SYNTHESIS OF BENZOHETEROCYCLES USING INTRAMOLECULAR CYCLISATION OF ARYL RADICALS

by

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SUMMARY

The purpose of the research was to investigate the synthesis of novel benzo 6- and 7-membered heterocycles with the aim of testing these compounds for biological activity at the Boots Company Plc Research Department.

The use of Bu_3SnH (tri-n-butyl tin hydride) was investigated for the synthesis of benzoheterocycles through radical cyclisation *via* aryl radicals.

The method was developed and the mechanism investigated using the cyclisation of N-(2-halogenophenyl)-thiobenzamide to yield 2-phenyl-benzothiazole. A pseudo $S_{RN}1$ mechanism has been proposed as a possible mechanism. The analogous carboxamide did not cyclise under any conditions but gave the non-cyclised reduced material, benzanilide.

N-(2-Halogenophenyl)-N-methyl-benzamides and thiobenzamides were cyclised *via* the corresponding aryl radicals to give N-methyl-6(5H)-phenanthridinone and thiophenanthridinone. A pseudo $S_{RN}1$ mechanism has also been proposed for this cyclisation. The use of DABCO [1,4-diazobicyclo(2.2.2)octane] to replace Bu_3SnH as a base in the cyclisation was partially successful in the cyclisation to N-methyl-6(5H)-phenanthridione. However, in the analogous N-(2-halogenophenyl)-N-methyl-thiobenzamide reactions, abstraction of the N-methyl group followed by $S_{RN}1$ cyclisation, gave 2-phenylbenzothiazole.

Attempts to extend this synthetic route to heterocyclic analogues of N-(2-halogenophenyl)-benzamide (phenyl replaced by pyridyl, pyrrolyl and furyl) failed.

Initial attempts using thiohydroxamate esters to replace Bu_3SnH for the generation of intermediate aryl radicals were not successful but further studies are required.

The use of Bu_3SnH was successfully extended to the synthesis of oxindoles from N-(2-halogenophenyl)-N-alkyl-α,β-unsaturated amides *via* the cyclisation of *ortho*-aryl radicals onto the β-position of the α,β-unsaturated N-alkyl amide side chain.

The cyclisations were fully investigated in order to determine the synthetic utility and mechanistic parameters. The following parameters were investigated: replacement of the amide oxygen by sulphur [N-(2-iodophenyl)-N-methyl-thiocinnamamide], replacement of the olefin by an acetylene group [N-(2-iodophenyl)-N-methyl-phenylpropynamide], variation of the N-substituent [N-benzyl-N-(2-iodophenyl)-cinnamamide], changes in β-substitution on the olefin of the α,β-unsaturated amide and the use of +I (e.g. Me) and -I (e.g. CO_2Me) groups, the effect of nucleofuge (I and Br), α,β-disubstitution [N-(2-iodophenyl)-N-methyl-cyclohex-1-ene-1-carboxamide], intermediate radical stability and bicyclisation *via* further cyclisation of the initial intermediate radical [N-(2-bromophenyl)-N-cinnamoyl-cinnamide].

ACKNOWLEDGEMENTS

I wish to thank the Technical and Academic staff of the Organic section of Loughborough University for their guidance and the Boots Company of Nottingham for their constant assistance, particularly with the recording of mass spectral and microanalytical data.

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CONTENTS

INTRODUCTION

Introduction

Although free radical chemistry has only developed relatively recently, its progress has been rapid. The beginnings of free radical chemistry, however are in the early 20th century.

Whilst anionic and cationic reactions were relatively easily studied and the mechanistic details elegantly explained in the pre-war period, free radical chemistry was largely unknown. Many reactions which could not be attributed to classical interpretations, were later to be explained by radical chemistry.

$$Ph_3C\text{–}CPh_3 \ [1] \rightleftharpoons 2\ Ph_3C^{\cdot} \ [2] \qquad (1)$$

Gomberg's [1] initial work on the equilibrium of "hexaphenylethane" [1] and triphenylmethyl radical [2] (Equation 1), highly stabilised and unreactive due to delocalisation of the unpaired electron, gave the chemical establishment the first tentative explanation for the evidence of free radicals.

It was not until Paneth's and Hofeditz [2] work some thirty years after Gomberg's first reports that conclusive proof of the existence of methyl radicals was offered along with their half life.

Definition of Radicals

In order to attempt to define free radicals it is necessary to explain how a bond can be broken. A bond between two atoms X and Y joined by a single sigma bond can be considered as a model. The bond can be fragmented by three different methods; by unequal fragmentation (heterolytic) (Equations 2 and 3) giving (negatively charged) anions and (positively charged) cations, and by equal fragmentation (homolytically) (Equation 4), two radicals are formed.

$$X\text{—}Y \longrightarrow X^{\ominus} + Y^{\oplus} \qquad (2)$$

$$X\text{—}Y \longrightarrow X^{\oplus} + Y^{\ominus} \qquad (3)$$

$$X\text{—}Y \longrightarrow X^{\cdot} + Y^{\cdot} \qquad (4)$$

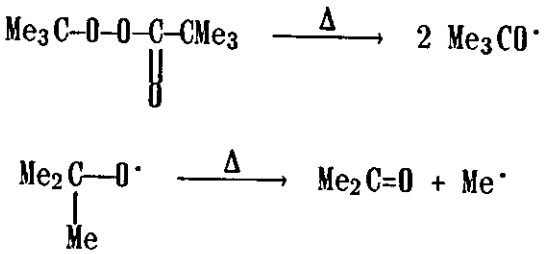
A free radical can be defined as an atom, molecule or complex which contains one or more unpaired electrons. This definition encompasses a huge area of research but for our purposes only organic radicals, and even more specifically, aryl radicals, will be dealt with.

Classification of Radical Reactions

There are several ways of describing radical reactions. One method is outlined by Sykes [3], and a more recent method, by Giese [4]. Sykes divides radical reactions into two main groups, unimolecular and bimolecular (which can be further subdivided). Giese divides radical reactions into: reactions of radicals with radicals, leading to non-chain "dead-end" reactions, and reactions between radicals and non-radicals which have the ability to self-perpetuate themselves in chain reactions.

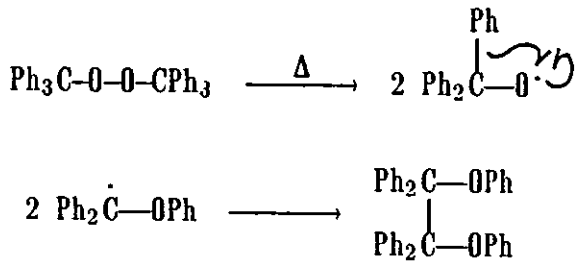
a. Unimolecular reactions

The main reaction type encompassed in this section is fragmentation [5], e.g. decomposition of t-butoxyl, formed by thermolysis of di-t-butyl peroxide at 130 °C, to yield acetone and methyl radicals (Scheme 1).



SCHEME 1

Rearrangement [6] of the radical can take place along with fragmentation. It is thought that the rearrangement proceeds by a bridged transition state with the driving force being the greater stability of the end product (Scheme 2).

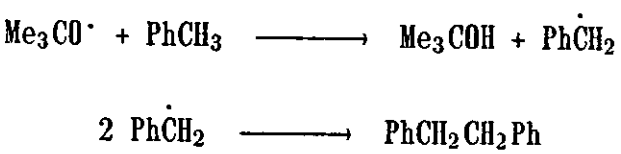


SCHEME 2

b. Bimolecular reactions between radicals

One type of bimolecular reaction is the generation of radicals which react with themselves thereby giving rise to a neutral moiety. Combination of radicals is assisted by high concentrations of radicals along with radicals with an increased life-time [7]. For example, dimerisation of benzyl radicals, formed by the reaction between t-butoxyl radicals and toluene at 100 °C, yields dibenzyl (Scheme 3). Another type of bimolecular reaction is disproportionation [8], e.g. Equation 5.

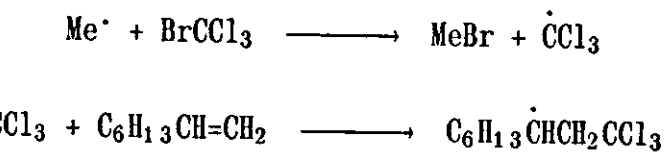
$$CH_2\dot{C}H_2 + H\text{–}CH_2\text{–}\dot{C}H_2 \longrightarrow CH_3CH_3 + CH_2{=}CH_2 \qquad (5)$$



SCHEME 3

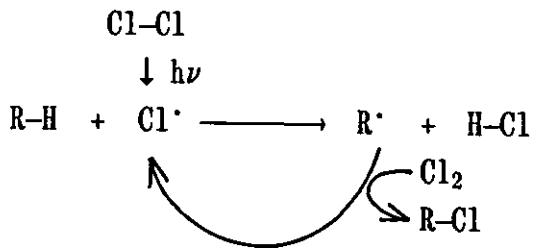
c. Bimolecular reactions between radicals and molecules

This category encompasses addition [9], displacement [10] and atom (often hydrogen) abstraction [11] reactions. There is usually a high probability of radical-molecule reactions taking place as opposed to radical-radical reactions. The two types of reaction are balanced by concentration factors. An example of abstraction and addition is shown in Scheme 4.



SCHEME 4

Most displacements are achieved by addition followed by abstraction, as in the chlorination of alkanes. The H-abstraction by the chlorine radical is followed by alkyl radical abstraction[12] of a chlorine atom from Cl_2, thereby generating chlorine radicals to maintain the chain (Scheme 5).



SCHEME 5

d. Redox reactions

Reduction of a radical by an electron gives an anion, and reduction of a neutral molecule yields a radical-anion, as shown in Equation 6. Oxidation of a radical by electron removal gives a cation, and oxidation of a neutral molecule yields a radical-cation, as shown in Equation 7.

$$R^{\cdot} + e^{-} \longrightarrow R^{-}$$
$$M + e^{-} \longrightarrow M^{-\cdot} \qquad (6)$$

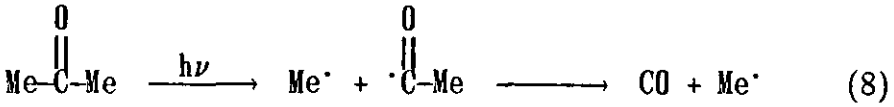
$$R^{\cdot} - e^{-} \longrightarrow R^{+}$$
$$M - e^{-} \longrightarrow M^{+\cdot} \qquad (7)$$

Radical Formation

Radical formation falls into three general methods; photolysis[13], thermal[14] and redox [14] generation of free radicals.

a. Photolysis

Photolysis of molecules with ultraviolet or visible radiation can bring about their fragmentation to radicals, e.g. the decomposition of acetone in the vapour phase with light at 320 nm (Equation 8).

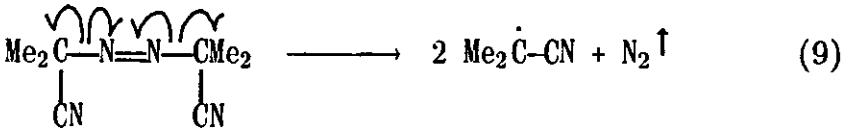


(8)

The advantage of photolysis is that bonds are fragmented at reasonable temperatures and that the energy applied is of a level that does not normally interfere with other parts of the molecule.

b. Thermolysis

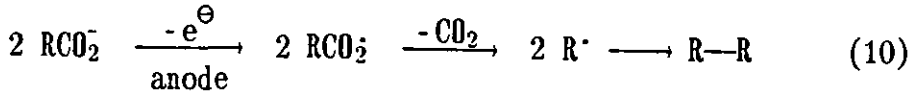
Thermolysis involves the use of heat to dissociate bonds of low dissociation energy, an example being an azo compound such as azobisisobutyronitrile (AIBN) which dissociates to radicals (often used as inhibitors) and nitrogen (Equation 9).



(9)

c. Redox methods

The use of redox reactions to generate radicals is also possible. Probably the best example in this area is the Kolbe electrolysis of acyclic carboxylic acids to give hydrocarbons [16] (Oxidation, Equation 10) and the accelerated decomposition of acyl peroxides using Cu^+ ion [3] (Reduction, Equation 11).



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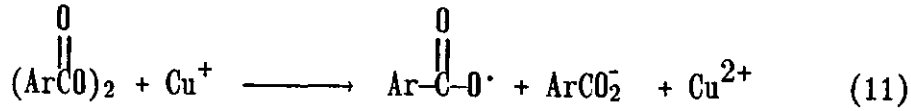

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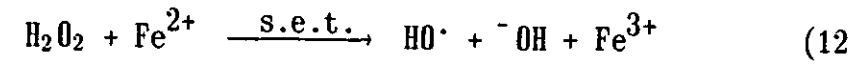


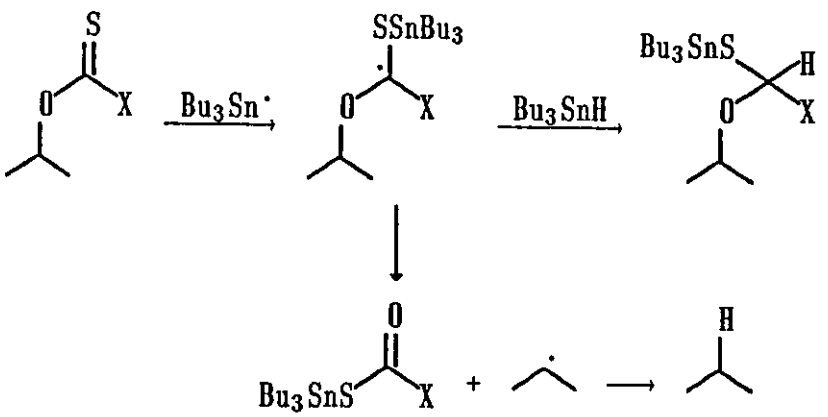
(12)

Reduction can also be used, e.g. Fenton's reagent [17] (Equation 12). All involve the generation of radicals by a single electron transfer (s.e.t.).

The Barton-McCombie Reaction

Deoxygenation of alcohols *via* xanthate esters and related thiocarbonates has been pioneered by Barton and McCombie [18]. The reaction is seldom attempted for tertiary alcohols, but deoxygenation of secondary alcohols is possible with moderate yields obtainable.

Bachi and Bosch [18] have put forward substantial evidence which suggests that the reduction process proceeds by the following mechanism (Scheme 6).



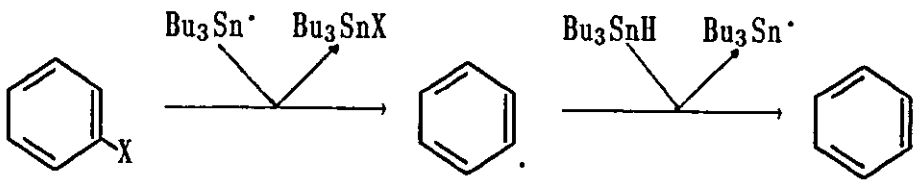
SCHEME 6

Some Modern Methods for the Generation of Radicals

Important recent advances in radical generation include the use of tri-n-butyltin hydride [19] (Bu_3SnH) and the Barton method [20] (using 2-mercapto-pyridine-N-oxide). These two methods are now used widely in radical reactions for carbon-carbon bond formation.

a. Tri-n-butyltin hydride

Radicals can be generated chemically by the removal of a halogen from an alkyl or aromatic halide by the use of Bu_3SnH (Equation 13).



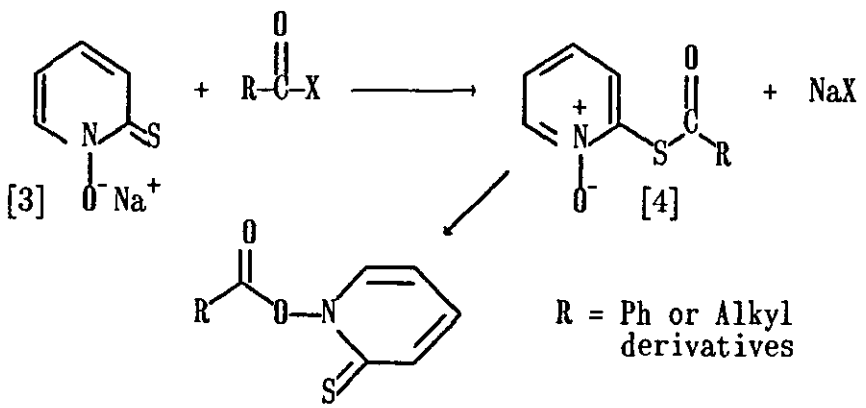
X = I,Br

(13)

It was found that the ease of generation of the aryl radicals from the corresponding aromatic halides was I > Br > Cl/F, which reflects the relative strength of the C-X bond. This selectivity will be discussed in greater detail later on.

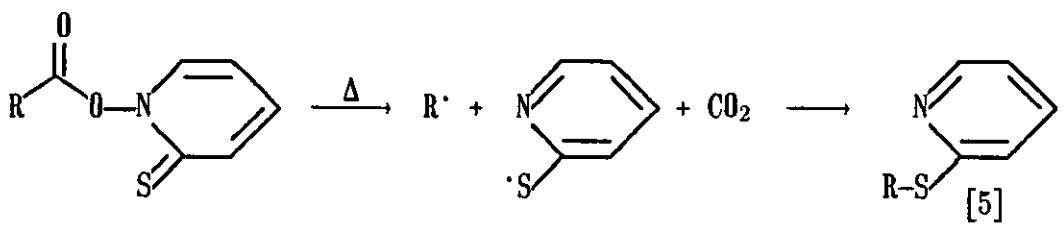
b. The Barton method.

The use of activated carboxylic acids to generate alkyl radicals was initially reported by Barton, Crich and Motherwell [20]. Reaction of carboxylic acid chlorides with the commercially available sodium salt of 2-mercaptopyridine-N-oxide [3] yields O-acyl thiohydroxamate esters [4] (Scheme 7).

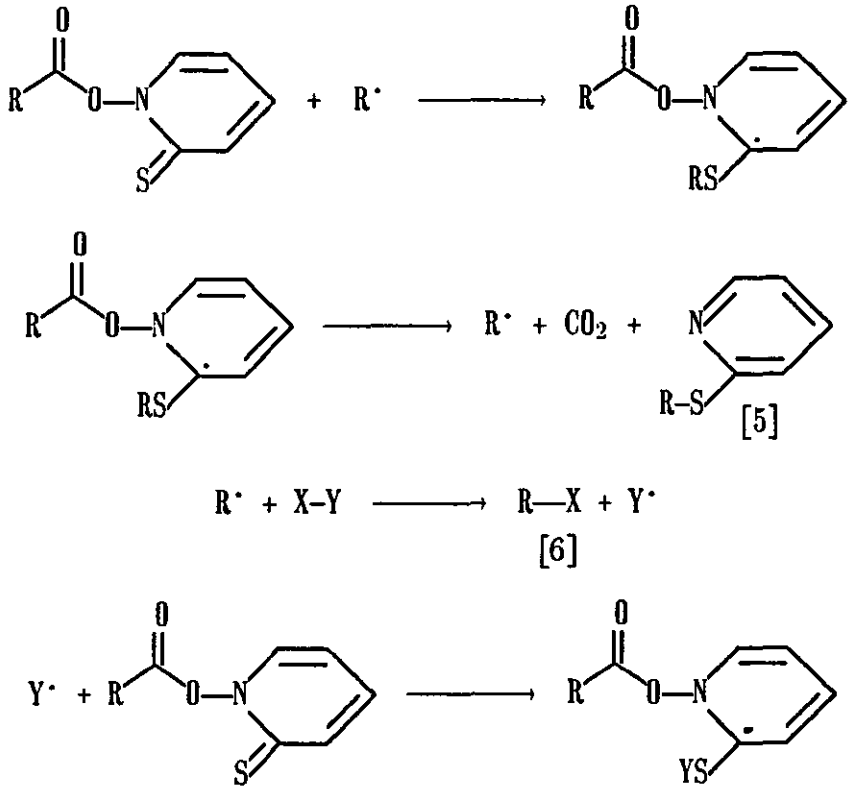


SCHEME 7

The esters can be isolated but are normally broken down to give alkyl radicals *via* their fragmentation under various conditions (e.g. photolysis and thermolysis) in suitable solvents (Scheme 8), the radical thus generated can also react with neutral moieties as indicated (Scheme 9) to give functionally substituted alkyl moieties [6].



SCHEME 8



SCHEME 9

The real advantage of the Barton method is the ability to use readily available starting materials, i.e. an almost unlimited supply of carboxylic acids. The Barton method differs from the use of trialkyltin radicals as chain-transfer agent since its application is very general and there is a variety of possible transformations of the intermediate radicals. There is an excellent review on the subject by Crich [21].

An enthalpic driving force for the reaction is provided by the formation of carbon dioxide and the aromatisation of the mercaptopyridine and an entropic driving force is provided by the formation of two molecules, carbon dioxide and the intermediate [5] from one starting material, as shown in Scheme 8.

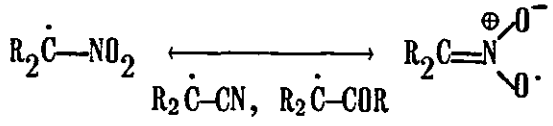
Radical Stabilisation

The stability of alkyl radicals depends on several factors: electron donating groups, release of strain, delocalisation of unpaired electrons and configuration of the unpaired electron. The stability of alkyl radicals [$R_3C\cdot > R_2CH\cdot > RCH_2\cdot > CH_3\cdot$] indicates the stabilising effects of electron donating groups as well as the

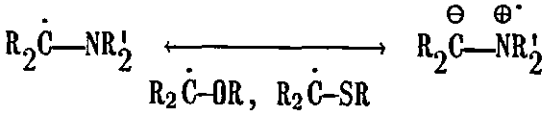
release of strain when the radical is formed (R = large group) on going from the sp^3-hybridised precursor to an sp^2-hybridised radical. However, the degree of H, as compared with carbonium ions is small. Delocalisation of the unpaired electron is the most important factor in the stabilisation of radicals. The more stable a radical, the less susceptible the radical is to reaction, i.e. more stable and less reactive.

The two best examples are allylic and benzylic radicals which delocalise the single electron over the π-orbitals. The systems are planar with sp^2-hybridisation, thereby giving rise to the maximum pπ and orbital overlap. The greater the radical delocalisation the greater the stability, e.g. $Ph_3C^{\cdot} > Ph_2CH^{\cdot} >> PhCH_2^{\cdot}$.

Radicals are also stabilised by conjugation with electron withdrawing groups but the effect is much less than allylic or benzylic conjugation [I]. Electron donating groups such as amines, ethers and thioethers strongly stabilise radicals [II]. Radicals in sp^2-hybridised bonds have some stabilisation but the effect is small [III].



(I)



(II)

(III)

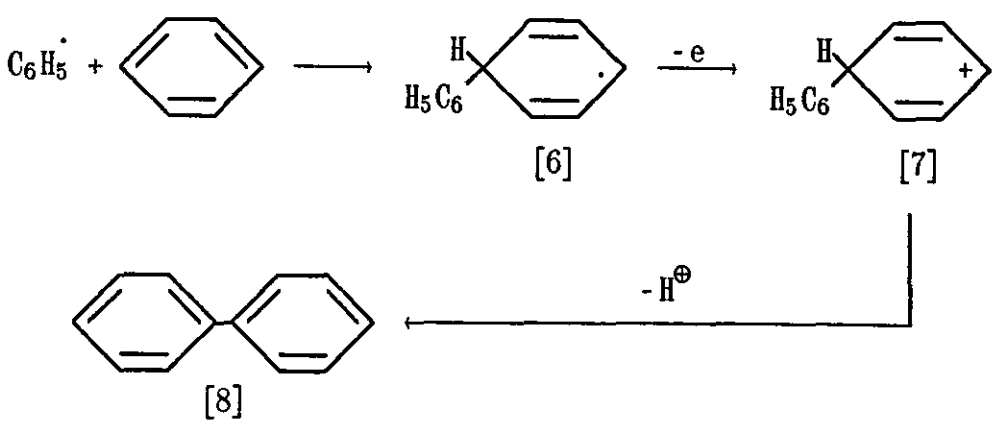
Aryl Radicals

The area of interest to our research is carbon σ aryl radicals [22]. These are carbon centred radicals in which the unpaired electron is in a σ-orbital of the ring system. Aryl radicals are not greatly stabilised and are therefore very unreactive and rapidly attack unsaturated, neutral or charged carbon atoms, e.g. arenes and alkenes. Aryl radicals are formed using the usual methods as described previously. The use of aryl radicals offers an alternative route for carbon-carbon bond

formation from ionic methods of carbon-carbon formation (e.g. Friedel-Craft reactions [23]).

One of the earliest examples of an aryl radical carbon-carbon formation was the Bamberger phenylation [24] of benzene using N-nitrosoacetanilide. However, it was not until Hey [25] proposed the phenyl radical as the intermediate that the reaction could be explained. The elucidation of the mechanism took right up until the 1970's and then only with the work of several free radical researchers [25,26] (Scheme 10).

The proposed mechanism in the literature [27] involves reaction between the radical and arene to give a radical adduct [6] which is then oxidised by a diazonium ion to give the cyclohexadienyl cation [7], followed by deprotonation to give the biphenyl [8].



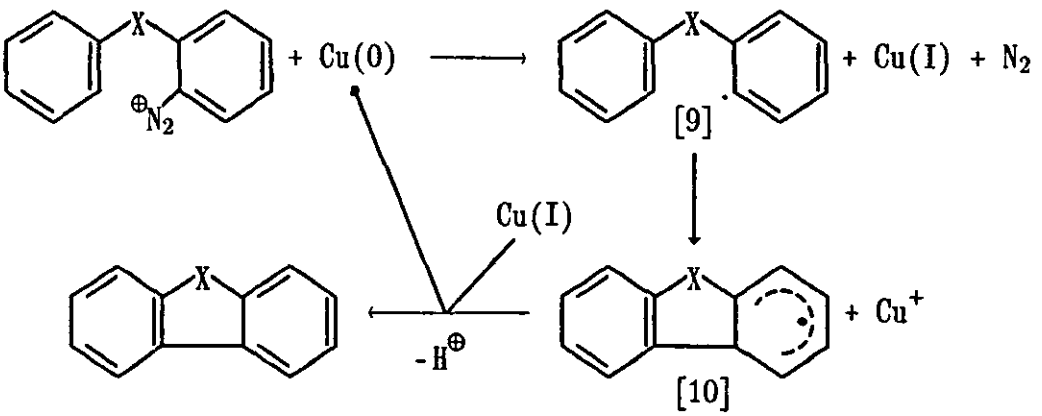
SCHEME 10

However, there is little selectivity in intramolecular radical arylations due to the small polar effects in the reactions, e.g. as in the Gomberg-Backmann [27] reaction. Selectivity of arylation occurs in intramolecular reactions such as the Pschorr ring closure [28] (Equation 14) with yields of above 40%.

(14)

Z = CH=CH, CH_2CH_2, NH, C=O and CH_2

The rate limiting reaction is attack of the radical [9]. Loss of a hydrogen atom from the delocalised cyclohexadienyl radical intermediate [10] to yield the substantial product is not spontaneous and occurs by hydrogen abstraction. This step is not rate limiting since no significant k_H/k_D kinetic isotope effect is observed [29]. A proposed mechanism is shown in Scheme 11. Product mixtures arising from arylation or phenylation of substituted aromatic species can be complex.



SCHEME 11

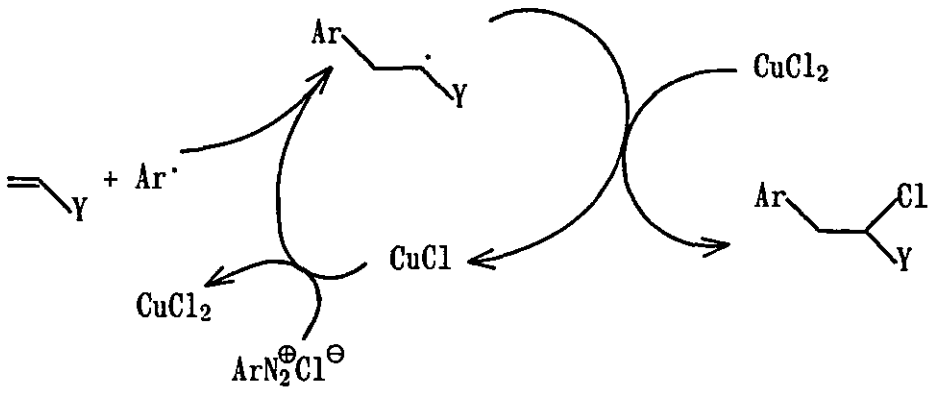
In the substitution of the benzene ring, the radical attack shows little selectivity whether the substituent is electron withdrawing or donating. Attack is also predominantly *ortho* or *para* to the substituent which is explained by the unpaired electron in the intermediate being delocalised and stabilised by either electron withdrawing or donating substituents. Homolytic aromatic substitution gives some formation of all three isomers unlike nucleophilic or electrophilic aromatic substitutions which are much more selective.

Reactions of Sigma-Aryl Radicals

a. Reactions between diazonium salts and unsaturated moieties in the presence of cuprous chloride

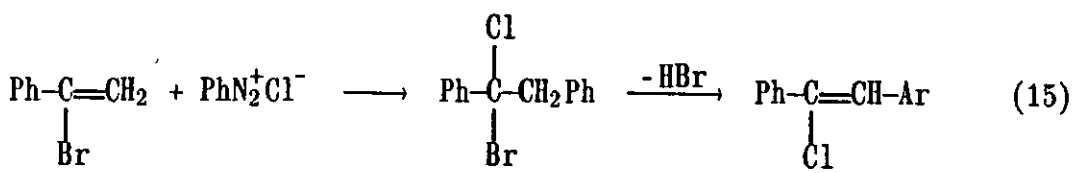
These reactions are an extension of the Gomberg-Backmann reaction [30]. Olefins activated by electron-withdrawing conjugating groups (X = Ar, C=C, halogen, C=O, C=N etc.) can be reacted by treatment with a diazonium salt and cupric chloride as the catalyst [31]. These types of reactions come under the heading of Meerwein arylation reactions. The most likely mechanism for the reaction is

attack by the aryl radical on the unsaturated moiety forming an adduct which can then react with cupric chloride to give addition or elimination products (Scheme 12).



SCHEME 12

Addition is often followed by spontaneous elimination as in the reaction forming α-chlorostilbene [32] (Equation 15).

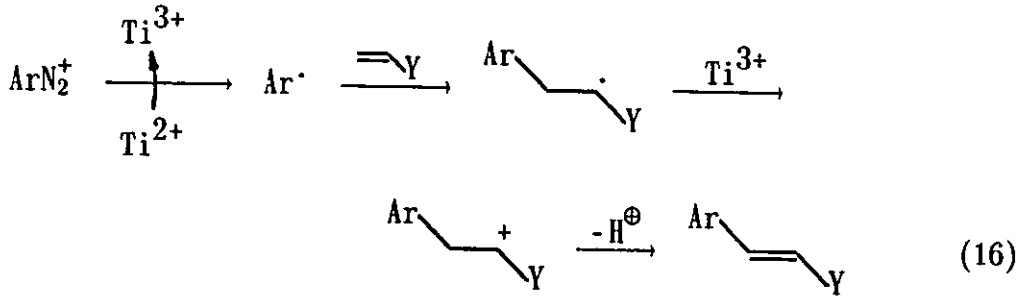


(15)

In the reaction with styrenes, the yields of carbon-carbon formation depends only slightly on the nature of substituent of the aryl diazonium salt [33]. It is this independence from the nature of substitution that has made the Meerwein reactions synthetically useful [34]. Optimisation of the reaction has been achieved by generation of the diazonium salt *in situ* in aprotic organic solvents, e.g. THF with alkyl nitrites [35], although acidic aqueous medium with sodium nitrite is still used.

Aryl radicals are so reactive that a large variety of alkenes are suitable for use as the unsaturated moiety. Alkenes substituted with chloro, acetoxy, phenyl, pyridyl, aldehyde, ketone, carboxylic acid, ester, amide, nitrile, sulphone and phosphonate substituents have been used; even ethylene [36] has been used. In some cases, elimination reactions occur during or after the radical steps. Ti(III) salts have been used by Citterio [37] as an alternative to the Meerwein reaction. The

Ti(III) salt reduces the diazonium salt to aryl radical, however, unlike $CuCl_2$ reactions, Ti(III) is not a catalyst and has to be used in at least stoichiometric to excess quantities (Equation 16).



(16)

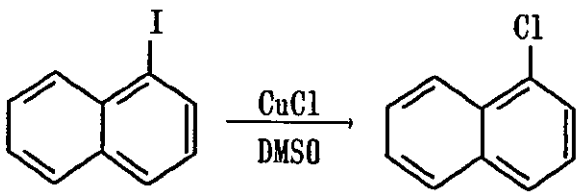
b. Aromatic substitution using aryl halides and copper compounds

Aromatic nucleophilic substitution on aryl halides can be catalysed by cuprous salts and by cuprous salts with copper powder (Equation 17). This area has been comprehensively reviewed by Lindley [38].

$$ArX + Cu(I)Nu^- \longrightarrow ArNu + Cu(I)X \qquad (17)$$

X = I, Br and Cl
Nu = RS, RO and RCYZ

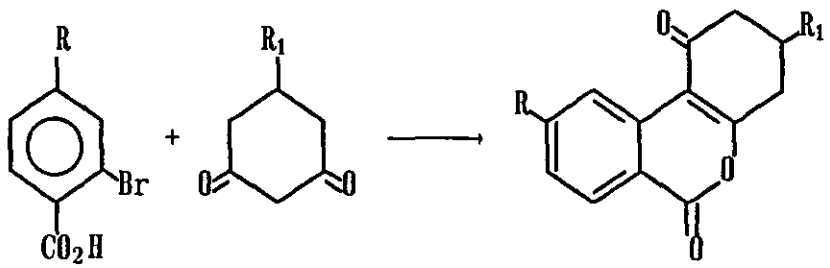
The leaving group ability in these reactions is I > Br > Cl. Halogen exchange in 1-halogenonaphthalenes promoted by copper(I) compounds established that the ease of displacement of halogen from the aryl halide is I > Br > Cl and that the ease of entry is exactly the opposite as shown in Equation 18. There are also phosphorus-centred anions, e.g. as shown in Equation 19. Many carbon-centred nucleophiles such as active methylene carbanions have also been used (Equation 20).



(18)

$$Ar\text{–}I + (RO)_2PO^- \xrightarrow{Cu(I)} Ar\text{–}\underset{\underset{O}{\|}}{P}(OR)_2 \qquad (19)$$

The original work of Hurtley [39] on 2-bromobenzoic acid with anions of β-diketo derivatives (e.g. ethyl acetoacetate) has progressed to the most recent application of activated methylene moieties in Adam's cannabinoid synthesis [40] as shown in Equation 20.

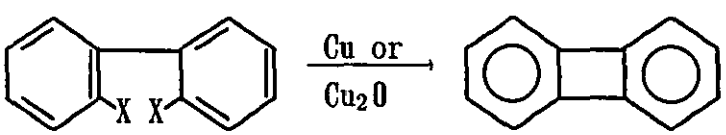


(20)

However the classic reaction is the formation of biaryl from halobenzenes by the Ullman [41] reaction (Equations 21 and 22). The mechanism of the Ullman reaction is thought to involve the initial formation of an aryl copper species which then effects a nucleophilic substitution on a second molecule of the aryl halide (Equation 23).

$$2\ \text{Ar–I} \xrightarrow{\Delta\ /\ \text{Cu}} \text{Ar–Ar} \qquad (21)$$

intermolecular reaction



(22)

intramolecular reaction

$$\text{Ar–I} + 2\ \text{Cu} \longrightarrow \text{ArCu} + \text{CuI}$$

$$\text{ArCu} + \text{ArI} \longrightarrow \text{ArAr} + \text{CuI} \qquad (23)$$

The mechanism of Cu(I) catalysed substitutions is still an area of debate. A possible mechanism proceeding *via* a Cu(III) species has been proposed by several researchers [38,42] (Scheme 13).

$$ArX + Cu(I)Nu \longrightarrow [Ar\text{--}X\text{--}Cu\text{--}Nu]^{\ddagger}$$

$$\Downarrow$$

$$Ar\text{–}Cu(III)NuX \rightleftharpoons [Ar^{\cdot} + Cu(II)NuX]$$

$$\Uparrow$$

$$[Ar\text{--}Nu\text{--}Cu\text{--}X]^{\ddagger} \longrightarrow Ar\text{–}Nu + Cu(I)X$$

SCHEME 13

The Ullman ether synthesis [43] (Equation 24) is also promoted by copper salts and it has been suggested that an aryloxycopper(I) species [11] is the reactive intermediate although several other mechanisms have been suggested in the literature [42].

$$CuX + ArO^{-} \longrightarrow \underset{[11]}{CuOAr} \xrightarrow{ArBr} ArOAr \qquad (24)$$

c. Reactions of arene diazonium salts catalysed by copper halides and copper

Treatment of diazonium salts with cuprous chloride or bromide leads to aryl chlorides or bromides respectively. The reaction is the well-known Sandmeyer reaction [44]. A similar reaction can also be carried out with copper powder and HBr or HCl, in which case it is called the Gattermann [44] reaction. The Sandmeyer reaction is not useful for the preparation of fluorides or iodides but for bromides and chlorides it is of wide use and is probably the best way of introducing bromine or chlorine into an aromatic ring. The yields are usually high.

A mechanism has been proposed in which the copper(I) halide undergoes a s.e.t. with the arene diazonium salt and generates an aryl radical which in turn reacts with the copper(II) halide to give the aryl halide and regenerate the catalytic copper(I) halide (Scheme 14).

$$ArN_2^{+}\ X^{-} + Cu(I)X \longrightarrow Ar^{\cdot} + N_2 + Cu(II)X_2$$

$$Ar^{\cdot} + Cu(II)X_2 \longrightarrow ArX + Cu(I)X$$

SCHEME 14

Aryl bromides can be prepared from primary aromatic amines in one step by two procedures:

(i) By treatment of the amine with a complex of $CuBr_2$ and NO^+ and is carried out at room temperature

(ii) By treatment of the amine with pentyl nitrite in the presence of bromofuran and is carried out at 100 °C [46].

Although the Gattermann reaction is a variation of the Sandmeyer reaction, when diazonium salts are treated with cuprous ion, two products are possible: biaryl- and azo-compounds (Equation 25).

$$2\ ArN_2^+ \xrightarrow[\text{or } Cu/H^+]{Cu^+} \begin{matrix} Ar\text{–}Ar + 2\ N_2\uparrow \\ \text{or} \\ Ar\text{–}N{=}N\text{–}Ar + N_2\uparrow \end{matrix} \qquad (25)$$

If the ring contains electron withdrawing groups, the main product is the biaryl, but the presence of electron donating groups leads mainly to the azo compound. Both products originate from ArN_2^+ and the mechanism probably involves free radicals [47].

d. The $S_{RN}1$ reaction

Further advancement in aromatic substitution of aromatic substrates *via* aryl radicals came from the $S_{RN}1$ (substitution, radical nucleophilic, unimolecular) reaction originally pioneered and developed by Bunnett and Kim [48]. They found some interesting results whilst working on amination of 5- and 6-iodo pseudo-cumenes with potassium amide in liquid ammonia. A common aryne intermediate was expected, and therefore, for both the bromo and chloro substituted pseudo-cumenes the ratio of 6-amino to 5-amino pseudo-cumenes was as expected. However, the iodo substituted substrates gave unrearranged products in high regioselective yields suggesting a non-aryne mechanism was operating. It could, however, be explained by the attack of an intermediate aryl radical on a nucleophile to give a radical anion. The radical anion undergoes a s.e.t. to the original substrate and yields the substitution product. Cleavage of the Ar-X bond

in the radical anion brings about the chain reaction (Scheme 15).

$$ArX + e^{\ominus} \longrightarrow [ArX]^{-\cdot}$$

$$[ArX]^{-\cdot} \longrightarrow Ar^{\cdot} + X^{-}$$

$$Ar^{\cdot} + Nu^{\ominus} \longrightarrow [ArNu]^{-\cdot}$$

$$[ArNu]^{-\cdot} + ArX \xrightarrow{s.e.t.} ArNu + [ArX]^{-\cdot}$$

Ar = aryl species;
Nu = nucleophile;
X = leaving group

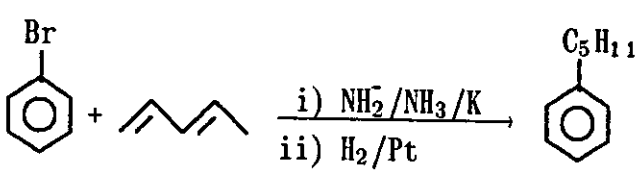
SCHEME 15

The $S_{RN}1$ reaction in an analogous form has been used to explain the substitution reactions of p-nitrobenzyl halides and 2-halogeno-2-nitropropanes by Kornblum [49] and Russell [50].

Although the standard, and most suitable solvent used is liquid ammonia, other solvents can be used, such as DMSO, DMF, THF and butyl alcohol. The syntheses can be promoted by electron donation from potassium metal, electrochemically, and by irradiation to stimulate the electron transfer step [51] between nucleophile and aryl halide.

i. $S_{RN}1$ reactions with conjugated hydrocarbons

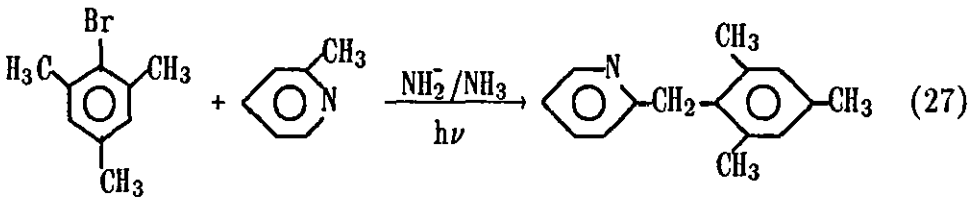
Reaction of arylbromides with a conjugated hydrocarbon in liquid ammonia gave rise to carbon-carbon bond formation, e.g. the formation of 1-phenylpentane (Equation 26) proceeds in high yield (74%) from bromobenzene and 1,3-pentadiene [52].



(26)

ii. $S_{RN}1$ reactions of picoline anions

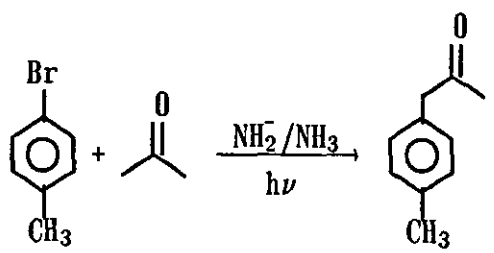
Picolines can be arylated on the methyl group using $S_{RN}1$ reactions (Equation 27) in good yield (89%) [53]. The reaction of 2-bromomesitylene shows that $S_{RN}1$ reactions are not hindered by small *ortho* substituents.



(27)

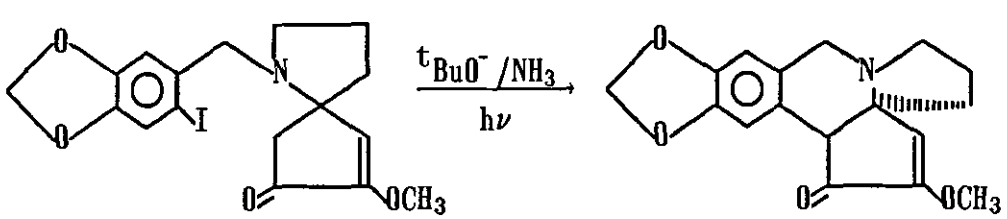
iii. Preparation of β-aryl ketones using $S_{RN}1$ substitutions

The best procedure for achieving arylation of ketones involves the generation of the enolate using potassium tertiary butoxide in liquid ammonia, followed by addition of the aromatic substrate and photolysis [54] (Equation 28).

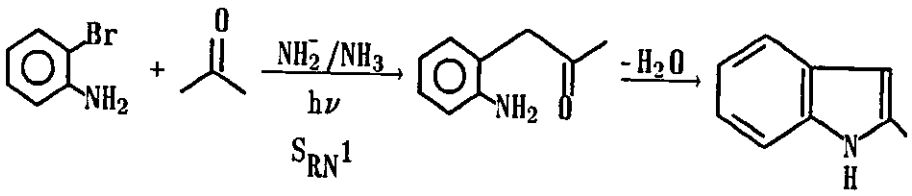


(28)

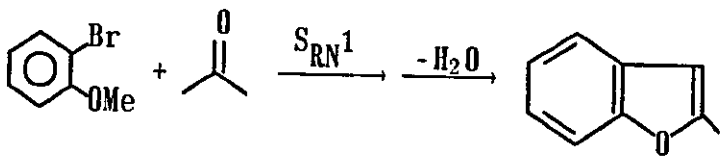
Heterocyclic halides also undergo $S_{RN}1$ reactions with enolates in comparable yields to that of aryl precursors [55]. Intramolecular reactions can also be achieved using $S_{RN}1$ reactions. Successful syntheses of alkaloid and benzoheterocycles have been achieved. The synthesis of the alkaloid (±)-cephalotaxinone [56] is shown in Equation 29. Successful syntheses of 2-substituted indoles [57] and benzofurans [56] have been achieved (Equations 30 and 31).



(29)



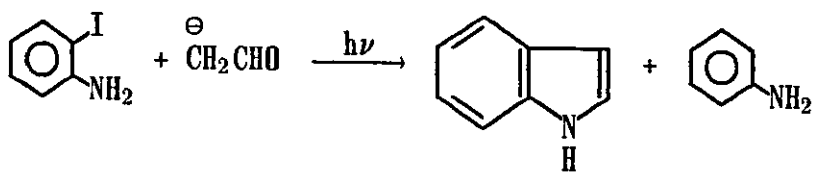
(30)



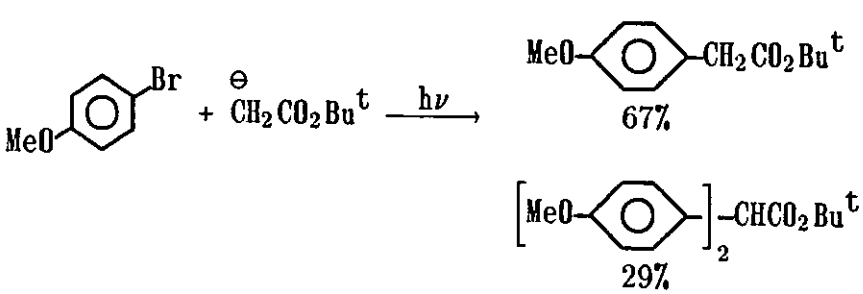
(31)

iv. $S_{RN}1$ reactions of the anions of aldehydes, esters and amides

The anions of aldehydes, amides and esters are as widely used in $S_{RN}1$ syntheses as ketones. Reduction of the halogenobenzene and disubstitution limit their application (Equations 32 and 33).



(32)



(33)

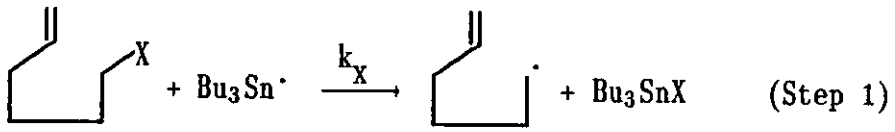
e. Bu_3SnH reactions

The synthetic use of tin hydrides was pioneered by Kuivila [58]. The literature has seen an explosion or research reporting the use of tri-n-butyltin hydride [59] (Bu_3SnH) for the generation of aryl and alkyl radicals. This reagent has proved useful for synthetic purposes due to its low toxicity, cheapness and ease of storage. The cyclisation of the 5-hexenyl radicals (Scheme 16) provides a good example of the use of Bu_3SnH.

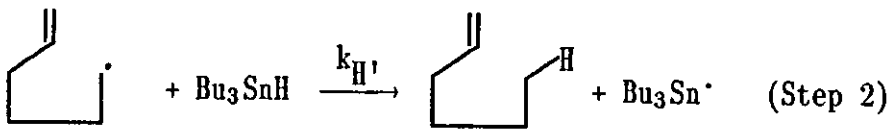
Initiation: $Bu_3SnH \xrightarrow{In^{\cdot}} Bu_3Sn^{\cdot} + In\text{-}H$

In = AIBN/Δ

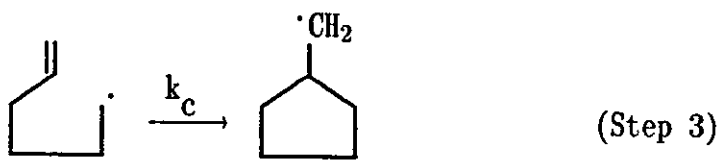
Propagation:



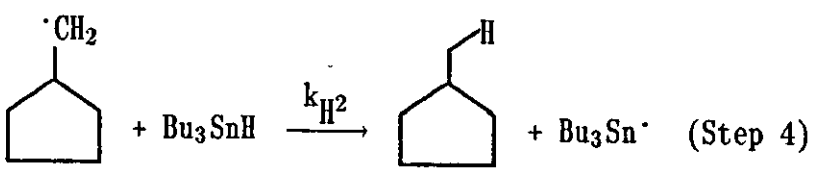
(Step 1)



(Step 2)



(Step 3)



(Step 4)

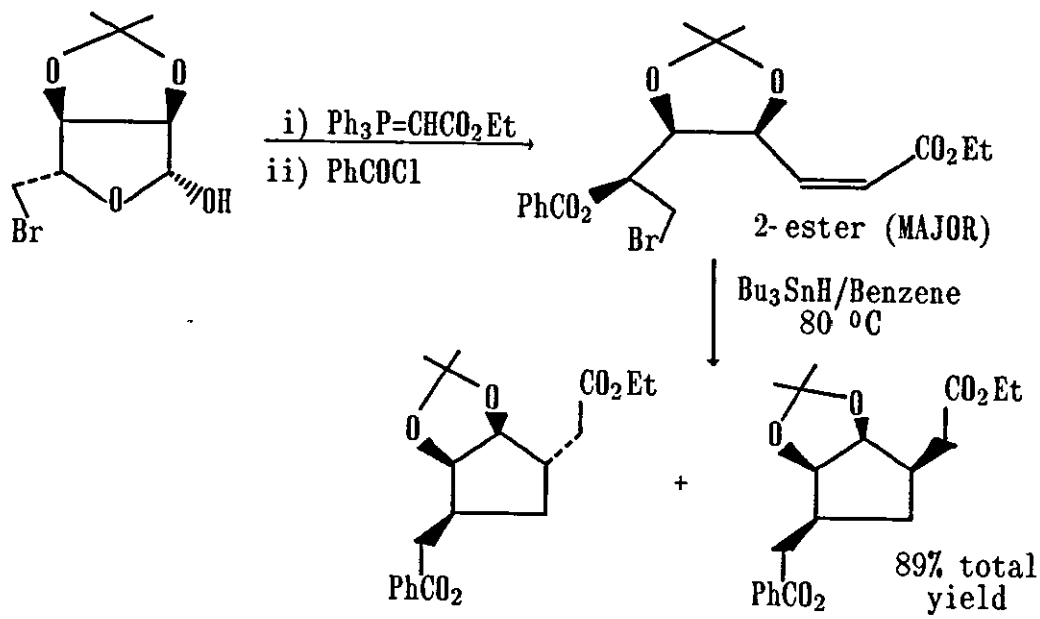
SCHEME 16

The chain carrier, the stannane radical, is generated by the use of AIBN (azobisisobutyronitrile) or other suitable radical-initiating species. In Step 1, the 5-hexenyl radical is generated and is followed by either reduction as in Step 2, or cyclisation to the intermediate 5-membered ring radical (Step 3). This cyclised radical can then undergo reduction by Bu_3SnH with the formation of more stannane radical ($Bu_3Sn^{\cdot}$) which acts as the chain carrier (Step 4).

The reason for the preference of 5-*exo* cyclisation over 6-*endo* cyclisation will be discussed later on in the introduction. However, at very high concentrations (> 5 M) reduction will predominate over cyclisation, and at low concentration (0.05 M) cyclisation is predominant. This control of the selectivity of product formation by the variation of [Bu_3SnH] has assisted the elucidation of the mechanism of Bu_3SnH as a radical cyclising agent.

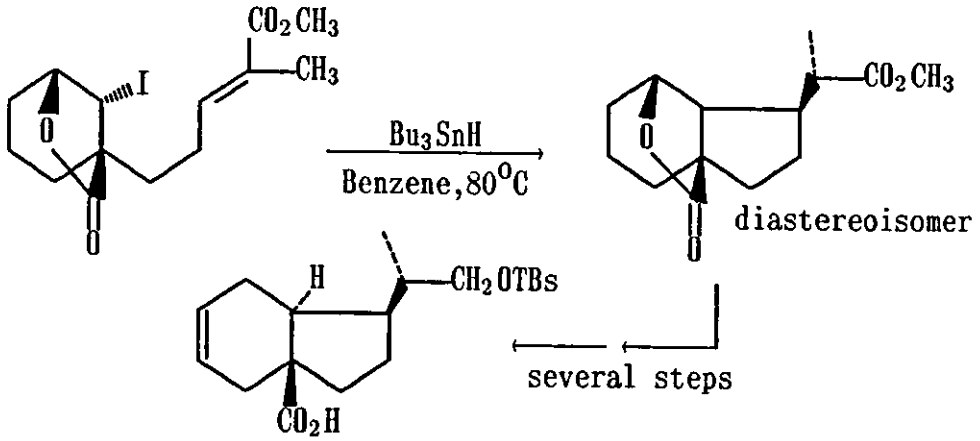
Some of the leaving groups that can be abstracted by $Bu_3Sn^{\cdot}$ to generate radicals are I, Br, SePh, Cl and SPh. The best leaving group has been found to be iodine. In order to lower the concentration of Bu_3SnH, to encourage cyclisation of the intermediate radical, various methods can be used. Bu_3SnH can be added to a large amount of solvent or added slowly over a long period of time. Recently the use of polymer bound tin hydride [60] has allowed new scope for synthetic reactions. It has also been the practice to use Bu_3SnCl in catalytic quantities with the generation of Bu_3SnH in catalytic quantities by reduction with $NaBH_4$ or $Na(CN)BH_3$ [60].

The area of work for which Bu_3SnH has been used is now so large that an overview is all that can be attempted. Bu_3SnH can be used to generate radicals from a wide variety of precursors and then cyclise onto a vast array of moieties such as alkenes, alkynes and α,β-unsaturated ketones and nitriles. Bu_3SnH can be used to bring about difficult reactions with stereoselectivity. A good example is shown in Scheme 17, the formation of a carbocycle from a sugar moiety.



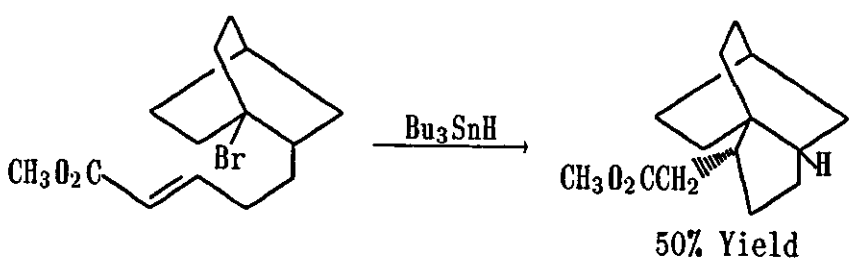
SCHEME 17

The cyclisation would be difficult by classical practice. Hart [62], for example, has shown through his synthesis of *trans*-hydroindane (Scheme 18) that stereoselectivity can be excellent.



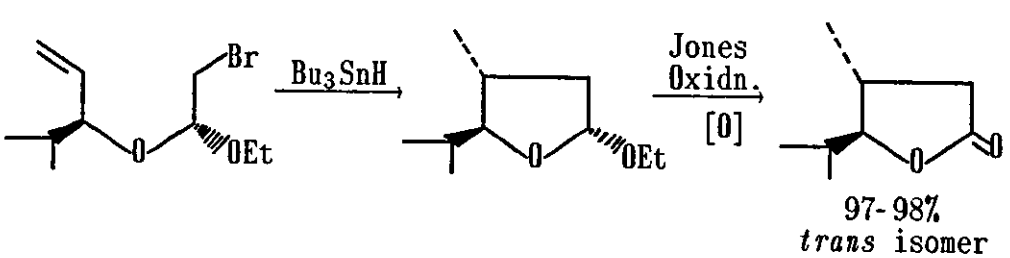
SCHEME 18

Kraus and Hon [63] have shown that the formation of carbon-carbon bonds in transannular cyclisations can be successfully achieved using an α,β-unsaturated ester (activated esters) as shown in Equation 34.



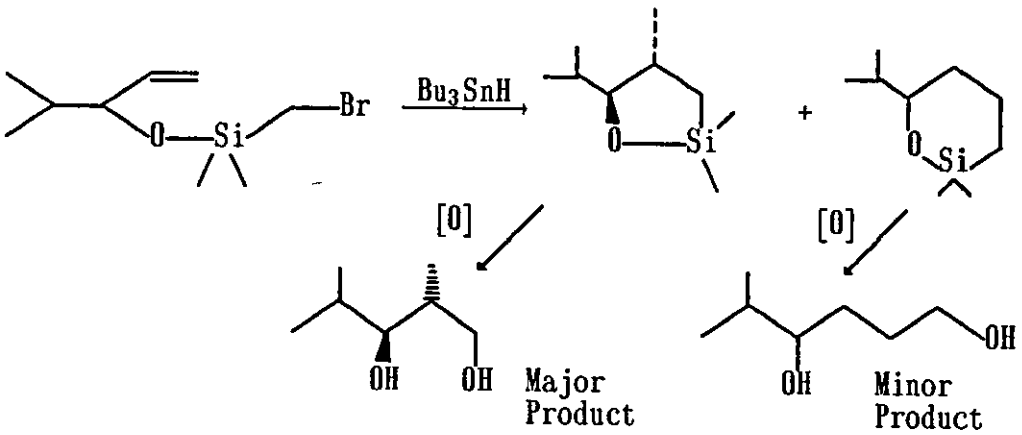
(34)

The use of Bu_3SnH to synthesise heterocycles has been a very fruitful area of research. It has allowed complicated heterocycles to be synthesised with ease such as the Stork and Veno [64] studies on γ-lactones (Equation 35). The bromoacetal method is used because direct cyclisation of the α-bromo esters is unfavourable.



(35)

The use of silylmethyl radicals as an indirect method for acyclic stereo-control [65] has been advanced by Nishiyama [66]. The cyclisation of a bromomethyl-dimethylsilyl ether produced the 5-*exo trans* over the 6-*endo cis* as the major product (Scheme 19).



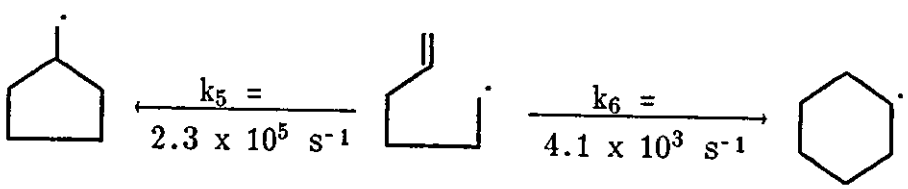
SCHEME 19

Ring Formation

There are many examples of the use of Bu_3SnH to synthesise 5-membered ring systems. However, the formation of 3- and 4-membered ring systems is found to be unfavourable and is not normally attempted. This is probably due to the strain engendered in the transition state. 6-Membered ring systems can be synthesised, but only by taking appropriate precautions in the design of cyclisation precursors or when an *exo* 6-membered ring is favoured over an *endo* 7-membered ring in the cyclisation process.

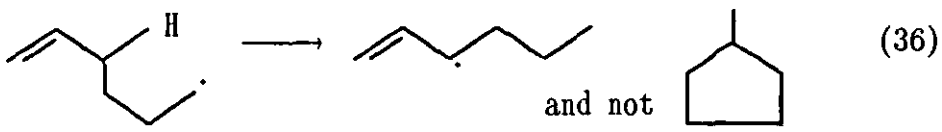
Two major problems are observed in the cyclisations:

i. Cyclisation to the 6-membered ring as compared to the 5-membered ring is one order of magnitude slower [67] as shown in Scheme 20.



SCHEME 20

ii. Allylic atom abstraction through a 5- or 6-membered ring transition state can become a serious, even dominant, competing reaction as the work of Livinghouse and Leonard [68] has indicated as shown in Equation 36.

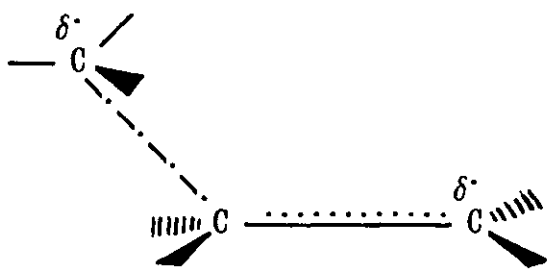


(36)

The solution to these problems can be achieved by several methods such as (a) removal of all appropriately located allylic hydrogen atoms, and (b) introduction of an activating group on the alkene acceptor which favours *exo* 6-ring cyclisation [69].

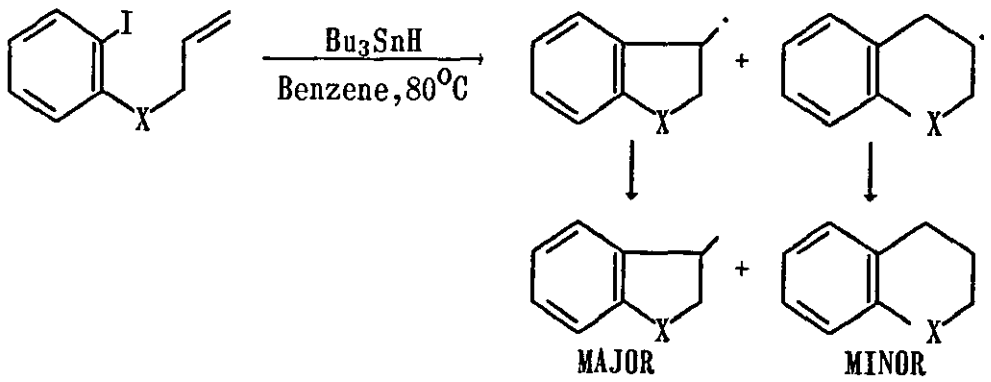
Regioselectivity of Intramolecular Radical Reactions

Nearly ten years ago a paper by Beckwith and co-workers [70] discussed the theory that the direction of cyclisation of hex-5-enyl radicals is determined by the ease of approach of the radical centre towards the olefinic bond along an axis extending vertically from the terminal atoms and lying within the plane of the π-orbital (Scheme 21).



SCHEME 21

Beckwith [70] used the cyclisation of *ortho*-alkenyliodobenzene (X = O, CH_2 and NMe as models) (Scheme 22). Evidence was provided to show that the aryl iodide interacted with the Bu_3Sn· radical to yield aryl radicals, and not a 4-centre concerted process as originally proposed. The conclusions drawn from this work were that the regioselectivity exhibited in the reactions studied was due partly to the differences in the value of H in the transition state for the two modes of cyclisation. The result also implies that the preferred transition state for alkyl radical addition to a double bond comprises a triangular array of centres arising from an initial interaction of the half-filled p orbital with one lobe of the antibonding π-orbital.

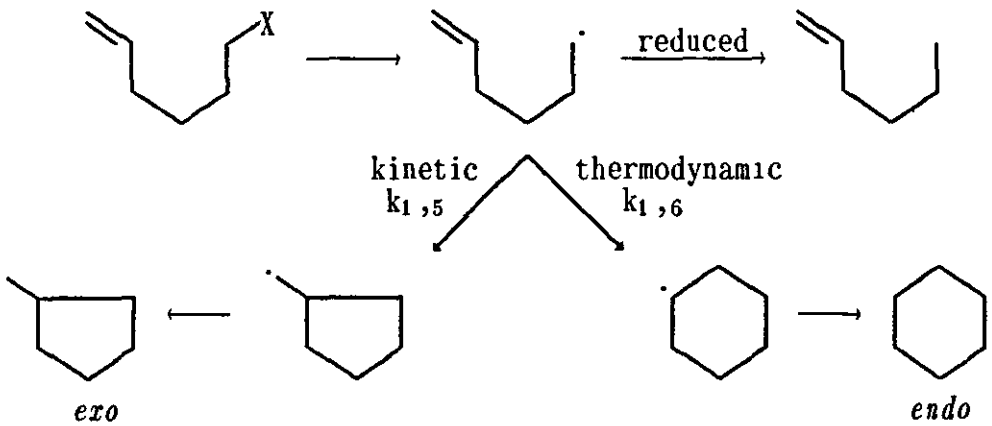


SCHEME 22

All the cyclisations studied specifically afforded products in which the newly formed radical centre is exocyclic to the new ring. The reasoning for this exhibition of high-level regioselectivity is because the proposed transition state, which requires the orbitals containing the three electrons involved in the redistribution process to lie in the one plane, is readily accommodated in pathways leading to exocyclic radicals, but not on those leading to endocyclic radicals.

In changing from intermolecular to intramolecular radical reactions, selectivity can be increased. The original idea that intramolecular reactions were being governed primarily by thermochemical factors was a misconception [71]. The real control of the regio- and stereo-selectivity comes from steric and stereoelectronic effects [72].

There are a number of factors associated with the regio- and stereo-chemical course of free radical reactions which are outlined using a model reaction, that of the hex-5-enyl radical (Scheme 23) which shows a very high regioselectivity for the 1,5-cyclisation. By reaction between 1-bromohex-5-ene and Bu_3SnH it was possible to generate the hex-5-enyl radical. The intermediate radical can react by three routes: direct reduction, 1,5-ring closure and 1,6-ring closure. The 1,5-ring closure is under kinetic control and leads to the *exo* product (methyl cyclopentane) whereas 1,6-ring closure is under thermodynamic control and leads to the *endo* product (cyclohexane).



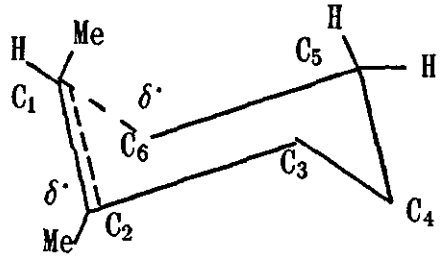
SCHEME 23

Therefore, unimolecular ring closure competes with bimolecular H-atom transfer from the stannane, and by increasing the stannane concentration, the proportion of cyclised material, as opposed to reduced product, will decrease [73]. It was also deduced that the relative amounts of 1,5- and 1,6-ring closure were constant and not dependent on temperature [72]. Therefore, it can be inferred that each mode of ring closure is irreversible. A complex is not involved since electron spin resonance (E.S.R.) spectroscopy at low temperature of the hex-5-enyl radical in solution shows that at varying temperatures only the cyclopentylcarbinyl radical is a detectable intermediate. Therefore, why does the hex-5-enyl radical ring closure proceed in this highly regioselective fashion to afford the least stable product? This observation is opposite to the accepted views of intermolecular reactions. Three explanations have been put forward to try to explain the results: firstly, the entropically favoured small ring theory of Capon and Rees [74], secondly Julia's [75] unfavourable transition state theory, and finally the stereoelectronic theory put forward by a number of authors [75].

Firstly, Capon and Rees' explanation is that small rings are more favourable entropically. Intramolecular reactions generally occur more readily than their bimolecular intermolecular counterparts because the latter involves substantial loss of translational entropy whereas the former involves the loss of internal rotational degrees of freedom. The entropy change associated with the loss of rotational freedom becomes increasingly unfavourable with increasing size of the ring being formed. It is reasonable, therefore, to expect that both ΔS and ΔH of

the intermediate will be more favourable for 1,5-ring closure of the hex-5-enyl radical than for 1,6-ring closure.

Secondly, Julia's explanation was a development of Le Bels hypothesis [75]. The explanation rests on the unfavourable non-bonded interaction between the pseudo-axial proton at C(2) and the *syn* proton at C(6) will destabilise the transition state for 1,6- as opposed to 1,5-ring closure (Scheme 24).



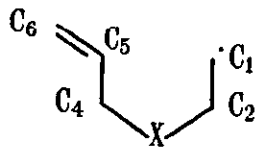
SCHEME 24

Finally, the stereoelectronic theory states that the strain engendered in accommodating the mandatory disposition of the reactive centres within the intermediate complex for 1,6-ring closure outweighs those of steric or thermodynamic factors expected to assist the formation of the more stable possible products.

There was initially, however, no real evidence to back the claims made in the hypothesis that there was an intermediate transition state for the addition incorporating the three participating atoms at the vertices of an obtuse triangle orthogonal to the nodal plane of the system. However, support came later on from theoretical calculations [76]. The transition state complex was found to be polar and calculations indicated that the required disposition of the centres could be more readily accommodated in the transition state complex for 1,5-ring closure as opposed to 1,6-ring closure [77]. Baldwin arrived at the same conclusions by the use of vector analysis [78]. From these explanations a representation of the radical intermediate can be drawn, as shown in Scheme 21.

The preference for the *exo* mode over the *endo* mode is greater in the cyclisation when oxygen is substituted at C(3) and even more where nitrogen is positioned at C(3). This can be explained by the shorter C(1)-C(6) distance, which

decreases the bond angle between C(2) and C(4) and then shortens the C-O bond as compared with the C-C bond (Scheme 25).

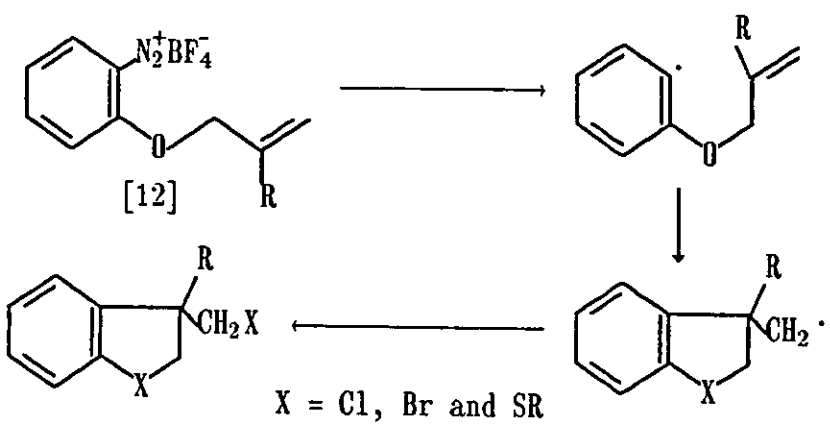


SCHEME 25

The Cyclisation of O-Alkenylaryl Radicals

The cyclisation of O-alkenylaryl radicals has been under intensive study over the last few years [79]. There are two areas of study: firstly synthetic potential [80] and secondly mechanistic studies in order to explain the regioselectivity of cyclisation, i.e. the governing factor for *exo* and *endo* cyclisation [81].

It has been found that in the radical cyclisation of O-(2-propenyloxy)-benzenediazonium tetrafluoroborate [12, R = H or Me] using copper(II) halides or thiolates, specific *exo*-ring cyclisation takes place as shown in Scheme 26.

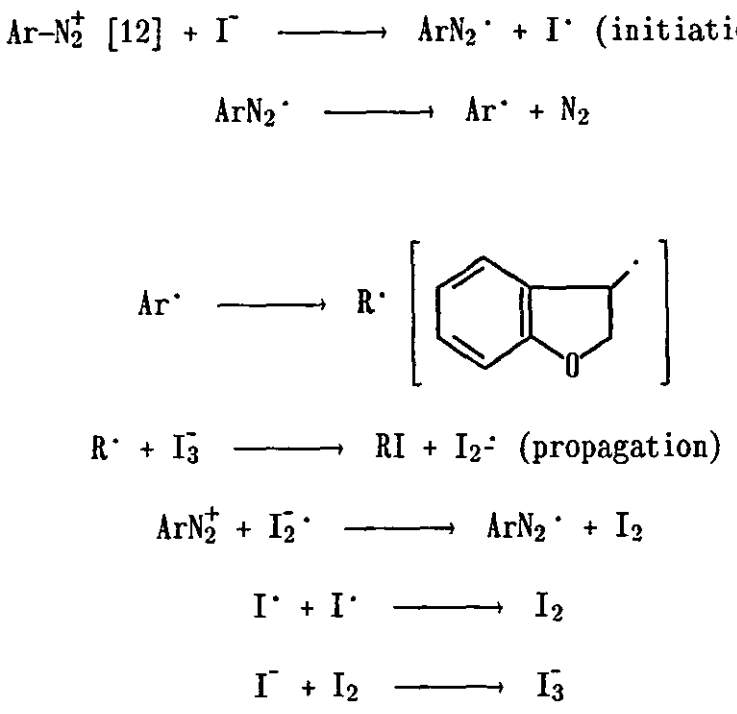


SCHEME 26

This reaction gave rise to functionalisation on the site of the cyclised radical. Previous examples in the literature [82] had indicated that sodium iodide could generate aryl radicals from arene diazonium salts by iodide de-diazoniation and that the subsequent site of the cyclised radical is functionalised. The whole

hypothesis cited that the rate of cyclisation would be more rapid than direct iodination [80] of the non-cyclised aryl radical. Reaction between benzenediazonium salts [12] and sodium iodide in acetone gave a rapid reaction to yield the *exo*-ring cyclised substituted product, 3-(iodomethyl)-2,3-dihydrobenzofuran in good yield with no detectable *endo* or non-cyclised iodoarene present.

When the benzenediazonium fluoroborate [12, R = H] was subjected to cyclisation under Bu_3SnH conditions, it was found that 3-methyl-2,3-dihydro-benzofuran and not the iodo derivative was formed. The literature [80] proposes the following mechanism, as shown in Scheme 27. The literature [83] explanation of the mechanism rests on the ability of the iodide ion to act as a one electron reductant.



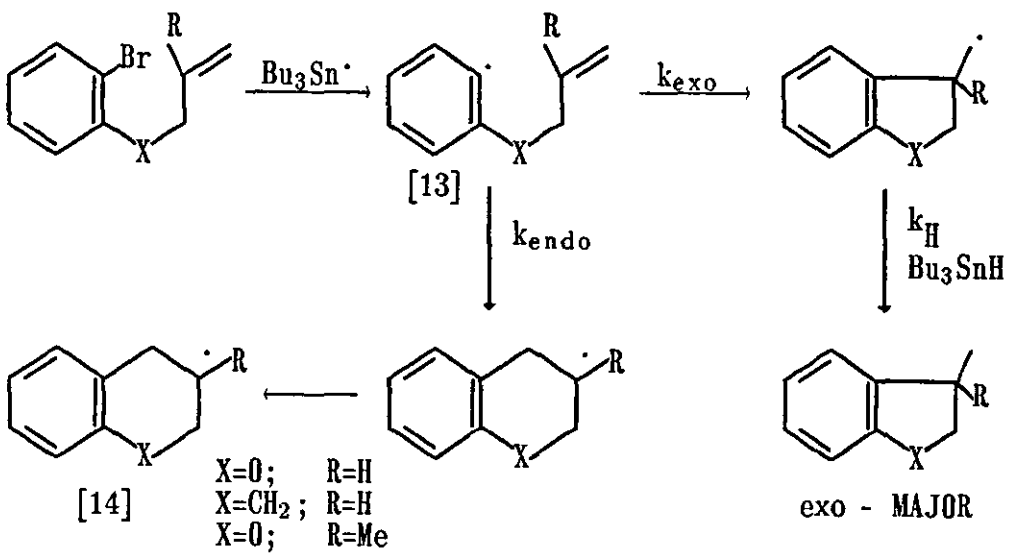
SCHEME 27

A variety of substituents were examined, all indicating a preference for 5- over 6-membered rings and the products isolated have good scope for elaboration and therefore have synthetic potential.

Beckwith and co-workers [79] have also shown that the apparent *endo*-ring closure of O-alkenyloxyaryl radicals by reaction between tributylstannane and

bromoarenes takes place *via exo*-cyclisation followed by neophyll rearrangement of initial products.

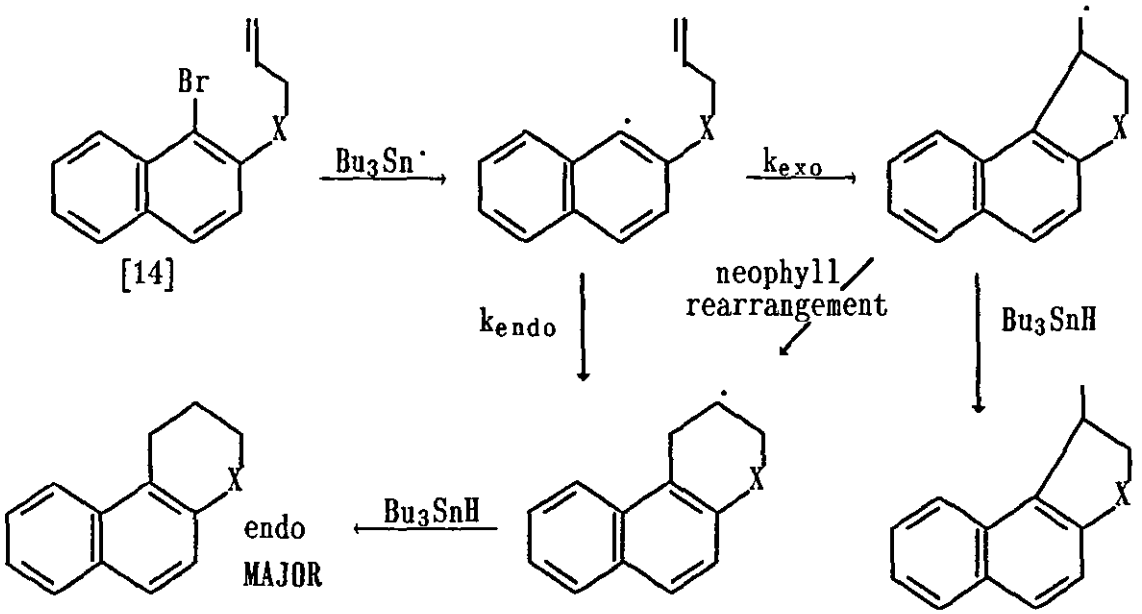
A few cases have indicated that in those compounds in which there is a substituent on the terminus of the double bond nearer to the aryl group, significant amounts of *endo* product are formed. It was found that substituted phenyl radical [13] under similar experimental conditions gave only *exo*-products as shown in Scheme 28. However, 1-bromo-2(prop-2-enyloxy)-naphthalene [14] gave the *endo* product as shown in Scheme 29.



SCHEME 28

The difference in behaviour on similar treatment with Bu_3SnH was initially thought to be due to steric interaction C(8) (of the naphthalene) and the terminal vinyl methylene in the side chain might destabilise the transition structure for 1,5-*exo* cyclisation [84]. However, Beckwith and co-workers [80] have shown that the reaction between bromoarenes and Bu_3SnH gave *endo* products, both by direct *endo*-cyclisation and by *exo*-cyclisation followed by neophyll rearrangement. The neophyll rearrangement is more enhanced by a naphthalene nucleus than by a phenyl group in the radical, and is facilitated by electron withdrawing substituents. However, the *endo*-cyclisation process is not the major cyclisation unless the [Bu_3SnH] is very low (to prevent rapid reduction of the *exo*-radical) and

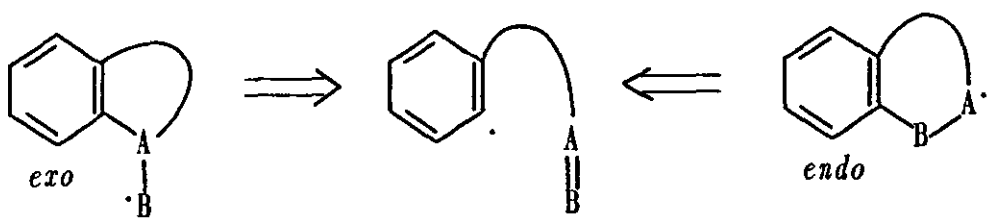
temperatures are high in order to stop competing intramolecular cyclisations and to encourage the rearrangement.



SCHEME 29

The Aim of the Research

The Boots Company are interested in novel benzoheterocyclic systems which are capable of elaboration. The procedures for the synthesis of these compounds are limited using classical methods. The central aim of the research was to develop new synthetic methods for benzoheterocyclic compounds, which would possibly exhibit biological activity. Benzoheterocycles containing a 7-membered ring and or a tricyclic ring system were of particular interest. The general synthetic route was based on the retrosynthetic analysis shown below using cyclisation of radicals onto saturated side chains (Scheme 30).



SCHEME 30

Beckwith's [85] studies have shown that *exo* cyclisation of aryl radicals onto side chain non-conjugated alkenes is a synthetically useful route to novel benzoheterocycles. One of the initial aims was to study whether heteroatoms could be in the unsaturated bond on the side chain and whether the cyclisation could be perturbed towards *endo* rather than *exo*-cyclisation. Both of these achievements would considerably widen the scope of the general preparation route. A few reports in the literature [85] had indicated that in the cyclisation to 7-membered rings, *endo*-cyclisation predominated over *exo*-cyclisation. Also, it was hoped that strong stabilisation of the intermediate free radicals produced by *endo*-cyclisation might bring thermodynamic control into play in the cyclisations and thus favour the *endo*-radical route.

Some of the parameters that we hoped to study were:

1. Effects of heteroatoms on the cyclisation, i.e. could they replace carbon in the unsaturated bond?
2. Effect of stabilisation of the radicals.
3. Effect of ring size and spiro rings.
4. Preference between *exo*- and *endo*-cyclisation.
5. Effect of conjugation on the side chain unsaturation.

A summary of the aims were:

1. Development of the known methods of generating aryl radicals and their application to simple cyclisations.
2. Application of the synthetic procedures to cyclisations that would test the above parameters and also provide useful products.
3. Possible preparation of the benzoheterocycles with 7-membered rings.
4. All the products would be tested for their biological activity by the Boots Company Plc.

DISCUSSION

Introduction

The work was initiated by attempting known synthetic methods to gain experience before applying to new benzoheterocyclic syntheses. The most useful syntheses for generating aryl radicals to react with unsaturated side chains appeared to be:

a. Halogenoarenes and Bu_3SnH.

b. Arene diazonium salts and Bu_3SnH.

c. Iodoarenes and methoxide (Bunnett method).

d. Arene carbonyl chlorides and the sodium salt of 2-mercaptopyridine-N-oxide (Barton method).

Part One of the discussion section describes initial reactions to check for suitable reaction conditions etc., using known methods. Part Two describes the application of the halogenoarenes and Bu_3SnH to a simple system. Part Three of the discussion section describes the cyclisation of *ortho*-aryl radicals onto α,β-unsaturated amides. Part Four describes the cyclisation of *ortho*-aryl radicals onto α,β-unsaturated esters. Part Five gives examples of the ^1H and ^{13}C N.M.R. spectroscopic data for the interesting compounds synthesised from Parts Three and Four, with literature references where applicable.

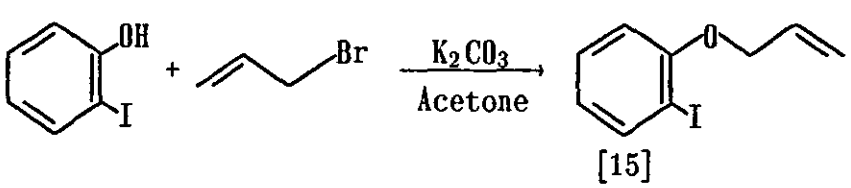
PART ONE:

INVESTIGATION OF METHODS FOR ARYL RADICAL CYCLISATION

a. Cyclisation of 2-Iodophenyl allyl ether using Bu_3SnH

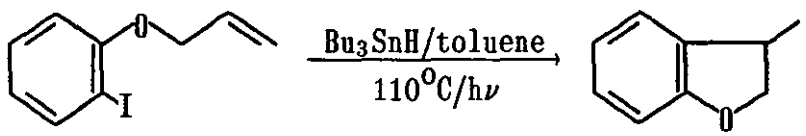
The first "known" reaction to be studied was the generation of an aryl radical intermediate from 2-iodophenyl allyl ether [15] using Bu_3SnH and cyclisation to 3-methyl-2,3-dihydrobenzofuran [16].

2-Iodophenyl allyl ether [15] was prepared as shown in Equation 37 in a good yield using a literature procedure [86].



[15] (37)

The allyl ether [15] was dissolved in deoxygenated toluene under nitrogen and the solvent heated to reflux whereupon Bu_3SnH (1.1 equiv.) and AIBN (0.3 equiv.) were added. The reaction was maintained at reflux and illuminated (2 x 150 W tungsten lamps) for 24 hours. (From now on this procedure is known as the "standard Bu_3SnH" conditions). After purification by distillation, the reaction yielded 3-methyl-2,3-dihydrobenzofuran [16] as described above (Equation 38).



[15] [16] (38)

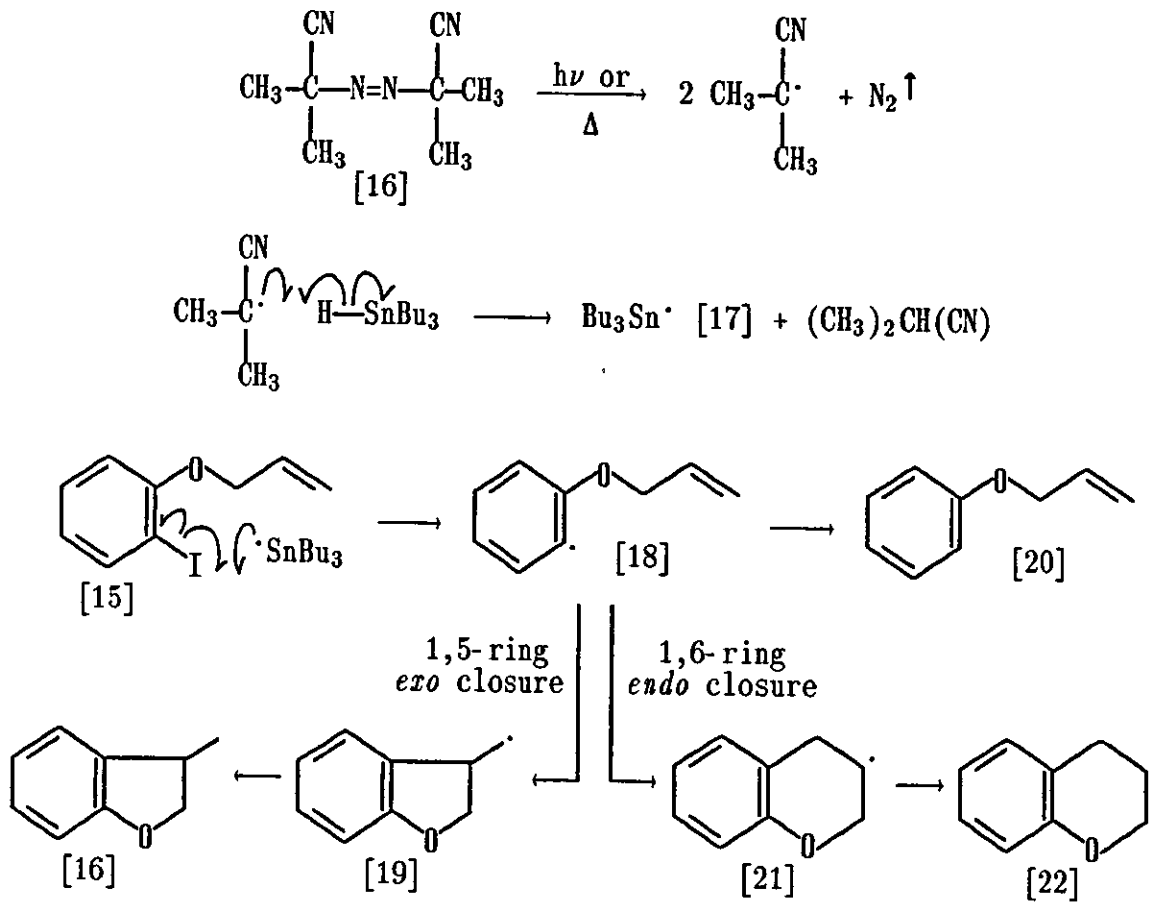
The reaction had been originally developed by Beckwith and co-workers and was repeated to gain practical experience of a known aryl cyclisation using Bu_3SnH. The original researchers had measured the yields of products using g.l.c. analysis. However, we attempted to isolate the material in a pure state from the stannane residues, which had not, to our knowledge, been attempted for this reaction. It was hoped that several procedures outlined in the literature could be used to isolate the benzofuran [16] from the tin residues in good yield. The procedures were:

a. The acetonitrile/hexane wash procedure of Berge and Roberts [87] in which the crude material is dissolved in CH_3CN and washed with hexane to remove the stannane residues.

b. The silica gel chromatography procedures of Fung *et al.* [88]. The authors suggested that the stannane residues could be separated from products on silica gel and so allow the pure material to be eluted free from contaminants.

Both procedures were found to be ineffective for the purification of the benzofuran [16]. The initial simplicity of the silica gel chromatography method was not found to be effective since most of the stannane residues, having a polarity very similar to the benzofuran [16], co-chromatograph with the products, as well as the rest of the tin residues streaking along the whole of the column or the preparative t.l.c plate from the baseline to the solvent front. The acetonitrile/hexane

procedure was also ineffective since the polarity of the benzofuran [16] was such that most of the material entered the hexane layer along with the tin residues and made a realistic yield unattainable by this procedure. Since the benzofuran was a liquid we attempted a Kugelruhr distillation of the material. This allowed several distillations to be achieved on a small sample of material *in vacuo*. Initially stannane residues were found to distil over with the product, as indicated by the literature [59], but after careful manipulation of the conditions of distillation, pure benzofuran [16] was achieved.



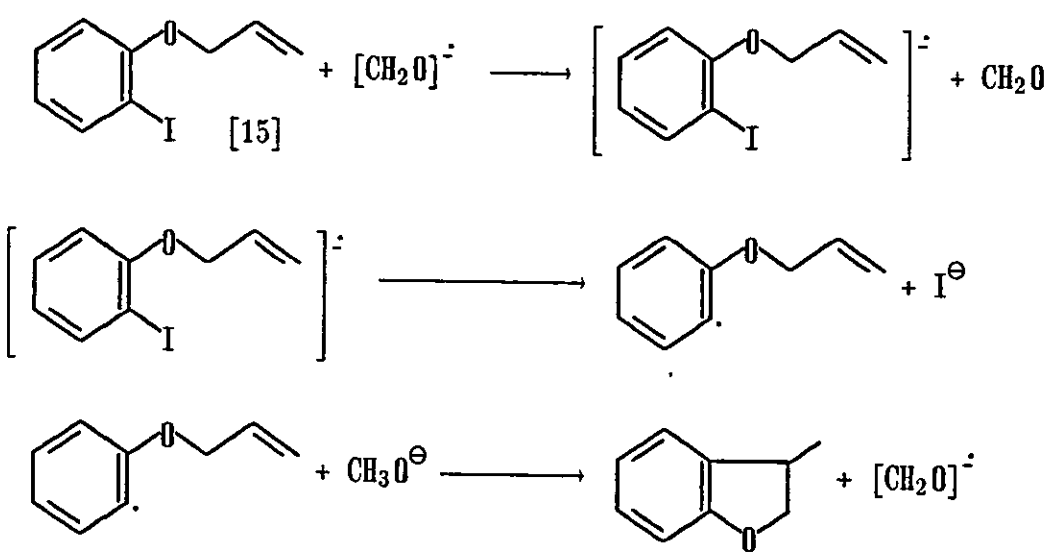
SCHEME 31

A possible mechanism for the reaction between the allyl ether [15] and Bu_3SnH is shown in Scheme 31. It involves the generation of the δ-aryl radical by the stannane radical [17], which had been generated by catalytic quantities of AIBN [18]. The stannane radical [17] then reacts with 2-iodoallyl phenyl ether [15] to give the aryl radical intermediate [18]. The intermediate [18] can then react

with the unsubstituted alkene moiety in an intramolecular ring cyclisation in two ways: the intermediate [18] can cyclise in an *exo* manner to give the 1,5-ring cyclised dihydrobenzofuran radical [19] which in turn goes to the dihydrobenzofuran [16] or can cyclise in an *endo* manner to give the 1,6-ring cyclised radical [21], which in turn goes to the 1,6-ring cyclised material, 2,3-dihydrobenzopyran [22]. The intermediate radical [18] could also be directly reduced, with no ring closure, to give the phenylallyl ether [20]. The reason behind the *exo* and *endo*-ring closure was comprehensively explained in the introduction.

b. Attempted cyclisation of 2-Iodophenyl allyl ether using the "Bunnett" procedure.

Bunnett and co-workers [89] have shown that iodoarenes can be reduced *via* the corresponding aryl radicals using methoxide with light catalysis and radical initiation. We therefore hoped to adapt the method to aryl cyclisation reactions.



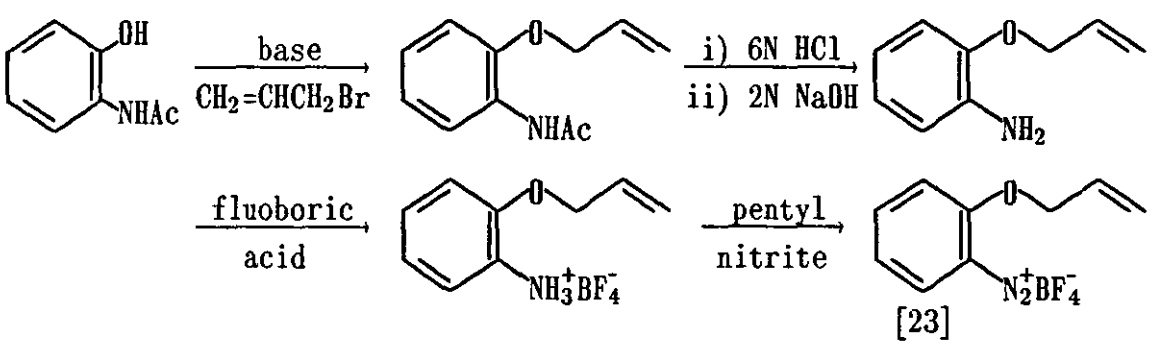
SCHEME 32

The allyl ether [15] was reacted with sodium methoxide whilst under illumination for 48 hours. Although the reaction quickly turned purple (an indication of iodine liberation), the preparative t.l.c. indicated that the sample in the reaction mixture had an R_f value corresponding with the reduced material, allylphenyl ether [20]. It was hoped that the methoxide would react with the

allylphenyl ether [15] to give the aryl radical [18], and after cyclisation, give rise to the *exo* product [16] as had been previously achieved using Bu_3SnH (Scheme 31). The expected mechanism is shown above (Scheme 32). It would appear that the intermediate aryl radical abstracts hydrogen ($H^{\cdot}$) from MeO^{-} faster than ring closure. If this is so, the method would have little use for cyclisation reactions. Further studies are required to elucidate the reaction mechanisms.

c. Cyclisation of 2-Allyloxybenzene diazonium fluoborate

The literature [90] had indicated that by changing the leaving group on the phenylallyl ether [15] from iodine to a diazonium fluoborate it would be possible to bring about the generation of the intermediate radical [18] and then the product, benzofuran [16] under milder conditions. This was found to be the case, and the diazonium fluoborate [23] was synthesised by the following route as indicated by Scheme 33.

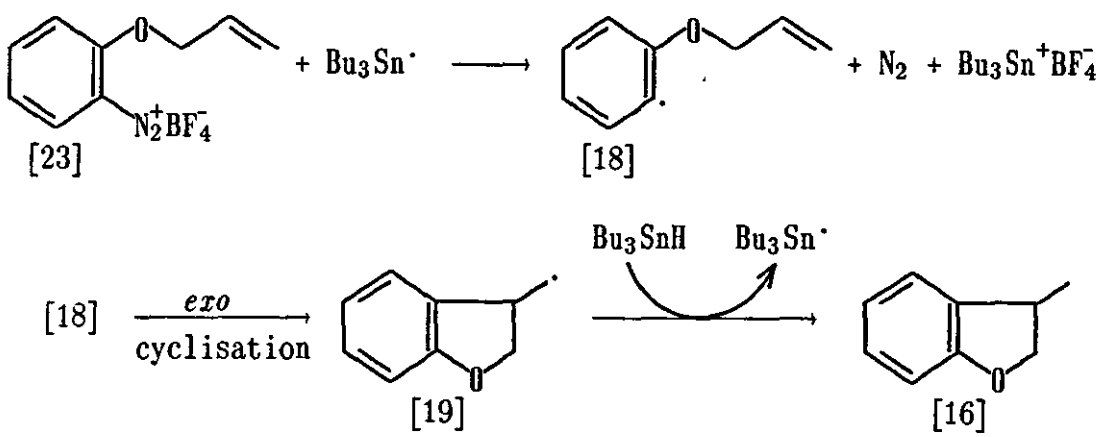


SCHEME 33

The diazonium fluoborate [23] was dissolved in THF and cautiously reacted with Bu_3SnH but without using the AIBN. The reaction was heated at reflux for 15 minutes and the product isolated by distillation as indicated previously. Compared to the reaction between iodoarenes and Bu_3SnH, the reaction time had been reduced considerably, i.e. from 24 hours to 15 minutes. The yield was slightly reduced in comparison to the reported reaction (58%) and the purity (90%) as indicated by g.l.c. lower than that achieved in the previous reaction using 2-iodophenyl allyl ether. However, the reaction showed that mild and effective

cyclisation could be achieved using an alternative leaving group.

There are several reasons for the mildness of the reaction which is best illustrated by looking at the proposed mechanism (Scheme 34). The diazonium fluoborate [23] reacts with a stannane radical to give the aryl radical [18], $Bu_3Sn^+BF_4^-$, and nitrogen. It is this evolution of nitrogen which pushes the reaction so rapidly along the path to the aryl radical [18]. Since this is an essentially irreversible, and energetically favoured reaction (evolution of nitrogen), there is a rapid conversion of the fluoborate [23] to the aryl radical [18]. The formation of the aryl radical is the rate limiting factor in the reaction sequence for the production of the benzofuran [16] using Bu_3SnH.



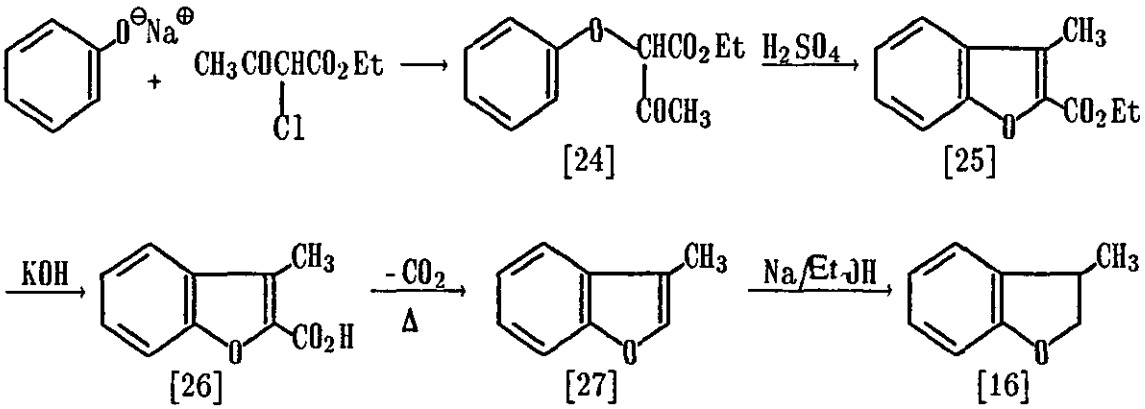
SCHEME 34

Although various aminoarenes are available as substrates, the diazotisation required in the sequence severely limits the possible structures/functional groups in the side-chain.

d. Classical synthesis of 3-Methyl-2,3-dihydrobenzofuran

Prior to the use of Bu_3SnH, the method, outlined below, was the best method for the synthesis of the benzofuran [16] by non-radical methods [91]. By reacting sodium phenoxide with ethyl α-chloroacetate, α-phenoxyacetoacetate was synthesised in good yield (90%) [24]. The ester [24] was reacted with sulphuric acid to give the ring cyclised ester, ethyl 3-methylcoumarilate [25], in moderate

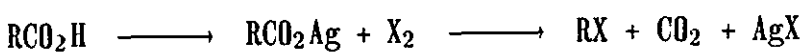
yield (43%). The ring cyclised ester [25] was reacted with base to give the acid [26], 3-methylcoumarilic acid, which in turn was decarboxylated to give 3-methylcoumarone [27]. The saturated coumarone was reduced using a reduction (Na in ethanol) to yield 3-methyl-2,3-dihydrobenzofuran [16] in a good yield (88%) and high purity (99% by g.l.c.). The different stages of the total synthesis are shown in Scheme 35. It shows the lengthy procedure required to obtain the benzofuran [16] by classical methods as shown in Scheme 35.



SCHEME 35

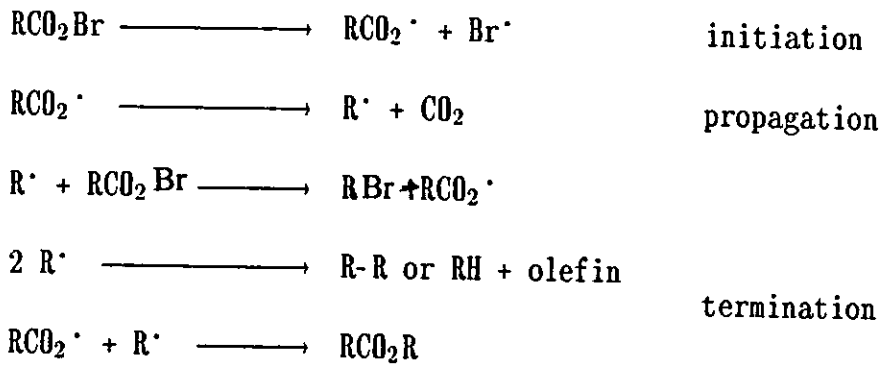
e. Attempted cyclisation of 2-Alloxybenzoic acid using the Barton procedure (using the sodium salt of 2-Mercaptopyridine-N-oxide)

The procedure developed by Barton and co-workers [92] appeared to be an alternative route for the production of aryl radicals, starting from arene carboxylic acids. Therefore, the procedure was examined using the models reported by Barton to gain practical experience in this area of chemistry. Four models were chosen to gain such experience. The Hundsdiecker reaction [93] has been used to convert carboxylic acids to alkyl halides with one less carbon atom as shown in Scheme 36.



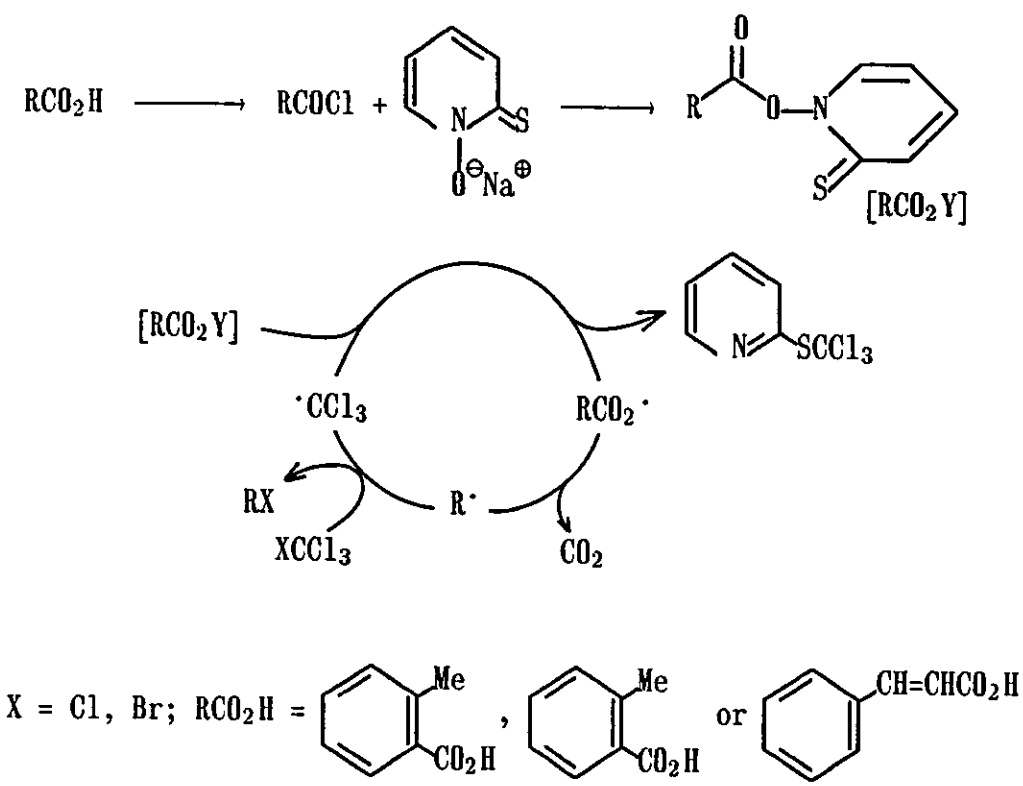
SCHEME 36

The mechanism proposed by Wilson and Cristol [92] proceeds *via* free radicals as shown in Scheme 37.



SCHEME 37

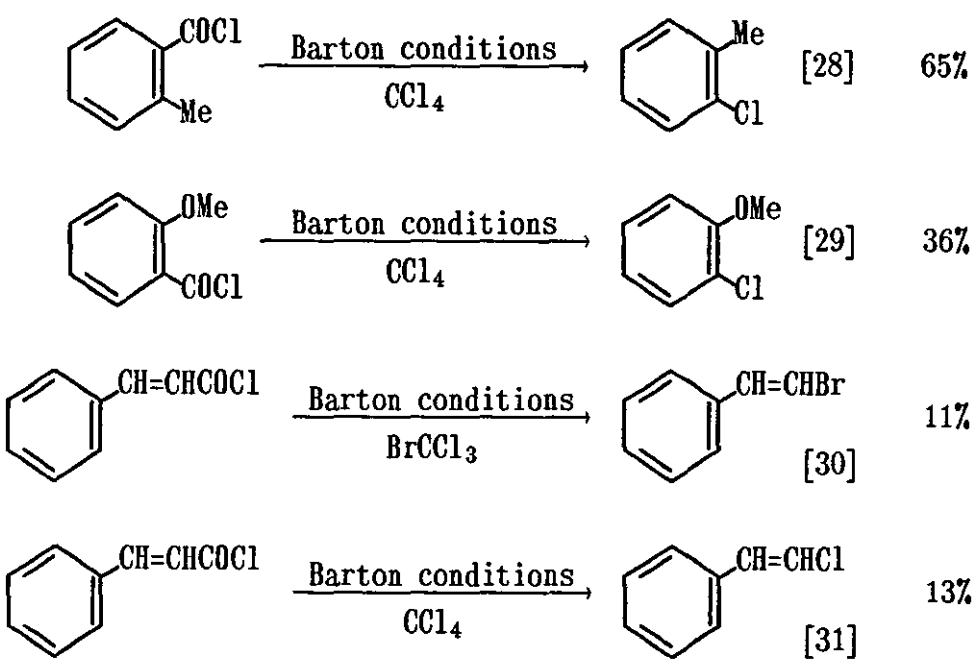
The mechanism helps to explain some of the by-products that have been isolated. Barton [92] proposed to modify the Hundsdiecker reaction so as to allow a one-pot synthesis of 2-chlorotoluene from 2-methylbenzoic acid. The procedure and the mechanism proposed by Barton [92] is shown in Scheme 38.



SCHEME 38

The reaction was monitored by observation of the development of a deep yellow colour on addition of the acid chloride derivative to the sodium salt of 2-mercaptopyridine-N-oxide. This colour indicated the formation of the

intermediate ester according to reports in a recent review, and that, when the colour subsides, the reaction is completed and ready for work-up. In the first of the four model reactions, 2-chlorotoluene [28] was synthesised from 2-methylbenzoyl chloride in CCl_4 in a good yield (65%). In the second model reaction chosen, anisoyl chloride in CCl_4 was reacted by the Barton procedure to give 2-chloroanisole [29] in moderate yield (36%). The third reaction, the synthesis of β-bromostyrene [30] from cinnamoyl chloride in bromotrichloromethane under the Barton conditions, gave a poor yield (11%). Finally the synthesis of β-chlorostyrene [31] from cinnamoyl chloride in carbon tetrachloride also gave a poor yield (13%). A summary of the model reactions is shown in Scheme 39.

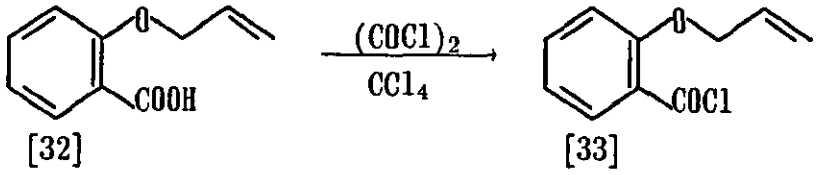


SCHEME 39

After the model systems had been mastered, the generation of a σ-aryl radical *ortho* to a known unsaturated system to synthesise a known compound, in this case the benzofuran [16], was attempted. We hoped that the Barton procedure could be applied to the field of aryl radical cyclisation and thereby eliminate the use of Bu_3SnH. 2-Allyloxybenzoic acid [32] was selected since it conformed to the two requirements previously stated above. It offered the same unsaturated moiety

previously found in [15] and also an *ortho* carboxylic group.

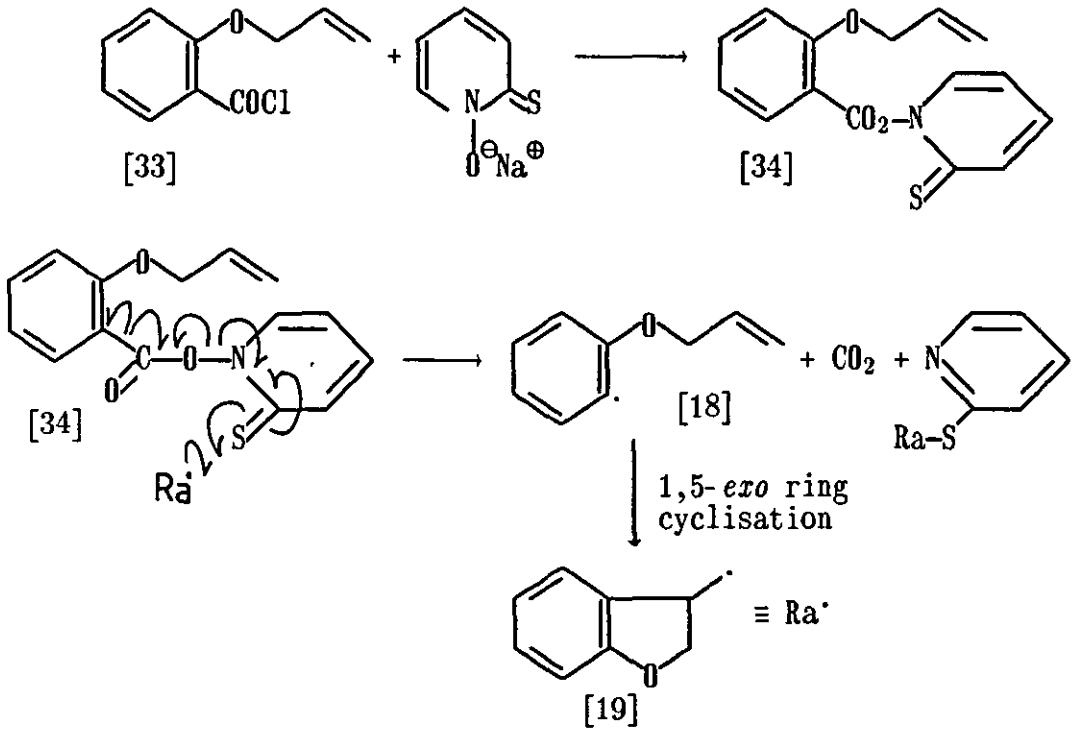
The acid chloride [33] was prepared from the acid [32] (Equation 39) using oxalyl chloride in CCl_4.



[32] [33] (39)

The acid chloride [33] was added to the sodium salt of 2-mercaptopyridine-N-oxide and reacted in the usual manner. The reaction only yielded some of the intermediate ester [34] along with an intractable gum. It should be noted that reviews of the Barton method often cite the failure of the procedure when applied to other systems. Practically, a great deal of investigation is still necessary in order to bring about successful cyclisation reaction using this procedure *via* aryl radicals. It was decided not to pursue this route further.

The proposed mechanism for the cyclisation using the Barton reagent is shown in Scheme 40.



SCHEME 40

There are several pitfalls to the scheme, e.g. it does not take into account the severity of the reaction conditions. The solvent, under the conditions of heat and illumination, could also generate radicals that would be equally available as the chain carrier, Ra· (Scheme 40). Direct reduction could lead to a build-up of reduced material. However, we feel that the real answer to the problem lies in what causes the intractable polymeric material. A possible explanation of our results was that the decomposition of the ester was faster than attack by the cyclised radical.

In conclusion, our initial investigations indicated that the use of Bu_3SnH on halogenoarenes would be the most successful method for generating aryl radicals for cyclisation reactions. Therefore, the cyclisation studies all use Bu_3SnH, even though there are considerable problems in separating products from the tin residues.

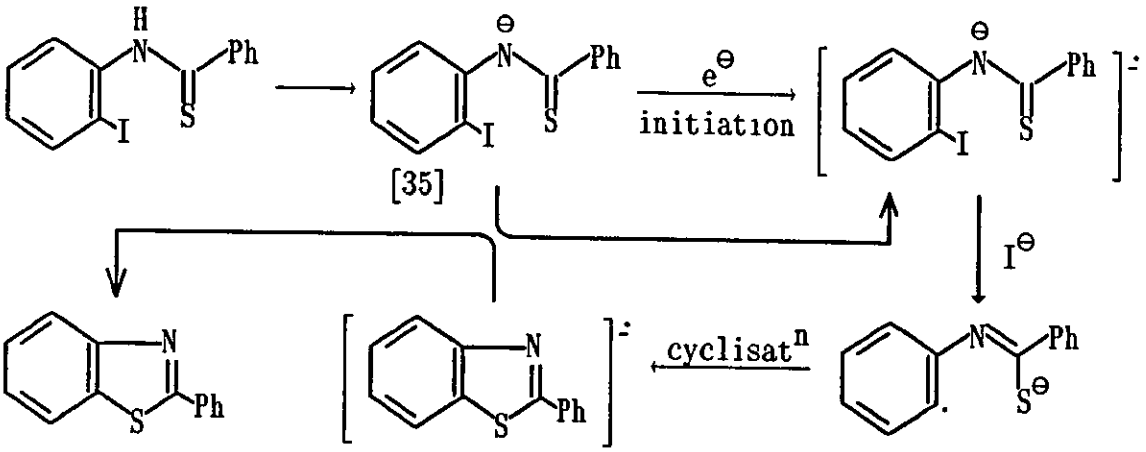
PART TWO:

INVESTIGATION OF THE ARYL RADICAL CYCLISATION OF AMIDES

In Part 1, the studies indicated that the use of iodoarenes and Bu_3SnH would be the most useful route for generating aryl radicals for cyclisation reactions. We therefore thought to apply this method to a previously studied cyclisation proceeding *via* an aryl radical intermediate. The anion of N-(2-iodophenyl)-thiobenzamide [35] had been cyclised by the $S_{RN}1$ reaction [94] and by use of Cu(I) or Cu(0) catalysis [94]. Although the exact mechanism of the copper catalysis is unknown, the general parameters are thought to be similar to those of the $S_{RN}1$ reaction.

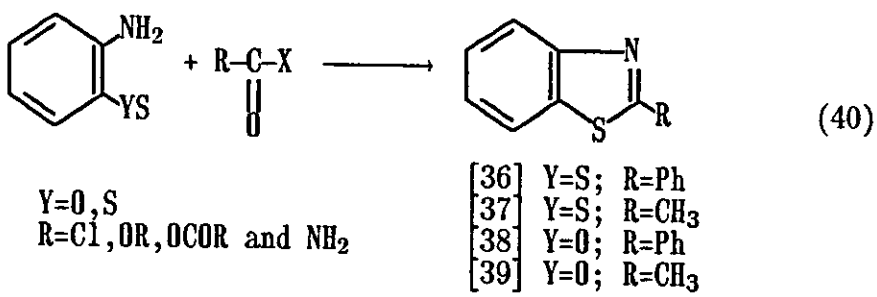
The $S_{RN}1$ mechanism is shown in Scheme 41. We decided that this reaction would provide a test for the Bu_3SnH route as well as indicate whether heteroatoms on the side-chain unsaturated group could participate in the cyclisation (Schemes 42 and 44).

The conventional method [95] for the preparation of 2-substituted benzothiazoles [36,37] and benzoxazoles [38,39] are achieved by reacting 2-aminothiophenols or 2-aminophenols with an acid derivative as depicted in Equation 40.

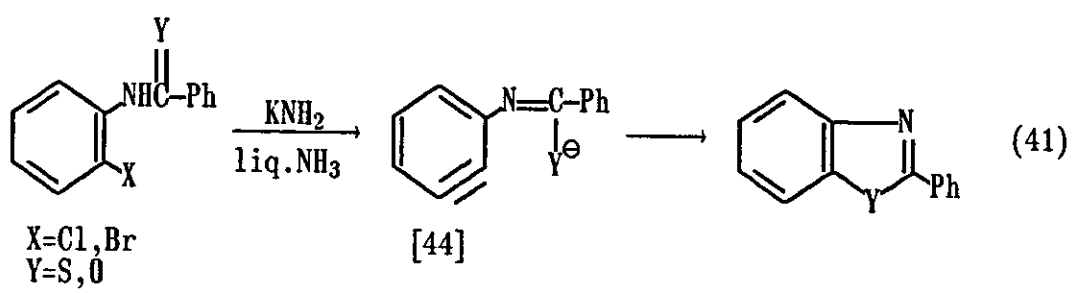


SCHEME 41

An alternative procedure developed by Bunnett and Hrutfiord [96] involves the cyclisation of thioamides and amides *via* benzyne intermediates [44] as shown in Equation 41. The yields of benzothiazole and benzoxazole vary between 62 and 90%.



(40)

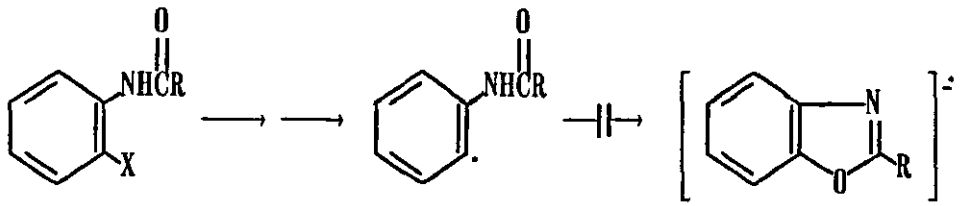


(41)

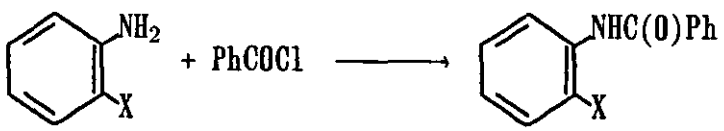
a. Preparation and attempted cyclisation of N-(2-Halogenophenyl)-benzamides

Although the $S_{RN}1$ reaction of the anions of N-(2-halogenophenyl)-benzamides were unsuccessful, it was decided to attempt the cyclisation using Bu_3SnH in order to determine whether the Bu_3SnH method was superior to $S_{RN}1$

reaction. The reason for the lack of cyclisation in the $S_{RN}1$ reaction was proposed to be due to the high energy required for the aryl radical to react with the stable carbonyl π-bond (Equation 42). N-(2-halogenophenyl)-benzamides [45,46] were easily prepared by the Schotten-Baumann [97] procedure as shown in Equation 43.



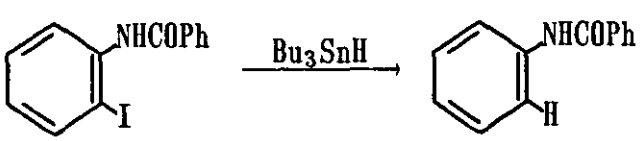
(42)



(43)

[45] X=I
[46] X=Br

The attempted cyclisation of the aryl radical derived from [45,46] onto the carbonyl functionality using Bu_3SnH was carried out under the standard conditions for Bu_3SnH. It was found that no ring cyclised material, and only reduced material, benzanilide [46], was synthesised in a good yield (46%) as shown in Equation 44.



(44)

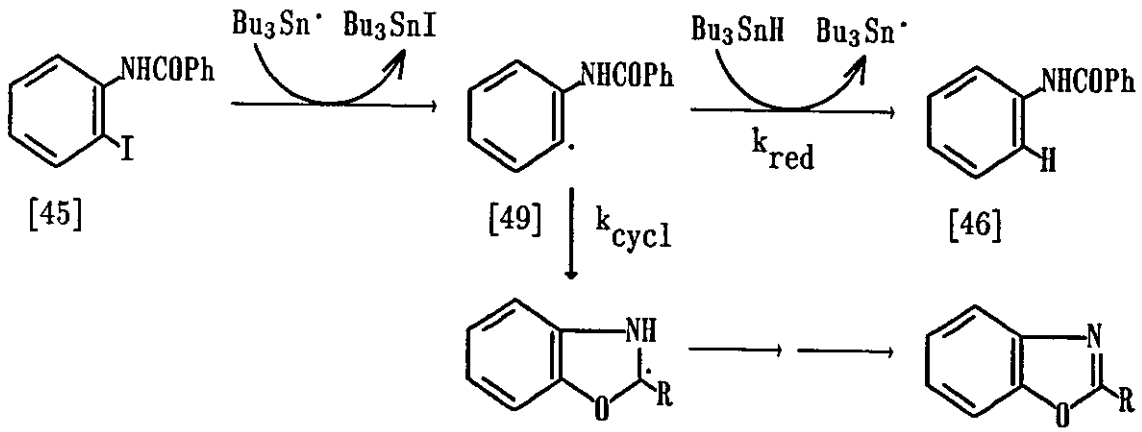
[45] [46]

The reason for the inactivity of the carbonyl moiety to the σ-aryl radical can be explained by the fact that the π-CO bonds are very stable and require a higher energy to homolytically alter the π-system.

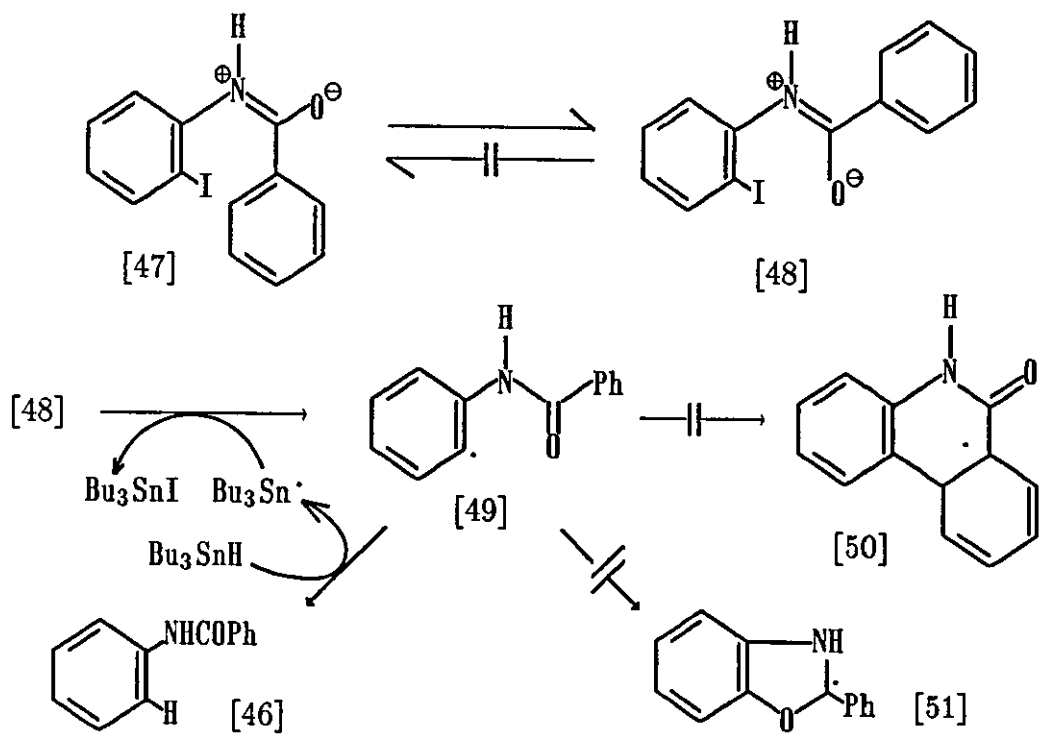
Therefore the absence of cyclisation can be explained by the faster relative rate of reduction versus the rate of cyclisation (Scheme 42) (i.e. $k_{redn} > k_{cycl}$).

If the rate of reduction is greater than that of cyclisation only benzanilide [46] will be formed, as shown by the experimental results. Benzanilides exhibit *cis* [47] and *trans* [48] isomerism and only the *trans* isomer is formed when a hydrogen

atom is present on the nitrogen atom. Therefore, though the oxygen atom is well set up for cyclisation onto the aryl radical [48] (Scheme 43), only reduction of the aryl radical takes place.



SCHEME 42

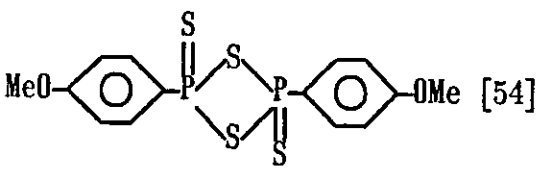


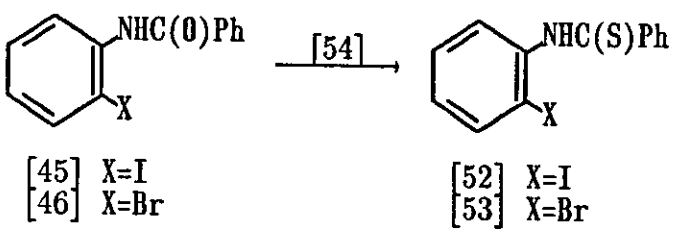
SCHEME 43

With the lack of success with the carboxamide system, we turned our attention to the thioamide analogues which were known to cyclise with difficulty by the $S_{RN}1$ mechanism.

b. Preparation and cyclisation under standard Bu_3SnH conditions of N-(2-Halogenophenyl)-thiobenzamides

The N-(2-halogenophenyl)-thiobenzamides [52] and [53] were prepared using Lawesson's reagent [54] on the corresponding benzamides [45,46] as shown in Equation 45. The reaction of N-(2-iodophenyl)-thiobenzamide [52] and N-(2-bromophenyl)-thiobenzamide [53] under standard Bu_3SnH conditions led to ring cyclisation to give 2-phenylbenzothiazole [56] as indicated in Scheme 44.

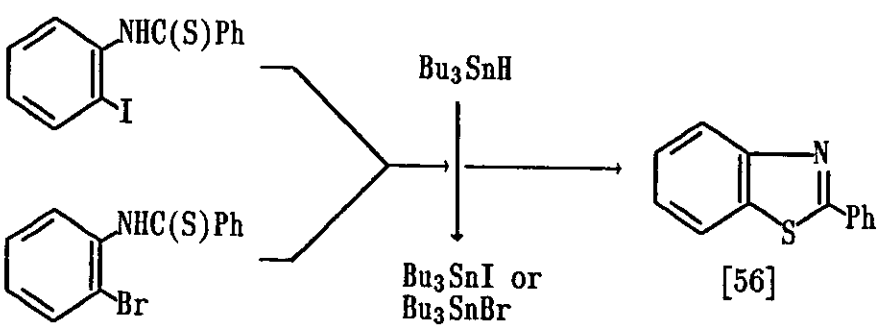




(45)

[45] X=I
[46] X=Br

[52] X=I
[53] X=Br

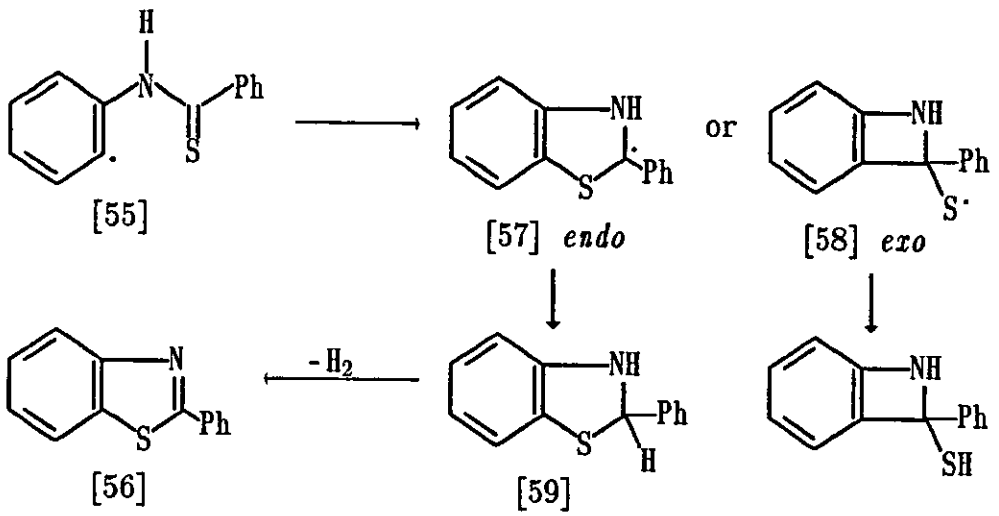


SCHEME 44

To explain the product formed, a number of mechanisms can be proposed in which a radical intermediate [55] plays a key role. As we saw earlier (Scheme 43) the generation of the aryl radical [55] leads to a number of reactions which could give rise to the expected product.

The expected cyclisation would give the initial products shown in Scheme 42. These intermediates for the formation of 2-phenylbenzothiazole [56], however, require further elaboration. Although the strain in the formation of the 4-

membered ring is large it might be possible that [58] is a transient intermediate that rearranges to give intermediate [57] which can then undergo reactions to form the product isolated [56]. The *exo*-cyclised radical [58] is not stabilised and rearrangement to the strongly stabilised *endo*-cyclised radical [57] should be thermodynamically favoured.



SCHEME 45

If the 2,3-dihydrobenzothiazole is the initial product of cyclisation an oxidation must take place on work-up (Scheme 45). Radical oxidation of [59] with atmospheric oxygen would be favourable because of the thermodynamic driving force to yield the fully aromatic benzothiazole. However, careful work-up under nitrogen only yielded the benzothiazole [56]. Therefore, a mechanism which yields [56] directly is most likely. The reaction was therefore studied under various conditions in order to understand the mechanism more fully. Results of our studies are discussed in the next section (see Table 1).

Cyclisations and attempted cyclisations of N-(2-halogenophenyl)-thiobenzamide under various conditions

General conditions for cyclisation

The material to be reacted was added to deoxygenated solvent (75 ml). The solvent was heated to reflux (or a specified temperature) whereupon Bu_3SnH, NaH or DABCO (as specified) and AIBN (as specified) were added. The reaction

	REACTION CONDITIONS §	AMOUNT OF S M. (mg) ¶	% S M. RECOVERED	% YIELD PRODUCT ¶
1.	Standard conditions	300 80	0 (<4)	69 (96)
2.	Absence of hv	200 76	20 (28)	15 (72)
3.	0.1 equiv. Bu_3SnH	400 85	0 (9)	80 (91)
4.	No AIBN	100	0	7
5.	No Bu_3SnH, 1.1 equiv. AIBN	350	0	65
6.	a) Toluene at 80 °C b) PhCl at 158 °C, 12h. c) PhH at 80 °C	300 62 400	(23) (6) (0)	(77) (94) (75)
7.	No Bu_3SnH, No AIBN	300	Polymeric material	
8.	No Bu_3SnH, 1.1 equiv. NaH	500	0	34
9.	Br in place of I Br, no hv	317 75	0 (40)	64 (60)
10.	No Bu_3SnH 1.1 equiv. DABCO	692	0	73
11.	No Bu_3SnH or AIBN 1.1 equiv. DABCO	145	0	55
12.	0 1 equiv. Bu_3SnH 1.1 equiv. DABCO	612	0 (9)	50 (91)

TABLE 1: Cyclisation and attempted cyclisation of N-(2-halogenophenyl)-thiobenzamide under various conditions

NOTES

S.M. Starting Material = N-(2-iodophenyl)-thiobenzamide

Product = 2-phenyl-1,3-benzothiazole

§ The conditions are those for the "standard" Bu_3SnH unless otherwise stated, i.e. 1.1 equivalents of Bu_3SnH, 0.2-0.3 equivalents of AIBN, hv, refluxing toluene, nitrogen, 24 h.

¶ The yields are pure isolated 2-phenyl-1,3-benzothiazole and the yields in parentheses are from repeat reactions using H.L.P.C. analysis.

was illuminated whilst maintaining the reaction at reflux (as specified) under nitrogen for the designated time (as specified). The solvent was removed *in vacuo* and the crude material recrystallised from a suitable solvent (pet. ether etc.) and characterised in the normal manner (I.R., N.M.R. and mass spectra). The results of which are explained in the next section (see Table 2).

Cyclisations of N-(2-halogenophenyl)-thiobenzanilide under various conditions and the material examined by H.P.L.C.

Some of the reactions originally performed above (Tables 1 and 2) were attempted under similar conditions but the crude material on removal of the solvent was redissolved in THF (100 ml) and analysed by H.P.L.C. (ODS column, 20 cm using 20% THF, 50% MeOH and 30% H_2O as the solvent system). An internal standard of acetanilide was used to calibrate the column initially and calibration curves drawn using standard concentrations of authentic materials; starting material, reduced material and cyclised material. The results of which are shown in Table 3 and discussed in the next section.

c. Cyclisation of N-(2-Iodophenyl)-thiobenzamide using Bu_3SnH under various conditions

The cyclisation of N-(2-iodophenyl)-thiobenzamide using Bu_3SnH was repeated under various conditions in order to gain some idea of the parameters and mechanism of the cyclisation reaction. The 2-phenylbenzothiazole was initially isolated, recrystallised and characterised using m.p., I.R., N.M.R. and mass spectroscopy. The results proved somewhat variable due to the lengthy purification due to the difficulty of separating out the tin residues.

Most of the reactions were repeated and the amount of 2-phenylbenzothiazole measured using H.P.L.C. (Table 3) on the crude reaction product. In this way the true amount of benzothiazole product could be measured without taking account of the variable separation problem.

Both sets of results are shown in Tables 1 and 2. The general method is detailed in the Experimental section. The normal procedure was the use of 1.1

[S.M] mg (mmol)	[Bu_3SnH] or reagent mg (mmol)	[AIBN] mg (mmol)	SOLVENT /TEMP °C	TIME (h)	% YIELD PRODUCT OR S M.
300 (0.9)	1.1 eq. 283 (0.97)	0.3 eq. 43 (0.26)	Toluene 110/hν	24	69% C.M.
200 (0.59)	1.1 eq. 188 (0.64)	0 2 eq. 20 (0.12)	Toluene 110/no hν	24	20% C.M. 5% S.M.
400 (1.2)	0.1 eq. 34 (0.12)	0.3 eq. 58 (0.35)	Toluene 110/hν	24	80% S.M.
100 (1.03)	1.1 eq. 377 (1.3)	None	Toluene 110/hν	24	7% R.M.
350 (1.03)	None	1.1 eq. 186 (1.13)	Toluene 110/hν	24	65% C.M. [5/19]
300 (0.88)	1.1 eq. 282 (0.37)	0.3 eq. 43 (0.26)	Toluene 80/hν	24	S.M.& C.M. ¶
300 (0.88)	None	None	Toluene 110/hν	24	Polymeric material
500.2 (14)	1.1 eq. NaH 370 (15.4)	0.2 eq. 482 (2.9)	Toluene 110/hν	24	34% C.M.
317 (1.08)	1.1 eq. 346 (1.18)	0.3 eq. 58 (0.35)	Toluene 110/hν	24	64% C.M.
200 (0.62)	1.1 eq. 198 (0.68)	0.3 eq. 30 (0.19)	Toluene 110/hν	24	64% R.M. benzanilide
400 (1.2)	1.1 eq. 377 (1.3)	0.3 eq. 58 (0.35)	Toluene 80/hν	24	75% C.M.
692 (2 04)	1.1 eq. 251 (2.24)	0.2 eq. 66 (0.4)	Toluene 110/hν	24	73% C.M.
145 (0.43)	1.1 eq. 53 (0.47)	None	Toluene 110/hν	24	55% C.M.
612 (1.8)	1.1 eq. 222 (1.98) Bu_3SnH 0.1 eq. 52 (0.18)	0.2 eq. 59 (0.36)	Toluene 110/hν	24	50% C.M.
	1 1 eq. 100 (0.89)	None	Toluene 110/hν	48	35% C.M.

TABLE 2: Cyclisations of N-(2-halogenophenyl)-thiobenzamide under various conditions and the material examined by H P.L.C.

nb. C.M. = Cyclised Material; R.M. = Reduced material; S.M. = Starting material recovered.
¶ from t l.c. evidence only (not isolated); see H.P.L.C. studies

[S.M.] mg (mmol)	[Bu_3SnH] mg (mmol)	[AIBN] mg (mmol)	SOLVENT /TEMP °C	TIME (h)	% YIELD S.M.	C.M.
1. 80 (0.235)	1.1 eq. 75 (0 26)	0.3 eq. 11 (0.07)	Toluene 110/hv	24	4	96
2. 76 (0 24)	1.1 eq. 71 (0.25)	0.3 eq. 12 (0.075)	Toluene 110/no hv	24	72	28
3. 85 (0.25)	0.1 eq. 7 (0.025)	0.3 eq. 12 (0.075)	Toluene 110/hv	24	91	9
4 65 (0.19)	1.1 eq. 61 (0.21)	0.3 eq. 9 (0.057)	Toluene 80/hv	24	23	77
5. 62 (0.18)	1.1 eq. 58 (0.20)	0.3 eq. 9 (0 054)	Chlorotoluene 157-159/hv	12	6	94
6. 65 (0.19)	0.1 eq. 3 (0.019)	0.3 eq. 9 (0.057)	Toluene hv	24	9	91
7. 75 (0.26)	1.1 eq. 83 (0.27)	0.3 eq. 13 (0.78)	Toluene 110/hv	24	40	60

TABLE 3: Cyclisation of N-(2-Iodophenyl)-thiobenzamide using Bu_3SnH under various conditions and examined by H.P.L.C.

equivalents of Bu_3SnH, 0.2-0.3 molar equivalents of AIBN, refluxing toluene, light catalysis and a dry nitrogen atmosphere.

TABLE 1

In Experiment 2 the use of standard Bu_3SnH conditions on N-(2-iodophenyl)-thiobenzamide in the absence of light gave rise to evidence that light was required to bring about completion of the reaction but it is not essential since 20% of the material cyclised product was obtained. There was a 15% recovery of starting material.

Initiation problems can be ruled out since the initiator AIBN breaks down readily under both heat and light catalysis to give initiator radicals. In Experiment 3 the use of catalytic quantities of both Bu_3SnH and AIBN gave almost no cyclisation with 80% recovery of starting material which suggests that Bu_3SnH was needed in stoichiometric amounts and was not acting in a catalytic role to perpetuate the chain reaction.

In Experiment 4, AIBN was excluded which gave rise to a poor yield of cyclised material (7%) and recovered starting material. This indicates that AIBN is required as an initiator for a free radical reaction. This result indicates a mechanism involving initiation *via* homolytic cleavage of the C-I bond in the starting material is likely to be much slower.

In Experiment 5, in which no Bu_3SnH was used and AIBN was used in excess, a comparable yield to that of the standard reaction (Experiment 1) was obtained. This indicated that the AIBN generated radicals are capable of removing or facilitating in the removal of iodine from the starting material, thereby generating the aryl radical necessary to form 2-phenylbenzothiazole. This would tend to indicate that AIBN was more important than Bu_3SnH in the reactions studied. However both Experiments 4 and 5 indicate the necessity of both components.

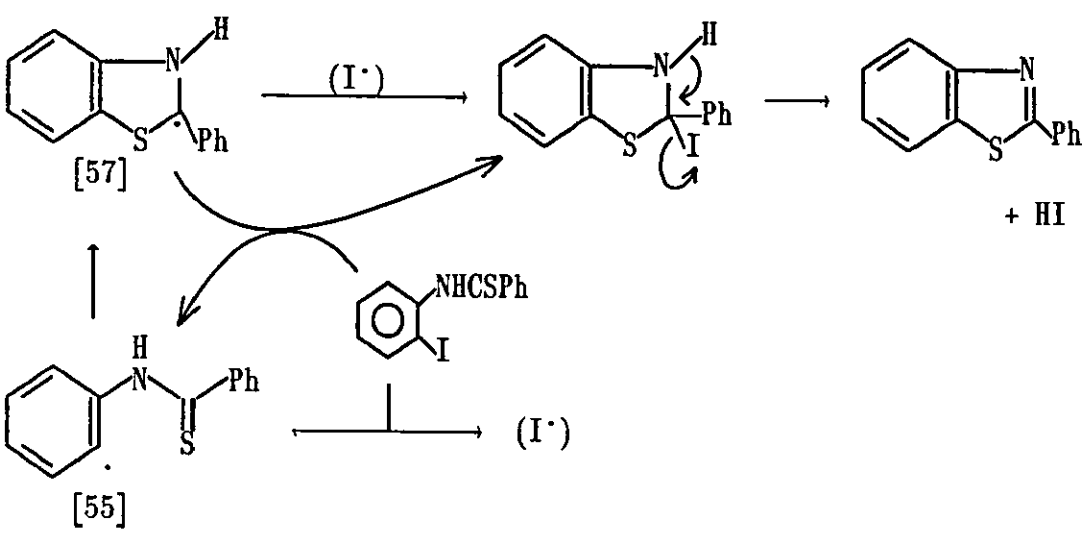
In Experiment 6a the standard reaction was attempted but using a lower temperature (80 ^{o}C) to observe what effects temperature would have on the yield of cyclised material. Although isolation was problematic, H.P.L.C. studies (Experiment 4, Table 3) indicate slightly lower yields of cyclised material than that

of the standard reactions (Experimental 1, Table 3).

In Experiment 6c the standard conditions were also used, except that benzene (80 °C) was used as the solvent, and gave an excellent yield (75%). This was used as a comparable result with that of the standard reaction with toluene at 80 °C (Experiment 6a).

This was exemplified by the reaction carried out under standard conditions with 2-chlorotoluene (157-159 °C) as a solvent (Experiment 6b). The reaction gave the same yield of product as that of the standard Bu_3SnH reaction in toluene but in a shorter reaction time (12 hours instead of 24 hours). The temperature studies suggest that temperature rather than solvent is the determining factor. Experiment 9 indicates that the reaction with bromine in place of iodine is slower as expected for the strong C-Br bond.

In Experiment 7 no reagents were used and the starting material alone was refluxed in solvent. Only polymeric material was isolated, clearly indicating that a mechanism proceeding by iodine radical generation is not possible under these conditions (Scheme 46).



SCHEME 46

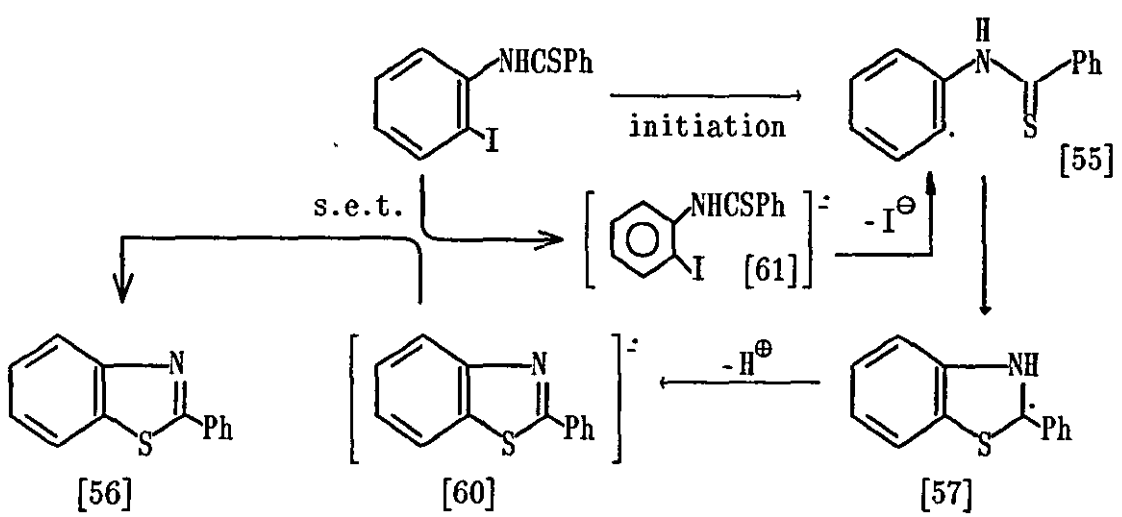
In Experiment 8, the use of sodium hydride as a base and catalytic AIBN in toluene gave the cyclised material in moderate yield (34%). Sodium hydride

deprotonates the thioamide to give an anion which reacts *via* an $S_{RN}1$ mechanism as shown above (Scheme 41). This is the first example of an $S_{RN}1$ reaction in a non-polar solvent such as toluene. There is no evidence that Bu_3SnH acts in a similar way.

Bu_3SnH has not been reported to react with acidic hydrogens thereby forming the anion of N-(2-iodophenyl)-thiobenzamide which can enter a $S_{RN}1$ mechanism. However, thioamides are more acidic than carboxamides and deprotonation is possible, but unlikely.

DABCO was used in place of Bu_3SnH (Experiments 10-12) with reasonable results suggesting either deprotonation and an $S_{RN}1$ reaction or deprotonation at some later stage in the mechanism is likely. The mechanism with DABCO could possibly be $S_{RN}1$ but that with Bu_3SnH is unlikely to be so.

Several experiments (3-7) indicate that a radical abstraction of iodine radical is required to initiate the reaction and yield an intermediate aryl radical. The route after the formation of the aryl radical is not however clear. The results with varying amounts of Bu_3SnH and AIBN were not conclusive. A chain mechanism is most likely in a free radical reaction and therefore we suggest that the intermediate aryl radical [55] cyclises to form a new radical [57] as shown in Scheme 47. Various mechanisms can be invoked to explain how the cyclised radical [57] is converted to 2-phenyl-1,3-benzothiazole.



SCHEME 47

Disproportionation of the cyclised radical [57] could give product [56] and the oxidisable [59]. There was no evidence for the formation of [59]. This observation coupled with the fact that this would not be a chain mechanism indicated that this explanation is unlikely.

Abstraction of the hydrogen ($H^{\cdot}$) from the nitrogen in intermediate [57] by the stannane radical was also considered but dropped after realising the energy barrier for loss of $H^{\cdot}$ is much higher than for the loss of H^{+} and that it would not be a chain reaction.

It is also possible that the intermediate radical [57] could abstract iodine from the starting material [52] giving rise to the benzothiazole [56] after loss of HI, as well as a chain-carrying radical [55] (see Scheme 46).

The Bu_3SnH would be required to mop up HI. Another possible mechanism is a concerted mechanism in which the stannane radical attacks the hydrogen on the thioamide causing simultaneous attack by the C=S group onto the aryl radical to give the product and Bu_3SnH.

There was little evidence for this mechanism since stoichiometric quantities of Bu_3SnH were required to bring about a successful yield of 2-phenylbenzothiazole. This mechanism also does not explain how $Bu_3Sn^{\cdot}$ would be regenerated to carry on the reaction.

Finally, there is homolytic cleavage of the carbon-iodine bond to give the aryl radical, which cyclises to give the radical intermediate [57]. This cyclised radical could then be attacked by the iodine radical on the amide hydrogen to give the cyclised product. Reaction between hydrogen iodide and Bu_3SnH to give Bu_3SnI and hydrogen gas would complete the reaction. Experiment 7 suggests that auto-homolysis is unlikely to account for the speed of the reaction.

In conclusion, the formation of 2-phenyl-1,3-benzothiazole cannot be explained by a normal Bu_3SnH mechanism. As explained the results suggest a chain free radical reaction involving initiation from AIBN to yield aryl radical [55] which cyclises to yield radical [57]. As proton loss appears to be important we suggest that a "pseudo $S_{RN}1$" mechanism is a likely explanation in which the aryl radical [55] is regenerated *via* a radical anion as shown in Scheme 47. Loss of H^{+}

(Bu_3SnH or DABCO) is probably the least energetic step for the radical [57]. The resulting radical anion [60] is known to be able to transfer an electron to the anion of the starting material [98] and is therefore even more likely to transfer an electron to the neutral (rather than anionic) starting material. The chain would be completed by loss of I^- from the new radical anion [61].

The central difference between this mechanism and the $S_{RN}1$ mechanism (Scheme 41) is that cyclisation takes place from a radical to yield a radical rather than from a radical anion to yield a radical anion.

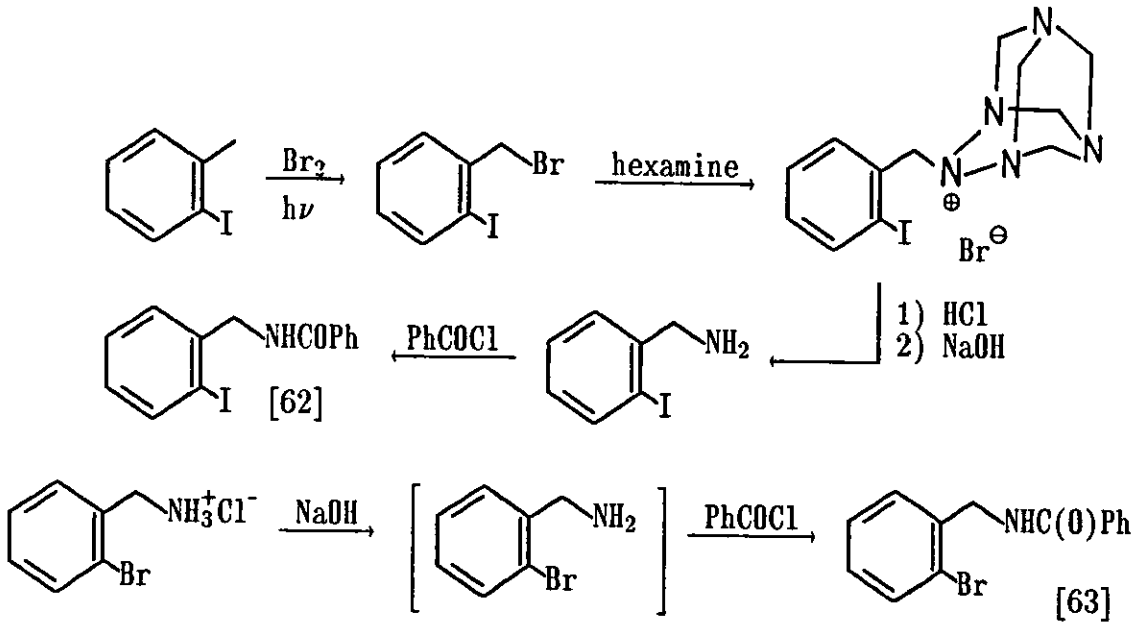
The evidence does not prove the "pseudo $S_{RN}1$" mechanism or exclude other mechanisms. However, it does explain all the evidence and is further supported by the reactions reported below (Sections d and e).

Absence of cyclisation of the aryl radical [55] onto the other aromatic ring (Section g) is explained as for the carboxamide analogue. The radical intermediate [55] is in the strongly preferred *trans* conformation which places the C=S group, rather than the other aromatic ring, in the correct position for cyclisation. The barrier for rotation to the *cis* conformation of the thioamide is likely to be too high.

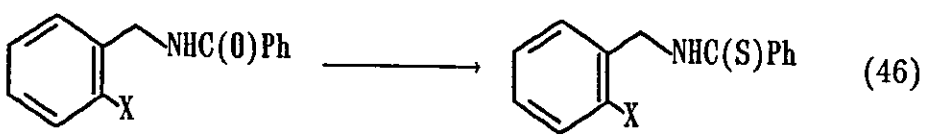
d. Cyclisation reaction of N-(2-Halogenophenyl)-methylbenzamide and N-(2-Halogenophenyl)-methylthiobenzamide

On the basis of the N-(2-halogenophenyl)-thiobenzamide cyclisations it was hoped that the synthesis of six-membered rings could be achieved by using N-(2-halogenophenyl)-methylbenzamides and -thiobenzamides. The synthesis followed a conventional method for both the N-(2-iodophenyl)-methylbenzamide [62] and the N-(2-bromophenyl)-methylbenzamide [63] as indicated by Scheme 48.

The thio-analogues [64,65] were synthesised using Lawesson's reagent to give N-(2-iodophenyl)-methylthiobenzamide [64] and the N-(2-bromophenyl)-methyl-thiobenzamide [65] as indicated by Equation 46.



SCHEME 48

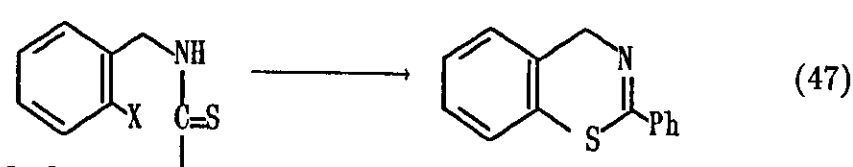


[62] X=I
[63] X=Br

[64] X=I
[65] X=Br

Our earlier studies showed that C=O moieties as unsaturated groups for cyclisation were ineffective for attack by the aryl radical. Therefore the cyclisation of N-(2-bromophenyl)-methylbenzamide [63] using the standard Bu_3SnH conditions was not attempted. However, the use of DABCO [1,4-diaza-bicyclo(2.2.2)octane] as a base, to replace Bu_3SnH and AIBN, was attempted. This reaction was studied to see whether the use of the base would bring about a $S_{RN}1$ type reaction. The reaction was unsuccessful and gave an almost quantitative recovery of starting material.

The cyclisation of both the thio-analogues, [64] and [65], were successful under the standard conditions using Bu_3SnH (Equation 47).

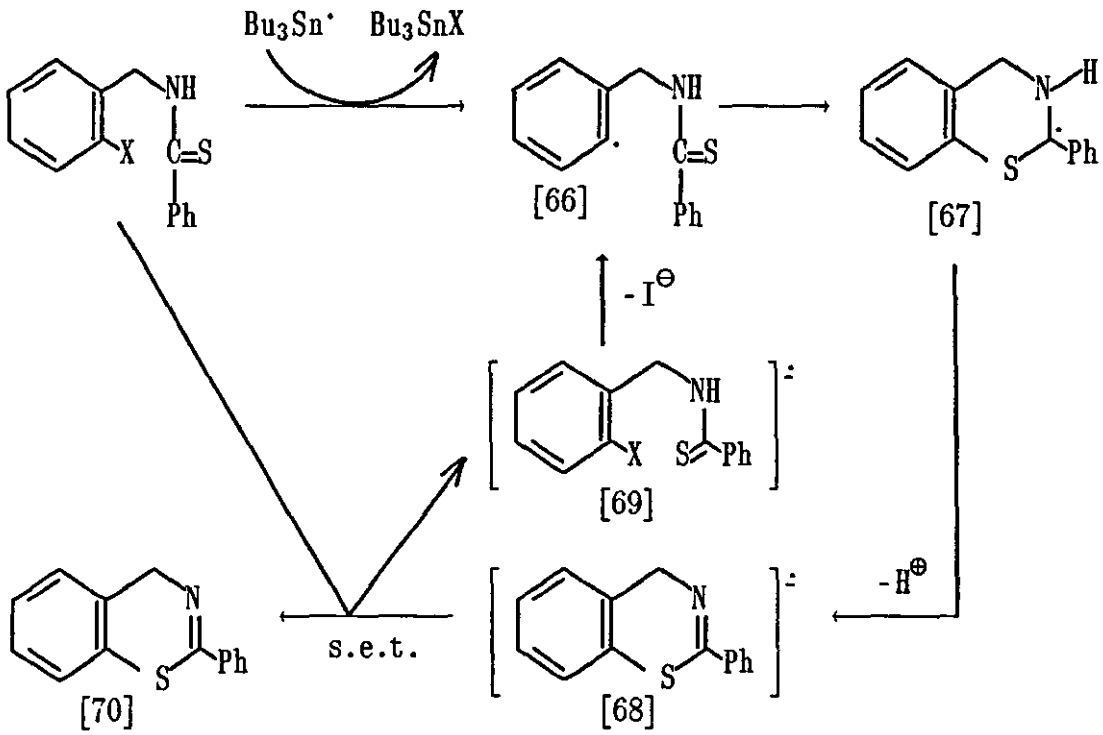


[64] X=I
[65] X=Br

[70]

The iodothio- analogue [64] cyclised to yield the six-membered ring 2-phenyl-4H-1,3-benzothiazine [70] in 31% yield and the corresponding bromothio-analogue [65] gave a slightly better yield (41%).

We propose that the mechanism is similar to that of the cyclisation of N-(2-halogenophenyl)-thiobenzamide and is illustrated in Scheme 49, i.e. a "pseudo $S_{RN}1$" mechanism.



SCHEME 49

The N-(2-halogenophenyl)-methylthiobenzamide reacts with a $Bu_3Sn^{\cdot}$ radical to give the aryl radical [66] which ring cyclises to the ring-cyclised radical intermediate [67] which in turn is deprotonated to give the radical anion [68]. The radical anion [68] undergoes s.e.t. to give the product, 2-phenyl-4H-3-benzothiazine [70] and the radical anion [69] to propagate the chain reaction.

The attempted $S_{RN}1$ cyclisation of the anion of [64] has been reported to be unsuccessful under various conditions [99]. This strongly suggests that a normal $S_{RN}1$ is not a likely mechanism of the reaction.

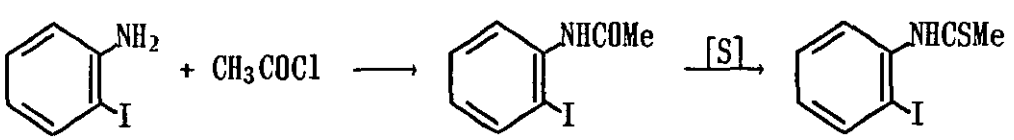
This cyclisation indicates that these cyclisation reactions may be applicable to other similar systems thereby providing a new synthetic method.

The cyclisation of N-(2-bromophenyl)-methylthiobenzamide [65] using DABCO in place of Bu_3SnH as a base was unsuccessful and gave unaltered starting material [65] in an almost quantitative yield (99%). This reaction strongly suggests that initial deprotonation does not take place, thereby ruling out an $S_{RN}1$ mechanism for the Bu_3SnH ring closure. This latter compound does not undergo $S_{RN}1$ cyclisation even under forcing conditions [99]. These results provide further evidence for the "pseudo" $S_{RN}1$ mechanism.

e. Cyclisation of N-(2-Iodophenyl)-thioacetamide and the attempted cyclisation of N-(2-Iodophenyl)-N-methylthioacetamide

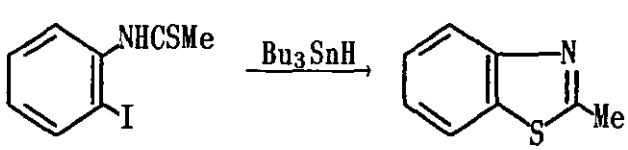
The cyclisation of the methyl analogue of the N-(2-iodophenyl)-thiobenzamide was studied to observe the generality of the reaction. The aim was also to prepare the N-methyl analogue to study whether the loss of the N-hydrogen was essential to the proposed "pseudo $S_{RN}1$" mechanism, i.e. loss of Me^+ is extremely unlikely and therefore other products would be predicted.

N-(2-Iodophenyl)-acetamide [71] was synthesised from 2-iodoaniline and acetyl chloride and treatment with Lawesson's reagent gave N-(2-iodophenyl)-thioacetamide [72] (Equation 48).



(48)

[71] 28% [72] 41%



(49)

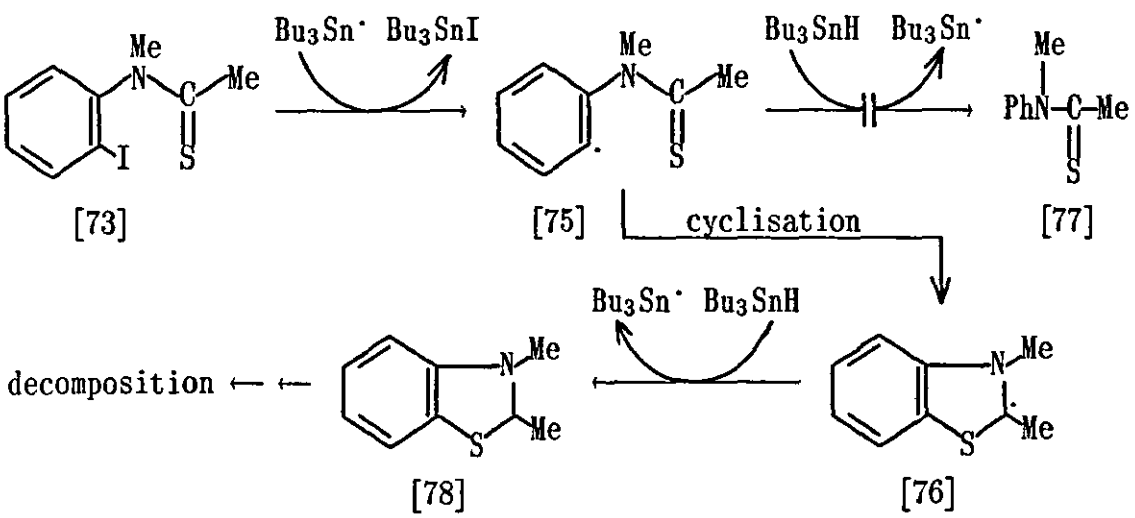
[72] [74]

The thioacetamide [72] was reacted under standard Bu_3SnH conditions to give 2-methylthiobenzothiazole [74] in good yield (43%) as in Equation 49. The mechanism is likely to be the same as illustrated previously in Scheme 44 for the phenyl analogue.

The attempted cyclisation of N-(2-iodophenyl)-N-methylthioacetamide [73] using the standard Bu_3SnH conditions was unsuccessful and gave only an intractable polymeric gum (Scheme 50). N-(2-iodophenyl)-N-methylthioacetamide [73] was prepared by the usual method using sodium hydride and methyl iodide as shown in Equation 50.

(50)

[72] [73]



[73] [75] [77] [78] [76]

SCHEME 50

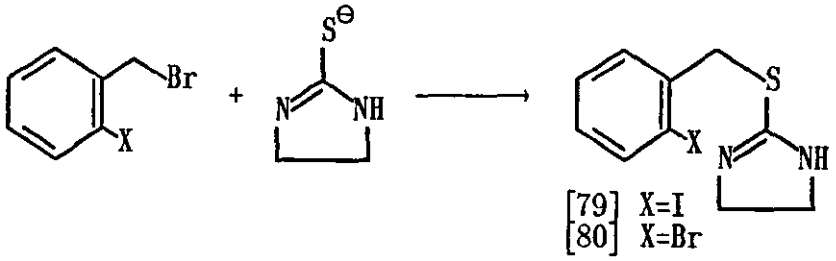
The problems associated with this cyclisation can be explained as shown in Scheme 50. Reaction between the stannane radical and the thioamide [73] gives the radical [75] which cyclises to the intermediate radical [76] faster than reduction to N-methylthioacetanilide [77]. This radical is likely to be reduced to 2,3-dihydro-2,3-dimethylbenzothiazole [78] which decomposes to unidentifiable materials on work-up.

So in summary, the reaction between Bu_3SnH and N-(2-iodophenyl)-thioacetamide [74] yielded 2-methylbenzothiazole in good yield (43%) but when a similar reaction was attempted with N-(2-iodophenyl)N-methylthioacetamide an intractable gum was obtained. These reactions support the proposition of a

"pseudo $S_{RN}1$" mechanism. If the aryl radical [75] generated in the latter reaction does not cyclise onto the C=S group then "normal" reduction to N-methyl-thioacetanilide would have been expected (Scheme 50). The lack of ability of the cyclised radical to lose Me^+ prevents aromatisation to 2-methylbenzothiazole and reduction probably takes place to yield an unstable product which decomposes.

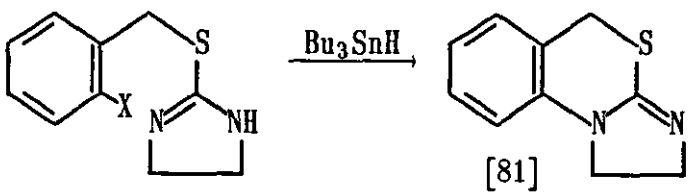
f. Attempted cyclisation of S-(2-Halogenophenyl)-methyl-2-imidazolidinethione

S-(2-Halogenophenyl)-methyl-2-imidazolidinethiones [79,80] were prepared as indicated in Equation 51 in a further attempt to study the scope of the Bu_3SnH catalysed cyclisations.



(51)

[79] X=I
[80] X=Br



(52)

[81]

Both the iodo and bromo derivatives [79,80] were reacted with Bu_3SnH under standard conditions with the aim of preparing a tricyclo derivative as shown in Equation 52. The reaction was unsuccessful and decomposition resulted with the evolution of a "thiol-like" smell. We have no explanation for the unsuccessful reaction and no further studies were carried out. Cu(I) catalysis of the reaction of the anion of [80] has been reported to yield the tricyclo compound [81] indicating that cyclisation is possible [100].

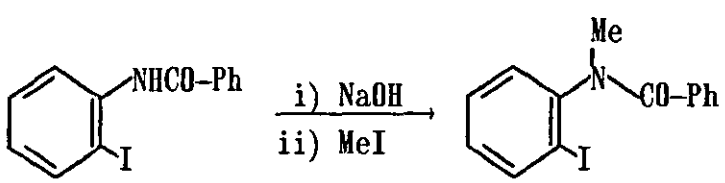
g. The cyclisation of N-(2-Iodophenyl)-N-methylbenzamide

The N-methyl derivatives of the N-(2-halogenophenyl)-benzamides were prepared and studied to further ascertain what effect the removal of the N-hydrogen would be in the proposed "pseudo $S_{RN}1$" mechanism. These results were initially unexpected but investigation of the literature [101] provided ample known precedents. The cyclisation of the aryl radical, generated using Bu_3SnH, onto the other aryl ring is discussed in this section.

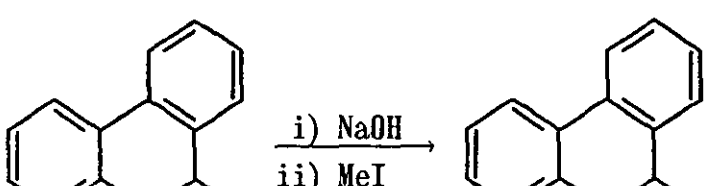
The cyclisation of both the thioamide and carboxamide derivatives were studied. Once we realised that the C=S bond was not involved in the cyclisation of N-(2-iodophenyl)-N-methylthiobenzamide, the study was extended to the carboxamide analogues as well.

The synthesis of N-(2-iodophenyl)-N-methylbenzamide [82] was achieved using the standard procedure with NaH/MeI in DMSO as indicated in Equation 53.

The synthesis of N-methyl-6(5H)-phenanthridinone [84] was instigated for comparison purposes, with the product of the cyclisation of the aryl radical of [82] onto the other phenyl ring (Equation 54).



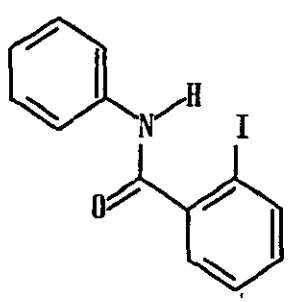
[45] [82] (53)



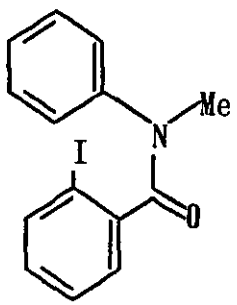
[83] [84] (54)

The cyclisation of the N-methylbenzamide [82] under the standard Bu_3SnH conditions gave the phenanthridinone [84] on work-up in a good yield (45%). This indicated that the aryl radical of [82] would cyclise onto the other phenyl ring when an N-methyl group, but not an N-hydrogen, was present.

Hey *et al.* [102] has suggested that in the photolysis of N-(2-iodophenyl)-N-methylbenzamide [82] in benzene or in the copper catalysed decomposition of the analogous 2-diazonium fluoborate gave a product inconsistent to that of Kharasch's photolysis [103] of non-methylated iodobenzanilide which gave benzanilide. They explain the results by suggesting that the N-methylation has a profound effect on the competition between intramolecular and intermolecular reactions. More recent evidence [103] suggests that the non-methylated amide strongly prefers the *trans* arrangement of the aryl groups as shown in Scheme 51 (Structure 1), from which intramolecular arylation may occur only after rotation about the amide bond, but that with the N-methylated case the preferred geometry is the *cis* arrangement as shown in Scheme 51 (Structure 2).



Structure 1



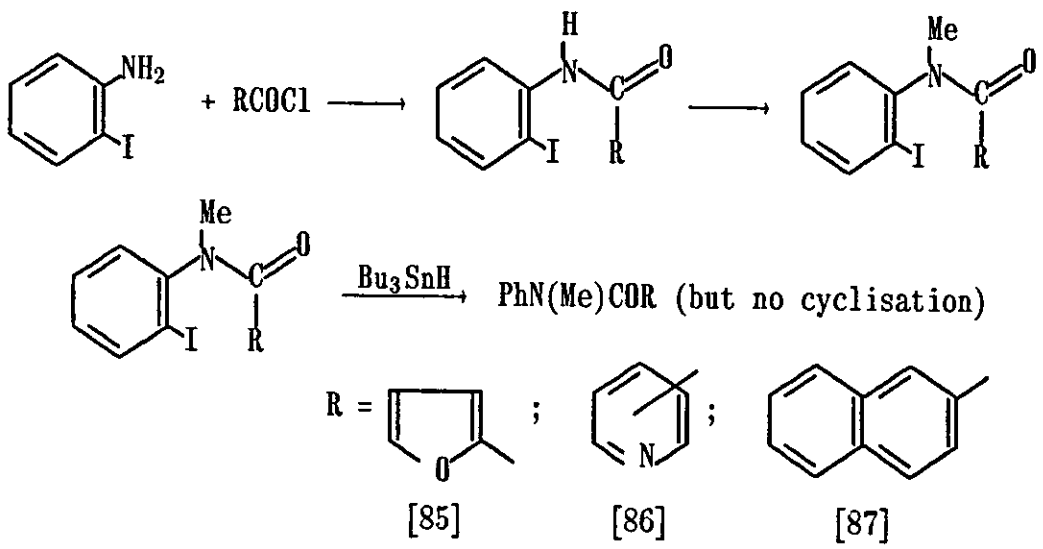
Structure 2

SCHEME 51

Oki [104] has recently put forward quantitative evidence that unsymmetrical amides, $RCONR_1R_2$, give two diastereoisomers that differ in their populations. Phenyl groups which are inductively electron withdrawing, enhance the barrier to rotation about an amide C-N bond.

We suggest that although reaction takes place *via* the *cis*-amide, the *trans*-isomer predominates. However, the N-methyl group, unlike the NH, competes with the phenyl group, for the *cis*-position because the energy barrier is low enough under the conditions of the reaction. Therefore, as the *cis*-isomer reacts, the predominant *trans* isomer equilibrates to the *cis*-stereochemistry. In contrast the energy barrier for rotation of the *trans*-NH diastereoisomer is too high to allow even a small amount of the *cis*-isomer for cyclisation.

The cyclisation of σ-arylamido radicals to phenanthridinone analogues using Bu_3SnH appears to be limited to aryl rings and when polynuclear or heteroaryl rings replaced the aryl ring (Scheme 52), cyclisation was not successful. Work on these reactions was abandoned because further advances did not appear likely. The respective N-methylamides were prepared as shown in Scheme 52 and the cyclisations attempted under "standard" Bu_3SnH conditions. We have no obvious explanation for the lack of success.

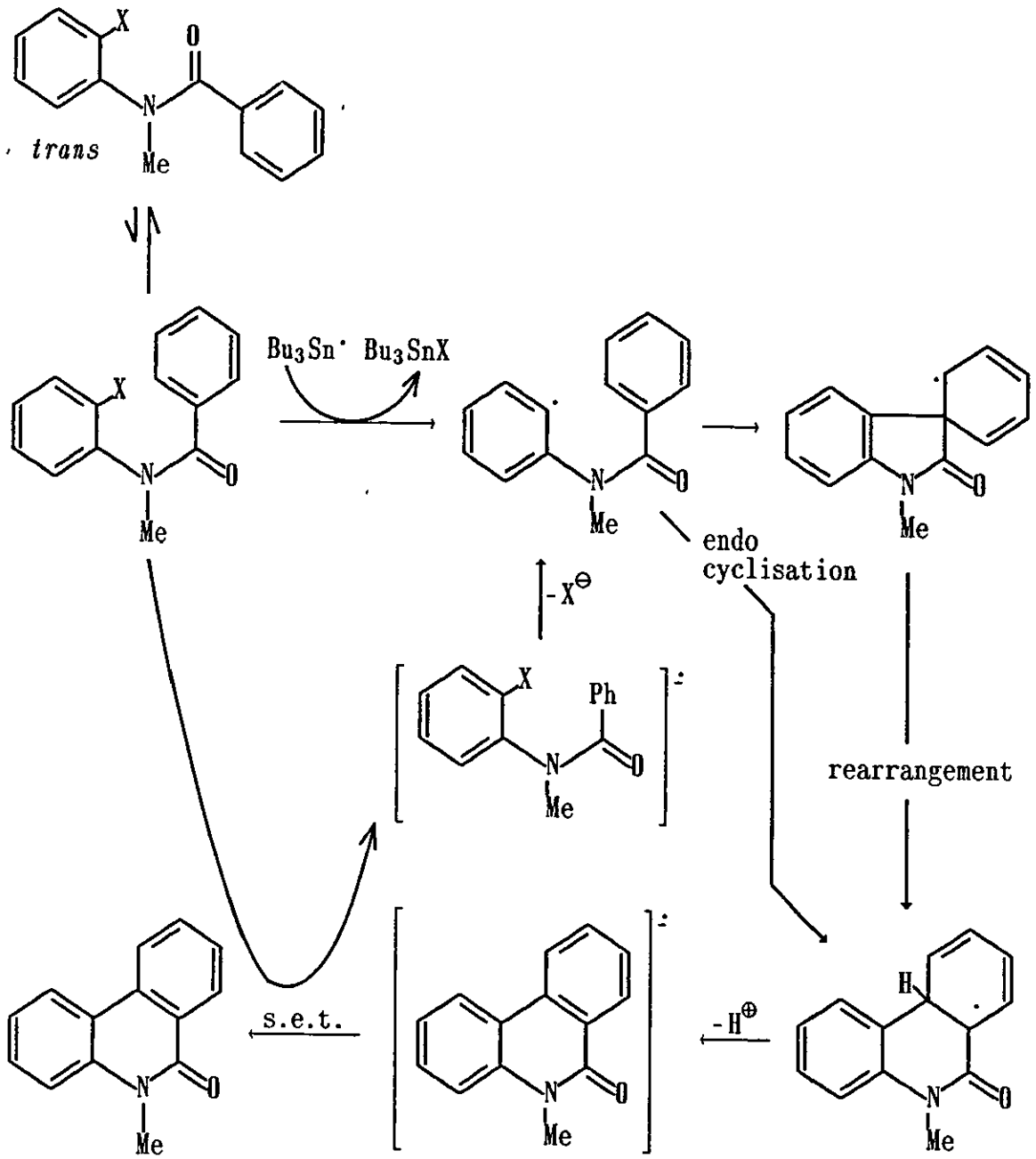


SCHEME 52

One obvious route ahead was to attempt the cyclisation of aryl radicals onto the double bond of N-(2-halogenophenyl)-α,β-unsaturated carboxamides and thioamides instead of onto aryl rings. It was envisaged that cyclisation onto a non-aromatic double bond may be more facile, which in fact turned out to be the case. This work is fully described in the next section.

A proposed "pseudo" $S_{RN}1$ mechanism for the cyclisation of N-(2-iodophenyl)-N-methylbenzamide is illustrated in Scheme 53. Alternative mechanisms cannot be ruled out. However, in this system an $S_{RN}1$ mechanism is not a possible alternative. The spiro-intermediate has been observed by Hey [102] but there was no evidence for it in our reactions. A rapid rearrangement as shown may explain the absence of products derived from it. The "pseudo $S_{RN}1$" mechanism is supported by the aromatisation driving force created by the loss of a

proton to yield the intermediate phenanthridinone radical anion. All the other reports propose the cyclised radical intermediate but none indicate how the hydrogen is lost. We suggest that loss of a proton is most likely and a relatively low energy route. The final s.e.t. should be facile and iodoaryl radical anions are well known to dissociate to aryl radicals and iodine [103].



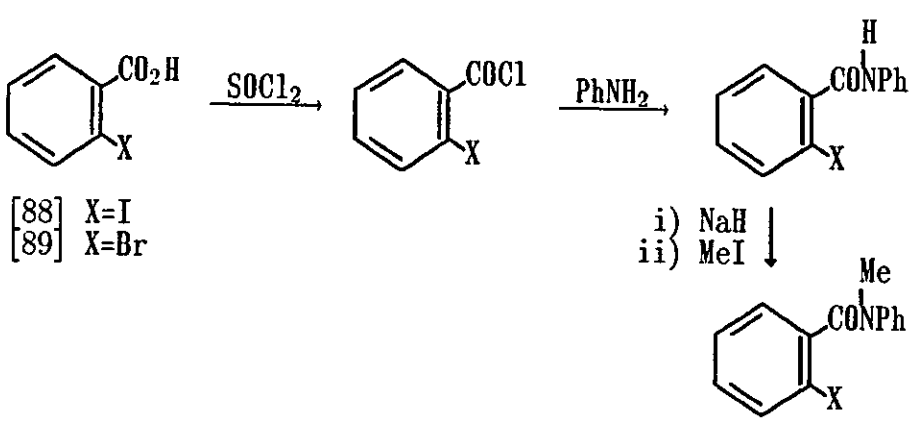
SCHEME 53

The mechanism is analogous to the "pseudo $S_{RN}1$" mechanism proposed for the cyclisation of N-(2-iodophenyl)-thiobenzamide in that both lose H^+ from the initially cyclised radical to form a stabilised (aromatic) radical anion. Loss of H^+ is usually a less energetic process than loss of hydrogen ($H^{\cdot}$). These results provide extra evidence that the "pseudo $S_{RN}1$" mechanism explains the cyclisations of N-(2-halogenophenyl)-thiobenzamides to 2-phenyl-1,3-benzothiazole.

Further studies were investigated under a variety of conditions: DABCO (1.1 equiv.) and AIBN (0.3 equiv.); Bu_3SnH (0.1 equiv.), AIBN and DABCO (1.1 equiv.); and finally the use of Bu_3SnH (0.1 equiv.), $NaBH_4$ (1.1 equiv.) and AIBN (0.3 equiv.). However all of these reactions gave recovery of the starting material. DABCO does not therefore appear to be able to replace Bu_3SnH, nor can Bu_3SnH/DABCO be used in catalytic amounts.

h. Cyclisation of N-Methyl-N-phenyl-2-iodobenzamide

Hey's [102] work has shown that the σ-aryl radical on either the carboxyl, or the amino aryl ring, leads to cyclisation. Therefore N-methyl-N-phenyl-2-iodo-benzamide [88] and N-methyl-N-phenyl-2-bromobenzamide [89] were synthesised as shown in the general scheme (Scheme 54).



SCHEME 54

The cyclisation of N-methyl-N-phenyl-2-iodobenzamide [88] was carried out under standard Bu_3SnH reaction. The yield of the phenyl cyclised material, N-

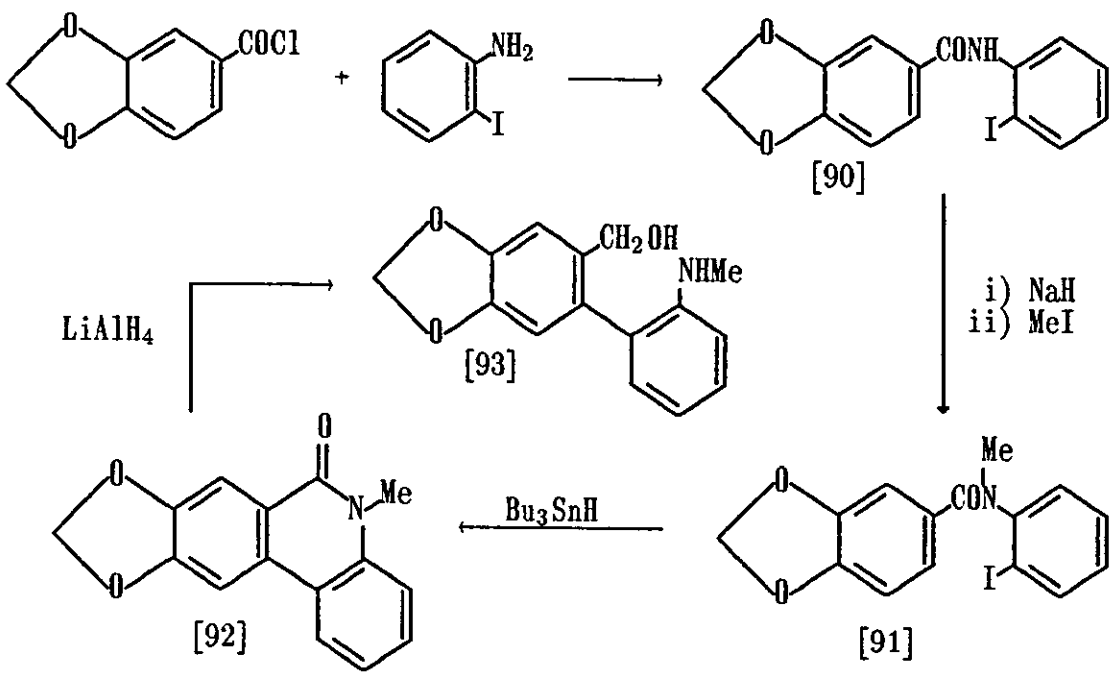
methylphenanthridinone (15%) and the recovery of starting material (38%), was measured by analysing the crude product mixture with a known amount of an added internal standard.

The reason for the difference in yields for the cyclisation reaction of the isomer [88] as compared with isomer [82], was possibly due to the variation of the nucleophilicity of the attacking radical (i.e. the o-carbonyl withdraws electron density from the aryl radical whereas an o-amino group will donate electron density thereby enhancing aryl nucleophilicity).

Therefore, a higher yield may be predicted for the cyclisation of [82] [nucleophilic radical cyclising onto a more electrophilic aryl ring (-I group = o-CO) as opposed to [88]; less nucleophilic radical cyclising onto a more nucleophilic aryl ring (+M group = o-NH)].

i. The attempted synthesis of the alkaloid, Ismine

It was realised that the synthetic utility of the radical cyclisation of these N-methylbenzamides [88,89] could be possibly used in the synthesis of Ismine [93], an *Amaryllidaceae* alkaloid, as shown in Scheme 55.

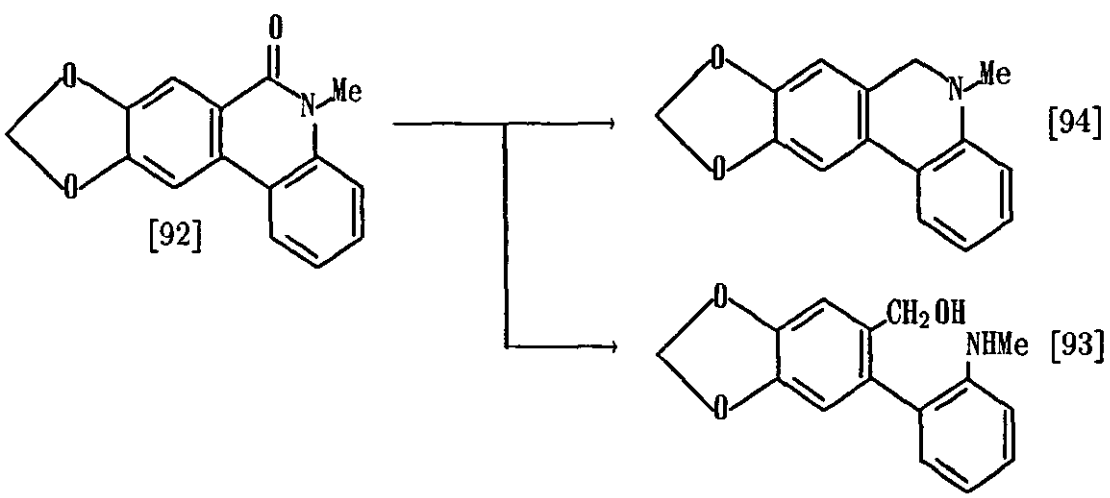


SCHEME 55

N-(2-Iodophenyl)-N-methyl-2,3-methylenedioxybenzamide [91] was synthesised according to Scheme 55. The cyclisation of N-(2-iodophenyl)-N-methyl-2,3-methylenedioxybenzamide under standard Bu_3SnH conditions gave a reasonable yield (29%) of the cyclised material, 5-methyl-2,3-methylene-phenanthridinone [92]. The literature [105] has cited [92] as a product isolated in the structural elucidation studies of lycorine and other *Amaryllidaceae* alkaloids.

We propose that the mechanism is similar to that previously shown in Scheme 53. The attempted cyclisation of the benzamide [91] using U.V. light only in toluene at room temperature gave rise to the recovery of starting material (59%). The photolysis was not very effective since it did not cleave the carbon-iodine bond at a sufficient rate to allow cyclisation.

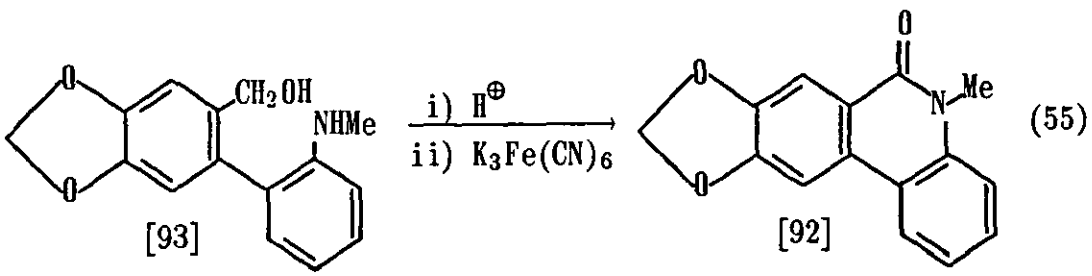
By treatment of the phenanthridinone [92] with $LiAlH_4$ in THF with a trace of water to generate LiOH, it was hoped to bring about the ring opening of the amide with subsequent reduction to yield ismine [93]. However, the reduction gave rise to the non-ring cleaved reduced material, 2,3-methylenedioxy-5,6-dihydrophenanthridinone [94] in good yield (70%) as depicted in Scheme 56. The use of $LiAlH_4$ in rigorously dried THF gave a similar result.



SCHEME 56

The phenanthridinone [92] has been used as evidence for the structural elucidation of ismine in the literature [106] and is a natural product in its own right. This synthesis therefore represents the formal preparation of a minor alkaloid.

The reaction of acid and then $K_3Fe(CN)_6$ on ismine gives the phenanthridinone as shown in Equation 55.

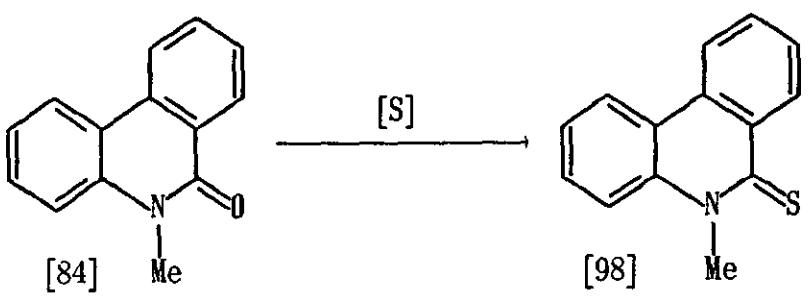


[93] [92] (55)

j. The cyclisation of N-(2-Halogenophenyl)-N-methylthiobenzamide

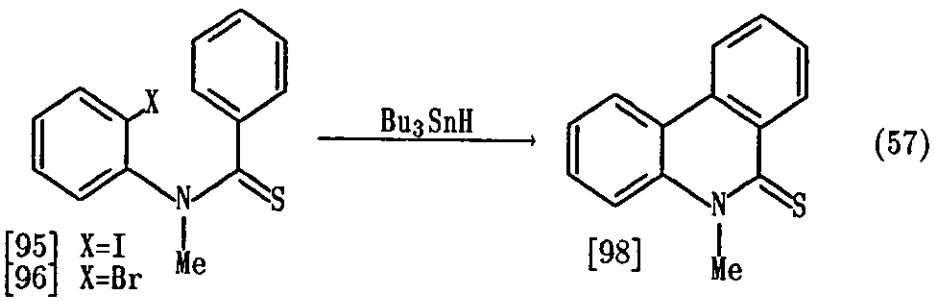
It was decided to attempt the cyclisation of the thioamide analogue of the previously successful carboxamide analogue. It was also a way of testing the theory that the benzamides exist in *cis* and *trans* isomers and react accordingly, i.e. the conversion to C=S allows another option for cyclisation, that of cyclisation onto the C=S bond. This does not happen since the reaction goes exclusively onto the phenyl ring indicating that the phenyl is more extensively available and/or reacts faster than the C=S bond.

N-(2-Iodophenyl)-N-methylthiobenzamide [95] and N-(2-bromophenyl)-N-methylthiobenzamide [96] were synthesised in the usual way from their respective benzamides. In order to have an authentic sample of the expected ring cyclised material, N-methyl-6(5H)-thiophenanthridinone [98] was synthesised as indicated in Equation 56 using Lawesson's reagent.



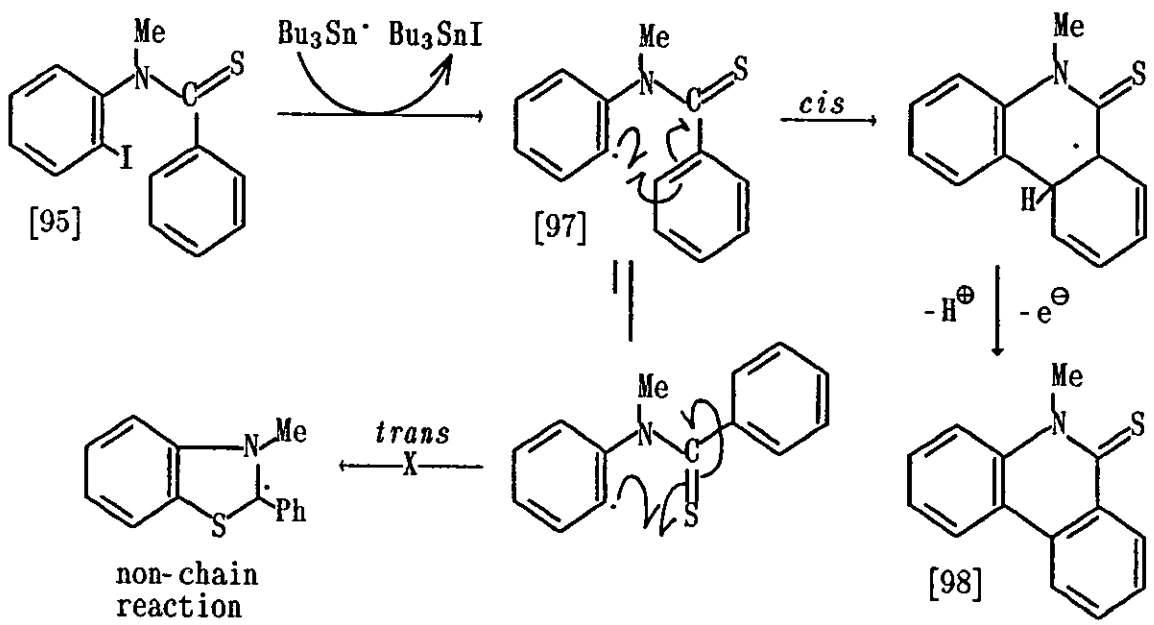
[84] [98] (56)

The cyclisation of the thioamides [95,96] under standard Bu_3SnH conditions gave N-methyl-6(5H)-thiophenanthridinone [98] in a 19-31% yield as shown in Equation 57.



(57)

We propose that this cyclisation also proceeds by a "pseudo $S_{RN}1$" mechanism. The thiobenzamide [95] on reaction with the stannane radical gives the aryl radical [97] which can react with either the C=S or the phenyl groups. However, as has been indicated previously in the cyclisation of benzamide using Bu_3SnH, N-methylation allows the *cis* conformation thereby putting the C=S out of easy reaction distance in comparison with the phenyl ring shown in Scheme 57.

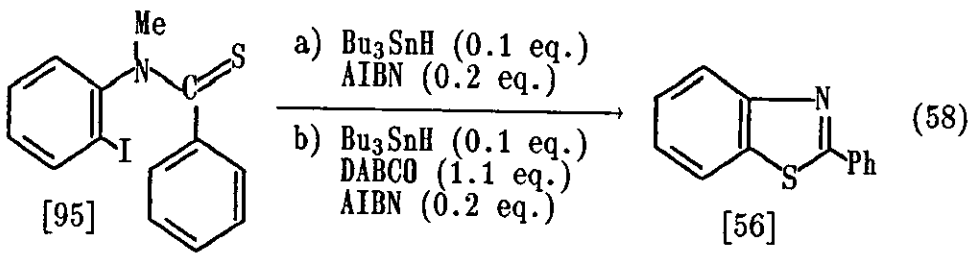


SCHEME 57

The results of these cyclisations are perhaps surprising but do provide evidence for the "pseudo $S_{RN}1$" mechanism. The intermediate aryl radical appears to cyclise faster on the phenyl ring (*cis* conformation) than onto the C=S group

(*trans* conformation). The latter route cannot enter a chain reaction because no H^+ can be lost. The cyclisation onto C=S is unlikely to be reversible because of the high energy required to go from a highly stabilised carbon radical (α-S, α-N and α-Ph) to the highly unstable aryl radical. Therefore, we suggest that this cyclisation is unlikely.

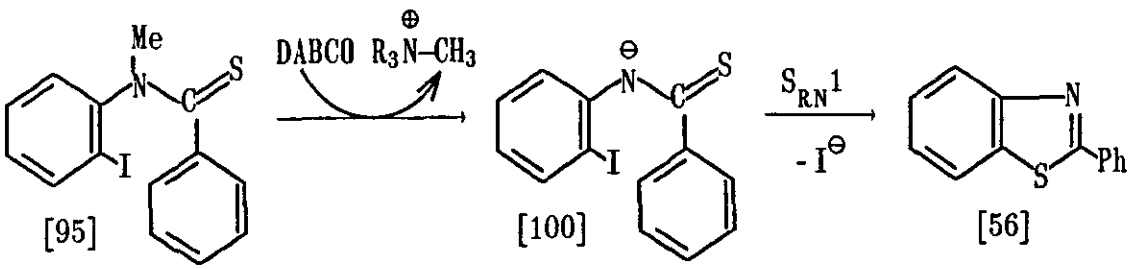
In the non-N-methyl compound only the *trans* conformation exists, thereby preventing cyclisation onto the phenyl ring, but allowing the slower addition onto C=S. The thiobenzamide [95] was then reacted under various conditions to further evaluate the mechanism of cyclisation. By using Bu_3SnH (0.1 equiv.) and AIBN (0.2 equiv.) with all other conditions being that of the standard conditions it was found that the thiobenzamide [95] would cyclise not to the thiophenanthridinone [98] but instead gave 2-phenylbenzothiazole [56] (30%) as shown in Equation 58. The N-methyl group is labile and can form an anion [100] which in turn cyclises to the benzothiazole [56] (Scheme 58).



(58)

The use of Bu_3SnH (0.1 equiv.), DABCO (1.1 equiv.) and AIBN (0.3 equiv.) as cyclising reagents on thiobenzamide [95] also gave rise to a 24% yield of 2-phenylbenzothiazole [56]. The use of only DABCO (1.1 equiv.) and AIBN (0.3 equiv.) as a cyclising reagent on the thiobenzamide [95] gave 2-phenylbenzothiazole [56] in an improved yield (47%) indicating that the Bu_3SnH was not required. The proposed mechanism is shown in Scheme 58 and shows demethylation of the starting material by DABCO to give the anion [100] which undergoes a similar $S_{RN}1$ mechanism as shown previously in Scheme 41. The methiodide of DABCO was isolated and identified providing some evidence for this proposal. This is the first aromatic $S_{RN}1$ reaction reported to take place in a non-polar solvent. The equivalent reaction does not take place for the

carboxamide analogue probably because the carboxamide anion is a considerably poorer leaving group than the thioamide anion.



SCHEME 58

The cyclisation of N-(2-bromophenyl)-N-methylthiobenzamide [96] was achieved using the standard Bu_3SnH conditions and gave the thiophenanthridione [98] in poor yield (13%). When the thiobenzamide [96] was treated with DABCO (1.1 equiv.) and no Bu_3SnH, 2-phenylbenzothiazole was formed in almost quantitative yield. To confirm the feasibility of an aromatic $S_{RN}1$ reaction in a non-polar solvent such as toluene, as an intermediate route in the above reaction, N-(2-iodophenyl)-thiobenzamide was treated with NaH in toluene, which gave a 34% yield of 2-phenylbenzothiazole. This result indicates that initial demethylation to yield the thiobenzamide anion [100] and subsequently $S_{RN}1$ is a likely mechanism.

PART THREE:

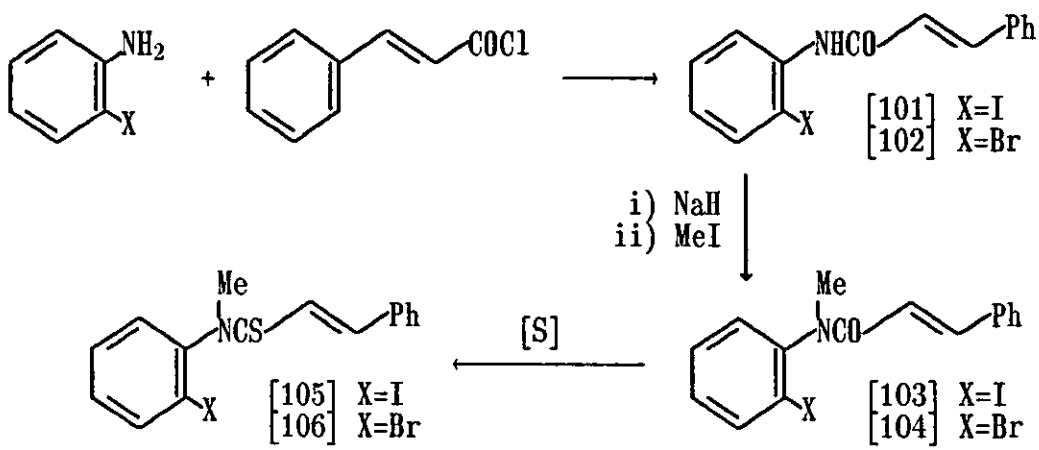
CYCLISATION OF O-ARYL RADICALS ONTO α,β-UNSATURATED AMIDES

In Section Two we showed that aryl radicals generated from N-(2-halogenophenyl)-N-methylbenzamide cyclised onto the second aryl ring. It was a natural extension to introduce the modification of a conjugated double bond in place of a conjugated aromatic ring for cyclisation as shown below in Scheme 59. Surprisingly, there is little precedent for cyclisation onto conjugated double bonds whereas there are a large number of examples of cyclisation of radicals onto isolated double bonds.

SCHEME 59

Initial studies with N-(2-halogenophenyl)-N-methylcinnamamide [105,106] indicated an interesting cyclisation as compared to the cyclisations of N-(2-halogenophenyl)-N-methylbenzamides. The former underwent "Bu_3SnH-type" cyclisation whereas the latter underwent a "pseudo $S_{RN}1$" type cyclisation.

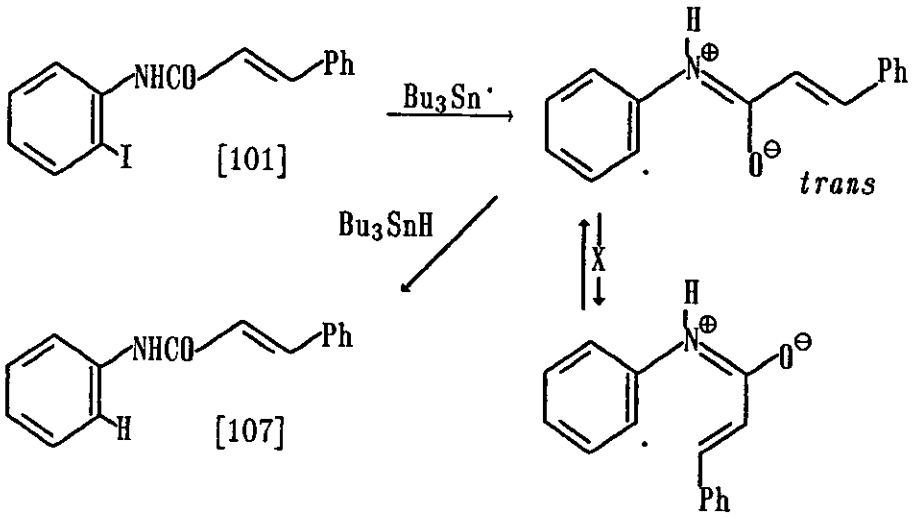
The cinnamamides were prepared in accordance with Scheme 60. N-(2-Iodophenyl)-N-methylcinnamamide [103] was prepared from the corresponding amide [101] using conventional procedures as shown in Scheme 60. The N-methylcinnamamide [103] was converted to the thio analogue, 2-iodo-N-methylthiocinnamamide [105] in the usual manner using Lawesson's reagent as shown in Scheme 60.



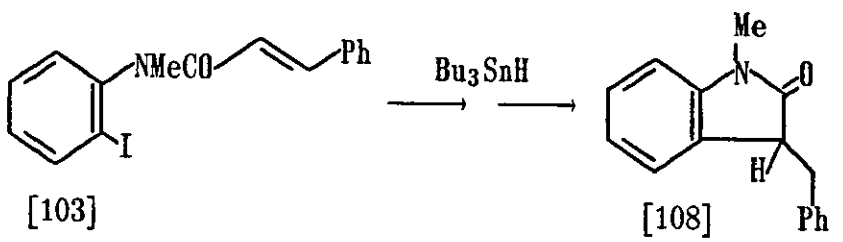
SCHEME 60

The cyclisation of the cinnamamide [101] was attempted using the standard Bu_3SnH conditions. However, only reduction took place to give the cinnamamide [107] in a poor yield (25%) as shown in Equation 59. The result was not unexpected since the previous amide reactions attempted, and the literature [107], indicated that reduction almost always takes place. The lack of cyclisation is due to the barrier to rotation of the low-energy *trans*-isomer of the amide to the less stable *cis*-isomer required for cyclisation.

Cyclisation of the N-methylcinnamamide [103] under standard Bu_3SnH conditions gave 3-benzyl-1-methyloxindole [108] in a fair yield (33%) as shown in Equation 60.



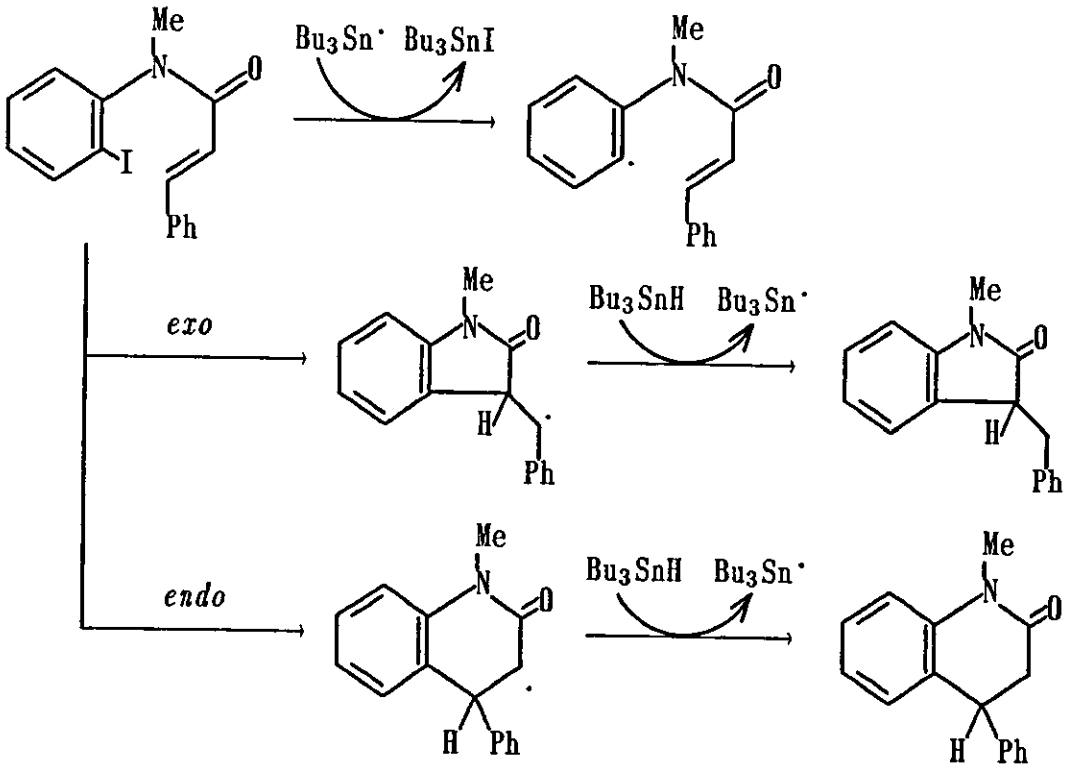
(59)



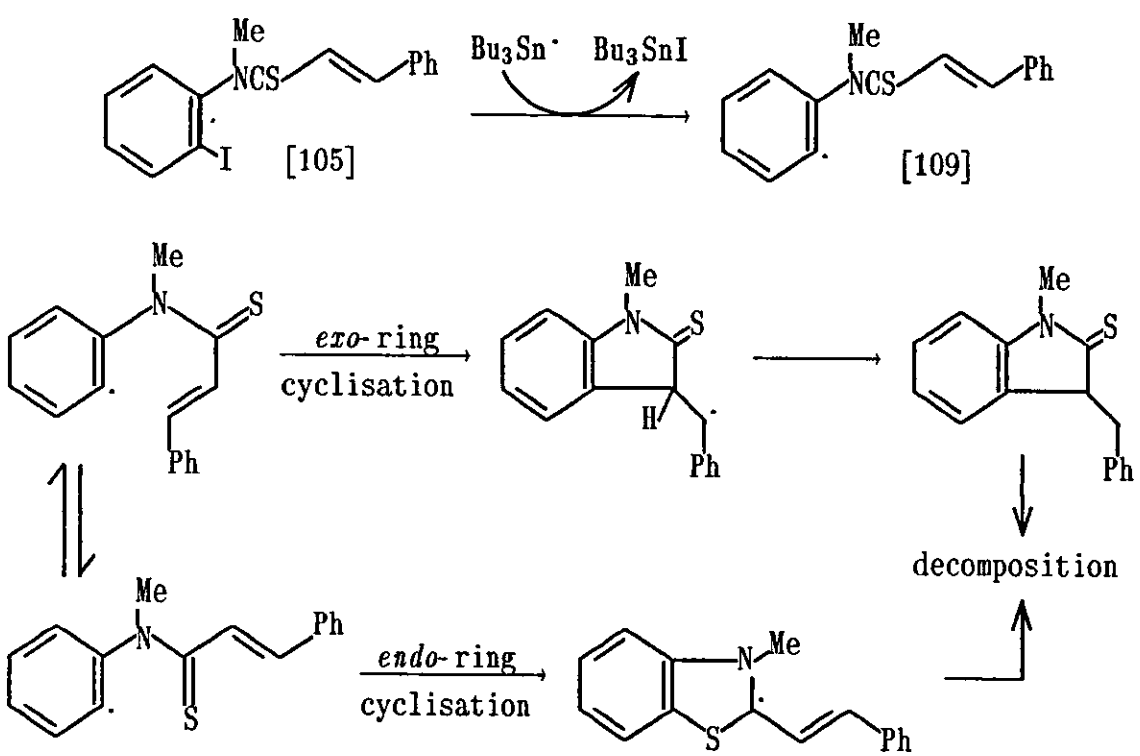
(60)

The explanation for the cyclisation of the α,β-unsaturated amide [103] to the oxindole [108] lies in the *cis/trans* ratio as discussed previously, the strong bias for *exo*-ring cyclisation as opposed to *endo* cyclisation, and due to the intermediate radical for *exo*-ring cyclisation being stabilised by the delocalisation of the radical over the phenyl substituent, as shown in Scheme 61. The mechanism for the cyclisation follows that normally observed in Bu_3SnH cyclisation [108].

The attempted cyclisation of N-(2-iodophenyl)-N-methylthiocinnamamide [105] gave a polymeric gum on work-up. The intermediate aryl radical [109] can cyclise onto the alkene or onto C=S (Scheme 62). Both products are likely to be unstable. The reaction was not further investigated.



SCHEME 61

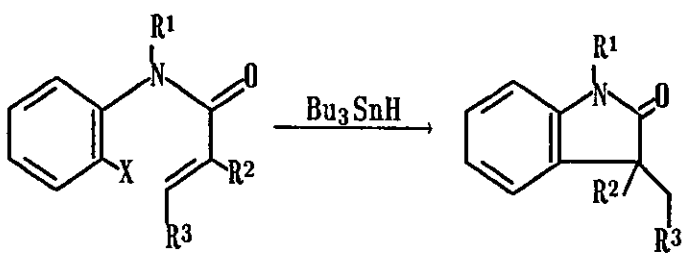


SCHEME 62

Further cyclisations of N-(2-Halogenophenyl)-α,β-unsaturated amides

After these exploratory reactions we realised that the reaction could be applied to general synthesis of oxindoles. Therefore, the following factors were investigated, and the general scheme is shown in Scheme 63.

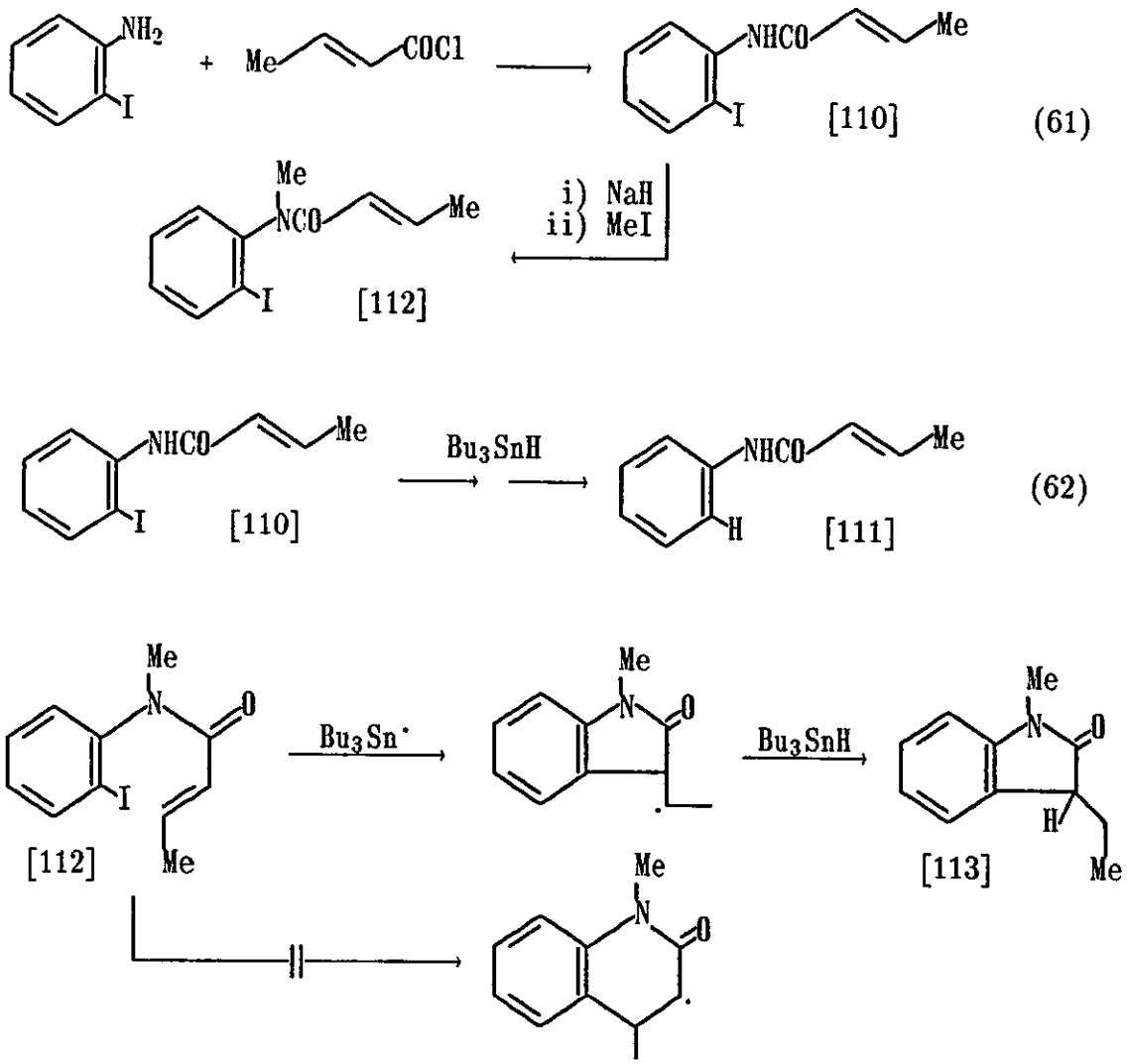
1. Effect of β-substitution on the α,β-unsaturated amide (+I group, R^3 = Me; -I group, $R^3 = CO_2Me$).
2. α,β-disubstitution.
3. Replacement of the olefin with an acetylene.
4. Other N-substituents.
5. Effect of the nucleofuge.
6. Effects of radical stabilisation.



SCHEME 63

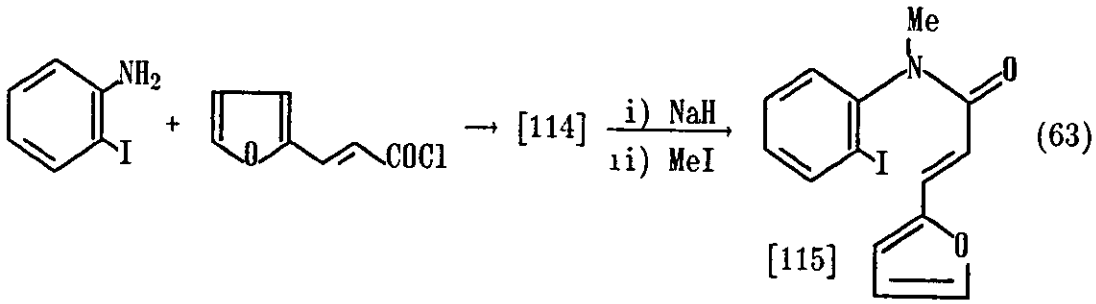
1. N-(2-Iodophenyl)-crotonamide [110] and the N-methyl derivative, N-(2-iodophenyl)-N-methylcrotonamide [112] were synthesised as indicated in Equation 61. The attempted cyclisation under standard Bu_3SnH conditions of the crotonamide [101] gave only the reduced material, crotonamide [111], in a good yield (65%) which was in line with the previous results of amide derivatives (Equation 62).

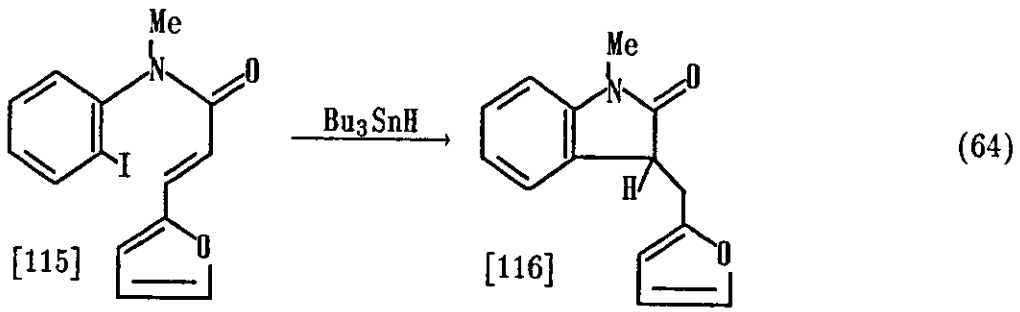
   The cyclisation of the N-methyl derivative [112] gave 1-methyl-3-ethyloxindole [113] in 23% yield (Scheme 64). The change in substituents causes a change in the radical stability of the intermediate radical, i.e. the stability is reduced since the intermediate radical cannot be delocalised as with R^3 = Ph. In this case the *endo*-radical could be more stable than the *exo*-radical but no product deriving from an *endo*-cyclisation was observed.



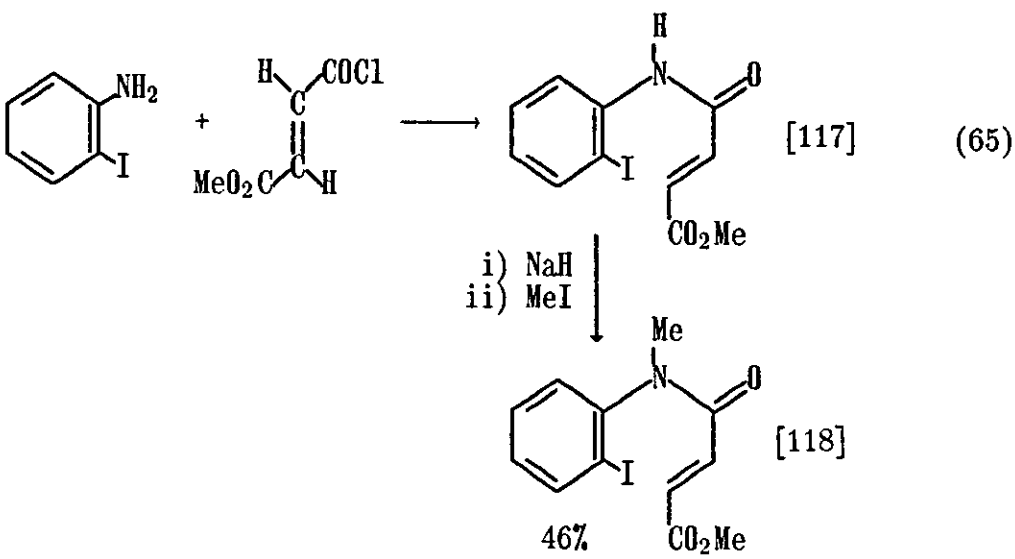
SCHEME 64

2. N-(2-Iodophenyl)-N-methyl-2-(2-furyl)-propenamide [115] was synthesised as shown (Equation 63) in a 25% yield. This reaction replaces a β-phenyl group with the heterocyclic 2-furyl ring. The cyclisation of the propenamide [115] under the standard Bu_3SnH conditions gave exclusively the *exo*-product, 1-methyl-3-(2-furylmethyl)-oxindole [116] (18%) as expected, since previous models had indicated that the variation in β-substitution had little effect on *exo*- versus *endo*- cyclisation (see Equation 64). However, the yield (18%) is by no means a reflection of the cyclisation rate nor actual yield but of the partition of the reaction mixture in the acetonitrile/pet. ether wash. It was found that large amounts of cyclised material [116] were being washed out.

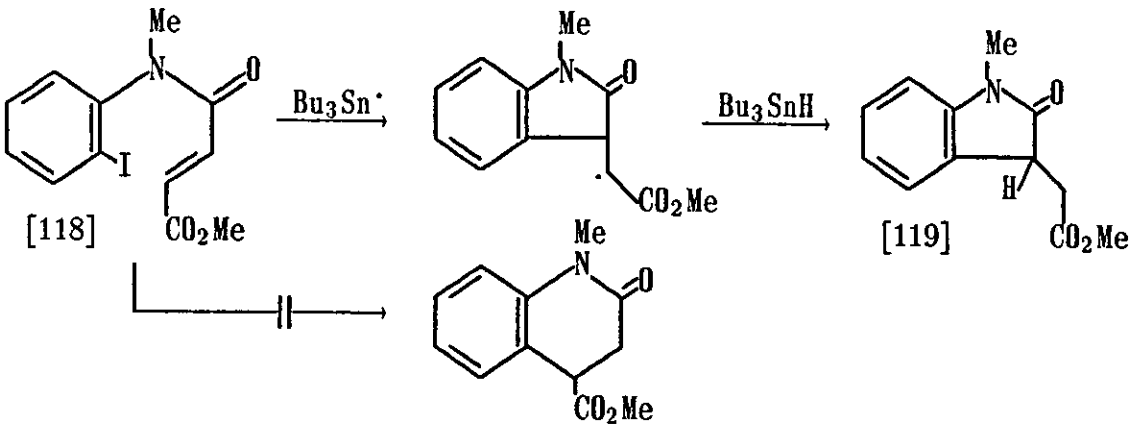




3. N-(2-Iodophenyl)-N-methyl-3-carboxymethyl-propenamide [118] was prepared from the corresponding propenamide [117] as indicated in Equation 65. This preparation allows the study of the effect of an -I group ($R^3 = CO_2Me$) as compared with the +I group (R^3 = Me) of the reaction reported above.

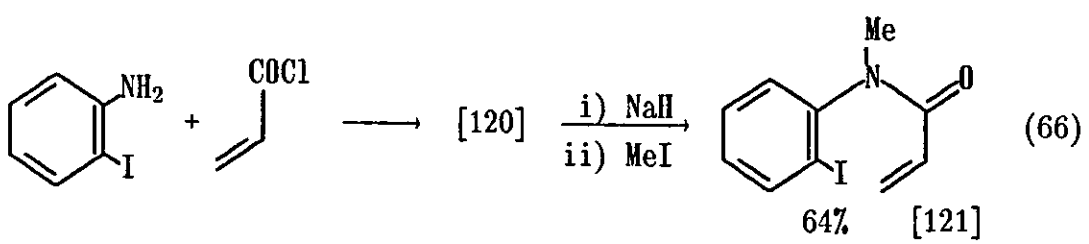


The cyclisations of the N-methyl-propenamide [118] using the standard Bu_3SnH conditions gave the corresponding *exo*-ring cyclised oxindole [119] in a fair yield (44%) as indicated by Scheme 65. These experiments suggest that the electron -withdrawing or -donating ability of the -R group is not important.



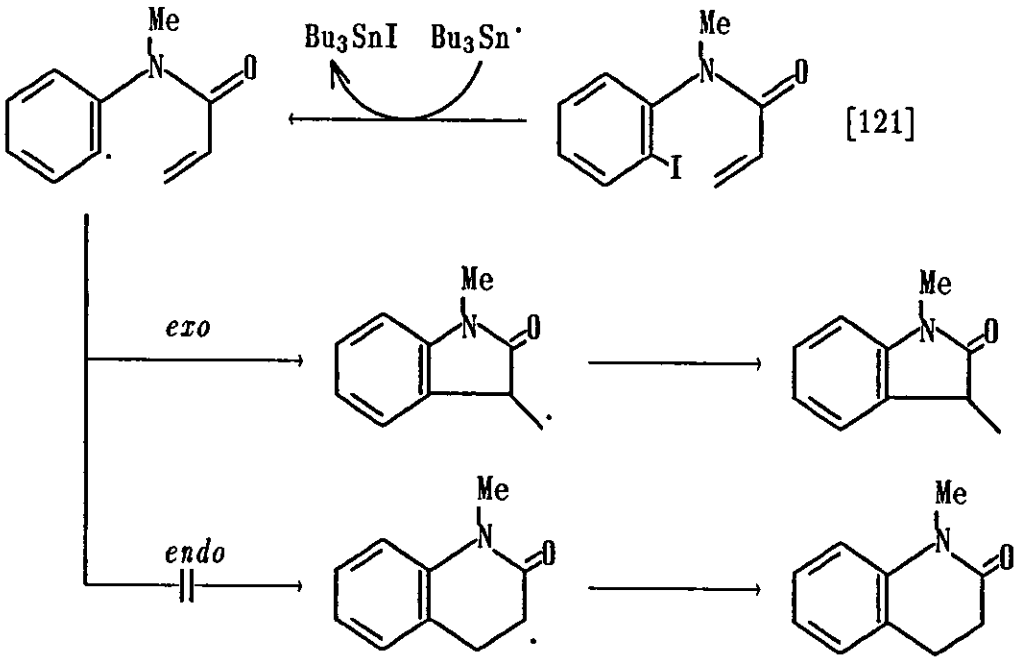
SCHEME 65

4. N-(2-Iodophenyl)-N-methylacrylamide [121] was synthesised as shown in Equation 66 to study the effect of decreasing the bias even further than with R^3 = Me towards *endo*- over *exo*-cyclisation. Therefore, when R^3 = H there is thermodynamic bias towards *endo*-cyclisation proceeding *via* a secondary alkyl radical relative to *exo*-cyclisation *via* a less stable primary alkyl radical intermediate, and kinetic (or stereoelectronic) bias towards *exo*-cyclisation.



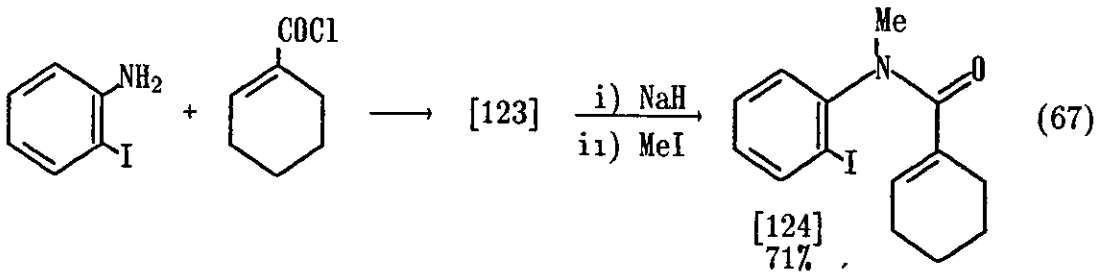
(66)

The acrylamide [121] was cyclised under standard Bu_3SnH conditions to give exclusively the *exo*-ring cyclised material, 1,3-dimethyloxindole in a good yield (67%) as shown in Scheme 66. The exclusive *exo*-cyclisation shows that stereoelectronic effects appear to be completely dominant over thermodynamic factors.

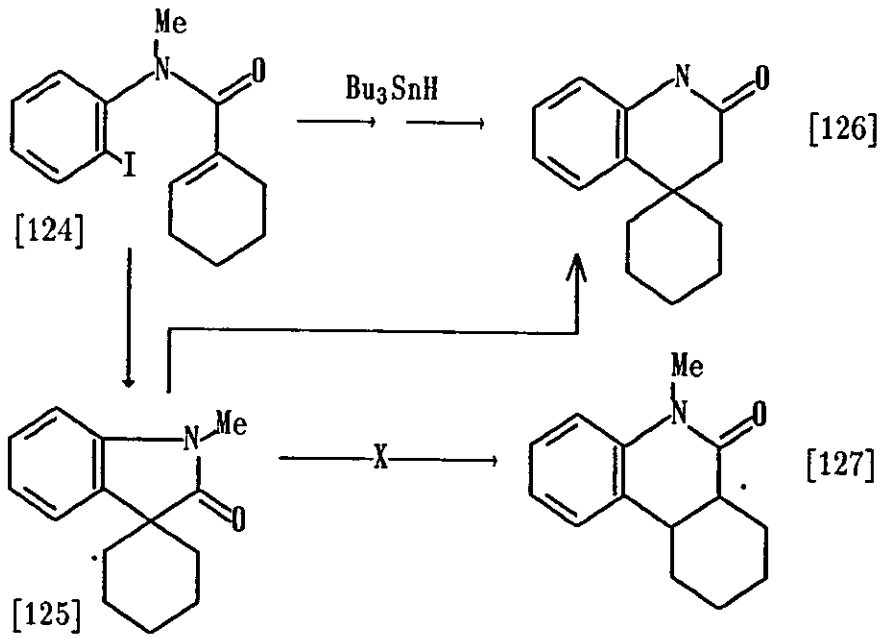


SCHEME 66

5. N-(2-Iodophenyl)-N-methyl-cyclohex-1-ene-1-carboxamide [124] was synthesised as shown in Equation 67 in order to study the effect of α,β-disubstitution and a spiro-ring intermediate.

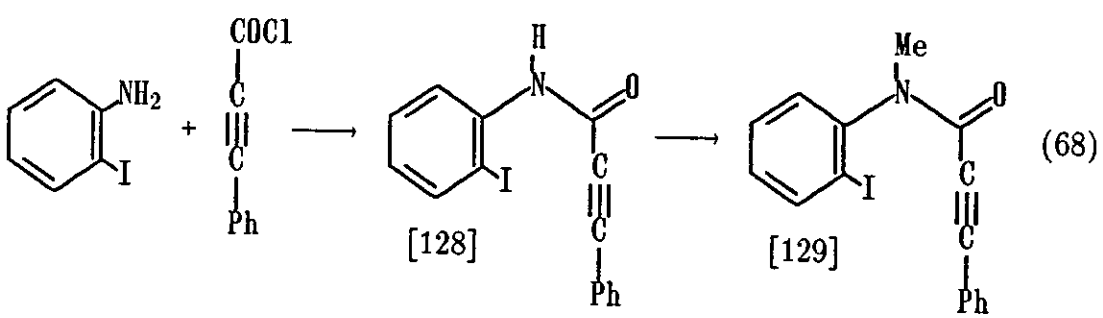


The cyclisation of the carboxamide [124] was carried out under the standard Bu_3SnH conditions to give the *exo*-ring cyclised product [126] in a 23% yield as shown in Scheme 67. This result underlines the fact that α,β-disubstitution has no effect on *exo*- versus *endo*-ring cyclisation since none of the *endo* product was isolated. A possible "*neophyll*" type rearrangement was also possible but not observed [109]. The t.l.c. of the reaction mixture and ^1H N.M.R. spectrum of the reaction crude product, indicated a single material, i.e. a possible *endo*-product was not lost on purification.

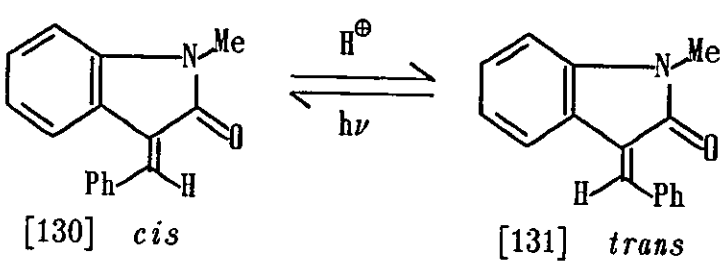


SCHEME 67

6. Replacement of the olefin group with that of an acetylene group was attempted to see what effect this would have on the products isolated. N-(2-Iodophenyl)-N-methyl-phenylpropynamide [129] was synthesised according to the route shown in Equation 68. The acid chloride, phenylpropioloyl chloride was reacted with 2-iodoaniline to give the amide, N-(2-iodophenyl)-phenylpropynamide (44%) [128] which was N-methylated by the normal method to yield N-(2-iodophenyl)-N-methyl-phenylpropynamide (73%) [129].

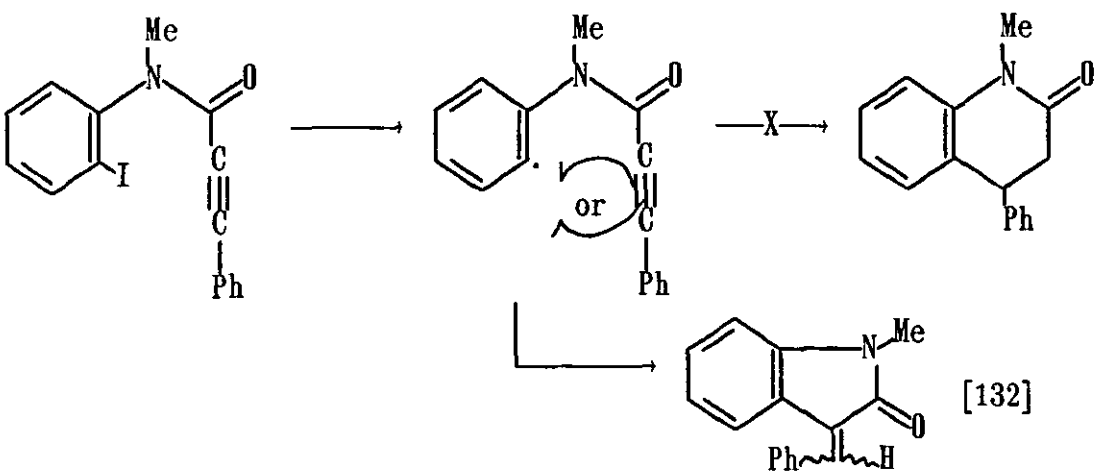


(68)



(69)

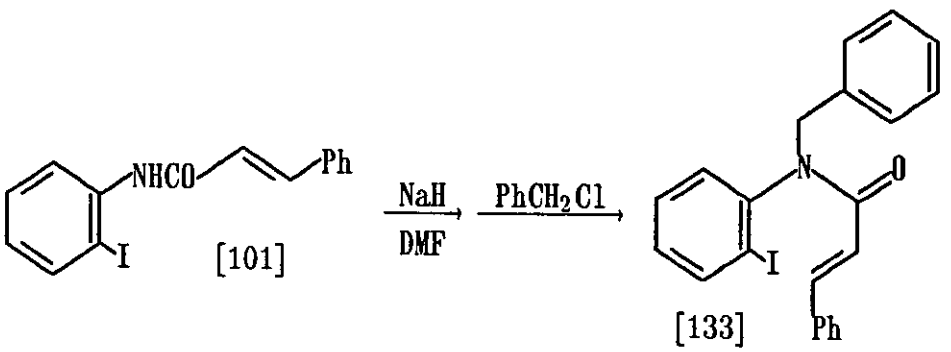
The N-methyl-phenylpropynamide [129] was cyclised using the standard Bu_3SnH conditions to give the *exo*-cyclised product, 3-benzyladine-1-methyloxindole [132] (Scheme 68). However, since the intermediate aryl radical can attack the alkyne in a manner that can give both *cis* and *trans* isomers of the *exo* product [132] it was not surprising that two isomers were isolated. The fast running dark yellow spot (on t.l.c.) of the *trans* isomer was isolated in good yield (32%) and the slow running pale yellow spot (on t.l.c.) of the *cis* isomer in a poor yield (5%). It was found that two isomers of [132] were interconvertible by exposure to light and acid as indicated in Equation 69. In acidic solution, the more stable *trans* isomer results form thermodynamic control *via* an intermediate cation. The *cis* isomer results from photolysis as is commonly observed when the *trans* isomer absorbs light in the visible region more effectively than the *cis* isomer.



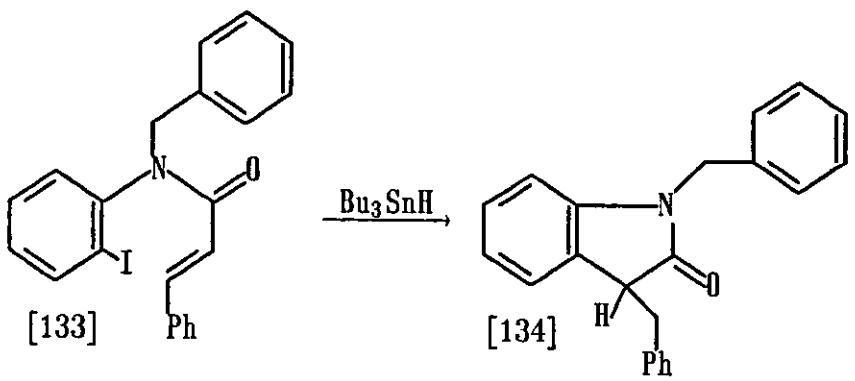
SCHEME 68

The poor yield of the reaction (Scheme 68) was not a reflection of the true yield. Once more the t.l.c. and weight of crude product indicated an almost quantitative yield of [132], but that the purification by acetonitrile/hexane wash treatment causes a large loss of the material [132]. This reaction illustrates that cyclisation *via* a vinyl radical is perfectly feasible as has been observed in the cyclisation of aliphatic alkyl radicals onto non-conjugated alkynes.

7. In order to show that the variation of N-substituent had little effect on the cyclisation product, N-benzyl-N-(2-iodophenyl)-cinnamamide [133] was prepared as shown in Equation 70 in a moderate yield (52%). The cyclisation of the N-benzylanilide [133] under the standard Bu_3SnH conditions gave the *exo* ring cyclised material, 1,3-dibenzyloxindole [134] in good yield (88%) as shown in Equation 71. As expected, the N-benzyl group has a similar effect to N-methyl substitute and leads to the *exo* product [134].

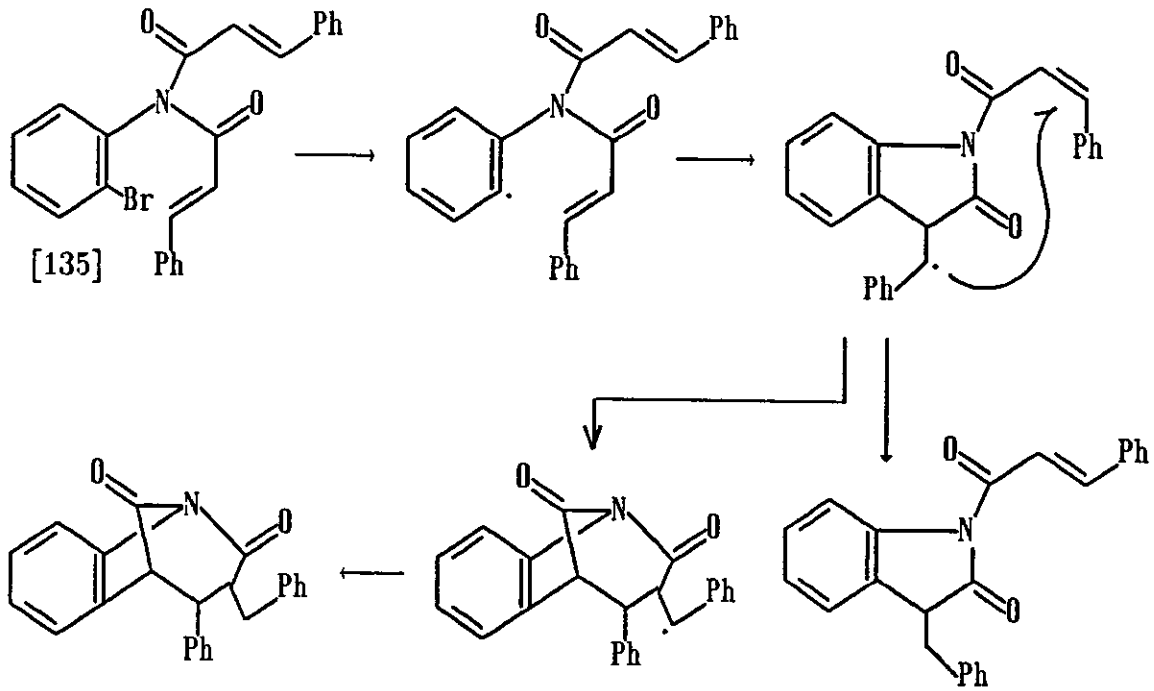


(70)



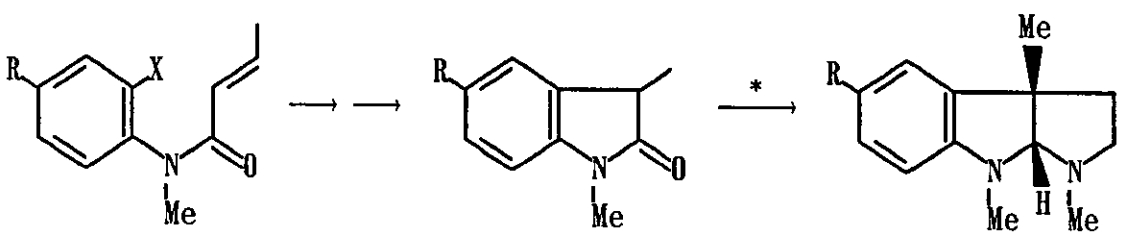
(71)

8. An attempt was made to carry out a "tandem" radical cyclisation as shown in Scheme 69. The di-cinnamoylamide [135] was prepared by treatment of N-(2-bromophenyl)-cinnamamide with NaH followed by cinnamoyl chloride. Cyclisation of [135] using the standard Bu_3SnH conditions gave a mixture of products but purification into isolated components was not achieved.



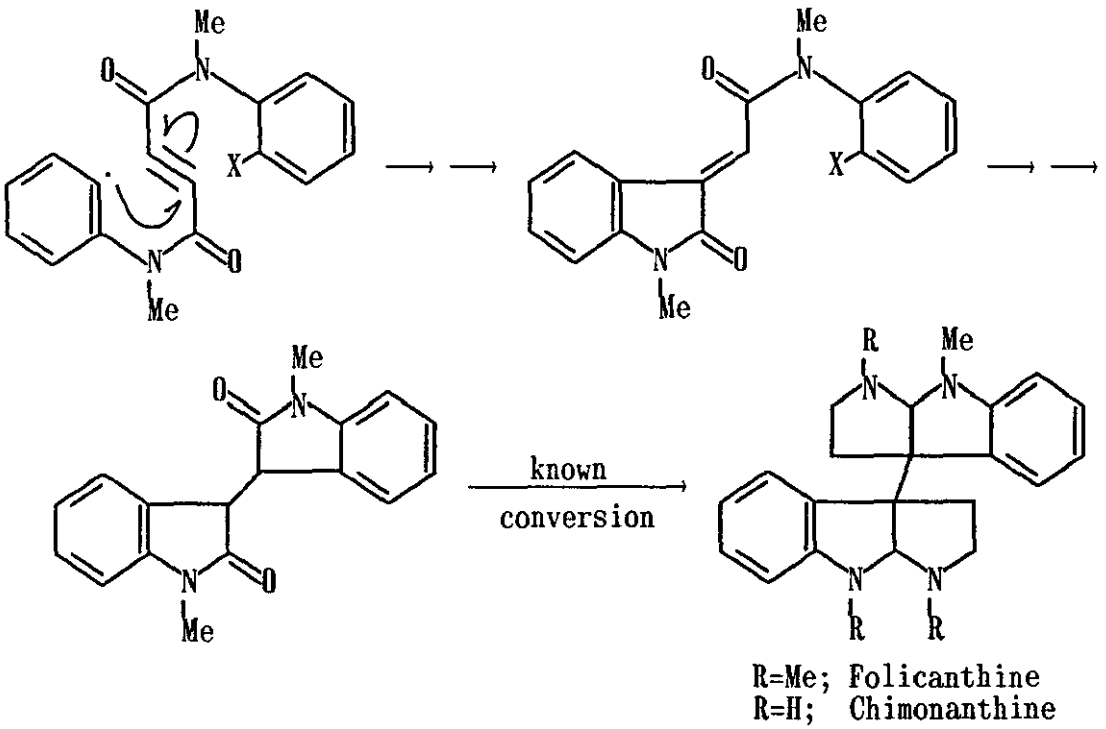
SCHEME 69

9. An attempt was made to apply our oxindole synthesis to a number of alkaloids as shown (Equation 72). The crotonamide cyclisation could be adapted to the preparation of the calabar alkaloid, phytostigmine [110], if required.



R = OCONHMe (Phytostigmine)
* = known cyclisation (Ref.110)

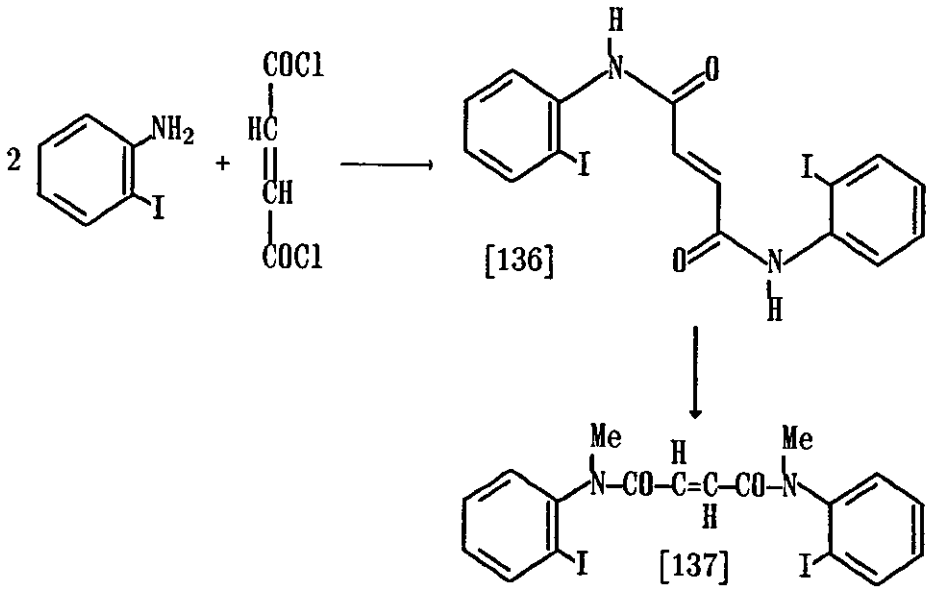
We were interested to prepare the skeleton of the ergot alkaloids, folicanthine (R = Me) and chimonanthine (R = H) *via* a "bicyclisation" as shown (Scheme 70). Known elaboration would allow conversion of the bicyclised indole to be converted to these alkaloids.



SCHEME 70

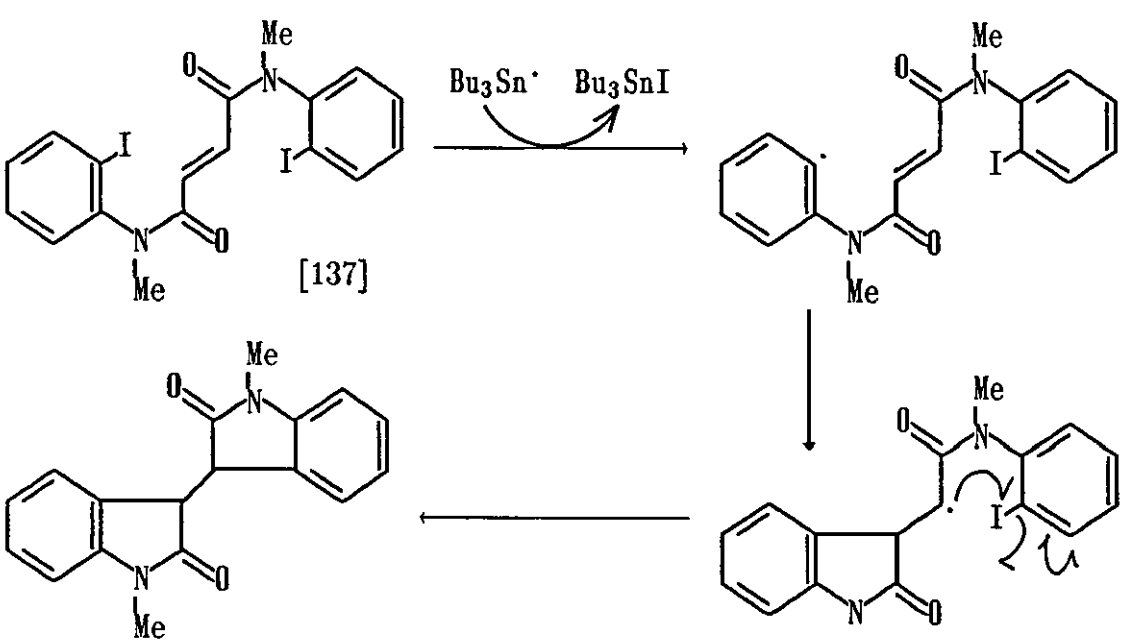
The synthesis of the starting material was envisaged as shown below. However, a major problem arose in the very first reaction of this scheme for alkaloid synthesis in that the available starting material for the acetylene group was only available as a diester, dimethyl acetylenedicarboxylate. The reaction between the $MeO_2C\text{-}C{\equiv}C\text{-}CO_2Me$ and the amine (2-iodoaniline) gave a very exothermic reaction in which a "Michael" type reaction probably took place [111]. Copious gas was evolved (possibly CO_2). Reactions with this acetylene diester were abandoned. Acetylenedicarboxylic acid was available and is reported to be very unstable. We then attempted to get round the problem by the use of a double bond instead of a triple bond.

N,N^1-di(2-iodophenyl)-N,N^1-dimethyl-*trans*-butenediamide [137] (27%) was prepared according to the route shown in Equation 73 from fumaroyl chloride and 2 equivalents of 2-iodoaniline to give the amide [136] (61%), which was subsequently N-methylated in the usual manner to give the amide [137].



(73)

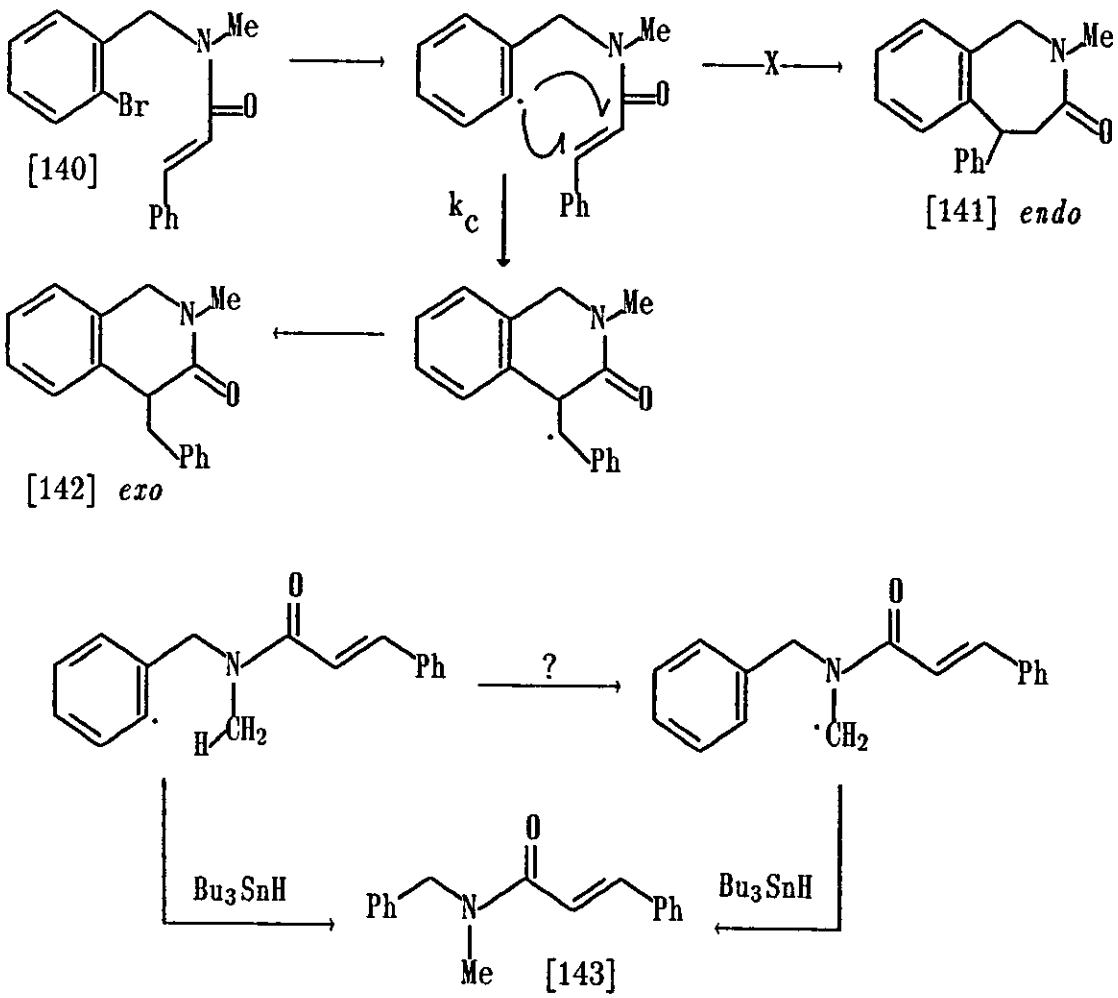
We had hoped that the N-methylated butenediamide [137] would cyclise once in an *exo* ring cyclisation and that the intermediate radical intermediate would undergo a homolytic aromatic substitution as shown in Scheme 71. However, the reaction yielded a polymeric gum on various attempts to bring about the cyclisation of [137] using various conditions with Bu_3SnH. If further time had been available, correct reaction conditions could possibly have been elucidated.



SCHEME 71

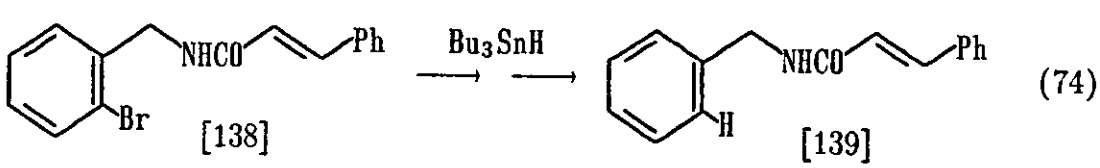
Cyclisation reactions of N-[(2-Halogenophenyl)-methyl]cinnamamides

Our next set of reactions was designed to test cyclisation of aryl radicals onto α,β-unsaturated amides to give 6- or 7-membered rings as shown in Scheme 72.



SCHEME 72

The attempted cyclisation of N-[(2-bromophenyl)-methyl]cinnamamide under the standard Bu_3SnH conditions gave a similar result to that of the primary amide, i.e. only reduction to the non-cyclised N-phenylcinnamamide [139] resulted (70%) as shown in Equation 74. Presumably the same explanation as for the N-(2-halogenophenyl)-cinnamamides applies, i.e. a very stable *trans* conformation.

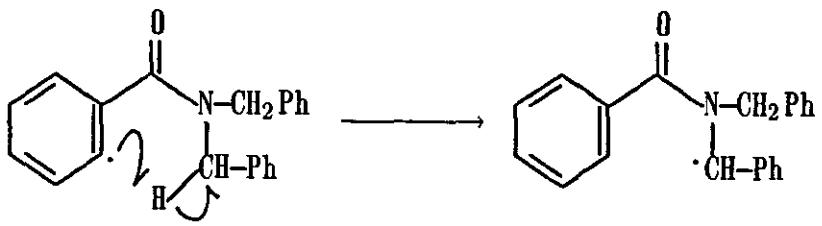


(74)

The cyclisation of the N-methyl derivative of [139], N-[(2-bromobenzyl)-N-methyl]cinnamamide [140] was more fruitful. The reduction of the amide [140] under standard conditions gave two products, the directly reduced non-cyclised material, N-benzyl-N-methylbenzamide [143] (22%) and the six-membered ring cyclised material, 4-benzyl-2-methyl-3-keto-1,2,3,4-tetrahydroisoquinoline [142] (15%) as depicted in Scheme 72.

This result may indicate that the rate of abstraction of hydrogen from Bu_3SnH (k_H) by the aryl radical intermediate is comparable to the rate of *exo*-cyclisation (k_6) to a six-membered ring but is much slower than *endo*-cyclisation to a five-membered ring ($k_5 >> k_H >> k_6$).

An alternative explanation is that a hydrogen is abstracted from the N-methyl group to yield a stabilised radical which is then reduced by Bu_3SnH as shown in Scheme 73. The hydrogen abstraction is favoured because a six-membered ring transition state is involved. The literature [112] provides a roughly similar precedent for this abstraction. This hydrogen abstraction would not be expected in the reactions of N-(2-halogenophenyl)-N-methylamides because hydrogen abstraction is not as rapid *via* a 5-membered ring transition state.

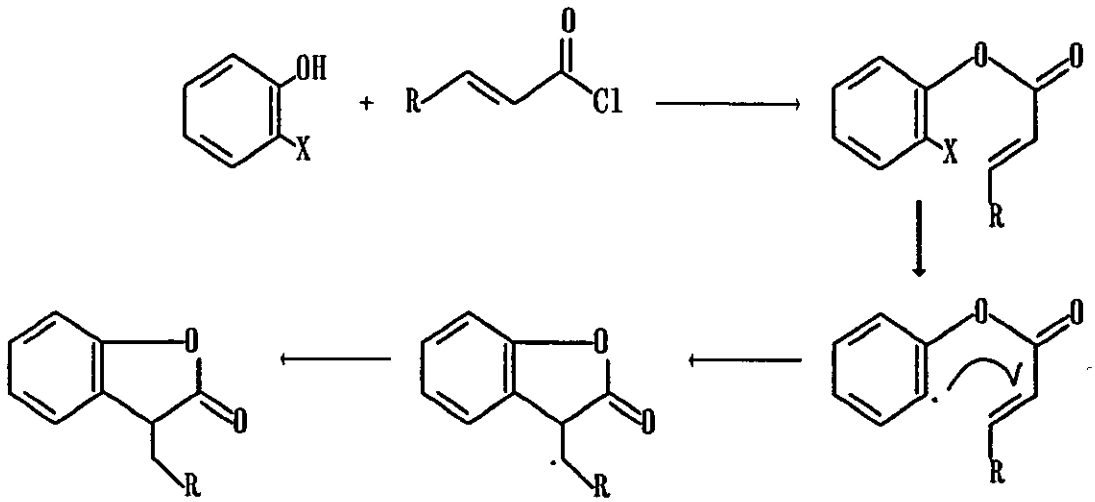


SCHEME 73

PART FOUR:

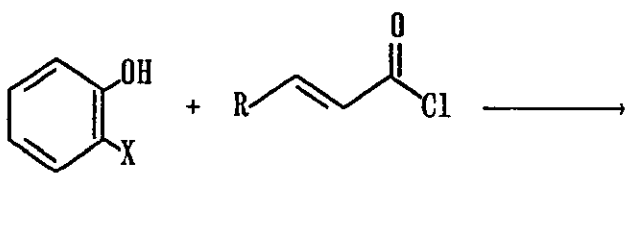
CYCLISATION OF O-ARYL RADICALS ONTO α,β-UNSATURATED ESTERS

In this section, we investigated whether the cyclisation of aryl radicals onto the α-position of N-alkyl-α,β-unsaturated amides to form oxindoles could be extended to form other benzo-fused heterocycles by using α,β-unsaturated side chains. The most obvious extension was to use α,β-unsaturated esters to form coumaran-2-ones etc. as shown in Scheme 74.



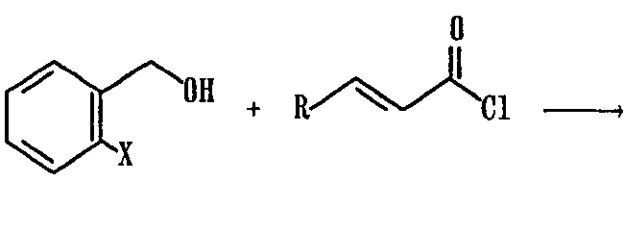
SCHEME 74

. Therefore, a number of suitable substrates were prepared to test the scope of this general synthetic method. Several esters (R = Ph and Me) were synthesised in accordance with Equations 75-77.



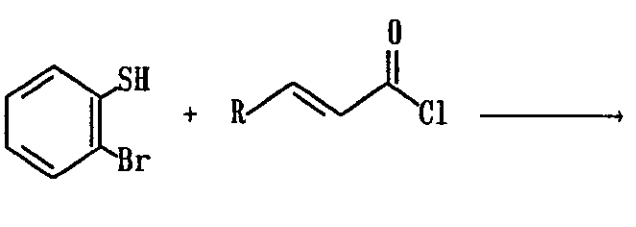
(75)

[144] R=Ph; X=I (60%)
[145] R=Me; X=I (22%)
[146] R=Me; X=Br (32%)



(76)

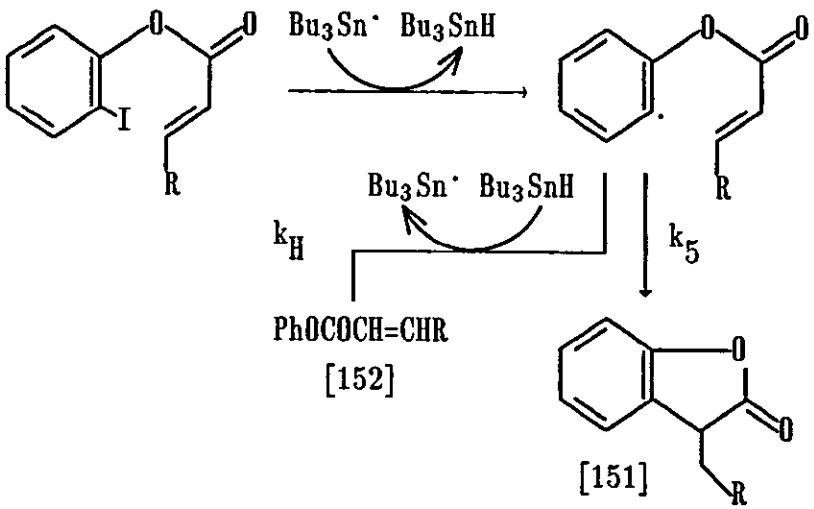
[147] R=Ph; X =I (24%)
[148] R=Me; X =Br (20%)



(77)

[149] R=Ph (77%)
[150] R=Me (35%)

After synthesising a number of different esters, cyclisation reactions were performed under various conditions and the yields measured by g.l.c. Cyclisation of [144, R = Ph] and [145, R = Me], was carried out under the standard Bu_3SnH conditions. The phenyl derivative gave the *exo*-cyclised material, 3-benzyl-coumaran-2-one [151] (26%) and the reduced material, phenyl cinnamate [152] (69%), as indicated in Equation 78.



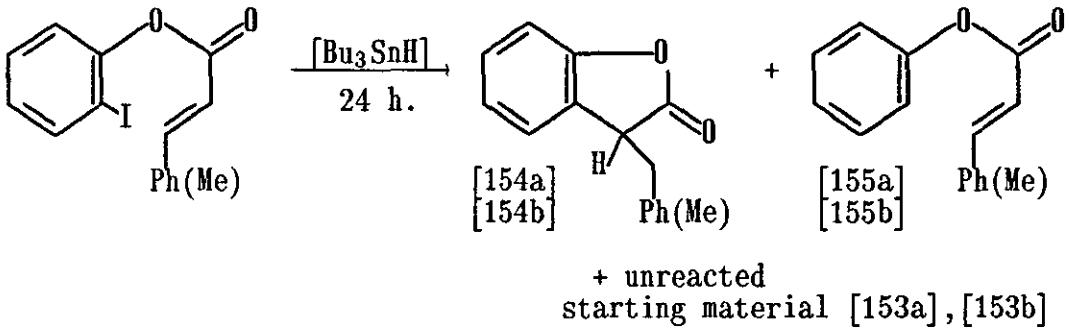
(78)

The results indicated that although the *exo*-cyclisation was taking place, it was limited in comparison to the N-alkyl-α,β-unsaturated amides, with reduction becoming the major route, perhaps because the conformation is not as well positioned as in N-methyl-α,β-unsaturated amides as previously described.

When the ester [146, R = Me] was used, the result was even more disappointing, in that *exo*-cyclisation to 3-ethylcoumaran-2-one was only 1% with both unaltered starting material (14%) and reduced material (52%) predominating. This could be due to several factors, e.g. the variation of stability of the intermediate radical in going from R = Ph to R = Me.

The effects upon cyclisation of 2-Iodophenyl Cinnamate and 2-Iodophenyl Crotonate by variation of [Bu_3SnH]

2-Iodophenyl cinnamate and crotonate were reacted in the usual way, Scheme 75, and the reaction mixtures analysed using g.l.c. (3% OV17 on gas chrom. Q 100/120 mesh at 225 ^{o} C) and compared with authentic materials.



SCHEME 75

RESULTS OF TABLE 4

We next studied what would happen when dilution was increased (Experiment 2 and Experiment 6). Increased dilution as seen in Experiment 2 gave similar results to Experiment 1 (standard reaction), which also corresponds with the failure to improve the yield in Experiment 6 in comparison to Experiment 5.

In Experiment 3, the use of standard concentrations with benzene as the solvent instead of toluene, gave a predictable result, in that some starting material was still in the reaction mixture (21%) but the amount of cyclised material (21%) and reduced material (57%) varied little compared to Experiment 1. The results indicated that the only difference between toluene and benzene was the slower rate in refluxing benzene. Abstraction of hydrogen from toluene (excluded in benzene) is not a factor in the high yield of reduced material.

In Experiment 4, extremely high dilution gave no cyclised material only unaltered starting material (73%) and phenyl cinnamate (27%). The slower rate of reaction is expected at low dilution but cyclisation would also be expected to increase relative to direct reduction. The results of the ester cyclisation do not appear to follow expected trends, of dilution/cyclisation versus direct reduction. No clear explanation is obvious to us and further work is required. Similarly, the reason for the poorer cyclisation observed for the α,β-unsaturated esters as compared to the α,β-unsaturated amides is not obvious. The *cis* N-alkylamides are possibly held in a conformation favourable to cyclisation.

EXPT.	S.M. mg (mmol)	Bu_3SnH mg (mmol)	SOLVENT (ml)	% YIELDS [153a]	[154a]	[155a]
1	115.2 (3.29)	1.1 eq. 105 (3.62)	Toluene (75)	0	26	69
2	500 (1.42)	1.1 eq. 457 (1.57)	Toluene (200)	0	24	69
3	500 (1.42)	1.1 eq. 457 (1.57)	Benzene (75)	21	21	57
4	105 (0.3)	1.1 eq. 96 (0.33)	Toluene (300)	73	0	27

EXPT.	S.M. mg (mmol)	Bu_3SnH mg (mmol)	SOLVENT (ml)	% YIELDS [153b]	[154b]	[155b]
5	113.2 (3.9)	1.1 eq. 125.8 (4.2)	Toluene (75)	14	1	52
6	500 (1.7)	1.1 eq. 556 (1.9)	Toluene (200)	13	1.5	53

TABLE 4: The effects upon cyclisation of 2-Iodophenyl cinnamate and 2-Iodophenyl crotonate by variation of [Bu_3SnH].

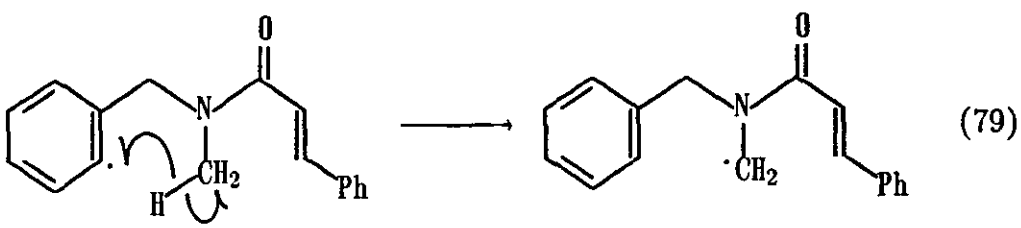
NOTES

S M. = Starting Material (Experiments 1-4) = 2-iodophenyl cinnamate [153a]
(Experiments 5-6) = 2-iodophenyl crotonate [153b]

Products
3-Benzylcoumaran-2-one [154a]
Phenyl cinnamate [155a]
3-Ethylcoumaran-2-one [154b]
Phenyl crotonate [155b]

The attempted cyclisation of 2-bromophenyl thiocinnamate [149] under the standard Bu_3SnH conditions led to decomposition of the starting material. This could possibly be due to the stannane radical reacting with the sulphur as observed for the reactions with thioamides.

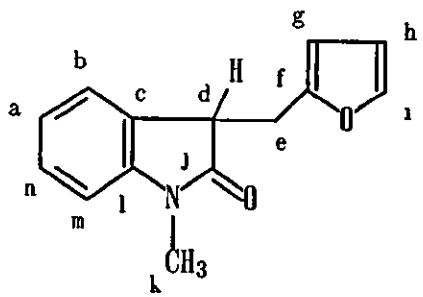
The attempted cyclisation of 2-iodobenzyl cinnamate [147] under standard Bu_3SnH conditions led to the direct reduction of the starting material to benzyl cinnamate in a 32% yield. This was not an expected result. The lack of cyclisation in the six (or seven) membered ring system parallels the results observed for the analogous α,β-unsaturated N-methyl analogue. For the analogous N-methylamide, $k_6 \approx k_H > k_7$, was observed. A 1,5-hydrogen abstraction was however, also possible, which could have explained the higher amount of reduced material (Equation 79). In this ester experiment no 1,5-hydrogen abstraction is possible, and therefore, $k_H >> k_6, k_7$.



(79)

The similar relative reactivity for both α,β-unsaturated esters and amides indicates that anti-Michael cyclisation onto the β-position *via* 1,5-cyclisation is strongly favoured over 1,6-cyclisation. Again, the reasons for these observations are not obvious. The work was terminated at this point due to shortage of time. However, future work should investigate the use of this cyclisation on other α,β-unsaturated systems.

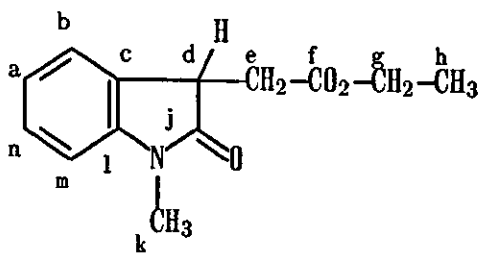
PART FIVE:
DIAGRAMS OF COMPOUNDS SHOWING UNUSUAL ^{13}C N.M.R. VALUES



1-Methyl-3-(3-Furylmethyl)-Oxindole

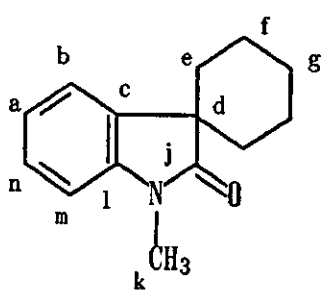
a = 120 ppm	f = 150 ppm	k = 26 ppm
b = 122 ppm	g = 106 ppm	l = 142 ppm
c = 126 ppm	h = 106 ppm	m = 109 ppm
d = 44 ppm	i = 139 ppm	n = 126 ppm
e = 29 ppm	j = 173 ppm	

Ref (^{13}C NMR, 3-methyloxindole): P.G. Gassman, D.P. Gilbert and T.Y. Luh, *J.Org. Chem.*, 42, 1340 (1977).



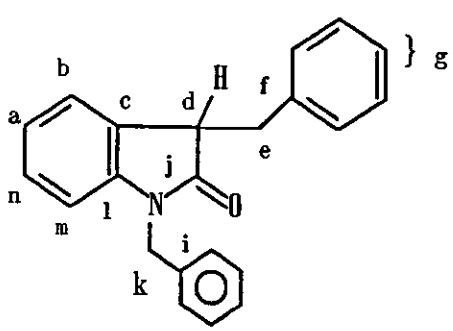
1-Methyl-3-Ethylate-Oxindole

a = 122 ppm	f = 171 ppm	k = 26 ppm
b = 124 ppm	g = 35 ppm	l = 144 ppm
c = 128 ppm	h = 14 ppm	m = 108 ppm
d = 42 ppm		n = 128 ppm
e = 61 ppm	j = 177 ppm	



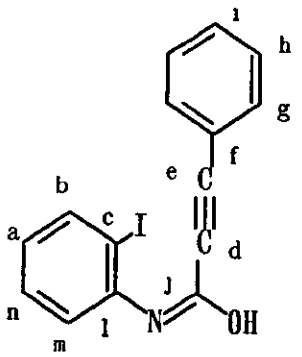
N-Methyl-Oxindole-3-Spiro-Cyclohexane

a = 127 ppm	f = 24 ppm	k = 26 ppm
b = 124 ppm	g = 25 ppm	l = 143 ppm
c = 135 ppm		m = 108 ppm
d = 47 ppm		n = 123 ppm
e = 33 ppm	j = 181 ppm	



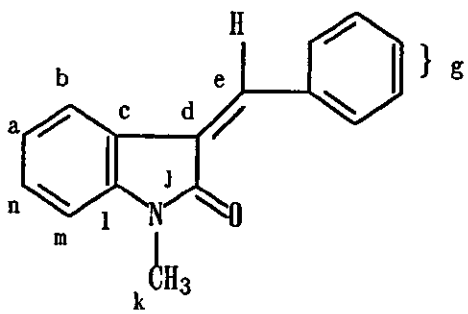
N-Benzyl-N-(2-Iodophenyl)-Cinnamamide

a = 124 ppm	f = 137 ppm	k = 36 ppm
b = 122 ppm	g = 127-133	l = 143 ppm
c = 128 ppm		m = 108 ppm
d = 42 ppm	i = 135 ppm	n = 127 ppm
e = 43 ppm	j = 177 ppm	



N- (2- Iodophenyl)- Phenylpropynamide

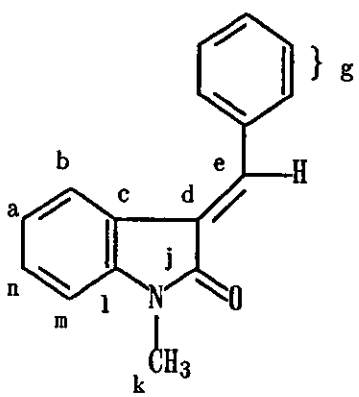
a = 124 ppm	f = 116 ppm	
b = 136 ppm	g = 130 ppm	l = 148 ppm
c = 84 ppm	h = 126 ppm	m = 120 ppm
d = 81 ppm	i = 128 ppm	n = 126 ppm
e = 88 ppm	j = 134 ppm	



***Trans*- 3- Benzyladine- 1- Methyloxindole**

a = 121 ppm		k = 26 ppm
b = 118 ppm	g = 128- 129	l = 142 ppm
c = 133 ppm		m = 108 ppm
d = 137 ppm		n = 128 ppm
e = 119 ppm	j = 166 ppm	

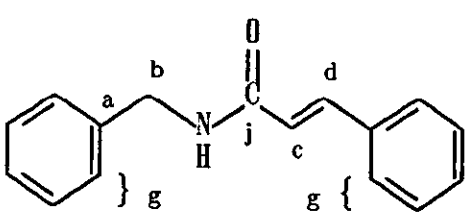
Ref: Expt.106



***Cis*- 3- Benzyladine- 1- Methyloxindole**

a = 122 ppm		k = 26 ppm
b = 123 ppm	g = 128- 129	l = 144 ppm
c = 130 ppm		m = 108 ppm
d = 135 ppm		n = 127 ppm
e = 121 ppm	j = 169 ppm	

Ref: Expt.106



a = 139 ppm	d = 139 ppm
b = 43 ppm	g = 126- 129 ppm
c = 122 ppm	j = 166 ppm

EXPERIMENTAL

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Gener.

All solvents were dried and distilled by conventional methods. Melting points were determined on a Kofler block and are uncorrected. Infrared spectra were recorded as KBr of Nujol mulls (solids) or thin films (liquids) on a Phillips 3956 with IBM Computer Interface and printout.

^{1}H Nuclear Magnetic Resonance spectra were determined using tetramethylsilane (TMS) as the internal standard. 100 MHz spectra were recorded on a Varian EM 360A instrument, 90 MHz spectra on a Bruker AM.90 instrument, 200 MHz spectra on a Bruker WP-200SY and 360 MHz spectra on a Bruker AM.360 spectrometer using TMS as an internal standard.

Mass spectra were recorded using a Kratos MS80 spectrometer linked to a DS-55 data system and a Finnigen MS8200 linked to a Lincos data system. H.P.L.C. analyses (high pressure liquid chromatography) were performed using a Waterman analytical H.P.L.C. with U.V. detection.

Analyses were performed by the microanalytical department, Manchester University. Nitrogen gas was deoxygenated by bubbling through gas washing bottles containing Fieser's solution and sodium hydroxide pellets.

"Petrol" refers to the 60-80°C boiling fraction unless otherwise stated. "Illumination" in the text refers to 2 x 150 W tungsten lamps. "Dried" in the text refers to treatment of the solvent with anhydrous magnesium sulphate. "SiO_2 flash" in the text refers to Merck silica gel 230-400 mesh according to the method of Still *et al.*[113].

Preparative and analytical thin layer chromatography was performed using Merck alumina 60_{PF254} (Type E) and Merck silica gel 60_{PF254} and 60_{PF366}. "Basic Al_2O_3" in the text refers to chromatographic grade basic Al_2O_3 and "neutral Al_2O_3" refers to chromatographic grade neutral Al_2O_3.

When only "cyclisation" is used in the text, this means that cyclisation conditions of Bu_3SnH (1.1 equiv.) and AIBN (0.2 to 0.3 equiv.) were being used to achieve cyclisation.

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Common Abbreviations Used in the Experimental Section

DMF	N,N-Dimethylformamide
DMSO	Dimethylsulphoxide
Et_2O	Diethyl ether
THF	Tetrahydrofuran
EtOAc	Ethyl acetate
CH_2Cl_2	Dichloromethane
$CHCl_3$	Trichloromethane
$CDCl_3$	Deuterochloroform
$BrCl_3$	Monobromotrichloromethane
NaOH	Sodium hydroxide
KOH	Potassium hydroxide
Bu_3SnH	Tri-n-butyltin hydride
Bu_3SnCl	Tri-n-butyltin chloride
DABCO	1,4-Diazobicyclo[2.2.2]octane
AIBN	Bis-azoisobutyronitrile
$LiAlH_4$	Lithium aluminium hydride
$NaBH_4$	Sodium borohydride

1. Preparation of 2-Iodophenyl allyl ether

A solution of 2-iodophenol (5g, 0.2 mmol) and K_2CO_3 (3.31g, 0.2 mmol) in acetone (100 ml) was heated under reflux for 1h. Allyl bromide (1.85g, 0.22 mmol) was added dropwise over 30 min. and refluxed for a further 32h.

After cooling, the reaction mixture was diluted with water (250 ml) and extracted with Et_2O (3 x 35 ml). The organic layer was washed with 10% aq. NaOH and water, dried, and the solvent removed *in vacuo* to yield a crude oil which on distillation gave 2-iodophenyl allyl ether b.p. (18) 141-144 °C [lit.[114] b.p. (18) 141-144 °C] (4.49g, 93%); ν_{max} (thin film): 3060-2864 (C-H stretch), 1646 (C=C stretch), 1580 (C-H stretch) and 748 cm^{-1} (4 adjacent H); δ_H (60 MHz, $CDCl_3$): 4.4-4.6 (2H, m, OCH_2), 5.1-5.4 (2H, m, $HC=CH_2$), 5.5-6.2 (1H, m, $CH=CH_2$) and 6.2-7.9 (4H, m, aromatic H).

2a. Cyclisation of 2-Iodophenyl allyl ether

2-Iodophenyl ether (3.1g, 12 mmol) was dissolved in deoxygenated toluene (75 ml) under nitrogen. The solvent was heated to reflux and Bu_3SnH (1.1 equiv., 3.84g, 13.2 mmol) and AIBN (0.3 equiv., 394 mg, 2.4 mmol) were added whilst irradiating with light for 24h. The reaction mixture was cooled, poured into ice/water and extracted with Et_2O (3 x 10 ml). The solvent was then evaporated *in vacuo*. The remaining oil was distilled to give 3-methyl-2,3-dihydrobenzofuran (1.34g, 83%), [b.p. (16) 86-87 °C], [lit.[115] b.p. (12) 78 °]; ν_{max} (thin film): 1460 (C-H deformation) and 745-750 cm^{-1} (Four adjacent H); δ_H (60 MHz, $CDCl_3$): 1.3 (3H, s, CH_3), 3.45 (1H, m, H_B), 4.0 (1H, m, H_A), 4.6 (1H, m, H_X) and 6.6-7.3 (4H, m, aromatic H).

2b. Attempted cyclisation of 2-Iodophenyl allyl ether using the "Bunnett" procedure

2-Iodophenyl allyl ether (580 mg, 2.23 mmol) was added dropwise to a deoxygenated solution of sodium methoxide [sodium metal (2 equiv., 103 mg, 4.48 mmol) in MeOH (40 ml)] over 15 min. The mixture was heated under reflux and

illuminated for 48h. The mixture was periodically monitored by t.l.c. (Al_2O_3, basic, pet. ether). After 24h. the solution had changed from a clear solution to a purple coloured solution.

The crude reaction mixture was poured into water (600 ml) and extracted with CH_2Cl_2 (3 x 25 ml). The organic layer was washed with water (x2), dried, and evaporated *in vacuo* to give a crude oil (440 mg) which was distilled to give phenyl allyl ether (242 mg, 81%), [b.p. (1.5) 14-150 °C] [lit.[116] b.p. 192-195 °]; ν_{max} (thin film): 2990-2860 (C-H stretch), 1580 (C=C stretch) and 750 cm^{-1} (4 adjacent H); δ_H (60 MHz, $CDCl_3$): 4.5-4.7 (2H, d, J = 4 Hz, X-C<u>H</u>$_3$-Y), 5.12-5.65 (2H, m, Y-<u>H</u>C=C<u>H</u>$_2$), 5.7-6.25 (1H, m, C<u>H</u>) and 6.7-7.8 (4H, m, aromatic H).

3. Preparation of 2-Acetamidophenyl allyl ether

2-Acetamidophenol (5g, 40 mmol), K_2CO_3 (6g, 30 mmol) and acetone (100 ml) were vigorously stirred whilst allyl bromide (4g, 30 mmol) was added dropwise over 1h. and the reaction heated at a gentle reflux for 8h. The mixture was cooled, water (150 ml) was added, extracted with Et_2O (3 x 50 ml). The organic extract was washed with 10% aq. NaOH and water, dried, and the solvent evaporated *in vacuo* to yield a brown oil which crystallised on standing. Recrystallation from pet. ether gave 2-acetamidophenyl allyl ether as colourless chalky crystals (4.52g, 72%), m.p. 51-52 °C [lit.[117] m.p. 50-51 °C]; ν_{max} (KBr): 3350-3440 (N-H stretch) and 750 cm^{-1} (4 adjacent H); δ_H (60 MHz, $CDCl_3$): 2.2 (3H, s, CH_3), 4.6 (2H, d, J = 6 Hz, CH_2), 5.2-5.6 (3H, m, CH=CH_2), 7.0-7.1 (4H, m, aromatic H) and 8.7 (1H, brs, amide H).

4. Preparation of 2-Allyloxyaniline

A mixture of 2-acetamidophenyl allyl ether (10g, 50 mmol) was heated to reflux for 70 mins. in 6N hydrochloric acid (40 ml). The resulting solution was made alkaline with 2N aq. NaOH solution and a red oil separated which was extracted with EtOAc (3 x 50 ml). The organic layer was washed with 10% aq. NaOH and water, dried, concentrated by evaporation of the solvent *in vacuo*, and finally

distilled to yield the 2-allyloxyaniline as a colourless oil (5.6g, 72%), b.p. (0.4) 80-85 °C [lit.[118] b.p. (0.6) 84-85 °]; ν_{max} (thin film): 3350-3440 (C-H stretch), 1580 (C=C stretch), 1610 (C=C stretch), 1200 (C-O stretch) and 750 cm^{-1} (4 adjacent H); δ_H (60 MHz, $CDCl_3$): 4.4 (2H, d, J = 5 Hz, $OC\underline{H}_2$), 5.0-6.3 (7H, m, aromatic H and $HC=C\underline{H}_2$).

5. Preparation of 2-Allyloxybenzene diazonium fluoborate

2-Allyloxyaniline (4g, 27 mmol) was dissolved in 40% aq. HBF_4 (20 ml) at 0 °C. The mixture was cooled to -5 °C after 10 min. and a white precipitate was filtered off. The precipitate was dried overnight over P_2O_5 giving the amino fluoborate derivative (5.2g). The fluoborate was dissolved in THF (15-20 ml), cooled to -5 °C and pentyl nitrite (1 mol excess) added over 15 min. The mixture was stirred until a precipitate formed which was filtered and dried (P_2O_5) to give 2-allyloxybenzene diazonium fluoborate (3.1g, 54%); ν_{max} (KBr): 2240 (N=N stretch), 1625 (C=C stretch) and 760 cm^{-1} (4 adjacent H); δ_H (60 MHz, $(CD_3)_2C=O$) 4.5-5.7 (5H, m, $C\underline{H}$-$C\underline{H}_2$=CH_2) and 5.8-6.8 (4H, m, aromatic H). All data corresponded with the literature data [119].

6. Cyclisation of 2-Allyloxybenzene diazonium fluoborate

2-Allyloxybenzene diazonium fluoborate (3g, 20 mmol) was stirred in deoxygenated THF (40 ml) and Bu_3SnH (1 equiv., 3.77g, 20 mmol) added. After 15 min. under illumination the reaction was heated to 68 °C for 15 min. and the product isolated in the normal way [Expt. 2a] to yield 3-methyl-2,3-dihydrobenzofuran (1g, 58%) [g.l.c. purity of 90% (10% carbowax 20 m on 100-120 Aeropack 30, 20' x 1/8" in stainless steel)]; ν_{max} (thin film): 1460 (C-H deformation), 1225 (C-O stretch) and 745 cm^{-1} (4 adjacent H); δ_H (60 MHz, $CDCl_3$): 1.3 (3H, m, $C\underline{H}_3$); 3.45 (1H, m, $C\underline{H}$=CH_3); 4.0 [1H, m, CH_2 (a)]; 4.6 [1H, m, CH_2 (b)], J_{AX} = 7.0 and J_{XY3} = 7.0 Hz; 6.6-7.3 (4H, m, aromatic H). All data corresponded with the literature data[120].

"Classical" synthesis of 3-Methyl-2,3-dihydrobenzofuran

7a. Preparation of Ethyl 3-methylcoumarilate

Dry sodium phenolate (116g, 1 mol) was added to benzene (1 L) and the solution brought to reflux. Ethyl chloroacetoacetate (165g, 1 mol) was added and the reaction was maintained at reflux for a further 4h. after addition of the chloro-ester. The light brown suspension was cooled to room temperature, extracted with water (2 x 500 ml). The organic layer was dried and the solvent removed by evaporation *in vacuo* leaving the crude ethyl phenoxyacetoacetate (200g, 90%). The product was added to concentrated sulphuric acid (195 ml) at 0-5 °C through a dropping funnel over a period of 1 h. whilst stirring with a mechanical stirrer.

The mixture soon solidified and was allowed to stand in the ice bath for 1h. longer. Ice (500 mg) and water (500 ml) were added with stirring and external cooling. The mixture was extracted with benzene (2 x 250 ml). The combined extracts were washed with water (100 ml), a saturated solution of $NaHCO_3$ (100 ml), dried, and the solvent evaporated *in vacuo*. The residue was distilled to give a pale yellow oil [b.p. (16) 162-167 °C] which solidified on cooling. The product was triturated with pet. ether and dried in a vacuum desiccator to give colourless rhombic plates of ethyl 3-methylcoumarilate (75g, 43%), m.p. 49-51 °C [lit.[121], m.p. 49-51 °C].

7b Preparation of 3-Methylcoumarilic acid

Ethyl 3-methylcoumarilic acid (70g, 0.34 mol) in 10% aq. KOH (500 ml) solution was refluxed for 1h. The clear yellow solution was acidified while hot with a slight excess of concentrated hydrochloric acid to precipitate the 3-methylcoumarilic acid. The suspension was cooled to room temperature and the colourless solid was filtered off. The filter cake was re-suspended in cold water (500 ml), stirred vigorously for several minutes, and filtered again. The colourless powder was dried under vacuum. This gave a good yield of 3-methylcoumarilic acid (57g, 95%), m.p. 192-193 °C [lit. [122], m.p. 192-193 °C].

7c Preparation of 3-Methylcoumarone

Dry 3-methylcoumarilic acid (50g) was distilled at 280 °C using a Wood's metal bath. Carbon dioxide was evolved and a cloudy liquid distilled at 190-220 °C. The crude product was purified by redistillation through a Vigreux column giving a clear colourless distillate of 3-methylcoumarone (33g, 88%), b.p. 195-197 °C [lit. [123], b.p. 195-197 °C].

7d Preparation of 3-Methyl-2,3-dihydrobenzofuran

Sodium (2g, 90 mmol) was introduced to 3-methylcoumarone (1g, 7.6 mmol) in absolute ethanol (5 ml) and the mixture heated under reflux for 1 h. The mixture was cooled, poured into water (150 ml), and extracted with Et_2O (3 x 50 ml). The organic layer was washed with brine and then water, dried, and concentrated by removal of the solvent *in vacuo*. The crude material was distilled to give 3-methyl-2,3-dihydrobenzofuran as a colourless oil (80 mg, 88%) [b.p. (12) 78 °C] [lit.[124] b.p. (12) 78 °C]; ν_{max} (thin film): 1460 (C-H deformation), 1225 (C-O stretch) and 745 cm^{-1} (4 adjacent H); δ_H (60 MHz, $CDCl_3$): 1.3 (3H, m, CH_3); 3.45 (1H, m, C<u>H</u>=CH_3); 4.0 [1H, m, CH_2 (a)]; 4.6 [1H, m, CH_2 (b)], J_{AB} = 8.5, J_{AX} = 9.0, J_{BX} = 7.0 and J_{XY3} = 7.0 Hz; 6.6-7.3 (4H, m, aromatic H). The distilled material was analysed for purity by g.l.c. (10% carbowax 20 m on 100-120 Aeropack 30, 20'x1/8" in stainless steel) and indicated a single peak.

8. Preparation of 2-Methylbenzoyl chloride

2-Methylbenzoic acid (4.7g, 30 mmol) was added to thionyl chloride (100 ml) and the reaction heated under reflux overnight. The solvent was removed and the acid chloride distilled to give 2-methylbenzoyl chloride (3.17g, 60%), b.p. (760) 206-208 °C [lit.[125] b.p. (762) 212 °C]; ν_{max} (thin film): 2960 (C-H and N-H stretch), 1800-1795 (C-O stretch), 750, 690 and 680 cm^{-1} (4 adjacent H).

9a. Preparation of 2-Chlorotoluene using the "Barton-Hundsdiecker" reaction

The sodium salt of 2-mercaptopyridine-N-oxide (1.2 equiv., 1.18g, 7.9 mmol) and 4-dimethylaminopyridine (0.3 equiv., 230 mg, 1.89 mmol) were added to refluxing deoxygenated CCl_4 (75 ml) under nitrogen. 2-Methylbenzoyl chloride (1 equiv., 970 mg, 6.3 mmol) was added dropwise over 15 min. during which time an intense yellow colour developed. The reaction mixture was illuminated and maintained at reflux for 2h. The crude product was poured into 2N hydrochloric acid (100 ml) and extracted with CCl_4 (50 ml). The organic layer was washed with 2N hydrochloric acid (x2), water (x2), a saturated solution of $NaHCO_3$ (x2) and water, dried, and the solvent evaporated *in vacuo*. The crude oil was distilled to give 2-chlorotoluene (520 mg, 65%), b.p. (760) 159 °C [lit.[126] b.p. (760) 159 °C]. All spectroscopic data agreed with that of the literature [126].

9b. Preparation of 2-Chloroanisole using the "Barton-Hundsdiecker" reaction

Anisoyl chloride (1 equiv., 500 mg, 293 mmol) and AIBN (0.3 equiv., 144 mg, 0.88 mmol) in CCl_4 (50 ml) were added to a suspension of the sodium salt of 2-mercaptopyridine-N-oxide (1.1 equiv., 479 mg, 3.22 mmol) in refluxing CCl_4 (100 ml) over 20 min. under nitrogen. The reaction was maintained until the bright yellow colour had subsided. The reaction mixture was filtered and the solvent evaporated *in vacuo* to leave an oil which was distilled to give 2-chloroanisole (152 mg, 36%), b.p. (11) 87-88 °C, [lit.[127] b.p. 195-196 °C]. All spectroscopic data agreed with that of the literature [127].

9c. Preparation of β-Bromostyrene using the "Barton-Hundsdiecker" reaction

Cinnamoyl chloride (1g, 0.6 mmol) and AIBN (0.3 equiv., 296 mg, 0.18 mmol) in $BrCCl_3$ (50 ml) were added to a suspension of the sodium salt of 2-mercaptopyridine-N-oxide (1.1 equiv., 984 mg, 0.66 mmol) in refluxing deoxygenated $BrCCl_3$ (50 ml) under nitrogen. A bright yellow colour was produced which subsided to an almost colourless reaction mixture after 2h. The

reaction mixture evaporated *in vacuo* to give a semi-crystalline material which was distilled to give β-bromostyrene (1.17 mg, 11%), b.p. (15) 120-130 °C, [lit.[128] b.p. (20) 110-112 °C]. All spectroscopic data agreed with that of the literature [128].

9d. Preparation of β-Chlorostyrene using the "Barton-Hundsdiecker" reaction

Cinnamoyl chloride (500 mg, 0.3 mmol) and AIBN (0.3 equiv., 148 mg, 0.09 mmol) in CCl_4 (50 ml) were added to a suspension of the sodium salt of 2-mercaptopyridine-N-oxide (1.1 equiv., 447 mg, 0.09 mmol) in refluxing CCl_4 (100 ml). A bright yellow colour was produced which subsided to an almost colourless reaction mixture after 3h. The reaction was evaporated *in vacuo* to give an oil which was distilled to give β-chlorostyrene (55 mg, 13%), b.p. (15) 85-87 °C, [lit.[129] b.p. (18) 90 °C]. All spectroscopic data agreed with that of the literature [129].

10. Preparation of 2-Allyloxybenzoic acid

Allyl bromide (1 equiv., 26.6g, 0.22 mmol) was added to a suspension of the sodium salt of salicylic acid (20g, 0.12 mmol) in DMF (100 ml) over 30 min. The solvent was heated at 100 °C for 12h. The solvent was removed *in vacuo*, methanolic KOH solution (4g in 75 ml) added, and the reaction heated under reflux for a further 12 h. The mixture was cooled and poured into iced water (100 ml) and neutralised to pH 3 with 2N hydrochloric acid. The aqueous mixture was extracted with Et_2O (5 x 25 ml) and the organic layer dried, evaporated to dryness, and the resulting residue recrystallised from aqueous EtOH to yield 2-allyloxybenzoic acid (11g, 56%), m.p. 63-65 °C [lit. [130], m.p. 60-62 °C]. ν_{max} (Nujol mull): 3300 (O-H stretch), 1700 (C=O stretch) and 1670 (C=C stretch) cm^{-1}; δ_H (60 MHz, $CDCl_3$): 4.6-6.4 (5H, m, O-CH_2CH=CH_2), 6.8-8.2 (4H, m, aromatic H) and 10.0 (1H, brs, CO_2H).

11. Preparation of 2-Allyloxybenzoyl chloride

2-Allyloxybenzoic acid (8.9g, 50 mmol) was dissolved in thionyl chloride (50 ml) and the reaction heated under reflux for 3h. The solvent was evaporated *in vacuo* and the oil distilled to give 2-allyloxybenzoyl chloride (7.07g, 72%). B.p. (1.5-2.5) 130-160 °C; ν_{max} (thin film): 1780 (C=O stretch), 1600 (C=C stretch), 760 and 720 cm^{-1} (5 adjacent H); δ_H (90 MHz, $CDCl_3$): 4.5-6.2 (5H, m, $C\underline{H}_2$) and 6.5-8.1 (4H, m, aromatic H); m/z 198 (M^+, ^{37}Cl) and 196 (M^+, ^{35}Cl).

12. Preparation of the thiohydroxamic ester of 2-Allyloxybenzoic acid and attempted cyclisation

Oxalyl chloride (1.5 equiv., 473 mg, 3.8 mmol) was added dropwise to a solution of 2-allyloxybenzoic acid (500 mg, 2.5 mmol) in chlorobenzene (25 ml) under reflux for 12 h. under nitrogen to yield the acid chloride. To the refluxing solution of the acid chloride was added the sodium salt of 2-mercaptopyridine-N-oxide (1.1 equiv., 343 mg, 2.8 mmol) with illumination by light over 3h. The mixture was cooled and the solvent evaporated *in vacuo*. The crude material was dissolved in CH_2Cl_2 (50 ml), washed with water (x3), dried, and the solvent evaporated *in vacuo*. The product was subjected to preparative t.l.c. (SiO_2, pet. ether/Et_2O, 1:1). The preparative t.l.c. yielded products that indicated a mixture of the ester derivative and an intractable gum which was not characterised.

13a. Preparation of N-(2-Iodophenyl)-benzamide

2-Iodoaniline (5g, 22.8 mmol) was suspended in 10% aq. NaOH (70 ml) and benzoyl chloride (1.1 equiv., 3.69g, 26.3 mmol) was added dropwise over a period of 2h. and stirred for a further 2h. The suspension was filtered and washed with water. The crude material was recrystallised from aqueous EtOH to give N-(2-iodophenyl)-benzamide as colourless crystals (4.98g, 68%), m.p. 140-141.5 °C [lit.[131] m.p. 139 °C]; ν_{max} (Nujol mull): 3210 (N-H stretch) and 1645 cm^{-1} (C=O stretch); δ_H (60 MHz, $CDCl_3$/d^6-DMSO) 6.6-8.65 (m, aromatic and amide H).

13b. Preparation of N-(2-Bromophenyl)-benzamide

Benzoylation of 2-bromoaniline gave N-(2-bromophenyl)-benzamide as colourless needles on recrystallisation from absolute EtOH (69%), m.p. 116-118 °C [lit.[132] m.p. 116 °C]; ν_{max} (Nujol mull): 3220 (N-H stretch) and 1650 cm^{-1} (C=O stretch); δ_H (60 MHz, $CDCl_3/d^6$-DMSO) 6.5-8.8 (10H, m, aromatic and amide H).

14. Attempted cyclisation of N-(2-Iodophenyl)-benzamide

N-(2-Iodophenyl)-benzamide (800 mg, 2.5 mmol) was dissolved in deoxygenated toluene (75 ml) and the solvent heated to reflux under nitrogen whereupon Bu_3SnH (1.1 equiv., 815 mg, 2.8 mmol) and AIBN (0.2 equiv., 82 mg, 0.5 mmol) were added. The reaction mixture was maintained at reflux whilst illuminating with light for 48 h. The crude material was evaporated to dryness to yield, on recrystallisation from absolute EtOH, N-(2-iodophenyl)-benzamide (223 mg, 46%), m.p. 163-165 °C [lit.[133] m.p. 161-164 °C]; ν_{max} (KBr): 3500 (N-H stretch), 1650 (C=O stretch), 750, 720 and 700 cm^{-1} (5 adjacent H); δ_H (60 MHz, $CDCl_3/d^6$-DMSO) 6.8-8.1 (m, aromatic H) and 9.8 (1H, brs, amide H).

The reaction was repeated several times and gave yields from 46-76%. All spectroscopic data agreed with that of the literature [133].

15. Preparation of N-(2-Iodophenyl)-thiobenzamide using Lawesson's reagent

N-(2-Iodophenyl)-benzamide (2g, 6.2 mmol) and Lawesson's reagent (0.7 equiv., 0.89g, 4 mmol) were dissolved in deoxygenated toluene under nitrogen and the solvent refluxed for 4 h. The yellow solution was cooled and the toluene removed *in vacuo*. The residue was taken up into CH_2Cl_2 (20 ml) and chromatographed on a short column (Al_2O_3,neutral, CH_2Cl_2). The eluant was evaporated to dryness to yield the crude thioamide which was recrystallised from absolute EtOH to yield N-(2-iodophenyl)-thiobenzamide as yellow crystals (1.18g, 56%), m.p. 92-96 °C [lit.[134] m.p. 96-99 °C]. All spectroscopic data agreed with that

of the literature [134].

16. Cyclisations and attempted cyclisations of N-(2-Halogenophenyl)-thiobenzamides: General conditions for cyclisation

The material to be reacted was added to deoxygenated solvent (75 ml). The solvent was heated to reflux (or as specified) whereupon Bu_3SnH or NaH or DABCO (as specified) and AIBN (as specified) were added. The reaction was illuminated whilst maintaining the reaction at reflux (as specified) under nitrogen for the designated time (as specified). The solvent was removed *in vacuo* and the crude material recrystallised from a suitable solvent [pet. ether etc.] and characterised in the normal manner (I.R., N.M.R. and mass spectra), the results of which are explained in the discussion [p. 48].

17. Cyclisations of N-(2-Halogenophenyl)-thiobenzanilide under various conditions and examination by H.P.L.C.

Some of the reactions performed previously by isolating the products of the reaction (Expt. 16) were attempted under a similar procedure except that the crude material on removal of the solvent was redissolved in THF (100 ml) and analysed by H.P.L.C. (ODS column, 20 cm using 20% THF, 50% MeOH and 30% H_2O as the solvent system). An internal standard of acetamide was used to calibrate the column initially and calibration curves drawn using standard concentrations of authentic materials; starting materials; reduced material and cyclised material. The results are explained in the discussion [p. 50].

18. Preparation of 2-Iodobenzylbromide

2-Iodotoluene (8.16g, 37.4 mmol) and bromine (11.95g, 74.8 mmol) were dissolved in CCl_4 (40 ml) and the reaction heated under reflux and nitrogen, illuminating with light for 30 h. The crude reaction mixture was washed with a saturated solution of sodium metabisulphite followed by sodium bicarbonate and water. The organic layer was dried and the solvent evaporated *in vacuo* to yield an

orange oil. Distillation of the oil yielded unreacted starting material as a pale red oil (1.2g, 15% recovery) [b.p. (1.4) 40-80 °C], and 2-iodobenzylbromide as a pale yellow oil [b.p. (10.4) 98-105 °C] which crystallised on standing (6.8g, 66%), m.p. 48-53 °C [lit.[135] m.p. 55.5 °C]; ν_{max} (thin film): 1565 (aryl-H vibration), 1440 (C-H deformation) and 760 cm^{-1} (4 adjacent H); δ_H (60 MHz, $CDCl_3$): 4.46 (2H, s, $C\underline{H}_2Br$) and 6.6-7.86 (4H, m, aromatic H).

19. Preparation of 2-Iodobenzylamine

2-Iodobenzylbromide (3.4g, 11.45 mmol) was added dropwise to a solution of hexamine (1.1 equiv., 1.7g, 12.6 mmol) in CCl_4 (45 ml). The reaction mixture was then heated under reflux for 30 min. A colourless precipitate formed after 10 min. The reaction mixture was then heated under reflux for a further 5 h., and then cooled. The hexamine adduct was collected by filtration of the colourless crystals (4.06g, 81%), m.p. 158-163 °C. The adduct was refluxed for 5 h., in a mixture of ethanol (20 ml), water (4 ml) and concentrated HCl (10 ml). The ethanol was removed by evaporation *in vacuo*.

The semi-crystalline residue was basified to pH 9 with 10% aq. NaOH, whereupon a thick, pale yellow precipitate formed. The mixture was extracted with Et_2O (3 x 50 ml). The organic extracts were washed with water (x2) and extracted with 2N hydrochloric acid (3 x 50 ml). The aqueous extracts were basified to pH 14 with 10% aq. NaOH and extracted with Et_2O (4 x 50 ml). The organic extracts washed with water (x2), dried and the solvent evaporated *in vacuo* to yield the crude amine as a pale yellow oil (1.57g, 59%). Kugelruhr distillation under reduced pressure yielded 2-iodobenzylamine as a pale yellow oil (0.66g, 25%), b.p. (1.5) 92 °C; ν_{max} (thin film): 3385 (N-H stretch), 3290 (C-H stretch) and 750 cm^{-1} (4 adjacent H); δ_H (60 MHz, $CDCl_3$): 1.45 (2H, brs, NH_2); 3.76 (2H, d, J = 4 Hz, CH_2NH_2) and 6.64-7.87 (4H, m, aromatic H). The product was authenticated by the preparation of the benzoyl derivative by benzoyl chloride (Expt. 20a).

20a. Preparation of N-(2-Iodobenzyl)-benzamide

2-Iodobenzylamine (520 mg, 2.2 mmol), benzoyl chloride (1.1 equiv., 360 mg, 2.6 mmol) and 10% aq. NaOH (17 ml) were reacted in the usual Schotten Baumann procedure to afford the crude amide which was recrystallised from EtOAc to yield colourless crystals of N-(2-iodobenzyl)-benzamide (300 mg, 40%), m.p. 157-159 °C [lit.[136] m.p. 154 °C]; ν_{max} (Nujol mull): 3260 (N-H stretch), 1635 (C=O stretch) and 1435 cm^{-1} (C-H deformation); δ_H (60 MHz, $CDCl_3$): 4.6 (2H, d, J = 6 Hz, CH_2NH), and 6.35-7.92 (10H, m, aromatic and amide H).

20b. Preparation of N-(2-Bromobenzyl)-benzamide

Benzoyl chloride (1.5 equiv., 4.73g, 33 mmol) was added dropwise to 2-bromobenzylamine hydrochloride (5g, 22 mmol) dissolved in 2N aq. NaOH (100 ml) stirred at room temperature. The reaction mixture was stirred for a further 1.5 h. The crude reaction mixture was poured into Et_2O (150 ml), washed with 2N hydrochloric acid (500 ml), 2N aq. NaOH (200 ml) and water (x2), dried and evaporated to dryness. The crude material was recrystallised from absolute EtOH to give N-(2-bromobenzyl)-benzamide as colourless crystals (4.34g, 67%), m.p. 141-142 °C; Analysis found: C, 58.4; H, 4.3; N, 5.0; Br, 27.8; $C_{14}H_{12}BrNO$ requires: C, 58.2; H, 4.2; N, 4.8; Br, 27.5%; ν_{max} (Nujol mull): 3290 (N-H stretch), 1630 (C=O stretch), 750, 720, 690 and 655 cm^{-1} (4 and 5 adjacent H); δ_H (60 MHz, $CDCl_3$): 4.6-4.7 (2H, d, J = 6 Hz, CH_2) and 6.8-7.9 (10H, m, aromatic and amide H); m/z 210 $[(M-Br)^+, 92\%]$.

21a. Preparation of N-(2-Iodobenzyl)-thiobenzamide

N-(2-Iodobenzyl)-benzamide (700 mg, 2.1 mmol) and Lawesson's reagent (0.7 equiv., 600 mg, 1.5 mmol) were dissolved in deoxygenated toluene (20 ml) under nitrogen. The solvent was heated under reflux for 2 h. as previously described (Expt. 15a) to yield the crude product as a yellow oil on removal of the solvent *in vacuo*. Purification by chromatography (Al_2O_3, basic, Et_2O/pet. ether, 1:1)

afforded N-(2-iodobenzyl)-thiobenzamide as yellow crystals (670 mg, 91%), m.p. 97-100 °C [lit.[137] m.p. 97-110 °C]. The spectroscopic data agreed with that of the literature [137].

21b. Preparation of N-(2-Bromobenzyl)-thiobenzamide using Lawesson's reagent

N-(2-Bromobenzyl)-benzamide (1.54g, 5.31 mmol) and Lawesson's reagent (0.7 equiv., 1.56g, 3.72 mmol) were dissolved in deoxygenated toluene (75 ml) under nitrogen and the reaction heated under reflux for 5 h. The solvent was evaporated *in vacuo* to give a yellow oil which was dissolved in CH_2Cl_2 (10 ml) and chromatographed down a short column (Al_2O_3, basic, CH_2Cl_2). The eluant was evaporated to dryness and recrystallised from absolute EtOH to give N-(2-bromobenzyl)-thiobenzamide (1.34g, 82%), m.p. 87-88 °C; Analysis found: C, 55.1; H, 4.0; N, 4.5; S, 10.2; $C_{14}H_{12}BrNS$ requires: C, 54.9; H, 3.9; N, 4.55; S, 10.45%; ν_{max} (KBr): 3250 (N-H stretch), 1520, 1465 and 1375 (C=S), 750 and 720 cm^{-1} (4 adjacent H); δ_H (60 MHz, $CDCl_3$): 5.0 (2H, d, J = 6 Hz, CH_2) and 7.0-8.2 (10H, m, aromatic H); m/z 226 [(M^+-Br), 100%].

22a. Cyclisation of N-(2-Iodobenzyl)-thiobenzamide

N-(2-Iodobenzyl)-thiobenzamide (600 mg, 1.7 mmol) was dissolved in deoxygenated toluene (75 ml) under nitrogen and the solvent heated to reflux, whereupon Bu_3SnH (1.1 equiv., 524 mg, 1.8 mmol) and AIBN (0.2 equiv., 56 mg, 0.3 mmol) were added. The reaction mixture was maintained at reflux whilst illuminating with light for 24 h. The solvent was removed *in vacuo* to leave a purple-red oil which was distilled to give 2-phenyl-4H-1,3-benzothiazine as a light yellow oil (119 mg, 31%), b.p. (26) 40.8-42.6 °C [lit. [138] b.p. 243-245 °C]. There were some small traces of impurity in the oil even after redistillation. ν_{max} (thin film): 2980-2820 (C-H stretch), 1574 and 1430 cm^{-1} (C=S); δ_H (60 MHz, $CDCl_3$): 4.7 (2H, s, CH_2N); 6.9-7.4 (7H, m, aromatic H) and 7.8-8.0 (2H, m, aromatic H).

22b. Cyclisation of N-(2-Bromobenzyl)-thiobenzamide

N-(2-Bromobenzyl)-thiobenzamide (200 mg, 0.7 mmol) was dissolved in deoxygenated toluene (75 ml) under nitrogen. The solvent was heated to reflux whereupon Bu_3SnH (1.1 equiv., 209 mg, 0.77 mmol) and AIBN (0.2 equiv., 21 mg, 0.13 mmol) were added, and the reaction was illuminated with light for 48 h. The solvent was removed *in vacuo* to leave the crude oil which was distilled to give 2-phenyl-4H-1,3-benzothiazine as a light yellow oil (60 mg, 41%). All spectroscopic data agreed with that of previously prepared material (Expt. 22a).

23. Attempted cyclisation of N-(2-Bromobenzyl)-benzamide using DABCO (1.1 equiv.) in toluene

N-(2-Bromobenzyl)-benzamide (252 mg, 0.97 mmol) was dissolved in deoxygenated toluene (75 ml) under nitrogen and the reaction heated to reflux whilst adding DABCO (1.1 equiv., 147 mg, 0.96 mmol). The reaction was heated under reflux and illuminated for 48 h. The crude material was poured into water (100 ml) and extracted with Et_2O (3 x 50 ml). The organic layers were washed with 2N hydrochloric acid and water (x2), dried, evaporated to dryness, and the residue crystallised from absolute EtOH to give the recovered starting material (230 mg, 91%), m.p. 142-144 °C [lit.[139] m.p. 141-142 °C]; ν_{max} (Nujol mull): 3290 (N-H stretch), 1630 (C=O), 740, 725 and 690 cm^{-1} (4 and 5 adjacent H); δ_H (60 MHz, $CDCl_3$): 4.6-4.8 (2H, d, J = 6 Hz, CH_2); and 6.8-7.9 (10H, m, aromatic and amide H). All spectroscopic data agreed with that of previously prepared material (Expt. 22a).

24. Attempted cyclisation of N-(2-Bromobenzyl)-thiobenzamide using DABCO (1.1 equiv.) in toluene

N-(2-Bromobenzyl)-thiobenzamide (288 mg, 0.94 mmol) was dissolved in deoxygenated toluene (75 ml) under nitrogen and the solvent heated to reflux, whilst adding DABCO (1.1 equiv., 170 mg, 1.03 mmol). The reaction was heated under reflux and illuminated with for 48 h. The crude material was poured into

water (100 ml) and extracted with Et_2O (3 x 50 ml). The organic layers were washed with 2N hydrochloric acid and water (x2), dried, evaporated to dryness, and the residue recrystallised from absolute EtOH to give recovery of starting material (280 mg, 97%), m.p. 88-89 °C [lit.[140] m.p. 87-88 °C]. All spectroscopic data agreed with that of starting material (Expt. 21b).

25. Preparation of N-(2-Iodophenyl)-acetamide

Crotonyl chloride (1.1 equiv., 1.963g, 25 mmol) was added to a solution of 2-iodoaniline (5g, 22.8 mmol) in pyridine (75 ml) over 20 min. at room temperature and the reaction stirred for 24 h. The reaction mixture was poured into water (500 ml) and extracted with Et_2O (4 x 100 ml). The organic layers were washed with 2N hydrochloric acid (x4), 2N aq. NaOH (x4) and water (x3), dried, evaporated to dryness, and the residue recrystallised from absolute EtOH to give N-(2-iodophenyl)-acetamide (1.65g, 28%), m.p. 111-113 °C; Analysis found: C, 36.8; H, 3.1; N, 5.4; I, 48.5; C_8H_8INO required: C, 36.8; H, 3.05; N, 5.35; I, 48.6%; ν_{max} (KBr): 3272 (N-H stretch), 1658 (C=O stretch) and 752 cm^{-1} (4 adjacent H); δ_H (90 MHz, $CDCl_3$): 2.21 (3H, s, CH_3) and 6.68-8.32 (5H, m, aromatic and amide H); m/z 261 (M^+, 24%) and 134 [(M^+-I), 100%].

26. Preparation of N-(2-Iodophenyl)-thioacetamide using Lawesson's reagent

N-(2-Iodophenyl)-acetamide (846 mg, 32.4 mmol) and Lawesson's reagent (0.7 equiv., 916 mg, 2.27 mmol) were dissolved in deoxygenated toluene (75 ml) under nitrogen and the reaction heated under reflux for 6 h. The crude reaction mixture was evaporated to dryness, redissolved in CH_2Cl_2 (20 ml) and chromatographed down a short column (Al_2O_3, basic, CH_2Cl_2). The eluant was evaporated to dryness and the residue recrystallised from water to give N-2-(iodophenyl)-thioacetamide (365 mg, 41%), m.p. 101-102 °C; Analysis found: C, 42.1; H, 3.8; N, 6.3; I, 55.2; S, 14.1; C_8H_8INS requires: C, 42.3; H, 3.4; N, 6.1; I, 55.9; S, 14.1%; ν_{max} (Nujol mull): 3128 (N-H stretch), 1553 (C=S), 770 and 725

cm^{-1} (4 adjacent H); δ_H (60 MHz, $CDCl_3$): 2.3 and 2.8 (3H, 2s, CH_3) and 6.9-8.3 (5H, m, aromatic and amide H); m/z 150 [(M^+-I), 100%].

27. Cyclisation of N-(2-Iodophenyl)-thioacetamide

N-(2-Iodophenyl)-thioacetamide (300 mg, 1.08 mmol) was dissolved in deoxygenated toluene (75 ml) and the solvent heated to reflux whereupon Bu_3SnH (1.1 equiv., 346 mg, 1.18 mmol) and AIBN (0.3 equiv., 53 mg, 0.32 mmol) were added. The reaction was maintained at reflux whilst illuminating for 24 h. The solvent was evaporated *in vacuo* to give a yellow oil which was distilled to give partially purified 2-methylbenzothiazole (250 mg), b.p. (0.7) 120 °C [lit.[141] b.p. 238 °C]. The oil was then dissolved in acetonitrile (20 ml) and washed with pet. ether (4 x 100 ml). The acetonitrile fraction was evaporated *in vacuo* to give a light yellow oil of pure 2-methylbenzothiazole (70 mg, 43%). All spectroscopic data agreed with that of the literature [141].

28. Preparation of N-(2-Iodophenyl)-N-methylacetamide

N-(2-Iodophenyl)-acetamide (3.38g, 12 mmol) in DMSO (10 ml) was added to a stirred suspension of sodium hydride (1.1 equiv., 342 mg, 14 mmol) in DMSO (50 ml) over 20 min. under nitrogen and stirred for a further 1 h. Methyl iodide (2 equiv., 3.42g, 24 mmol) was added to the reaction mixture and stirred for 20 min. The reaction mixture was poured into water (500 ml) and extracted with EtOAc (3 x 25 ml). The organic extract was washed with 2N hydrochloric acid and water, dried, evaporated to dryness, and the residue recrystallised from aqueous MeOH to give N-2-(iodophenyl)-N-methylacetamide (1.49g, 45%), m.p. 60-64 °C; Analysis found: C, 39.3; H, 3.7; N, 5.0; I, 45.1; $C_9H_{10}INO$ requires: C, 39.3; H, 3.6; N, 5.1; I, 45.2%; ν_{max} (KBr): 2924 (C-H stretch), 1646 (C=O stretch) and 776 cm^{-1} (4 adjacent H); δ_H (90 MHz, $CDCl_3$): 1.8 (3H, s, CH_3), 3.2 (3H, s, NCH_3), 6.8-7.5 (3H, m, aromatic H) and 7.7-7.9 (1H, d, J = 8 Hz, *ortho*-H to iodine); m/z 148 [(M^+-I), 100%].

29. Attempted cyclisation of N-(2-Iodophenyl)-N-methylacetamide

N-(2-Iodophenyl)-N-methylacetamide (732 mg, 2.52 mmol) was dissolved in deoxygenated toluene (75 ml) under nitrogen. The solvent was heated to reflux whereupon Bu_3SnH (1.1 equiv., 805 mg, 2.76 mmol) and AIBN (0.3 equiv., 124 mg, 0.75 mmol) were added. The reaction mixture was illuminated whilst maintaining the solvent at reflux for 24 h. The solvent was evaporated *in vacuo* and redissolved in acetonitrile (20 ml) and washed with hexane (4 x 100 ml). The acetonitrile layer was evaporated *in vacuo* to give a red oil and was subjected to preparative t.l.c. (SiO_2, pet. ether/EtOAc, 3:1). No pure material was present in the eluants as shown by t.l.c.

30. Preparation of N-(2-Iodophenyl)-N-methylthioacetamide

N-(2-Iodophenyl)-N-methylacetamide (1.29g, 4.69 mmol) and Lawesson's reagent (0.7 equiv., 1.34g, 3.2 mmol) were stirred in refluxing benzene (75 ml) under nitrogen for 5 h. The solvent was evaporated *in vacuo* and the crude orange oil chromatographed (Al_2O_3, basic, pet. ether/EtOAc, 3:1). The separated material was recrystallised twice form absolute EtOH to give N-(2-iodophenyl)-N-methylthioacetamide (905 mg, 66%), m.p. 120-122 ^oC; Analysis found: C, 37.0; H, 3.5; N, 4.6; S, 11.2; I, 43.0; $C_9H_{10}INS$ requires: C, 37.1; H, 3.45; N, 4.8; S, 11.0; I, 43.65%; ν_{max} (KBr): 1486, 1462 and 1438 (C=S stretch) and 766 cm^{-1} (4 adjacent H); δ_H (90 MHz, $CDCl_3$): 2.3 (3H, s, CH_3), 3.66 (3H, s, NCH_3), 7.0-7.6 (3H, m, aromatic H) and 7.9-8.16 (1H, d, J = 8 Hz, *ortho*-H to iodine); m/z 291 (M^+, 3%) and 164 (82).

31. Attempted cyclisation of N-2-(Iodophenyl)-N-methylthioacetamide

N-(2-Iodophenyl)-N-methylthioacetamide (300 mg, 1.03 mmol) was dissolved in deoxygenated toluene (75 ml) and the solvent heated to reflux under nitrogen whereupon Bu_3SnH (1.1 equiv., 330 mg, 1.1 mmol) and AIBN (0.2 equiv., 34 mg, 0.2 mol) were added. The reaction mixture was maintained at reflux whilst

illuminating with light for 24 h. The solvent was evaporated *in vacuo* and the reaction product analysed by t.l.c. (SiO_2, pet. ether/EtOAc, 2:1). This indicated that the reaction products had decomposed to an intractable gum. Further purification was not pursued.

32a. Preparation of S-(2-Iodobenzyl)-2-imidazolidinethione

2-Iodobenzylbromide (3.04 mg, 10.2 mmol), ethylene thiourea (1.1 equiv., 1.12g, 11 mmol) and absolute ethanol (30 ml) were refluxed for 3 h. and then cooled. The volume of the solvent was reduced to half *in vacuo* and the resulting colourless crystals were collected by filtration and washed with cold ethanol. The hydrobromide salt was obtained as colourless crystals (3.69g, 91%), m.p. 195-200 ^{o}C. The hydrobromide salt (2g, 0.5 mmol) was suspended in water (70 ml) and the mixture acidified to pH 3 with concentrated hydrochloric acid to aid dissolution. Solid $NaHCO_3$ was added to the mixture to bring the pH up to 8-9. The resulting mixture was extracted with CH_2Cl_2 (3 x 20 ml). The organic extracts were washed with water (x2), dried, and the solvent evaporated *in vacuo* to yield S-(2-iodobenzyl)-2-imidazolidinethione as colourless crystals after recrystallisation from absolute EtOH (1.44g, 90%), m.p. 98-99 ^{o}C [lit.[142] m.p. 98-101 ^{o}C]; ν_{max} (Nujol mull): 3160 (N-H stretch), 1670 (C=N stretch), 1440 (C-H deformation) and 765 cm^{-1}; δ_H (60 MHz, $CDCl_3$): 3.62 (4H, s, $\underline{CH_2}\underline{CH_2}$), 4.07 (1H, brs, amide H), 4.37 (2H, s, $\underline{CH_2}S$) and 6.7-7.9 (4H, m, aromatic H).

32b. Preparation of S-(2-Bromobenzyl)-2-imidazolidinethione

A similar procedure was used as detailed in Expt. 32a. The hydrobromide salt was obtained as colourless crystals (81%), m.p. 195-200 ^{o}C and S-(2-bromobenzyl)-2-imidazolidinethione in a good yield (99%), m.p. 95-98 ^{o}C; Analysis found: C, 44.6; H, 4.0; N, 10.5; Br, 29.6; $C_{10}H_{11}BrN_2S$ requires: C, 44.3; H, 4.05; N, 10.35; Br, 29.5%; ν_{max} (Nujol mull): 3160 (N-H stretch), 1665 (C=N stretch), 1440 (C-H deformation) and 765 cm^{-1} (4 adjacent H); δ_H (60 MHz, $CDCl_3$): 3.62 (4H, s, $\underline{CH_2}\underline{CH_2}$), 4.07 (1H, brs, amide H), 4.37 (2H, s, $\underline{CH_2}S$) and 6.67-7.9 (4H, m,

aromatic H); m/z 191 [(M^+-Br), 100%].

33a. Attempted cyclisation of S-2-(Iodobenzyl)-2-imidazolidinethione

S-(2-Iodobenzyl)-2-imidazolidinethione (947 mg, 3 mmol) was dissolved in deoxygenated toluene (75 ml) and the solvent heated to reflux under nitrogen whereupon Bu_3SnH (1.1 equiv., 952 mg, 3.27 mmol) and AIBN (0.2 equiv., 97 mg, 0.6 mmol) were added. The reaction mixture was maintained at reflux whilst illuminating with light for 24 h. The solvent was evaporated *in vacuo* and the resulting creamy coloured gum was triturated with hexane and subsequently washed several times with cold hexane. The product was filtered to yield a cream coloured powder (476 mg). However, on continued exposure to the atmosphere a thiol-like smell was evolved. The product eluded characterisation due to its instability.

33b. Attempted cyclisation of S-(2-Bromobenzyl)-2-imidazolidinethione

The same conditions as used for the iodo derivative (Expt. 33a) were used. An intractable gum ensued on work up and eluded characterisation.

34. Preparation of N-(2-Iodophenyl)-N-methylbenzamide

To a stirred solution of sodium hydride (1.65g, 86 mmol) in DMSO (150 ml) was added N-(2-iodophenyl)-benzamide in DMSO (20 ml). The reaction mixture was stirred at room temperature for 2 h. under nitrogen until an orange colour was formed. The addition of methyl iodide (1.5 equiv., 13.2g, 93 mmol) caused the colour to subside and the mixture was stirred for a further 1 h. The crude reaction mixture was poured into water (200 ml) and extracted with EtOAc (3 x 50 ml). The organic layer was washed with water (x7), dried and the solvent removed *in vacuo* to give crude material (17.2g). This was recrystallised from absolute EtOH to give N-(2-iodophenyl)-N-methylbenzamide (13.7g, 66%), m.p. 138-139 °C; Analysis found: C, 49.9; H, 3.6; N, 4.2; I, 38.0; $C_{14}H_{12}INO$ requires: C, 49.85; H,

3.55; N, 4.15; I, 37.7%; ν_{max} (KBr): 2950 (N-CH_3 stretch), 1628 (C=O stretch), 772, 724 and 710 cm^{-1} (4 and 5 adjacent H); δ_H (60 MHz, $CDCl_3$): 3.4 (3H, s, CH_3) and 6.5-8.0 (9H, m, aromatic H); m/z 210 (M^+I, 96%), 105 (100) and 77 (48).

35. Preparation of N-Methyl-6(5H)-Phenanthridinone

6(5H)-Phenanthridinone (500g, 2.56 mmol) in DMF (10 ml) was added dropwise over 15 min. to a suspension of sodium hydride (1.1 equiv., 67 mg, 2.8 mmol) in DMF (40 ml) under nitrogen. The reaction was stirred for 2 h., methyl iodide (1.1 equiv., 399 mg, 2.8 mmol) added, and stirred overnight. The crude product was poured into water (500 ml) and extracted with CH_2Cl_2 (3 x 20 ml). The organic layer was washed with water (x7), dried, evaporated to dryness and the residue recrystallised from absolute EtOH to give N-methyl-6(5H)-phenanthridinone (300 mg, 56%), m.p. 108.5 °C; Analysis found: C, 80.0; H, 5.5; N, 6.6; $C_{14}H_{11}NO$ requires: C, 80.3; H, 5.26; N, 6.6%; ν_{max} (CH_2Cl_2) 2980-2860 (C-H and N-CH_3 stretch), 1650 (C=O stretch), 770, 720 and 650 cm^{-1} (4 adjacent H); δ_H (60 MHz, $CDCl_3$): 3.75 (3H, s, N-CH_3), 7.05-7.75 (5H, m, aromatic H), 8.05-8.25 (2H, d, J = 8 Hz, aromatic H) and 8.35-8.55 (1H, d, J = 8 Hz, aromatic H); m/z 209 (M^+, 100%), 178 (22), 152 (15) and 113 (10).

36. Cyclisation of N-(2-Iodophenyl)-N-methylbenzamide

N-(2-Iodophenyl)-N-methylbenzamide (562 mg, 1.7 mmol) was dissolved in deoxygenated toluene (50 ml) and the reaction heated to reflux under nitrogen whereupon Bu_3SnH (1.1 equiv., 533 mg, 1.9 mmol) and AIBN (0.2 equiv., 56 mg, 0.34 mmol) were added. The reaction mixture was illuminated and maintained at reflux for 24 h. The solvent was evaporated *in vacuo* to give a brown oil which was dissolved in acetonitrile (50 ml) and washed with pet. ether (4 x 20 ml). The acetonitrile fraction was evaporated *in vacuo* and the material chromatographed (SiO_2, flash, pet. ether, followed by pet. ether/EtOAc, 3:1) to give N-methyl-6(5H)-phenanthridinone (153 mg, 45%), m.p. 88-92 °C [lit.[143] m.p. 108.5 °C]. All spectroscopic data agreed with that of authentic material (Expt. 35).

37. Attempted cyclisation of N-(2-Iodophenyl)-N-methylbenzamide using DABCO (1.1 equiv.) and AIBN (0.2 equiv.) in toluene

N-(2-Iodophenyl)-N-methylbenzamide (400 mg, 1.22 mmol) was dissolved in deoxygenated toluene (50 ml). The reaction was heated to reflux whereupon DABCO (1.1 equiv., 150 mg, 1.34 mmol) and AIBN (0.2 equiv., 40 mg, 0.24 mmol) were added. The solvent was maintained at reflux and illuminated for 24 h. The solvent was evaporated to dryness and the residue recrystallised from pet. ether/EtOH to give recovered N-(2-iodophenyl)-N-methylbenzamide (217 mg, 52% recovery), m.p. 130-132 °C [lit. [144] m.p. 138-139 °C]. All spectroscopic data agreed with that of authentic material (Expt. 34).

38. Attempted cyclisation of N-(2-Iodophenyl)-N-methylbenzamide using Bu_3SnH (0.1 equiv.), AIBN (0.2 equiv.) and DABCO (1.1 equiv.) in toluene

N-(2-Iodophenyl)-N-methylbenzamide (300 mg, 0.92 mmol) was dissolved in deoxygenated toluene (50 ml) and the reaction heated to reflux whereupon Bu_3SnH (0.1 equiv., 26 mg, 0.09 mmol), AIBN (0.2 equiv., 30 mg, 0.18 mmol) and DABCO (1.1 equiv., 113 mg, 1.01 mmol) were added. The solvent was maintained at reflux whilst illuminating for 24 h. The solvent was filtered and the filtrate evaporated to dryness and the resulting N-(2-iodophenyl)-N-methylbenzamide recrystallised from pet. ether/EtOH (80 mg, 27% recovery), m.p. 130-132 °C [lit.[142] m.p. 138-139 °C]. All spectroscopic data agreed with that of authentic material (Expt. 34).

39. Attempted cyclisation of N-(2-Iodophenyl)-N-methylbenzamide using Bu_3SnCl (0.1 equiv.), $NaBH_4$ (1.1 equiv.) and AIBN (0.2 equiv.) in toluene

N-(2-Iodophenyl)-N-methylbenzamide (300 mg, 0.92 mmol) was dissolved in deoxygenated toluene (50 ml) and the solvent heated to reflux whereupon Bu_3SnCl (0.1 equiv., 30 mg, 0.09 mmol), $NaBH_4$ (1.1 equiv., 38 mg, 1.09 mmol) and AIBN (0.2 equiv., 30 mg, 0.18 mmol) were added. The solvent was maintained at reflux and illuminated for 24 h. The solvent was filtered, evaporated to dryness and the resulting N-(2-iodophenyl)-N-methylbenzamide recrystallised from absolute EtOH

(195 mg, 58% recovery), m.p. 131-132 °C [lit.[145] m.p. 138-139 °C]. All spectroscopic data agreed with that of authentic material (Expt. 34).

40a. Preparation of N-Methyl-N-phenyl-2-iodobenzamide

The sodium salt of 2-iodobenzoic acid (6g, 22 mmol) was suspended in toluene (70 ml) to which pyridine (0.5 equiv., 87 mg, 1.1 mmol) and oxalyl chloride (2.2 equiv., 7g, 48 mmol) were added. The reaction was heated under reflux for 2 h. The reaction mixture was filtered and the solvent removed *in vacuo*. The crude acid chloride was distilled to give the pure acid chloride (5.15g, 19 mmol), b.p. (27) 159 °C, which crystallised on cooling.

The acid chloride (5.15g, 19 mmol) was dissolved in toluene (30 ml) heated to reflux, whilst adding N-methylaniline (1.1 equiv., 2.24g, 21 mmol) over 15 min. The reaction was allowed to cool and poured into water (150 ml), washed with water (x3), dried and evaporated *in vacuo* to give a brown oil which was recrystallised from pet. ether to give N-methyl-N-phenyl-2-iodobenzamide (5.33g, 83%), m.p. 69-70.5 °C [lit.[146] m.p. 69-71 °C]; ν_{max} (thin film): 3058-2932 (C-H and N-CH_3 stretch), 1662 (C=O stretch), 740 and 638 cm^{-1} (4 and 5 adjacent H); δ_H (60 MHz, $CDCl_3$): 3.0 (3H, s, N-CH_3) and 6.5-7.97 (9H, m, aromatic H).

40b. Preparation of 2-Bromophenyl-N-methylbenzamide

To a suspension of 2-bromobenzoic acid (4.64g, 23 mmol) in toluene (75 ml) was added oxalyl chloride (2.5 equiv., 7.27g, 50 mmol). The reaction was heated under reflux for 2 h. under nitrogen. The solvent was removed *in vacuo* and the crude material distilled to give the pure acid chloride (2.92g, 58%) [b.p. (1) 30 °C]. The acid chloride (2.92g, 13 mmol) was dissolved in toluene (70 ml) and pyridine (10 ml) and N-methylaniline (1.4g, 13 mmol) added dropwise in toluene (70 ml). The reaction was stirred for 3 h. The crude material was poured into water (100 ml) and extracted with CH_2Cl_2 (3 x 50 ml). The organic layer was washed with 2N hydrochloric acid, 2N aq. NaOH solution, and water (x2), dried and evaporated to dryness. The residue was recrystallised from a pet. ether/EtOH mixture to give

methyl-N-phenyl-2-bromo-N-benzamide as colourless crystals (1.7g, 45%), m.p. 51-52 °C; Analysis found: C, 57.5; H, 4.1; N, 4.5; Br, 27.3; $C_{14}H_{12}BrNO$ requires: C, 57.9; H, 4.1; N, 4.8; Br, 27.6%; ν_{max} 3056-2980 (C-H and N-CH_3 stretch), 1652 (C=O stretch), 770, 748, 732, 698, 672 and 640 cm^{-1} (4 and 5 adjacent H); δ_H (60 MHz, $CDCl_3$): 3.5 (3H, brs, N-CH_3), 6.9-7.73 (9H, m, aromatic H); m/z 290 (M^+, 5%), 210 [$(M-Br)^+$, 22%] and 183 [$(C_7H_4BrO)^+$, 100%].

41. Cyclisation of N-Methyl-N-phenyl-2-iodobenzamide

N-Methyl-N-phenyl-2-iodobenzamide (482 mg, 1.4 mmol) was dissolved in deoxygenated toluene (75 ml) under nitrogen. The solvent was heated to reflux whereupon DABCO (1 equiv., 160 mg, 1.4 mmol) and AIBN (0.2 equiv., 5 mg, 0.28 mmol) were added. The reaction mixture was evaporated *in vacuo* to yield the crude material to which was added phthalide as an N.M.R. spike and analysed by N.M.R. This gave the cyclised product, N-methyl-phenanthridinone (15%) and recovery of starting material (38%).

42. Preparation of N-(2-Bromobenzyl)-N-methylbenzamide

N-(2-Bromobenzyl)-benzamide (1.733g, 5.98 mmol) in DMF (10 ml) was added to a suspension of sodium hydride (1.1 equiv., 151 mg, 6.6 mmol) in DMF (60 ml) under nitrogen at 0 °C. The reaction mixture was stirred for 2 h., methyl iodide (2 equiv., 1.87g, 13 mmol) added dropwise over 15 min., and stirred for a further 2 h. The reaction mixture was poured into water (500 ml) and extracted with Et_2O (3 x 75 ml). The organic layers were washed with water (x7), dried, evaporated to dryness, and recrystallised from absolute EtOH to give N-(2-bromobenzyl)-N-methylbenzamide (1.118g, 65%), m.p. 70-71 °C; Analysis found: C, 59.3; H, 4.6; N, 4.7; Br, 26.3; $C_{15}H_{14}BrNO$ requires: C, 59.2; H, 4.6; N, 4.6; Br, 26.3%; ν_{max} (KBr): 1620 (C=O stretch), 1450 (C-H deformation), 755, 700 and 670 cm^{-1} (4 and 5 adjacent H); δ_H (60 MHz, $CDCl_3$): 3.0 (3H, s, N-CH_3), 4.5-5.0 (2H, brs, CH_2) and 7.0-8.2 (9H, m, aromatic H); m/z 304 (M^+, 3%), and 224 [$(M-Br)^+$, 100%].

43. Preparation of N-(2-Bromobenzyl)-N-methylthiobenzamide

N-(2-Bromobenzyl)-N-methylbenzamide (417 mg, 1.37 mmol) and Lawesson's reagent (0.7 equiv., 388 mg, 0.925 mmol) were dissolved in deoxygenated toluene (75 ml) and the reaction heated under reflux under nitrogen for 5 h. The solvent was evaporated *in vacuo* to give a yellow oil, which was redissolved in CH_2Cl_2 (25 ml) and chromatographed through a short column (Al_2O_3, neutral, CH_2Cl_2). The solvent was evaporated *in vacuo* to give N-(2-bromobenzyl)-N-methylthiobenzamide as a light yellow gum (400 mg, 91%); Analysis found: C, 56.3; H, 4.7; N, 4.35; S, 10.05; $C_{15}H_{14}BrNS$ requires: C, 56.25; H, 4.35; N, 4.35; S, 10.0%; ν_{max} (thin film): 1469 and 1396 (C=S), 762, 736, 698 and 662 cm^{-1} (4 and 5 adjacent H); δ_H (60 MHz, $CDCl_3$): 3.0 (3H, s, N-CH_3), 4.6-5.0 (2H, brs, CH_2) and 6.9-7.7 (9H, m, aromatic H); m/z 240 [(M^+-Br), 100%].

44. Preparation of N-(2-Iodophenyl)-2,3-methylenedioxybenzamide

Piperonylic acid (4.09g, 25 mmol) was dissolved in thionyl chloride (100 ml) and then reacted under reflux for 5 h. under nitrogen. The solvent was removed *in vacuo* to leave a crude oil which was distilled to give the pure piperonyl chloride (3.131g, 84%) [b.p. (0.5) 40 °C] which crystallised on cooling, m.p. 78-79 °C [lit. [147] m.p. 80 °C].

The acid chloride (3.131g, 17 mmol) was added dropwise to a solution of 2-iodoaniline (1.1 equiv., 4.09g, 18.7 mmol) and pyridine (5 ml) in toluene (70 ml) under nitrogen. The reaction mixture was stirred for 2 h., poured into water (500 ml), washed with 2N hydrochloric acid, 2N aq. NaOH and water (x2), dried, evaporated to dryness, and the residue recrystallised from absolute EtOH to give N-(2-iodophenyl)-2,3-methylenedioxybenzamide (2.373g, 38%), m.p. 123-124 °C; Analysis found: C, 45.5; H, 2.9; N, 3.85; I, 34.6; $C_{14}H_{10}INO_3$ requires: C, 45.8; H, 2.7; N, 3.8; I, 34.95%; ν_{max} (Nujol mull): 3200 (N-H stretch), 1645 (C=O stretch), 755, 725 and 680 cm^{-1} (4 adjacent H); δ_H (60 MHz, $CDCl_3$): 6.0-6.1 (2H, s, CH_2) and 6.6-8.5 (8H, m, aromatic and amide H); m/z 367 (M^+, 10%), 240 [(M^+-I),

37%], 149 (100), 121 (18), 91 (12) and 65 (19).

45. Preparation of N-(2-Iodophenyl)-N-methyl-2,3-methylenedioxybenzamide

N-(2-Iodophenyl)-2,3-methylenedioxybenzamide (12.75g, 35 mmol) in DMF (10 ml) was added dropwise to a suspension of sodium hydride (1.1 equiv., 924 mg, 39 mmol) in DMF (75 ml) under nitrogen at 0 °C. The reaction mixture was stirred for 2 h., methyl iodide (2 equiv., 9.94g, 70 mmol) added, and the reaction mixture stirred for 2 h., gradually allowing the reaction mixture to reach room temperature. The crude material was poured into water (500 ml) and extracted with CH_2Cl_2 (4 x 50 ml). The organic layers were washed with water (x7), dried, evaporated to dryness, and the residue recrystallised from absolute EtOH to give N-(2-iodophenyl)-N-methyl-2,3-methylenedioxybenzamide (7.15g, 54%), m.p. 97-97.5 °C; Analysis found: C, 47.5; H, 3.3; N, 3.7; I, 33.7; $C_{15}H_{12}INO_3$ requires: C, 47.25; H, 3.15; N, 3.65; I, 33.35%; ν_{max} (Nujol mull): 1640 (C=O stretch), 750 and 715 cm^{-1} (4 adjacent H); δ_H (60 MHz, $CDCl_3$): 3.4 (3H, s, N-CH_3), 5.9 (2H, s, CH_2) and 6.3-7.9 (7H, m, aromatic H); m/z 252 [(M^+-I), 100%].

46a. Cyclisation of N-(2-Iodophenyl)-N-methyl-2,3-methylenedioxybenzamide

N-(2-Iodophenyl)-N-methyl-2,3-methylenedioxybenzamide (244 mg, 0.64 mmol) was dissolved in deoxygenated toluene (100 ml) under nitrogen. The solvent was heated to reflux and Bu_3SnH (1.1 equiv., 205 mg, 0.70 mmol) and AIBN (0.2 equiv., 21 mg, 0.128 mmol) added. The reaction mixture was illuminated whilst maintaining the solvent at reflux for 48 h. The solvent was evaporated to dryness and the crude material recrystallised from absolute EtOH to give 5-methyl-2,3-methylenedioxy-phenanthridinone (47 mg, 29%), m.p. 245-247 °C [lit.[148] m.p. 244-245 °C]; ν_{max} (KBr): 2785 (C-H stretch), 1647 (C=O stretch), 778, 757 and 736 cm^{-1} (4 adjacent H); δ_H (60 MHz, $CDCl_3$): 3.8 (3H, s, N-CH_3), 6.2 (2H, s, CH_2) and 7.2-8.2 (6H, m, aromatic H); m/z 253 (M^+, 100%).

46b. Attempted cyclisation of N-(2-Iodophenyl)-N-methyl-2,3-methylenedioxybenzamide Using U.V. Light in toluene

N-(2-Iodophenyl)-N-methyl-2,3-methylenedioxybenzamide (32 mg, 0.08 mmol) in toluene (75 ml) under nitrogen was irradiated with U.V. light (Hanovia 1 litre photochemical reactor, medium pressure, 100 W) for 25 h. The crude reaction mixture was evaporated *in vacuo*. The crude semi-solid was redissolved in CH_2Cl_2 (70 ml), washed with a saturated solution of sodium metabisulphite, saturated aq. $NaHCO_3$ and water, dried, evaporated to dryness, and the residue recrystallised from absolute EtOH to give the unaltered starting material (19 mg, 59% recovery), m.p. 90-94 °C. All spectroscopic data agreed with that of the starting material (Expt. 46a).

47. Attempted reduction of 5-Methyl-2,3-methylenedioxy-phenanthridinone to Ismine using a $LiAlH_4$ in THF/water mixture

5-Methyl-2,3-methylenedioxy-phenanthridinone (1 equiv., 99 mg, 3.9 mmol) was added to a suspension of $LiAlH_4$ (2 equiv., 297 mg, 7.8 mmol) in THF (60 ml) and the reaction kept under nitrogen for 1 h. To the stirred suspension was then added water (2 ml) and the reaction stirred for a further 24 h. under nitrogen. The material was then quenched by careful addition of water until a gelatinous white precipitate formed, then 2N hydrochloric acid was added until pH 5 was reached. The mixture was filtered and extracted with CH_2Cl_2 (5 x 50 ml). The organic layer was then washed with water (x4), dried, evaporated to dryness and recrystallised from n-hexane/benzene mixture to give the non-ring closed reduced material, 2,3-methylenedioxy-5,6-dihydrophenanthridinone (65 mg, 70%), m.p. 84-85 °C; Analysis found: C, 75.0; H, 5.3; N, 5.7; $C_{15}H_{13}NO_3$ requires: C, 75.3; H, 5.4; N, 5.0%; ν_{max} (CH_2Cl_2) 2890-2790 (C-H stretch and N-CH_3 stretch), 1605-1600 (C-H deformation), 750 and 740 cm^{-1} (4 adjacent H); δ_H (60 MHz, $CDCl_3$/d^6-DMSO) 2.9 (3H, s, N-CH_3), 4.1 (2H, s, CH_2), 5.9 (2H, s, O-CH_2O), 6.5-7.55 (6H, m, aromatic H); m/z 239 (M^+, 100%).

48a. Preparation of N-(2-Iodophenyl)-N-methylthiobenzamide

N-(2-Iodophenyl)-N-methylbenzamide (4g, 12 mmol) and Lawesson's reagent (0.7 equiv., 3.46g, 8.5 mmol) were dissolved in toluene (75 ml) and heated to reflux under nitrogen for 6 h. The solvent was removed *in vacuo* and the resulting crude yellow oil chromatographed (Al_2O_3, basic, pet. ether/EtOAc, 1:1). The eluant was removed *in vacuo* and the crude material was recrystallised from aqueous EtOH to give N-(2-iodophenyl)-N-methylthiobenzamide (2.1g, 50%), m.p. 140-141 °C; Analysis found: C, 47.8; H, 3.6; N, 4.1; I, 35.6; S, 8.8; $C_{14}H_{12}INS$ requires: C, 47.59; H, 3.4; N, 3.95; I, 36.0; S, 9.06%; ν_{max} (KBr): 2920 (N-CH_3 stretch), 1570, 1470, 1375 (C=S stretch), 765 and 720 cm^{-1} (4 and 5 adjacent H); δ_H (90 MHz, $CDCl_3$): 3.4 and 3.8 (total 3H, 2 x s, CH_3) and 6.65-8.2 (9H, m, aromatic H); m/z 226 [(M-I)$^+$, 100%].

48b. Preparation of N-(2-Bromophenyl)-N-methylthiobenzamide

A solution of N-(2-bromophenyl)-N-methylbenzamide (2.064g, 7.11 mmol) and Lawesson's reagent (0.7 equiv., 2.013g, 5 mmol) in toluene (75 ml) were heated to reflux over 6 h. under nitrogen. The solvent was removed *in vacuo* and the resulting crude yellow oil dissolved in CH_2Cl_2 (10 ml) and chromatographed (Al_2O_3, basic, CH_2Cl_2). The crude eluant was evaporated to dryness and recrystallised from pet. ether/toluene to give N-(2-bromophenyl)-N-methyl-thiobenzamide (1.14g, 43%), m.p. 110-111 °C; Analysis found: C, 48.0; H, 3.4; N, 3.95; S, 9.4; $C_{14}H_{12}BrNS$ requires: C, 47.6; H, 3.4; N, 3.95; S, 9.0%; ν_{max} (Nujol mull): 1460, 1375 and 1305 (C=S band), 760, 725 and 700 cm^{-1} (4 and 5 adjacent H); δ_H (60 MHz, $CDCl_3$): 3.8 (3H, s, CH_3) and 6.9-7.85 (9H, m, aromatic H); m/z 226 [(M^+-Br), 100%].

49. Preparation of N-Methyl-6(5H)-thiophenanthridinone

N-Methyl-6(5H)-phenanthridinone (118 mg, 0.565 mmol) was added to a deoxygenated solution of Lawesson's reagent (0.7 equiv., 160 mg, 3.95 mmol) in

toluene (40 ml) and heated under reflux for 4 h. The toluene was removed *in vacuo* to give an oil which was chromatographed down a short column (Al_2O_3, basic, CH_2Cl_2). The eluant was evaporated to dryness and the residue recrystallised from absolute EtOH to give N-methyl-6(5H)-thiophenanthridinone (32 mg, 25%), m.p. 194-195 °C; Analysis found: C, 74.5; H, 5.1; N, 6.2; S, 15.4; $C_{14}H_{11}NS$ requires: C, 74.6; H, 4.8; N, 6.2; S, 14.2%; ν_{max} (Nujol mull): 1455, 1375 and 1335 (C=S), 740 and 710 cm^{-1} (4 adjacent H); δ_H (60 MHz, $CDCl_3$): 4.35 (3H, s, N-CH_3), 7.3-7.9 (5H, m, aromatic H), 8.1-8.2 (2H, t, J = 8 Hz, aromatic H) and 9.0-9.3 (1H, d, J = 8 Hz, aromatic H); m/z 225 (M^+, 100%).

50a. Cyclisation of N-(2-Iodophenyl)-N-methylthiobenzamide

N-(2-Iodophenyl)-N-methylthiobenzamide (300 mg, 0.85 mmol) was dissolved in deoxygenated toluene (75 ml) under nitrogen. The solvent was heated to reflux whereupon Bu_3SnH (1.1 equiv., 272 mg, 99.3 mmol) and AIBN (0.1 equiv., 14 mg, 0.085 mmol) were added. The reaction mixture was evaporated *in vacuo* to yield semi-crystalline material which was recrystallised from pet. ether/toluene to give N-methyl-6(5H)-thiophenanthridinone (53 mg, 29%), m.p. 103-105 °C [lit.[149] m.p. 108.5 °C]; ν_{max} (Nujol mull): 1645 (C=O stretch), 745, 725 and 685 cm^{-1} (4 adjacent H); δ_H (60 MHz, $CDCl_3$): 3.8 (3H, s, N-CH_3) and 7.1-8.7 (9H, m, aromatic H); m/z 209 (M^+, 100%).

50b. Cyclisation of N-(2-Iodophenyl)-N-methylthiobenzamide using Bu_3SnH (0.1 equiv.) and AIBN (0.2 equiv.) in toluene

A similar procedure was used to that described above (Expt. 50a). N-(2-Iodophenyl)-N-methylthiobenzamide (300 mg, 0.85 mmol) was dissolved in deoxygenated toluene and the solvent heated to reflux whereupon Bu_3SnH (0.1 equiv., 25 mg, 0.85 mmol) and AIBN (0.2 equiv., 27 mg, 0.17 mmol) were added. The solvent was maintained at reflux and illuminated for 24 h. The solvent was evaporated *in vacuo* to give a semi-crystalline material which was crystallised from absolute EtOH to give 2-phenylbenzothiazole (30%), m.p. 115-116 °C [lit.[150] m.p.

111-113 °C]. All spectroscopic data agreed with that of the literature [150].

50c. Cyclisation of N-(2-Iodophenyl)-N-methylthiobenzamide using Bu_3SnH (0.1 equiv.), DABCO (1.1 equiv.) and AIBN (0.3 equiv.) in toluene

N-(2-Iodophenyl)-N-methylthiobenzamide (300 mg, 0.85 mmol) was dissolved in deoxygenated toluene and the solvent heated to reflux whereupon Bu_3SnH (0.1 equiv., 25 mg, 0.85 mmol), DABCO (1.1 equiv., 104 mg, 0.94 mmol) and AIBN (0.3 equiv., 42 mg, 0.26 mmol) were added. The solvent was maintained at reflux and the reaction illuminated for 24 h. The solvent was evaporated *in vacuo* to give a semi-crystalline material which was crystallised from absolute EtOH to give 2-phenylbenzothiazole (24%), m.p. 107-110 °C [lit.[151] m.p. 111-113 °C]. All spectroscopic data agreed with that of the literature [151].

50d. Cyclisation of N-(2-Iodophenyl)-N-methylthiobenzamide using DABCO (1.1 equiv.) and AIBN (0.3 equiv.) in toluene

N-(2-Iodophenyl)-N-methylthiobenzamide (300 mg, 0.85 mmol) was dissolved in deoxygenated toluene and the solvent brought to reflux whereupon DABCO (1.1 equiv., 104 mg, 0.94 mmol) and AIBN (0.3 equiv., 42 mg, 0.26 mmol) were added. The solvent was evaporated *in vacuo* to give a semi-crystalline material which was crystallised from absolute EtOH to give 2-phenylbenzothiazole (47%), m.p. 115-117 °C [lit.[152] m.p. 111-113 °C]. All spectroscopic data agreed with that of the literature [152].

51. Cyclisation of N-(2-Bromophenyl)-N-methylthiobenzamide

N-(2-Bromophenyl)-N-methylthiobenzamide (400 mg, 13 mmol) was dissolved in deoxygenated toluene and the solvent heated whereupon Bu_3SnH (1.1 equiv., 418 mg, 14.4 mmol) and AIBN (0.3 equiv., 64 mg, 3.9 mmol) were added. The solvent was evaporated *in vacuo* to give a semi-crystalline material which was recrystallised from pet. ether/toluene to give N-methyl-6(5H)-thiophenanthridinone in moderate yield (13%), m.p. 188-189 °C [lit.[153] m.p. 194-195 °C]. All spectroscopic data

agreed with that of an authentic sample [153].

52a. Cyclisation of N-(2-Bromophenyl)-N-methylthiobenzamide using DABCO (1.1 equiv.)

N-(2-Bromophenyl)-N-methylthiobenzamide (400 mg, 13 mmol) and DABCO (1.1 equiv., 161 mg, 14.4 mmol) were dissolved in deoxygenated toluene under nitrogen and the reaction heated under reflux whilst illuminating with light for 48 h. The solvent was evaporated *in vacuo* and the resulting crude residue recrystallised from absolute EtOH to give 2-phenylbenzothiazole (99%), m.p. 109-111 °C [lit.[154] m.p. 111-113 °C]. All spectroscopic data agreed with that of the literature [154].

52b. Cyclisation of N-(2-Bromophenyl)-N-methylthiobenzamide using Bu_3SnH (0.1 equiv.), AIBN (0.2 equiv.) and DABCO (1.1 equiv.) in toluene

N-(2-Bromophenyl)-N-methylthiobenzamide (400 mg, 13 mmol) was dissolved in deoxygenated toluene under nitrogen and the reaction was heated to reflux whereupon Bu_3SnH (0.1 equiv., 38 mg, 1.3 mmol), AIBN (0.2 equiv., 43 mg, 2.6 mmol) and DABCO (1.1 equiv., 160 mg, 14 mmol) were added. The reaction was heated under reflux and illuminated for 48 h. The resulting crude material was recrystallised from absolute EtOH to give N-methyl-6(5H)-thiophenanthridinone as a light yellow coloured powder (19%), m.p. 194-195 °C [lit.[155] m.p. 194-195 °C]. All spectroscopic data agreed with that of an authentic sample [155].

53a. Preparation of N-(2-Iodophenyl)-pyridine-2-carboxamide

2-Picolinic acid (15g, 0.122 mol) was dissolved in methanol (100 ml) and gaseous HCl bubbled through the solution over a period of 2 h. until the pH of the methanol solution was positively acidic. The methanol was removed *in vacuo* to yield the salt (17.5g, 90%), m.p. 190-200 °C (dec). The hydrochloride salt (17.5g, 0.11 mol) was dissolved in thionyl chloride (150 ml) and the reaction heated under reflux for 4 h. The solvent was removed *in vacuo* and the resulting acid chloride hydrochloride salt subjected to a pressure of 1-2 mm Hg for 1 h. in order to remove

traces of thionyl chloride.

The acid chloride hydrochloride salt was suspended in toluene (60 ml) and 2-iodoaniline (0.8 equiv., 19.28g, 88 mmol) in Et_3N (50 ml) added dropwise over 15 min. A blue precipitate was formed immediately and the reaction was stirred vigorously over 2 h. The crude mixture was poured into water (100 ml) and extracted with CH_2Cl_2 (3 x 50 ml). The organic layers were shaken with 2N aq. NaOH and water, dried, evaporated to dryness, and the residue recrystallised from absolute EtOH to give N-(2-iodophenyl)-pyridine-2-carboxamide (18.2g, 51%), m.p. 135-137 °C; Analysis found: C, 40.0; H, 2.5; N, 8.3; I, 39.0; $C_{12}H_9INO$ requires: C, 44.4; H, 2.8; N, 8.6; I, 39.2%; ν_{max} (KBr): 3270 (N-H stretch), 1685 cm^{-1} (C=O stretch); δ_H (90 MHz, $CDCl_3$): 6.71-8.88 (8H, m, aromatic and heterocyclic H) and 10.5 (1H, brs, amide H); m/z 324 (M^+, 9%) and 197 [(M^+-I), 100%].

53b. Preparation of N-(2-Bromophenyl)-pyridine-2-carboxamide

2-Picolinic acid was treated as described in Expt. 53a and reacted with 2-bromoaniline to give, on recrystallisation from absolute EtOH, N-(2-bromophenyl)-pyridine-2-carboxamide in moderate yield (18%), m.p. 117-120 °C; Analysis found: C, 51.6; H, 3.3; N, 10.4; Br, 28.4; $C_{12}H_9BrNO_2$ requires: C, 52.0; H, 3.3; N, 10.1; Br, 28.8%; ν_{max} (KBr): 3284 (N-H stretch), 1688 (C=O stretch), 752 and 680 cm^{-1} (4 adjacent H); δ_H (60 MHz, $CDCl_3$): 6.7-8.7 (9H, m, aromatic and heterocyclic H) and 10.6 (1H, brs, amide H); m/z 277 (M^+, 4%) and 197 [(M^+Br), 100%].

54. Preparation of N-(2-Iodophenyl)-pyridine-3-carboxamide

2-Iodoaniline (16.2g, 80 mmol) in toluene (10 ml) and Et_3N (10 ml) was added to a stirred suspension of nicotinoyl chloride hydrochloride salt (17.2g, 96 mmol) in toluene (30 ml) at 0 °C. The reaction mixture was stirred overnight and the precipitate was filtered off, redissolved in water (500 ml). The solution was basified with 2N aq. NaOH to pH 11, and extracted with CH_2Cl_2 (3 x 50 ml). The organic layers were dried, evaporated to dryness, and the residue recrystallised

from absolute EtOH to give N-(2-iodophenyl)-pyridine-3-carboxamide (6.25g, 25%), m.p. 142-144 °C; Analysis found: C, 44.65; H, 3.0; N, 8.6; I, 39.35; $C_{12}H_9INO_2$ requires: C, 44.4; H, 2.7; N, 8.64; I, 39.19%; ν_{max} (KBr): 3290 (N-H stretch), 1635 (C=O stretch), 760, 720, 705 and 650 cm^{-1} (4 adjacent H); δ_H (90 MHz, d^6-DMSO/$CDCl_3$): 6.8-9.5 (8H, m, aromatic and heterocyclic H) and 10.5 (1H, brs, amide H); m/z 325 (M^+, 2%) and 197 [(M^+-I), 100%].

55. Preparation of N-(2-Iodophenyl)-N-methylpyridine-2-carboxamide

N-(2-Iodophenyl)-pyridine-2-carboxamide (1g, 3.08 mmol) in DMSO (10 ml) was added dropwise to a suspension of sodium hydride (1.1 equiv., 122 mg, 3.3 mmol) in DMSO (50 ml) at 0 °C under nitrogen and the reaction stirred for 2 h. Methyl iodide (1.5 equiv., 656 mg, 4.62 mmol) was added and the reaction mixture stirred overnight. The crude reaction was poured into water (100 ml) and extracted with CH_2Cl_2 (3 x 50 ml). The organic layers were washed with water (x7), dried, evaporated to dryness, and the residue recrystallised from absolute EtOH to give N-(2-iodophenyl)-N-methylpyridine-2-carboxamide (570 mg, 55%), m.p. 100-105 °C; Analysis found: C, 46.2; H, 3.4; N, 8.4; I, 37.4; $C_{13}H_{12}INO_2$ requires: C, 46.15; H, 3.25; N, 8.28; I, 37.57%; ν_{max} (KBr): 2950-2860 (C-H stretch), 1645 (C=O stretch), 755 and 680 cm^{-1} (4 adjacent H); δ_H (60 MHz, $CDCl_3$): 3.3 (3H, s, N-CH_3) and 6.0-8.2 (10H, m, aromatic and heterocyclic H); m/z 211 [(M^+-Br), 100%].

56. Preparation of N-(2-Iodophenyl)-N-methylpyridine-3-carboxamide

N-(2-Iodophenyl)-pyridine-3-carboxamide (10.3g, 31 mmol) in DMSO (10 ml) was added dropwise to a stirred suspension of sodium hydride (1.1 equiv., 818 mg, 34 mmol) in DMSO (50 ml) at 0 °C under nitrogen. The reaction mixture was stirred for 2 h., methyl iodide (1.2 equiv., 5.28g, 37 mmol) added stirred for a further 2 h. The crude reaction was poured into water (300 ml) and extracted with CH_2Cl_2 (3 x 50 ml). The organic layers were washed with water (x7), dried, evaporated to dryness, and the residue recrystallised from absolute EtOH to give

N-(2-iodophenyl)-N-methylpyridine-3-carboxamide (5.32g, 51%), m.p. 75-80 °C; Analysis found: C, 46.0; H, 3.3; N, 8.2; I, 37.3; $C_{13}H_{12}INO_2$ requires: C, 46.1; H, 3.25; N, 8.28; I, 37.57%; ν_{max} (KBr): 2950-2855 (C-H and N-CH_3 stretch) and 1654-1640 cm^{-1} (C=O stretch); δ_H (90 MHz, $CDCl_3$): 3.25 (3H, s, N-CH_3) and 6.7-8.8 (8H, m, aromatic and heterocyclic H); m/z 339 [(M^++H), 100%].

57. Attempted cyclisation of N-(2-Iodophenyl)-N-methylpyridine-2-carboxamide

N-(2-Iodophenyl)-N-methylpyridine-2-carboxamide (250 mg, 0.74 mmol) was dissolved in deoxygenated toluene (100 ml) under nitrogen. The solvent was heated to reflux whereupon Bu_3SnH (1.1 equiv., 236 mg, 0.81 mmol) and AIBN (0.3 equiv., 3 mg, 0.02 mmol) was added. The reaction was maintained at reflux and illuminated for 24 h. The solvent was evaporated *in vacuo* to give a brown oil which was subjected to preparative t.l.c. (Al_2O_3, pet. ether/EtOAc, 3:1) and indicated a polymeric mixture, which was not pursued.

58. Attempted cyclisation of N-(2-Iodophenyl)-N-methylpyridine-3-carboxamide

The same procedure was carried out as described in Expt. 57. N-(2-Iodophenyl)-N-methylpyridine-3-carboxamide was dissolved in deoxygenated toluene under nitrogen. The solvent was heated to reflux whereupon Bu_3SnH and AIBN were added. The reaction was maintained at reflux and illuminated for 24 h. The solvent was evaporated *in vacuo* to give a dark oil which was subjected to preparative t.l.c. (Al_2O_3, pet. ether/EtOAc, 3:1) and indicated a polymeric mixture, and was not pursued.

59a. Preparation of N-(2-Bromophenyl)-furan-2-carboxamide

2-Furoyl chloride (1.1 equiv., 20.9g, 0.16 mmol) was added dropwise to a stirred suspension of 2-bromoaniline (25g, 0.145 mmol) in 2N aq. NaOH (100 ml). The reaction mixture was stirred overnight and the precipitate filtered off and

recrystallised from pet. ether/Et_2O to give N-(2-bromophenyl)-furan-2-carboxamide (12.637g, 32%), m.p. 94-95 °C; Analysis found: C, 49.9; H, 3.0; N, 5.3; Br, 30.3; $C_{11}H_8BrNO_2$ requires: C, 49.6; H, 3.0; N, 5.25; Br, 30.05%; ν_{max} (KBr): 3200 (N-H stretch), 1690 (C=O stretch), 1570 (C=C stretch) and 780 cm^{-1} (4 adjacent H); δ_H (60 MHz, $CDCl_3$): 6.5-8.9 (9H, m, aromatic, heterocyclic and amide H); m/z 264 (M^+, 10%) and 186 [(M^+-Br), 86%].

59b. Preparation of N-(2-Iodophenyl)-furan-2-carboxamide

The same procedure was used as described in Expt. 59a. 2-Furoic acid and chloride was added dropwise to a stirred suspension of 2-iodoaniline in 2N aq. NaOH. The reaction mixture was stirred overnight and the precipitate filtered off and recrystallised from pet. ether/Et_2O to give N-(2-iodophenyl)-furan-2-carboxamide (33%), m.p. 86-87 °C; Analysis found: C, 42.5; H, 2.7; N, 4.5; I, 40.2; $C_{11}H_7INO_2$ requires: C, 42.2; H, 2.57; N, 4.47; I, 40.55%; ν_{max} (KBr): 3360 (N-H stretch), 3120 (C-H stretch), 1670 (C=O stretch), 1520 (C=C stretch), 770 and 750 cm^{-1} (4 adjacent H); δ_H (90 MHz, $CDCl_3$): 6.52-8.72 (m, aromatic, heterocyclic and amide H), D_2O exchange removed the peak at 8.5; m/z 312 (M^+, 16%) and 186 [(M^+-I), 98%].

60a. Preparation of N-(2-Bromophenyl)-N-methylfuran-2-carboxamide

N-(2-Bromophenyl)-furan-2-carboxamide (3.69g, 14 mmol) in DMF (10 ml) was added dropwise to a stirred suspension of sodium hydride (1.1 equiv., 366 mg, 15 mmol) in DMF (30 ml) and the reaction stirred at 0 °C under nitrogen for 2 h. Methyl iodide (2.2 equiv., 4.374g, 30 mmol) was added and the reaction stirred for a further 2 h. The crude material was poured into water (500 ml) and extracted with CH_2Cl_2 (3 x 50 ml). The organic extracts were washed with water (x7), dried, evaporated to dryness, and the residue recrystallised from pet. ether/Et_2O to give N-(2-bromophenyl)-N-methylfuran-2-carboxamide (3.311g, 85%), m.p. 121-122 °C; Analysis found: C, 51.7; H, 3.65; N, 4.9; Br, 28.4; $C_{12}H_{10}BrNO_2$ requires: C, 51.45; H, 3.65; N, 5.10; Br, 28.55%; ν_{max} (KBr): 2950-2850 (C-H stretch and N-

CH_3), 1640 (C=O stretch), 770 and 740 cm^{-1} (4 adjacent H); δ_H (60 MHz, $CDCl_3$): 3.4 (3H, s, NCH_3), 5.8-6.2 (3H, m, heterocyclic H) and 6.8-7.9 (4H, m, aromatic H); m/z 280 (M^+, 1%) and 200 [(M^+-Br), 100%].

60b. Preparation of N-(2-Iodophenyl)-N-methylfuran-2-carboxamide

The same procedure was used as described in Expt. 60a. N-(2-Iodophenyl)-furan-2-carboxamide in DMF was added dropwise to a stirred suspension of sodium hydride in DMF and the reaction stirred at 0 °C under nitrogen for 2 h. Methyl iodide was added and the reaction stirred for a further 2 h. The crude was poured into water and extracted with CH_2Cl_2. The organic extracts were washed with water, dried, evaporated to dryness, and the residue recrystallised from pet. ether/Et_2O to give N-(2-iodophenyl)-N-methylfuran-2-carboxamide (47%), m.p. 139-141.5 °C; Analysis found: C, 44.5; H, 3.15; N, 4.2; I, 36.2; $C_{12}H_{10}INO_3$ requires: C, 44.0; H, 3.10; N, 4.2; I, 38.8%; ν_{max} (KBr): 3120-2920 (C-H and N-CH_3 stretch), 1630 (C=O stretch), 1560 (C=C stretch), 770, 720 and 700 cm^{-1} (4 adjacent H); δ_H (90 MHz, $CDCl_3$): 3.4 (3H, s, NCH_3), 5.7-6.0 (1H, s, heterocyclic H, position 5), 6.2-6.37 (1H, q, heterocyclic H, position 4), 7.0-7.68 (4H, m, aromatic H) and 7.97-8.14 (1H, d, J = 2.6 Hz, heterocyclic H, position 3); m/z 200 [(M^+-I), 100%] and 95 (48).

61. Preparation of N-(2-Bromophenyl)-furan-2-carboxamide

2-Furoic acid (21g, 0.17 mmol) was dissolved in thionyl chloride (200 ml) and the reaction heated under reflux under nitrogen for 5 h. The crude material was evaporated *in vacuo* and the resulting crude oil distilled to give the pure 2-furoic acid chloride (23g, 94%), b.p. (10) 68 °C [lit.[156] b.p. (10) 66 °C].

2-Furoic acid chloride (1.5 equiv., 4.4g, 33 mmol) was added dropwise to a stirred solution of 2-bromobenzylamine hydrochloride (5g, 22 mmol) in NaOH (3.5 equiv., 3.14g, 77 mmol) in water (100 ml) over 20 min. The reaction mixture was stirred overnight and the precipitate filtered off and recrystallised from pet. ether/Et_2O to give N-(2-bromobenzyl)-furan-2-carboxamide as white crystals

(6.02g, 95%), m.p. 121-122 °C; Analysis found: C, 51.4; H, 3.5; N, 4.8; Br, 29.3; $C_{12}H_{10}BrNO_2$ requires: C, 51.45; H, 3.55; N, 5.0; Br, 28.6%; ν_{max} (KBr): 3250 (N-H stretch), 1645 (C=O stretch), 1575 (C=C stretch) and 750 cm^{-1} (4 adjacent H); δ_H (60 MHz, $CDCl_3$): 4.65-4.75 (2H, d, J = 8 Hz, CH_2) and 6.4-7.71 (8H, m, aromatic, heterocyclic and amide H); m/z 200 [(M^+-Br), 100%] and 95 (67).

62. Preparation of N-(2-Bromobenzyl)-N-methylfuran-2-carboxamide

N-(2-Bromobenzyl)-furan-2-carboxamide (3.692g, 13 mmol) in DMF (10 ml) was added dropwise to a stirred suspension of sodium hydride (1.1 equiv., 334 mg, 15 mmol) in DMF (40 ml). The reaction was stirred for 2 h., methyl iodide (2.2 equiv., 4.124g, 29 mmol) added, and stirred for a further 2 h. The crude material was poured into water (500 ml) and extracted with CH_2Cl_2 (3 x 50 ml). The organic layers were washed with water (x7), dried, evaporated to dryness, and the residue recrystallised from absolute EtOH to give N-(2-bromobenzyl)-N-methylfuran-2-carboxamide (3.22g, 83%), m.p. 96-98 °C; Analysis found: C, 53.4; H, 4.1; N, 4.7; Br, 26.9; $C_{13}H_{12}BrNO_2$ requires: C, 53.05; H, 4.1; N, 4.75; Br, 27.2%; ν_{max} (Nujol mull): 2950-2770 (C-H stretch and N-CH_3), 1630 (C=O stretch), 760 and 660 cm^{-1} (4 adjacent H); δ_H (60 MHz, $CDCl_3$): 3.2 (3H, s, NCH_3), 4.75 (2H, s, CH_2) and 6.15-8.05 (7H, m, aromatic and heterocyclic H); m/z 214 [(M^+-Br), 100%].

63. Attempted cyclisation of N-(2-Iodophenyl)-N-methylfuran-2-carboxamide

N-(2-Iodophenyl)-N-methylfuran-2-carboxamide (535 mg, 1.63 mmol) was added to deoxygenated toluene (70 ml) and the solvent brought to reflux under nitrogen whereupon Bu_3SnH (1.1 equiv., 523 mg, 1.8 mmol) and AIBN (0.1 equiv., 28 mg, 1.63 mmol) were added and the reaction illuminated for 48 h. The solvent was evaporated *in vacuo* to give a semi-crystalline oil. The oil was redissolved in acetonitrile (50 ml) and washed with pet. ether (4 x 20 ml). The acetonitrile portion was evaporated to dryness and the residue recrystallised from aqueous EtOH to give recovered starting material (120 mg, 25% recovery), m.p. 140-142

°C. All the spectroscopic data agreed with that of the starting material (Expt. 60b).

64. Preparation of N-(2-Iodophenyl)-thiophene-2-carboxamide

Thiophene-2-carboxylic acid (21.5g, 0.1 mmol) was dissolved in thionyl chloride (250 ml) and the reaction heated under reflux for 3 h. The solvent was removed *in vacuo* to give a dark oil which was distilled to give 2-thiophenecarbonyl chloride (22.9g, 94%), b.p. (12) 120-125 °C [lit.[157] b.p. 206-208 °C]. The acid chloride was added dropwise to a solution of 2-iodoaniline (1.1 equiv., 37.7g, 0.17 mmol) in toluene (50 ml) and triethylamine (20 ml). The reaction was stirred overnight. The crude material was poured into hexane (100 ml) and the precipitate filtered off. The precipitate was redissolved in CH_2Cl_2 (150 ml) basified with a saturated solution of $NaHCO_3$ to pH 8, washed with water, dried, and the solvent evaporated *in vacuo* to give a red oil, which on cooling, gave a brown solid. The solid was recrystallised from absolute EtOH to give N-(2-iodophenyl)-thiophene-2-carboxamide (26.17g, 51%), m.p. 97.5-98 °C; Analysis found: C, 40.3; H, 2.6; N, 4.3; I, 38.6; S, 9.4; $C_{11}H_8INOS$ requires: C, 40.12; H, 2.43; N, 4.25; I, 38.6; S, 9.72%; ν_{max} (KBr): 3260 (N-H stretch), 1650 (C=O stretch), 1590 (C=C stretch), 750 and 720 cm^{-1} (4 adjacent H); δ_H (90 MHz, $CDCl_3$): 6.6-8.5 (m, aromatic, heterocyclic and amide H); m/z 329 (M^+, 1%), 202 [(M^+-I), 66%] and 110 (100).

65. Preparation of N-(2-Iodophenyl)-N-methylthiophene-2-carboxamide

N-(2-Iodophenyl)-thiophene-2-carboxamide (20.34g, 62 mmol) in DMSO (20 ml) was added dropwise to a stirred suspension of sodium hydride (1.1 equiv., 1.63g, 68 mmol) in DMSO (100 ml) over a period of 20 min. under nitrogen and the reaction stirred for 1 h. Methyl iodide (1.5 equiv., 13.18g, 92 mmol) was added and the reaction stirred for a further 1 h. The crude product was then poured into water (x7), dried, evaporated to dryness, and the residue recrystallised from absolute EtOH to give N-(2-iodophenyl)-N-methylthiophene-2-carboxamide as light brown crystals (125.09g, 75%), m.p. 110-112 °C; Analysis found: C, 42.3; H,

3.2; N, 4.2; I, 36.6; S, 9.0; $C_{12}H_{10}INOS$ requires: C, 41.92; H, 2.91; N, 4.07; I, 36.97; S, 9.31%; ν_{max} (KBr): 2950 (C-H and N-CH_3 stretch), 1620 (C=O stretch), 1520 (C=C stretch), 746 and 720 cm^{-1} (4 adjacent H); δ_H (90 MHz, $CDCl_3$): 3.3 (3H, s, N-CH_3) and 6.7-8.0 (7H, m, aromatic and heterocyclic H); m/z 216 [(M^+-I), 76%] and 110 (100).

66. Attempted cyclisation of N-(2-Iodophenyl)-N-methylthiophene-2-carboxamide

N-(2-Iodophenyl)-N-methylthiophene-2-carboxamide (2.43g, 7.70 mmol) was added to deoxygenated toluene (75 ml) and the solvent heated to reflux under nitrogen whereupon Bu_3SnH (1.1 equiv., 2.05g, 7.78 mmol) and AIBN (0.1 equiv., 116 mg, 0.71 mmol) were added and the reaction illuminated for 24 h. The solvent was then evaporated *in vacuo* to give an orange oil which was redissolved in acetonitrile (50 ml) and shaken with hexane (4 x 50 ml). The acetonitrile fraction was evaporated to dryness. The product eluded identification because the starting material had decomposed on attempted cyclisation as indicated by preparative t.l.c. (SiO_2, pet. ether/EtOAc, 3:1).

67. Preparation of N-(2-Bromophenyl)-1-naphthalenecarboamide

α-Naphthoic acid (15.4g, 90 mmol) was dissolved in thionyl chloride (100 ml) and the reaction heated under nitrogen for 5 h. The solvent was evaporated *in vacuo* and the crude acid chloride distilled to give the pure acid chloride (14.2g, 83%), b.p. (1) 120 °C [lit.[158] b.p. (10) 163 °C].

The acid chloride (1.1 equiv., 6.9g, 36 mmol) was added to a solution of 2-bromoaniline (5.7g, 33 mmol) in toluene (75 ml) and pyridine (0.05 equiv., 130 mg, 1.65 mmol) over 20 min. The reaction was stirred for a further 2 h. The crude reaction mixture was poured into water (500 ml) and extracted with CH_2Cl_2 (3 x 50 ml). The organic extracts were washed with 2N hydrochloric acid, water (x3), dried, evaporated to dryness, and the residue recrystallised form absolute EtOH to give N-(2-bromophenyl)-1-naphthalenecarboamide (10g, 92%), m.p. 157-158 °C;

Analysis found: C, 61.9; H, 3.6; N, 4.2; Br, 24.9; $C_{17}H_{12}BrNO$ requires: C, 62.6; H, 3.7; N, 4.2; Br, 24.55%; ν_{max} (Nujol mull): 3260 (N-H stretch), 1645 (C=O stretch), 745 and 655 cm^{-1} (4 adjacent H); δ_H (60 MHz, $CDCl_3$): 6.8-8.7 (m, aromatic and heterocyclic H); m/z 197 [(M^+-Br), 100%].

68. Preparation of N-(2-Bromophenyl)-N-methyl-1-naphthalenecarboamide

N-(2-Bromophenyl)-1-naphthalenecarboamide (3.689g, 11 mmol) in DMF (10 ml) was added dropwise to a stirring suspension of sodium hydride (1.1 equiv., 290 mg, 12 mmol) in DMF (40 ml) over 15 min. The reaction was stirred for 2 h. under nitrogen, methyl iodide (1.1 equiv., 1.76g, 12 mmol) added and stirred for a further 2 h. The reaction mixture was poured into water (500 ml) and extracted with CH_2Cl_2 (3 x 50 ml). The organic layers were washed with water (x7), dried, evaporated to dryness, and the residue recrystallised from absolute EtOH to give N-(2-bromophenyl)-N-methyl-1-naphthalenecarboamide (2.8g, 72%), m.p. 95-96 ^oC; Analysis found: C, 63.1; H, 4.3; N, 4.3; Br, 23.1; $C_{18}H_{14}BrNO$ requires: C, 63.5; H, 4.1; N, 4.1; Br, 23.5%; ν_{max} (KBr): 2950-2845 (C-H and N-CH_3 stretch), 1645 (C=O stretch), 770, 725, 640 and 600 cm^{-1} (4 adjacent H); δ_H (60 MHz, $CDCl_3$): 3.5 (3H, brs, N-CH_3) and 6.7-8.3 (11H, m, aromatic H); m/z 260 [(M^+-Br), 100%].

69. Attempted cyclisation of N-(2-Bromophenyl)-N-methyl-1-naphthalene-carboamide

N-(2-Bromophenyl)-N-methyl-1-naphthalenecarboamide (2.78g, 8.17 mmol) was dissolved in deoxygenated toluene (75 ml) and the solvent heated to reflux under nitrogen whereupon Bu_3SnH (1.1 equiv., 2.614g, 8.9 mmol) and AIBN (0.3 equiv., 402 mg, 2.5 mmol) were added. The solvent was maintained at reflux whilst illuminating for 48 h. The solvent was evaporated *in vacuo* and the residue redissolved in acetonitrile (50 ml) and washed with pet. ether (x5). The acetonitrile fraction was evaporated *in vacuo* and analysed by preparative t.l.c. The t.l.c. indicated a large number of spots characteristic of a polymeric mixture. The reaction was not pursued or the products characterised.

70a. Preparation of N-(Iodophenyl)-cinnamamide

Cinnamoyl chloride (1 equiv., 16.6g, 99 mmol) in toluene (100 ml) was added dropwise to a stirred solution of 2-iodoaniline (21.81g, 99 mmol) in toluene (60 ml) over 15 min. The crude reaction mixture was poured into water (200 ml) and the organic layer was washed with a saturated solution of $NaHCO_3$ and then water, dried, evaporated to dryness and the residue recrystallised from aqueous EtOH to give N-(2-iodophenyl)-cinnamamide (23.12g, 67%), m.p. 155-157 °C; Analysis found: C, 51.4; H, 3.6; N, 4.0; I, 34.8; $C_{15}H_{12}INO$ requires: C, 51.5; H, 3.43; N, 4.01; I, 36.3%; ν_{max} (KBr): 3500 (N-H stretch), 3250-3000 (C-H stretch), 1665 (C=O stretch), 770 and 720 cm^{-1} (4 and 5 adjacent H); δ_H (90 MHz, d^6-DMSO/$CDCl_3$): 2.51 (1H, q, alkene H), 3.37 (1H, s, alkene H) and 6.85-9.77 (10H, m, aromatic and amide H), D_2O exchange removed the peak at 9.2-9.77; m/z 350 [(M^+-I), 100%], 222 (30) and 131 (10).

70b. Preparation of N-(2-Bromophenyl)-cinnamamide

The same procedure was used as described for Expt. 70a. Cinnamoyl chloride in toluene was added dropwise to a stirred solution of 2-bromoaniline in toluene over 15 min. The crude reaction mixture was poured into water and the organic layer was washed with a saturated solution of $NaHCO_3$ and then water, dried, evaporated to dryness and the residue recrystallised from absolute EtOH to give N-(2-bromophenyl)-cinnamamide (45%), m.p. 150-152 °C; Analysis found: C, 57.9; H, 3.8; N, 4.5; Br, 26.1; $C_{15}H_{12}BrNO$ requires: C, 59.6; H, 3.95; N, 4.65; Br, 26.5%; ν_{max} (KBr): 3224(N-H stretch), 1660 (C=O stretch), 1626 (C=C stretch), 760, 740 and 690 cm^{-1} (4 and 5 adjacent H); δ_H (60 MHz, d^6-DMSO/$CDCl_3$): 7.9-9.1 (11H, m, aromatic and alkene H) and 10.5 (1H, brs, amide H); m/z 301 (M^+, 7%) and 222 [(M^+-Br), 5%].

71. Preparation of N-(2-Iodophenyl)-N-methylcinnamamide

N-(2-Iodophenyl)-cinnamamide (43.48g, 0.125 mmol) was added to a stirred suspension of sodium hydride (1.5 equiv., 448 mg, 0.1868 mmol) in DMSO (200 ml), stirred at 40 °C for 1 h. under nitrogen. The reaction was cooled to room temperature whereupon methyl iodide (2 equiv., 41.18g, 0.29 mol) was added to the reaction mixture. The crude reaction mixture was poured into water (200 ml) and extracted with EtOAc (3 x 50 ml). The organic layer was washed with water (x7), dried, evaporated to dryness, and the residue recrystallised from absolute EtOH to give N-(2-iodophenyl)-N-methylcinnamamide (19.59g, 43%), m.p. 105-107 °C; Analysis found: C, 53.2; H, 4.0; N, 3.8; I, 35.0; $C_{16}H_{14}INO$ requires: C, 52.6; H, 3.8; N, 3.85; I, 34.98%; ν_{max} (KBr): 3100-2790 (C-H and N-CH_3 stretch), 1660 (C=O stretch), 770 and 710 cm^{-1} (4 and 5 adjacent H); δ_H (90 MHz, $CDCl_3$): 3.1 (3H, s, N-CH_3), 6.02-6.2 (2H, d, J = 16 Hz, alkene H) and 7.02-8.11 (10H, m, aromatic H); m/z 364 [(M^+-H), 100%], 252 (22), 248 (100), 238 (22), 234 (30), 164 (25) and 122 (17).

72. Preparation of N-(2-Iodophenyl)-N-methylthiocinnamamide

N-(2-Iodophenyl)-N-methylcinnamamide (3g, 8.3 mmol) and Lawesson's reagent (0.7 equiv., 2.34g, 5.7 mmol) were dissolved in toluene (100 ml) and the reaction heated under reflux under nitrogen for 2 h. The solvent was then evaporated *in vacuo* to give an orange oil which was taken up in CH_2Cl_2 and chromatographed down a short column (Al_2O_3, basic, CH_2Cl_2). The eluant was evaporated to give an orange oil which was triturated with hexane to give a solid orange powder which was recrystallised from absolute EtOH to give N-(2-iodophenyl)-N-methylthiocinnamamide (2.2g, 70%), m.p. 90-91 °C; Analysis found: C, 50.3; H, 4.0; N, 3.6; I, 33.7; S, 8.8; $C_{16}H_{14}INS$ requires: C, 50.65; H, 3.7; N, 3.7; I, 33.5; S, 8.45%; ν_{max} (KBr): 1615 (C=C stretch), 1465, 1430 and 1370 cm^{-1} (C=S stretch); δ_H (60 MHz, $CDCl_3$): 3.2 (3H, s, N-CH_3), 6.02-6.2 (2H, d, J = 16 Hz, alkene H) and 7.1-8.11 (9H, m, aromatic H); m/z 379 (M^+, 3%), 252 [(M^+-I), 100%], 147 (20), 126 (11), 115 (11), 103 (13), 91 (11) and 77 (13).

73. Preparation of N-(2-Bromobenzyl)-cinnamamide

Cinnamoyl chloride (1.1 equiv., 16.5g, 98 mmol) in toluene (75 ml) was added to a stirred suspension of 2-bromobenzylamine hydrochloride (20g, 89 mmol) in toluene (100 ml). The reaction mixture was stirred vigorously whilst triethylamine (2.2 equiv., 19.7g, 0.2 mol) was added and stirring continued for 3 h. at room temperature. The suspension was filtered, dissolved in EtOAc (200 ml) and washed with a saturated solution of $NaHCO_3$ (x5). The organic layer was dried, evaporated to dryness, and the residue recrystallised from absolute EtOH to give N-(2-bromobenzyl)-cinnamamide as colourless crystals (5.6g, 20%), m.p. 158-159 ^oC; Analysis found: C, 60.6; H, 4.6; N, 4.5; Br, 25.5; $C_{16}H_{14}BrNO$ requires: C, 60.75; H, 4.4; N, 4.45; Br, 25.5%; ν_{max} (KBr): 3260 (N-H stretch), 2910 (C-H stretch) and 1650 cm^{-1} (C=O stretch); δ_H (60 MHz, $CDCl_3$): 4.35-4.75 (2H, d, J = 8 Hz, CH_2), 6.15-6.55 (2H, d, J = 16 Hz, alkene H) and 7.0-7.55 (11H, m, aromatic and alkene H); m/z 236 [(M^+-Br), 100%], 131 (81), 107 (27), 103 (52) and 77 (32).

74. Preparation of N-(2-Bromobenzyl)-N-methylcinnamamide

N-(2-Bromophenyl)-cinnamamide (4.774g, 15 mmol) in DMSO (10 ml) was added to a suspension of sodium hydride (1.1 equiv., 398 mg, 16.6 mmol) in DMSO (30 ml) over 30 min. under nitrogen and the reaction stirred for a further 1 h. Methyl iodide (1.2 equiv., 256 mg, 18 mmol) was added and the reaction stirred for a further 1 h. The reaction mixture was poured into water (500 ml) and extracted with Et_2O (3 x 100 ml). The organic layers were washed with water (x7), dried, evaporated to dryness, and the residue recrystallised from EtOH/pet. ether to give N-(2-bromobenzyl)-N-methylcinnamamide as colourless crystals (2.9g, 59%), m.p. 69-70 ^oC; Analysis found: C, 59.5; H, 4.7; N, 4.5; Br, 26.6; $C_{15}H_{14}BrNO$ requires: C, 59.2; H, 4.6; N, 4.6; Br, 26.3%; ν_{max} (KBr): 3056-2810 (C-H stretch), 1646 (C=O stretch), 1602 (C=C stretch), 760, 700 and 670 cm^{-1} (4 and 5 adjacent H); δ_H (90 MHz, $CDCl_3$): 3.13 (3H, s, N-CH_3), 4.7-5.0 (2H, brs, CH_2) and 7.0-8.1 (11H, m, aromatic and alkene H); m/z 224 [(M^+-Br), 100%].

75. Attempted cyclisation of N-(2-Iodophenyl)-cinnamamide

N-(2-Iodophenyl)-cinnamamide (1g, 2.87 mmol) was dissolved in deoxygenated toluene (50 ml) and the reaction heated to reflux under nitrogen whereupon Bu_3SnH (1.1 equiv., 920 mg, 3.16 mmol) and AIBN (0.2 equiv., 94 mg, 0.57 mmol) was added. The solvent was maintained at reflux and illuminated for 24 h.

The solvent was evaporated *in vacuo* and the crude material dissolved in acetonitrile (50 ml) and washed with pet. ether (5 x 20 ml). The acetonitrile fraction was then evaporated *in vacuo* and the material chromatographed (SiO_2, flash, pet. ether/EtOAc, 3:1) to give cinnamanilide which was recrystallised from absolute EtOH (161 mg, 25%), m.p. 145-150 °C [lit.[159] m.p. 150-151 °C]; Analysis found: C, 80.7; H, 6.1; N, 5.8; $C_{15}H_{13}NO$ requires: C, 80.7; H, 5.85; N, 6.3%; ν_{max} (KBr): 3270 (N-H stretch), 2920 (C-H stretch), 1655 (C=O), 760 and 695 cm^{-1} (5 adjacent H); δ_H (60 MHz, $CDCl_3$): 6.5-8.0 (12H, m, aromatic and alkene H) and 8.5 (1H, brs, amide H); m/z 222 (M^+, 1%), 131 [(M^+-C_5H_7O), 100%], 103 (43), 96 (26) and 76 (28).

76. Cyclisation of N-(2-Iodophenyl)-N-methylcinnamamide

N-(2-Iodophenyl)-N-methylcinnamamide (5.412g, 15 mmol) was dissolved in deoxygenated toluene (75 ml) and the reaction heated to reflux under nitrogen whereupon Bu_3SnH (1.1 equiv., 4.77g, 16.4 mmol) and AIBN (0.3 equiv., 733 mg, 4.5 mmol) was added. The solvent was maintained at reflux and illuminated for 24 h. The solvent was evaporated *in vacuo* to give an orange oil which was redissolved in acetonitrile (20 ml) and extracted with pet. ether (3 x 100 ml). The acetonitrile fraction was evaporated *in vacuo* and the residue material distilled to give a semi-crystalline material [b.p. (0.01) 175-200 °C] which was triturated with hexane to give 3-benzyl-1-methyl-oxindole as light orange crystals (1.161g, 33%), m.p. 67-69 °C; Analysis found: C, 80.6; H, 6.5; N, 6.0; $C_{16}H_{13}NO$ requires: C, 81.0; H, 6.36; N, 5.9%; ν_{max} (KBr): 1700 (C=)), 1580 (C=C) and 750, 700 and 666 cm^{-1} (4 and 5 adjacent H); δ_H (90 MHz, $CDCl_3$): 2.5-3.8 (6H, m, methyl, methylene,

C-H on 5 ring system) and 6.5-7.3 (9H, m, aromatic H); m/z 238 [(M^+-H), 100%].

77. Attempted cyclisation of N-(2-Iodophenyl)-N-methylthiocinnamamide

N-(2-Iodophenyl)-N-methylthiocinnamamide (500 mg, 1.3 mmol) was dissolved in deoxygenated toluene (75 ml) under nitrogen. The solvent was heated to reflux whereupon Bu_3SnH (1.1 equiv., 422 mg, 1.45 mmol) and AIBN (0.3 equiv., 65 mg, 0.04 mmol) were added. The reaction mixture was illuminated whilst maintaining the reaction at reflux for 24 h. The solvent was evaporated to dryness, the residue redissolved in acetonitrile (20 ml) and washed with hexane (4 x 50 ml). The acetonitrile fraction was evaporated to dryness and chromatographed (SiO_2, t.l.c. grade, pet. ether/EtOAc, 3:1). However, the material was found to be polymeric and eluded characterisation.

78. Attempted cyclisation of N-(2-Bromobenzyl)-cinnamamide

N-(2-Bromobenzyl)-cinnamamide (1g, 3.16 mmol) was dissolved in deoxygenated toluene (75 ml) under nitrogen. The reaction was heated to reflux whereupon Bu_3SnH (1.1 equiv., 1.013g, 3.48 mmol) and AIBN (0.2 equiv., 103 mg, 0.632 mmol) were added. The reaction was heated under reflux whilst illuminating for 48 h. The solvent was then evaporated *in vacuo* to give a semi-solid which was redissolved in acetonitrile (50 ml) and washed with pet. ether (5 x 100 ml). The acetonitrile fraction was evaporated to dryness and the resulting residue subjected to preparative t.l.c. (SiO_2, pet. ether/EtOAc, 3:1). Recrystallisation from pet. ether (100-110 °C) of the main fraction gave N-benzyl-cinnamamide (519 mg, 70%), m.p. 111-114 °C; Analysis found: C, 80.4; H, 6.4; N, 6.1; $C_{16}H_{15}NO$ requires: C, 81.0; H, 6.35; N, 5.9%; ν_{max} (KBr): 3296 (N-H stretch), 1650 (C=O stretch), 760 and 698 cm^{-1} (5 adjacent H); δ_H (90 MHz, d^6-DMSO) 4.4-4.6 (2H, d, J = 6 Hz, CH_2), 6.4-6.6 (1H, d, J = 16 Hz, alkene H) and 7.1-7.9 (10H, m, aromatic H); m/z 237 (M^+, 82%), 236 [(M^+-H), 5%], 131 [($C_9H_7O^+$), 100%] and 106 [($C_7H_8N^+$), 74%].

79. Cyclisation of N-(2-Bromobenzyl)-N-methylcinnamamide

N-(2-Bromobenzyl)-N-methylcinnamamide (4.744g, 1.5 mmol) was dissolved in deoxygenated toluene (75 ml) under nitrogen and the reaction heated to reflux whereupon Bu_3SnH (1.1 equiv., 485 mg, 1.6 mmol) and AIBN (0.2 equiv., 50 mg, 0.304 mmol) were added. The solvent was maintained at reflux whilst illuminating for 24 h. The solvent was evaporated *in vacuo* to give an oil which was redissolved in acetonitrile (20 ml) and washed with pet. ether (4 x 75 ml). The acetonitrile fraction was evaporated *in vacuo* and the residual oil subjected to preparative t.l.c. to give two fractions.

The top fraction consisted of the non-cyclised reduced material, N-benzyl-N-methylcinnamamide as a gum (83 mg, 22%); Analysis found: C, 81.0; H, 6.5; N, 5.3; $C_{17}H_{17}NO$ requires: C, 81.2; H, 6.8; N, 5.6%; ν_{max} (thin film): 3024-2920 (C-H stretch), 1648 (C=O stretch), 1608 (C=C stretch), 764 and 686 cm^{-1} (5 adjacent H); δ_H (60 MHz, $CDCl_3$): 3.13 (3H, s, N-CH_3), 4.76 (2H, s, CH_2) and 6.8-8.26 (12H, m, aromatic and alkene H); m/z 251 (M^+, 92%), 131 [($C_9H_7O^+$), 100%], 103 (52), 77 (27) and 69 (86).

The bottom fraction consisted of the cyclised material, 4-benzyl-2-methyl-3-keto-1,2,3,4-tetrahydroisoquinoline as a gum (56 mg, 15%); Analysis found: C, 81.0; H, 6.4; N, 5.2; $C_{17}H_{17}NO$ requires: C, 81.2; H, 6.8; N, 5.6%; ν_{max} (thin film): 3060-2924 (C-H stretch), 1644 (C=O stretch), 748 and 702 cm^{-1} (4 and 5 adjacent H); δ_H (60 MHz, $CDCl_3$): 2.1 (3H, s, N-CH_3), 2.4-3.6 (3H, m, ABX system, CH-CH_2-Ph), 4.5 (2H, s, CH_2-N-CH_3) and 6.6-7.7 (9H, m, aromatic H); m/z 251 (M^+, 44%), 190 (34), 160 (60), 131 (25), 118 (34), 91 (100) and 84 (47).

80. Preparation of N-(2-Iodophenyl)-crotonamide

Dimethylaminopyridine (0.2 equiv., 556 mg, 4.5 mmol) followed by crotonyl chloride (1.1 equiv., 2.61g, 25 mmol) was added to a stirred solution of 2-iodoaniline (5g, 23 mmol) in Et_2O (100 ml) over 20 min. The reaction mixture was poured into water (250 ml) and extracted with EtOAc (3 x 20 ml). The organic layer was washed with water (x2), 2N hydrochloric acid (x5) and water (x3), dried,

and the residue recrystallised from absolute EtOH to give N-(2-iodophenyl)-crotonamide as colourless crystals (1.24g, 19%), m.p. 132-134 °C; Analysis found: C, 41.4; H, 3.3; N, 4.7; I, 44.0; $C_{10}H_{10}INO$ requires: C, 41.8; H, 3.5; N, 4.9; I, 44.25%; ν_{max} (KBr): 3244 (N-H stretch), 1670 (C=O stretch), 1640 (C=C stretch) and 746 cm^{-1} (4 adjacent H); δ_H (60 MHz, $CDCl_3$): 1.7-2.5 (3H, d, J = 6 Hz, CH_3), 5.6-6.1 (1H, d, J = 16 Hz, alkene H), 6.4-8.4 (5H, m, aromatic and alkene H) and 9.5 (1H, brs, amide H); m/z 287 (M^+, 1%), 160 [(M^+-I), 85%], 69 (100) and 41 (45).

81. Preparation of N-(2-Iodophenyl)-N-methylcrotonamide

N-(2-Iodophenyl)-crotonamide (2.742g, 9.5 mmol) in DMSO (10 ml) was added to a stirred suspension of sodium hydride (2 equiv., 459 mg, 19 mmol) in DMSO (75 ml) over 10 min. The reaction was stirred for 2 h. under nitrogen. The reaction mixture was poured into water (500 ml) and extracted with Et_2O (3 x 25 ml). The organic layers were washed with water (x7), dried, evaporated to dryness, and the residue recrystallised from aqueous EtOH to give colourless crystals of N-(2-iodophenyl)-crotonamide (1.23g, 43%), m.p. 106-108 °C; Analysis found: C, 43.75; H, 4.0; N, 4.6; I, 41.5; $C_{11}H_{12}INO$ requires: C, 43.85; H, 4.0; N, 4.6; I, 41.5%; ν_{max} (KBr): 1660 (C=O stretch), 1616 (C=C stretch) and 774 cm^{-1} (4 adjacent H); δ_H (90 MHz, $CDCl_3$): 1.54-1.81 (3H, d, J = 8 Hz, CH_3), 3.24 (3H, s, N-CH_3), 5.3-5.75 (1H, d, J = 16 Hz, alkene H) and 6.36-8.18 (5H, m, aromatic and alkene H); m/z 174 [(M^+-I), 100%].

82. Attempted cyclisation of N-(2-Iodophenyl)-crotonamide

N-(2-Iodophenyl)-crotonamide (697 mg, 0.24 mmol) was dissolved in deoxygenated toluene (75 ml) under nitrogen. The solvent was heated to reflux whereupon Bu_3SnH (1.1 equiv., 757 mg, 0.26 mmol) and AIBN (0.2 equiv., 79 mg, 0.048 mmol) were added. The reaction was heated under reflux and illuminated for 24 h. The solvent was evaporated *in vacuo* and the resulting crude oil redissolved in acetonitrile (20 ml) and washed with pet. ether (3 x 100 ml). The

acetonitrile layer was evaporated to dryness and the residue recrystallised from absolute EtOH to give crotonamide (250 mg, 65%), m.p. 115-117 °C [lit.[160] m.p. 115 °C]; ν_{max} (KBr): 3284 (N-H stretch), 1670 (C=O stretch), 1638 (C=C stretch), 752, 694 and 675 cm^{-1} (4 and 5 adjacent H); δ_H (60 MHz, $CDCl_3$): 1.63-2.0 (3H, br, J = 6 Hz, CH_3), 5.88 and 6.2 (2H, 2 x s, alkene H) and 6.6-7.86 (6H, m, aromatic and amide H).

83. Cyclisation of N-(2-Iodophenyl)-N-methylcrotonamide

N-(2-Iodophenyl)-N-methylcrotonamide (1.524g, 5.06 mmol) was dissolved in deoxygenated toluene (75 ml) and the reaction heated to reflux whereupon Bu_3SnH (1.1 equiv., 1.62g, 5.56 mmol) and AIBN (0.3 equiv., 249 mg, 1.51 mmol) were added. The reaction was maintained at reflux and illuminated for 24 h. The solvent was evaporated *in vacuo* and the crude material redissolved in acetonitrile (20 ml) and shaken with pet. ether (4 x 100 ml). The acetonitrile fraction was evaporated *in vacuo* and distilled to give 1-methyl-3-ethyl-oxindole (200 mg, 23%), b.p. (0.03) 140-150 °C [lit.[161] b.p. 280-285 °C]; ν_{max} (thin film): 1710 (C=O stretch) and 750 cm^{-1} (4 adjacent H); δ_H (90 MHz, $CDCl_3$): 0.7-0.9 (3H, t, CH_3), 1.8-2.2 (2H, q, CH_2), 3.1-3.4 (4H, s and t, N-CH_3 and C-H of 5-ring system) and 6.7-7.3 (4H, m, aromatic H); m/z 75 (M^+, 60%) and 147 [(M^+-C_2H_4), 100%].

84. Preparation of 2-(2-Furyl)-acryloyl chloride

Furylacrylic acid (10.7g, 76 mmol) was dissolved in thionyl chloride (100 ml) and the reaction heated under reflux nitrogen overnight. The solvent was removed *in vacuo* and the residual oil distilled to give 2-(2-furyl)-acryloyl chloride as a light brown semi-solid (10.4g, 87%), b.p. (26) 110-120 °C [lit.[162] b.p. (10) 105-106 °C]; ν_{max} (thin film): 1744 (C=O stretch) and 1626 cm^{-1} (C=C stretch).

85. Preparation of N-(2-Iodophenyl)-2-(2-furyl)-propenamide

2-(2-Furyl)-acryloyl chloride (3.5g, 21 mmol) was added over 15 min. to a solution of 2-iodoaniline (2.1 equiv., 10g, 45.6 mmol) in Et_2O (100 ml) at room temperature and stirred for 2 h. The reaction mixture was poured into water (500 ml) and extracted with EtOAc (3 x 25 ml). The organic layers were washed with water (x3), 2N hydrochloric acid (x4) and water (x2), dried, evaporated to dryness, and the residue recrystallised from absolute EtOH to give N-(2-iodophenyl)-2-(2-furyl)-propenamide (5.408g, 75%), m.p. 152-154 °C; Analysis found: C, 46.1; H, 3.1; N, 4.15; I, 37.0; $C_{13}H_{10}INO_2$ requires: C, 46.0; H, 2.95; N, 4.15; I, 37.45%; ν_{max} (KBr): 3292 (N-H stretch), 1656 (C=O stretch), 1614 (C=C stretch) and 748 cm^{-1} (4 adjacent H); δ_H (90 MHz, d^6-DMSO/$CDCl_3$): 6.4-8.06 (7H, m, aromatic and heterocyclic H) and 9.1 (1H, brs, amide H); m/z 121 [(M^+-I), 100%].

86. Preparation of N-(2-Iodophenyl)-N-methyl-2-(2-furyl)-propenamide

N-(2-Iodophenyl)-phenylpropynamide (3.84g, 11 mmol) in DMSO (10 ml) was added over 20 min to a suspension of sodium hydride (1.1 equiv., 348 mg, 12 mmol) in DMSO (75 ml) under nitrogen and the reaction stirred for 1 h. Methyl iodide (1.2 equiv., 1.9g, 13.2 mmol) was added and the reaction stirred for a further 1 h. The crude reaction mixture was poured into water (500 ml) and extracted with EtOAc (3 x 30 ml). The organic layers were washed with water (x7), dried, evaporated to dryness, and the residue recrystallised from absolute EtOH to give N-(2-iodophenyl)-N-methyl-2-(2-furyl)-propenamide (984 mg, 25%), m.p. 121.5-122 °C; Analysis found: C, 47.6; H, 3.6; N, 3.9; I, 35.85; $C_{14}H_{12}INO_2$ requires: C, 47.6; H, 3.4; N, 3.95; I, 36.0%; ν_{max} (KBr): 1654 (C=O stretch), 1680 (C=C stretch) and 748 cm^{-1} (4 adjacent H); δ_H (90 MHz, $CDCl_3$): 3.3 (3H, s, N-CH_3), 5.8-6.7 [3H, m, furan (position 3) and alkene H], 6.9-8.23 [6H, m, aromatic and furan (2 and 5 position on the furan)]; m/z 226 (M^+, 0.5%), 226 [(M^+-I), 64%] and 198 [(226-CO^+), 10%].

87. Cyclisation of N-(2-Iodophenyl)-N-methyl-3-(3-furyl)-propenamide

N-(2-Iodophenyl)-N-methyl-3-(3-furyl)-propenamide (3.3g, 9.3 mmol) was dissolved in deoxygenated toluene (75 ml). The reaction was heated to reflux whereupon Bu_3SnH (1.1 equiv., 2.98g, 10 mmol) and AIBN (0.3 equiv., 301 mg, 1.86 mmol) were added. The solvent was removed *in vacuo* and the resulting crude oil redissolved in acetonitrile (100 ml) and washed with pet. ether (6 x 100 ml). The acetonitrile portion was then evaporated *in vacuo* to leave an orange oil which was chromatographed (SiO_2, flash, pet. ether/EtOAc, 1:1) to give one major fraction (535 mg), which was recrystallised from pet. ether (b.p. 80-100 °C) to give 1-methyl-3-(3-furylmethyl)-oxindole (377 mg, 18%), m.p. 82-84 °C; Analysis found: C, 72.4; H, 4.8; N, 6.2; $C_{14}H_{13}NO_2$ requires: C, 74.0; H, 5.75; N, 6.15%; ν_{max} (KBr): 2930 (C-H stretch), 1705 (C=O stretch), 1610 (C=C stretch) and 752 cm^{-1} (4 adjacent H); δ_H (90 MHz, $CDCl_3$): 2.7-3.85 [3H, m, (ABX spectrum), CH_2 and H(position 3)], 3.15 (3H, s, N-CH_3), 5.9-6.5 [1H, d, J = 16 Hz, furan H (position 5)], 6.15-6.3 [1H, t, furan H (position 4)] and 6.5-7.35 [5H, m, aromatic and furan H (position 2)]; m/z 227 (M^+, 100%), 146 (24) and 81 (100).

88. Preparation of Fumaroyl chloride monoethylester

Fumaric acid monoethylester (12g, 83 mmol) was dissolved in thionyl chloride (100 ml). The reaction was heated under reflux for 3 h. under nitrogen. The solvent was evaporated *in vacuo* to give a dark orange yellow oil which was distilled to give fumaroyl chloride monoethylester as a colourless oil (10.53g, 78%), b.p. (22) 70-80 °C; ν_{max} (thin film): 1764 (C=O stretch) and 1728 cm^{-1} (C=C stretch).

89. Preparation of N-(2-Iodophenyl)-3-carboxymethyl-propenamide

Fumaroyl chloride monoethylester (4.15g, 25 mmol) in Et_2O (50 ml) was added to a stirred solution of 2-iodoaniline (2.1 equiv., 11.7g, 53 mmol) in Et_2O (100 ml). The organic layer was washed with 2N hydrochloric acid (x3) and water

(x3), dried, evaporated *in vacuo*, and the residue recrystallised from absolute EtOH to give N-(2-iodophenyl)-3-carboxymethyl-propenamide (3.54g, 41%), m.p. 155-157 °C; Analysis found: C, 41.7; H, 3.6; N, 4.1; I, 36.45; $C_{12}H_{12}INO_3$ requires: C, 41.75; H, 3.5; N, 4.05; I, 36.8%; ν_{max} (KBr): 3276 (N-H stretch), 1710 (C=O ester), 1668 (C=O amide), 1640 (C=C stretch) and 746 cm^{-1} (4 adjacent H); δ_H (90 MHz, $CDCl_3$): 1.16-1.56 (3H, t, CH_3), 4.06-4.6 (2H, q, CH_2) and 6.3-8.1 (6H, m, aromatic and alkene H), 9.6 (1H, brs, amide H); m/z 218 [(M^+-I), 100%] and 57 25).

90. Preparation of N-(2-Iodophenyl)-N-methyl-3-carboxymethyl-propenamide

N-(2-Iodophenyl)-3-carboxymethyl-propenamide (6.96g, 20 mmol) was added to a stirred suspension of sodium hydride (1.2 equiv., 576 mg, 24 mmol) in DMSO (75 ml) under nitrogen at room temperature for 1 h. Methyl iodide (1.5 equiv., 4.26g, 30 mmol) was added to the reaction mixture and stirred for 1 h. The reaction mixture was poured into water (500 ml) and extracted with Et_2O (3 x 50 ml). The organic extracts were washed with water (x7), dried, evaporated to dryness, and the residue recrystallised from absolute EtOH to give N-(2-iodophenyl)-N-methyl-3-carboxymethyl-propenamide as a colourless powder (3.32g, 46%), m.p. 94-95 °C; Analysis found: C, 43.3; H, 3.9; N, 3.9; I, 35.5; $C_{13}H_{14}INO_3$ requires: C, 43.45; H, 3.9; N, 3.9; I, 35.4%; ν_{max} (KBr): 3056-2984 (C-H stretch), 1722 (C=O stretch), 1662 (C=O amide), 1630 (C=C stretch) and 770 cm^{-1} (4 adjacent H); δ_H (90 MHz, $CDCl_3$): 1.06-1.43 (3H, t, OCH_3), 3.3 (3H, s, N-CH_3), 3.96-4.43 (2H, s, CH_2) and 6.26-8.16 (6H, m, aromatic H); m/z 232 [(M^+-I), 100%].

91. Cyclisation of N-(2-Iodophenyl)-N-methyl-3-carboxymethyl-propenamide

N-(2-Iodophenyl)-N-methyl-3-carboxymethyl-propenamide (2.5g, 6.96 mmol) was dissolved in deoxygenated toluene (75 ml) and the reaction heated to reflux whereupon Bu_3SnH (1.1 equiv., 2.23g, 7.6 mmol) and AIBN (0.3 equiv., 3.42 mg, 2 mmol) were added. The reaction was maintained at reflux and illuminated for 24 h. The solvent was evaporated *in vacuo* and the crude oil redissolved in

acetonitrile (20 ml) and washed with pet. ether (4 x 100 ml). The acetonitrile fraction was evaporated *in vacuo* to give an oil which distilled to give 1-methyl-3-carboxymethyl-oxindole (719 mg, 44%), b.p. (0.5) 195-200 °C; Analysis found: C, 66.45; H, 6.4; N, 6.1; $C_{13}H_{15}NO_3$ requires: C, 66.9; H, 6.45; N, 6.0%; ν_{max} (thin film): 1710 (C=O ester), 1612 (C=O amide) and 752 cm^{-1} (4 adjacent H); δ_H (90 MHz, $CDCl_3$): 1.0-1.4 (3H, t, OCH_3), 2.7-3.1 (2H, dd, $\underline{CH_2}$-CH_3), 3.36 (3H, s, N-CH_3), 3.6-4.43 (3H, m, $\underline{CH}$-$\underline{CH_2}$) and 6.7-7.52 (4H, m, aromatic H); m/z 233 (M^+, 37%).

92. Preparation of N-(2-Iodophenyl)-acrylamide

Acryloyl chloride (5g, 55 mmol) was added to a solution of 2-iodoaniline (2.1 equiv., 25g, 0.16 mmol) in Et_2O (100 ml) under nitrogen over 30 min. at 0 °C and the reaction warmed to room temperature. The crude reaction mixture was poured into water (500 ml) and extracted with EtOAc (3 x 25 ml). The organic layer was washed with 2N hydrochloric acid (x3) and water (x2), dried, evaporated to dryness, and the residue recrystallised from absolute EtOH to give N-(iodophenyl)-acrylamide as colourless crystals (6.97g, 46%), m.p. 101-103 °C; Analysis found: C, 39.7; H, 3.1; N, 5.2; I, 46.3; C_9H_8INO requires: C, 39.55; H, 2.95; N, 5.15; I, 46.5%; ν_{max} (KBr): 3268 (N-H stretch), 1664 (C=C stretch) and 754 cm^{-1} (4 adjacent H); δ_H (60 MHz, $CDCl_3$): 5.6-5.8 (m, aromatic and alkene H); m/z 273 (M^+, 14%) and 146 [(M^+-I), 92%].

93. Preparation of N-(2-Iodophenyl)-N-methylacrylamide

N-(2-Iodophenyl)-acrylamide (5g, 18.3 mmol) in DMSO (10 ml) was added to a suspension of sodium hydride (1.2 equiv., 660 mg, 22.9 mmol) in DMSO (50 ml) under nitrogen at room temperature. The reaction was stirred for 1 h., methyl iodide (1.4 equiv., 4.5g, 28.5 mmol) added, and stirring continued for a further 20 min. The reaction was poured into water (500 ml) and extracted with Et_2O (3 x 25 ml). The organic layer was washed with water (x7), dried and evaporated *in vacuo* to give a thick brown oil which was chromatographed (Al_2O_3, basic, pet. ether/-

EtOAc, 3:1) to give N-(2-iodophenyl)-N-methylacrylamide (3.49g, 64%); Analysis found: C, 42.05; H, 3.5; N, 4.9; I, 43.7; $C_{10}H_{10}INO$ requires: C, 41.8; H, 3.5; N, 4.9; I, 44.25%; ν_{max} (thin film): 2850 (C-H stretch), 1660 (C=O stretch), 1616 (C=C stretch) and 768 cm^{-1} (4 adjacent H); δ_H (90 MHz, $CDCl_3$): 3.26 (3H, s, N-CH_3), 5.23-6.53 (3H, m, alkene H), 6.83-7.56 (3H, m, aromatic H) and 7.7-8.0 (1H, d, J = 8 Hz, aromatic H); m/z 233 [(M^+-C_3H_2O), 16%], 160 [(M^+-I), 100%] and 55 (43).

94. Cyclisation of N-(2-Iodophenyl)-N-methylacrylamide

N-(2-Iodophenyl)-N-methylacrylamide (1g, 3.48 mmol) was dissolved in deoxygenated toluene (75 ml) under nitrogen. The solvent was heated to reflux whereupon Bu_3SnH (1.1 equiv., 1.115g, 3.8 mmol) and AIBN (0.3 equiv., 171 mg, 1.04 mmol) were added. The reaction was illuminated whilst maintaining the reaction at reflux for 24 h. The solvent was evaporated *in vacuo* and the resulting crude oil redissolved in acetonitrile (20 ml) and washed with pet. ether (4 x 100 ml). The acetonitrile layer was evaporated *in vacuo* to give 1,3-dimethyloxindole as an orange oil (375 mg, 67%), b.p. (0.7) 120-130 °C [lit.[163] b.p. (11) 136-138 °C]; Analysis found: C, 74.2; H, 6.9; N, 8.6; $C_{10}H_{11}NO$ requires: C, 74.55; H, 6.85; N, 8.7%; ν_{max} (thin film): 1716 (C=O stretch) and 752 cm^{-1} (4 adjacent H); δ_H (90 MHz, $CDCl_3$): 1.3-1.7 (3H, d, J = 8 Hz, N-CH_3), 3.13-3.73 (4H, m, CH and CH_3) and 6.7-7.53 (4H, m, aromatic H); m/z 161 (M^+, 100%), 146 (40), 134 (41), 118 (44), 91 (23) and 77 (28).

95. Preparation of 1-Cyclohexene-1-carboxoyl chloride

1-Cyclohexene-1-carboxylic acid (3g, 23.8 mmol) was dissolved in thionyl chloride (50 ml) and the reaction heated to reflux for 3 h. The solvent was evaporated *in vacuo* and the residue distilled to give 1-cyclohexene-1-carboxoyl chloride (3.24g, 94%), b.p. (11) 86-89 °C [lit.[164] b.p. (11) 86 °C].

96. Preparation of N-(2-Iodophenyl)-1-cyclohexene-1-carboxamide

1-Cyclohexene-1-carboxoyl chloride (1 equiv., 3.24g, 22 mmol) was added to a suspension of 2-iodoaniline (1 equiv., 4.9g, 22 mmol) in 10% aq. NaOH solution (100 ml) and stirred for 2 h. The crude reaction mixture was poured into water (100 ml) and extracted with Et_2O (3 x 20 ml). The organic layer was shaken with 2N hydrochloric acid, 2N NaOH and water (x2), dried, evaporated to dryness to give N-(2-iodophenyl)-1-cyclohexene-1-carboxamide as white crystals (2.34g, 33%), m.p. 50-55 °C; ν_{max} 3375 (N-H stretch), 2870 (C-H stretch), 1680 (C=O stretch), 1630 (C=C stretch) and 750 cm^{-1} (4 adjacent H); δ_H (90 MHz, $CDCl_3$): 1.1-2.6 (8H, m, cyclohexene ring), 6.6-7.9 (4H, m, aromatic and alkene H) and 8.2-8.4 (1H, d, J = 8 Hz, *ortho*-proton to iodine on aromatic OH); m/z 327 (M^+, 23%), 200 [(M^+-I), 85%], 109 (100), 91(7), 81 (73) and 79 (20). Full elemental analysis was carried on the N-methyl derivative to establish the authenticity of the compound (Expt. 97).

97. Preparation of N-(2-Iodophenyl)-N-Methyl-1-cyclohexene-carboxamide

N-(2-Iodophenyl)-1-cyclohexene-1-carboxamide (2.3g, 7 mmol) in DMSO (10 ml) was added to a suspension of sodium hydride (1.1 equiv., 186 mg, 7.7 mmol) in DMSO (30 ml) under nitrogen and stirred for 1 h., methyl iodide (1.1 equiv., 1.093g, 7.7 mmol) was added and the reaction stirred for 20 min., then poured into water (500 ml) and extracted with Et_2O (3 x 75 ml). The organic layer was washed with water (x7), dried and evaporated to dryness and recrystallised from cyclohexane to give N-(2-iodophenyl)-N-methyl-1-cyclohexene-1-carboxamide as a light brown solid (1.7g, 71%), m.p. 95-97 °C; Analysis found: C, 49.4; H, 4.7; N, 4.2; I, 37.7; $C_{14}H_{16}INO$ requires: C, 49.5; H, 4.7; N, 4.1; I, 37.25%; ν_{max} (KBr): 2910 (C-H stretch), 1630 (C=O stretch), 1580 (C=C stretch) and 770 cm^{-1} (4 adjacent H); δ_H (60 MHz, $CDCl_3$): 1.1-2.46 (8H, m, cyclohexane ring), 3.27 (3H, s, N-CH_3), 5.8-6.1 (1H, m, C=C<u>H</u>), 6.83-7.6 (3H, m, aromatic H) and 7.8-8.06 (1H, d, J = 8 Hz, *ortho*-proton to iodine on aromatic ring); m/z 234 [(M^+-I, 100%], 109 [($C_7H_9O^+$, 82%], 81 (65) and 79 (19).

98. Cyclisation of N-(2-Iodophenyl)-N-methyl-1-cyclohexene-1-carboxamide

N-(2-Iodophenyl)-N-methyl-1-cyclohexene-1-carboxamide (248 mg, 0.72 mmol) was dissolved in deoxygenated toluene (75 ml) under nitrogen and the reaction heated to reflux whereupon Bu_3SnH (1.1 equiv., 233 mg, 0.8 mmol) and AIBN (0.2 equiv., 24 mg, 0.014 mmol) was added. The solvent was maintained at reflux and illuminated for 10 h. The solvent was evaporated *in vacuo* to give a dark oil which was redissolved in acetonitrile (20 ml) and shaken with pet. ether (4 x 100 ml). The acetonitrile fraction was evaporated *in vacuo* and the oil subjected to preparative t.l.c. (SiO_2, EtOAc/pet. ether, 1:2) to give clear oil of the *exo* material, N-methyl-oxindole-3-spiro-cyclohexane (35 mg, 23%); Analysis found: C, 77.7; H, 7.9; N, 6.1; $C_{14}H_{16}NO$ requires: C, 78.1; H, 7.9; N, 6.5%; ν_{max} (thin film): 2920 (C-H stretch), 1710 (C=O stretch) and 760 cm^{-1} (4 adjacent H); δ_H (90 MHz, $CDCl_3$): 1.0-2.3 (10H, m, cyclohexane ring H), 3.2 (3H, s, N-CH_3), 6.6-7.5 (4H, m, aromatic H); δ_C (360 MHz, $CDCl_3$): [see Part 5]; m/z 215 (M^+, 57%), 160 (100) and 147 (16).

99. Preparation of N-(2-Bromophenyl)-N-cinnamoyl-cinnamamide

N-(2-Bromophenyl)-cinnamamide (1g, 3.3 mmol) in THF (10 ml) was added to a suspension of sodium hydride (1.5 equiv., 119 mg, 5 mmol) in THF (20 ml) under nitrogen and the reaction stirred for 1 h. Cinnamoyl chloride (1.1 equiv., 604 mg, 3.63 mmol) was added to the reaction mixture and stirred for a further 1 h. The reaction was poured into water (500 ml) and extracted with Et_2O (3 x 75 ml). The organic layers were washed with water (x6), dried, evaporated to dryness and recrystallised from EtOH/pet. ether to give N-(2-bromophenyl)-N-cinnamoyl-cinnamamide as colourless crystals (596 mg, 42%), m.p. 168-170 ^oC; Analysis found: C, 66.3; H, 4.2; N, 3.2; Br, 18.1; $C_{24}H_{18}BrNO_2$ requires: C, 66.7; H, 4.2; N, 3.2; Br, 18.5%; ν_{max} (KBr): 3060 (C-H stretch), 1680 (C=O stretch), 1610 (C=C stretch), 786, 762, 740 and 700 cm^{-1} (4 and 5 adjacent H); δ_H (60 MHz, $CDCl_3$): 6.8-8.2 (m, aromatic and alkene H); m/z 432 (M^+, 1%), 131 [(C_9H_7O), 100%] and 103 (20).

100. Attempted cyclisation of N-(2-Bromophenyl)-N-cinnamoyl-cinnamamide

N-(2-Bromophenyl)-N-cinnamoyl-cinnamamide (217 mg, 0.5 mmol) was dissolved in deoxygenated toluene under nitrogen. The solvent was heated to reflux whereupon Bu_3SnH (1.1 equiv., 161 mg, 0.55 mmol) and AIBN (0.2 equiv., 16 mg, 0.1 mmol) were added. The reaction was maintained at reflux with illumination for 24 h. The reaction mixture was evaporated *in vacuo* and the crude material redissolved in acetonitrile (20 ml) and subsequently washed with pet. ether (5 x 15 ml). The acetonitrile fraction was evaporated *in vacuo* and the crude material purified using preparative t.l.c. (SiO_2, pet. ether/EtOAc, 2:1) to give a single spot material (42 mg), m.p. 183-185 °C; Analysis found: C, 80.6; H, 6.0; N, 3.9; $C_{24}H_{21}NO_2$ requires: C, 81.15; H, 5.9; N, 3.95%; ν_{max} (KBr): 3040-2910 (C-H stretch), 1730 (C=O stretch), 1680 (C=O stretch), 750 and 695 cm^{-1} (4 and 5 adjacent H); δ_H (90 MHz, $CDCl_3$): 2.6-3.3 (5H, m, C<u>H</u>-C<u>H</u>, C<u>H</u>-C<u>H</u>$_2$) and 6.3-7.4 (14H, m, aromatic H); m/z 355 (M^+, 34%), 131 [($C_9H_7O^+$, 100%], 91 (38) and 43 (60). There has been no reasonable explanation for the results of the reaction. However, the results are discussed in the discussion [see Parts 3 and 4].

101. Preparation of N-Benzyl-N-(2-iodophenyl)-cinnamamide

N-(2-Iodophenyl)-cinnamamide (3g, 8.5 mmol) in DMSO (10 ml) was added to a suspension of sodium hydride (1.2 equiv., 247 mg, 10 mmol) in DMSO (75 ml) over 20 min. under nitrogen and the reaction stirred for 1 h. Benzyl bromide (1.1 equiv., 1.47g, 9.35 mmol) was added to the reaction mixture which was stirred for a further 1 h. The reaction mixture was then poured into water (100 ml) and extracted with Et_2O (4 x 75 ml). The organic layers were washed with water (x5), dried, evaporated to dryness, and the residue recrystallised from absolute EtOH to give N-benzyl-N-(2-iodophenyl)-cinnamamide (1.96g, 52%), m.p. 110-113 °C; Analysis found: C, 60.4; H, 4.1; N, 3.2; I, 28.0; $C_{22}H_{18}INO$ requires: C, 60.15; H, 4.1; N, 3.2; I, 28.95%; ν_{max} (KBr): 2920-2850 (C-H stretch), 1655 (C=O stretch) and 1610 cm^{-1} (C=C stretch); δ_H (90 MHz, $CDCl_3$): 4.06-4.3 (2H, d, J = 14 Hz, CH_2), 5.7-6.2 (2H, m, alkene H) and 6.76-8.23 (18H, m, aromatic H); m/z 439

(M^+, 26%) and 312 [(M^+-I), 68%].

102. Cyclisation of N-Benzyl-N-(2-iodophenyl)-cinnamamide

N-Benzyl-N-(2-iodophenyl)-cinnamamide (500 mg, 1.1 mmol) was dissolved in deoxygenated toluene (75 ml) under nitrogen. The solvent was heated to reflux whereupon Bu_3SnH (1.1 equiv., 365 mg, 1.2 mmol) and AIBN (0.2 equiv., 37 mg, 0.23 mmol) were added. The reaction was heated under reflux and illuminated for 24 h. The solvent was evaporated *in vacuo* to give an orange oil which was redissolved in acetonitrile (10 ml) and washed with pet. ether (5 x 50 ml). The acetonitrile fraction was evaporated *in vacuo* and the resulting crude oil subject to preparative t.l.c. (SiO_2, pet. ether/EtOAc, 1:1) to give 1,3-dibenzyloxindole as a thick orange oil (310 mg, 88%); Analysis found: C, 84.0; H, 5.5; N, 4.6; $C_{22}H_{19}NO$ requires: C, 84.3; H, 6.1; N, 4.5%; ν_{max} (thin film): 1710 (C=O stretch), 1612 (CH_2 deformation), 752 and 700 cm^{-1} (4 and 5 adjacent H); δ_H (90 MHz, $CDCl_3$): 2.9-4.0 [3H, m, (ABX system), $X\underline{H}_2$-C$\underline{H}$], 4.4-5.2 (2H, s, benzyl-CH_2) and 6.25-7.7 (14H, m, aromatic H); m/z 313 (M^+, 39%) and 222 [(M^+-C_7H_7), 52%].

103. Preparation of Phenylpropioloyl chloride

Phenylpropiolic acid (20.8g, 14.2 mmol) was dissolved in thionyl chloride (100 ml) and the reaction heated under reflux for 24 h. under nitrogen. The solvent was evaporated *in vacuo* and the resulting crude oil distilled to give pure phenylpropioloyl chloride as a colourless oil (20.3g, 87%), b.p. (16) 104 °C [lit.[165] b.p. (17) 115-116 °C]; ν_{max} (thin film): 2200 (C=C stretch) and 1760 cm^{-1} (C=O stretch).

104. Preparation of N-(2-Iodophenyl)-phenylpropynamide

Phenylpropioloyl chloride (500 mg, 3.03 mmol) was added to a solution of 2-iodoaniline (2.2 equiv., 1.46g, 6.6 mmol) in Et^2O (25 ml) at 0 °C over 20 min. The reaction was stirred for 2 h. at room temperature. The reaction mixture was

poured into water (50 ml) and extracted with EtOAc (3 x 30 ml). The organic layers were washed with 2N hydrochloric acid, water (x3), dried, evaporated to dryness, and the residue recrystallised from absolute EtOH to give N-(2-iodophenyl)-phenylpropynamide as colourless crystals (467 mg, 44%), m.p. 108-111 °C; Analysis found: C, 51.9; H, 2.94; N, 4.0; I, 36.0; $C_{15}H_{10}INO$ requires: C, 51.85; H, 2.9; N, 4.05; I, 36.6%; ν_{max} (KBr): 3184-3008 (N-H stretch), 2260-2150 (C-C stretch) and 1624 cm^{-1} (C=O stretch); δ_H (90 MHz, $CDCl_3$): 6.6-8.51 (m, aromatic and amide H); m/z 347 (M^+, 7%), 220 [(M^+-I), 57%], 129 (100), 75 (14), 71 (11), 57 (16) and 43 (11).

105. Preparation of N-(2-Iodophenyl)-N-methylphenylpropynamide

N-(2-Iodophenyl)-phenylpropynamide (9.94g, 28.6 mmol) was added to a stirred suspension of sodium hydride (1.2 equiv., 825 mg, 34 mmol) in DMSO (75 ml) under nitrogen at room temperature. The mixture was warmed to 40 °C and then cooled to 0 °C whereupon methyl iodide (2 equiv., 8.12g, 57.2 mmol) was added, and the stirring continued for 1 h. The reaction mixture was poured into water (500 ml) and extracted with EtOAc (3 x 20 ml). The organic layers were washed with water, 2N hydrochloric acid (x3) and water (x2), dried, evaporated to dryness, and the residue recrystallised from absolute EtOH to give N-(2-iodophenyl)-N-methylphenylpropynamide (7.57g, 73%), m.p. 125-126 °C; Analysis found: C, 53.2; H, 3.5; N, 3.9; I, 35.0; $C_{15}H_{10}INO$ requires: C, 53.2; H, 3.3; N, 3.9; I, 35.2%; ν_{max} (KBr): 3010-2950 (C-H and N-CH_3 stretch), 2212 (C=C stretch), 1628 (C=O stretch), 774 and 754 cm^{-1} (4 and 5 adjacent H); δ_H (60 MHz, $CDCl_3$): 3.3 (3H, s, N-CH_3), 6.9-7.6 (8H, m, aromatic H) and 7.9-8.1 (1H, d, J = 8 Hz, *ortho*-H to iodine); m/z 234 [(M^+-I), 100%] and 129 (100).

106. Cyclisation of N-(2-Iodophenyl)-N-methylphenylpropynamide

N-(2-Iodophenyl)-N-methylphenylpropynamide (5.09g, 14 mmol) was dissolved in deoxygenated toluene (75 ml) under nitrogen. The solvent was maintained at reflux whilst illuminating for 24 h. The solvent was removed *in*

vacuo and the crude oil redissolved in acetonitrile (200 ml) and washed with pet. ether (6 x 50 ml). The acetonitrile layer was evaporated *in vacuo* and the orange oil distilled to give a light orange oil, a mixture of *cis*- and *trans*-3-benzyladine-1-methyloxindole (1.54g, 47%), b.p. (0.05) 195-200 °C; Analysis found: C, 78.3; H, 5.7; N, 5.6; $C_{16}H_{13}NO.1/2H_2O$ requires: C, 78.7; H, 5.75; N, 5.75%; ν_{max} (thin film): 3056-2932 (C-H stretch), 1704 (C=O stretch), 1606 (C=C stretch), 778, 748 and 698 cm^{-1} (4 and 5 adjacent H); δ_H (90 MHz, $CDCl_3$): 3.2 (3H, s, N-CH_3) and 6.6-8.5 (10H, m, aromatic and alkene H).

The mixture was separated using preparative t.l.c (SiO_2, pet. ether/EtOAc, 3:1) to give two fractions; (a) the fast running yellow spot was the *trans* isomer (1.04g, 32%); Analysis found: C, 75.5; H, 5.6; N, 5.25; $C_{16}H_{13}NO.1/2H_2O$ requires: C, 78.7; H, 5.75; N, 5.75%; ν_{max} (thin film): 3050-2928 (C-H stretch), 1706 (C=O stretch), 1632(C=C stretch), 778, 748, 720 and 698 cm^{-1} (4 and 5 adjacent H); δ_H (90 MHz, $CDCl_3$): 3.2 (3H, s, N-CH_3), 6.7-7.5 (8H, m, aromatic H), 7.8-8.2 (2H, *ortho*-proton on phenyl substituent and alkene H); δ_C (360 MHz, $CDCl_3$): [see discussion for details]; m/z 235 (M^+, 100%), 158 (34), 146 (27), 129 (44) and 55 (22); (b) the slow running yellow spot was the *cis* isomer (159 mg, 5%); Analysis found: C, 78.3; H, 5.5; N, 5.4; $C_{16}H_{13}NO.1/2H_2O$ requires: C, 78.7; H, 5.75; N, 5.75%; ν_{max} (thin film): 3020-2870 (C-H stretch), 1710 (C=O stretch), 1634(C=C stretch), 778, 748, 720 and 698 cm^{-1} (4 and 5 adjacent H); δ_H (90 MHz, $CDCl_3$): 3.2 (3H, s, N-CH_3), 6.7-7.8 (10H, m, aromatic and alkene H); δ_C (360 MHz, $CDCl_3$): [see page 96 for details]; m/z 235 (M^+, 100%), 158 (34), 129 (44) and 55 (22).

107. Preparation of Fumaroyl chloride

Fumaric acid (20g, 17.2 mmol) was dissolved in thionyl chloride (150 ml) and the reaction heated under reflux over 2 h. The solvent was then evaporated *in vacuo* and the residual oil distilled to give fumaroyl chloride (11.47g, 44%), b.p. 161-164 °C [lit.[165] b.p. 161-164 °C]. All spectroscopic data agreed with the literature [165].

108. Preparation of N,N^1-Di(2-iodophenyl)-*trans*-butenediamide

Fumaroyl chloride (1g, 6.58 mmol) was added to a stirred solution of 2-iodoaniline (4.1 equiv., 5.9g, 26.9 mmol) in toluene (50 ml) at room temperature over 20 min. and the reaction stirred for 1 h. The precipitate was filtered off, washed with 1N aq. NaOH (100 ml), 1N hydrochloric acid (100 ml) and water (100 ml). The insoluble material was dried (P_2O_5) to give N,N^1-di(2-iodophenyl)-*trans*-butenediamide (2.07g, 61%), m.p. 320-348 °C; ν_{max} (KBr): 3256 (N-H stretch), 1638 (C=O stretch) and 1578 cm^{-1} (C=C stretch); δ_H (90 MHz, d^6-DMSO at 110 °C), 6.89-8.4 (m, aromatic and amide H); m/z 391 [(M^+-I), 100%], 264 [(M^+-I_2), 29%].

109. Preparation of N,N^1-Di(2-iodophenyl)-N,N^1-dimethyl-*trans*-butenediamide

N,N^1-Di(2-iodophenyl)-*trans*-butenediamide (805 mg, 1.6 mmol) in DMSO (10 ml) was added to a suspension of sodium hydride (2.2 equiv., 101 mg, 3.5 mmol) in DMSO (50 ml) under nitrogen at room temperature. The reaction was stirred for 1 h., methyl iodide (2.5 equiv., 568 mg, 4 mmol) added, and stirring continued for 20 min. The crude material was filtered and washed with water and recrystallised from aqueous MeOH to give N,N^1-di(2-iodophenyl)-N,N^1-dimethyl-*trans*-butenediamide as a colourless powder (234 mg, 27%), m.p. 265-272 °C (dec); Analysis found: C, 39.0; H, 2.95; N, 5.0; I, 46.0; $C_{18}H_{16}I_2N_2O_2$ requires: C, 39.55; H, 2.95; N, 5.0; I, 46.0%; ν_{max} (KBr): 3200 and 3080 (C-H stretch), 1640 (C=O stretch), 1575 (C=C stretch) and 770 cm^{-1} (4 adjacent H); δ_H (90 MHz, d^6-DMSO at 110 °C) 3.1 (6H, s, N-CH_3) and 7.05-8.2 (6H, m, aromatic and alkene H); m/z 546 (M^+, 0.5%), 419 [(M^+-I), 100%] and 292 [(M^+-I_2), 44%].

110. Attempted cyclisation of N,N^1-Di(2-iodophenyl)-N,N^1-dimethyl-*trans*-butenediamide

N,N^1-Di(2-iodophenyl)-N,N^1-*trans*-butenediamide (300 mg, 0.55 mmol) was partially dissolved in deoxygenated toluene (75 ml). The solvent was heated to

reflux whereupon Bu_3SnH (1.1 equiv., 194 mg, 0.67 mmol) and AIBN (20%, 0.2 equiv., 18 mg, 0.11 mmol) added. The solvent was evaporated *in vacuo* and the residual material redissolved in acetonitrile (20 ml) and washed with pet. ether (4 x 100 ml). A red solid was isolated which eluded identification.

111a. Preparation of 2-Iodophenyl cinnamate

Cinnamoyl chloride (1.1 equiv., 9.99g, 60 mmol) in toluene (50 ml) was added dropwise to a stirred solution of 2-iodophenol (12 g, 54 mmol) in toluene (100 ml) over 30 min. Et_3N (1.2 equiv., 6.5g, 64 mmol) was added and the stirring continued for 1 h. The crude reaction was poured into water (200 ml). The organic layer was shaken with a saturated solution of $NaHCO_3$ (x4), dried, evaporated to dryness, and the residue recrystallised from absolute EtOH/pet. ether to give 2-iodophenyl cinnamate (11.4g, 60%), m.p. 70-72 °C; Analysis found: C, 51.7; H, 3.3; I, 36.5; $C_{15}H_{11}IO_2$ requires: C, 51.45; H, 3.15; I, 36.3%; ν_{max} (KBr): 1740 (C=O stretch), 1630 (C=C stretch), 750, 710, 685 and 650 cm^{-1} (4 and 5 adjacent H); δ_H (60 MHz, $CDCl_3$): 6.4-8.2 (m, aromatic and alkene H); m/z 350 (M^+, 2%) and 131 [(M^+-C_9H_7O), 100%]. The above procedure was used to prepare the esters in Expts. 111b-115.

111b. Preparation of 2-Iodobenzyl cinnamate

2-Iodobenzylalcohol (1.01g, 4.3 mmol) was reacted with cinnamoyl chloride (1.1 equiv., 790 mg, 4.7 mmol) to yield 2-iodobenzyl cinnamate (378 mg, 24%), b.p. (0.5) 250 °C. The distilled oil crystallised out on standing to give light yellow crystals (m.p. 55-58 °C); Analysis found: C, 52.7; H, 3.7; I, 33.7; $C_{16}H_{13}IO_2$ requires: C, 52.75; H, 3.55; I, 34.9%; δ_{max} (KBr): 1715 (C=O stretch), 1665 (C=C stretch), 750, 710, 685 and 650 cm^{-1} (4 and 5 adjacent H); δ_H (60 MHz, $CDCl_3$): 5.3 (2H, s, CH_2), 6.3-6.7 (1H, m, alkene H) and 7.1-8.0 (9H, m, aromatic H); m/z 237 [(M^+-I), 49%], 131 [(M^+-$C_9H_7O_2$), 100%], 103 (28), 90 (19), 76 (20) and 69 (24).

112. Preparation of 2-Bromophenyl thiocinnamate

2-Bromothiophenol (2g, 10.05 mmol) was reacted with cinnamoyl chloride (1.2 equiv., 2.12g, 12.6 mmol) to yield 2-bromophenyl thiocinnamate (2.6g, 77%), m.p. 75-77 °C; Analysis found: C, 56.8; H, 3.4; Br, 24.8; S, 9.95; $C_{15}H_{11}BrOS$ requires: C, 56.43; H, 3.45; Br, 25.1; S, 10.05%; ν_{max} (KBr): 1690 (C=O stretch), 1615 (C=C stretch), 750 and 690 cm^{-1}; m/z 131 [(M^+-$C_9H_7O_2$), 100%].

113a. Preparation of 2-Iodophenyl crotonate

2-Iodophenol (1.1g, 4.98 mmol) was reacted with crotonyl chloride (1.1 equiv., 569g, 5.4%) to yield 2-iodophenyl crotonate (310 mg, 22%), b.p. (0.2) 180 °C; Analysis found: C, 42.01; H, 3.3; I, 43.9; $C_{10}H_9IO^2$ requires: C, 41.65; H, 3.1; I, 44.1%; ν_{max} (thin film): 2912 (C-H stretch), 1736 (C=O stretch), 1654 (C=C stretch), 754 and 738 cm^{-1} (4 adjacent H); δ_H (60 MHz, $CDCl_3$): 1.8-2.1 (13H, d, J = 8 Hz, CH_3), 5.9-6.26 (1H, d, J = 16 Hz, alkene H) and 6.8-7.9 (5H, m, aromatic and alkene H); m/z 288 (M^+, 6%) and 69 [(M^+-C_4H_5), 100%].

113b. Preparation of 2-Bromophenyl crotonate

2-Bromophenol (1g, 5.7 mmol) was reacted with crotonyl chloride (1.5 equiv., 652 mg, 6.3 mmol) to yield 2-bromophenyl crotonate (320 mg, 32%), b.p. (0.2) 140 °C; Analysis found: C, 49.9; H, 3.7; Br, 32.3; $C_{10}H_9BrO^2$ requires: C, 49.8; H, 3.75; Br, 33.2%; ν_{max} (thin film): 1740 (C=O stretch), 1655 (C=C stretch), 755 and 740 cm^{-1} (4 adjacent H); δ_H (60 MHz, $CDCl_3$): 1.7-2.1 (3H, d, J = 9 Hz, CH_3), 5.83-6.26 (1H, d, J = 15 Hz, alkene H) and 6.8-7.6 (5H, m, aromatic and alkene H); m/z 242 (M^+, 2%) and 69 [(M^+-C_4H_5O), 100%].

114. Preparation of 2-Bromophenyl thiocrotonate

2-Bromothiophenol (2g, 1.05 mmol) was reacted with crotonyl chloride (1.2 equiv., 1.33g, 1.33 mmol) to yield 2-bromophenyl thiocrotonate (400 mg, 35%), b.p. (1) 200-220 °C; Analysis found: C, 46.5; H, 3.4; Br, 31.0; S, 12.4; $C_{10}H_9BrOS$

requires: C, 46.7; H, 3.5; Br, 31.1; S, 12.5%; ν_{max} (thin film): 1685 (C=O stretch), 1635 (C=C stretch), 770 and 745 cm^{-1} (4 and 5 adjacent H); δ_H (60 MHz, $CDCl_3$): 1.73-2.0 (3H, d, J = 8 Hz, CH_3), 5.9-6.33 (1H, brd, J = 16 Hz, alkene H), 6.63-7.76 (7H, m, aromatic and alkene H); m/z 257 (M^+, 1%) and 69 [(M^+-C_4H_5O), 100%].

115. Preparation of 2-Iodobenzyl crotonate

2-Iodobenzylalcohol (1g, 4.2 mmol) was reacted with crotonyl chloride (1.1 equiv., 498 mg, 4.7 mmol) to yield 2-iodobenzyl crotonate (250 mg, 20%), b.p. (0.05) 140-150 °C; Analysis found: C, 43.8; H, 3.64; I, 42.15; $C_{11}H_{11}IO_2$ requires: C, 43.7; H, 3.62; I, 42.05%; ν_{max} (thin film): 2980 (C-H stretch), 1736 (C=O stretch), 1640 (C=C stretch) and 750 cm^{-1} (4 adjacent H); δ_H (90 MHz, $CDCl_3$): 2.95-3.35 (3H, d, J = 8 Hz, CH_3), 4.95-5.0 (2H, s, CH_2), 5.5-6.3 (1H, m, alkene H) and 6.7-8.0 (5H, m, aromatic and alkene H); m/z 301 (M^+, 2%), 175 [(M^+-I), 85%], 107 (93), 90 (72), 89 (30) and 69 (25).

116. Cyclisations of 2-Iodophenyl cinnamate and 2-Iodophenyl crotonate under various conditions.

For the conditions used and results, see discussion (page xx). 2-Iodophenyl cinnamate/crotonate (as specified) under nitrogen. The solvent was heated to reflux whereupon Bu_3SnH (as specified) and AIBN (as specified) was added. The solvent was maintained at reflux with illumination for 24 h. The reaction mixtures were then analysed using GLC (3% OV17 on gas chrom Q 100/120 mesh at 120 °C) and compared with authentic materials.

117. Attempted cyclisation of 2-Bromophenyl thiocinnamate

2-Bromophenyl thiocinnamate (600 mg, 1.9 mmol) was dissolved in deoxygenated toluene (75 ml) under nitrogen. The solvent was heated to reflux whereupon Bu_3SnH (1.1 equiv., 602 mg, 2.1 mmol) and AIBN (0.3 equiv., 93 mg, 0.57 mmol) was added. The solvent was maintained at reflux whilst illuminating for 24 h. The reaction mixture was then examined by preparative t.l.c. (SiO_2 or Al_2O_3,

pet. ether/EtOAc, 2:1) which indicated the material had decomposed to a polymeric mixture which was not pursued.

118. Attempted cyclisation of 2-Iodobenzyl cinnamate

2-Iodobenzyl cinnamate (600 mg, 1.6 mmol) was dissolved in deoxygenated toluene (75 ml) under nitrogen. The solvent was heated to reflux whereupon Bu_3SnH (1.1 equiv., 528 mg, 1.8 mmol) and AIBN (0.3 equiv., 79 mg, 0.48 mmol) was added. The solvent was maintained at reflux and illuminated for 24 h. The solvent was evaporated *in vacuo* and the material redissolved in acetonitrile (20 ml) and shaken with pet. ether (5 x 100 ml). The acetonitrile fraction was evaporated *in vacuo* and the material chromatographed (SiO_2, t.l.c. grade, pet. ether/EtOAc, 2:1) and gave the reduced material benzyl cinnamate as a colourless oil (210 mg, 32%); Analysis found: C, 80.5; H, 5.6; $C_{16}H_{14}O_2$ requires: C, 80.7; H, 5.9%; ν_{max} (thin film): 2950 (C-H stretch), 1705 (C=O ester), 1620 (C=C stretch), 780 and 720 cm^{-1} (5 adjacent H); δ_H (60 MHz, $CDCl_3$): 5.36 (2H, s, CH_2), 6.4-6.73 (1H, d, J = 16 Hz, alkene H), 7.0-8.0 (11H, m, aromatic and alkene H); m/z 238 (M^+, 41%), 91 (100) and 77 (22).

119. Preparation of $\underline{N}^1$-(2-Bromophenyl)-$\underline{N}^2$-cinnamoylhydrazine

2-Bromophenylhydrazine hydrochloride (5g, 22.4 mmol) and cinnamoyl chloride (1.1 equiv., 4.1g, 24.6 mmol) were added simultaneously to a solution of KOH in water (2.2 equiv., 2.76g, 49.2 mmol in 75 ml) and stirred for 1 h. The resulting yellow precipitate was filtered off and recrystallised twice from absolute EtOH to give $\underline{N}^1$-(2-bromophenyl)-$\underline{N}^2$-cinnamoylhydrazine as colourless crystals (1.83g, 26%); ν_{max} (KBr): 3240 (N-H stretch), 3024 (C-H stretch), 1692 (C=O stretch), 1628 (C=C stretch), 768, 740 and 710 cm^{-1} (4 and 5 adjacent H). Authentication was achieved by full characterisation of the mono-$\underline{N}$-methyl compound (Expt. 120).

120. Preparation of $\underline{N}^1$-(2-Bromophenyl)-$\underline{N}^2$-cinnamoyl-$\underline{N}^2$-methylhydrazine

To a suspension of sodium hydride (1.1 equiv., 152 mg, 6.3 mmol) in DMSO (75 ml) was added $\underline{N}^1$-(2-bromophenyl)-$\underline{N}^2$-cinnamoylhydrazine (1.83g, 5.7 mmol) and the reaction stirred under nitrogen for 1 h. To the reaction mixture was added dropwise methyl iodide (1.2 equiv., 1.62g, 6.9 mmol) and stirring continued for a further 1 h. The crude material was then poured into water (100 ml) and extracted with Et_2O (4 x 50 ml). The organic layer was then washed with water (4 x 100 ml), dried and the solvent evaporated *in vacuo* to give the crude material, which was recrystallised from absolute EtOH to give pure $\underline{N}^1$-(2-bromophenyl)-$\underline{N}^2$-cinnamoyl-$\underline{N}^2$-methylhydrazine (490 mg, 26%), m.p. 120-122 °C; Analysis found: C, 58.3; H, 4.1; N, 8.1; Br, 24.6; $C_{16}H_{15}N_2Br$ requires: C, 58.0; H, 4.5; N, 8.5; Br, 24.2%; ν_{max} (KBr): 3236 (N-H stretch), 2920 (C-H stretch), 1646 (C=O stretch), 1606 (C=C stretch), 760 and 682 cm^{-1} (4 and 5 adjacent H); δ_H (90 MHz, $CDCl_3$): 3.25 (3H, s, CH_3), 6.2-7.8 (12H, m, aromatic and alkene H); m/z 331 (M^+, 11%), 251 [(M^+-Br), 2%], 200 [(M^+-$C_9H_7O^+$), 10%], 131 (100), 103 (25) and 43 (27).

121. Attempted cyclisation of $\underline{N}^1$-(2-Bromophenyl)-$\underline{N}^2$-cinnamoyl-$\underline{N}^2$-methylhydrazine

$\underline{N}^1$-(2-Bromophenyl)-$\underline{N}^2$-cinnamoyl-$\underline{N}^2$-methylhydrazine (127 mg, 0.38 mmol) was dissolved in deoxygenated toluene (75 ml) under nitrogen. The solvent was heated to reflux whereupon Bu_3SnH (1.1 equiv., 123 mg, 0.4 mmol) and AIBN (0.3 equiv., 18 mg, 0.1 mmol) were added. The reaction was maintained at reflux and illuminated for 48 h. The reaction was then evaporated *in vacuo* to give a yellow gum. The material was subjected to preparative t.l.c. (SiO_2, pet. ether/EtOAc, 3:1) and gave two fractions. Fraction (1) consisted of a polymeric mixture which was not characterised. Fraction (2) consisted of starting material (9 mg, 7% recovery) as indicated by comparison with an authentic sample of starting material.

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