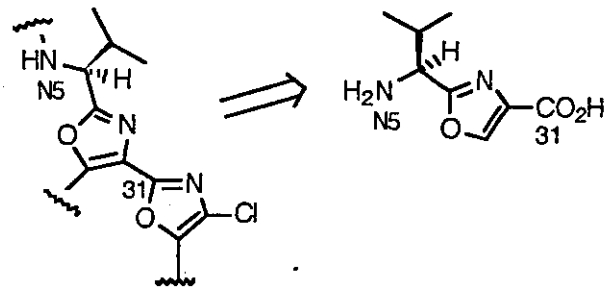
Scheme 83

Initial studies on this system using *N*-chlorosuccinimide yielded an inseparable mixture thought to contain the 2-chlorinated product and a product derived from chlorination on the aryl ring. Further investigations along this line may prove fruitful.

4.3 Valine Oxazole Portion.

4.3.1 Introduction

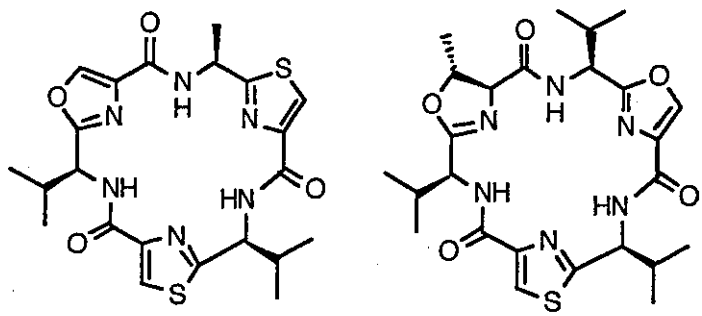
In the diazonamides, the oxazole portion, from C31 to N5 is based around (*S*)-valine. This heterocycle represented a new class of modified amino acids, not previously seen in the vast array of cyclic peptides, reported up to this time (1991).[126] (Figure 22).



Diazonamides

Figure 22

However this substructure was reported, in 1992 by Ireland *et al.*[127] in the macrocyclic hexapeptides, bistratamides C **199** and D **200**, isolated from the ascidian, *Lissoclinum bistratum.* (Figure 23).

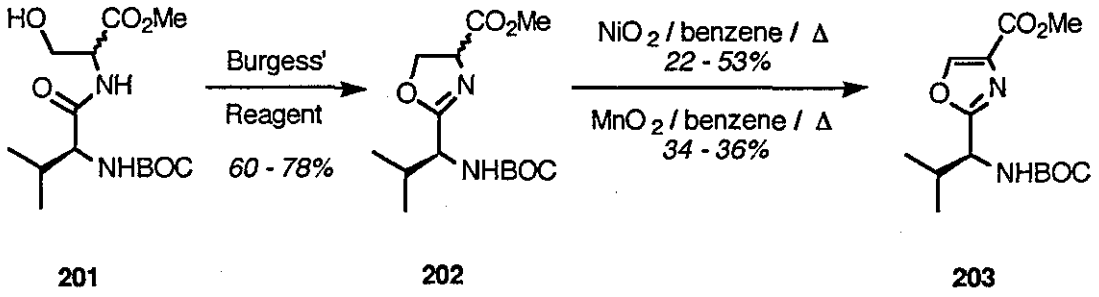


199 **200**

Figure 23

(-)-Bistratamide C **199** has recently succumbed to total synthesis by Meyers and Aguilar.[128] They prepared the modified oxazole amino acid **203** by, firstly, transformation to the oxazoline **202.** This was achieved by treating the valine-serine derived dipeptide **201** with

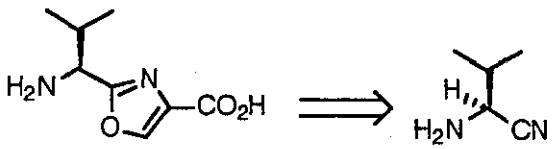
Burgess' Reagent, yielding **202** in 60 - 78%. Oxidation using either nickel(IV) oxide in benzene or manganese(IV) oxide in benzene gave the oxazole **203** in variable yield. (Scheme 84).



201 **202** **203**

Scheme 84

It was intended to prepare derivatives of this oxazole amino acid by use of rhodium carbenoid methodology. This would require the synthesis of a protected form of the nitrile based on (*S*)-valine, **204**, and to study its effectiveness of oxazole formation. (Figure 24).

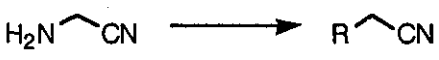


204

Figure 24

4.3.2 Preparation of (S)-Valine Nitrile.

Initial studies were carried out into the suitability of various protecting group on nitrogen, and their effect upon oxazole formation. The commercially available aminoacetonitrile (glycine nitrile) **205** was converted to the *N*-phthaloyl **206a**, *N-tert*-butoxycarbonyl **206b** and *N*-benzyloxycarbonyl **206c** protected forms, by conventional chemistry.[129] (Table 32).

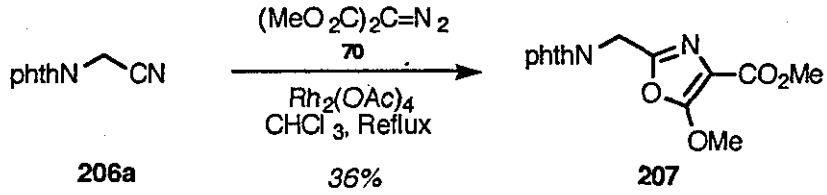


205 **206**

R	Nitrile	Yield (%)
phthN	**206a**	84
^{t}BuOCONH	**206b**	81
PhCH$_2$OCONH	**206c**	79

Table 32

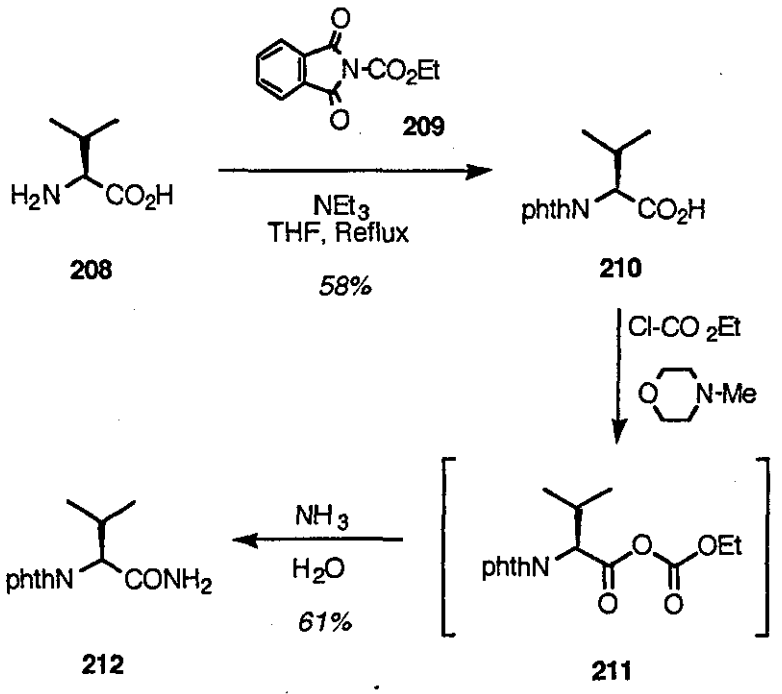
The ability of **206a** - **206c** to undergo oxazole formation was studied using dimethyl diazomalonate **70**. Of these, only **206a** was found to react, yielding the oxazole **207** in 36%. The reactions were conducted using rhodium(II) acetate as catalyst in refluxing chloroform. (Scheme 85).



206a *36%* **207**

Scheme 85

The aim was to prepare *N*-phthaloyl protected (*S*)-valine nitrile **213**, which was achieved in three steps from (*S*)-valine **208**. Reacting (*S*)-valine **208**, *N*-carboethoxyphthalimide **209** and triethylamine, in refluxing THF gave *N*-phthaloyl (*S*)-valine ($[\alpha]_D^{20}$ = -53.9, c=1.2, $CHCl_3$) **210** in 58% yield.[130] Conversion of **210** to the corresponding amide **212** was achieved in 61% yield by use of a mixed anhydride method.[131] The carboxylic acid **210** was added to a mixture of 4-methylmorpholine and ethyl chloroformate at -15°C to give the intermediate mixed anhydride **211**. Reaction of **211** with aqueous ammonia yielded the amide ($[\alpha]_D^{20}$ = +26.5, c=0.9, $CHCl_3$) **212**. (Scheme 86).



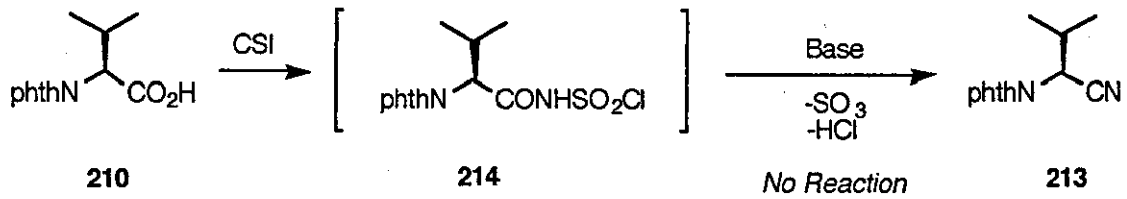
Scheme 86

Dehydration of the amide **212** lead to the isolation of the nitrile **213**. The reaction could be carried out with a variety of reagents. The use of tosyl chloride in refluxing pyridine gave **213** in 74% yield,[131] the use of trifluoroacetic anhydride and pyridine in THF at 0°C yielded **213** in 89%,[132] whilst use of Burgess' Reagent allowed the isolation of **213** in 87% yield.[133] The use of both tosyl chloride in pyridine and Burgess' Reagent in the preparation of α-chiral nitriles has been demonstrated in the literature.[131,133] (Table 33).

Reagent	*Yield (%)*	$[\alpha]_D$
TsCl / py. / Reflux	74	+18.6, c=1.3
$(CF_3CO)_2O$ / py. / THF/ 0°C	89	+20.6, c=1.9
Burgess' Reagent / THF / 0°C	87	+20.4, c=1.5

Table 33

It had been hoped to use the known reaction of chlorosulfonyl isocyanate (CSI) in the one step conversion of 1-chiral acids into 1-chiral nitriles.[134] The reaction works by formation of an intermediate *N*-chlorosulfonyl carboxamide **214**, which reacts under basic conditions to yield the nitrile. However application of this reaction on **210**, did not result in the isolation of the nitrile **213**. (Scheme 87).



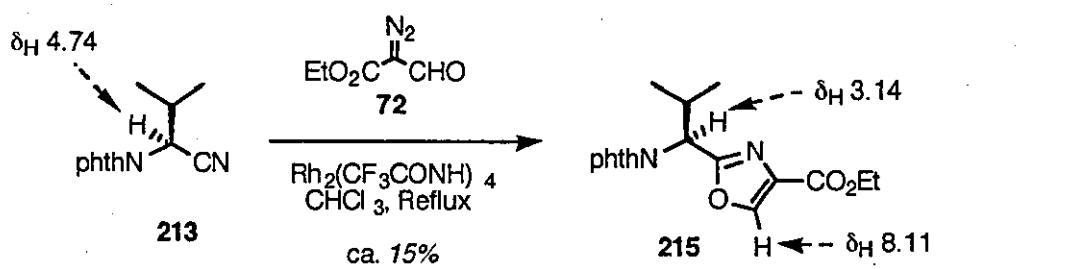
CSI = Cl-SO_2-N=C=O : Base = DMF, NEt_3 or ($^iPr)_2NEt$

Scheme 87

4.3.3. Studies of (S)-Valine Nitrile in Oxazole Formation.

The ability of the nitrile **213** to undergo oxazole formation with ethyl 1-formyldiazoacetate **72** and dimethyl diazomalonate **70** under rhodium catalysis was studied. The catalysts screened were the carboxylate catalysts, rhodium(II) acetate and rhodium(II) perfluorobutyrate **180** and the carboxamide catalyst rhodium(II) trifluoroacetamide **124**.

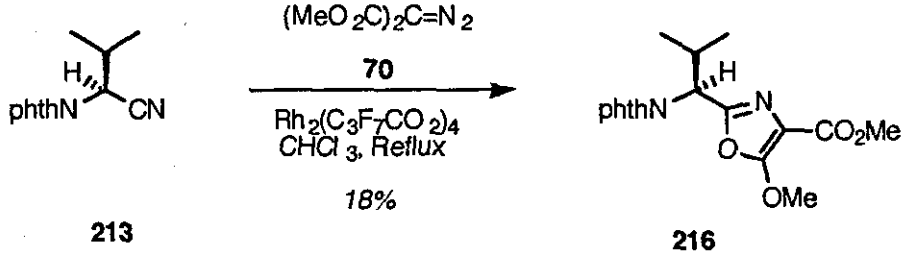
Analysis of the crude reaction mixture from the reaction between involving ethyl 1-formyldiazoacetate **72**, under rhodium(II) trifluoroacetamide **124** catalysis, by proton nmr showed that oxazole formation had taken place. However, the oxazole **215** could not be isolated from the reaction, in an analytically pure form. (Scheme 88).



Crude mixture : [$\alpha]_D^{20}$ = -23.4 (c=0.43, $CHCl_3$)

Scheme 88

In the reaction involving dimethyl diazomalonate **70**, the use of the modified carboxylate catalyst, rhodium(II) perfluorobutyrate **180**, allowed isolation of the oxazole **216** as an oil ($[\alpha]_D^{20}$ = -43.2, c=1.50, $CHCl_3$), in 18% yield. The oxazole was found to be contaminated with *ca.* 2% of an impurity, thought to be derived from OH-insertion into the diazomalonate. (Scheme 89).



213 **216**

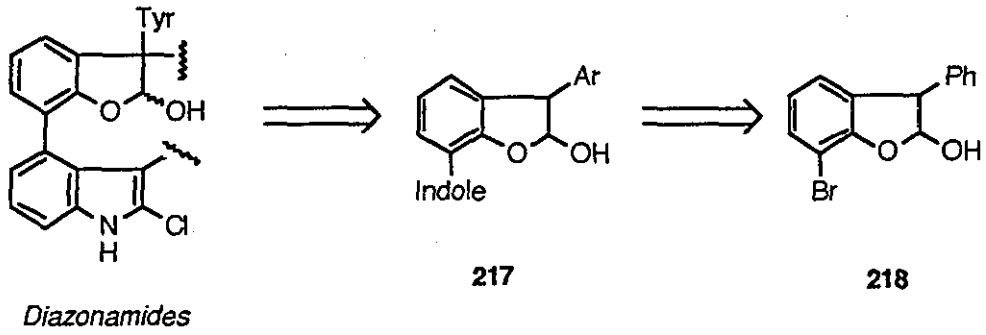
Scheme 89

Due to the isolation difficulties encountered, the optical purity of the heterocyclic systems **215** and **216** could not be determined. It seems that the ring formation did occur with some retention of chirality, as both systems showed an optical rotation.

4.4 Studies Towards the Benzofuranol Portion

4.4.1 Introduction

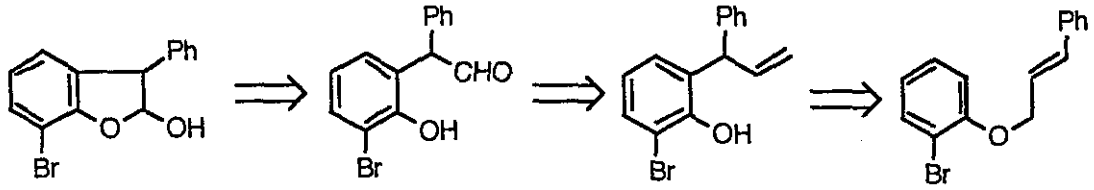
Analysis of the 2-benzofuranol section, C10 - C17, leads to the system **217.** Work within the group has shown that arylbromides, after conversion to the corresponding boronic acid, will undergo coupling, using Suzuki conditions, with 4-haloindoles.[117] On the basis of this work, the 2-benzofuranol **218** was deemed a suitable model system. (Figure 25).



217 **218**

Figure 25

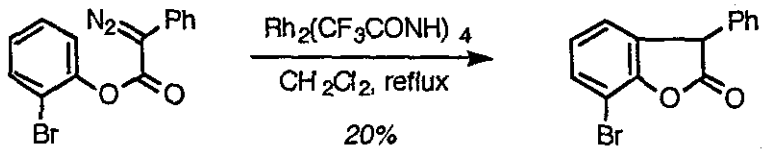
The 2-benzofuranol **218** can be formed by cyclisation of the corresponding phenolic aldehyde **219**. Ozonolysis on the phenol **220**, which in turn could be obtained from a Claisen rearrangement on the ether **221**, would possibly lead to the phenolic aldehyde, and hence the required benzofuranol. (Figure 26).



218 **219** **220** **221**

Figure 26

The corresponding 2-benzofuranone of **218**, 7-bromo-3-phenylbenzo[b]furan-2-one **223**, has previously been prepared within the group by the use of rhodium carbenoid methodology. This was achieved by aromatic C-H insertion of the diazoester **222**, using rhodium(II) trifluoroacetamide catalysis **124**, in 20% yield. (Scheme 90).

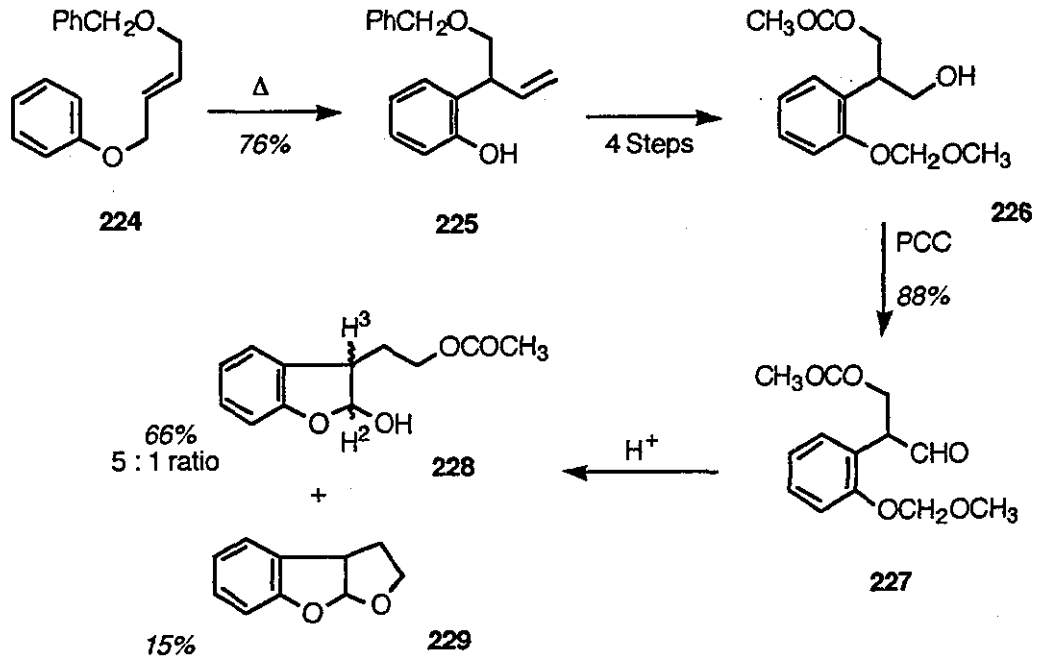


222 **223**

Scheme 90

It was intended for this Claisen approach to 2-benzofuranols as outlined above, to complement this existing chemistry.

A review of the literature shows only one previous study towards 2-benzofuranols, by the use of the Claisen rearrangement. In their studies of biogenetic precursors of aflatoxin B_1, Gorst-Allman and Steyn[135] used a Claisen rearrangement on the ether **224** to yield the phenol **225**, in 76%. Manipulation upon **225**, gave the alcohol **226**. Oxidation, using pyridinium chlorochromate (PCC) led to the aldehyde **227** in 88% yield. Acidic removal of the methoxymethyl group, gave the benzofuranol **228** in 66% yield, as well as a 15% yield of the tetrahydrobisfuran **229**. (Scheme 91).

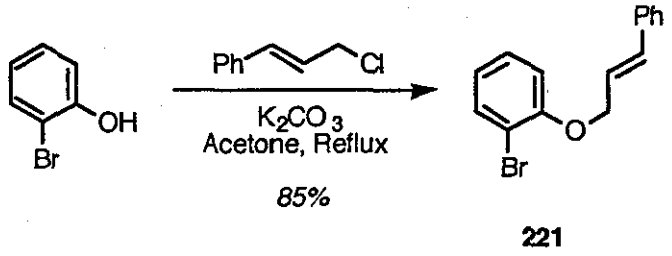


Scheme 91

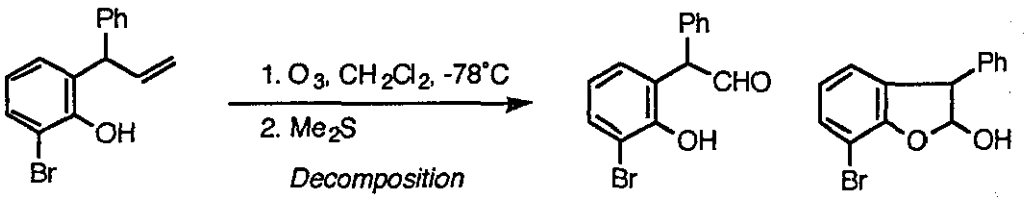
The authors found that the 2-benzofuranol **228** existed as two diastereomers, in *ca.* 5 :1 ratio. The major epimer had a 2.18 Hz coupling constant between H2 and H3, and the minor diastereomer had a coupling constant of 6.26 Hz. From these observations, they suggest that the hydroxy group is pseudoaxial in the major diastereomer, and pseudoequatorial in the minor diastereomer.

4.4.2 Synthetic Studies

The starting ether **221**, was readily prepared from 2-bromophenol and cinnamyl chloride, in 85% yield. (Scheme 92).



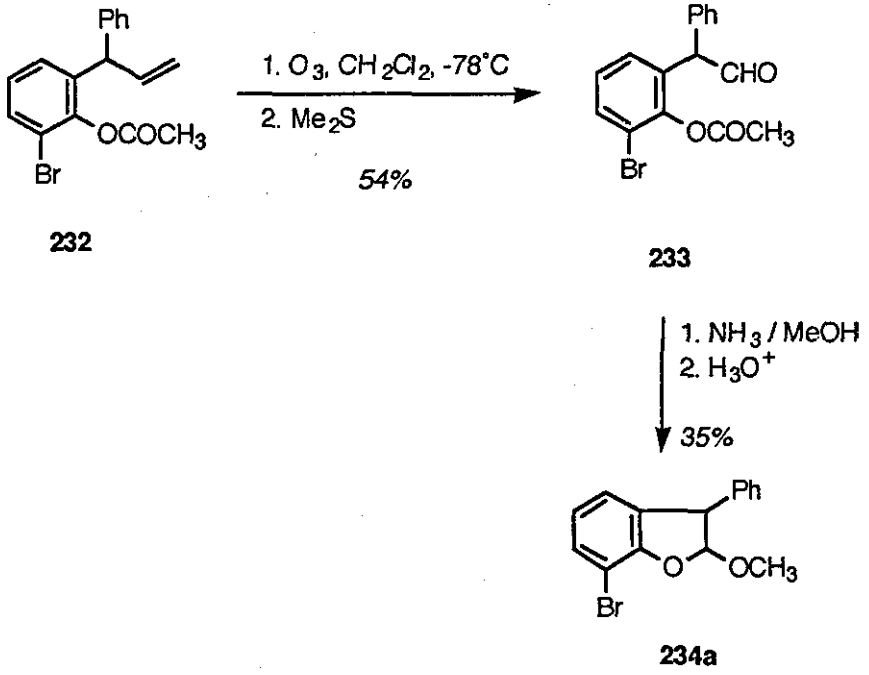
Scheme 92



220 **219** **218**

Scheme 95

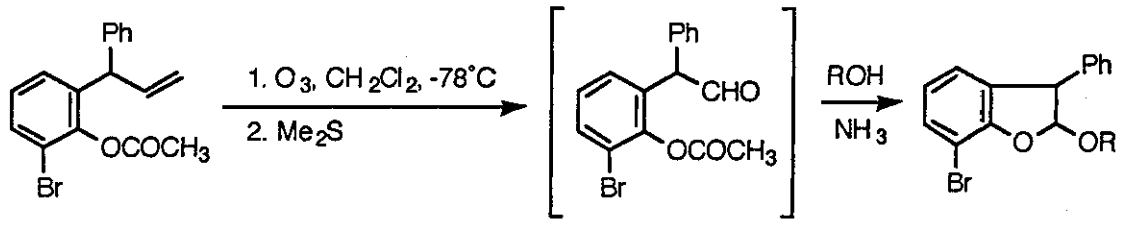
However, ozonolysis of the *O*-acetate **232**, followed by dimethylsulfide workup, allowed the isolation of the aldehyde **233** in 54% yield after chromatography. Unfortunately, this aldehyde was found to decompose rapidly making spectroscopic analysis difficult. Deprotection of the *O*-acetate group of **233**, using methanolic ammonia, yielded 7-bromo-2-methoxy-3-phenyl-2,3,-dihydrobenzo[b]furan **234a** in 35%. (Scheme 96).



232 **233** **234a**

Scheme 96

Instead of isolation of the intermediate aldehyde **233**, it was decided to deprotect the crude mixture after ozonolysis, without purification. The deprotection was attempted using both methanolic and ethanolic ammonia. This allowed isolation of the 2-methoxybenzofuranol **234a** in 36% and the 2-ethoxybenzofuranol **234b** in 15%, overall yields, over the three steps. (Scheme 97).



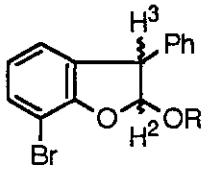
232 **233** **234**

R	*Product*	*Overall Yield (%)*
Me	**234a**	36 (19)[a]
Et	**234b**	15

[a] = yield with isolation of intermediate aldehyde

Scheme 97

Both **234a** and **234b** were found to have been formed as a mixture of diastereomers, in a ratio of 16 :1 for **234a**, and 20 : 1 for **234b**. The proton nmr data (250 MHz) for the major diastereomers is shown. (Table 36).

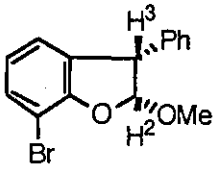


234

R	*System*	*Ratio*	*δH (ppm)*		*J (Hz)*	
		Major : Minor	H^2	H^3	H^2	H^3
Me	**234a**	16 : 1	5.59 (d)	4.65 (d)	6.2	6.4
Et	**234b**	20 : 1	5.71 (d)	4.63 (d)	6.5	6.3

Table 36

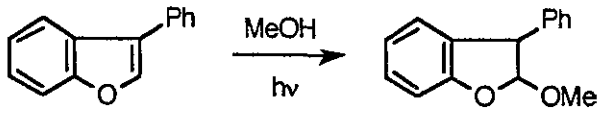
An nOe experiment on **234a** was conducted to determine the stereochemical relationship of the major diastereomer. Irradiation of the doublet at 5.59 ppm, corresponding to the CH at the 2-position, caused an enhancement of 4.4% on the doublet at 4.65 ppm, which corresponds to the CH at the 3-position. This result suggests the major diastereomer obtained is of *cis* relationship between the two hydrogens at the 2- and 3-position. (Figure 27).



(±) *cis*-**234a**

Figure 27

The debrominated equivalent of **234a**, 2-methoxy-3-phenyl-2,3-dihydrobenzo[b]furan **236**, has been prepared by Arnold *et al.*[137] by the photolysis of 3-phenylbenzo[b]furan **235** in methanol. (Scheme 98).

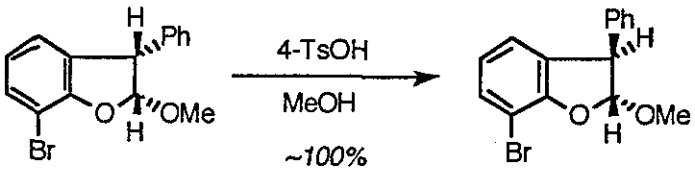


235 **236**

Scheme 98

The benzofuranol **236** was found to exist as a mixture of diastereomers, described as *cis* and *trans*. These isomers were separable by chromatography, the *trans* isomer having a coupling constant of 2.4 Hz, whilst the *cis* isomer has a coupling constant of 6.5 Hz. This is in agreement with the coupling constants observed with **234a** and **234b**.

Dissolving *cis*-**234a** and 4-toluenesulfonic acid in methanol, and allowing to stand for seven days caused conversion into the other diastereomer. This time the ratio was 27 : 1, in favour of the previously 'minor' diastereomer. Analysis of the *trans* isomer by δ_H (250 MHz) showed a doublet at 4.45 (J = 2.1 Hz) and a doublet at 5.52 (J = 2.5 Hz), showing that this is the *trans* isomer. Since the *cis* isomer, under acid catalysis, had transformed to the *trans* isomer it can be postulated that the *trans* isomer is the thermodynamically favoured diastereomer. (Scheme 99).

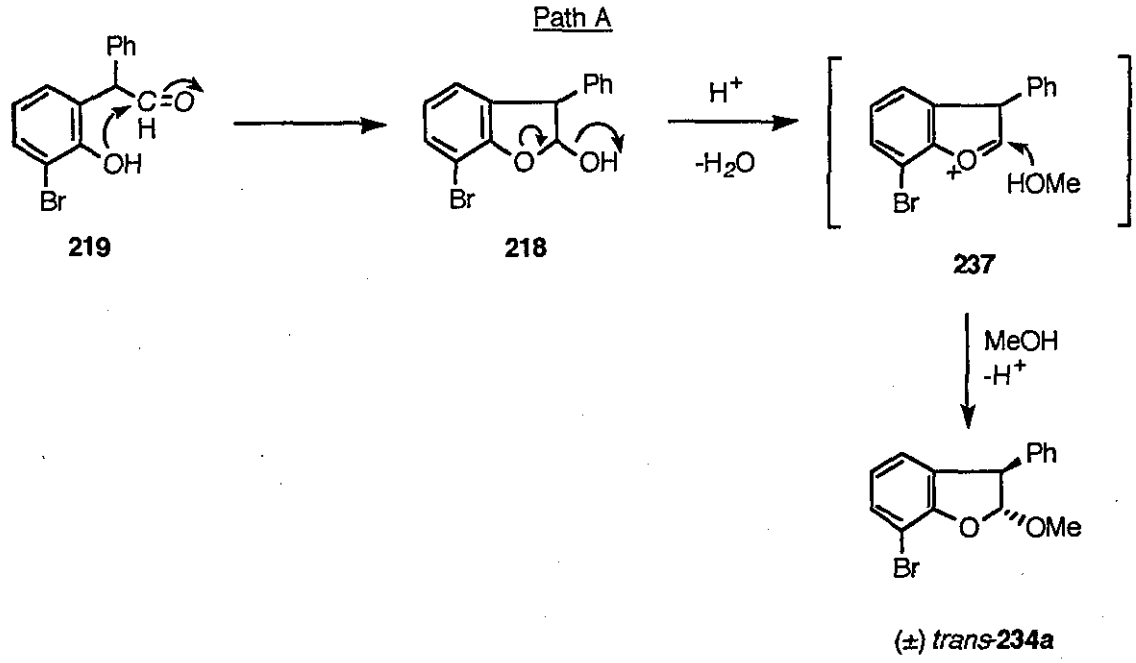


(±) *cis*-**234a** (±) *trans*-**234a**

Scheme 99

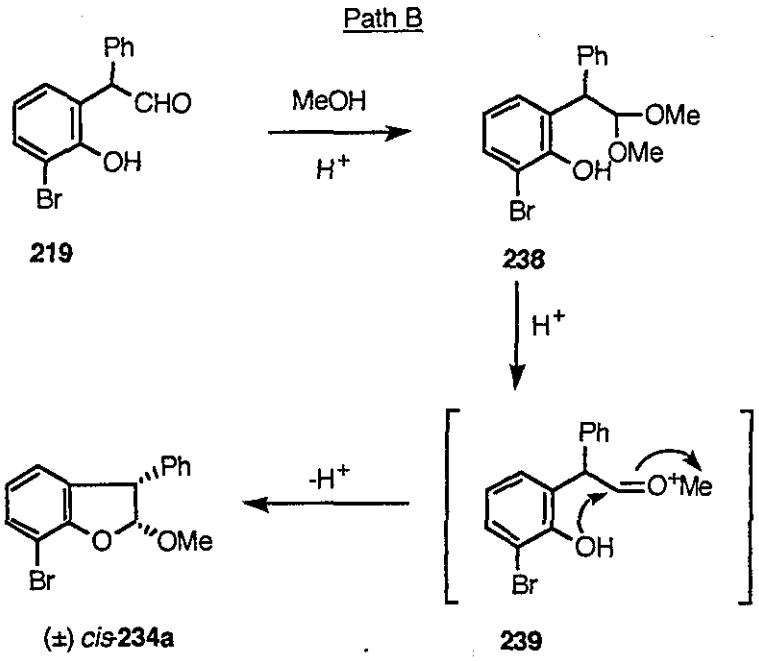
An nOe experiment conducted on *trans*-**234a** confirmed the assigned stereochemical relationship of H2 and H3. Irradiation of the doublet at 5.52, corresponding to the CH at the 2-position caused no enhancement of the doublet at 4.45, the H3 proton, giving agreement with the assignment of a *trans* relationship.

Since the *trans* isomer is thermodynamically favoured, the initial formation of the *cis* isomer must be conducted under kinetic conditions. It is assumed that there is initial deprotection of the O-acetate **233** yielding the phenolic aldehyde **219**. This system then undergoes cyclisation, yielding (±) *cis*-**234a**, as the kinetic isomer. There are two possible mechanisms for this cyclisation. Path A involves intramolecular attack of the phenol upon the aldehyde, giving the 7-bromo-2-hydroxy-2,3-dihydrobenzo[b]furan **218**. This undergoes acid catalysed displacement leading to the cyclic oxonium ion **237**. Nucleophilic attack by the methanol gives **234a**. However, this attack would occur, preferably, from the least hindered side, i.e. that opposite the phenyl group at C3, leading to the *trans* isomer as the favourable product. (Scheme 100).



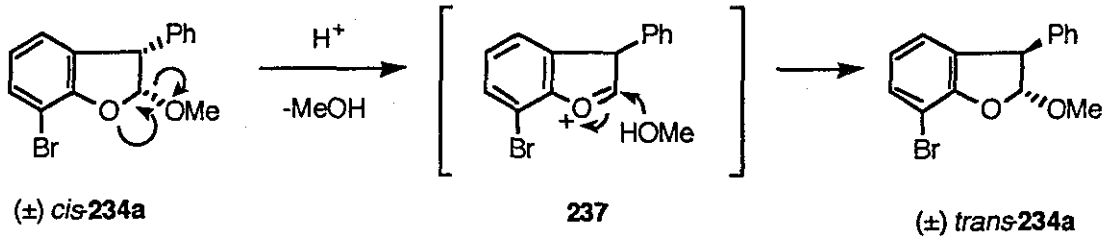
Scheme 100

Path B involves formation of the methoxyoxonium ion **239**, probably *via* the intermediate acetal **238**. This oxonium ion would undergo an intramolecular *exo*-cyclisation by the phenol, leading to **234a**. The cyclisation would take place from the least hindered side of the oxonium ion, i.e. on the opposite side to the phenyl group at C3 giving the *cis* isomer as the favourable product. (Scheme 101).



Scheme 101

The diastereomer ratio after the ozonolysis is in favour of the *cis*-isomer, whilst the preferred thermodynamic product is the *trans*-isomer. It seems plausible then, that path B is in operation on the phenolic aldehyde **219** faster than path A, leading to the initially formed kinetic isomer, (±) *cis*-**234a**. The transformation of the *cis* isomer to the *trans* under thermodynamic conditions, probably occurs by a mechanism similar to that described in path A. Under acidic conditions, the methoxy group is displaced giving the intermediate cyclic oxonium ion **237**. Intermolecular attack of the methoxy group will occur on the opposite side to the phenyl group at C3, leading to the thermodynamically preferred, *trans* isomer. (Scheme 102).



Scheme 102

It was intended for a system incorporating tyrosine, or a model for it, to partake in this Claisen rearrangement route to the benzofuranol skeleton, to provide a diazonamide mimic. Unfortunately, time was not available to bring this to fruition.

4.5 Conclusion.

Unlike in the case of the oxazolylindole alkaloids, **1a** - **1c**, the preparation of a functionalised oxazolylindole system by the use of rhodium carbenoid methodology proved elusive. One of the possible explanations for this was an interaction of the halide atom with the diazo group forming an cyclic halonium ylide, although this was unproven. It is hoped, however, that other methods of ketocarbene formation may allow preparation of these functionalised oxazolylindole systems

The formation of oxazoles, by use of a rhodium(II) catalysed reaction, has allowed the preparation of oxazoles based around (*S*)-valine. This involved the synthesis of a protected form of (*S*)-valine nitrile. Due to isolation difficulties encountered, and the lack time, these heterocyclic systems were not investigated further.

A Claisen rearrangement approach to benzofuranols allowed the synthesis of a model system, based on the diazonamides. A one step deprotection and cyclisation led to the synthesis of a protected benzofuranol. It was hoped to incorporate tyrosine, or a model for it, in this system, but lack of time prevented this study.

Chapter 5

Experimental

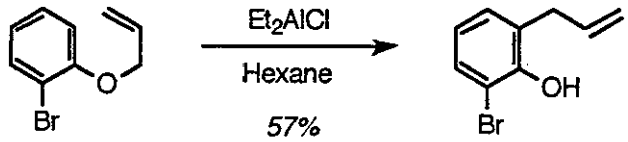
5.1 General Information.

Solvents and Reagents: Commercially available solvents and reagents were used throughout without further purification, except for those described below which were purified as described. 'Light petroleum' refers to the fraction boiling between 40 and 60°C, and was distilled through a 36 cm Vigreux column before use. Ethyl acetate was distilled, from calcium chloride, through a 36 cm Vigreux column before use. Xylene, mesitylene and toluene were dried where necessary by storage over sodium wire for several days. Both diethyl ether, referred to as 'ether', and THF were distilled from sodium benzophenone ketyl under nitrogen, prior to use. Dichloromethane was distilled from phosphorous pentoxide. DMF was dried by stirring over calcium hydride for 15 h, decanted, and distilled under reduced pressure before storage over activated 4 Å molecular sieves under nitrogen. Pyridine and triethylamine were distilled from, and stored over, potassium hydroxide pellets. Methanol and ethanol were distilled from magnesium turnings and iodine, and stored over activated 4 Å molecular sieves under nitrogen. Ethanol-free chloroform was used, and distilled from phosphorous pentoxide when necessary. Acetonitrile was distilled from phosphorous pentoxide, before storage over activated 4 Å molecular sieves under nitrogen. *N,N*-Dimethylaniline was freshly distilled before use.

Chromatographic Procedures: Analytical thin layer chromatography was carried out using aluminium-backed plates coated with Merck Kieselgel 60 GF_{254}. Plates were visualised under UV light (at 254 and/or 360 nm) or by staining with 'vanillin dip' or phosphomolybdic acid reagent, followed by heating. Flash chromatography, referring to the technique described by Still *et al.*,[138] was carried out using Merck Kieselgel 60 H silica or Sorbsil C 60 silica gel. Pressure was applied at the column head with hand bellows. Samples were applied as saturated solutions in an appropriate solvent. Dry flash chromatography refers to the technique as described by Harwood.[139]

Spectroscopic techniques: IR spectra were recorded in the range 4000-600 cm^{-1} using a Nicolet FT-205 spectrometer, with internal calibration. Spectra were recorded as either solutions in chloroform, deuterochloroform or thin films, between sodium chloride plates, or as KBr discs. Elemental analyses were carried out on a Perkin-Elmer 2400 Elemental Analyser. ^{1}H and ^{13}C NMR spectra were recorded using Bruker AC-250 and Bruker WH-400 (SERC NMR Spectroscopy Centre, Warwick) instruments. ^{1}H spectra are referenced against residual undeuterated solvent; in the case of deuterochloroform this is 7.260 ppm. Signals are described as multiplets (m), singlets (s), doublets (d), triplets (t), double doublets (dd) etc.; J values are recorded in Hz. In ^{13}C spectra CX signifies a quaternary peak. High- and low-resolution mass spectra were recorded on a Kratos MS80 instrument or on a VG

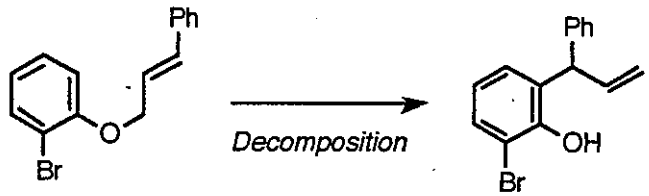
A study initially on *O*-allyl-2-bromophenol **230** had shown that the Claisen rearrangement by thermolysis, either neat or in mesitylene was unsuccessful. The rearrangement took place, however, by use of the Lewis acid, diethylaluminium chloride, at room temperature, allowing the isolation of the 2-bromophenol **231**, in 57% yield. (Scheme 93).



230 **231**

Scheme 93

Unfortunately, translating these conditions to **221** in an attempt to initiate the Claisen rearrangement proved unsuccessful. The use of diethylaluminium chloride or thermolysis, either neat or in mesitylene, caused decomposition of the allyl ether. (Table 34).



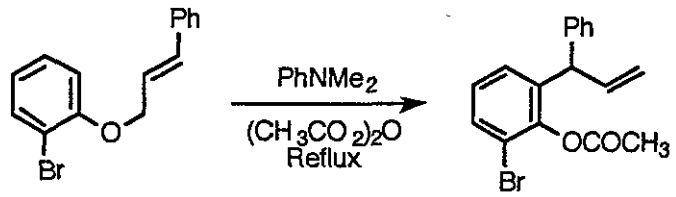
221 **220**

Conditions	*Yield (%)*
Et_2AlCl, Hexane	0
Δ, neat	0
Δ, mesitylene	0

Table 34

Claisen rearrangement of ethers which bear γ-alkyl substituents are often complicated by further rearrangements of the initial phenolic product, the so-called abnormal Claisen rearrangement. However, these subsequent rearrangements can be prevented if an efficient trapping agent is employed to intercept the initial phenolic product. Although **221** does not bear any γ-alkyl substituent, and hence should not participate in any further sigmatropic process, the formation of the phenolic group is thought to be detrimental to the outcome of the initial rearrangement.

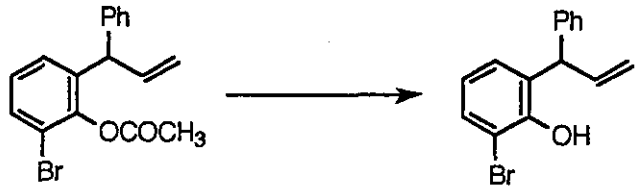
Acetic anhydride, in *N,N*-dimethylaniline (1 : 1 v/v) has been shown to be an effective trapping agent,[138] allowing the isolation of 'normal' Claisen products, as their *O*-acetate. This system proved effective upon the ether **221**, yielding the *O*-acetate **232** in 81% yield. (Scheme 94).



221 **232**

Scheme 94

Deprotection of the *O*-acetate **232** to the phenol **220** using sodium hydrogencarbonate in methanol proved ineffective, but was achieved using methanolic ammonia in 89% yield. (Table 35).



232 **220**

Conditions	*Yield (%)*
$NaHCO_3$ / MeOH	0
NH_3 / MeOH	89

Table 35

Ozonolysis of the phenol **220** in dichloromethane at -78°C, using the neutral work-up of dimethylsulfide on the intermediate ozonide, resulted in decomposition. Neither the aldehyde **219** or the benzofuranol **218** could be isolated. (Scheme 95).

Analytical ZAB-E instrumental (SERC Mass Spectrometry Service, Swansea), low-resolution mass spectra were also recorded on a Fisons GC-MS 800. Melting points were measured on a Reichert-Kofler hot stage apparatus or on an Electrothermal digital melting point apparatus and are uncorrected.

5.2 General Reagents.

Rhodium(II) trifluoroacetamide ***124***

Prepared by adaptation of a procedure, as described by Bear *et al.*[85] Rhodium(II) acetate and trifluoroacetamide (100 equiv.) were placed in a flask, placed in a heated oil bath (*ca.* 150°C), put under vacuum and stirred for 6 h. After this time an equal ammount of trifluoroacetamide was added, and the mixture stirred for a further 6 h. The purple solid remaining, was removed and sublimed *in vacuo*, to remove excess trifluoroacetamide, and then purified by flash chromatography (eluant ethyl acetate : light petroleum). The remaining solid was then recrystallised (methanol or acetone / water) and dried under vacuum, yielding the *title compound* as a sky blue solid.

$$Rh_2(OAc)_4 \longrightarrow Rh_2(NHCOCF_3)_4$$

Rhodium(II) perfluorobutyrate ***180***

Prepared by the procedure as described by Drago *et al.*[140] Rhodium(II) acetate was refluxed in a solution of perfluorobutyric acid : perfluorobutyric anhyride (10 : 1 v/v) for 15 min under a nitrogen atmosphere. Excess solvent was removed by distillation, and the remaining solution was cooled to -20°C for 24 h. The resultant dark blue solid was filtered, washed with cold pentane, recrystallised from toluene and dried *in vacuo*, over NaOH. This yielded the *title compound* as a yellow-green solid, which readily picks up water from the atmosphere to form a blue adduct.

$$Rh_2(OAc)_4 \longrightarrow Rh_2(C_3F_7CO_2)_4$$

4-Acetomidobenzenesulfonyl azide ***111***

Prepared by the procedure as described by Davies *et al.*[78] To a stirred solution of 4-acetomidobenzenesulfonyl chloride (50.0 g, 214 mmol) in acetone (500 mL) was added sodium azide (**CAUTION**; 14.9 g, 1.1 equiv.) as a solution in water (150 mL). After stirring for 18 h, the reaction mixture was poured into a stirred solution of water (1000 mL). A colourless precipitate formed, which was collected by filtration, washed with water (3 x 100

mL), and dried over phosphorous pentoxide *in vacuo.* Recystallisation from toluene gave the *title compound* as a colourless solid (35.4 g, 69%); spectral data identical to that given.

1-Ethyl-2-chloropyridinium tetrafluoroborate ***113***

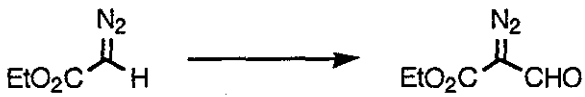
Prepared by the procedure as described by Monteiro.[79] A solution of triethyloxonium tetrafluoroborate[141] (17.0 g, 90 mmol) in DCM (50 mL) was stirred at 0°C, under a nitrogen atmosphere. To this was added 2-chloropyridine (10.2 g, 1 equiv.) dropwise over 20 min, then the reaction mixture was heated to reflux for 1 h. After cooling ether (20 mL) was added, and the mixture stirred at 0°C for 3 h, after which time a crystalline mass had formed. The supernatant liquid was removed *via* use of a cannula, and the resultant solid collected by filtration and washed with ether (2 x 10 mL). Drying *in vacuo* gave the *title compound* as a hygroscopic colourless solid (18.6 g, 90%); spectral data identical to that given.

Dimethyl diazomalonate ***70***

To a solution of dimethyl malonate (5.0 g, 37.8 mmol) and 4-acetomindobenzenesulfonyl azide **111** (10.0 g, 1.1 equiv.) in acetonitrile (100 mL) at 0°C was added triethylamine (6.33 mL, 1.2 equiv.) dropwise. After stirring for 16 h, the solution was concentrated *in vacuo*, and the resultant solid was washed with ether : light petroleum (4 x 75 mL, 1 :1 v/v). The combined organics were concentrated under reduced pressure, and purified by flash chromatography (eluant ethyl acetate : light petroleum) This yielded the *title compound* as a low melting yellow solid (4.9 g, 82%), $\nu_{max.}$ (thin film) 2147, 1739 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 3.87 (3 H, s, CH_3); δ_C (62.9 MHz: $CDCl_3$) 52.2 (CH_3) (diazo and carbonyl carbons not observed).

Ethyl 1-formyldiazoacetate ***72***

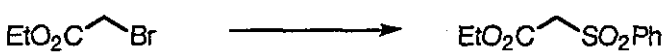
Prepared by a modified procedure as described by Helquist *et al.*[67] To a stirred solution of (chloromethylene)dimethylammonium chloride (5.0 g, 39 mmol) in chloroform (19.5 mL, 2.0M solution) was added ethyl diazoacetate (8.21 mL, 2 equiv.) over 45 min, keeping the temperature around 0°C. After the addition was complete, the solution was stirred for 1 h, then concentrated *in vacuo.* and the oily residue obtained was extracted with ether (5 x 75 mL). The combined organics were washed with brine (50 mL), $NaHCO_3$ (10%, 2 x 30 mL), water (50 mL) and dried ($MgSO_4$). Concentration under reduced pressure, followed by purification by bulb-to-bulb distillation (bath temp. 65°C @ 0.8 mmHg) gave the *title compound* as a pale yellow oil (1.39 g, 25%); spectral data identical to that given.



5.3 Chapter 2 Experimental.

Ethyl benzenesulfonyl acetate ***110***

A solution of ethyl bromoacetate **109** (5.0 g, 30 mmol) and benzenesulfinic acid, sodium salt (5.9 g, 1.2 equiv.) in ethanol (200 mL) was refluxed for 3 h. Excess solvent was removed *in vacuo*. The remaining precipitate was dissolved in ether (200 mL) and washed with water (2 x 200 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The product was then recrystallised from dichloromethane to give the *title compound* as a colourless crystalline solid (5.92 g, 86%), m.p. 39 - 41°C; $\nu_{max.}$ (KBr) 3006, 1742, 1325, 1154 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.17 (3H, t, J 7.1, CH_3), 4.05 - 4.17 (4H, m, 2 x CH_2), 7.55 - 7.69 (3H, m, ArH), 7.93 - 7.97 (2H, m, ArH); δ_C (62.9 MHz; $CDCl_3$) 13.8 (CH_3), 61.0 (OCH_2), 62.3 (CH_2), 128.5 (CH), 129.2 (CH), 134.3 (CH), 139.1 (CX), 162.6 (ester); *m/z* (EI) 229 (MH^+, 80%), 164 (80), 141 (100), 91 (95), 78 (75); (Found: M^+ 228.0456. $C_{10}H_{12}O_4S$ requires 228.0456).

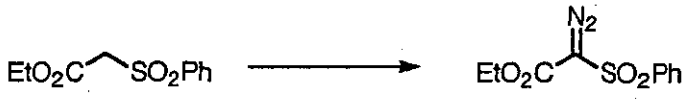


Ethyl diazo(benzenesulfonyl) acetate ***103***

(a) To a stirred solution of **110** (5.8g, 25.4 mmol) and 4-acetamidobenzenesulfonyl azide **111** (9.16g, 1.5 equiv.) in acetonitrile (200 mL) at 0°C, was added triethylamine (5.31 mL, 1.5 equiv.) dropwise. The reaction mixture was then stirred at room temperature for 16 h. After this time it was concentrated *in vacuo*, and the resulting precipitate was triturated (3 x 200 mL, 1 : 1 ether : light petroleum). The combined organics were concentrated under reduced

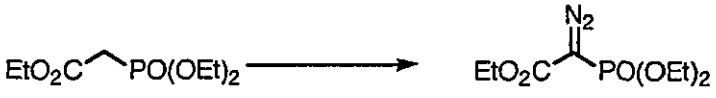
pressure. Purification by flash chromatography (eluant ether : light petroleum) yielded the *title compound* as a pale yellow solid (4.76g, 74%); spectral data given below.

(b) A solution of 1-ethyl-2-chloro pyridinium tetrafluoroborate **113** (2.40 g, 1.2 equiv.) and sodium azide (678 mg, 1.2 equiv.) in methanol (70% solution, 100 mL), at 0°C, was stirred for 10 min, forming 1-ethyl-2-azidopyridinium tetrafluoroborate **112** *in situ*. Ethyl benzenesulfonyl acetate **110** (2.0 g, 8.7 mmol) and sodium acetate (856 mg, 1.2 equiv.) were added as a solution in methanol (70% solution, 50 mL). The reaction mixture was stirred for 24 h, after which time excess solvent was removed under reduced pressure. The residue was diluted with ether (150 mL) and washed with water (2 x 50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The product was purified by flash chromatography (eluant ethyl acetate : light petroleum) to yield the *title compound* as a yellow solid (1.45 g, 65%), m.p. 51 - 53°C; $\nu_{max.}$ ($CHCl_3$) 2400, 2129, 1416, 1345, 1160 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.25 (3H, t, J 7.1, CH_3), 4.18 (2H, q, J 7.1, OCH_2), 7.53 - 7.66 (3H, m, ArH), 8.01 - 8.05 (2H, m, ArH); δ_C (62.9MHz; $CDCl_3$) 14.0 (CH_3), 62.0 (CH_2), 127.0 (CH), 129.0 (CH), 133.9 (CH), 142.0 (CX) (diazo and carbonyl carbons not observed); *m/z* (EI) 254 (M^+, 20%), 226 (10), 209 (20), 182 (20), 141 (100); (Found: M^+ 254.0362. $C_{10}H_{10}N_2O_4S$ requires 254.0361).



Triethyl diazophosphonoacetate ***104***

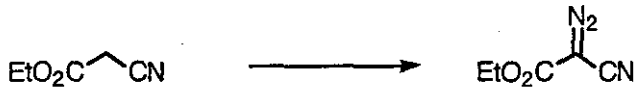
Triethyl phosphonoacetate **119** (1.9 g, 8.5 mmol) was added to a stirred suspension of azidotris(diethylamino)phosphonium bromide **120** (3.36 g, 1.1 equiv.) in ether (20 mL). Small portions of potassium *tert*-butoxide were added until a pale yellow colouration took place. The reaction mixture was stirred for 20 h, after which time sodium sulfate was added (5.0 g) and the mixture stirred for a further 10 min. After filtration the solution was concentrated i*n vacuo*. Purification by flash chromatography (eluant ethyl acetate : light petroleum) gave the *title compound* as a pale yellow oil (1.9 g, 93%); spectral data identical to that in reference 76.



Ethyl diazocyanoacetate ***105***

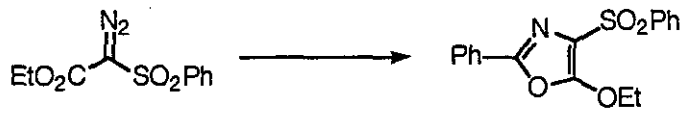
A mixture of 1-ethyl-2-chloropyridinium tetrafluoroborate **113** (12.1 g, 1.2 equiv.) and sodium azide (3.4 g, 1.2 equiv.) in methanol (70% solution, 140 mL), at 0°C, was stirred for

15 min. Ethyl cyanoacetate **122** (5 g, 44.2 mmol) and sodium acetate (4.3 g, 1.2 equiv.) was added to the reaction mixture as a solution in methanol (70% solution, 60 mL). After stirring for 15 min, the reaction mixture was diluted with ether (100 mL). The organic layer was washed with water (70 mL), brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by dry-flash chromatography (gradient of light petroleum to light petroleum-ethyl acetate) gave the *title compound* as a yellow oil (4.89 g, 80%), $\nu_{max.}$ (thin film) 2230, 2137, 1719 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.34 (3 H, t, J 7.1, CH_3), 4.35 (2 H, q, J 7.2, OCH_2); δ_C (62.9 MHz; $CDCl_3$) 14.3 (CH_3), 63.45 (OCH_2), 107.4 (CN) (diazo and carbonyl carbons not observed); *m/z* (EI) 139 (*M* +, 30%), 94 (20), 44 (30), 129 (100); (Found: *M* + 139.03817. $C_5H_5N_3O_2$ requires 139.03817).



4-Benzenesulfonyl-5-ethoxy-2-phenyloxazole ***106a***

To a refluxing solution of benzonitrile (0.510 mL, 5 equiv.) and rhodium(II) acetate (3 mg, 1% molar equiv.) in chloroform (3 mL) was added a solution of ethyl diazo(benzenesulfonyl) acetate **103** (254 mg, 1 mmol) in chloroform (7 mL) over a 7 h period. After the addition was complete, the reaction mixture was refluxed for a further hour, and then concentrated *in vacuo*. Purification by flash chromatography (eluant ethyl acetate : light petroleum) followed by recrystallisation from ethyl acetate gave the *title compound* as a colourless solid (233 mg, 71%), m.p. 110-112°C; (Found: C, 61.8; H, 4.64; N, 4.2. $C_{17}H_{15}NO_4S$ requires C, 62.0; H, 4.59; N, 4.2%); $\nu_{max.}$ (KBr) 1615, 1343, 1163 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.54 (3 H, t, J 7.1, CH_3), 4.58 (2 H, q, J 7.1, OCH_2), 7.40 - 7.57 (6 H, m, ArH), 7.88 - 7.92 (2 H, m, ArH), 8.06 - 8.10 (2 H, m, ArH); δ_C (62.9 MHz; $CDCl_3$) 14.9 (CH_3), 71.1 (OCH_2), 116.0 (CX), 126.0 (CH), 127.5 (CH), 128.7 (CH), 129.1 (CH), 130.8 (CH), 133.3 (CH), 141.5 (C-4), 151.5 (C-5), 158.0 (C-2); *m/z* (FAB) 330 (*MH* +, 100%), 284 (M-45, 40), 154 (35), 122 (45); (Found: *M*+ 329.0721. $C_{17}H_{15}NO_4S$ requires 329.0722).



Diethyl 5-ethoxy-2-phenyloxazole-4-phosphonate ***107a***

(a) To a refluxing solution of benzonitrile (309 mg, 1.5 equiv) and rhodium(II) trifluoroacetamide **124** (13 mg, 1% mol equiv) in chloroform (5 mL) was added a solution of triethyl diazophosphonate **104** (468 mg, 2 mmol) in chloroform (16 mL) over a 6 h period. The reaction mixture was refluxed for a further hour, after which time it was concentrated *in*

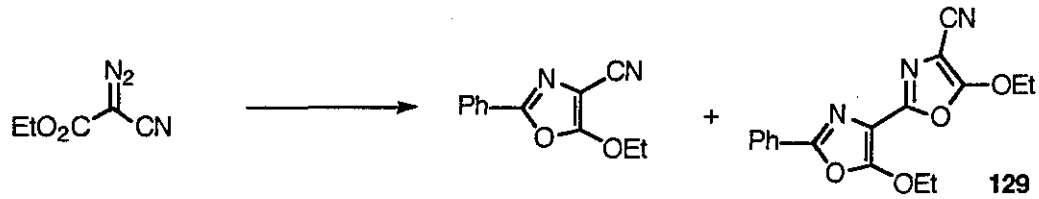
vacuo. Purification by flash chromatography (eluant ethyl acetate: light petroleum) gave the *title compound* as an oil (254 mg, 53%), $\nu_{max.}$ (thin film) 2985, 1614, 1248, 1023, 735 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.37 (6 H, dt, J 2.6, 2 x CH_3), 1.51 (3 H, t, J 7.1, CH_3), 4.14 - 4.30 (4 H, m, 2 x OCH_2), 4.54 (2 H, q, J 7.1, OCH_2) , 7.41 - 7.44 (3 H, m, ArH), 7.93 - 7.97 (2 H, m, ArH); δ_C (62.9 MHz; $CDCl_3$) 14.1 (CH_3), 16.1 (CH_3), 16.2 (CH_3), 62.4 (OCH_2), 62.9 (OCH_2), 70.2 (OCH_2), 125.7 (CH), 126.5 (CX), 128.6 (CH), 130.1 (CH), 131.8 (C-4), 152.6 and 153.0 (C-5, J_{CP} 22.6), 163.1 and 163.6 (C-2, J_{CP} 34.5); *m/z* (FAB); 326 (*MH* +, 100%), 297 (*M* -28, 8), 280 (*M* -45, 15); (Found:MH^+ 326.1157. $C_{15}H_{20}NO_5P$ + *H* requires 326.1157).

(b) The above reaction was carried out on the 3mmol scale using rhodium(II) acetate (26 mg, 2% mol equiv.) as catalyst, to give the *title compound* (161 mg, 16%).

(i) 5-Ethoxy-2-phenyloxazole-4-carbonitrile ***108a*** and *(ii) 5-Ethoxy-2-[5-ethoxy-2-phenyloxazol-4-yl]oxazole-4-carbonitrile* ***129***

To a refluxing solution of benzonitrile (1.21 g, 3 equiv) and rhodium(II) acetate (86.2 mg, 5% molar equiv.) in chloroform (4 mL) was added a solution of ethyl diazocyanoacetate **105** (546 mg, 4 mmol) in chloroform (10 mL) over a 10 h period. After addition was complete, the reaction mixture was refluxed for a further hour. After this time it was concentrated *in vacuo* to yield a crude mixture. Purification by flash chromatography (eluant ether : light petroleum) yielded the (i) *title compound* as a colourless crystalline solid (209 mg, 25%), m.p. 78 - 80°C; (Found C, 67.3, H, 4.6, N, 13.1. $C_{12}H_{10}N_2O_2$ requires C, 67.3, H, 4.7, N, 13.1 %); $\nu_{max.}$ (KBr) 2989, 2223, 1616, 1604, 1568 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.55 (3 H, m, CH_3), 4.62 (2 H, q, J 7.0, OCH_2), 7.41 - 7.50 (3 H, m, ArH), 7.88 - 7.96 (2 H, m, ArH); δ_C (62.9 MHz; $CDCl_3$) 14.7 (CH_3), 70.0 (OCH_2), 113.1 (CN), 125.8 (C-5), 126.0 (CH), 128.9 (CH), 131.0 (CH), 152.3 (C-4), 164.0 (C-2); *m/z* (EI); 214 (*M*+, 20%), 186 (40), 105 (100); (Found: M^+ 214.0742. $C_{12}H_{10}N_2O_2$ requires 214.0742) and (ii) *5-ethoxy-2-[5-ethoxy-2-phenyloxazol-4-yl]oxazole-4-carbonitrile* **129** as a colourless glassy solid (64 mg, 20%); spectral data given below.

(b) The above reaction was carried out using rhodium(II) trifluoroacetamide **124** (26 mg, 1% molar equiv.), as catalyst, to give only the (i) *title compound* **108a** (26 mg, 12%).



108a **129**

GENERAL PROCEDURE FOR THE PREPARATION OF 4-(BENZENESULFONYL)OXAZOLES

4-Benzenesulfonyl-5-ethoxy-2-ethyloxazole ***106b***

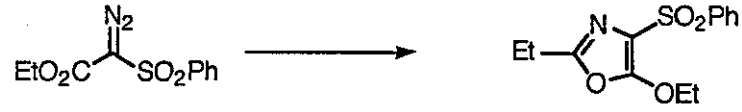
(a) To a refluxing solution of propionitrile (0.357 mL, 5 equiv.) and rhodium(II) acetate (3 mg, 1% molar equiv.) in chloroform (3 mL) was added a solution of **103** (254 mg, 1 mmol) in chloroform (7 mL) over a 7 h period. After the addition was finished, the reaction mixture was refluxed for a further hour, after which time it was concentrated *in vacuo*. Purification by flash chromatography (eluant ethyl acetate : light petroleum) followed by recrystallisation from ethyl acetate gave the *title compound* as a colourless solid (147 mg, 52%), m.p. 101-103°C; (Found C, 55.6; H, 5.10; N, 4.9. $C_{13}H_{15}NO_4S$ requires C, 55.5; H, 5.37; N, 5.0 %); $\nu_{max.}$ (KBr) 2360, 1633, 1327, 1150 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.26 (3 H, t, J 7.6, $CH_2\underline{CH_3}$), 1.47 (3 H, t, J 7.1, $OCH_2\underline{CH_3}$), 2.65 (2 H, q, J 7.6, $\underline{CH_2}CH_3$), 4.45 (2 H, q, J 7.1, OCH_2CH_3), 7.48 - 7.59 (3 H, m, ArH), 8.01 - 8.04 (2 H, m, ArH); δ_C (62.9 MHz; $CDCl_3$) 13.8 ($CH_2\underline{CH_3}$), 14.8 ($OCH_2\underline{CH_3}$), 63.4 ($\underline{CH_2}CH_3$), 70.7 ($O\underline{CH_2}CH_3$), 114.1 (CX), 127.4 (CH), 129.0 (CH), 131.4 (CH), 141.5 (C-4), 155.7 (C-5), 157.9 (C-2); *m/z* (FAB) 282 (*MH*+, 100%), 236 (*M*-45, 10), 197 (20), 135 (25), 125 (20); (Found: *MH* + 282.080. $C_{13}H_{15}NO_4S$ + *H* requires 282.0799).

(b) The above reaction was carried out using rhodium(II) trifluoroacetamide **124** (6.5 mg, 1% molar equiv.) as catalyst to give the *title compound* (180 mg, 64%).

(c) The above reaction was carried out using rhodium(II) (*S*)-mandalate **125** (8.1 mg, 1% molar equiv.) as catalyst to give the *title compound* (190 mg, 68%).

(d) The above reaction was carried out using rhodium(II) 1-naphthoate **126** (8.9 mg, 1% molar equiv.) as catalyst to give the *title compound* (183 mg, 65%).

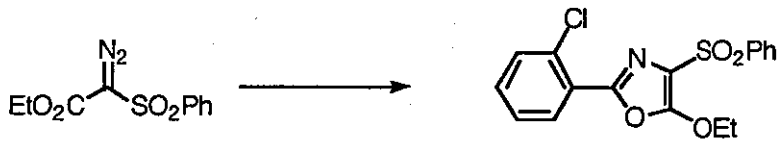
(e) The above reaction was carried out using rhodium(II) 1-benzenesulfonylprolinate **127** (12.0 mg, 1% molar equiv.) as catalyst to give the *title compound* (125 mg, 44%).



4-Benzenesulfonyl-2-(2-chlorophenyl)-5-ethoxyoxazole ***106c***

Yield 56%

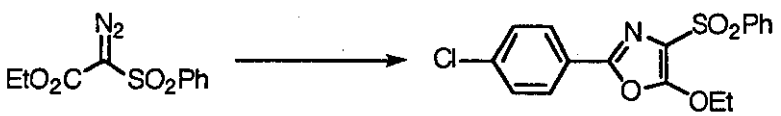
m.p. 145-147°C; (Found C, 56.2; H, 4.0; N, 3.8. $C_{17}H_{14}ClNO_4S$ requires C, 56.1; H, 3.9; N, 3.85 %); $\nu_{max.}$ (KBr) 1612, 1341, 1157 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.53 (3 H, t, J 7.1, CH_3), 4.59 (2 H, q, J 7.1, OCH_2), 7.32 - 7.58 (6 H, m, ArH), 7.92 (1 H, m, ArH), 8.07 -8 .11 (2 H, m, ArH); δ_C (100 MHz; $CDCl_3$) 14.7 (CH_3), 70.8 (OCH_2), 115.3 (CX), 124.8 (CX), 126.8 (CH), 127.4 (CH), 128.9 (CH), 130.8 (CH), 131.0 (CH), 131.5 (CH), 132.0 (CX), 133.2 (CH), 141.3 (C-4), 149.3 (C-5), 158.0 (C-2); *m/z* (EI) 363 (*M* +, 30%), 358 (50), 286 (100); (Found: *MH* + 364.041. $C_{17}H_{14}ClNO_4S + H$ requires 364.0410).



4-Benzenesulfonyl-2-(4-chlorophenyl)-5-ethoxyoxazole ***106d***

Yield 46%

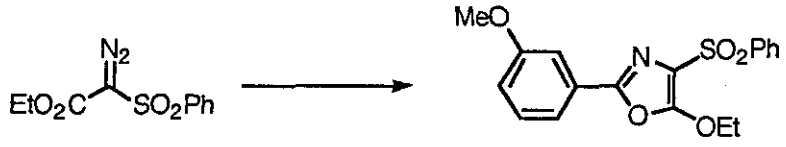
m.p. 127-129°C (decomposes); $\nu_{max.}$ (KBr) 1622, 1302, 1155 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.53 (3 H, t, J 7.1, CH_3), 4.57 (2 H, q, J 7.1, OCH_2), 7.36 - 7.40 (1 H, m, ArH), 7.53 - 7.60 (4 H, m, ArH), 7.81 - 7.84 (1 H, m, ArH), 7.93 - 7.96 (2 H, m, ArH), 8.05 (1 H, m, ArH); δ_C (62.9 MHz; $CDCl_3$) 14.9 (CH_3), 71.2 (OCH_2), 124.4 (CX), 127.2 (CH), 127.4 (CH), 128.7 (CX), 129.0 (CH), 133.3 (CH), 136.9 (CX), 141.2 (C-4), 150.6 (C-5), 158.0 (C-2); *m/z* (FAB) 364 (*MH* +, 100%), 318 (*M* -45, 6), 307 (18), 289 (18); (Found: *MH* + 364.041. $C_{17}H_{14}ClNO_4S + H$ requires 364.0410).



4-Benzenesulfonyl-5-ethoxy-2-(3-methoxyphenyl)oxazole ***106e***

Yield 24%

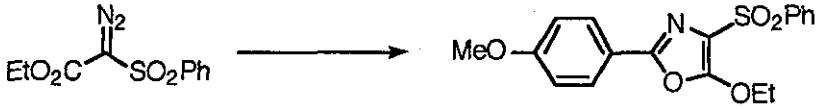
m.p.121-123°C; (Found C, 59.9; H, 4.7; N, 3.9. $C_{18}H_{17}NO_5S$ requires C, 60.2; H, 4.8; N, 3.9 %); $\nu_{max.}$ (KBr) 2957, 1618, 1345, 1157 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.53 (3 H, t, J 7.1, CH_3) 3.84 (3 H, s, OCH_3), 4.57 (2 H, q, J 7.1, OCH_2) 6.99 (1 H, m, ArH), 7.31 - 7.60 (6 H, m, ArH) 8.05 - 8.09 (2 H, m, ArH); δ_C (100 MHz; $CDCl_3$) 14.8 (CH_3), 55.3 (OCH_3), 71.0 (OCH_2), 110.7 (CH), 116.0 (CH), 117.0 (CH), 118.3 (CX), 127.0 (CH), 127.4 (CH), 128.9 (CH), 129.7 (CH), 133.1 (CX), 141.3 (C-4), 151.3 (C-5), 157.8 (CX), 159.7 (C-2); (Found: *MH* + 360.091. $C_{18}H_{17}NO_5S + H$ requires 360.0905).



4-Benzenesulfonyl-5-ethoxy-2-(4-methoxyphenyl)oxazole ***106f***

Yield 28%

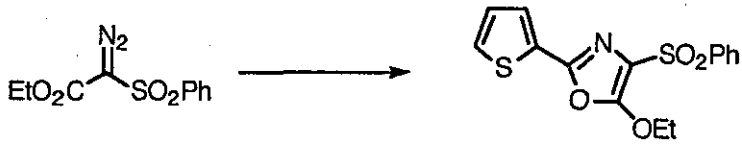
m.p. 125-127°C; (Found C, 60.1; H, 4.74; N, 4.0. $C_{18}H_{17}NO_5S$ requires C, 60.2; H, 4.77; N, 3.9 %) $\nu_{max.}$ (KBr) 3003, 1605, 1323, 1155 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.53 (3 H, t, J 7.1, CH_3), 3.84 (3 H, s, OCH_3), 4.55 (2 H, q, J 7.1, OCH_2), 6.90 - 6.93 (2 H, m, ArH), 7.52 - 7.59 (3 H, m, ArH), 7.82 - 7.85 (2 H, m, ArH), 8.06 - 8.10 (2 H, m, ArH); δ_C (100 MHz; $CDCl_3$) 14.9 (CH_3), 55.3 (OCH_3), 71.0 (OCH_2), 114.1 (CH), 118.6 (CX), 127.4 (CH), 127.7 (CH),128.9 (CH), 129.0 (CX), 133.1 (CH), 141.4 (C-4), 151.8 (C-5), 157.6 (CX), 161.6 (C-2); *m/z* (FAB) 360 (MH^+, 85%), 314 (M-45, 10), 135 (100); *m/z* (EI) 359 (M^+, 30%), 286 (100); (Found: MH^+ 360.0906. $C_{18}H_{17}NO_5S + H$ requires 360.0905).



4-Benzenesulphonyl-5-ethoxy-2-(2-thienyl)oxazole ***106g***

Yield 22% (pale brown crystals)

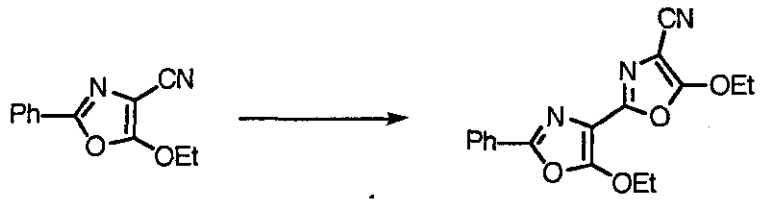
m.p. 96-98°C; $\nu_{max.}$ (KBr) 1621, 1331, 1160 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.53 (3H, t, J 7.0, CH_3), 3.48 (2H, q, J 7.0, OCH_2), 7.07 (1H, dd, J 3.7, J' 4.9, ArH), 7.41 (1H, dd, J 1.2, J' 5.0, ArH), 7.49 - 7.63 (4H, m, ArH), 8.05 - 8.10 (2H, m, ArH) ; δ_C (62.9 MHz; $CDCl_3$) 14.8 (CH_3), 71.3 (OCH_2), 116.0 (CH), 127.4 (CH), 127.8 (CH), 128.3 (CH), 128.9 (CH), 129.0 (CH), 133.3 (CX), 141.2 (C-5), 148.0 (C-4), 157.4 (C-2) ; *m/z* (EI) 336 (MH^+, 100%), 272 (25), 168 (30), 111 (10); (Found MH^+ 336.0364. $C_{15}H_{13}NO_4S_2 + H$ requires 336.0364).



5-Ethoxy-2-[5-ethoxy-2-phenyloxazol-4-yl]oxazole-4-carbonitrile ***129***

To a refluxing solution of 5-ethoxy-2-phenyloxazole-4-carbonitrile **108a** (80 mg, 0.37 mmol) and rhodium(II) acetate (8.0 mg, 5% molar equiv.) in chloroform (1 mL) was added a solution of ethyl diazocyanoacetate **105** (103.9 mg, 2.0 equiv.) in chloroform (6 mL) over a 6

h period. After the addition was complete the reaction mixture was refluxed for a further 4 h. The reaction mixture was allowed to cool, then concentrated *in vacuo*. Purification by flash chromatography (eluant ethyl acetate : light petroleum) gave the *title compound* as a crystalline solid (19 mg, 16%), $\nu_{max.}$ ($CDCl_3$) 2254, 1629, 1618, 1348 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.52-1.58 (6 H, m, 2 x CH_3), 4.59 (4 H, m, 2 x OCH_2), 7.43 - 7.53 (3 H, m, ArH), 7.80 - 7.99 (2 H, m, ArH); δ_C (100 MHz; $CDCl_3$) 14.6 (CH_3), 14.9 (CH_3), 70.0 (OCH_2), 70.35 (OCH_2), 112.9 (CN), 125.8 (CH), 126.2 (CX), 128.5 (CX), 128.7 (CX), 130.4 (CH), 146.3 (CX), 152.3 (CX), 157.2 (CX), 163.3 (CX); *m/z* (FAB) 326 (*MH*+, 65%), 281 (40), 207 (25), 147 (35), 136 (35), 105 (65), 73 (100); (Found *MH* + 326.114. $C_{17}H_{15}N_3O_4 + H$+ requires 326.114.)



Methyl diazocyanoacetate ***130***

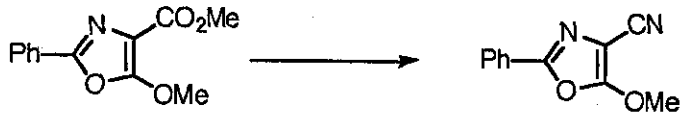
A mixture of 1-ethyl-2-chloropyridinium tetrafluoroborate **113** (7.64 g, 1.1 equiv.) and sodium azide (2.19 g, 1.1 equiv.) in acetonitrile : water solution (7:3, 200 mL), at 0°C, was stirred for 15 min. Methyl cyanoacetate (3.0 g, 30.3 mmol) was added to the solution, followed by a catalytic amount of potassium carbonate. After stirring for 10 min, the reaction mixture was diluted with ether (100 mL). The organic layer was washed with water (70 mL), brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by dry-flash chromatography (gradient of light petroleum to light petroleum : ethyl acetate) gave the *title compound* as a yellow oil (2.37 g, 62%), $\nu_{max.}$ (thin film) 2231, 2142, 1729 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 3.90 (3 H, s, OCH_3); δ_C (62.9 MHz, $CDCl_3$) 53.6 (OCH_3) (nitrile, diazo and carbonyl carbons not observed); *m/z* (EI) 125 (*M*+, 50%), 97 (*M* -28, 15), 94 (20), 54 (100); (Found *M* + 125.0223. $C_4H_3N_3O_2$ requires 125.0225).

5-Methoxy-2-phenyloxazole-4-carbonitrile ***131***

(a) To a refluxing solution of benzonitrile (3.3 g, 2 equiv.) and rhodium(II) acetate (70 mg, 1% molar equiv.) in chloroform (10 mL) was added a solution of methyl diazocyanoacetate **130** (2.0 g, 16 mmol) in chloroform (40 mL) over a 20 h period. The reaction mixture was refluxed for a further 2 h, after which time it was then concentrated *in vacuo*. The product

was purified by flash chromatography (eluant light petroleum : ethyl acetate) to yield a crystalline compound. Recrystallisation from light petroleum gave the *title compound* as a colourless crystalline solid (1.10 g, 35%); spectral data given below.

(b) To a stirred solution of ammonium chloride (57.3 mg, 2.5 equiv) in xylene (10 mL), under a nitrogen atmosphere, was added trimethyl aluminium (2.0 M solution in toluene, 0.535 mL, 2.5 equiv). The reaction mixture was stirred for 15 min, then oxazole-4-ester **71a** (100 mg, 0.43 mmol) was added and the reaction mixture was heated to reflux for 2 h. After cooling, the mixture was quenched with HCl (2 M, 10 mL) and diluted with water (10 mL). After extraction with ethyl acetate (3 x 10 mL), the combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (eluant ethyl acetate : light petroleum) gave the *title compound* as a colourless crystalline solid (58 mg, 68%), m.p. 107-108°C, (Found; C, 66.0; H, 4.0; N, 13.9. $C_{11}H_8N_2O_2$ requires C, 66.0; H, 4.0; N, 14.0%); $\nu_{max.}$ (KBr) 2228, 1628 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 4.31 (3 H, s, OCH_3), 7.44 - 7.48 (3 H, m, ArH), 7.88 - 7.93 (2 H, m, ArH); δ_C (62.9 MHz; $CDCl_3$) 59.3 (OCH_3), 112.8 (CN), 125.5 (CX), 125.8 (CH), 128.8 (CH), 130.9 (CH), 152.5 (C-5), 162.1 (C-2); *m/z* (EI) 200 (*M* +, 100%), 157 (*M*-43, 30), 105 (*M*-95, 100); (Found: *M* + 200.0586. $C_{11}H_8N_2O_2$ requires 200.0586).



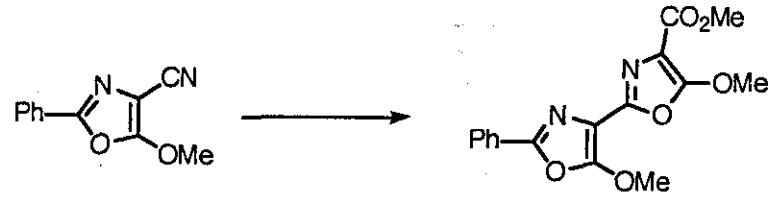
Methyl 2-phenyl-5-methoxyoxazole-4-carboxylate ***71a***

To a refluxing solution of benzonitrile (940 mg, 9.2 mmol) and rhodium(II) acetate (20.3 mg, 5% molar equiv.) in chloroform (5 mL) was added a solution of dimethyl diazomalonate **70** (2.0 g, 13.8 mmol) in chloroform (25 mL) over a 12 h period. After addition was complete, the reaction mixture was refluxed for a further 3 h. After concentration *in vacuo*, the reaction was purified by flash chromatography (eluant ethyl aceate : light petroleum). Recrystallisation from ethyl acetate gave the *title compound* as a colourless solid (1.19 g, 82%), m.p. 97 - 98°C (lit.;[67] 98 - 99°C); $\nu_{max.}$ (KBr) 1718, 1623, 1609, 1450 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 3.92 (3 H, s, CO_2CH_3), 4.27 (3 H, s, OCH_3), 7.42 - 7.47 (3 H, m, ArH), 7.96 - 8.00 (2 H, m, ArH); δ_C (62.9 MHz; $CDCl_3$) 51.8 ($CO_2\underline{C}H_3$), 59.8 (OCH_3), 107.4 (C-4), 125.8 (CH), 126.3 (CX), 128.7 (CH), 130.4 (CH), 150.8 (C-5), 161.8 and 161.9 (C-2 and ester).

Methyl 5-methoxy-2-[5-methoxy-2-phenyloxazol-4-yl]oxazole-4-carboxylate ***135***

To a refluxing solution of 5-methoxy-2-phenyloxazole-4-carbonitrile **131** (150 mg, 0.75 mmol) and rhodium(II) trifluoroacetamide **124** (9.8 mg, 2% molar equiv) in chloroform (3 mL) was added a solution of dimethyl diazomalonate **70** (216.2 mg, 2 equiv) in chloroform (10 mL) over a 10 h period. The reaction mixture was refluxed for a further 2 h, after which time it was concentrated *in vacuo*. The residue was purified by flash chromatography (eluant light petroleum : ethyl acetate) to give the *title compound* as a colourless crystalline compound (131 mg, 53%), m.p. 144-146°C; (Found C, 58.3; H, 4.12; N, 8.4. $C_{16}H_{14}N_2O_6$ requires C, 58.2; H, 4.27; N, 8.5 %); $\nu_{max.}$ (KBr) 2956, 1713, 1615 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.88 (3 H, s, CO_2CH_3), 4.25 (3 H, s, OCH_3), 4.26 (3 H, s, OCH_3), 7.43 - 7.45 (3H, m, ArH), 7.98 - 7.99 (2H, m, ArH); δ_C (100 MHz; $CDCl_3$) 51.5 ($CO_2\underline{C}H_3$), 59.8 (OCH_3), 60.0, (OCH_3) 104.8 and 107.0 (C-5 and C-5'), 125.6 (CH), 126.4 (CX), 128.6 (CH), 130.2 (CH), 144.8 (C-4), 151.7 (C-4'), 157.5 (ester), 161.3 and 161.7 (C-2 and C-2'); *m/z* (EI) 330 (*M* +, 50%), 287 (*M* -43, 30), 202 (50), 105 (100); (Found: *M* + 330.0850. $C_{16}H_{14}N_2O_6$ requires 330.0852).

(b) The above reaction was carried out on the 0.85 mmol scale using rhodium(II) acetate (11.2 mg, 3% molar equiv.), as catalyst, to give the *title compound* (136 mg, 48%).



2-(2-Phenyloxazol-4-yl)oxazole-4-methanol ***136***

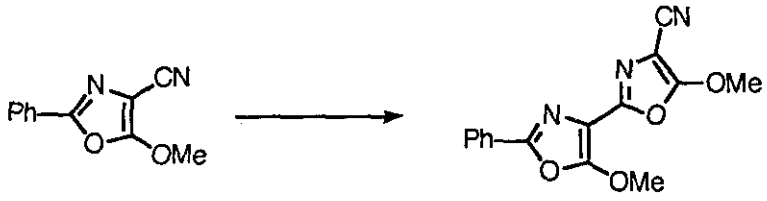
To a stirred solution of methyl 5-methoxy-2-[5-methoxy-2-phenyloxazol-4-yl] oxazole-4-carboxylate **135** (43 mg, 0.13 mmol) in THF (5 mL) at -78°C under a nitrogen atmosphere, was added lithium aluminium hydride (0.195 mL, 1.0 M solution in THF, 2 equiv). The reaction mixture was stirred at -70°C for 1.5 h, then allowed to warm up to room temperature. The reaction was then worked-up by the successive addition of water (0.1 mL), NaOH solution (15%; 0.1 ml) then diluted with ether (20 mL), which was then filtered. The organic layer was then washed with brine (10 mL) and dried ($MgSO_4$), then concentrated under reduced pressure. The residue was purified by flash chromatography (eluant light

petroleum : ethyl acetate) to yield the *title compound* as a colourless solid (13 mg, 38%), m.p. 142-144°C, $\nu_{max.}$ (KBr) 3293, 1635, 1523, 1456, 1330, 1114, 1034 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 2.26 (1H, br s, exchangeable D_2O, OH), 4.69 (2H, s, CH_2), 7.44 - 7.52 (3H, m, ArH), 7.67 (1H, s, ArH), 8.12 - 8.17 (2H, m, ArH), 8.27 (1H, s, ArH); δ_C (100 MHz; $CDCl_3$) 56.9 (CH_2), 126.3 (CX), 126.8 (CH), 128.7 (CH), 131.0 (CX), 131.5 (CH), 134.9 (CH), 138.2 (CH), 141.4 (CX), 155.6 (CX), 162.7 (CX); *m/z* (EI) 242 (*M* +, 100%), 172 (*M* -70, 80), 80 (50); (Found: *M* + 242.0690. $C_{13}H_{10}N_2O_3$ requires 242.0691).

5-Methoxy-2-[5-methoxy-2-phenyloxazol-4-yl]oxazole-4-carbonitrile ***137***

To a refluxing solution of 5-methoxy-2-phenyloxazole-4-carbonitrile **131** (250 mg, 1.25 mmol) and rhodium(II) acetate (27.6 mg, 5% molar equiv.) in chloroform (5 mL) was added a solution of methyl diazocyanoacetate **130** (187 mg, 1.2 equiv.) in chloroform (10 mL) over a 10 h period. After the addition was complete the reaction mixture was refluxed for a further 4 h. The reaction mixture was allowed to cool, then concentrated *in vacuo*. Purification by flash chromatography (eluant ethyl acetate : light petroleum) gave the starting material (137 mg), and the *title compound* as a colourless solid (104 mg, 28%, 62% based upon recovered starting material), m.p. 140-142 °C; (Found C, 60.6; H, 3.60; N, 14.1. $C_{15}H_{11}N_3O_4$ requires C, 60.6; H, 3.73; N, 14.2 %); $\nu_{max.}$ (KBr) 2230, 1654, 1627, 1582, 1377, 1221, 1138, 1041, 700 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 4.27 (3H, s, OCH_3), 4.28 (3H, s, OCH_3), 7.43 - 7.46 (3H, m, ArH), 7.95 - 8.00 (2H, m, ArH); δ_C (100 MHz; $CDCl_3$) 60.1 (OCH_3), 60.1 (OCH_3), 104.4 (CX), 112.6 (CX), 114.6 (CN), 125.7 (CH), 126.1 (CX), 128.7 (CH), 130.4 (CH), 146.2 (CX), 152.0 (CX), 157.8 (CX), 163.9(CX), 166.4 (CX); *m/z* (EI) 297 (*M*+, 40%), 254 (*M*-43, 50), 105 (100); (Found *M*+ 297.0750. $C_{15}H_{11}N_3O_4$ requires 297.0749).

(b) The above reaction was carried out on the 1.2 mmol scale, using rhodium(II) trifluoroacetamide (7.3 mg, 1% molar equiv.) as catalyst, to give the *title compound* (17 mg, 5%).

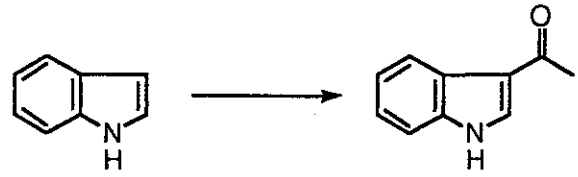


5.4 Chapter 3 Experimental.

3-Acetylindole ***152***

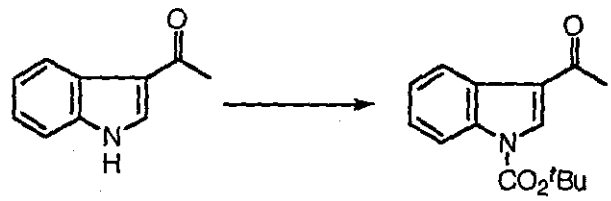
Prepared *via* a modified procedure as described in reference 142, as follows:

To a stirred solution of phosphorus oxychloride (39 mL, 3.3 equiv.) in chloroform (150 mL) was added *N,N*-dimethyl acetamide (39 mL, 3.3 equiv.) dropwise, keeping the temperature below 10°C. After the addition was complete, the reaction mixture was stirred for 10 min to allow complete formation of the greenish yellow Vilsmeier complex. Then indole **151** (15.0 g, 128 mmol) in chloroform (150 mL) was added to the reaction mixture dropwise over 1.5 h, keeping the reaction mixture around 10°C. The reaction mixture was then refluxed for 5 h. After cooling, it was extracted with water (3 x 200 mL). The combined aqueous phases were taken to pH 5 using sodium acetate. The resulting suspension was allowed to stand at room temperature overnight. The suspension was filtered and recrystallised from chloroform. This yielded the *title compound* as a colourless solid (16.3 g, 80%), m.p. 187 - 189°C; $\nu_{max.}$ (KBr) 3193, 1618, 1460 cm^{-1}; δ_H (250 MHz; $CDCl_3$/DMSO) 2.04 (3 H, s, CH_3), 2.99 (1 H, s, exchangeable in D_2O, NH), 6.73 - 6.77 (2 H, m, ArH), 6.98 - 7.02 (1 H, m, ArH), 7.49 (1 H, s, H-2), 7.82 (1 H, m, ArH); δ_C (62.9 MHz; $CDCl_3$/DMSO) 27.3 (CH_3), 111.9 (CH), 117.2 (CX), 121.6 (CH), 121.8 (CH), 122.9 (CH), 125.4 (CX), 133.1 (CH), 136.8 (CX), 193.2 (ketone); *m/z* (EI) 159 (M^+, 30%), 144 (70), 116 (30).



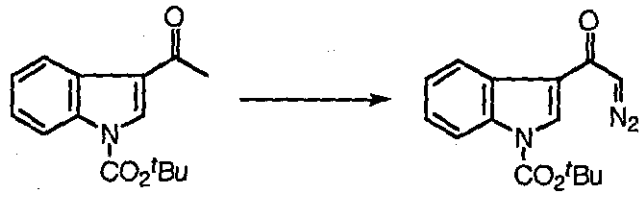
tert-*Butyl 3-acetylindole-1-carboxylate* ***153***

To a stirred suspension of 3-acetylindole **152** (3.0 g, 18.8 mmol) and di-*tert*-butyl pyrocarbonate (4.93 g, 1.2 equiv.) in acetonitrile (50 mL) was added 4-dimethylamino pyridine (230.2 mg, 10% molar equiv.). After 30 min, diethylethylenediamine (350 mg) was added and the reaction mixture was stirred for a further 10 min. After this time, the reaction mixture was diluted with ether (100 mL). The organic layer was washed in succession by $KHSO_4$ (1M, 3 x 50 mL), water (50 mL), saturated $NaHCO_3$ (50 mL), brine (50mL) then dried ($MgSO_4$) and concentrated *in vacuo*. Recrystallisation from ethyl acetate gave the *title compound* as a colourless solid (3.70g, 76%), m.p. 146 - 148°C; $\nu_{max.}$ (KBr) 1736, 1659, 1449 cm^{-1}: δ_H (250 MHz; $CDCl_3$) 1.72 (9 H, s, $C(CH_3)_3$), 2.57 (3 H, s, CH_3), 7.32 - 7.42 (2 H, m, ArH), 8.09 - 8.14 (1 H, m, ArH), 8.23 (1 H, s, ArH), 8.34 - 8.39 (1 H, m, ArH); δ_C (62.9 MHz; $CDCl_3$) 27.7 (CH_3), 28.1 ($C(\underline{C}H_3)_3$), 85.4 ($\underline{C}(CH_3)_3$), 115.0 (CH), 120.7 (CX), 122.7 (CH), 124.4 (CH), 125.5 (CH), 127.4 (CX), 132.4 (CH), 135.6 (CX), 149.2 (carbamate), 193.7 (ketone); *m/z* (EI) 259 (M^+, 10%), 203 (20), 159 (30), 144 (50), 57 (100); (Found: M^+ 259.12083. $C_{15}H_{17}NO_3$ requires 259.12083).



tert-*Butyl 3-diazoacetylindole-1-carboxylate* ***150a***

A solution of LiHMDS was prepared *in situ* by the dropwise addition of butyl lithium (1.6M solution, 6.36 mL, 1.2 equiv.) to a stirred solution of 1,1,1,3,3,3-hexamethyldisilazane (2.37 mL. 1.2 equiv.) in THF (20 mL) at 0°C under a nitrogen atmosphere. After stirring for 15 min at this temperature, the solution was cooled down to -78°C. At this temperature, *tert*-butyl 3-acetylindole-1-carboxylate **153** (2.20 g, 8.48 mmol) was added dropwise as a solution in THF (30 mL). The reaction mixture was stirred at -78°C for 30 min and then 2,2,2-trifluoroethyl trifluoroacetate (1.36 mL, 1.2 equiv.) was added rapidly in one portion. After stirring for 10 min the mixture was diluted with ether (40 mL) and washed with HCl (5% solution, 40 mL). The aqueous layer was extracted with ether (2 x 40 mL). The combined organics were washed with brine (40 mL) and concentrated *in vacuo*. The resulting solid was then suspended in acetonitrile (40 mL) to which was added water (0.152 mL, 1 equiv.) and triethylamine (1.77 mL, 1.5 equiv.). To this stirred solution was added mesyl azide (1.81 g, 1.5 equiv.) dropwise as a solution in acetonitrile (20 mL) over a 20 min period. After the addition was complete, the resulting mixture was stirred for 16h. The reaction mixture was then diluted with ether (100 mL) and washed with NaOH (15% solution, 3 x 50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography (eluant ethyl acetate : light petroleum) gave the *title compound* as a yellow solid (2.05 g, 85%); spectral data identical to that given in reference 97.



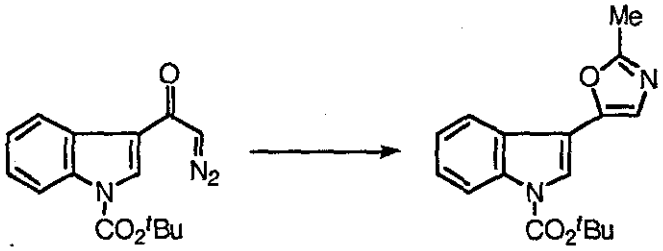
*2-Methyl-5-(3-(1-*tert*-butoxycarbonyl)indoyl) oxazole* ***157a***

(a) To a stirred solution of acetonitrile (5 mL) and rhodium(II) trifluoroacetamide **124** (6.5 mg, 1% molar equiv.) at 80°C was added *tert*-butyl 3-diazoacetylindole-1-carboxylate **150a** (285 mg, 1 mmol) dropwise as a solution in chloroform (5 mL) over a 5 h period. After the addition was complete, the reaction mixture was stirred for a further 3 h. After concentration under reduced

pressure, purification by flash chromatography (eluant ether : dichloromethane) gave the *title compound* as a pale brown solid (108 mg, 36%); spectral data given below.

(b) The above reaction was carried out on the 4.3 mmol scale using rhodium(II) acetate (39 mg, 2% molar equiv.) as catalyst, to give the *title compound* (478 mg, 37%); spectral data given below.

(c) To a stirred solution of acetonitrile (5 mL) and rhodium(II) trifluoroacetamide **124** (2.2 mg, 1% molar equiv.) at 25°C, was added *tert*-butyl 3-diazoacetylindole-1-carboxylate **150a** (100 mg, 0.35 mmol) dropwise as a solution in chloroform (1 mL) over an hour period. After the addition was complete the reaction mixture was stirred for a further 2 h. After this time it was concentration *in vacuo* and followed by purification by flash chromatography (eluant ethyl acetate : light petroleum). This gave the *title compound* as a pale brown solid (48 mg, 46%), m.p. 110 - 112°C; $\nu_{max.}$ (KBr) 1720, 1453, 1371 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.69 (9 H, s, $C(CH_3)_3$), 2.56 (3 H, s, CH_3), 7.24 (1 H, s, ArH)7.25 - 7.38 (2 H, m, ArH), 7.75 (1 H, d, J 7.8, ArH), 7.85 (1 H, s, ArH), 8.21 (1 H, d, J 7.9, ArH); δ_C (62.9 MHz; $CDCl_3$) 14.0 (CH_3), 29.2 ($C(\underline{C}H_3)_3$), 84.3 ($\underline{C}(CH_3)_3$), 109.6 (CX), 115.5 (CH), 120.1 (CH), 122.2 (CH), 123.3 (CH), 125.1 (CH), 126.7 (CX), 135.6 (CX), 145.8 (C-5), 149.3 (carbamate), 160.2 (C-2); *m/z* (EI) 299 (*MH*$^+$, 60%), 199 (50), 179 (100); (Found *MH*$^+$ 299.1396. $C_{17}H_{18}N_2O_3$ + *H* requires 299.1396).

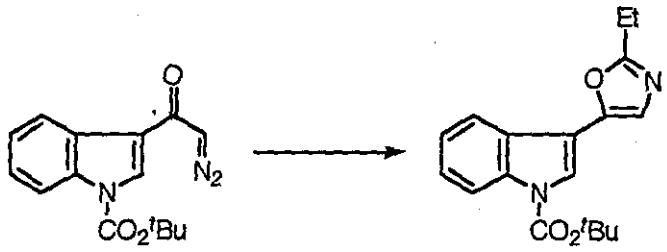


*2-Ethyl-5-(3-(1-*tert*-butoxycarbonyl)indoyl) oxazole* ***157b***

(a) To a stirred solution of proprionitrile (5 mL) and rhodium(II) trifluoroacetamide **124** (12 mg, 1% molar equiv.) at 80°C was added *tert*-butyl 3-diazoacetylindole-1-carboxylate **150a** (570 mg, 2 mmol) dropwise as a solution in chloroform (10 mL) over a 10 h period. After the addition was complete, the reaction mixture was stirred for a further 4 h. After concentration under reduced pressure, purification by flash chromatography (eluant ether : dichloromethane) gave the *title compound* as a pale brown glassy solid (340 mg, 55%); spectral data given below.

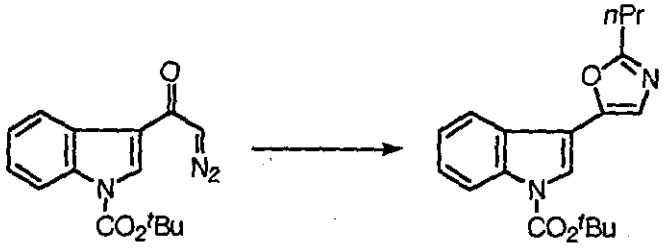
(b) To a stirred solution of propionitrile (5 mL) and rhodium(II) trifluoroacetamide **124** (2.2 mg, 1% molar equiv.) at 25°C, was added *tert*-butyl 3-diazoacetylindole-1-carboxylate **150a** (100 mg, 0.35 mmol) dropwise as a solution in chloroform (1 mL) over an hour period, then reaction mixture was stirred for a further 2 h. Concentration *in vacuo*, followed by purification by flash chromatography (eluant ethyl acetate : light petroleum) gave the *title compound* as a pale brown glassy solid (100 mg, 90%), $\nu_{max.}$ ($CDCl_3$) 1744, 1451, 1370 cm^{-1}, δ_H (250 MHz; $CDCl_3$) 1.42

(3 H, t, J 7.5, CH_3), 1.70 (9 H, s, $C(CH_3)_3$), 2.90 (2 H, q, J 7.6, CH_2), 7.31 - 7.43 (3 H, m, ArH), 7.80 (1 H, d, J 7.1, ArH), 7.86 (1 H, s, ArH), 8.21 (1 H, d, J 7.8, ArH); *m/z* (EI) 312 (M^+, 20%), 256 (30), 212 (40), 57 (100); (Found: M^+ 312.1474. $C_{18}H_{19}N_2O_3$ requires 312.1474).



*2-n-Propyl-5-(3-(1-*tert*-butoxycarbonyl)indolyl)oxazole* ***157c***

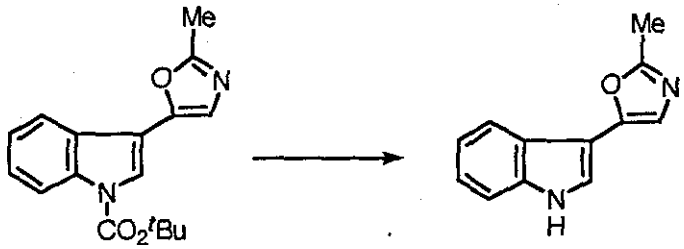
To a stirred solution of butyronitrile (5 mL) and rhodium(II) trifluoroacetamide **124** (12 mg, 1% molar equiv.) in chloroform (5 mL) at 25°C, was added *tert*-butyl 3-diazoacetylindole-1-carboxylate **150a** (570 mg, 2 mmol) dropwise as a solution in chloroform (20 mL) over a 2 h period. After stirring for 12 h the reaction mixture was concentration *in vacuo*. Purification by flash chromatography (eluant dichloromethane : diethyl ether) gave the *title compound* as a pale brown glassy solid (153 mg, 24%), $\nu_{max.}$ ($CDCl_3$) 1743, 1451, 1371 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.05 (3 H, t, J 7.4, CH_3), 1.71 (9 H, s, $C(CH_3)_3$), 1.80 - 1.95 (2 H, m, CH_2), 2.82 (2 H, t, J 7.4, CH_2), 7.31 - 7.39 (2 H, m, ArH), 7.74 - 7.78 (1 H, m, ArH), 7.84 (1 H, s, ArH), 8.21 - 8.28 (2 H, m, ArH); *m/z* (EI) 326 (M^+, 10%), 270 (40), 226 (40), 57 (100); (Found: M^+ 326.16303. $C_{19}H_{22}N_2O_3$ requires 326.16303).



Pimprinine [2-methyl-5-(3-indolyl) oxazole] ***1a***

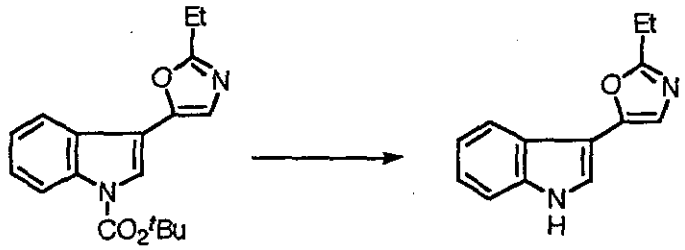
To a stirred solution of 2-methyl-5-(3-(1-*tert*-butoxycarbonyl)indoyl) oxazole **157a** (86 mg, 0.29 mmol) in THF (5 mL) under a nitrogen atmosphere was added sodium methoxide (30 % solution in methanol, 1.5 mL, 3 equiv.) dropwise. After 15 min the reaction mixture was diluted with ether (3 mL) and washed with water (2 x 3 mL), brine (3 mL), dried ($MgSO_4$) and then concentrated *in vacuo*. Purification by flash chromatography (eluant ethyl acetate) gave the *title compound* (42 mg, 74%), m.p. 202 - 203°C (lit.;[90] 204-205°C), $\nu_{max.}$ (KBr) 3426, 1638, 1453, 1023 cm^{-1}, δ_H (400 MHz; $CDCl_3$), 2.53 (3 H, s, CH_3), 7.14 (1 H, s, ArH),

7.21 - 7.29 (2 H, m, ArH), 7.42 (1 H, d, J 7.5, ArH), 7.50 (1 H, d, J 2.6, ArH), 7.82 (1 H, d, J 7.7, ArH); δ_C (100 MHz; $CDCl_3$) 13.9 (CH_3), 106.0 (C-3'), 111.4 (C-7'), 119.9 (C-5'), 120.0 (C-4'), 120.8 (C-2'), 121.3 (C-6'), 123.0 (C-4), 124.0 (C-3A'), 136.1 (C-7A'), 147.2 (C-5), 159.1 (C-2); (Found: MH^+ 199.0871. Calc. for $C_{12}H_{10}N_2O + H$, 199.0871).



Pimprinethine [2-ethyl-5-(3-indolyl) oxazole] ***1b***

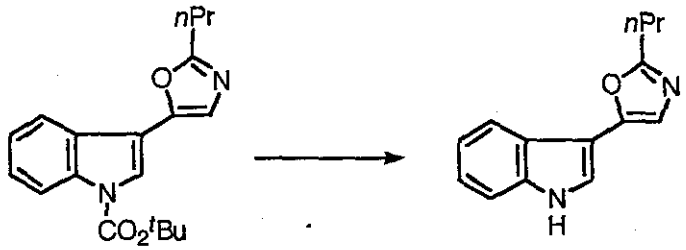
To a stirred solution of 2-ethyl-5-(3-(1-*tert*-butoxycarbonyl)indoyl) oxazole **157b** (100 mg, 0.32 mmol) in THF (5 mL) under a nitrogen atmosphere was added sodium methoxide (30 % solution in methanol, 1.5 mL, 3 equiv.) dropwise. After 15 min the reaction mixture was diluted with ether (3 mL) and washed with water (2 x 3 mL), brine (3 mL), dried ($MgSO_4$) and then concentrated *in vacuo*. Purification by flash chromatography (eluant ethyl acetate) gave the *title compound* (53 mg, 78%), m.p. 152 - 154°C (lit.;[91] 161°C), $\nu_{max.}$ (KBr) 3174, 1635, 1444, 1351, 1117 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.41 (3 H, t, J 7.6, CH_3), 2.87 (2 H, q, J 7.6, CH_2), 7.14 (1 H, s, ArH), 7.25 (2 H, m, ArH), 7.42 (1 H, m, ArH), 7.50 (1 H, d, J 2.6, ArH), 7.83 (1 H, d, J 7.7, ArH), 8.36 (1 H, s, NH); δ_C (100 MHz; $CDCl_3$) 11.2 (CH_3), 21.6 (CH_2), 106.1 (C-3'), 111.4 (C-7'), 119.8 (C-5'), 119.9 (C-4'), 120.7 (C-2'), 121.3 (C-6'), 122.9 (C-4), 124.0 (C-3A'), 136.1 (C-7A'), 147.0 (C-5), 163.6 (C-2); *m/z* (EI) 212 (M^+, 100%), 197 (30), 142 (40); (Found 212.0950. Calc. for $C_{13}H_{12}N_2O$, 212.0950).



WS-30581A [2-n-propyl-5-(3-indolyl) oxazole] ***1c***

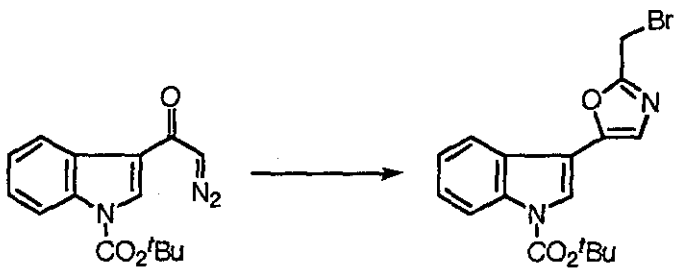
To a stirred solution of 2-*n*-propyl-5-(3-(1-*tert*-butoxycarbonyl)indoyl) oxazole **157c** (153 mg, 0.48 mmol) in THF (5 mL) under a nitrogen atmosphere was added sodium methoxide (30 % solution in methanol, 2.0 mL, 3 equiv.) dropwise. After 15 min the reaction mixture was diluted with ether (3 mL) and washed with water (2 x 3 mL), brine (3 mL), dried ($MgSO_4$) and then

concentrated *in vacuo*. Purification by flash chromatography (eluant ethyl acetate : light petroleum) gave the *title compound* (52 mg, 47%), m.p. 131 - 133°C (lit.;[90] 128-130°C); $\nu_{max.}$ (KBr) 3150, 1637, 1617, 1459, 1252 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.06 (3 H, t, J 7.3, CH_3), 1.87 (2 H, m, CH_2), 2.84 (2 H, t, J 7.3, CH_2), 7.18 (1 H, s, ArH), 7.21 - 7.31 (2 H, m, ArH), 7.43 (1 H, dd, J 1.9, J' 6.2, ArH), 7.52 (1 H, d, J 2.6, ArH), 7.85 (1 H, dd, J 2.7, J' 6.8, ArH), 9.93 (1 H, br s, NH); δ_C (62.9 MHz; $CDCl_3$) 13.7 (CH_3), 20.6 (CH_2), 30.1 (CH_2), 105.8 (C-3'), 111.5 (C-7'), 119.6 (C-5'), 119.9 (C-4'), 120.7 (C-2'), 121.6 (C-6'), 122.8 (C-4), 124.1 (C-3A'), 136.2 (C-7A'), 147.2 (C-5), 162.7 (C-2); *m/z* (EI) 226 (*M*+, 100%), 197 (50), 142 (80); (Found: M^+ 226.11061. Calc. for $C_{14}H_{14}N_2O$, 226.11060).



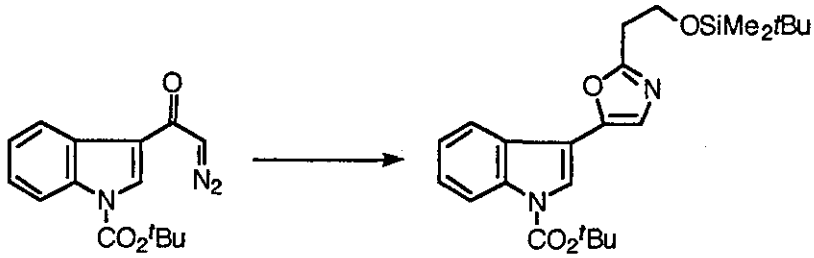
*2-(Bromomethyl)-5-(3-(1-*tert*-butoxycarbonyl)indolyl) oxazole* ***157d***

To a stirred solution of freshly distilled bromoacetonitrile (2 mL) and rhodium(II) trifluoroacetamide **124** (11.4 mg, 1% molar equiv.) at 25°C, was added *tert*-butyl 3-diazoacetylindole-1-carboxylate **150a** (500 mg, 1.7 mmol) dropwise as a solution in chloroform (8 mL) over a 4 h period. After addition, the reaction mixture was stirred for a further 2 h. Concentration *in vacuo*, followed by purification by flash chromatography (eluant ethyl acetate : light petroleum) gave the *title compound* as a pale yellow solid (120 mg, 19%), m.p. 150°C (dec.); (Found C, 54.0; H, 4.37; N, 7.2. $C_{17}H_{17}BrN_2O_3$ requires C, 54.1; H, 4.54; N, 7.4 %); $\nu_{max.}$ (KBr) 1717, 1626, 1450 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.70 (9 H, s, $C(CH_3)_3$), 4.56 (2 H, s, CH_2), 7.33 - 7.42 (3 H, m, ArH), 7.78 (1 H, dd, J 1.1, J' 7.2, ArH), 7.93 (1 H, s, ArH), 8.21 (1 H, d, J 8.1, ArH); δ_C (100 MHz, $CDCl_3$) 20.5 (CH_2), 28.1 ($C(\underline{C}H_3)_3$), 84.5 ($\underline{C}(CH_3)_3$), 108.8 (CX), 115.5 (CH), 119.9 (CH), 123.0 (CH), 123.2 (CH), 123.4 (CH), 125.2 (CH), 126.4 (C-5), 135.5 (carbamate), 149.1 (C-2); *m/z* (CI) 378 (^{81}Br, M^+, 70%), 376 (^{79}Br, M^+, 70), 299 (100), 199 (100); (Found: ^{79}Br MH^+ 377.051. $C_{17}H_{17}BrN_2O_3$ + *H* requires 377.051).



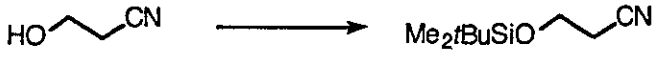
*2-(2-*tert*-Butyldimethylsilyloxyethyl)-5-(3-1-*tert*-butoxycarbonyl) indolyl) oxazole* ***157e***

To a stirred solution of 2-*tert* butyldimethylsilyloxypropane-1-carbonitrile **159** (487 mg, 5 molar equiv.) and rhodium(II) trifluoroacetamide **124** (3.4 mg, 1% molar equiv.) in chloroform (2 mL) at 25°C, was added *tert*-butyl 3-diazoacetylindole-1-carboxylate **150a** (150 mg, 0.52 mmol) dropwise as a solution in chloroform (4 mL) over a 3 h period. After addition, the reaction mixture was stirred for a further 12 h. Concentration *in vacuo*, followed by purification by flash chromatography (eluant ethyl acetate : light petroleum) gave the *title compound* as a pale brown oil (47 mg, 20%), $\nu_{max.}$ (thin film) 1739, 1453, 1369 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 0.00 (6 H, s, 2 x $SiCH_3$), 0.83 (9 H, s, $SiC(CH_3)_3$), 1.61 (9 H, s, $OC(CH_3)_3$), 3.04 (2 H, t, J 6.8, CH_2), 4.03 (2 H, t, J 6.9, CH_2), 7.21 - 7.76 (1 H, m, ArH), 7.72 - 7.76 (1 H, m, ArH), 7.82 (1 H, s, ArH), 8.17 (1 H, d, J 7.7, ArH); δ_C (62.9 MHz; $CDCl_3$) -5.5 (2 x $SiCH_3$), 18.1 ($SiC(\underline{C}H_3)_3$), 25.7 ($OC(\underline{C}H_3)_3$), 28.1 ($Si\underline{C}(CH_3)_3$), 32.1 (CH_2), 60.7 (CH_2), 84.2 ($O\underline{C}(CH_3)_3$), 109.7 (CX), 115.4 (CH), 120.0 (CH), 122.2 (CH), 122.3 (CH), 123.0 (CH), 125.0 (CH), 126.6 (CX), 135.5 (CX), 145.7 (C-5), 149.3 (carbamate), 161.3 (C-2); *m/z* (EI) 442 (M^+, 10%), 329 (80), 285 (100); (Found M^+ 442.22877. $C_{24}H_{34}N_2O_4Si$ requires 442.22877).



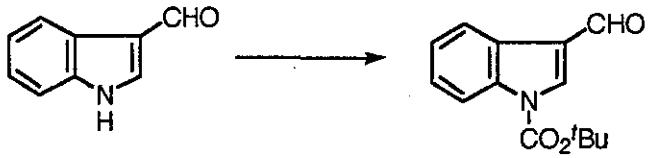
*3-*tert *Butyldimethylsilyloxypropane-1-carbonitrile* ***159***

A solution of 3-hydroxy propane-1-carbonitrile (5.0 g, 70.3 mmol), *tert*-butyldimethylsilyl chloride (18.7 g, 1.2 equiv.) and imidazole (7.18 g, 1.5 equiv.) in DMF (100 mL) was stirred for 12 h. After this period of time, the reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (200 mL). The organic layer was washed with water (4 x 100 mL), brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by bulb-to-bulb distillation (bath temp. 90°C @ 0.2 mmHg) gave the *title compound* as a clear oil (10.4 g, 80%), $\nu_{max.}$ (thin film) 2360, 1472, 1255 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 0.00 (6 H, s, 2 x $SiCH_3$), 0.81 (9 H, s, $SiC(CH_3)_3$), 2.44 (2 H, t, J 6.2, CH_2), 3.74 (2 H, t, J 6.1, CH_2); δ_C (62.9 MHz; $CDCl_3$) -5.3 (2 x $SiCH_3$), 21.7 (CH_2), 25.7 ($SiC(\underline{C}H_3)_3$), 58.5 (CH_2), 64.7 ($Si\underline{C}(CH_3)_3$), 118.0 (CN); (Found: M^+ 185.12385. $C_9H_{19}NO^{28}Si$ requires 185.1236).



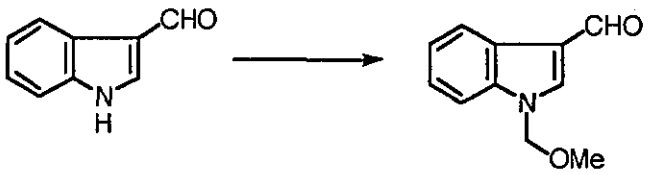
tert *Butyl indole-1-carboxylate-3-carboxyaldehyde* ***164a***

To a stirred solution of indole-3-carboxyaldehyde **166** (2.0 g, 13.7 mmol), and 4-dimethyl aminopyridine (1.67 g, 1 equiv.) in dichloromethane (100 mL), was added di-*tert* butyl pyrocarbonate (3.29 g, 1.1 equiv.) dropwise as a solution in dichloromethane (15 mL). After 20 min, the reaction mixture was washed with water (2 x 100 mL), brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Recrystallisation from ethanol gave the *title compound* as a colourless crystalline compound (2.14 g, 64%); spectral data identical to that given in reference 111.



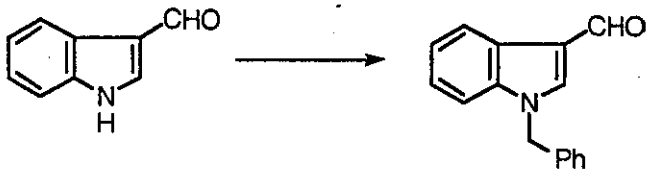
1-Methoxymethylindole-3-carboxaldehyde ***164b***

To a stirred suspension of sodium hydride (60% suspension in light petroleum, 1.38 g, 1.5 equiv.) in DMF (45 mL), under a nitrogen atmosphere, was added indole-3-carboxyaldehyde **166** (5.0 g, 34.5 mmol) dropwise, as a solution in DMF (50 mL) over 20 min. After stirring for 30 min, methyl chloromethyl ether (**CAUTION**, 3.40 mL, 1.3 equiv) was added dropwise as a solution in DMF (50 mL), over 15 min. The reaction mixture was stirred for 12 h, then diluted with water (140 mL) and extracted with ether (3 x 200 mL). The combined organics were washed with water (3 x 100 mL), brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Recrystallisation from ethanol gave the *title compound* as a pale brown solid (3.35 g, 52%), m.p. 79 - 81°C; $\nu_{max.}$ (KBr) 1648, 1534, 1457 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 3.28 (3 H, s, OCH_3), 5.47 (2 H, s, NCH_2), 7.30 - 7.38 (2 H, m, ArH), 7.48 - 7.53 (1 H, m, ArH), 7.78 (1 H, s, ArH), 8.29 (1 H, m, ArH), 10.00 (1 H, s, CHO); δ_C (62.9 MHz; $CDCl_3$) 56.3 (OCH_3), 78.3(NCH_2), 110.7 (CH), 118.6 (CX), 122.1 (CH), 123.4 (CH), 124.5 (CH), 125.6 (CX), 137.2 (CX), 138.6 (CH), 185.1 (aldehyde); *m/z* (EI) 189 (M^+, 100%), 174 (40), 158 (80), 130 (40).



1-Benzylindole-3-carboxaldehyde ***164c***

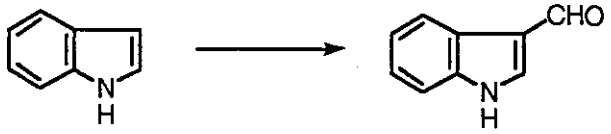
To a stirred solution of sodium hydride (60% suspension in light petroleum, 1.24 g, 1.5 equiv) in THF (50 mL) was added indole-3-carboxylate **166** (3.0 g, 20.7 mmol) over 45 min. After stirring for a further 15 min , benzyl bromide (2.94 mL, 1.2 equiv.), as a solution in THF (50 mL), was added dropwise over 15 min. The reaction mixture was stirred for 16 h, then diluted with water (100 mL) and extracted with ether (3 x 100 mL). The combined organics were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo.* Recrystallisation from ethanol gave the *title compound* as a pale brown solid (4.0 g, 83%), m.p. 109 - 110°C; $\nu_{max.}$ (KBr) 1655, 1535, 1401 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 5.32 (2 H, s, CH_2), 7.15 (2 H, m, ArH), 7.24 - 7.32 (6 H, m, ArH), 7.68 (1 H, s, ArH), 8.31 (1 H, m, ArH), 9.97 (1 H, s, CHO); δ_C (62.9 MHz; $CDCl_3$) 50.8 (CH_2), 110.3 (CH), 118.4 (CX), 122.1 (CH), 123.0 (CH), 124.1 (CH), 125.4 (CX), 127.2 (CH), 128.3 (CH), 129.0 (CH), 135.3 (CX), 137.4 (CX), 138.5 (CH), 184.6 (aldehyde); *m/z* (EI) 235 (30%), 91 (100), 65 (10); (Found M^+ 235.09971. $C_{16}H_{13}NO$ requires 235.09971).



Indole-3-carboxaldehyde ***166***

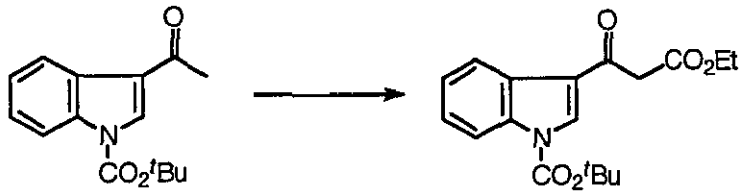
Prepared *via* a modified procedure as described in reference 142, as follows:

To a stirred solution of DMF (60 mL), at 0°C, was added phosphorous oxychloride (17 mL, 1 equiv) dropwise over 30 min. After this time, indole **151** (20 g, 170 mmol) in DMF (20 mL), was added to the reaction mixture over 30 min, not allowing the reaction temperature to rise above 10°C. After the addition was complete the mixture was heated to 35°C for 45 min to allow formation of the yellow Vilsmeier complex. After cooling, ice-water (120 mL) was added followed by, firstly, dropwise addition of NaOH (1.5 M, 200 mL) until the reaction mixture turned yellow at which point the rest of the NaOH was added in a single portion. After rapid heating of the solution to its boiling point for 5 min, the mixture was cooled down to -20°C for 16 h. The resulting suspension was filtered re-suspended in water (400 mL), re-filtered, washed (3 x 150 mL) and dried *in vacuo.* Recrystallisation from ethanol gave the *title compound* as solid (21.0 g, 85%).



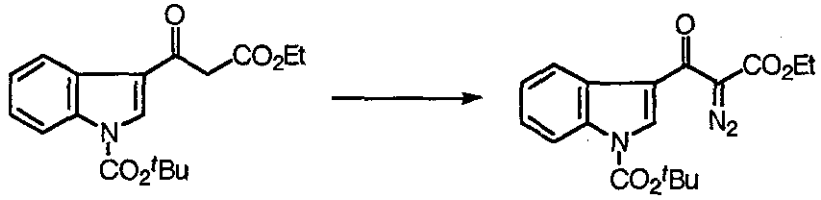
tert-*Butyl 3-(2-ethoxycarbonyl-1-oxoethyl)indole-1-carboxylate* ***165a***

A solution of LiHMDS was prepared from the addition of butyl lithium (1.6M, 2.41 mL, 2 equiv.) to a solution of 1,1,1,3,3,3-hexamethyldisilazane (0.813 mL, 2 equiv.) at 0°C in THF (10 mL) under a nitrogen atmosphere. After stirring for 15 min, the solution was cooled down to -78°C. To this was added *tert*-butyl 3-acetylindole-1-carboxylate **153** (500 mg, 1.93 mmol) dropwise as a solution in THF (10 mL). After 30 min, DMPU (0.233 mL, 1 equiv.) and ethyl cyanoacetate (0.381 mL, 2 equiv.) were added. After stirring for 15 min the reaction was quenched with water (25 mL) and extracted with ether (3 x 30 mL). The combined organics were washer with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (eluant ethyl acetate ; light petroleum) gave the *title compound* as a colourless solid (600 mg, 94%), m.p. 80 - 82°C; $\nu_{max.}$ (KBr) 1747, 1732, 1667, 1450 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.29 (3 H, t, J 7.1, CH_3), 1.71 (9 H, s, $C(CH_3)_3$), 3.91 (2 H, s, CH_2), 4.23 (2 H, q, J 7.1, OCH_2), 7.32 - 7.43 (2 H, m, ArH), 8.10 - 8.14 (1 H, m, ArH), 8.28 (1 H, s, ArH), 8.34 - 8.38 (1 H, m, ArH); δ_C (62.9 MHz; $CDCl_3$) 14.0 (CH_3), 28.0 ($C(\underline{C}H_3)_3$), 47.2 (CH_2), 61.4 (OCH_2), 85.6 ($\underline{C}(CH_3)_3$), 114.9 (CH), 118.7 (CX), 122.6 (CH), 124.5 (CH), 125.7 (CH), 127.2 (CX), 132.9 (CH), 135.5 (CX), 148.8 (carbamate), 167.3 (ester), 187.5 (ketone); *m/z* (E.I.) 332 (MH^+, 50%), 232 (100), 160 (50); (Found: MH^+ 332.1498. $C_{18}H_{21}NO_5 + H$ requires 332.1498).



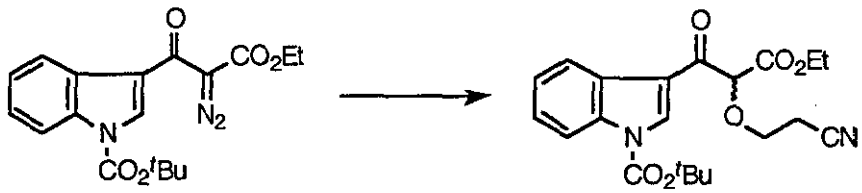
tert-*Butyl 3-(2-diazo-2-ethoxycarbonyl-1-oxoethyl)indole-1-carboxylate* ***163a***

To a stirred solution of indole ester **165a** (500 mg, 1.5 mmol) and 4-acetomidobenzenesulfonyl azide **111** (471 mg, 1.3 equiv.) in acetonitrile (40 mL) at 0°C was added triethylamine (0.315 mL, 1.5 equiv.). After stirring for 12 h, the reaction mixture was concentrated *in vacuo*. The residue was washed with ether : light petroleum (1 : 1, 70 mL). Concentration of the combined organic solution under reduced pressure, followed by purification by flash chromatography (eluant light petroleum : ethyl acetate) gave the *title compound* as a pale yellow oil (336 mg, 62%), $\nu_{max.}$ 2139, 1743, 1717, 1591 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.29 (3 H, t, J 7.1, CH_3), 1.70 (9 H, s, $C(CH_3)_3$), 4.31 (2 H, q, J 7.1, OCH_2), 7.29 - 7.40 (2 H, m, ArH), 8.13 (1 H, m, ArH), 8.21 (1 H, m, ArH), 8.62 (1 H, s, ArH); δ_C (62.9 MHz; $CDCl_3$) 14.2 (CH_3), 28.0 ($C(\underline{C}H_3)_3$), 61.4 (OCH_2), 85.1 ($\underline{C}(CH_3)_3$), 114.7 (CH), 117.4 (CX), 122.0 (CH), 124.0 (CH), 125.1 (CH), 128.4 (CX), 133.5 (CH), 134.8 (CX), 149.0 (carbamate), 161.2 (ester), 179.0 (ketone).



tert-Butyl (2-[3-cyanopropoxy]-2-ethoxycarbonyl-1-oxoethyl)indole-1-carboxylate ***170***

To a refluxing solution of 3-hydroxyproprionitrile (481 mg, 3 equiv.) in chloroform (4 mL) was added *tert*-butyl 3-(2-diazo-2-ethoxycarbonyl-1-oxoethyl)indole-1-carboxylate **163a** (400 mg, 1.12 mmol) as a solution in chloroform (12 mL) dropwise over 12 h. When the addition was complete the reaction mixture was refluxed for a further 4 h. After this time, the mixture was cooled and concentrated *in vacuo*. Purification by flash chromatography (eluant ethyl acetate : light petroleum) gave the *title compound* as a clear oil (300 mg, 67%), $\nu_{max.}$ (thin film) 2254, 1747, 1731 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.29 (3 H, t, J 7.1, CH_3), 1.67 (9 H, s, $C(CH_3)_3$), 2.04 (2 H, q, J 7.0, OCH_2), 4.28 (2 H, m, CH_2), 4.37 (2 H, m, CH_2), 4.93 (1 H, s, CH), 7.27 (2 H, m, ArH), 7.34 (1 H, d, J 7.1, ArH), 7.60 (1 H, s, ArH), 7.79 (1 H, m, ArH); δ_C (62.9 MHz; $CDCl_3$) 14.1 (CH_3), 17.8 (CH_2), 28.1 ($C(\underline{C}H_3)_3$), 49.2 (CH), 59.9 (CH_2), 62.3 (CH_2), 84.0 ($\underline{C}(CH_3)_3$), 111.4 (CN), 115.3 (CH), 116.3 (CX), 119.3 (CH), 112.8 (CH), 124.8 (CH), 125.5 (CH), 128.8 (CX), 135.5 (CX), 149.3 (carbamate), 167.2 (ester); *m/z* (EI) 300 (M^+, 40%), 227 (100), 202 (50), 130 (90); (Found: M^+ 400.16342. $C_{21}H_{24}N_2O_6$ requires 400.1628).



5.5 Chapter 4 Experimental.

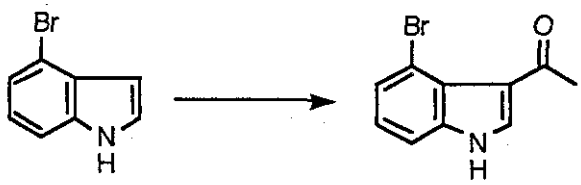
4-Bromoindole ***178***

To a solution of 4-bromo-2-nitrotoluene **177** (10.0 g, 46 mmol) in DMF (30 mL) was added DMF-dimethyl acetal (18.4 mL, 3 equiv.) and pyrrolidine (3.8 mL, 1 equiv.), which was then heated to 110°C for 4 h. The reaction mixture was then cooled, diluted with ether (150 mL) and washed with water (4 x 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude enamine, thus obtained, was dissolved in aqueous acetic acid (80% solution, 300 mL) and heated to 75°C. Zinc dust (25.5 g, 8.5 equiv.) was added portionwise over 1 h, after which time the reaction temperature was risen to 85°C and stirring

was continued for a further 2 h. Cooling and filtering gave a filtrate which was then diluted with ether (150 mL), washed with water (2 x 100 mL) and then saturated $NaHCO_3$ (2 x 100mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography (eluant dichloromethane : light petroleum) gave the *title compound* (7.93 g, 88%); spectral data identical with that given in reference 118.

4-Bromo-3-acetylindole ***179***

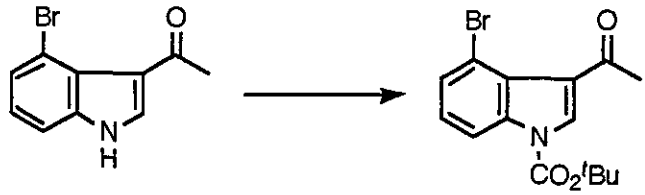
To a stirred solution of phosphorus oxychloride (4.71 mL, 3.3 equiv.) in chloroform (50 mL) was added dimethyl acetamide (4.69 mL, 3.3 equiv.) dropwise, keeping the temperature below 10°C. After the addition was complete, the reaction mixture was stirred for 10 min to allow complete formation of the greenish yellow Vilsmeier complex. Then 4-bromoindole **178** (3.0 g, 15.3 mmol) in chloroform (50 mL) was added to the reaction mixture dropwise over 30 min, keeping the reaction mixture around 10°C. The reaction mixture was then refluxed for 4 h. After cooling, it was extracted with water (3 x 100 mL). The combined aqueous phases were taken to pH 5 using sodium acetate and allowed to stand at room temperature overnight. The suspension was then filtered, collected and recrystallised from chloroform. This yielded the *title compound* as a colourless solid (2.55 g, 70%), m.p. 184 - 186°C; (Found C, 50.2; H, 3.23; N, 6.3. $C_{10}H_8BrNO$ requires C, 50.45; H, 3.39; N, 5.9 %); $\nu_{max.}$ (KBr) 3270, 1644, 1435 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 2.24 (3 H, s, CH_3), 2.84 (1 H, br s. exchangeable with D_2O, NH), 6.71 - 6.80 (1 H, m, ArH), 7.06 - 7.15 (2 H, m, ArH), 7.80 (1 H, s, ArH); δ_C (62.9 MHz; $CDCl_3$) 29.6 (CH_3), 111.4 (CH), 114.2 (CX), 118.5 (CX), 123.8 (CH), 124.5 (CX), 126.9 (CH), 133.5 (CX), 138.8 (CX), 192.2 (ketone); *m/z* (EI) 239 (^{81}Br M^+, 30%), 237 (^{79}Br M^+, 35), 224 (100), 222 (100); (Found: ^{79}Br M^+ 236.979. $C_{10}H_8{}^{79}BrNO$ requires 236.9790).



tert-*Butyl 3-acetyl-4-bromoindole-1-carboxylate* ***174***

To a stirred suspension of 3-acetyl-4-bromoindole **179** (2.0 g, 18.8 mmol) and di-*tert*-butyl pyrocarbonate (2.02 g, 1.2 equiv.) in acetonitrile (50 mL) was added 4-dimethylamino pyridine (102.6 mg, 10% molar equiv.). After 30 min the reaction mixture was diluted with ether (50

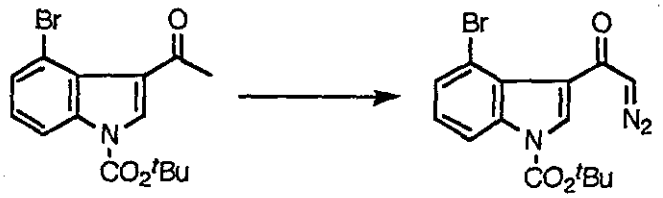
mL). The organic layer was washed in succession by $KHSO_4$ (1M, 3 x 50 mL), water (50 mL), saturated $NaHCO_3$ (50 mL), brine (50mL) then dried ($MgSO_4$) and concentrated *in vacuo*. Recrystallisation from ethyl acetate gave the *title compound* as a colourless solid (2.68 g, 94%), m.p. 70 - 72°C; $\nu_{max.}$ (KBr) 1750, 1685, 1541, 1420 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.69 (9 H, s, $C(CH_3)_3$), 2.64 (3 H, s, CH_3), 7.19 - 7.25 (1 H, m, ArH), 7.51 - 7.54 (1 H, m, ArH), 8.03 (1 H, s, ArH), 8.18 - 8.22 (1 H, m, ArH); δ_C (62.9 MHz; $CDCl_3$) 28.0 ($C(\underline{C}H_3)_3$), 31.2 (CH_3), 85.6 ($\underline{C}(CH_3)_3$), 114.4 (CH), 114.7 (CX), 123.3 CX), 126.4 (CH), 127.2 (CX), 129.0 (CH), 130.4 (CH), 137.0 (carbamate), 194.7 (ketone); *m/z* (EI) 340 (^{81}Br MH^+, 30%), 338 (^{79}Br MH^+, 30). 240 (100), 238 (100); (Found: ^{79}Br M^+ 337.0314. $C_{15}H_{16}{}^{79}BrNO_3$ requires 337.0314).



tert-*Butyl 4-bromo-3-diazoacetylindole-1-carboxylate* ***176b***

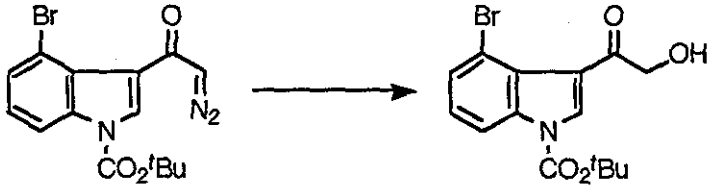
A solution of LiHMDS was prepared *in situ* by the dropwise addition of butyl lithium (1.6 M solution, 6.65 mL, 1.2 equiv.) to a stirred solution of 1,1,1,3,3,3-hexamethyldisilazane (2.25 mL, 1.3 equiv.) in THF (30 mL) at 0°C under a nitrogen atmosphere. After stirring for 15 min at this temperature, the solution was cooled down to -78°C. At this temperature, *tert*-butyl 3-acetyl-4-bromoindole-1-carboxylate **174** (3.0 g, 8.87 mmol) was added dropwise as a solution in THF (70 mL), over a 20 min period. The reaction mixture was stirred at -78°C for 30 min and then 2,2,2-trifluoroethyl trifluoroacetate (1.43 mL, 1.2 equiv.) was added rapidly in one portion. After stirring for 10 min the mixture was diluted with ether (40 mL) and washed with HCl (5% solution, 40 mL). The aqueous layer was extracted with ether (2 x 40 mL). The combined organics were washed with brine (20 mL) and concentrated *in vacuo*. The resulting solid was then suspended in acetonitrile (40 mL) to which was added water (0.160 mL, 1 equiv.) and triethylamine (1.85 mL, 1.5 equiv.). To this stirred solution was added mesyl azide (1.90 g, 1.5 equiv.) dropwise as a solution in acetonitrile (20 mL) over a 20 min period. After the addition was complete, the resulting mixture was stirred for 12 h. The reaction mixture was then diluted with ether (100 mL) and washed with NaOH (15% solution, 4 x 30 mL), brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography (eluant ethyl acetate : light petroleum) gave the *title compound* as a pale yellow solid (2.40 g, 74%), m.p. 131-133°C; (Found C, 49.7; H, 3.83; N, 11.6. $C_{15}H_{14}BrN_3O_3$ requires C, 49.5;, H, 3.87; N, 11.5 %); $\nu_{max.}$ 2099, 1740, 1622, 1421 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.67 (9 H, s, $C(CH_3)_3$), 5.67 (1 H, s, CH), 7.23 (1 H, m, ArH), 7.48 (1 H, m, ArH), 7.90 (1 H, s, ArH), 8.18 (1 H, m, ArH); δ_C (62.9 MHz; $CDCl_3$) 28.0 ($C(\underline{C}H_3)_3$), 58.3 (CH), 85.4 ($\underline{C}(CH_3)_3$), 114.0 (CX), 114.4 (CH), 126.1 (CH), 128.2 (CH), 128.3 (CH), 148.5 (CX); *m/z* (EI) 366 (^{81}Br MH^+, 100%), 364 (^{79}Br MH^+,

100), 210 (60), 208 (60); (Found ^{79}Br MH^+ 364.0297. $C_{15}H_{14}{}^{79}BrN_3O_3$ + H requires 364.0297).



tert-*Butyl 4-bromo-3-(2-hydroxy-1-oxoethane)indole-1-carboxylate* ***183***

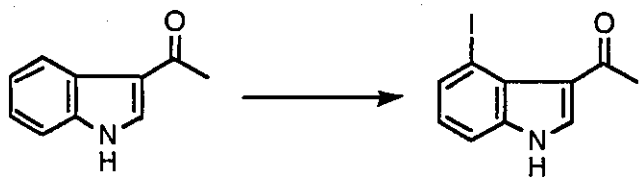
$\nu_{max.}$ (KBr) 3448, 1735, 1664 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.65 (9 H, s, $C(CH_3)_3$), 4.04 (2 H, s, CH_2), 7.13 (1 H, t, J 8.1, ArH), 7.37 (1 H, m, ArH), 7.58 (1 H, s, ArH), 8.18 (1 H, d, J 8.5, ArH); δ_C (62.9 MHz; $CDCl_3$) 28.0 ($C(\underline{C}H_3)_3$), 31.9 (CH_2), 84.2 ($\underline{C}(CH_3)_3$), 112.9 (CX), 114.0 (CX), 114.6 (CH), 125.3 (CH), 126.0 (CX), 126.7 (CH), 129.4 (CX), 134.0 (CX), 136.6 (CX), 148.8 (ketone); *m/z* (CI) 373 (^{81}Br $M+NH_4^+$, 50%), 371 (^{79}Br $M+NH_4^+$, 50), 273 (100), 271 (100); (Found: ^{79}Br $M+NH_4^+$ 371.0606. $C_{15}H_{16}{}^{79}BrNO_4+NH_4$ requires 371.0607).



3-Acetyl-4-iodoindole ***185***

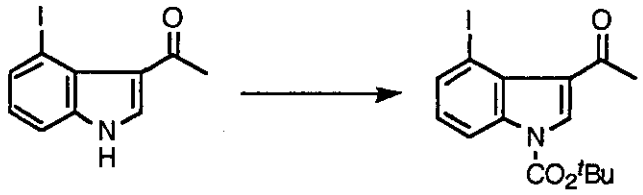
To a stirred solution of thallium(III) trifluoroacetate (**CAUTION**, 4.78 g, 1.2 equiv.) in trifluoroacetic acid (10 mL) was added 3-acetylindole **152** (1.15 g, 7.2 mmol) portionwise, the reaction mixture was protected from light and stirred for 2.5 h. After cooling down to -10°C, to allow crystallisation of intermediate thallium compound **184**, potassium iodide (8.3 g, 7 equiv.) as a solution in water (25 mL) was added and the resultant solution was allowed to stir for a further 30 min. The reaction was made basic using NaOH (15% solution, 20 mL). The resultant mixture was filtered, and the filtrate was extracted with dichloromethane (3 x 30 mL). The combined organics were washed with water (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Recrystallisation from ethanol gave the *title compound* as a beige solid (563 mg, 27%), m.p. 204 °C; $\nu_{max.}$ (KBr) 3146, 1646, 1402 cm^{-1}; δ_H (250 MHz: $CDCl_3$ / DMSO) 2.72 (3 H, s, CH_3), 6.59 (1 H, t, J 7.8, ArH), 7.15 (1 H, d, J 8.4, ArH), 7.43 (1 H, d, J 7.8, ArH), 7.59 (1 H, s, ArH), 11.21 (1 H, br s, NH); δ_C (62.9 MHz; $CDCl_3$ / DMSO) 29.6 (CH_3), 84.8 (CX), 111.9 (CH), 118.7 (CX), 123.9 (CH), 134.1 (CH), 137.8 (CX), 191.8

(ketone); *m/z* (EI) 285 (M^+, 40%), 270 (50), 259 (60), 159 (50), 144 (100); (Found : 284.96524. $C_{10}H_8INO$ requires 284.96524).



tert-*Butyl 3-acetyl-4-iodoindole-1-carboxylate* ***186***

To a stirred suspension of 3-acetyl-4-iodoindole **185** (248 mg, 0.87 mmol) and di-*tert*-butyl pyrocarbonate (228 mg, 1.2 equiv) in acetonitrile (10 mL) was added 4-dimethylamino pyridine (10.6 mg, 10% molar equiv.). After 30 min the reaction mixture was diluted with ether (10 mL). The organic layer was washed in succession by $KHSO_4$ (1M, 3 x 10 mL), water (10 mL), saturated $NaHCO_3$ (10 mL), brine (10mL) then dried ($MgSO_4$) and concentrated *in vacuo*. Recrystallisation from ethyl acetate gave the *title compound* as a colourless solid (314 mg, 94%), m.p. 94 - 96°C; $\nu_{max.}$ (KBr) 1750, 1678, 1446, 1370 cm^{-1}; δ_H (250 MHz: $CDCl_3$) 1.68 (9 H, s, $C(CH_3)_3$), 2.62 (3 H, s, CH_3), 7.04 (1 H, t, J 7.7, ArH), 7.85 (1 H, m, ArH), 8.03 (1 H, s, ArH), 8.74 (1 H, m, ArH); δ_C (62.9 MHz; $CDCl_3$) 28.0 ($C(\underline{C}H_3)_3$), 31.6 (CH_3), 86.8 ($\underline{C}(CH_3)_3$), 114.9 (CH), 126.3 (CH), 130.2 (CH), 136.4 (CH), 158.2 (CX).



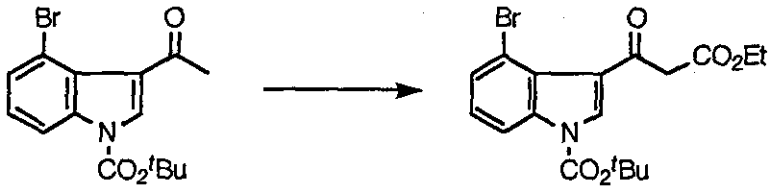
tert-*Butyl 3-diazoacetyl-4-iodoindole-1-carboxylate* ***176b***

A solution of LiHMDS was prepared *in situ* by the dropwise addition of butyl lithium (1.6M solution, 0.56 mL, 1.2 equiv.) to a stirred solution of 1,1,1,3,3,3-hexamethyldisilazane (0.188 mL, 1.3 equiv.) in THF (3 mL) at 0°C under a nitrogen atmosphere. After stirring for 15 min at this temperature, the solution was cooled down to -78°C. At this temperature, *tert*-butyl 3-acetyl-4-iodoindole-1-carboxylate (250 mg, 0.68 mmol) was added dropwise as a solution in THF (10 mL), over a 5 min period. The reaction mixture was stirred at -78°C for 30 min and then 2,2,2-trifluoroethyl trifluoroacetate (0.120 mL, 1.2 equiv.) was added rapidly in one portion. After stirring for 10 min the mixture was diluted with ether (10 mL) and washed with HCl (5% solution, 10 mL). The aqueous layer was extracted with ether (2 x 10 mL). The combined organics were washed with brine (10 mL) and concentrated *in vacuo*. The

resulting solid was then suspended in acetonitrile (10 mL) to which was added water (0.013 mL, 1 equiv.) and triethylamine (1.85 mL, 1.5 equiv.). To this stirred solution was added mesyl azide (160 mg, 1.5 equiv.) dropwise as a solution in acetonitrile (5 mL) over a 5 min period. After the addition was complete, the resulting mixture was stirred for 12 h. The reaction mixture was then diluted with ether (20 mL) and washed with NaOH (15% solution, 4 x 10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography (eluant ethyl acetate : light petroleum) gave the *title compound* as a pale yellow glassy solid (90 mg, 22%) contaminated with traces of methanesulfonyl azide, $\nu_{max.}$ 2106, 1744, 1623 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.64 (9 H, s, $C(CH_3)_3$), 5.62 (1 H, s, CH), 7.02 (1 H, d, J 7.0, ArH), 7.74 (1 H, d, J 7.2 , ArH), 7.86 (1 H, s, ArH), 8.20 (1 H, d, J 8.5, ArH).

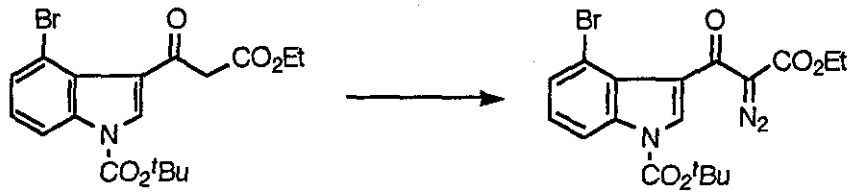
tert-*Butyl (2-ethoxycarbonyl-1-oxoethyl)-4-bromoindole-1-carboxylate* ***189***

A solution of LiHMDS was prepared from the addition of butyl lithium (1.6M, 4.25 mL, 2 equiv.) to a solution of 1,1,1,3,3,3-hexamethyldisilazane (1.43 mL, 2 equiv.) at 0°C in THF (30 mL) under a nitrogen atmosphere. After stirring for 30 min, the solution was cooled down to -78°C. To this was added *tert*-butyl 3-acetyl-4-bromoindole-1-carboxylate **174** (1.15 g, 3.40 mmol) dropwise as a solution in THF (30 mL). After 30 min, DMPU (0.411 mL, 1 equiv.) and ethyl cyanoacetate (0.671 mL, 2 equiv.) were added. After stirring for 15 min the reaction was warmed to -20°C, then quenched with saturated NH_4Cl (25 mL) and diluted with water (50 mL) and ether (50 mL), followed by extraction with ether (3 x 50 mL). The combined organics were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (eluant ethyl acetate ; light petroleum) gave the *title compound* as a colourless oil (1.10 g, 79%, *ca.* 7 : 3 ratio of *keto* : *enol* form), $\nu_{max.}$ (thin film) 1744, 1690, 1648, 1638 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.26 (3 H, m, *keto-enol*, $OCH_2\underline{C}H_3$), 1.67 (9 H, s, $C(CH_3)_3$), 3.95 (2 H, s, *keto*, $OC\underline{H}_2CH3$), 4.15 (2 H, q, J 7.3, *keto*, $OC\underline{H}_2CH3$), 4.22 (2 H, q, J 3.3, *enol*, $OC\underline{H}_2CH3$), 5.42 (1 H, m, *enol*, CH), 7.48 - 7.52 (1 H, m, ArH), 8.01 (1 H, s, *enol*, ArH), 8.10 (1 H, s, *keto*, ArH), 8.19 (1 H, m, ArH); δ_C (62.9 MHz; $CDCl_3$) 14.8 *keto* (CH_3), 14.9 *enol* (CH_3), 28.7 ($C(\underline{C}H_3)_3$), 50.6 *keto* (CH_2), 61.0 *enol* (CH_2), 62.1 *keto* (CH_2), 85.7 *enol* ($\underline{C}(CH_3)_3$), 86.6 *keto* ($\underline{C}(CH_3)_3$), 115.0 *keto* (CH), 115.2 *enol* (CH), 127.1 *keto* (CH), 128.8 *enol* (CH), 129.6 *enol* (CH), 129.8 *keto* (CH), 131.0 *enol* (CH), 131.9 *keto* (CH), 137.6 (CX), 149.0 (carbamate), 167.6 (ester). 189.1 *keto* (ketone).



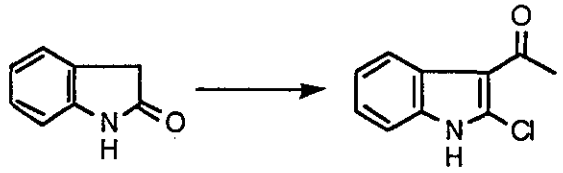
tert-*Butoxy (2-diazo-2-ethoxycarbonyl-1-oxoethyl)-4-bromoindole-1-carboxylate* ***190***

To a stirred solution of indole ester **189** (800 mg, 1.95 mmol) and 4-acetomidobenzenesulfonyl azide **111** (562 mg, 1.2 equiv.) in acetonitrile (20 mL) at 0°C was added triethylamine (0.407 mL, 1.5 equiv.). After stirring for 12 h, the reaction mixture was concentrated *in vacuo*. The residue was triturated with ether : light petroleum (1 : 1, 70 mL). Concentration of the organic solution under reduced pressure, followed by purification by flash chromatography (eluant light petroleum : ethyl acetate) gave the *title compound* as a pale yellow oil (702 mg, 83 %), $\nu_{max.}$ (thin film) 2137, 1743, 1695, 1630, 1423 cm^{-1}; δ_H (250MHz; $CDCl_3$) 0.93 (3 H, t, J 7.1, $OCH_2\underline{CH_3}$), 1.52 (9 H, s, $C(CH_3)_3$), 3.98 (2 H, q, J 7.1, $OC\underline{H_2}CH_3$), 7.20 (1 H, m, ArH), 7.43 (1 H, d, J 7.6, ArH), 7.84 (1 H, s, ArH), 8.21 (1 H, d, J 8.3, ArH); δ_C (62.9 MHz; $CDCl_3$) 13.8 ($OCH_2\underline{C}H_3$), 27.9 ($C(\underline{C}H_3)_3$), 61.4 ($O\underline{C}H_2CH_3$), 85.1 ($\underline{C}(CH_3)_3$), 114.5 (CH), 120.7 (CX), 125.7 (CH), 127.4 (CH), 127.5 (CH), 135.7 (CX), 148.5 (carbamate), 160.7 (ester), 182.2 (ketone).



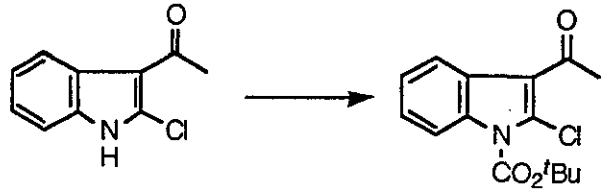
3-Acetyl-2-chloroindole ***194***

To a stirred solution of phosphorus oxychloride (67 mL, 3.3 equiv.) in chloroform (200 mL) was added *N,N*-dimethyl acetamide (66.8 mL, 3.3 equiv.) dropwise, keeping the temperature below 10°C. After the addition was complete, the reaction mixture was stirred for 10 min to allow complete formation of the greenish yellow Vilsmeier complex. Then oxindole **194** (29 g, 218 mmol) in chloroform (250 mL) was added to the reaction mixture dropwise over 1.5 h, keeping the reaction mixture around 10°C. The reaction mixture were then refluxed for 2 h. After cooling, it was extracted with water (3 x 500 mL). The combined aqueous phases were taken to pH 5 using potassium acetate. The resulting suspension was filtered, collected, triturated with hot chloroform (500 mL) and refiltered. This yielded the *title compound* as a pale green solid (20.5 g, 48 %); data identical to that given in reference 123.



tert-*Butyl 3-acetyl-2-chloroindole-1-carboxylate* ***195***

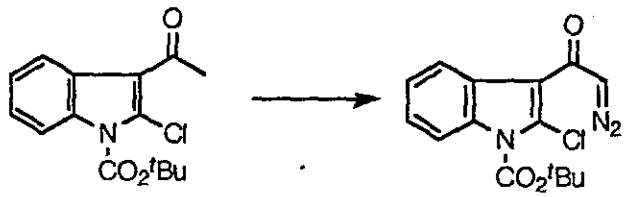
To a stirred suspension of 3-acetyl-2-chloroindole **194** (5.0 g, 25.8 mmol) and di-*tert*-butyl pyrocarbonate (6.20 g, 1.1 equiv.) in acetonitrile (50 mL) was added 4-dimethylamino pyridine (404 mg, 10% molar equiv.). After 1 h the reaction mixture was diluted with ether (100 mL). The organic layer was washed in succession by $KHSO_4$ (1M, 3 x 50 mL), water (50 mL), saturated $NaHCO_3$ (50 mL), brine (50mL) then dried ($MgSO_4$) and concentrated *in vacuo*. Recrystallisation from ethyl acetate gave the *title compound* as a pale pink solid (4.02 g, 53%), $\nu_{max.}$ (KBr) 1674, 1614, 1439 cm^{-1}; δ_H (250 MHz: $CDCl_3$) 1.71 (9 H, s, $C(CH_3)_3$), 2.73 (3 H, s, CH_3), 7.32 (2 H, m, ArH), 7.96 (1 H, m, ArH), 8.29 (1 H, s, ArH); δ_C (62.9 MHz; $CDCl_3$) 28.0 ($C(\underline{C}H_3)_3$), 31.6 (CH_3), 83.0 ($\underline{C}(CH_3)_3$), 114.0 (CH), 121.8 (CH), 124.4 (CH), 125.3 (CH); *m/z* (CI) 294 (*MH*$^+$, 10%), 194 (100), 160 (80); (Found: *MH*$^+$ 294.0897. $C_{15}H_{16}ClNO_3$ + *H* requires 294.0897).



tert-*Butyl 2-chloro-3-diazoacetylindole-1-carboxylate* ***192***

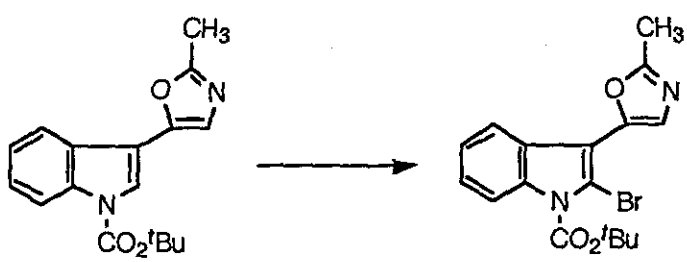
A solution of LiHMDS was prepared *in situ* by the dropwise addition of butyl lithium (1.6M solution, 4.42 mL, 1.2 equiv.) to a stirred solution of 1,1,1,3,3,3-hexamethyldisilazane (1.49 mL, 1.3 equiv.) in THF (15 mL) at 0°C under a nitrogen atmosphere. After stirring for 15 min at this temperature, the solution was cooled down to -78°C. At this temperature, *tert*-butyl 3-acetyl-2-chloroindole-1-carboxylate **195** (1.73 g, 5.90 mmol) was added dropwise as a solution in THF (30 mL), over a 20 min period. The reaction mixture was stirred at -78°C for 30 min and then 2,2,2-trifluoroethyl trifluoroacetate (0.95 mL, 1.2 equiv.) was added rapidly in one portion, After stirring for 10 min the mixture was diluted with ether (30 mL) and washed with HCl (5% solution, 30 mL). The aqueous layer was extracted with ether (2 x 20 mL). The combined organics were washed with brine (20 mL) and concentrated *in vacuo*. The resulting solid was then suspended in acetonitrile (20 mL) to which was added water (0.011 mL, 1 equiv.) and triethylamine (1.23 mL, 1.5 equiv.). To this stirred solution was added mesyl azide (1.26 g, 1.5 equiv.) dropwise as a solution in acetonitrile (20 mL) over a

20 min period. After the addition was complete, the resulting mixture was stirred for 12 h. The reaction mixture was then diluted with ether (40 mL) and washed with NaOH (15% solution, 4 x 20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography (eluant ethyl acetate : light petroleum) gave the *title compound* as a pale red solid (523 mg, 28%), m.p. < 15°C, $\nu_{max.}$ 2109, 1747, 1665 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.72 (9 H, s, $C(CH_3)_3$), 6.16 (1 H, s, CH), 7.32 (2 H, m, ArH), 7.99 (1 H, m, ArH), 8.16 (1 H, m, ArH); δ_C (62.9 MHz; $CDCl_3$) 28.0 ($C(\underline{C}H_3)_3$), 57.5 (CH), 86.2 ($\underline{C}(CH_3)_3$), 114.3 (CH), 121.1 (CH), 122.0 (CX), 124.2 (CH), 125.3 (CH); *m/z* (CI) 320 (MH^+, 80%), 218 (80), 164 (100); (Found: MH^+ 320.0802. $C_{15}H_{14}ClN_3O_3 + H$ requires 320.0802).



*2-Methyl-5-(*N-tert *butoxycarbonyl 2-bromoindolyl)oxazole* ***198***

A solution of **157a** (50 mg, 0.17 mmol), *N*-bromosuccinimide (36 mg, 1.2 equiv.) and *tert*-butyl peroxide (1 drop) in tetrachloromethane (4 mL) were refluxed in the presence of a bright light for 5 h. After cooling, the reaction mixture was concentrated *in vacuo* and then purified by flash chromatography (eluant ethyl acetate : light petroleum). This yielded the *title compound* as a glassy pale yellow solid (39 mg, 64%), δ_H (400 MHz; $CDCl_3$) 1.70 (9 H, s, $C(CH_3)_3$), 2.59 (3 H, s, CH_3), 7.38 (3 H, m, ArH), 8.00 (1 H, d, J 7.6, ArH), 8.20 (1 H, s, ArH); δ_C (100 MHz; $CDCl_3$) 14.1 (CH_3), 28.0 ($C(\underline{C}H_3)_3$), 84.5 ($\underline{C}(CH_3)_3$), 107.8 (CX), 110.4 (CX), 115.2 (CH), 121.0 (CH), 123.2 (CH), 123.8 (CH), 125.1 (CH), 127.1 (CX), 134.9 (CX), 143.3 and 149.9 (C-5 and carbamate), 160.0 (C-2); *m/z* (CI) 378 (^{81}Br M^+, 20%), 376 (^{79}Br M^+, 20), 278 (50), 276 (50), 199 (100); (Found: M^+ 376.0423. $C_{17}H_{17}{}^{79}BrN_2O_3$ requires 376.0423).



N-*Phthaloylaminoacetonitrile* ***206a***

To a stirred solution of aminoacetonitrile hydrochloride **205** (2.0 g, 21.6 mmol) and phthalic anhydride (3.20 g, 1 equiv.) in chloroform was added triethylamine (3.01 mL, 1 equiv.)

dropwise. The reaction mixture was then refluxed for 48 h. After cooling the reaction mixture was diluted with dichloromethane (50 mL), washed with $NaHCO_3$ (10% solution, 2 x 50 mL), water (50 mL), brine (50 mL) and dried (Na_2SO_4). Filtration and concentration *in vacuo* gave the *title compound* as a colourless crystalline solid (3.40 g, 84 %), m.p 126 - 128°C; $\nu_{max.}$ (KBr) 1778, 1721, 1422 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 4.59 (2 H, s, CH_2), 7.79 - 7.84 (3 H, m, ArH), 7.89 - 7.94 (2 H, m, ArH); δ_C (62.9 MHz; $CDCl_3$) 25.1 (CH_2), 114.0 (CN), 124.1 (CH), 131.3(CX), 134.9 (CH), 167.0 (carbonyl); *m/z* (EI) 186 (M^+, 100%), 132 (70), 104 (90); (Found M^+ 186.0249. $C_{10}H_6N_2O_2$ requires 186.0249).

N-tert *Butoxycarbonylaminoacetonitrile* ***206b***

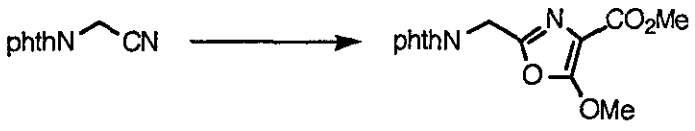
To stirred solution of NaOH (475 mg, 1.1 equiv.) in water (10 mL) was added aminoacetonitrile hydrochloride **205** (1.0 g, 10.8 mmol). The reaction mixture was then diluted with *tert*-butyl alcohol (8 mL) and stirred for 15 min. After this time di-*tert*-butyl pyrocarbonate (2.35 g, 1 equiv.) was added. After stirring for 16 h, HCl (2M 10 mL) was added, and the solution extracted with ether (3 x 20 mL). The combined organics were washed with saturated $NaHCO_3$ (10 mL), water (2 x 20 mL), brine (20 mL) and dried ($MgSO_4$). Concentration *in vacuo* followed by flash chromatography (eluant ethyl acetate : light petroleum) gave the *title compound* as a colourless solid. (1.36 g, 81%), m.p. 38 - 40°C; δ_H (250 MHz; $CDCl_3$) 1.43 (9 H, s, $C(CH_3)_3$), 4.01 (2 H, d, J 5.5, CH_2), 5.39 (1 H, s, NH); δ_C (62.9 MHz; $CDCl_3$) 28.2 ($C(\underline{C}H_3)_3$), 29.0 (CH_2), 81.2 ($\underline{C}(CH_3)_3$), 116.6, (CN), 155.0 (carbamate); *m/z* (EI) 157 (MH^+, 20%), 156 (M^+, 5), 101 (100); (Found: M^+ 159.0916. $C_7H_{12}N_2O_2$ requires 156.0899).

N-*Benzyloxycarbonylaminoacetonitrile* ***206c***

To stirred solution of NaOH (258 mg, 1.1 equiv.) in water (6.5 mL) was added aminoacetonitrile hydrochloride **205** (542 mg, 5.85 mmol). The reaction mixture was then diluted with *tert*-butyl alcohol (5 mL) and stirred for 15 min. After this time benzyl chloroformate (0.837 mL, 1 equiv.) was added. After stirring for 16 h, HCl (2M 5 mL) was added, and the solution extracted with ether (3 x 10 mL). The combined organics were washed with saturated $NaHCO_3$ (10 mL), water (2 x 10 mL), brine (20 mL) and dried ($MgSO_4$). Concentration *in vacuo* followed by flash chromatography (eluant ethyl acetate : light petroleum) gave the *title compound* as a colourless solid. (880 mg, 79%); spectral data identical to that given in reference 129

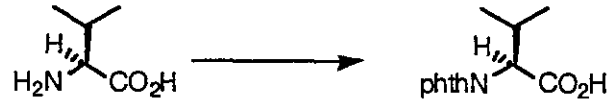
Methyl 5-methoxy-2-[N-phthaloyl methylamine] oxazole-4-carboxylate ***207***

To a refluxing solution of *N*-phthaloylaminoacetonitrile **206a** (200 mg, 1.07 mmol) and rhodium(II) acetate (23.7 mg, 5 % molar equiv.) in chloroform (7 mL) was added a solution of dimethyl diazomalonate **70** (232.2 mg, 1.5 equiv.) in chloroform (5 mL) over a 5 h period. The reaction mixture was refluxed for an additional 2 h. Concentration *in vacuo* of the reaction mixture, followed by flash chromatography (eluant light petroleum : ethyl acetate) gave the *title compound* as a pale yellow solid (121 mg, 36%), m.p. 143 - 145°C; $\nu_{max.}$ (KBr) 1771, 1723, 1422 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 3.76 (3H, s, CO_2CH_3), 4.09 (3H, s, OCH_3), 4,94 (2H, s, CH_2), 7.68 - 7.75 (3H, m, ArH), 7.80 - 7.85 (2H. m, ArH); δ_C (62.9 MHz; $CDCl_3$) 34.4 (CH_2), 51.6 ($CO_2\underline{C}H_3$), 59.9 (OCH_3), 106.5 (C-5), 123.6 (CH), 131.7 (CX), 134.3 (CH), 147.2 (C-4), 161.4 (ester), 161.6 (C-2), 167.0 (carbonyl); *m/z* (EI) 317 (*MH*$^+$, 100%), 284 (60); (Found *MH*$^+$ 317.0774. $C_{15}H_{12}N_2O_6$ + *H* requires 317.07735).



N-*Phthaloyl-2(S)-2-amino-3-methylbutanoic acid* ***210***

A solution of (*S*)-valine **208** (1.24 g, 10.6 mmol), *N*-carboethoxyphthalimide **209** (2.32 g, 1 equiv.), triethylamine (2.06 mL. 1.4 equiv.) in THF (30 mL) was refluxed for 24 h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was dissolved in dichloromethane (50 mL) and extracted with $NaHCO_3$ (10% solution, 3 x 50 mL). The extracted was acidified to pH 2 with dilute HCl (2 M), and extracted with dichloromethane (3 x 50 mL). The organic extract was washed with water (50 mL) and dried (Na_2SO_4). Concentration *in vacuo* followed by recrystallisation from toluene gave the *title compound* as a colourless solid (1.36 g, 58%), m.p. 106 - 108°C; $[\alpha]_D^{20}$ = -53.9 (c=1.2, $CHCl_3$); $\nu_{max.}$ (KBr) 3234, 1771, 1759, 1696, 1397 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 0.92 (3H, d, J 6.8, $CH(C\underline{H}_3)_2$), 1.17 (3H, d, J 6.7, $CH(C\underline{H}_3)_2$), 2.75 (1H, m, $C\underline{H}(CH_3)_2$), 4.63 (1 H, d, J 8.4, CH), 7.72 - 7.77 (3H, m, ArH), 7.83 - 7.89 (2H, m, ArH); δ_C (62.9 MHz; $CDCl_3$) 19.4 ($CH(\underline{C}H_3)_2$), 20.8 ($CH(\underline{C}H_3)_2$), 28.3 ($\underline{C}H(CH_3)_2$), 57.4 (CH), 123.5 (CH), 131.5 (CH), 134.1 (CX), 167.7 (carbonyl), 173.8 (acid)



N-*Phthaloyl-2(*S*)-2-amino-3-methylbutane-1-carboxamide* ***212***

To a stirred solution of 4-methylmorpholine (1.43 mL, 1 equiv.) and ethyl chloroformate (1.65 mL, 1 equiv.) at -15°C, under a nitrogen atmosphere, was added *N*-phthaloyl-2(*S*)-2-amino-3-methylbutanoic acid **210** (3.35 g, 15 mmol) as a solution in THF (2 mL) dropwise keeping the temperature at -15°C. After stirring for 10 min, aqueous ammonia (30% solution, 2 mL) in THF (4 mL) was added to the reaction mixture. The resulting solution was stirred at room temperautre for 12 h. After this time ethyl acetate (30 mL) and water (50 mL) were added and the reaction mixture was extraction with ethyl acetate (2 x 30 mL). The combined organic layers were washed with $NaHCO_3$ (10% solution, 30 mL), brine (30 mL), HCl (1 M, 30 mL), brine (30 mL) and dried (Na_2SO_4). Concentration *in vacuo* gave the *title compound* as a colourless solid (2.24g, 61%), m.p. 170°C; (Found C, 63.1; H, 5.64; N, 11.3. $C_{13}H_{14}N_2O_3$ requires C, 63.4; H, 5.73; N, 11.4 %); $[\alpha]_D^{20}$ = +26.5 (c=0.9, $CHCl_3$); $\nu_{max.}$ (KBr) 3203, 1773, 1717, 1653, 1471 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 0.35 (3 H, d, J 6.7, $CH(C\underline{H}_3)_2$), 0.61 (3 H, d, J 6.6, $CH(C\underline{H}_3)_2$), 2.33 (2 H, m, $C\underline{H}(CH_3)_2$), 3.83 (2 H, d, J 9.9,CH), 6.24 (1 H, br s, NH), 6.73 (1 H, br s, NH); δ_C (62.9 MHz; $CDCl_3$) 19.0 ($CH(\underline{C}H_3)_2$), 20.1 ($CH(\underline{C}H_3)_2$), 26.9 ($\underline{C}H(CH_3)_2$), 60.3 (CH), 122.8 (CH), 131.1 (CX), 133.8 (CH), 167.6 (carbonyl), 170.1 (acid); *m/z* (EI) 247 (*MH*$^+$, 100%), 202 (30), (Found: *MH*$^+$ 247.1083. $C_{13}H_{14}N_2O_3$ + *H* requires 247.10825).

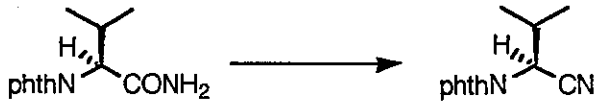
N-*Phthaloyl-2(*S*)-2-amino-3-methylbutane-1-carbonitrile* ***213***

(a) A mixture of *N*-phthaloyl-2(*S*)-2-amino-3-methylbutane-1-carboxamide **212** (1.5 g, 6.1 mmol) and 4-toluenesulphonyl chloride (1.39 g, 1.2 equiv.) in pyridine (10 mL) was heated to reflux for 12 h. After dilution with ether (50 mL) the reaction mixure was extracted with copper(II) sulphate solution (5 x 50 mL). The remaining organic layer was washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo.* The resulting precipitate was diluted with ethyl acetate (40 mL) then washed with hydrochloric acid (2M, 30 mL), water (3 x 30 mL) and saturated NH_4Cl (20 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography (eluant ether : light petroleum) gave the *title compound* as a colourless solid (1.03g, 74%), $[\alpha]_D^{20}$ = +18.6 (c=1.3, $CHCl_3$); other spectral data given below.

(b) To a stirred solution of *N*-phthaloyl-2(*S*)-2-amino-3-methylbutane-1-carboxamide **212** (1.5 g, 6.1 mmol) and pyridine (1.03 mL, 2.1 equiv.) in THF (15 mL) at -10°C was added

trifluoroacetic anhydride (0.936 mL, 1.1 equiv.) dropwise. After stirring for 1 h, the solution was diluted with HCl (2.0 M, 25 mL) and ether (70 mL). The organic layer was separated, washed with water (30 mL), brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (eluant ethyl acetate : light petroleum) gave the *title compound* as a colourless solid (1.24 g, 89%), $[\alpha]_D^{20}$ = +20.6 (c=1.9, $CHCl_3$); other spectral data given below.

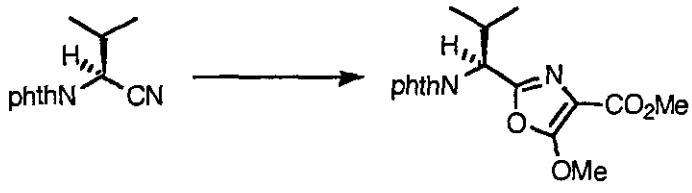
(c) To a stirred solution of *N*-phthaloyl-2(*S*)-2-amino-3-methylbutane-1-carboxamide **212** (206 mg, 0.84 mmol) in THF (5 mL) at -10°C, under a nitrogen atmosphere, was added Burgess' Reagent ([methoxycarbonylsulfamoyl]triethylammonium hydroxide inner salt, 500 mg, 2.5 equiv.) portionwise over 1 h. After the addition was complete, the solution was stirred for a further 5 min, then applied straight onto a silica column. Purification by flash chromatography (eluant ethyl acetate : light petroleum) gave the *title compound* as a colourless solid (179 mg, 87%), m.p. 99 - 101°C; (Found C, 68.3: H, 5.34: N, 11.85. $C_{13}H_{12}N_2O_2$ requires C, 68.4: H, 5.30: N, 12.3 %); $[\alpha]_D^{20}$ = +20.4 (c=1.5, $CHCl_3$); $\nu_{max.}$ (KBr) 2353, 1775, 1728 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 0.93 (3H, d, J 6.7, $CH(C\underline{H}_3)_2$), 1.26 (3H, d, J 6.7, $CH(C\underline{H}_3)_2$), 2.67 (1H, m, $C\underline{H}(CH_3)_2$), 4.74 (1H, d, J 5.2, CH), 7.73 - 7.81 (2H, m, ArH), 7.88 - 7.93 (2H, m, ArH); δ_C (62.9 MHz; $CDCl_3$) 18.6 ($CH(\underline{C}H_3)_2$), 19.6 ($CH(\underline{C}H_3)_2$), 30.6 ($\underline{C}H(CH_3)_2$), 46.5 (CH), 115.6 (CN), 124.0 (CH), 131.2 (CX), 134.8 (CH), 166.2 (carbonyl); *m/z* (EI) 246 (100%, $M+NH_4^+$), 202 (30), 188 (10); (Found $M+NH_4^+$ 246.1243 $C_{13}H_{12}N_2O_2 + NH_4^+$ requires 246.1243).



Methyl 5-methoxy-2-(1(S)-N-phthaloyl-1-amino-2-methyl propane)oxazole-1-carboxylate ***216***

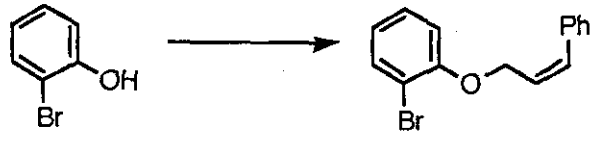
To a refluxing solution of *N*-phthaloyl-2(*S*)-2-amino-3-methylbutane-1-carbonitrile **213** (250 mg, 1.09 mmol) and rhodium(II) perfluorobutyrate **180** (23 mg, 1% molar equiv.) in chloroform (5 mL), was added a solution of dimethyl diazomalonate **70** (190 mg, 1.1 equiv.) in chloroform (6 mL) dropwise over 6 h. After the addition was complete, the reaction was refluxed for a further 2 h, cooled and concentrated *in vacuo*. Purification by flash chromatography (eluant ethyl acetate : light petroleum) gave the *title compound* as an oil (70 mg, 18%) contaminated with *ca.* 2% of an impurity, $[\alpha]_D^{20}$ = -43.2 (c=1.5, $CHCl_3$); $\nu_{max.}$ (thin film) 1768, 1721, 1630, 1384 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 0.85 (3 H, d, J 6.6, $CH(C\underline{H}_3)_2$), 0.97 (3 H, d, J 6.2, $CH(C\underline{H}_3)_2$), 3.07 (1 H, m, $C\underline{H}(CH_3)_2$), 3.85 (3 H, s,

CO_2CH_3), 4.17 (3 H, s, OCH_3), 5.05 (1 H, d, J 10.4, CH), 7.76 (2 H, m, ArH), 7.84 (2 H, m, ArH); δ_C (62.9 MHz; $CDCl_3$) 19.1 ($CH(\underline{C}H_3)_2$), 20.3 ($CH(\underline{C}H_3)_2$), 28.2 ($\underline{C}H(CH_3)_2$), 51.6 ($CO_2\underline{C}H_3$), 53.0 (CH), 59.8 (OCH_3), 123.4 (CH), 131.4 (CX), 134 (CH), 149.6 (C-4), 161.3 (C-5), 164.3 and 167.2 (carbonyl and C-2); *m/z* (EI) 358 (M^+, 20%), 202 (100), 160 (50); (Found: M^+ 358.1165. $C_{18}H_{18}N_2O_6$ requires 358.1165).



O-*(3-Phenyl prop-2-ene)-2-bromophenol* ***221***

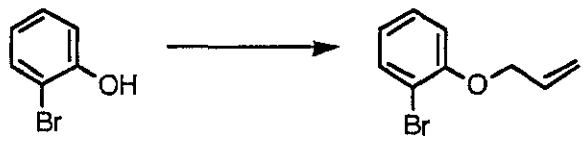
A solution of 2-bromophenol (10.0 g, 57.8 mmol), cinnamyl chloride (8.82 g, 1 equiv), anhydrous potassium carbonate (7.99 g, 1 equiv.) in acetone (30 mL) was refluxed for 12 h. After cooling, the reaction mixture was poured into water (100 mL) and extracted with ether (3 x 20 mL). The combined organics were washed with NaOH (40% solution, 2 x 30 mL), brine (40 mL) and dried ($MgSO_4$). Filtration, followed by concentration *in vacuo*, gave the *title compound* as a pale yellow viscous oil, which crystallised at 5°C (14.14 g, 85%), m.p 48 - 50°C; $\nu_{max.}$ (thin film) 1479, 1244, 1031 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 4.79 (2 H, d, J 5.4, OCH_2), 6.46 (1 H, m, CH), 6.72 (2 H, m, ArH), 6.91 (1 H, m, CH), 7.25 - 7.58 (6 H, m, ArH), 7.60 (1 H, d, 7.9, ArH); δ_C (62.9 MHz; $CDCl_3$) 69.7 (OCH_2), 112.4 (CX), 113.8 (CH), 122.1 (CH), 123.7 (CH), 126.6 (CH), 127.9 (CH), 128.2 (CH), 128.4 (CH), 133.0 (CH), 133.4 (CH), 136.4 (CX), 155.0 (CX).



O-*(1-Prop-2-ene)-2-bromophenol* ***230***

A solution of 2-bromophenol (10.0g, 57.8 mmol), 3-bromoprop-1-ene (5.0 mL, 1 equiv.), anhydrous potassium carbonate (7.99g, 1 equiv.) in acetone (20 mL) was refluxed for 2 h. After cooling, the reaction mixture was poured into water (100 mL) and extracted with ether (3 x 20 mL). The combined organics were washed with NaOH (40% solution, 2 x 30 mL), brine (40 mL) and dried ($MgSO_4$). Filtration, followed by concentration *in vacuo*, gave the *title compound* as a pale yellow oil (11.0g, 89%), $\nu_{max.}$ (thin film) 1587, 1479 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 4.62 (2 H, m, $OC\underline{H}_2CH$), 5.34 (1 H, dq, J 1.6, J' 10.5, *Z* $CH=C\underline{H}_2$), 5.48 (1 H, dq, J 1.6, J' 17.1, *E* $CH=C\underline{H}_2$), 6.08 (1 H, m, $C\underline{H}=CH_2$), 6.68 (2 H, m, ArH), 7.24 (1 H, m,

ArH), 7.56 (1 H, dd, J 1.6, J' 7.7, ArH); δ_C (62.9 MHz; $CDCl_3$) 69.7 ($O\underline{C}H_2CH$), 112.4 (CX), 113.7 (CH), 117.7 ($CH=\underline{C}H_2$), 122.0 (CH), 128.4 (CH), 132.7 (CH), 133.5 (CH), 155.0 (CX).



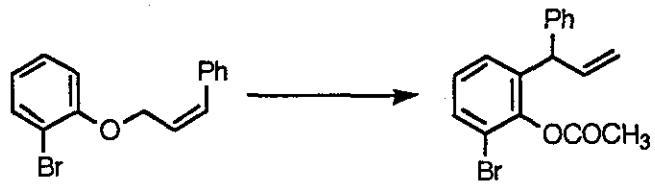
2-(1-Prop-2-ene)-6-bromophenol ***231***

To a stirred soution of *O*-(1-prop-2-ene)-2-bromophenol **230** (2.5 g, 11.7 mmol) in hexane (50 mL) under a nitrogen atmosphere, was added diethylaluminium chloride (1.0M solution in hexane, 23.5 mL, 2 equiv) dropwise. After stirring for 45 min, the reaction mixture was cooled down to 0°C, then quenched by the slow addition of HCl (2M, 20mL). The aqueous layer was then extracted with ether (3 x 20 mL). The combined organics were washed with brine (40 mL), dried ($MgSO_4$) and concentrated i*n vacuo*. Purification by bulb-to-bulb distillation (bath temp. 125°C @ 3mmHg) gave the *title compound* as a clear oil (1.43 g, 57%), $\nu_{max.}$ (thin film) 3510, 1451, 1238 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 3.46 (2 H, d, J 6.5, $PhCH_2$), 5.08 (1 H, m, $CH=C\underline{H}_2$), 5.14 (1 H, m, $CH=C\underline{H}_2$), 5.61 (1 H, br s, OH), 6.02 (1 H, m, $C\underline{H}=CH_2$), 6.77 (1 H, t, J 7.8, ArH), 7.10 (1 H, d, J 7.2, ArH), 7.34 (1 H, dd, J 1.4, J' 8.1, ArH); δ_C (62.9 MHz; $CDCl_3$) 34.9 ($PhCH_2$), 110.5 (CX), 116.1 ($CH=\underline{C}H_2$), 121.4 (CH), 127.8 (CX), 129.6 (CH), 129.9 (CH), 135.9 (CH), 150.1 (CX).

1-Acetyl-2-(1-phenyl prop-2-ene)-6-bromophenol ***232***

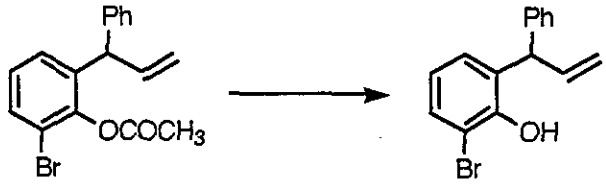
A soution of *O*-(3-phenyl prop-2-ene)-2-bromophenol **221** (2.0 g, 6.9 mmol), acetic anhydride (6 mL) and *N,N*-dimethyl aniline (6 mL) were heated to reflux under a nitrogen atmosphere for 19 h. After cooling, the reaction mixture was poured into ice-water (50 mL) and stirred for 10 min. After extraction with ether (100 mL), the organic layer was washed with HCl (5% solution, 4 x 20 mL), saturated $NaHCO_3$ (3 x 20 mL), dried ($MgSO_4$), then concentrated *in vacuo*. Purification by flash chromatography (eluant ether : light petroleum) gave the *title compound* as a pale yellow oil (1.87 g, 81 %), $\nu_{max.}$ (thin film) 1772, 1441, 1190, 1167 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 2.20 (3 H, s, $OCOCH_3$), 4.89 (1 H, d, J 6.7, ArCHPh), 4.98 (1 H, dt, J 1.1, J' 17.9, *E* $CH=C\underline{H}_2$), 5.30 (1 H, dt, J 1.4, J' 10.3, *Z* $CH=C\underline{H}_2$), 6.26 (1 H, m, $C\underline{H}=CH_2$), 7.10 (1 H, m, ArH), 7.16 - 7.23 (3 H, m, ArH), 7.25 - 7.37 (3 H, m, ArH), 7.52 (1 H, dd, J 1.7, J' 7.7, ArH); δ_C (62.9 MHz; $CDCl_3$) 20.5 ($OCOCH_3$), 49.3

(ArCHPh), 117.3 (CH), 126.7 (CH), 127.1 (CH), 128.4 (CH), 128.5 (CH), 128.9 (CH), 131.5 (CH), 137.9 (CX), 138.8 (CH), 141.4 (CX), 146.5 (CX), 167.6 (carbonyl); *m/z* (CI) 350 (^{81}Br *M*+NH_4^+, 90%), 348 (^{79}Br *M*+NH_4^+, 100), 224 (20); (Found: ^{79}Br *M*+NH_4^+ 348.0599. $C_{17}H_{15}{}^{79}BrO_2$ + NH_4 requires 348.0600).



6-Bromo-2-(1-phenylprop-2-ene)phenol ***220***

To a stirred solution of **232** (1.09 g, 3.29 mmol) in methanol (30 mL) was added aqueous ammonia (30% solution, 5 mL) dropwise. After 12 h, HCl (2M, 10 mL) was added and the solution was extracted with ether (3 x 30 mL). The combined organics were washed with water (30 mL), brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (eluant ethyl acetate : light petroleum) gave the *title compound* as a pale yellow oil (850 mg, 89%), $\nu_{max.}$ (thin film) 3510, 1493, 1448 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 4.95 (1 H, dt, J 1.5, J' 17.0, *Z* CH=C<u>H</u>$_2$), 5.12 (1 H, d, J 6.6, ArCHPh), 5.23 (1 H, dt, J 1.2, J' 10.0, *E* CH=C<u>H</u>$_2$), 5.61 (1 H, br s, OH), 6.28 (1 H, m, C<u>H</u>=CH$_2$), 6.76 (1 H, t, J 7.9, ArH), 7.07 (1 H, dd, J 1.4, J' 7.7, ArH), 7.16 - 7.35 (7 H, m, ArH).

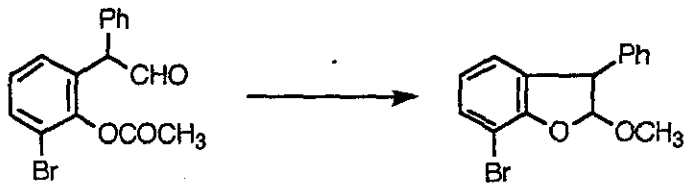


1-Acetyl-2-(phenylmethyl-1-carboxaldehyde)-6-bromo phenol ***233***

Ozone was bubbled through a stirred solution of alkene **232** (250 mg, 0.75 mmol) in dichloromethane (10 mL) at -78°C. After all the starting material had been consumed, as indicated by tlc and the reaction mixture turning deep blue, due to excess ozone being present. The excess ozone was removed by bubbling nitrogen gas through the mixture for 1 min, after which time dimethyl sulfide (0.5 mL, 10 equiv.) was added and the solution was allowed to warm to room temperature slowly. The reaction mixture was then washed with water (10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield the crude *title compound* as an oil (134 mg, 54%), $\nu_{max.}$ (thin film) 1770, 1731, 1443 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 2.30 (3 H, s), 4.95 (1 H, d, J 2.0), 7.08 - 7.78 (8 H, m), 9.88 (1 H, d, J 2.1).

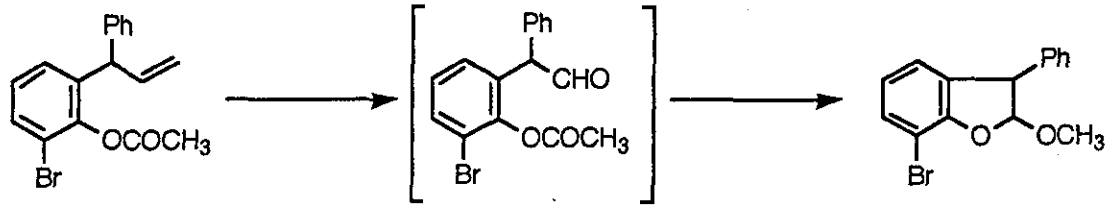
2-Methoxy-3-phenyl-2,3-dihydrobenzo[b]furan ***234a***

(a) To a stirred solution of aldehyde **233** (130 mg, 0.39 mmol) in methanol (5 mL) was added aqueous ammonia (1 mL). After stirring for 12 h, HCl (2 M, 2 mL) was added and the solution was extracted with ether (3 x 10 mL). The combined organics were washed with water (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (eluant ethyl acetate : light petroleum) gave the *title compound* as a clear oil (41 mg, 35%. 16 : 1 ratio; *cis* : *trans*); spectral data given below.

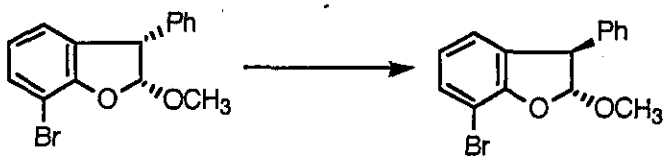


(b) Ozone was bubbled through a stirred solution of alkene **232** (250 mg, 0.75 mmol) in dichloromethane (10 mL) at -78°C. After all the starting material had been consumed, as indicated by tlc and the reaction mixture turning deep blue, due to excess ozone being present. The excess ozone was removed by bubbling nitrogen gas through the mixture for 1 min, after which time dimethyl sulfide (0.5 mL, 10 equiv.) was added and the solution was allowed to warm to room temperature slowly. After concentration *in vacuo*, the crude aldehyde was dissolved in methanol (10 mL) to which was added aqueous ammonia (2 mL) and stirred. After stirring for 12 h, HCl was added (2 M, 3 mL) and the solution was extracted with ether (3 x 10 mL). The combined organics were washed with water (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (eluant ethyl acetate : light petroleum) gave the *title compound* as a clear oil (82 mg, 36% overall, 16 : 1 ratio *cis* : *trans*), $\nu_{max.}$ ($CDCl_3$) 1625, 1602, 1448 cm^{-1}; δ_H (250 MHz; $CDCl_3$) *cis*-**234a** 3.34 (3 H, s, OCH_3), 4.65 (1 H, d, J 6.4, CHPh), 5.59 (1 H, d, J 6.2, C<u>H</u>OCH_3), 6.68 (1 H, t, J 7.7, ArH), 6.79 (1 H, m, ArH), 7.14 - 7.27 (6 H, m, ArH): nOe experiment, irradiation at 5.59 caused enhancement at 4.65 (4.4%); *trans*-**234a** 3.60 (3 H, s, OCH_3), 4.46 (1 H, d, J 2.1, CHPh), 5.52 (1 H, d, J 2.5, C<u>H</u>OCH_3), 6.69 (1 H, t, J 7.7, ArH), 7.01 (1 H, d, J 7.2, ArH), 7.13 (6 H, m, ArH): nOe experiment, irradiation at 5.52 caused no enhancement at 4.46; δ_C (62.9 MHz; $CDCl_3$) *cis*-**xa** 53.8 (OCH_3), 56.5 (CHPh), 108.5 (<u>C</u>HOCH_3), 112.5 (CH), 124.0 (CH), 127.6 (CH), 128.1 (CH), 130.2 (CH), 131.4 (CH);

trans-**xa** 55.6 (OCH_3), 56.4 (CHPh), 103.2 ($CHOCH_3$), 114.1 (CH), 127.4 (CH), 127.6 (CH), 129.2 (CH), 131.7 (CH); *m/z* (EI) 306 (^{81}Br M^+, 20%), 304 (^{79}Br M^+, 30), 165 (100), 105 (40); (Found: ^{79}Br M^+ 304.0099. $C_{15}H_{13}{}^{79}BrO_2$ requires 304.0099).



(c) A mixture of the benzofuran (16 : 1 ratio *cis* : *trans*) was dissolved in methanol (3 mL) to which was added a catalytic amount of 4-methylbenzenesulfonic acid, and allowed to stand for 7 days. After this time the mixture was concentrated *in vacuo*. Analysis by δ_H (250 MHz) showed a ratio of 27 :1 *trans* : *cis*.

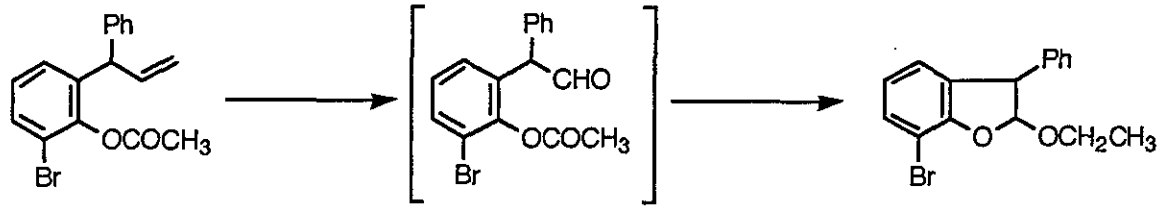


(±) (±)

2-Ethoxy-3-phenyl-2,3-dihydrobenzo[b]furan ***234b***

Ozone was bubbled through a stirred solution of alkene **232** (250 mg, 0.75 mmol) in dichloromethane (10 mL) at -78°C. After all the starting material had been consumed, as indicated by tlc and the reaction mixture turning deep blue, due to excess ozone being present. The excess ozone was removed by bubbling nitrogen gas through the mixture for 1 min, after which time dimethyl sulfide (0.5 mL, 10 equiv.) was added and the solution was allowed to warm to room temperature slowly. After concentration *in vacuo*, the crude aldehyde was dissolved in ethanol (10 mL) to which was added aqueous ammonia (2 mL) and stirred. After stirring for 12 h, HCl was added (2 M, 3 mL) and the solution was extracted with ether (3 x 10 mL). The combined organics were washed with water (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (eluant ethyl acetate : light petroleum) gave the *title compound* as a clear oil (36 mg, 15% overall, 20 : 1 ratio *cis* : *trans*), $\nu_{max.}$ (thin film) 1625, 1602, 1447 cm^{-1}; δ_H (250 MHz; $CDCl_3$) *cis*-**xb** 0.95 (3 H, t, J 7.0, CH_3), 3.40 (1 H, m, $CHOC\underline{H}_2$), 3.76 (1 H, m, $CHOC\underline{H}_2$), 4.63 (1 H, d, J 6.3, CHPh), 5.71 (1 H, d, J 6.5, $C\underline{H}OCH_2$), 6.65 - 6.79 (2 H, m, ArH), 7.16 - 7.27 (6 H, m); δ_C (62.9 MHz; $CDCl_3$) *cis*-**xb** 14.7 (CH_3), 53.8 (CHPh), 65.0

(CHO<u>C</u>H$_2$), 107.6 (<u>C</u>HOCH2), 122.3 (CH), 124.0 (CH), 125.8 (CH), 127.3 (CH), 130.2 (CH), 131.3 (CH); (Found : ^{79}Br M^+ 318.0255. $C_{16}H_{15}{}^{79}BrO_2$ requires 318.0256).



Chapter 6

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