Radical cyclisations onto imidazoles

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Radical Cyclisations onto Imidazoles

by

Fawaz Aldabbagh

A Doctoral Thesis

Submitted in partial fulfilment of the requirements for the award of

Doctor of Philosophy

at Loughborough University

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To mum, dad and Ameer.

family and friends
"you brought me fame, fortune and everything that goes with it, I thank you all."

"We are the Champions"  F. Mercury
Abstract

This thesis describes the development of new pathways towards the synthesis of novel antimicrobial (and anticancer) agents. Two synthetic protocols based on free radical chemistry are studied, which are used to access polycyclic heterocyclic compounds of potential biological importance. Both these procedures involve the generation of radicals using Bu$_3$SnH and AIBN initiators, and the subsequent intramolecular radical cyclisation onto the imidazole ring. Radical cyclisations onto benzimidazoles and pyrroles are also described.

Chapter One provides a general introduction to the research. It includes a description of the initial aims and objectives of the work, and a review of the literature in the areas of "bioreductive antimicrobial and anticancer agents," and "homolytic aromatic substitution reactions." The former outlines the current understanding of this biological activity, while the latter review's the basis of the free radical methodology used in this project.

Chapter Two describes the possibility of incorporating various ring systems onto nitroimidazoles by adapting synthetic procedures, which had already been used to synthesise mitomycin analogues. It describes the synthetic problems, and limitations of using nitroimidazole substrates with this methodology.

Chapter Three describes the first reported radical cyclisations onto imidazoles and benzimidazoles using "ipso" substitution at the C-2 position. This provides a new synthetic route to biologically important [1,2-α]fused benzimidazoles and imidazoles, and the potential synthesis of the targets given in Chapter Two. A mechanistic investigation into these intramolecular radical cyclisations using isotopic labelling studies is also described.

Chapter Four describes "oxidative radical cyclisations onto imidazoles and pyrroles using Bu$_3$SnH." The mechanism for such a transformation has been the subject of a great deal of literature speculation. A "pseudo SRN1 mechanism" is offered in this section. This synthetic protocol yielded a series of novel five, six and seven membered [1,2-α]fused imidazoles, which may be elaborated further to form new antimicrobial (and anticancer) agents. A description of the versatility and limitations of this methodology to access polycyclic heterocyclic systems is given.

Chapter Five provides a detailed description of all the experiments performed. All novel compounds reported in this chapter are fully characterised by IR, $_1^H$ and $_{13}C$ NMR, mass spectra and combustion analysis or accurate mass.
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Abbreviations

Ac  acetyl
AIBN azobisisobutyronitrile
Ar  aryl
Boc N-tert-butoxycarbonyl
bp  boiling point
Bu  butyl
DABCO 1,4-diazabicyclo[2.2.2]octane
DNA deoxyribonucleic acid
DMF N,N-dimethylformamide
DMSO dimethyl sulfoxide
EPR Electron Paramagnetic Resonance
equiv. equivalent
Et  ethyl
FT-IR Fourier Transform Infra-Red
GC-MS Gas Chromatography Mass Spectroscopy
IR  Infra-Red
lit. literature
LUMO Lowest Unoccupied Molecular Orbital
Me  methyl
mp  melting point
Mes mesyl
MS  Mass Spectroscopy
NBS N-bromosuccinimide
NMR Nuclear Magnetic Resonance
PCC pyridinium chlorochromate
Ph phenyl
Prep-TLC preparative Thin Layer Chromatography
TBS tert-butylsilyl
TEBA tetraethylbenzylammonium chloride
Tf triflate
THF tetrahydrofuran
TLC Thin Layer Chromatography
TMEDA N,N,N′,N′-tetramethylethylenediamine
Tol tolyl
Ts tosyl
UV Ultra-Violet
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1.0 General Introduction

1.1 Aims and Objectives of the Project

The long term aim of this research is the synthesis of novel antimicrobial (and anticancer) agents containing the combined structural features of mitomycins and nitroimidazoles necessary for biological activity. This objective can only be achieved by the development of new synthetic methodology to access such polycyclic heterocyclic systems. Thus, two synthetic protocols based on free radical chemistry had to be developed, which involved radical cyclisations onto several nitrogen containing heteroaromatic systems (imidazoles, benzimidazoles and pyrroles). The first synthetic protocol was an intramolecular aromatic "ipso-substitution" pathway, and the second involved "oxidative radical cyclisations" using Bu₃SnH. An understanding of the versatility and limitations of the two reaction protocols was essential. An assessment of the advantages of the two developed radical pathways against conventional syntheses of such heterocyclic systems, and an understanding of the mechanisms of these two radical protocols had also to be achieved.

1.2 Bioreductive Antimicrobial and Anticancer Agents

Bioreductive agents are compounds that require in vivo reduction in order to induce biological activity.¹ This may be antibiotic activity, which is the treatment of disease caused by microorganisms. The most widely used bioreductive antibiotics are nitroimidazoles, which are discussed in section 1.2.1. However, the term "bioreductive" was first applied to quinone compounds such as the anticancer drug mitomycin C, and so mitomycins are the subject of section 1.2.2.

1.2.1 Nitroimidazoles

Nitroimidazoles are antibiotics used clinically for treatment against anaerobic (without oxygen) bacteria, protozoal infection and in anticancer chemotherapy.¹ ² The specific mechanisms for these biological activities have not been clearly proven, nevertheless nitroimidazoles are an important group of antimicrobial and anticancer agents, which require reductive activation in vivo prior to reaction between the drugs and DNA (scheme 1). The initial stage in reductive activation often proceeds by a discrete one-electron transfer process that can be reversed by oxygen. This implies, that bioreductive drugs should be less potent in oxygenated cells. This is often the case and is the basis for the selectivity observed in experimental tumours.
Scheme 1. Reductive activation and oxidative deactivation

There are three possible isomeric structures with the nitro group at C-2 (1), C-4 (2) or C-5 (3) in the heterocyclic ring (figure 1). However, only 2- and 5-nitroimidazoles are biologically active.

Figure 1. Nitroimidazole structural isomers

The antibiotic azomycin (4) was the first nitroimidazole which was reported to be active against T. vaginalis. Nevertheless, the greatest advance in the chemotherapy of protozoan infections was made in about 1960 with the introduction of metronidazole (5). The latter was the first orally effective treatment of trichomoniasis and at higher dosage levels it proved to be most efficacious and tolerated treatment of amoebiasis. Metronidazole is still the market leader among nitroimidazole antibiotics because of its effectiveness, short duration of therapy, and low toxicity. However, several other 5-nitroimidazole analogues are commercially available (figure 2), the leading ones being tinidazole (6), ornidazole (7), nimorazole (8), and dimetridazole (9). There are less 2-nitroimidazoles in production, but misonidazole (10) is used as a substitute for metronidazole. Generally, 5-nitroimidazoles possess greater therapeutic advantage over 2-nitroimidazoles.

Figure 2. The market leading nitroimidazole antibiotics
The \textit{in vivo} reduction of nitroimidazoles does not require a nitroreductase enzyme, but is achieved by ferredoxin oxireductase (an Fe-S-protein acting as an electron transfer agent), which has a reduction potential of around -430 mV. This should be compared to the lowest reduction potential discovered in aerobic cells at -350 mV. Therefore, aerobic cells clearly possess insufficient reduction potential, and this would explain the lack of activity towards aerobes. Furthermore, the inactivity of 4-nitroimidazoles is explained, since it has a higher reduction potential than 2- or 5-nitroimidazoles. Therefore, nitroimidazoles act as electron acceptors from ferredoxin oxireductase, so interfering with the metabolic pathways of anaerobes without affecting the human host. These bioreductive drugs can function as either hypoxic (oxygen depleted) cell radiation sensitizers or as hypoxic-cytotoxins. Most biologically active nitroimidazoles exhibit both types of behaviour to varying degrees.

\textbf{a) Radiosensitization}

This represents an increase in the efficiency of radiation-induced DNA damage. This sensitisation is usually not observed in oxygenated cells, so this is the basis for tumour selectivity. It was suggested that a redox process was involved in which the efficiency of mammalian cell radiosensitization increases with the electron affinic properties of the nitro compounds used.\textsuperscript{5} Therefore, there is a clear dependence between the efficiency of sensitisation and one-electron reduction potentials.

\textbf{b) Hypoxic Cytotoxicity}

A vast array of compounds have been used to kill hypoxic mammalian cells. However, despite the efficiency of these hypoxic cytotoxins being directly related to the electron affinities of the compounds, the mechanisms involved are quite different from those of radiosensitization.\textsuperscript{1,6} This is because the critical step in hypoxic toxicity is enzyme-mediated reductive activation. This explains the process being much slower, highly temperature-dependent, and showing a much greater cell-line variability than is observed in hypoxic cell radiosensitization.

The only defined part of the mode of action of nitroimidazoles is the requirement that the nitroimidazole is reduced prior to any observable activity. The initial nitro radical anion (12) formed undergoes a reduction sequence (scheme 2) similar to that observed in many other aromatic nitro compounds. This consists of a series of single electron transfer (SET), protonation and dehydration reactions. There is no clear evidence published to date to which of the possible reduced species is the reactive intermediate in the mode of action of nitroimidazoles, although several proposals have been put forward. For instance, the nitro radical anion (12) is a likely reactive intermediate, since it is well known that many electrophiles and radicals readily react with DNA. Studies using electron paramagnetic resonance (EPR) spectroscopy have detected the presence of nitro radical anions in protozoal and anaerobic bacterial cells.\textsuperscript{1,7} This suggests that they are relatively stable, and may survive long enough to react with some intracellular species. Furthermore, EPR spectroscopy work by Bowman and Symons\textsuperscript{8} has suggested that the nitro radical anion is more stable than might otherwise have been expected (scheme 3).
There have been only a few reports in the literature claiming that the nitroso derivative (13) is the reactive intermediate, probably because it has never been isolated in reduction studies. This is due to the fact that the nitroso species is rapidly reduced to the hydroxylamino compound (14) in reduction studies, and this reactivity has led to it not being considered as a serious reactive intermediate. Nevertheless, it has been shown that hydroxylamino derivatives require oxidation prior to becoming active, which supports the case for the nitroso species (13) being the reactive
intermediate. Furthermore, nitroso analogues of 4- and 5-nitroimidazoles have been synthesised and proved to have a much greater biological activity against a number of anaerobic micro-organisms. These results provide further evidence for the reductive potential being the primary factor in determining the activity of nitroimidazoles, and suggests that the nitroso species is the reactive intermediate. There is however good evidence to eliminate the amino derivative (15) from suspicion of being an active intermediate, since Sullivan et al. have prepared the amine derivative of metronidazole (5, figure 2), and found it to be biologically inactive.

1.2.2 Mitomycins

Mitomycins, exemplified by mitomycin C (16a) and A (16b in figure 3) are a class of potent anti-tumour antibiotics. These bioreductive drugs are useful as chemotherapeutic agents for the treatment of various tumours. Once reductive activation has taken place, mitomycin reacts covalently with DNA, so exerting its cytotoxic action. Therefore, like nitroimidazoles, these compounds are selectively toxic to hypoxic cells because the oxygen in aerobic cells oxidises the reductively activated intermediates back to the neutral drugs, before they are able to react with DNA. There has been intense research into the synthesis of mitomycin analogues and other structurally related compounds as part of the quest for new therapeutically useful drug formulations with improved tumour specificity and cytotoxicity.

The proposed mechanism for mitomycin antitumour activity is shown in scheme 4. Activation occurs at the quinone group in a single electron reduction process, and subsequent loss of methanol, and opening of the aziridine ring provides electrophilic species (19). It is particularly noteworthy that all these steps occur at the radical anion stage, and that the intermediate aziridinomitosene semiquinone (17) can be reoxidised on exposure to air to aziridinomitosene (18). Isolation of mono DNA adducts such as (21) proved that nucleophilic moieties in DNA firstly alkylate position 1 in the electrophilic species (19), prior to the alkylation of position 10 to give the cross-linked DNA adduct (22). The latter occurs at the iminium species (20), which is formed by virtue of the push of the indole nitrogen electron pair causing the loss of the urethane group (CONH₂).
Scheme 4. Proposed mechanism for the activation-alkylation cascade of the mitomycins
1.3 Homolytic Aromatic Substitution

Homolytic aromatic substitution is an addition-elimination reaction, which can be represented by the general reaction given in scheme 5. The mechanism is based on studies performed by Hey et al\textsuperscript{12} in the 1930s on arylation (Rad \(*=\) Ar \(*, and various X) reactions. The synthetic interest of these reactions was however limited until the extensive work of the last twenty five years improved the reactivity and regioselectivity of these processes.

**Summary:**

\[ \text{Rad} \ast + \text{ArH} \rightarrow \text{ArHRad} \ast \]

Scheme 5. Homolytic aromatic substitution

A general mechanism for the addition of a radical to an aromatic system is given in scheme 6, which probably proceeds via several transition states and intermediates with reactivity and regioselectivity being determined by polar effects in the radical and substrate.\textsuperscript{13}

**Scheme 6. Radical addition followed by substitution**

Unlike, aromatic electrophilic substitution, which proceeds via a rapid extrusion of a proton to regain aromaticity, the expulsion of a hydrogen atom from a cyclohexadienyl radical requires the participation of a new reactant. Scheme 7 shows the two possible elimination processes; disproportionation or oxidation, where the oxidant can be e.g. oxygen, a nitro derivative, a peroxide or a metal salt. A good oxidant will enhance the yield of the substitution product. Oxidative radical cyclisations are the subject of section 1.3.2.

The two synthetic protocols used in this project are aromatic homolytic substitution (ipso-substitution), which is the subject of the next section, and 'oxidative radical cyclisations' using Bu\textsubscript{3}SnH, which is reviewed for the first time in section 1.3.3. The latter may proceed via a "pseudo S\textsubscript{RN}1 mechanism" consequently the mechanism of S\textsubscript{RN}1 reactions is briefly discussed in section 1.3.4.
1.3.1 Aromatic Homolytic 'ipso-Substitution'

'ipso-substitution' is substitution at a position already carrying a substituent. In the 1970s, Tiecco et al. \(^{14}\) extensively studied intermolecular aromatic ipso-substitution reactions, and provided the following conclusions:

1. Electroneutral radicals only give selective ipso attack in those cases in which addition affords a σ-complex intermediate of considerably greater stability than those derived from the addition at unsubstituted positions. 2. Ipso attack is particularly facilitated by polar effects that can intervene and stabilise the transition state of the addition. 3. Many examples have been reported of nucleophilic radicals easily undergoing ipso-substitution onto aromatic compounds containing electron withdrawing groups. 4. Fewer literature examples exist of polar effects facilitating the addition of electrophilic radicals at the ipso position of aromatic compounds holding electron-releasing substituents.

For example, the nucleophilic 1-adamantyl (Ad·) radical reacts with several 2-substituted benzothiazoles (23) to afford 2-(1-adamantyl)-benzothiazole (24), as a result of homolytic ipso-substitution (scheme 8).\(^ {15}\) The greatest yields were obtained with the strongest electron withdrawing leaving groups \(i.e.\) nitro (\(X=\text{NO}_2\)) and phenylsulfonyl (\(X=\text{PhSO}_2\)). The 1-adamantyl radical was generated via a redox reaction with silver nitrate in a solution of aqueous ammonia and ammonium sulfate in acetonitrile.

\[ \text{Scheme 8. \textit{ipso}-substitution in 2-substituted benzothiazole} \]

Therefore, on the basis of these results an addition-elimination sequence was proposed (scheme 9) in which radical anion (25) may be formed by the transfer of an electron from the
adamantyl radical to the benzothiazole, and this may play an important role in determining the ease of formation of the σ-complex intermediate (26). The subsequent formation of substituted benzothiazole (24) will be thus greatly facilitated by the superior leaving group ability of e.g. the PhSO₂ group.

![Chemical structure and reaction scheme](image)

**Scheme 9. Tiecco et al., 'addition-elimination' mechanism**

Watanabe et al. reacted electron deficient 2-(alkylsulfonyl)benzothiazoles (27) directly with Bu₃Sn• to give 2-(tributylstannyl)benzothiazole (28) in 67-79% yield (scheme 10). This synthetic methodology is important in overcoming the steric factors in carbon-tin bond formation between a bulky tin atom and a sterically hindered internal carbon atom.

![Chemical structure and reaction scheme](image)

**Scheme 10. Intermolecular 'ipso-substitution' using Bu₃Sn•**

Intramolecular ipso-substitution reactions have received greater attention in the last fifteen years. For example, ipso-substitution reactions were proposed for the formation of unexpected products such as the phenanthrene (31) via the postulated spiro intermediate (30) instead of the 'oxidative biaryl coupling reaction product' (29) in scheme 11 (also see scheme 44 in section 1.3.3.).

The synthetic utility of intramolecular ipso-substitution reactions was first demonstrated by Speckamp et al. (scheme 12), when a 1,4-aryl rearrangement was observed to quantitatively give the phenanthridine analogue (32).
A further example from Speckamp et al\textsuperscript{21} is illustrated in scheme 13, which can be adapted to the aryl shift depicted in scheme 12. The $\alpha$-halomethyl substituted piperidine sulfonamides (33) gave a mixture of the 1,6-addition products (35), the ipso-substitution, desulfonylation products (36), and the reduction compounds (34). Furthermore, it was found that if the ortho positions were blocked, as in compound (33e) the 'ipso-attack product' (36e) was the only compound obtained, and the 1,6-adduct (35e) and reduction compound (34e) were not formed. The absence of the latter may be due to an interaction of the radical intermediate with the aromatic substituent in such a way that steric factors prevent effective hydrogen transfer by the bulky tributyl tin hydride molecule.
This methodology has been extended by Motherwell et al\textsuperscript{22,23} in the area of biaryl couplings (scheme 14) in which competition is observed between [1,5]\textit{ipso}-substitution and [1,6]addition of aryl radicals (37). When $X = \text{O}$ or CH$_2$ only the direct addition products (39) were observed, and a mixture of (39) and (41) were obtained when $X = \text{NCH}_3$. These results may be compared to the decarboxylation of carbamoyloxyl radicals ($R_2\text{NCO}_2\cdot$) which are known to be faster than the analogous oxygen case ($\text{ROCO}_2\cdot$). Given the possibility of the interconversion of radical intermediates (38) and (40), and a similar rate difference for the extrusion of sulfur dioxide, the mechanisms shown in scheme 14 provide a reasonable explanation.
Attention was then shifted to the effect of incorporation of substituents on the aromatic acceptor ring,\textsuperscript{22,23} which proved that this strategy is of great synthetic value, since it encourages the formation of sterically congested products with both electron releasing and/or electron withdrawing groups sited either ortho and/or para to the sulfonyl substituted acceptor ring. These are both beneficial, and tolerant to the synthetic process. The formation of such molecules could prove difficult by non-radical metal mediated methods. Some of the results are shown in scheme 15. Particularly noteworthy was the location of methoxy substituent at the ortho position in biaryl compound (42), which yielded solely the ipso-substitution product (43). In contrast sulfonamide (44) with a meta carbomethoxy group yielded a mixture of the [1,5]ipso-substitution product (45), and [1,6]addition products (46) and (47). In the latter, there are two possible sites for [1,6]attack, but only one set of the possible rearomatised regioisomeric products was recovered. The dihydroaromatic compound (47) was isolated from the second set, since rearomatisation would lead to the introduction of a severe peri interaction from the carbomethoxy group. The formation of 'oxidative radical cyclisation' products using the reductive conditions of Bu$_3$SnH mediated reactions is the subject of section 1.3.3.

Furthermore, this strategy was extended to the synthesis of heterobiaryls by appropriate positioning of the heteroatom.\textsuperscript{23} A couple of representative examples are shown in scheme 16, and serve to reinforce the previously established reactivity pattern, \textit{i.e.} hetero atoms positioned ortho and/or para to the sulfonyl group yield largely or selectively the [1,5]ipso-substitution product.
Scheme 15. The influence of substituents on ipso-substitution during biaryl coupling

Scheme 16. Heterobiaryl couplings
Grimshaw et al.\textsuperscript{24} have carried out radical biaryl couplings electrochemically. The reduction of compounds (48) and (49), as shown in scheme 17 occurs at a mercury cathode in aprotic solvents and can lead to the formation of compounds (51), (52) and (53). The intermediate σ-radical (50) is derived from the radical anions (48) or (49). In the case of the amide (49), a halide anion is lost to give \textit{syn} and \textit{anti} radicals of (50). The formation of carbanions was considered unlikely, since nucleophilic substitution on an unactivated benzene ring is highly improbable. There was however, a considerable quantity of reduced amide (51) observed in these processes, which may be due to the rotation about the amide bonds adjoining the two benzene rings during radical cyclisation to give the \textit{anti} amide. The \textit{cis} conformation of the amide would give the greatest access to the [1,6]addition product (53). It is however particularly noteworthy, that these electrochemical biaryl coupling experiments give relatively large quantities of products formed as a consequence of \textit{ipso}-substitution, such as the biaryl (52), when there are substituents \textit{ortho} or \textit{para} in the starting compound. Such findings are in agreement with the biaryl couplings of Motherwell et al.\textsuperscript{22,23}

\begin{scheme}[h]
\centering
\includegraphics[width=\textwidth]{schematic.png}
\caption{Electrochemical biaryl couplings}
\end{scheme}
More recent work by Lee et al. on radical isomerisations by intramolecular *ipso*-substitution of aryl ethers$^{25}$ and *N*-arylamides$^{26}$, also proposed that the efficiency of *ipso* attack was greatly dependent upon the stability of the intermediate *spiro* cyclohexadienyl radical. The 3-aryloxypropyl radicals (54) can abstract hydrogen from Bu$_3$SnH to form aryl propyl ethers (55), or attack *ortho* or *ipso* aryl positions intramolecularly to form the fused (56) or *spiro* (57) cyclohexadienyl radicals (scheme 18). In agreement with the findings of Motherwell$^{22,23}$ and Grimshaw$^{24}$ both electron-withdrawing and -donating substituents on the aryl ring facilitate the *ipso* attack. Furthermore, captodative stabilisation can be achieved, when the *spiro* cyclohexadienyl radical intermediate (57) is strategically substituted by two groups with opposing electron demand (e.g. compound 58). This leads to the isolation of only the rearranged product (59) in high yield.$^{25}$

**Scheme 18.** Radical Isomerisation via *ipso*-substitution
A similar aryl shift to that first observed by Speckamp et al\textsuperscript{20,21} (schemes 12 and 13) may also be induced photochemically, and has proved to be an effective method for the arylation of 1,2-diketones.\textsuperscript{27} Scheme 19 shows the irradiation of 2-{(aryl sulfonyl)oxy} cyclohexanones (60) provided an excited triplet state (61), subsequent addition to the \textit{ips}o position provided intermediate (62), which can either revert to the starting material or eliminate sulfur dioxide and rearomatise to the enolisable diketone (63). Sensitisation and quenching experiments unambiguously proved the radical process and the formation of the excited lowest triplet state.

Vinyl radicals, generated by the regioselective addition of stannyl radicals to an appropriate alkyne, and subsequent intramolecular radical cyclisation onto a benzene ring have been the subject of detailed research.\textsuperscript{28,29} Such a process was carried out by Nanni et al\textsuperscript{29}, with aryl alkynyl sulfides and selenides. The latter is depicted in scheme 20, and it was concluded that a 5-exo cyclisation of (Z-) vinyl radicals (64) to form \textit{spiro} cyclohexadienyl radical (65) was a highly favoured process due to the heteroatom (selenium or sulfur) possessing empty low energy orbitals, which interact with the radical centre to facilitate such a ring closure. It can then be assumed that both 5- and 6-membered rings can be derived from the initial 5-exo cyclisation, and the virtual absence of the selenopyran (66) suggests that radical (65) was not subject to a competing ring expansion, presumably owing to the fairly low energy of the C-Se bond. On the contrary, nitrogen- and oxygen-containing vinyl radicals give only reduction products, while the hydrogen abstraction product (67) was absent. This can again be attributed to the powerful carbon radical and selenium atom interaction.
The free radical ipso-substitution of 2-substituted indoles carried out by Caddick et al.\textsuperscript{30,31} is shown in Scheme 21. The iodides (68) gave better yields of cyclised compounds (69) than analogous bromide radical precursors. The electron withdrawing SPh, SOPh and SO\textsubscript{2}Tol groups enhanced the electrophilicity at the indole-2-position thereby facilitating attack by the nucleophilic alkyl radicals. Therefore, this radical 'addition-elimination' sequence enabled the formation of five, six and seven membered fused [1,2-\textit{a}] indole systems (69). Generally, for any one substituent the yields of the six membered rings were greater than the five membered compounds. These findings reinforce the reactivity patterns found in other radical cyclisations onto indole systems.\textsuperscript{32,33} An explanation by Jones et al.\textsuperscript{33} proposed that there is considerable strain and distortion in the five membered ring product, and hence presumably the transition state. However, the favourability of such a cyclisation protocol was highlighted by the formation of the seven membered ring in moderate yields, when \( L = \text{SOPh} \) or \( \text{SO}_2\text{Tol} \). However, the attempted formation of the seven membered ring with \( L = \text{SPh} \) (68c) failed. The authors believe that this is due to the aryl sulfide moiety not being as strongly electron withdrawing as the higher valence sulfur forms (\textit{i.e.} SOPh and SO\textsubscript{2}Tol), consequently the rate of cyclisation would be low.
Scheme 21. The formation of [1,2-a] indoles by intramolecular ipso-substitution

The generality of this protocol was tested with the radical cyclisations detailed in scheme 22. Despite the formation of the tricycle (70) in good yield, only the reduced compound (72) was formed from the attempted cyclisation of amide (71). The reason for this anomaly is the restricted rotation about an amide bond, which forces the alkyl radical generated from (71) to take up a disfavoured trans conformation for radical cyclisation onto the aromatic ring.

Scheme 22. Testing the generality of aromatic ipso-substitution
1.3.2 Oxidative Radical Cyclisations onto Heteroaromatic Systems

The intermolecular and intramolecular addition of a radical onto an aromatic nucleus followed by oxidation of the new resonance stabilised π–radical intermediate back to the aromatic system (i.e. oxidative radical cyclisation) is a process which has considerable synthetic utility. Numerous methods have been employed to affect such cyclisations, and many of these methods will be discussed in this section.

Much of the basic understanding of intermolecular homolytic radical substitution reactions has been due to the extensive work of Minisci et al.35 In 1968 a preliminary report36 by this group proposed that regioselective reactions could only be achieved if a polar antagonism was created by allowing nucleophilic carbon centred radicals to attack electron deficient substrates. Therefore, olefins conjugated with electron withdrawing groups, protonated heteroaromatic bases, quinones and many other electron deficient heterocycles were thus employed as substrates. Intermolecular radical additions onto heteroaromatic rings have proved to be very facile, and most importantly it reproduces the Friedel-Crafts reaction, but with opposite reactivity and selectivity owing to the nucleophilic character of the reacting radicals. Furthermore, the similarity of such a process with the classical Friedel-Crafts reaction can be related by the fact that generally the more stable the carbonium ion the more nucleophilic the corresponding radical. Hence, it may be inferred the electrophilic species useful in the Friedel-Crafts reactions can be utilised, as corresponding radicals, for the selective substitution onto heteroaromatic bases (with exception to carbon centred radicals conjugated with electron withdrawing groups). The rates for alkyl and acyl radicals are usually extremely high, and this is coupled with high substrate and positional selectivity. A general oxidative homolytic substitution process with a protonated pyridine as the substrate is outlined in scheme 23. The pyridyl π–radical intermediate (73) is highly nucleophilic, and so only a mild oxidant is required to achieve selective rearomatisation.

Scheme 23. The general outline of an oxidative radical substitution onto protonated pyridines
Such a system can be mediated by Ti(III) and hydroxylamine in acid medium (scheme 24), which can generate alkyl radicals (74), and selectively rearomatise the quinoline intermediate (75).\textsuperscript{37}

\[
+\text{NH}_3\text{OH} + \text{Ti}^{3+} + \text{H}^+ \rightarrow \text{NH}_3 + \text{Ti}^{4+} + \text{H}_2\text{O}
\]

\[
\text{NH}_3 + R-H \rightarrow \text{NH}_4^+ + R^* \quad \text{74}
\]

\[
\text{74} = ^*\text{CH}_2\text{OH}, \text{CH}_3\text{CHOH},
\]

Overall reaction;

\[
\text{Overall reaction;}
\]

\[
\text{CH}_3
\]

\[
\text{NH}^+
\]

\[
\text{H}^+
\]

\[
\text{CH}_3
\]

\[
\text{R}^-
\]

\[
\text{74} = ^*\text{CH}_2\text{OH}, \text{CH}_3\text{CHOH},
\]

\[
\text{C-OR}
\]

\[
\text{C-OR}
\]

\[
\text{C-N}
\]

\[
\text{C-N^+}
\]

\[
\text{Figure 4}
\]

Moreover, the low oxidising character of this system allows the use of strongly nucleophilic radicals. This is advantageous because, often a marked increase in the nucleophilicity of radicals can cause synthetic limitations due to an increase in the stability of the radical, and consequently its oxidisability.\textsuperscript{38} The latter is particularly prevalent in radicals with oxygen and nitrogen atoms in the $\alpha$-position, as depicted in figure 4.
Furthermore, radicals that are too nucleophilic can be involved in electron transfer processes with heteroaromatic compounds of high electron affinity (schemes 9 and 25), which limits the substitution process.\textsuperscript{15,37}

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme25.png}
\end{center}

**Scheme 25.** Electron transfer process

Another method for the effective substitution of protonated heteroaromatic bases uses alkyl iodides in Fenton's reagent type conditions (scheme 26).\textsuperscript{39} This method may be also applied to complex alkyl iodides, such as iodo sugars that lead to C-nucleosides with interesting biological activities. The reaction depicted in scheme 26 proceeds through a complex pathway. Normally, a Fenton's reagent reaction as shown in scheme 27 (eq. 1) would produce highly reactive and none selective hydroxyl radicals ($\text{HO}^\cdot$) by the Fe(II) catalysed decomposition of hydrogen peroxide. The hydroxyl radical can thus react with substrates, such as the alkyl iodides. However, this reaction was minimised by using DMSO as the reaction solvent. Scheme 27 (eq. 2) shows the reaction of DMSO with the hydroxyl radical leads to fast $\beta$-scission, and the generation of a methyl radical ($\text{Me}^\cdot$). The methyl radicals generated are much more reactive than the alkyl radicals ($\text{R}^\cdot$), and consequently the abstraction of iodine from the alkyl iodides is fast.

However, in the studies of Minisci \textit{et al}\textsuperscript{35} the alkyl radical was always selectively introduced into the heteroaromatic ring because of its superior nucleophilicity over that of the methyl radical. Fe(III) compounds also serves as oxidants for the pyridyl radical intermediates (73, in scheme 23).\textsuperscript{39}

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme26.png}
\end{center}

**Scheme 26.** Fenton's conditions for intermolecular radical cyclisations.

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme27.png}
\end{center}

**Scheme 27.** The generation of methyl radicals using Fenton's type conditions
Scheme 28. Intramolecular radical cyclisations onto indoles and pyrroles using Fenton's conditions.
Muchowski et al.\textsuperscript{40} extended the use of the Fe(II) /DMSO /H$_2$O$_2$ system to intramolecular radical cyclisation reactions. This allowed the synthesis of a wide range of bicyclic indoles and pyrroles. A selection of the reactions carried out are shown in scheme 28. The regioselectivity of these reactions was in agreement with Frontier Molecular Orbital (FMO) calculations, which showed that indole compounds (76 and 78) possess a large LUMO coefficient at C-2. Therefore, the expected addition of the nucleophilic alkyl radical at this position was observed providing cyclised products (77) and (79) respectively. There was however, no correlation observed between the isolated yields and the magnitude of LUMO coefficients. Furthermore, indoles (80) and (82) possess a methyl and hydrogen substituent at the 3-position respectively, which results in the LUMO coefficient at C-2 and C-7 being almost identical. However, indoles (81) and (83) resulting from radical addition at C-2 were the only observed products, because the disruption of the heterocyclic system is always more favourable than the more resonance stabilised benzoid ring. Secondary radicals could also be cyclised under these conditions, but tertiary radicals (e.g. generated from compound 84) gave the expected cyclised compounds (e.g. 85) in poor yield due to the formation of the tertiary carbonium ion providing alkenes (86) and (87). The pyrrole (88) has similar LUMO coefficients at C-3 and C-5, but for steric reasons only the cyclised indole (89) was produced.

Manganese (III) based oxidative radical cyclisations have also been used to carry out intramolecular radical cyclisations onto pyrroles.\textsuperscript{41} The almost quantitative conversion of alkylmalonate (90) into cyclic diester (92) using manganese(III) acetate in acetic acid is shown in scheme 29. Cyclised diester (92) can also be obtained by bromine abstraction (Br *) from the bromomalonate (91) using a triethylborane/oxygen mediated oxidation process.

\begin{center}
\begin{tikzpicture}

\node[rectangle, draw, text width=4cm, align=center] (a) at (0,0) {
\[
\text{2 Mn(OAc)$_3$, HOAc / NaOAc}
\]};
\node[rectangle, draw, text width=4cm, align=center] (b) at (4,0) {
\[
\text{NaH, THF, NBS}
\]};
\node[rectangle, draw, text width=4cm, align=center] (c) at (0,-4) {
\[
\text{Et$_3$B / O$_2$}
\]};

\draw[->] (a) -- (b);
\draw[->] (b) -- (c);
\end{tikzpicture}
\end{center}

\textbf{Scheme 29. Intramolecular oxidative radical cyclisations of pyrroles}
The mechanism for triethylborane oxidative radical cyclisations is not fully understood. However, the most probable pathway is autoxidation. The ethyl radical generated (scheme 30) probably undergoes bromine abstraction from bromomalonate (91). The initiation process for such a mechanism remains largely unknown.

\[
\text{ROO}^\cdot + \text{Et}_3\text{B} \xrightarrow{\text{slow}} \text{ROO}^- \text{B} \text{Et}_2^+ + \text{Et}^\cdot \\
\text{Et}^\cdot + \text{O}_2 \xrightarrow{\text{fast}} \text{EtOO}^\cdot
\]

Scheme 30. Triethylborane autoxidation

The synthesis of indolo[2,3-a]isoquinolines via the Mn(III) mediated oxidative addition of dimethyl malonate radicals across the C-2 position of indole is shown in scheme 31. The cyclisation is again activated by the electron-withdrawing group (EWG) at C-3. The great advantage of these transition metal catalysed processes is that the reaction products are free of unwanted tin hydride reduction compounds, as is observed in the analogous Bu$_3$SnH mediated radical cyclisations.

\[
\text{EWG} \xrightarrow{\text{Mn(OAc)$_3$, CH$_2$(CO$_2$Me)$_2$}} \text{EWG}
\]

Scheme 31. Synthesis of indolo[2,3-a]isoquinolones

Minisci et al\textsuperscript{44} have also cyclohexylated a variety of heteroaromatic bases (e.g. quinoline, benzothiazole, isoquinoline ) (scheme 32) using cyclohexylthiocarbonate (94), and benzoyl peroxide (93). Cyclohexylthiocarbonate (94) was conveniently prepared \textit{in situ} from the reaction of cyclohexanol and dithiocarbonate under acidic conditions. The mechanism was proposed by Barton\textsuperscript{44} in which the rate of phenyl radical addition to the dithiocarbonate (94) is very high, since no phenylation of the heteroaromatic bases was observed. The nucleophilic cyclohexyl radical (R \cdot) generated now adds to the heteroaromatic base, which subsequently loses a proton. The final step of the mechanism involves a single electron transfer (SET) with the oxidising benzoyl peroxide (93) to regain the aromaticity of the heteroaromatic system. It may be speculated that this will lead to the formation of a benzoyl peroxide radical anion (95) which will then disintegrate to a phenyl radical and peroxy anion (PhCOO\textsuperscript{-}) in a process identical to that earlier proposed by Bowman et al.\textsuperscript{45} \textit{i.e.} the "\textit{pseudo} aromatic \textit{SN}_1" mechanism (see section 1.3.3).
1.3.3 'Oxidative Radical Cyclisations' using Bu₃SnH

The last section describes the wide variety of systems reported to perform radical cyclisations with oxidative rearomatisation. The conditions employed in most cases were oxidative, which is useful in regenerating the final aromaticity of the product. However, this project is concerned with 'oxidation' during 'reductive cyclisations' with Bu₃SnH.

The use of Bu₃SnH for the reductive cyclisations of a wide range of substrates has been widely reported, and is well used in synthetic organic chemistry. These reactions involve radical abstraction of a labile group (e.g. iodine, bromine and benzeneselanyl) by Bu₃Sn • radicals to yield an intermediate radical, cyclisation of the radical onto an unsaturated bond, and reduction of the new intermediate radical by abstraction from Bu₃SnH. Nevertheless, there has been an increasing number of reported Bu₃SnH mediated 'oxidative radical cyclisations'. This type of radical cyclisation has been shown to be synthetically very useful, and an understanding of the common aspects of its mechanism is of great interest.

The earliest literature example (scheme 33) is of radicals generated from 5'-deoxy-5'-iodoadenosine derivatives undergoing 5'-8-cyclisation to give mainly the reduction compounds (96) and (97), and a small amount of 'oxidative rearomatisation product' (98) in 16% yield. This was improved by Ueda et al with their stereospecific radical cyclisations of adenosine 5'-aldehyde (99) to yield the corresponding rearomatised 8,5'-cycloadenosine derivative (100) in good yield. An understanding of these reactions is important since radicals are effective nucleobase damaging agents.
The synthetic utility of these intramolecular radical cyclisations onto heteroaromatic systems was first demonstrated by Murphy and Sherburn⁴⁹ reporting the efficient formation of [6,5], [6,6], [6,7]-bicyclic pyridinium salts (scheme 34).

Most recently, pyridinium radicals have been generated from 2-bromo-\textit{N}-alkylpyridinium salts (101) (scheme 35), and shown to add to a benzene ring to give the fused tricyclic system (102) in good yield.⁵⁰
The first proposed mechanism for oxidative radical cyclisations using \( Bu_3SnH \) was the "pseudo \( S_{RN1} \) mechanism" given by Bowman \textit{et al.} It was first described for the addition of aryl radicals onto thioamides (scheme 36) to yield benzothiazoles (104) with no dihydro product being observed. This almost quantitative formation of the 'oxidised' product was carried out under conditions, which rigorously excluded oxygen.

\[ \begin{align*}
\text{H} & \quad \boxed{\text{Bu}_3\text{SnH}} \\
\text{Ph} & \quad \text{S} \\
\hline
\text{N} & \quad \boxed{\text{Ph}} \\
\text{S} & \quad \boxed{\text{Ph}}
\end{align*} \]

\textbf{Scheme 36.} Cyclisation of thioamide

The proposed mechanism (scheme 37) begins with \( S\text{H}_2 \) abstraction of halogen by \( \text{Bu}_3\text{Sn} \cdot \) to yield a very reactive \( \sigma \)-aryl radical (105), which undergoes addition to the sulfur in the C=S bond. It is proposed that a proton is lost from radical intermediate (106) to \( \text{Bu}_3\text{SnH} \) to evolve hydrogen gas, and yield a highly stable radical anion (107). The normal steps of \( S_{RN1} \) reactions are followed, that is the radical anion (107) undergoes a \text{SET} (single electron transfer) with a another molecule of substrate (103) to form the benzothiazole product (104), and a new radical anion of the substrate (103'). The latter loses halide anion rapidly to reform \( \sigma \)-aryl radical (105), and so completing the mechanistic cycle. The role of \( \text{Bu}_3\text{SnH} \) is only catalytic to the radical chain, and it is the only substance that can act both as a base and radical initiator. This was supported by the formation of benzothiazole (104) in good yield using only a catalytic amount of \( \text{Bu}_3\text{SnH} \) (0.1 equiv.), and DABCO (1.1 equiv.). It should be noted that in "normal" \( \text{Bu}_3\text{SnH} \) reductive cyclisations an acidic hydrogen is not present.

\[ \begin{align*}
\text{H} & \quad \boxed{\text{Bu}_3\text{SnH}} \\
\text{Ph} & \quad \text{S} \\
\hline
\text{N} & \quad \boxed{\text{Ph}} \\
\text{S} & \quad \boxed{\text{Ph}}
\end{align*} \]

\textbf{Scheme 37.} \textit{pseudo} \( S_{RN1} \) mechanism

27
Support for the "pseudo S_{RN}1 mechanism" has been offered by Beckwith and Storey\textsuperscript{51} (scheme 38) to explain the formation of oxindoles (111) from suitable o-bromo-N-methylanilides (108) using tandem translocation of the initially formed aryl radical (109), and subsequent intramolecular homolytic substitution. It was first shown that the intramolecular homolytic substitution was the rate determining step as opposed to the prior aryl radical translocation (or 1,5-hydrogen transfer). The reactions used di-tert-butyl peroxide as initiator, which would be a doubtful oxidant for intermediate cyclised radical (110). Therefore, on this evidence initiators such as AIBN may also not be involved in abstraction of hydrogen (H⁺).

\begin{center}
\includegraphics[width=\textwidth]{scheme38.png}
\end{center}

\textbf{Scheme 38. Radical synthesis of oxindoles}

\begin{center}
\includegraphics[width=\textwidth]{scheme39.png}
\end{center}

\textbf{Scheme 39. The fate of radicals generated next to carbonyls in o-iodoanilides}
The generation of radicals adjacent to carbonyls (113) via a highly favoured 1,5-hydrogen transfer reaction of \( \alpha \)-iodoanilides (112), which undergo tandem 1,5-exo and 1,7-cyclisation to give the radical intermediates (114) is shown in scheme 39. Contrary to the "pseudo SRN I mechanism" AIBN was proposed as a possible oxidant of the intermediate cyclised radical (114), since the reaction only reached completion with an excess of AIBN and prolonged heating. Other reactions involving oxidative rearomatisations do not occur in the absence of Bu\(_3\)SnH or AIBN and are low yielding in the presence of catalytic amounts of AIBN. Furthermore, AIBN has been shown to abstract hydrogens in radical reactions.

The work of Minisci et al\(^{35}\) in the area of oxidative intermolecular homolytic aromatic substitution reactions has proved to be fundamental. Section 1.3.2 discussed many of these reactions, however the alkyl radicals generated prior to aromatic substitution were always selectively derived from the respective alkyl iodides. Such reactions are not suitable for alkyl bromides, because bromine abstraction by aryl radical (e.g. from benzoyl peroxide) or methyl radical (e.g. from DMSO + H\(_2\)O\(_2\)) is slower than iodine abstraction. Therefore, these reactions are not selective, and compete with hydrogen abstraction from acidic C-H bonds or addition to double bonds and aromatic rings. This difference in behaviour would appear to be due more to a different mechanism of atom transfer than to bond strengths. A classical transition state was proposed for bromine atom transfer, while iodine abstraction was said to proceed by a much faster and more selective addition-elimination process (scheme 40).\(^{55}\)

\[
\begin{align*}
(1) & \quad \text{RBr} + \cdot \text{X} \quad \xrightarrow{\text{[R} \cdot \text{X} \cdot \text{Br]}^+} \quad \text{R} \cdot + \text{BrX} \\
(2) & \quad \text{RI} + \cdot \text{X} \quad \xrightarrow{\text{R} \cdot \text{I} \cdot \text{X}} \quad \text{R} \cdot + \text{IX}
\end{align*}
\]

Scheme 40. Mechanisms for bromine and iodine abstractions

Therefore, it follows that Minisci et al\(^{56}\) were obliged to use the standard radical conditions of Bu\(_3\)SnH and AIBN in order to achieve successful intermolecular homolytic aromatic substitution with alkyl bromides. Since, tin (and silicon) radicals can be utilised to achieve a high rate of bromide abstraction. However, the authors stressed the use of stoichiometric amounts of AIBN (scheme 41, also see scheme 32) in order to achieve hydrogen abstraction from the intermediate cyclohexadienyl radical ion (116) by the \( \alpha \)-cyanoisopropyl radical (115) to yield the rearomatised products (117). This result is in contradiction with the "pseudo SRN I mechanism" and in agreement with the findings of Curran et al.\(^{52}\) The \( \alpha \)-cyanoisopropyl radical (115) is deemed electrophilic by virtue of the proximity of the cyano group to the radical centre, and so it does not react with protonated heteroaromatic bases. Therefore, this is an important example of a regioselective "oxidative intermolecular radical substitution using Bu\(_3\)SnH."
Scheme 41. The role of AIBN in 'oxidative rearomatisation'.

Scheme 42. A mechanistic study of the synthesis of phenanthridines by radical Caryl - Caryl coupling
Most recently however, Lobo and Prabhakar et al\textsuperscript{57} gave evidence of the non-participation of ABCN in oxidative rearomatisation during the synthesis of phenanthridines by radical C\textsubscript{aryl}-C\textsubscript{aryl} coupling. The reaction (scheme 42) used was the radical cyclisation of o-bromobenzyl aniline (118), in which the aniline is substituted with deuterium, and employing 1,1-azobiscyclohexylcarbonitrile (ABCN, 120) as initiator. It was shown (scheme 42) that cleaved ABCN radical (121) was not implicated in the abstraction of deuterium from the intermediate radical (119), since (123), as opposed to (122) was given. Therefore, the carbon centred radical (121) was not the oxidising agent. Analogous initiators such as AIBN, are therefore unlikely to be taking part in such a process.

Castedo et al have also used intramolecular radical C\textsubscript{aryl}-C\textsubscript{aryl} couplings to generate various isoquinoline alkaloids\textsuperscript{58} and a wide range of phenanthrene ring systems (126).\textsuperscript{59} The free radical reaction of the haloketoester (124) gives the intermediate phenanthrolic methyl ester (125), and subsequent lactonisation yields phenanthrene ring systems (126). There is now also the potential for the synthesis of a wide range of pyrrolophenanthridone alkaloids by oxidative biaryl couplings using Bu\textsubscript{3}SnH mediated intramolecular radical cyclisations.\textsuperscript{33}

![Scheme 43. C\textsubscript{aryl} - C\textsubscript{aryl} coupling to generate phenanthrenes](image)

Hoshino et al\textsuperscript{19} used this synthetic methodology to yield novel polycyclic organosilicon compounds (scheme 44), and provided a mechanistic explanation for the formation of the three products (128), (130) and (131). An ipso-substitution pathway is predicted to yield compound (130), but no explanation is given for the loss of hydrogen (H \textbullet) to regenerate aromaticity from compound (127) to yield (128). Early work\textsuperscript{17} into Bu\textsubscript{3}SnH mediated biaryl couplings also yielded unexpected products derived from speculative ipso attack, and possible spiro intermediates such as (129). Later, rather than radical oxidative addition reactions, biraryl couplings were promoted via ipso substitution pathways (see section 1.3.1).\textsuperscript{22,23}
Scheme 44. The synthesis of novel polycyclic organosilicon compounds.
A most innovative radical reaction, which was developed by Curran et al., is shown in scheme 45 and is the tandem or cascade cyclisation to form camptothecins (135). These antitumor agents were synthesised via the initial formation of the pyridone radical (132), intermolecular reaction with phenyl isocyanide, and subsequent 5-exo radical cyclisation onto the N-propagyl group creates the vinyl radical (133). The latter cyclises onto the arene to form the radical (134), which undergoes rapid oxidative rearomatisation via an unknown pathway to yield the pentacyclic product (135). Vinyl radicals are widely studied intermediates that have been employed in other synthetically useful oxidative annihilations. Initiation for this cascade reaction is provided by hexamethylditin, and UV light. Therefore, there is no Bu3SnH or AIBN to be implicated in the final oxidation step.

Selenoimidates (scheme 46) have been used as radical precursors to generate imidoyl radicals, which undergo 6-exo radical cyclisation onto double bonds, followed by oxidative addition onto arenes to yield tetracycle (136).
Oxidative radical cyclisations mediated by Bu₃SnH have also found increasing use in the synthesis of indole based polycyclic systems (Scheme 47). Most notably, intramolecular radical cyclisations of haloarylindole-3-carbaldehyde (137) and haloalkylindole-3-carbaldehydes (139) to form isoindolo[1,2-a]indole (138) and tricyclic [1,2-a]fused indoles respectively (140). In both these examples homolytic radical cyclisation is followed by highly favoured oxidative rearomatisation, which may be explained using the "pseudo SRN 1 mechanism". Since, the intermediate radical anion formed will be highly stabilised as the ketyl radical anion, and the profound stability of such aromatic ketyl radicals has been proven by EPR spectroscopy.

This is in contrast to reductive radical cyclisations carried out by Ziegler et al. with allyl, dioxolanyl, and carbon centred oxiranyl and aziridinyl radicals onto the indole-2-position, which invariably gave predominantly dihydroindole products. Three such examples are shown in Scheme 48. Bu₃SnH mediated radical cyclisation of N-allylindole-3-carboxylate (141) yielded the dihydropyrrolo[1,2-a]indole (142). Furthermore, E and Z isomeric mixtures of bromoaziridine (143) were heated at reflux in toluene in the presence of Bu₃SnH and 1,1-azobiscyclohexylcarbonitrile (ABCN, 120) as initiator, the dimer (144), dihydroindole (145), and
uncyclised aziridine (146) were produced.\textsuperscript{68} The tendency for the cyclised benzylic radical to dimerize may be due to an additional captodative stability created by the nitrile group. Chiral carbon-centred epoxy radicals\textsuperscript{67} have been generated via photolysis of degassed solutions of Barton's ester (147), which along with the biproduct 2, 2'-dipyridinyl disulfide give symmetrical dimer (148), unsymmetrical dimer (149) and a trace of epoxyindole (150). Therefore, it can be inferred that oxidative radical cyclisations are far more favoured in the indole-3-carbaldehyde reactions (scheme 47), while 'reductive cyclisations' with Bu$_3$SnH occur with the poorer radical stabilising groups (i.e. COOMe, and CN in scheme 48). Nevertheless, the potential for the incorporation of three membered rings may be adapted to form a wide range of mitomycin analogues.

\[ \text{Scheme 48. Reductive cyclisations onto indoles} \]
Muchowski et al.\textsuperscript{69} have used the "pseudo \textit{S}_{RN1} mechanism" to explain oxidative radical cyclisations onto pyrroles. The radical cyclisation of 1-(2-bromobenzyl)-2-alkanesulfonylpyrroles (151) and 1-(4-bromobutyl)-2-methylsulfonylpyrroles (153) yielded the partial or complete reductive desulfonylation pyrrolizidine derivatives (152) and (154) respectively as the major products (scheme 49). The authors stress that the radical cyclisations occurred with no apparent oxidant nor were products indicative of disproportionation processes observed. Radical addition was proposed to occur at the $\alpha$-position of the pyrrole nucleus not bearing the sulfonyl group, and that sulfonyl group is lost via reduction in a second process after the oxidative radical cyclisation is complete. The "pseudo \textit{S}_{RN1} mechanism" would again suggest that the driving force of such radical cyclisations would be the thermodynamic stability of the intermediate ketyl radical anion.

\begin{equation}
R - Q
\end{equation}

\begin{equation}
R = \text{SO}_2\text{Me,} \\
R = \text{SO}_2\text{C}_6\text{H}_4\text{Me}
\end{equation}

Scheme 49. Oxidative radical cyclisations onto pyrroles using Bu\textsubscript{3}SnH

1.3.4 The Aromatic \textit{S}_{RN1} Mechanism

Before the introduction of the aromatic \textit{S}_{RN1} mechanism by Bunnett and Kim\textsuperscript{70} in 1970, there were three commonly known mechanistic pathways that nucleophilic aromatic substitution reactions could follow (scheme 50). These routes are shown in general, e.g. intermediates (156), (157) and (158) after one or several reaction steps give the nucleophilic substitution product (160). Aryl cations (156) are generally intermediates, when the aromatic substrates (155) has nitrogen as a leaving group (\textit{i.e.} $X = \text{N}_2^+$). Nucleophilic addition with the formation of $\sigma$-complex (157) only occurs, if aromatic substrate (155) possesses one or more electron withdrawing groups activating such an \textit{ipso}-attack. Finally, the removal of a proton, and the formation of a aryl carbanion (158) can only occur in strongly basic conditions. Consequently, the benzyne intermediate (159) is formed, which on nucleophilic substitution leads the formation of more than one regioisomer of (160).
Scheme 50. Nucleophilic Aromatic Substitution Pathways.

Initiation

\[ \text{ArX} + e^- \rightarrow (\text{ArX})^{--} \]

Propagation

\[ (\text{ArX})^{--} \rightarrow \text{Ar}^* + X^- \]

\[ \text{Ar}^* + \text{Nu}^- \rightarrow (\text{ArNu})^{--} \]

\[ (\text{ArNu})^{--} + \text{ArX} \xrightarrow{\text{SET}} \text{ArNu} + (\text{ArX})^{--} \]

Overall

\[ \text{ArX} + \text{Nu}^- \rightarrow \text{ArNu} + X^- \]

Scheme 51. The $S_{RN1}$ mechanism.
However, intense research by Bunnett et al.\textsuperscript{71} provided many reactions that could not be explained by the above processes. One such reaction is the nucleophilic substitution of unactivated aryl halides, which was not carried out under strongly basic conditions in a process conducive to any of the mechanism depicted in scheme 50. These reactions are explained by the SR\textsubscript{RN}1 mechanisms (scheme 51), which represents a Substitution, Radical, Nucleophilic, Unimolecular process, similar to SR\textsubscript{N}1. Since, the overall reaction is a nucleophilic aromatic substitution that involves radicals and radical anions, it follows that such reactions are suppressed by radical scavengers (e.g. di-tert-butyl nitroxide and O\textsubscript{2}) and strong electron acceptors (p-dinitrobenzene and O\textsubscript{2}).

Initiation can occur chemically, photochemically, electrochemically or simply by heating. A common initiation process is the solvation of potassium or sodium metal in liquid ammonia, which furnishes metal cations and solvated electrons. Combination of the solvated electrons with aryl halide molecules is represented in scheme 52. Therefore, generation of radical (R\textsuperscript{+}), radical anion (RX\textsuperscript{-}) or radical anion (RNu\textsuperscript{-}) allows entry to the propagation cycle. If the subsequent radical chain is long, then most of the reaction occurs in the propagation steps.

\[
\text{ArX} + \text{e}_{\text{NH}_3}^{-} \rightarrow (\text{ArX})^{--}
\]

\textbf{Scheme 52. Initiation using metal in ammonia}

A useful example of aromatic SR\textsubscript{RN}1 is illustrated in scheme 53, and is the photostimulated reaction of dihalobenzenes, such as \textit{m}-chloroiodobenzene (161) with thiophenyl anion (PhS\textsuperscript{-}) to give predominantly the disubstituted product (165).\textsuperscript{72} The radical anions are formed either by a single electron transfer (SET) process or the combination of an aromatic radical with PhS\textsuperscript{-}. The favourability of such a process depends on the relative energies of the radical anions formed. Therefore, this depends on the energy, and the location of the extra electron in the radical anions, which may either undergo a SET process or fragment by loss of a leaving group. Both these processes have been studied extensively,\textsuperscript{73} and depend on factors such as reduction potentials, solvent and temperature. Molecular orbital\textsuperscript{74} calculations and EPR spectroscopy\textsuperscript{75} have shown that this extra electron can either occupy a \pi* or \sigma* orbital. The extra electron in halobenzene radical anions (162) and (163) is said to undergo an intramolecular electron transfer process from the \pi* orbitals of the aromatic moiety to the \sigma* orbital of the C-X (X = I or Cl) bond. This leads to the rupture of the C-X bond, since the location of an electron in the \sigma* orbital is a repulsive state. The probability for such an electron transfer will depend on the relative energies of these molecular orbitals. If the energy of the \sigma* orbital is lower than that of the \pi* orbital, the radical anion will probably be a \sigma* radical anion. Therefore it follows that the disubstituted radical anion (164) is a \pi*-radical anion, since the SET process is much more favoured than the fragmentation process.
Scheme 53. The Aromatic $S_{RN1}$ mechanism with dihalobenzenes
2.0 Syntheses of Target 4(5)-Nitroimidazoles (168) and (170)

2.1 Introduction

The modes of action of bioreductive antimicrobial and anticancer agents were discussed in section 1.2.1 and 1.2.2. The design of more potent and selective antimicrobial (and anticancer) drugs could be feasible by understanding the common aspects of the molecular mechanisms. It was apparent that these mechanisms are dependent on certain structural features, and therefore an analysis of common structural features should provide a direction for designing the synthesis of new drugs. In particular, an oxidising group is essential, e.g. a nitro group in the nitroimidazoles and a quinone group in the indolequinones. Likewise, a strained three membered ring is present in mitomycins. If these features are central to the mode of action there is every possibility that they can be combined or are interchangeable. Therefore, the synthetic targets which are proposed in this chapter are based on this concept. In particular, the structures of the synthetic targets will combine the strained three membered moieties from mitomycins and mitosenes, and the oxidising moiety of nitroimidazoles. If these compounds prove to be equally potent and selective, they in turn provide evidence for the mechanism of bioreductive antimicrobial (and anticancer) drugs.

Aziridinomitosene (18) is formed by the reoxidation of reductively activated intermediate aziridinomitosene semiquinone (17, scheme 4, section 1.2.2). Interestingly, the aziridinomitosene (18) has been found to exhibit antitumour activity upon reductive activation. Therefore, a postulated nitroimidazole target will combine aziridinomitosene structural features that were necessary to its activity with those of nitroimidazole (Figure 5). Such a nitroimidazole target (166) has the quinone group replaced by the nitro-moiety (N=C-NO2). The 5-nitro target (167) also has the same structural features. The nitroimine (N=C-NO2) and nitroalkene (CH=C-NO2) moieties of 2- and 5-nitroimidazoles have been shown to readily accept electrons to form radical anions, and thus it should prove viable to replace the oxidising function of the quinone group. Analogues (166) and (167) have three potential sites for reaction with DNA (nitro-group, aziridine and benzylic carbon). Therefore, in order to simplify synthetic studies, the initial target did not contain the benzylic side chain, e.g. (168). This target still has two potential DNA alkylating sites. Once the synthetic methodology for adding the aziridine ring moiety is proven the syntheses can be repeated with a suitable protected benzylic side chain incorporated into the starting material.
Aziridinomitosene analogues in which the aziridine is replaced by a cyclopropane ring (i.e. so called cyclopropamitosene 169, figure 6) have proven to be especially potent bioreductive anticancer agents.\(^7\)\(^7\) Thus, using the same principles as outlined above, a second simplified target (170) was also considered for synthesis.

Therefore, initial synthetic studies aimed to synthesise nitroimidazole targets (168) and (170) by adapting methods that had already been successfully used by to make analogues of aziridinomitosene (18) and cyclopropamitosene (169).

### 2.2 Attempted Synthesis of Nitroimidazole (168)

**Scheme 54. Putative synthesis of nitroimidazole 168**

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The proposed synthesis of nitroimidazole (168) is shown in scheme 54. The first step in the synthesis involves the alkylation of 4(5)-nitro-1'H-imidazole (171), which proved problematic. This should not have been too surprising, since the regioselective N-alkylation of 4(5)-nitro-1'H-imidazoles has always been a problem of great significance, because of the chemotherapeutic and pharmacological advantage of 1-alkyl-5-nitro-1'H-imidazoles over 1-alkyl-4-nitro-1'H-imidazoles (see section 1.2.1). The reason for this is the existence of 4(5)-nitro-1'H-imidazole (171) as two tautomers (scheme 55) in acidic or neutral conditions by virtue of a 1,3-shift of the NH proton. The tautomeric system in which the NH bond is strongest predominates, and the two tautomers exist in an approximate ratio of 400 : 1 in favour of the 4-nitro isomer (171a).78

Alkylations under basic conditions gives 1-alkyl-4-nitro-1'H-imidazoles, since they proceed largely via the conjugate base of (171a), while under neutral or acidic conditions the formation of 1-alkyl-5-nitro-1'H-imidazole occurs via a more favoured substitution at the basic imine nitrogen (3-N) of (171a).79

The first step in the synthesis involved the formation of 2-(5-nitro-1'H-1-imidazolyl)-1-ethanol (175), which according to a literature procedure could be simply made by refluxing 4(5)-nitro-1'H-imidazole (171) in 2-chloroethanol. However, we discovered that this alkylation process only took place, when small amounts of potassium iodide were added to the refluxing solution (scheme 56). The iodide probably displaces the chlorine in 2-chloroethanol, and the resulting 2-iodoethanol was in turn undergoing an intramolecular displacement reaction to form ethylene oxide, since Giraldi et al have reported ethylene oxide as a successful alkylating agent of (171) to yield (175), as shown in scheme 57. Alternatively, the more reactive 2-iodoethanol undergoes Sn2 attack by the basic N-imine in 4(5)-nitroimidazole (171).
1-(2-Chloroethyl)-5-nitro-1H-imidazole (172) was made in moderate yield according to the method of Welch and Vatne. An attempt at increasing this yield by increasing the time the reaction was heated under reflux from 3 h to 54 h is shown in scheme 58. However, this led to the unexpected chlorination of the heteroaromatic ring to yield 2(4)-chloro-1-(2-chloroethyl)-5-nitro-1H-imidazole (176), as the sole product in 45% yield. The exact position of the new heteroaromatic chlorine substituent could not be deduced by relative chemical shifts in the $^1$H NMR and $^{13}$C NMR spectra. Consequently, this synthetic route was not pursued further, because these first steps proved fairly low yielding and capricious.

The next step in the synthesis was the hydroxymethylation of chloride (172), as shown in scheme 54, and is discussed in the next section. Simple oxidation of the resulting alcohol should form the aldehyde (173), which would facilitate the formation of the unsaturated pyrrolo[1,2-a]imidazole (174) via a proposed intramolecular Wittig reaction. "One-pot" alkylation-intramolecular Wittig reactions have been used to form similar fused heterocyclic systems. For example, the preparation of pyrrolizidine (178) from readily available pyrrole-2-carbaldehyde (177) by reaction with vinyltriphenylphosphonium bromide in the presence of sodium hydride is illustrated in scheme 59. More recently, this Schweizer-Light reaction has been extended to the formation of the biologically important pyrrolo[1,2-a]indole system (180). The initially formed 3H-isomer (179) isomerises to the more stable 9H-isomer (180).
Moreover, the formation of 5H-pyrrolo[1,2-a]imidazole (182) has been reported\(^8\) using the Schweizer-Light reaction, as shown in scheme 60. The latter literature procedure was repeated, and used as a guide to the formation of nitroimidazole (174) in scheme 54. Imidazole-2-carbaldehyde (181) was reacted with sodium hydride, and vinyltriphenylphosphonium bromide. Unfortunately, pyrrolizidine (182) could not be isolated, and the reaction gave unidentifiable products even under conditions which rigorously excluded air. Furthermore, it was suggested that pyrrolizidine (182) was air sensitive, and for this reason was rapidly catalytically hydrogenated to the stable heterocycle (183).\(^8\) Thus, the analogous nitroimidazole (174) was also likely to be highly unstable, and so difficult to handle. It was hoped that unsaturated pyrrolo[1,2-a]imidazole (174) could be converted to the proposed nitroimidazole target (168) by addition of the aziridine ring using standard methods\(^8\) (scheme 54), examples of which have been used in aziridinomitosene synthesis.\(^8\)

\[
\begin{align*}
\text{Scheme 59. The Schweizer-Light reaction}
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 60. Schweizer-Light reaction used to synthesise 5H-pyrrolo[1,2-a]imidazole (182)}
\end{align*}
\]

Therefore, we have obtained circumstantial evidence for the instability of synthetic intermediate (174), which is further reason to suspend the synthetic pathway presented in scheme 54.

Since, this work was carried out, synthetic work on mitomycins has suggested that aziridine target (168) may be obtained by another route. If applied to the nitroimidazole synthesis, the formation of unstable unsaturated system (174) would be avoided. Since, Wang and Jimenez\(^8\) have synthesised the aziridinomitosene analogue (189) using a diaklyvinylsulfoxonium salt (184 in scheme 61). Therefore, the reaction is similar to the Schweizer-Light reaction in that the
vinylsulfonium salt (184) undergoes a conjugate addition with the anionic indole to form the sulfur ylide (185) \textit{in situ} (phosphonium ylid in the intramolecular Wittig reaction). The sulfur ylid (185) then reacts at the carbonyl centre to form an alkoxide (186), which displaces dimethyl sulfide. The resultant oxirane (187) was then readily ring opened with a solution of sodium azide to yield azido the alcohol (188), which can readily form the aziridine ring via mesylation and reduction.

\[ \text{Scheme 61. An alternative route to aziridinomitosenes} \]
2.3 Attempted Synthesis of Nitroimidazole (170)

The synthetic route is based on the synthesis of cyclopropamitosene analogues carried out by Moody et al. However, once more the initial alkylation step proved troublesome.

1-Allyl-5-nitro-1H-imidazole (190) was prepared according to a literature procedure (Scheme 63), which involved heating 4(5)-nitro-1H-imidazole (171) and allyl-4-methyl-1-benzenesulphonate (193, allyl tosylate), under slightly acidic conditions at 130 °C. Yields of 1-allyl-5-nitro-1H-imidazole (190) were invariably low with a significant amount of the 4-nitro isomer (194) always given. Column chromatography and/or recrystallisation failed to separate pure 1-allyl-5-nitro-1H-imidazole (190) from the crude product mixture.

It has been reported in the literature that alkylations of 4(5)-nitro-1H-imidazole (171) in polar aprotic solvents (e.g. DMSO, DMF) improve the regioselective formation of the 1-alkyl-5-nitro-1H-imidazole isomer. Thus, the alkylation of 4(5)-nitro-1H-imidazole (171) with allyl bromide in DMF was carried out, but both yields and regioselectivity were very poor (Scheme 64).
Esters of polyphosphoric acid have also been used to carry out regioselective alkylations of 4(5)-nitro-1H-imidazoles to exclusively obtain the 1-alkyl-5-nitro isomer (Scheme 65). However, this method has been applied only to methylation and ethylation reactions, and was not attempted with our starting material (171).

Recent mechanistic studies by Singh et al. have shown that alkylation reactions are greatly affected by temperature. For instance, allylation of 2-methyl-4(5)-nitro-1H-imidazole (195) using allyl bromide in DMF / AcOH media yielded mainly the 2-methyl-1-allyl-5-nitro-1H-imidazole (196) at 80 °C, while at 140 °C the 4-nitro isomer (197) predominated. Below 70 °C, there was no allylation observed. The mechanism for such a transformation was shown to involve quaternization of the initially formed 1-allyl-5-nitro-1H-imidazole (196) followed by
preferential deallylation to yield the thermodynamically more stable 4-nitro-1\textit{H}-imidazole (197) at higher temperatures (scheme 66). Despite the increase in the overall yields of allylated products at higher temperatures, 2-methyl-1-allyl-5-nitro-1\textit{H}-imidazole (196) was never separated from the isomeric product mixture, and its overall yield remained low.

The first published hydroxymethylation procedure of 4(5)-nitro-1\textit{H}-imidazoles at the C-2 position was reported by Rufer\textit{et al.}\textsuperscript{93} Many such reactions have also been reported by Sehgal and Agrawal,\textsuperscript{94} and involve heating the 4(5)-nitro-1\textit{H}-imidazole (190) and paraformaldehyde in DMSO in a sealed tube at temperatures in an excess of 110°C. As the mixture of 1-allyl-5-nitro-1\textit{H}-imidazole (190) and the 4-isomer (194) could not be separated, the mixture was treated under similar conditions to form (1-allyl-5-nitro-1\textit{H}-2-imidazolyl)methanol (198) in moderate yield (scheme 67). Column chromatography of this reaction mixture allowed the clean separation of 1-allyl-4-nitro-1\textit{H}-imidazole (194), which did not undergo hydroxymethylation because the 4-nitro group is less able to stabilize a negative charge at C-2.

![Scheme 67](image)

**Scheme 67.** C-2 Hydroxymethylation of 4(5)-nitro-1\textit{H}-imidazole

![Scheme 68](image)

**Scheme 68.** Oxidation using manganese dioxide

Oxidation of alcohol (198) to the aldehyde (191), shown in scheme 68 was carried out using manganese dioxide (MnO\textsubscript{2}) in dichloromethane (the product mixture contained 64% of the aldehyde 191 and 1% of the alcohol 198). However, at this stage the synthesis was suspended, because of the low yields using this route. The prime problem was the poor yielding first step. Despite, regioselective preparations of 1-alkyl-5-nitro-1\textit{H}-imidazole being present in the literature, most of these syntheses are low yielding and capricious. However, the remaining steps should be synthetically feasible. There has been literature reports\textsuperscript{95} of 1-methyl-5-nitro-1\textit{H}-imidazolecarbaldehyde (199) reactions with mono and \(N,N\)-dialkylhydrazines to give the the respective hydrazones (200 in Scheme 69).
The required diazo moiety could be generated by a variation of the Bamford-Stevens reaction, namely the thermolysis of the sodium salt of tosylhydrazones. Padwa et al. reported that on heating tricyclic cyclopropane (203) was formed via pyrazoline (202) derived from a concerted 1,3-dipolar addition of a diazoalkane (201) to a double bond (scheme 70).

Moody et al. have taken advantage of this protocol to synthesise numerous analogues of cyclopropamitosenes from tosylhydrazones (scheme 71).

2.4 Conclusions

The synthesis of nitroimidazoles (168) and (170) proved difficult using the synthetic schemes described in sections 2.2 and 2.3. The main problem being the initial regioselective alkylation of 4(5)-nitro-1H-imidazole (171), which was invariably low yielding. Thus, the next two chapters report the development of two new routes to polycyclic diazole systems, which are based on free radical chemistry.
3.0 Intramolecular Radical Cyclisations by "ipso" Substitution at the C-2 Position of Imidazoles and Benzimidazoles.

3.1 Introduction

The last chapter described the difficulties encountered when attempting to synthesise new tricyclic nitroimidazole antimicrobial (and anticancer) agents by using conventional synthetic routes, which began with the alkylation of 4(5)-nitro-1H-imidazole (171). The overwhelming synthetic problem was that it was difficult to prepare pure samples of 1-alkyl-5-nitroimidazole in high yield, which could be converted to compounds for cyclisation after several synthetic steps. Therefore, a more accessible route to such [1,2-α]fused 5-nitroimidazole systems was required, which led us to consider radical cyclisations onto imidazole systems. A preliminary communication has already been published on this work.\textsuperscript{98} Moreover, in order to avoid the initial alkylation problems, it was decided to begin new syntheses on imidazoles without a nitro group, and perform the nitration reaction after the synthesis of the heterocyclic nucleus was complete. A putative retrosynthesis of nitroimidazole target (168) is shown in scheme 72. The key step is the cyclisation of the aziridinyl radical onto the electrophilic C-2 position of the imidazole ring.

![Scheme 72](image)

Scheme 72. A possible synthesis of nitroimidazole target (168) by radical cyclisation

A free radical pathway was chosen, since radical cyclisations have become a major route for the synthesis of heterocyclic systems.\textsuperscript{99} Section 1.3.1 reviewed the wide range of reactions reported to date, involving aromatic homolytic "ipso" substitution. Moreover, Caddick \textit{et al}\textsuperscript{30,31} have developed a novel approach to [1,2-α]fused indoles based on an intramolecular aromatic "ipso" substitution pathway (see scheme 21, section 1.3.1). The initial aim of our work was to adapt this protocol to provide a facile route to a number of [1,2-α]fused imidazole and benzimidazole systems. The chapter also details the understanding developed of the mechanism involved in this synthetic protocol.
3.2 Free Radical Route to Bicyclic [1,2-α]fused Imidazoles and Benzimidazoles

Scheme 73. The synthesis of [1,2-α]fused imidazoles by radical cyclisation

The free radical route chosen to [1,2-α]fused imidazoles is shown in scheme 73. The planned route was as follows; Trityl protection of imidazole (204) allows regioselective substitution at the C-2 position of the diazole ring with an electron withdrawing substituent (Z), which was to be accomplished by reacting the 1-(trityl)imidazole with n-butyl lithium (n-BuLi), and quenching the imidazole C-2 anion with a suitable electrophile. Removal of the trityl group, and subsequent alkylation provides the radical precursors, which can then be cyclised under standard radical conditions (i.e. slow syringe pump addition of Bu3SnH and AIBN to the refluxing reaction solution) to form a series of [1,2-α]fused imidazoles. This methodology was also adapted to form a series [1,2-α]fused benzimidazoles, which possess important biological activity.

3.3 The Synthesis of Bicyclic [1,2-α]fused Imidazoles

3.3.1 Examples of 5,6,7,8-tetrahydro[1,2-α]fused imidazoles

There have been two literature accounts of isolated natural products with 5,6,7,8-tetrahydro[1,2-α] fused imidazole structure (Figure 7, n = 2). The five and seven membered analogues are not known from natural sources.

Figure 7. The bicyclic [1,2-α] imidazole skeleton of interest
The first such compound was isolated from the fermentation broth of *Streptomyces amakusaensis* by Japanese workers\textsuperscript{100} in 1992, and was named "nagstatin" (205 in Figure 8). Nagstatin was discovered to be a specific inhibitor of the exoglucosidase enzyme NAG-ase (*N*-acetyl-β-D-glucosaminidase).\textsuperscript{100} Serum levels of such enzymes have been found to increase in diabetes mellitus,\textsuperscript{102} leukaemia\textsuperscript{103} and nephritis cancer.\textsuperscript{104} Thus, nagstatin may be an important inhibitor in gaining an understanding of the mechanisms of cancers and immune disorders.

![Figure 8. "nagstatin"](image)

In 1996, Keller and Hammann *et al*\textsuperscript{101} isolated the secondary metabolite sibyllimycine (208 in Scheme 74) from the fermentation broth of *Thermoactinomyces sp*. These organisms were found in the 60 °C hot springs of Lake Tanganyika in Cape Banza, Africa. Sibyllimycine has no known structural analogues from natural sources, and its biological activity is currently under screening. The structure of sibyllimycine (208) was verified by its synthesis from 4-methyl-1*H*-imidazole (206).\textsuperscript{101} The imidazole (206) was alkylated with 4-bromobutyronitrile, and deprotonated at the C-2 position with *n*-BuLi, which consequently lead to ring closure. The imine (207) was readily hydrolysed to the ketone, sibyllimycine (208).

![Scheme 74. The synthesis of sibyllimycine](image)
During the course of our research, a synthesis of bicyclic [1,2-α]imidazoles has also been reported by Hua et al,
which is shown in scheme 75. The synthesis involves the condensation of various lactams (209) with 2-aminoacetyladaldehyde diethyl acetal (210) in the presence of strong Lewis acids (SnCl₄ or TiCl₄). The mechanism of the reaction was suggested to involve nucleophilic attack by the lactam NH at C-1 of the oxonium ion derived from (210) and the Lewis acid, followed by ring closure of the amino group with the lactam carbonyl group. Dehydration, and elimination of ethanol led to the formation the various bicyclic imidazole products (183, and 211-214). The advantages of the synthetic protocol is that various functional groups such as hydroxyl and olefinic groups (compounds 215 and 216) have been found to tolerate these reaction conditions. Furthermore, the favourability of such cyclisations is exemplified by the formation of the seven, eight and nine membered ring compounds (products 212-214) in high yield. However, not all the lactams used are commercially available, and so must be synthesised prior to cyclisation.

Scheme 75. Lewis acid promoted condensation reaction to synthesise various fused imidazoles
3.3.2 The synthesis of 2-(tosyl)- and 2-(phenylsulfanyl)-1H-imidazole (221) and (222).

Reactions between organolithium reagents, and N-protected imidazoles have provided a valuable route to 1,2-disubstituted imidazoles. In 1978, Kirk was the first to establish the trityl group as an efficient N-protection of imidazole, but not until recently has it been widely used for imidazole protection. Thus, the trityl group was chosen as the N-protection for imidazole because of the following reasons:

1. 1-(Triphenylmethyl)imidazole [1-(trityl)imidazole, 217] can be readily prepared in high yield at room temperature using well documented literature procedures (scheme 76).

2. The reagents used in this reaction are very cheap commercially available materials.

3. The trityl group is resistant to the forcing conditions of ring metallation.

4. The trityl group is hydrolytically readily cleaved to form the unprotected 2-substituted-1H-imidazoles in high yield.

\[
\begin{array}{c}
\text{N} \\
\text{CPh}_3,
\end{array}
\]

Scheme 76. Synthesis of 1-(trityl)imidazole

It has long been recognised that the C-2 position on N-protected imidazole is the most acidic. The relatively high kinetic acidity of H-2, and subsequently its strikingly greater reactivity than that of H-4 or H-5 is due mainly to the inductive influence of the two nitrogen atoms on C-2, which will be far greater than that on C-4 or C-5. Furthermore, the C-H bond at C-2 also has slightly greater s-character than C-4 or C-5. Therefore, the lithiated C-2 anion of 1-(trityl)imidazole (217) was formed using n-BuLi in dry THF at -78 °C, and this was quenched using sulfur electrophiles at 0 °C, as shown in scheme 77. The use of tosyl fluoride gave the required 2-(tosyl)-1-(trityl)-1H-imidazole (218) in 33% yield, and diphenyl disulfide gave 2-(phenylsulfanyl)-1-(trityl)-1H-imidazole (219) in 46% yield. We tried to improve the yield of the imidazole (218) by using tosyl chloride in place of tosyl fluoride, however 2-chloro-1-(trityl)-1H-imidazole (220) was the only product obtained from this reaction. Thus, the lithiated imidazole anion is quenched by chlorine rather than the tosyl group, since the tosyl group is a better leaving group.

The trityl group was hydrolytically cleaved, as shown in scheme 78 by refluxing 2-(tosyl)-1-(trityl)-1H-imidazole (218) and 2-(phenylsulfanyl)-1-(trityl)-1H-imidazole (219) in acidic aqueous methanol over 2 hours. The novel imidazoles (221) and (222) formed, were found to be highly polar crystalline white solids, which were precipitated as the free bases from the aqueous layer on work up. This should have been expected since N-unsubstituted imidazoles are
stabilised by extensive hydrogen bonding, which provides them with the observed crystalline properties, as well as their ready solubility in aqueous solutions. Furthermore, this hydrogen bonding is lost in alkylated imidazoles, which are accordingly often liquids.

**Scheme 77.** 1-(Trityl)imidazole carbanion formation and quenching with electrophiles

3.3.3 Problems with 1-((w-haloalkyl)imidazole radical precursors.

The general procedure for the alkylation of 2-substituted imidazoles is exemplified by the synthesis of 1-(3-bromo-2-propenyl)-2-[(4-methylphenyl)sulfonyl]-1H-imidazole (223), which is depicted in scheme 79. The imidazole N-1 anion is formed using sodium hydride in dry THF, which in this case is quenched using a three fold excess of 1,3-dibromopropene. However, the radical cyclisation of bromide (223) failed. The synthesis of bicyclic imidazole (182) was also attempted using the Schweizer-Light reaction, as described section 2.2. Both these methods
failed to yield 5H-pyrrolo[1,2-a]imidazole (182), because the latter is thought to be too unstable to isolate.

Scheme 79. Attempted synthesis of 5H-pyrrolo[1,2-a]imidazole (182) by radical cyclisation

Consequently, our attention was turned to the synthesis of the more stable bicyclic [1,2-a]fused imidazole (183), which it was envisaged could be synthesised by the radical cyclisation of an alkyl iodide precursor, since Caddick et al. had successfully used 1-[ω-bromo(or iodo)alkyl]indoles as radical precursors. Firstly, chloride (224) was made by alkylation of 2-tosylimidazole (221), which was achieved using two different alkylating agents, as outlined in scheme 80. The greatest yield for chloride (224) was obtained when using 1-bromo-3-chloropropane, rather than 1-chloro-3-iodopropane. The latter alkylation procedure resulted in the formation of a considerable amount of the bisalkylated imidazole (225).

Scheme 80. The synthesis of 1-[3-(chloropropyl)]-2-tosyl-1H-imidazole (224)

The formation of bisalkylated imidazole (225) was attributed to the nucleophilic character of the displaced iodide anion during the alkylation process, which can lead to the speculative formation of alkyliodide (226), which then undergoes an SN2 reaction with another imidazole anion, as outlined in scheme 81.
The chloride (224) was converted to the iodide (226) by $S_N2$ displacement (Finkelstein reaction) using an excess of sodium iodide in acetone, as shown in scheme 82. However, iodide (226) was isolated in only poor yield, and rapidly darkened to yield an intractable mixture, despite being kept in the dark and under an atmosphere of nitrogen. Therefore, the synthesis of 6,7-dihydro-5$H$-pyrrolo[1,2-$a$]imidazole (183) using iodide (226) as a radical precursor is not a synthetically viable process. The $^1$H NMR spectrum indicated that iodide (226) was polymerising, due to the basic imine nitrogen undergoing $S_N2$ substitution displacing the iodide, which is a good leaving group. Unlike indoles, the extra basic nitrogen in imidazoles precludes the use of $\omega$-iodoalkyl side chains.

3.3.4 The synthesis of 1-[(co-phenylselanyl)alkyl]imidazole radical precursors (227-229).

The instability of iodide (226) led to the synthesis of 1-[(co-phenylselanyl)alkyl]imidazoles, which proved to be valuable radical precursors. The phenylselanyl (PhSe) group is an excellent leaving group in radical reactions but a poor leaving group in $S_N2$ reactions. The 1-[(co-phenylselanyl)alkyl]-2-tosyl-1$H$-imidazole radical precursors (227-229) were synthesised in moderate to good yields using sodium hydride and 1-(iodoalkyl)-co-phenylselenides (233-235), as shown in scheme 83.
The 1-(iodoalkyl)-ω-phenylselenides (233-235) were synthesised using methodology previously developed in the Bowman group,\textsuperscript{112} which is detailed in scheme 84. The iodine in 1-chloro-ω-iodoalkanes was displaced by the phenylselenide anion, which had been generated on reduction with sodium borohydride (eq. 1). The chlorides (230-232) were then converted to the iodides (233-235) by an S\textsubscript{N}2 displacement using an excess of sodium iodide in acetone (eq. 2).

Scheme 84. Synthesis of 1-iodoalkyl-ω-phenylselenides (233-235)

3.3.5 Radical cyclisations of 1-[(ω-phenylselanyl)alkyl]-2-tosyl-1\textsubscript{H}-imidazole radical precursors (227-229).

The phenylselenyl imidazole precursors (227-229) were treated with Bu\textsubscript{3}SnH under standard radical cyclisation conditions which provided the bicyclic imidazoles (183), (211) and (212) in good yields (scheme 85). The bicyclic [1,2-α]fused imidazoles formed were isolated cleanly after work up with no chromatography required. The work up procedure involved extraction of the imidazole products into acid in order to remove tributyltin residues, and subsequent basification gave the free imidazole base.
The mechanism for these intramolecular radical cyclisations by "ipso" substitution can be depicted using the mechanistic cycle illustrated in scheme 86. The initial $S_{H2}$ attack by the nucleophilic Bu$_3$Sn • radical results in the formation of Bu$_3$SnSePh, and creates a nucleophilic alkyl radical, which will readily cyclise onto the electron deficient C-2 position of the imidazole ring in the rate determining step. The C-2 position is deemed electrophilic by virtue of the inductive and mesomeric electron withdrawal of the tosyl group. The iminyl radical (236) will now rapidly rearomatise the imidazole ring with the elimination of a tosyl ($p$-TolSO$_2$ •) radical. The tosyl radical is strongly electrophilic and will attack the weak Sn-H bond so reforming the Bu$_3$Sn • radical to continue the mechanistic cycle.

These results can now be compared with the analogous radical cyclisations onto the indole 2-position (i.e. with indoles substituted with SO$_2$Tol at the 2-position) performed by Caddick et al.$^{,30,31}$ The yields reported by this group were much higher for the formation of the five and six membered bicyclic [1,2-α]indoles, but the yield for the seven membered indole cyclisation was
only 33% (scheme 21, section 1.3.1). In contrast, the analogous imidazole radical cyclisation occurred in better yield, and the reaction was free of any tin hydride reduction products. The imidazole radical cyclisation may be more favoured because of the greater resonance stabilisation, which exists in the iminyl radical intermediate (236), as compared with the less resonance stabilised indole intermediate (237) shown in scheme 87. Although, the addition time of the Bu₃SnH and AIBN to the refluxing reaction solution had to be increased from five to ten hours for the six and seven membered cyclisation so to avoid the formation of tin hydride reduction products.

![Scheme 87. Radical aromatic "ipso" substitution onto the C-2 position of indoles](image)

### 3.3.6 Radical cyclisations of 1-[3-(phenylselanyl)propyl]-2-(phenylsulfanyl) and -2-(phenylsulfonyl)imidazoles

The synthesis of 2-(phenylsulfanyl)-1H-imidazole (222) was discussed in section 3.3.2, and it was found that it could be synthesised in higher yields than 2-[(4-methylphenyl)sulfonyl]-1H-imidazole (2-tosylimidazole, 221). Consequently, it was important to assess its viability as an intermediate for the synthesis of bicyclic [1,2-a]fused imidazoles.

The oxidation of 2-(phenylsulfanyl)-1H-imidazole (222) was accomplished by the addition of an excess of oxone™ at 0 °C, and stirring of the reaction solution for 48 h at ambient temperature. Shorter reaction times gave mixtures of the arylsulfoxide (238) and arylsulfone (239), and difficulties were encountered in only getting the arylsulfoxide (238). At the longer reaction time, the arylsulfone (239) was formed in good yield, as shown in scheme 88. In contrast in the analogous indole reaction 30,31 the arylsulfoxide (240) was the only isolated product in 50-64% yield, as shown in scheme 89. The chemoselectivity of the commercially obtained oxone™ (potassium peroxymonosulfate, 2KHSO₅.KHSO₄.K₂SO₄) has been reported 113 to be highly dependent on the concentration of this oxidising agent, the reaction time and temperature used. Therefore, the more extreme conditions used in the imidazole reaction (scheme 88) allowed the oxidation of the initially formed arylsulfoxide (238) to the arylsulfone (239). These novel imidazole compounds may be readily separated by column chromatography, since the arylsulfoxide (238) is considerably more polar than the arylsulfone (239).
Scheme 88. The oxidation of arylsulfide (222)

Scheme 89. The Oxone™ oxidation of 2-(phenylsulfanyl)indole

Scheme 90. Radical cyclisation of the aryl sulfide (241) and the aryl sulfone precursors (239)

The alkylation of the arylsulfide (222), and the cyclisation of the phenyl selenide (241) is shown in scheme 90. The initial alkylation could be performed in good yield, however the radical cyclisation of phenyl selenide (241) was low yielding, and provided equal amounts of cyclised (183) and uncyclised imidazole (242). The result was in agreement with the findings of Caddick et al., since the analogous 2-indolyl aryl sulfide radical cyclisations were also generally
lower yielding than those using higher valence sulfur substituents [i.e. SO₂Tol, and S(O)Ph] at the 2-position of the indole ring. It was hypothesised⁹⁰,⁹¹ that the reason for this phenomena was that the arylsulfide moiety was not as strongly electron withdrawing in character, and possesses a considerable electron donating (M⁺) character. Hence, the rate of cyclisation of the nucleophilic alkyl radical onto the electrophilic 2-position, i.e. the rate determining step, is enhanced by the more electron withdrawing tosyl group, as compared to the aryl sulfide group.

Thus as expected, the arylsulfone (239) was alkylated and the phenyl selenide (243) was radically cyclised in good yield, with no uncyclised imidazole (242) being formed.

3.4 The Synthesis of Bicyclic [1,2-a]fused Benzimidazoles

3.4.1 Examples of pyrrolo[1,2-a]benzimidazoles

Pyrrolo[1,2-a]benzimidazoles are an important class of antitumour agents consisting of three main analogues (figure 9).¹¹⁴,¹¹⁵ The 6-aziridinyl analogues (244, PBIs) possess the most potent antitumour activity, requiring a two electron reductive activation.¹¹⁴ Like other bioreductive compounds, this cytotoxicity is selective to strictly anaerobic cells.¹,² The 6-acetamido (245, APBI) and the imino-6-acetamido (246, imino-APBI) derivatives are much less potent antitumour agents, but are still of interest due to their specific activity against certain cancer cells.¹¹⁵ However, APBI (245) and imino-APBI (246) are not bioreductively activated anticancer agents, since reductive activation is not required for them to manifest, their cytotoxicity. The mechanisms of biological activity remain under investigation.

![Figure 9. Pyrrolo[1,2-a]benzimidazole anticancer agents](image)

The first synthesis of the benzimidazole nucleus was carried out as early as 1928 by Phillips,¹¹⁶ and involved the acid catalysed condensation of o-phenylenediamine (247) with a carboxylic acid, as shown in scheme 91. "Internal Phillips reactions" have provided a facile route to various pyrrolo[1,2-a]benzimidazoles.¹¹⁷ For example, enantiomers of pyrrolo[1,2-a]benzimidazoles (248) can be formed with the (R) or (S) centre, and have proved important in the "structure-activity relationship" work carried out by Skibo et al.¹¹⁴,¹¹⁵
Much of the synthetic methodology used to access pyrrolo[1,2-a]benzimidazoles is based on the principle of placing substituents ortho to an aromatic amine to provide a means of cyclisation, and formation of nitrogen heterocycles. Such a synthetic protocol is the so called "t-amino effect", which is defined as "a nucleophilic reaction involving the tertiary nitrogen or the oxidation of a tertiary nitrogen to the iminium ion, which is then subjected to nucleophilic attack." The cyclisation reaction can be used to form the benzimidazole nucleus in the presence of a Lewis acid, and elaboration of the \( N,N \)-dialkylaniline substituent can provide a route to the pyrrolo[1,2-a]benzimidazole system, as shown in scheme 92.

Jackson et al have reported the synthesis of benzimidazoles with a five, six and seven membered fused alicyclic ring formed by rhodium catalysed hydroformylation of \( N \)-alkenyl-1,2-diaminobenzenes (249), as shown in scheme 93. The intramolecular cyclisation reaction which occurs involves initial imine formation, and the subsequent oxidative work up formed the benzimidazoles. However, the yields of target benzimidazoles (252) and (254) were particularly low by this method, which can be explained by the low regioselectivity of the initial hydroformylation, particularly with \( N \)-alkenyl-1,2-diaminobenzene (249c), which provided a significant quantity of benzimidazole (255). The hydroformylation of \( N \)-alkenyl-1,2-diaminobenzene (249a) also allowed the isolation of imine (250) and cyclic diamine (256), presumably resulting from hydrogenation of the intermediate imine (251). Nevertheless, benzimidazole (253) was isolated after chromatographic separation in good yield.
Most recently, Haque and Rasmussen\textsuperscript{122} have synthesised tricyclic [1,2-\textalpha]fused benzimidazoles by the intramolecular alkylation reaction of various 2,4-disubstituted benzimidazoles, as outlined in scheme 94. The ambident anion formed by the \textit{N}-1 deprotonation of the benzimidazole, and the subsequent regioselectivity of the intramolecular alkylation reaction was studied in detail. It was concluded that the constrained approach geometries involved in cyclisations to both \textit{N}-1 and \textit{N}-3 sites reduce the steric effect of the 4-substituent, particularly for the five-membered ring formation, allowing the electrostatic field and the electronic effect of the substituent to dominate regioselectivity. Thus, 4-nitrobenzimidazoles gave predominant alkylation at the more "crowded" \textit{N}-3 site, whereas the 4-amino system showed a definite preference for cyclisation at the less hindered \textit{N}-1 site. It follows that the more "electronically impartial" 4-methyl system showed less regioselectivity than the 4-nitro or amino substituted compounds. However, steric factors become dominant in the formation of six membered alicyclic rings, and so large \textit{N}-1 selectivity is exhibited by all three C-4 substituted benzimidazoles.
3.4.2 The synthesis of 2-(phenylsulfanyl)-1H-benzimidazole (261)

The synthetic route followed is described in section 3.2, which began with the initial trityl protection of imidazole (204) or benzimidazole (257). The methodology for imidazole trityl protection is outlined in section 3.3.2, and was carried out on benzimidazole (257) to readily form 1-(trityl)benzimidazole (258) on a multi-gram scale, as shown in scheme 95. However, the C-2 anion formed with n-BuLi could only be quenched with tosyl fluoride in poor yield, although 2-(phenylsulfanyl)-1-(trityl)benzimidazole (260) was formed in good yield. Acid hydrolysis of the protective trityl group allowed the isolation of 2-(phenylsulfanyl)-1H-benzimidazole (261) in excellent yield.

3.4.3. Problems with 1-(α-haloalkyl)benzimidazole radical precursors

The problems encountered using 1-(α-haloalkyl)imidazole radical precursors are described in section 3.3.3. Some of these problems also occurred when using benzimidazoles. For example, simple alkylation of benzimidazole (257) did not form the expected 1-(3-bromopropyl)-1H-benzimidazole (262), and resulted in the formation of either the bisalkylated benzimidazole (263) or the dialkylated salt (264), depending on the relative amount of 1,3-dibromopropane used, as outlined in scheme 96. The dialkylation problem is due to the second more basic imidazole nitrogen being susceptible to further alkylation and polymerisation reactions.\textsuperscript{123}
Scheme 95. Trityl protection and 2-substitution of benzimidazole

Scheme 96. Alkylation of benzimidazole (56) with 1,3-dibromopropane
The bromide radical precursor (266) was made via the chloride (265) as shown in scheme 97. The bromination followed a literature procedure, which had to be used in place of the typical SN2 displacement reaction using an excess of sodium bromide in acetone, i.e. the so called Finkelstein reaction conditions. The Finkelstein reaction usually utilises the solubility difference in acetone between NaI and NaCl, however the limiting factor in this approach is that an equilibrium is established between chloride (265) and bromide (266), and thus most of the chloride is recovered. Therefore, an additive is required in these reactions in order to shift the equilibrium towards the bromide (266), consequently ethylbromide was added to the reaction mixture in N-methylpyrrolidinone. Ethyl bromide reacts with displaced chloride ions (Cl-) to yield ethyl chloride, and both these low boiling point alkanes were removed by evaporation, and only a catalytic amount of sodium bromide is required to initiate this reaction. However, the extra cumbersome bromination step led us to use the more accessible benzeneselenides as radical precursors. Therefore, the conclusion from both our imidazole and benzimidazole studies was that the extra basic nitrogen in diazole precursors precludes the successful use of haloalkyl radical precursors.

![Scheme 97. Difficulties with bromide formation](image)

**3.4.4 Radical cyclisations of 1-[(ω-phenylselenanyl)alkyl]-2-(phenylsulfanyl)-1H-benzimidazole radical precursors (267-269).**

Generally, the alkylation of 2-(phenylsulfanyl)-1H-benzimidazole (261), and the subsequent radical cyclisation of 1-[(ω-(phenylselenanyl)alkyl]-2-(phenylsulfanyl)-1H-benzimidazoles (267-269) occurred in reasonable to good yield, as shown in scheme 98. Although the yield of the seven membered [1,2-α]fused benzimidazole (254) was poor, it is similar to the analogous result obtained with indoles. Therefore, it can be generally concluded that radical cyclisations onto
the benzimidazole 2-position do not require a strongly electron withdrawing high valence sulfur substituent, as was required with radical cyclisations onto imidazoles.

\[
\begin{align*}
\text{N} & \quad \text{SPh} \\
\text{I} & \quad \text{H} \\
\text{261}
\end{align*}
\]

\[
\begin{align*}
1. \text{NaH, acetonitrile} & \quad \text{SPh} \\
2. \text{ICH}_2(\text{CH}_2)_n\text{CH}_2\text{SePh} & \quad \text{N} \\
\rightarrow & \quad \text{N}
\end{align*}
\]

\[
\begin{align*}
n = 1, & \quad 267 (44\%) \\
n = 2, & \quad 268 (44\%) \\
n = 3, & \quad 269 (75\%)
\end{align*}
\]

\[
\begin{align*}
\text{Bu}_3\text{SnH, AIBN,} & \quad 5 \text{ h addition, toluene reflux} \\
\rightarrow & \quad \text{SePh}
\end{align*}
\]

\[
\begin{align*}
n = 1, & \quad 252 (49\%) \\
n = 2, & \quad 253 (54\%) \\
n = 3, & \quad 254 (17\%)
\end{align*}
\]

Scheme 98. The synthesis of tricyclic [1,2-\text{a}]benzimidazoles

3.4.5 A mechanistic study of homolytic aromatic "ipso" substitution reactions onto benzimidazoles

The following section examines the necessity for an electron withdrawing substituent and/or leaving group at the C-2 position of benzimidazoles. The synthesis, and attempted radical cyclisation 1-[3-(phenylselanyl)propyl]-1\text{H}-benzimidazole (271) is shown in scheme 99. The attempted radical cyclisation of phenylselenide (271) gave largely 1-propyl-1\text{H}-benzimidazole (273), and only a trace of the cyclised benzimidazole (252), which inferred that without the presence of an electron withdrawing group at the C-2 position of the benzimidazole ring, the rate of cyclisation was much slower than the rate of tin hydride reduction of intermediate radical (272). The yields of products (252) and (273) shown in scheme 99 were determined by \textsuperscript{1}H NMR spectroscopy.

However, in the intermediate radical (272) a [1,5]-hydrogen abstraction from the 2-position of the unsubstituted benzimidazole is possible, as outlined in scheme 100, which would lead to the formation of 1-propyl-1\text{H}-benzimidazole (273) in increased yield. We tested this hypothesis by placing a deuterium atom in the 2-position of benzimidazole, as detailed in scheme 101. The use of GC-MS analysis allowed us to deduce the level of deuterium incorporation, and its position in the benzimidazole (275).
Scheme 99. The attempted radical cyclisation of 1-(3-phenylselanyl)-1H-benzimidazole (271)

Scheme 100. [1,5]-Hydrogen abstraction
Reaction between the deuterated and non-deuterated benzimidazole mixture (275) and Bu₃SnH gave predominantly 2-deuterio-1-propylbenzimidazole (276), but surprisingly with a higher amount of 2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole (252) being formed, as shown in scheme 102. Analysis by GC-MS showed a 4:1 ratio of unyclised benzimidazole (276) and cyclised benzimidazole (252) had been obtained. The formation of deuterated benzimidazole (276) provided evidence that [1,5]-hydrogen abstraction was not occurring to any great extent, while the increased level of 2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole (252), as compared to the cyclisation shown in scheme 99, can be attributed experimental error. Although the addition time of the tin hydride and AIBN was kept constant in all these experiments, other factors remained variable, such as the quality of the commercially obtained tin hydride, and its concentration in the reaction mixture.

Further, unequivocal proof for the absence of [1,5]-hydrogen abstraction was obtained by treating 1-[3-(phenylselanyl)propyl]-1H-benzimidazoles (271) with tin deuteride (Bu₃SnD) under standard radical cyclisation conditions, as shown in scheme 103. The unyclised benzimidazole (277) was the major product, but with an increase in the formation of 2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole (252). The increased amount of observed cyclised product (252) is possibly explained by an isotope effect, since the Sn-D bond is stronger than the Sn-H bond, with a resultant decrease in the rate of reduction, i.e. reduction in the rate of D-abstraction from Bu₃SnD by intermediate radical (272) would allow increased time for cyclisation. The small amount of radical cyclisation observed in the reactions shown in schemes 99, 102 and 103 was due to the nucleophilic alkyl radical cyclising onto the electron deficient C-2 position of the benzimidazole ring, and the subsequent stability of intermediate cyclised radicals formed. According to the "pseudo S₉N₁" mechanism discussed in section 1.3.3 and chapter 4, the acidity of the C-2 position in benzimidazoles will facilitate the rearomatisation of any intermediate radical anion formed.
Scheme 102. Treatment of 2-deutero-1-[(3-(phenylselanyl)propyl)]-1H-benzimidazole (275) with Bu$_3$SnH

Scheme 103. Experimental evidence for the absence of [1,5]-hydrogen abstraction
3.5 Conclusions and Future Work

We have thus successfully extended the pioneering work of Caddick et al\textsuperscript{30,31} to provide a new route to [1,2-\textit{a}]fused imidazoles and benzimidazoles. The yields have not been optimised, and so the route described holds considerable synthetic promise. The use of bromo and iodo compounds was found to be problematic, and so new phenylselenides were synthesised, and have proved to be valuable radical precursors. Radical cyclisations onto benzimidazoles were carried out cleanly with a phenylsulfanyl substituent at the 2-position, while radical cyclisations onto imidazoles could only be carried out cleanly in the presence of higher valence sulfur substituents at the imidazole C-2 position. We can conclude that this was due to the fact that the imidazole ring in benzimidazoles is much less aromatic than in imidazole, and so the formation of the aromatic radical intermediate is easier. Therefore, radical cyclisation onto benzimidazoles takes place with 2-phenylsulfanyl substituent, and does not require the more electron withdrawing tosyl group.

The synthesised imidazoles may be converted into antimicrobial agents by using a literature\textsuperscript{105} bromination reaction followed by a lithium-halogen exchange reaction to introduce the nitro group into the C-3 position of the bicyclic imidazole (183), as outlined in scheme 104.

\begin{center}
\includegraphics[width=\textwidth]{scheme104.png}
\end{center}

Scheme 104. The nitration of bicyclic [1,2-\textit{a}]imidazoles
4.0 Oxidative Radical Cyclisations onto Imidazoles and Pyrroles using Bu$_3$SnH

4.1 Introduction

One of the long term interests of our group is the synthesis of polycyclic nitroimidazole analogues of the mitomycins, as described in section 2.1. The difficulties involved in the synthesis of such compounds by conventional means has led us to consider possible free radical routes. We have recently reviewed the increasing number of radical cyclisations used for the synthesis of heteroaromatic systems. A putative retrosynthesis of target nitroimidazole (280) is outlined in scheme 105, and involves the cyclisation of cyclopropanyl radical (279) onto the electrophilic 5-position of the imidazole ring. The radical cyclisations were carried out using the reductive conditions of Bu$_3$SnH, but only "oxidised aromatic heteroarene compounds" were isolated. The increasing number of reported oxidative radical cyclisations using Bu$_3$SnH were reviewed in section 1.3.3. These included oxidative radical cyclisations onto heteroarenes, e.g. pyridinium salts, pyrroles and indoles. The rate of radical cyclisation onto pyrroles and indoles has been shown to be greatly enhanced by the presence of an aldehyde or ketone substituent on the heteroaromatic ring. Therefore, our initial radical cyclisations contain an aldehyde group on the 4-position of the imidazole ring, which can be further elaborated to the urethane (OCONH$_2$) substituent in the nitroimidazole target (280). The synthesis of a series of novel bicyclic [1,2-c]fused imidazoles using radical cyclisations onto imidazole-4-carbaldehyde was carried out, and we have recently reported this work in a preliminary communication. For comparison purposes, radical cyclisations onto imidazole-5-carbaldehyde and imidazole-2-carbaldehyde were also carried out. Furthermore, radical cyclisations onto 4-phenylimidazole and onto pyrroles allowed us to gain an understanding of the versatility and limitations of this synthetic protocol.

\[
\begin{align*}
280 & \xrightarrow{\text{H$_2$NCONH$_2$}} \text{278} + \text{279} \\
& \xrightarrow{\text{Y}} \text{279} \\
& \xrightarrow{\text{X}} \text{280}
\end{align*}
\]

Scheme 105. A possible synthesis of nitroimidazole target (280) using radical cyclisation
The last chapter described the first reported radical cyclisations onto diazoles to form [1,2-a]fused imidazoles and benzimidazoles using ipso substitution at the C-2 position. However, there have been other recent reported syntheses of these [1,2-a]fused imidazoles and benzimidazoles by non-radical routes. The synthesis of imidazoles containing a [1,2-c]fused alicyclic ring has not been reported to our knowledge, apart from a free radical cyclisation carried out by Bowman and Taylor in 1990. The N-alkenyl-imidazol-5-yl radical (281) was readily generated using either Bu\(_3\)SnH or Na / NH\(_3\), which via 5-exo cyclisation, quantitatively gave pyrrolo[1,2-c]imidazole (283), as exemplified in scheme 106. The regioselectivity obtained indicated that the rate of 5-exo cyclisation of \(\sigma\)-radical (281) was far greater than the rate of reduction by Bu\(_3\)SnH, because no non-cyclised compound (284) was obtained. The unfavourability of the 6-endo cyclisation was confirmed by the absence of cyclised imidazole resulting from radical (282). The attempted cyclisation of 1-allyl-5-bromo-2-methyl-1H-imidazole (285) is shown in scheme 107 and resulted in only the Bu\(_3\)SnH reduction product (287) because the 5-endo and 4-exo are both unfavoured. The 4-exo cyclisation would have resulted in the highly strained 4-membered fused alicyclic system (286). Therefore, there is clearly the requirement for a more facile routes to [1,2-c]fused imidazole systems, which has led us to carry out the work described in the following sections.

Scheme 106. Cyclisation of N-(butyl-3-en-1-yl)-1-imidazol-5-yl radicals

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4.2 Radical Cyclisations using Imidazole-4(5)-carbaldehyde

4.2.1 Alkylation of imidazole-4(5)-carbaldehyde (278)

\[
\text{OHC}<\text{N}<\text{H} \quad \begin{align*}
\text{1. NaH, THF, reflux} & \rightarrow \text{OHC} \quad \text{N} \\
\text{2. Br(CH}_2\text{)_3Cl} & \rightarrow \text{Cl} \quad \text{Cl}
\end{align*}
\]

Scheme 108. Synthesis of 1-(3-chloropropyl)-1H-4-imidazolecarbaldehyde (288)

\[
\text{OHC}<\text{N}<\text{H} \quad \begin{align*}
\text{1. NaH, THF, reflux} & \rightarrow \text{OHC} \quad \text{N} \\
\text{2. BrCH}_2\text{(CH}_2\text{)_nCH}_2\text{Br} & \rightarrow \text{Br} \quad \text{Br}
\end{align*}
\]

Scheme 109. Synthesis of 1-(ω-bromoalkyl)-1H-4-imidazolecarbaldehydes

It has been known for many years that 4(5)-substituted imidazoles usually give mixtures of isomeric products when treated with alkylating agents. Product ratios are known to vary from substrate to substrate, and with reaction conditions and solvents used (see section 2.2)
The required 1-(ω-haloalkyl)-1H-4-imidazolecarbaldehyde radical precursors were formed using sodium hydride in THF to generate the N-1 anion of imidazole-4(5)-carbaldehyde (278), which was quenched using a large excess of dihaloalkane, as outlined in schemes 108 and 109. Thus, the alkylation of the imidazole-4(5)-carbaldehyde anion gave the 4-isomer, but in a couple of cases small amounts of the 5-isomer were also obtained. Column chromatography using neutral alumina gave the clean separation of the two isomers, with the 5-isomers always eluting first. The use of longer chain dibromoalkanes resulted in increased preference for the more nucleophilic imidazole nitrogen, which allowed for the regioselective synthesis of longer chain alkyl bromide radical precursors (294), (296) and (298) in excellent yields, as shown in scheme 109. The alkylation were not optimised but the reasonable yields and high regioselectivity provided a good route to the required radical precursors.

However, the isolation of useful quantities of ω-(haloalkyl)-1H-5-imidazolecarbaldehyde radical precursors proved more difficult. The imidazole alkylation had to be carried out under neutral conditions in order to force the alkylation onto the more basic "imine" nitrogen. The reaction between imidazole-4(5)-carbaldehyde (278) and 1-chloro-4-iodobutane in acetonitrile is shown in scheme 110, but only gave the desired 5-isomer in 15% yield. Imidazole-4(5)-carbaldehyde (278) was also refluxed over two days with 1-(phenylselanyl)-ω-iodoalkanes in THF, as shown in scheme 111. The use of 1-(phenylselanyl)-ω-iodoalkanes (233) and (234) as alkylating agents instead of 1-bromo-ω-iodoalkanes prevented the formation of dialkylation products. However, the yields of the desired 5-isomer remained very low even with these forcing conditions.

Scheme 110. Synthesis of 1-(4-chlorobutyl)-1H-5-imidazolecarbaldehyde (301)

Scheme 111. Synthesis of 1-[ω-(phenylselanyl)alkyl]-1H-5-imidazolecarbaldehydes
4.2.2 Radical cyclisations onto imidazole-4-carbaldehydes

The \( \omega \)-iodoalkyl radical precursors again proved difficult to handle. For example, 1-(3-iodopropyl)-1\( \text{H} \)-4-imidazolecarbaldehyde (306) was synthesised from the chloride (288) by \( \text{S}_{\text{N}}2 \) displacement with sodium iodide in acetone (Finkelstein conditions), as shown in scheme 112. The iodide (306) was formed in excellent yield, and was stored in the dark and under an atmosphere of nitrogen. However, the yellow oil of the iodide (306) rapidly darkened to form an intractable mixture, which could not be manipulated further. This led us to convert the chloride (288) into the iodide (306) \textit{in situ} prior to treatment with \( \text{Bu}_3\text{SnH} \) under standard radical conditions (scheme 113). Thus, iodide formation, and radical reaction were both carried out in the same solvent, \textit{i.e.} acetonitrile, but only yielded a mixture of the cyclised imidazole (307) and the \( \text{Bu}_3\text{SnH} \) reduction product (308) in very poor yield. Acetonitrile had to be used as a reaction solvent because of the increased polarity of these 4(5)-imidazolecarbaldehyde radical precursors, as compared to the 1-[(\( \omega \)-(phenylselanyl)alkyl)]imidazole radical precursors discussed in chapter 3.

The successful use of phenylselenides as radical precursors in the radical cyclisations onto imidazoles and benzimidazoles as described in chapter 3, led us to synthesise 1-[3-(phenylselanylpropyl)]-1\( \text{H} \)-4-imidazolecarbaldehyde (302). The phenylselenide radical precursor (302) was obtained from the bromide (290) via the oxidation of alcohol (309) with manganese dioxide, as shown in scheme 114. Treatment of phenylselenide (302) with \( \text{Bu}_3\text{SnH} \)
under standard radical conditions led to the isolation of 6,7-dihydro-5H-pyrrolo[1,2-c]imidazole-1-carbaldehyde (307) in 27% yield and 1-propyl-1H-4-imidazolecarbaldehyde (308) in 11% yield. Therefore, despite the phenylselenide radical precursor (302) giving an improved isolated yield of the cyclised imidazole (307), the synthesis still required improvement.

![Scheme 114](image)

**Scheme 114.** The synthesis of 1-[3-(phenylselanyl)propyl]-1H-4-imidazolecarbaldehyde (302), and radical cyclisation

1-(α-Bromoalkyl)-1H-4-imidazolecarbaldehydes were obtained in good to excellent yields by the alkylation of imidazole-4(5)-carbaldehyde (278), as shown in scheme 109. We found that treatment of bromide (290) with Bu3SnH gave improved yield of 6,7-dihydro-5H-pyrrolo[1,2-c]imidazole-1-carbaldehyde (307), as shown in scheme 115. The six membered radical cyclisation occurred in slightly higher yield and no Bu3SnH reduction products were formed. The six membered radical cyclisation is more favoured because of the inherent strain in the five membered ring product (307). Jones *et al*33 have offered a similar explanation for the preference of 6-endo radical cyclisations over 5-exo radical cyclisations onto indoles. The seven membered cyclised imidazole (312) was isolated cleanly after chromatography, but in poor yield, even when the rate of addition of Bu3SnH and AIBN to the reaction mixture was increased from 5 to 10 hours to limit the rate of tin hydride reduction. Generally, seven membered ring cyclisations are less favourable than five and six because of a less favoured entropy factor.
**Scheme 115.** The radical cyclisation of 1-(ω-bromoalkyl)-1H-4-imidazolecarbaldehydes

Intramolecular $S_{H2}^2$ macrocyclisations have been shown to be feasible when the radical cyclising ring closure is onto sterically unhindered and electronically activated double bonds.$^{128,129}$ Such a system is outlined in scheme 116 in which the attempted formation of six to nine membered lactones was unsuccessful.$^{129}$ However, the formation of ten to fifteen membered lactones was reported in 46-80% yield, since only for the longer alkyl chains was the desired disposition of reactive centres in the required s-Z conformation for radical cyclisation achieved. Therefore, in agreement with the lactone macrocyclisations, the unfavoured entropy for cyclisation led to the isolation of only the tin hydride reduction product (315) in our attempted eight membered radical cyclisation, shown in scheme 115. However, following the results for the macrocyclisations presented in scheme 116, the formation of the fourteen membered [1,2-κ]fused imidazole (316) was expected to be more favourable, but disappointingly only the reduction product (317) was isolated. The effect of the α,β-unsaturated ester as shown in scheme 116 is obviously much stronger than the effect of the α,β-unsaturated aldehyde moiety in 298.

**Scheme 116.** Intramolecular $S_{H2}^2$ Macrocyclisations

The regioselectivity of the radical cyclisation onto the 5-position, [1,2-κ]fused rather than [1,2-α] fused, could not be verified using $^1$H NMR and $^{13}$C NMR chemical shifts. The structure of
cyclosed imidazole (307) was confirmed using X-ray crystallography, as shown in figure 10. A 90° rotation of the molecule is also shown, which illustrated the profound planarity of the molecule.

The regioselectivity for radical cyclisation onto the 5-position rather than the 2-position for these imidazole-4-carbaldehyde radical precursors was further ascertained by blocking the 5-position with a methyl substituent. Attempted cyclisation of the 5-methylimidazole (318) led to only the formation of the tin hydride reduction product (319), and no cyclisation onto C-2 (scheme 117). Conversely, when the 2-position contained a methyl substituent, the radical cyclisation was observed to form the cyclosed imidazole (322) in excellent yield. The reactive aldehyde (321) was not isolated, since the more stable α,β-unsaturated methyl ketone adduct (322) was formed via an aldol type condensation reaction with acetone.

Scheme 117. Regioselective radical cyclisation onto the 5-position of imidazole-4-carbaldehydes

The synthesis of 1-(2-bromobenzyl)-1H-imidazolecarbaldehyde (323), and its attempted radical cyclisation is shown in scheme 118. The reasons for the failure of the radical cyclisation is unknown, since an analogous cyclisation has been reported on pyrrole-2-carbaldehyde (scheme 49, 1.3.3). Furthermore, molecular modelling studies have been carried out, which supported the favourability of the cyclisation.

Scheme 118. Synthesis and attempted radical cyclisation of 1-(2-bromobenzyl)-1H-4-imidazolecarbaldehyde
Figure 10. X-ray crystal structures of 6,7-dihydro-5H-pyrrolo[1,2-c]imidazole-1-carbaldehyde (307)
4.2.3 The mechanism for radical cyclisations onto imidazole-4-carbaldehyde

There is no definitive mechanism for oxidative radical cyclisations using Bu$_3$SnH. The many examples described in section 1.3.3 proceed to aromatic products which provides a strong driving force. The "pseudo SRN 1" mechanism$^{45}$ proposed for these reactions can be applied to radical cyclisations onto imidazole-4-carbaldehydes, as shown in scheme 119. The nucleophilic alkyl radical (325) is formed via S$_2$H abstraction of bromide by the nucleophilic Bu$_3$Sn • radical. The nucleophilic alkyl radical (325) cyclises regioselectively onto the β-position of the α,β-unsaturated aldehyde moiety in a Michael type manner. Consequently, the π-radical intermediate (326) is formed, and undergoes a rapid loss of a proton to Bu$_3$SnH, which gives the highly stabilised radical anion (327). The radical anion intermediate (327) is a highly stabilised entity by virtue of the delocalisation of the extra electron throughout the aromatic imidazole system and the conjugated aldehyde group. Consequently, radical anion (327) is a highly stabilised ketyl radical anion, and such radical intermediates are well known and have been observed by EPR spectroscopy.$^{64}$ The normal steps of a typical SRN 1 reaction$^{73}$ are then followed i.e. radical anion (327) undergoes a single electron transfer process (SET) with a molecule of substrate (290) to form the cyclised imidazole (307), and the substrate radical anion (328). The radical anion (328) dissociates to reform the initial nucleophilic radical, so sustaining the chain mechanism (see section 1.3.4)

Scheme 119. The "pseudo SRN 1" with 1-(3-bromopropyl)-1H-4-imidazolcarbaldehyde (290)
The most debatable step in the "pseudo $S_{RN}$ 1" mechanism is the loss of a proton from radical intermediate (326), which suggests that Bu$_3$SnH is both a radical initiator and a base. While, the acidity of radicals have not been extensively studied, a number of examples show that they are considerably more acidic than the corresponding non radical compounds, often by an order of $10^6$. The stability of the $\pi$-radical (326) is possibly similar to the $\pi^*$-radical anion (327), which suggests that the proton loss may be rapid. AIBN has also been proposed as a possible oxidant for radical intermediates such as (326), since certain reported oxidative radical cyclisation reactions using Bu$_3$SnH only reached completion with an excess of AIBN and prolonged heating (scheme 39, section 1.3.3). Furthermore, Engel and Wu have shown that AIBN abstracts hydrogens in radical reactions, as outlined in scheme 120. The authors reported the formation of benzhydryl radicals upon the photolysis of benzpinacol, followed by rapid hydrogen transfer from the benzhydryl radical to the least hindered nitrogen atom of the azo linkage in various azoalkanes. A second hydrogen abstraction gave the air sensitive hydrazine product.

\[ \begin{align*}
\text{Ph} & + \text{C} \rightarrow \text{C} + \text{Ph} & \Delta & \rightarrow & 2 \text{Ph} & \rightarrow \text{Ph}_2\text{CHOH} + \text{Ph}_2\text{CO} \\
& \downarrow & & & & & \downarrow \\
& \text{RN} \rightarrow \text{NR} & & & & & \text{RN} \rightarrow \text{NR} \\
& \text{Ph}_2\text{CO} + \text{RN} \rightarrow \text{RN} & & & & & \text{RN} \rightarrow \text{NR} \\
& \downarrow & & & & & \downarrow \\
& & \text{RN} \rightarrow \text{NR} & & & & & \text{RN} \rightarrow \text{NR}
\end{align*} \]

Scheme 120. Reduction of azoalkanes by benzhydryl radicals

Lobo, Prabhakar et al. in their recent studies of the syntheses of phenanthridines, which appear to proceed by the same oxidative cyclisation, have shown that the "hydrogen" which is lost in the oxidation is not abstracted by 2-cyanoprop-2-yl radicals (scheme 42, section 1.3.3). Alternatively, the radical intermediate (326) may be reduced by Bu$_3$SnH to form 4,5-dihydroimidazole (imidazoline, 329), as in normal Bu$_3$SnH reductive cyclisations (scheme 121). The radical cyclisations were carried out under an atmosphere of nitrogen using anhydrous solvents, thus the oxidative rearomatisation of intermediate (329) can only occur upon work up. Such 4,5-dihydroimidazoles (329) are unlikely reaction intermediates, since 4,5-dihydroimidazoles are known to be stable. Furthermore, the 4,5-dihydroimidazole system occurs in a number of pharmacologically active molecules. The 4,5-dihydroimidazole intermediate (329) may also form upon the disproportionation of radical intermediate (326), as shown in scheme 122.
4.2.4 Radical cyclisations of imidazole-5-carbaldehydes

The radical cyclisation of 1-[3-(phenylselanyl)propyl]-1H-5-imidazolecarbaldehyde (303) gave only the reduced imidazole (331), while the cyclisation of 1-[4-(phenylselanyl)butyl]-1H-5-imidazolecarbaldehyde (305) gave only the six membered cyclised [1,2-a]fused imidazole (332), as shown in scheme 123. Therefore, the five membered transition state leading to cyclised
imidazole (330) is less favoured due to strain and distortion, which does not occur in the six membered transition state leading to cyclised imidazole (332). The aldehyde group has a strong directing influence on the cyclisation of the nucleophilic alkyl radical onto the electrophilic 2-position of the imidazole ring, since the aldehyde group is fully conjugated with the imidazole 2-position. The "pseudo $S_{RN}1$" mechanism\(^{45}\) for phenylselenide radical cyclisations is shown in scheme 124, and there are two main differences to the mechanism described in scheme 119 for bromide radical precursors. The first difference is the phenylselenide anion (PhSe\(^{-}\)) can undergo a single electron transfer (SET) process, which follows well established $S_{RN}1$ reactivity patterns for phenylsulfide (PhS\(^{-}\)) and phenylselenide (PhSe\(^{-}\)) anions.\(^{134}\) The second difference is the (PhSe\(^{-}\)) anion is a strong base and is capable of proton abstraction, and the formation of the highly stabilised radical anion intermediate (334). The normal steps of $S_{RN}1$ reactions\(^{73}\) are then followed. The mechanism for phenylselenide radical cyclisations infers that $Bu_3SnH$ merely initiates the radical cyclisation, and thus future studies into proving the "pseudo $S_{RN}1$" mechanism should examine the possibility of performing radical cyclisations with phenylselenide substrates using only catalytic amounts of $Bu_3SnH$ or $(Bu_3Sn)_2$.

\[ \text{Scheme 124. The "pseudo } S_{RN}1 \text{" mechanism with 1-[4-(phenylselanyl)butyl]-1H-5-imidazolecarbaldehyde (305)} \]
4.3 Attempted Radical Cyclisations of Imidazole-2-carbaldehyde

The last section described the synthesis of imidazole-4-carbaldehyde and imidazole-5-carbaldehyde radical precursors, and the results obtained on treatment with Bu₃SnH under standard radical conditions. This section examines the possibility of radical cyclisations with the aldehyde group in the 2-position of the imidazole ring.

4.3.1 Preparation of imidazole-1H-2-carbaldehyde (181)

Imidazole-1H-2-carbaldehyde (181) can be commercially obtained, but is rather expensive (£25.50/g), and of dubious purity, so it was prepared according to a modified literature procedure shown in scheme 125. The overall yield was low, and other more recently reported syntheses of imidazole-1H-2-carbaldehyde (181) were attempted, but with no improvement on the yield. This included the synthesis of aldehyde (181) via a Comforth-Huang reaction to form 2-(dichloromethyl)imidazole (336), and in situ hydrolysis of imidazole (336), as shown in scheme 126.
Aldehyde (181) can also be obtained via aminal protection of imidazole, followed by a well documented C-2 lithiation and substitution, as shown in scheme 127. Hydrolysis of the aminal protecting group gave imidazole-1H-2-carbaldehyde (181). The reason for the low yields of aldehyde (181) in all these preparations was due to the considerable polarity and instability of this compound, which had to be precipitated as the free base from acidic solutions. Imidazole-1H-2-carbaldehyde (181) has also been reported to be highly unstable to various organic and aqueous bases.

4.3.2 Preparation of 1-[3-(phenylselanyl)propyl]-1H-2-imidazolecarbaldehyde (338)

The most obvious preparation of the required 1-[3-(phenylselanyl)propyl]-1H-2-imidazolecarbaldehyde (338) is by the alkylation of imidazole-1H-2-carbaldehyde (181). The attempted alkylation of imidazole-1H-2-carbaldehyde (181) by treatment with sodium hydride, and quenching of the imidazole N-1 anion with 3-iodo-1-(phenylselanyl)propane (233) failed to yield the desired imidazole (338), as shown in scheme 128. Bauer et al. have recently reported a similar observation shown in scheme 129. This involved the attempted sulfonylation of aldehyde (181) in the presence of either organic or aqueous bases, which resulted in intractable mixtures, which the authors suggested were due to the instability of the aldehyde (181) under alkaline conditions.
The alternative route to 1-[3-(phenylselanyl)propyl]-1H-2-imidazolocaraldehyde (338) shown in scheme 130 was also attempted. The initial alkylation of imidazole (204) occurred in reasonable yield using one equivalent of 3-iodo-1-(phenylselanyl)propane (233), but when two equivalents were used the dialkylated imidazole (340) was obtained, which was due to the extra basic nitrogen in imidazoles (see section 3.4.3). For unknown reasons, the attempted lithiation of the C-2 position of imidazole (339) with n-BuLi, and subsequent quenching of the lithiated anion with DMF failed to yield the desired aldehyde (338). This reaction was repeated several times, but only the starting imidazole (339) was recovered.

The successful preparation of 1-[3-(phenylselanyl)propyl]-1H-2-imidazolocarbaldehyde (338) was achieved via the initial literature preparation of acetal (341), as shown in scheme 131. The acetal was alkylated using sodium hydride and 3-iodo-1-(phenylselanyl)propane (233) to form 1-[(3-(phenylselanyl)propyl)-2-(diethoxymethyl)imidazole (342) in good yield. The acetal was then hydrolysed to form 1-[3-(phenylselanyl)propyl]-1H-2-imidazolocarbaldehyde (338), also in good yield.
4.3.3 Attempted radical cyclisation of 1-[3-(phenylselanyl)propyl]-1H-2-imidazolocarbaldehyde (338)

The attempted radical cyclisation of aldehyde (338) is shown in scheme 132. The aldehyde substituent in the 2-position of the imidazole ring proved unstable under these standard radical conditions, and was reduced to form imidazole (339). It can be inferred that the selective loss of the C-2 aldehyde is faster than S$_{1,2}$ abstraction of the phenylselenide group. The mechanism of the reaction is unknown, and not obvious. Because of the difficulty of the synthesis the reaction was not repeated once the synthesised material had been used up. Likewise, the more promising cyclisation of the 1-[4-(phenylselanyl)butyl]-1H-2-imidazolocarbaldehyde (338a) shown in scheme 132a was not contemplated for the same reasons. Although, the results described in the last section suggest that this may be a more favoured process. Unfortunately, the attempted cyclisation of 1-[3-(phenylselanyl)propyl]-1H-2-imidazolocarbaldehyde (338) was carried out before our successful 6-exo radical cyclisation of 1-[4-(phenylselanyl)butyl]-1H-5-imidazolocarbaldehyde (305 in scheme 123).
4.4 Radical Cyclisations onto 4-Phenylimidazole and 4-Nitroimidazole

The regioselective cyclisation of 1-(ω-bromoalkyl)-1H-4-imidazolocarbaldehydes onto the C-5 position of the imidazole ring is described in section 4.2.2. It was concluded that this was an addition of nucleophilic alkyl radicals onto the β-position of α,β-unsaturated aldehydes in a Michael type manner. The work described in this section aimed to test the regioselectivity of these radical cyclisations with two different substituents at the 4-position of the imidazole ring (i.e. phenyl and nitro groups).

The required 1-(ω-bromoalkyl)-4-phenyl-1H-imidazoles were obtained readily using sodium hydride in THF to generate the N-1 anion of 4-phenylimidazole (343), which was quenched using a large excess of ω-dibromoalkane, as shown in scheme 133. The regioselective formation of the 4-isomer was facilitated by the steric hindrance imposed by the phenyl group on the N-3 position, which prevented any formation of the 5-isomer.

The regioselective formation of 1-alkyl-5-nitroimidazoles proved difficult, as described in chapter 2. However, the regioselective formation of 1-alkyl-4-nitroimidazoles is a much easier process, and is well documented. Sodium hydride in THF was used to form the N-1 anion, which was quenched with an excess of 1,4-dibromobutane to form 1-(4-bromobutyl)-4-nitro-1H-imidazole (346 in scheme 134) in reasonable yield. The regioselectivity of the alkylation at the N-1 position rather than the N-3 position is due to the much greater basic and nucleophilic character of the N-1 anion (i.e. more distant from the electron withdrawing NO2 group). Furthermore, the N-3 anion is deactivated by the large inductive electron withdrawal of the adjacent nitro group.
The treatment of 1-(3-bromopropyl)-4-phenyl-1H-imidazole (344) with Bu₃SnH gave almost equal quantities of the cyclised [1,2-α]fused imidazole (347) and the uncyclised imidazole (348), as shown in scheme 135. In contrast, the treatment of 1-(4-bromobutyl)-4-phenyl-1H-imidazole with Bu₃SnH gave no uncyclised imidazole, and only the products of radical cyclisation onto the imidazole ring were obtained. Once more, the 5-membered ring cyclisation is less favoured than the six membered ring cyclisation because of strain. The 4-phenyl group has a much smaller directing influence on radical cyclisation onto the imidazole ring than the 4-aldehyde group, which resulted in some unexpected cyclisation onto the C-2 position in the six membered radical cyclisation. Cyclisation onto the C-2 position of the imidazole ring is facilitated by virtue of its electrophilic nature, which is due to the inductive influence of the adjacent nitrogen atoms. The two cyclised imidazoles (349) and (350) could not be separated by chromatography, and so the relative yields were estimated by GC-MS analysis.
The influence of the 4-phenyl substituent on the putative "pseudo-SRN\textsubscript{1} mechanism" is interesting. The phenyl group is +M, and therefore will not make the C-5 position more electrophilic to facilitate cyclisation, hence the competitive C-2 cyclisation occurred. The intermediate cyclised radical would be strongly stabilised by conjugation with the phenyl substituent, but much more so for cyclisations onto C-5 than C-2 (scheme 135a). This suggests that the stability of the intermediate cyclised radical is not crucial. The phenyl group also helps stabilise a radical anion by delocalisation.

![Scheme 135a. Resonance stabilised π-radical intermediates](image)

The attempted radical cyclisation of 1-(4-bromobutyl)-4-nitro-1\textit{H}-imidazole (346) using \textit{Bu}_3\textit{SnH} gave an intractable mixture, since the \textit{Bu}_3\textit{Sn} • radical can add onto the nitro group to yield unidentifiable products.\textsuperscript{138} Furthermore, the NO\textsubscript{2} group will form radical anions according to the "pseudo-SRN\textsubscript{1} mechanism," which may be too stable to undergo the required single electron transfer process.\textsuperscript{8,45}

4.5 Radical Cyclisation Reactions onto Pyrroles

The analogous oxidative radical cyclisations using \textit{Bu}_3\textit{SnH} were carried out on 3-acetylpyrroles and pyrrole-2-carbaldehydes for comparison purposes. The only previous examples of oxidative radical cyclisations onto pyrroles using the reductive conditions of \textit{Bu}_3\textit{SnH} addition have been reported by Muchowski \textit{et al}\textsuperscript{69} (see scheme 49, section 1.3.3). The development of new synthetic methodology towards new pyrrolizidines is important, since many natural products possess this structural unit.\textsuperscript{139} Some initial studies were carried out by Emma Mann, a final year project student. 

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4.5.1 The synthesis of 3-acetylpyrrole (353)

Pyrrole is an electron rich or \( \pi \)-excessive heterocycle and unlike imidazole, can easily undergo aromatic electrophilic substitution reactions. The preferred position for aromatic electrophilic substitution is at the C-2 position, consequently it is difficult to obtain preparatively useful amounts of 3-substituted pyrroles by direct substitution reactions. Hence, it was necessary to protect pyrrole with the electron withdrawing phenylsulfonyl group,\(^{140}\) which deactivates the \( \alpha \)-positions to acylation, and suppresses diacylation in the Friedel-Crafts reaction shown in scheme 136.\(^{141}\) The phenyl sulfonyl group was hydrolysed using sodium hydroxide solution to give 3-acetylpyrrole (353) in excellent yield.\(^{141}\)

![Scheme 136. The synthesis of 3-acetylpyrrole (353)](image)

The 3-acetylpyrrole radical precursors were used instead of the analogous aldehydes, because of the shorter synthesis of 3-acetylpyrrole (353). Pyrrole-3-carbaldehyde (355) can only be prepared via the synthesis of 1-[1-(sulfonylphenyl)-1\( H \)-pyrrololy]-1-ethanone (354), since it was reported in the literature\(^{142}\) that the synthesis of aldehyde (355) directly from a Friedel-Crafts reaction on 1-(sulfonylphenyl)pyrrole (352) had failed. A literature\(^{143}\) synthesis of pyrrole-3-carbaldehyde is outlined in scheme 137. Other syntheses of this compound have been reported.\(^{142}\)

![Scheme 137. The synthesis of pyrrole-3-carbaldehyde (355)](image)
4.5.2 Alkylations of 3-acetylpyrrole (353) and pyrrole-2-carbaldehyde (177)

\[
\begin{align*}
&\text{353} & \text{1. NaH, THF, reflux} & \text{177} \\
&\text{353} & \text{2. BrCH}_2(CH_2)_nBr & \text{357. } n = 1 (56\%) \\
& & & \text{358. } n = 2 (63\%) \\
& & & \text{359. } n = 1 (71\%) \\
& & & \text{360. } n = 2 (62\%) \\
& & & \text{361. } n = 3 (45\%)
\end{align*}
\]

Scheme 138. The alkylation of pyrroles

The alkylation of pyrroles is straightforward, unlike imidazoles which contain an extra basic nitrogen. Therefore, 1-[(o-bromoalkyl)-1H-pyrrolyl]-1-ethanones (356-358) and 1-(o-bromoalkyl)-1H-2-pyrrolecarbaldehydes (359-361) were obtained regioselectively in good to excellent yields, as shown in scheme 138.

4.5.3 Radical cyclisation of 1-[(o-bromoalkyl)-1H-pyrrolyl]-1-ethanones (356-358) and 1-(o-bromoalkyl)-1H-2-pyrrolecarbaldehydes (359-361).

The radical cyclisations onto 3-acetylpyrroles are shown in scheme 139 and are used as a comparison for the analogous imidazole-4-carbaldehyde reactions. The regioselectivity exhibited by the 3-acetyl pyrroles was found to be similar to that observed in the imidazole series, that is addition of the nucleophilic radical onto the $\beta$-position of the $\alpha,\beta$-unsaturated ketone in a Michael type manner. The cyclisation at the C-2 position was completely selective for the 6-membered cyclisation, and some uncyclised pyrroles were isolated in the 5- and 7-membered ring cyclisations. This again is due to strain in the five membered cyclisation, and a less favourable entropy factor in the seven membered cyclisation.
The radical cyclisation reactions onto pyrrole-2-carbaldehydes shown in scheme 140 are used as a comparison to the analogous imidazole-5-carbaldehyde reactions. The radical cyclisations were all regioselective with the highest yield obtained for the six membered ring cyclisation. The lowest yields were due to problems of separating tin residues from the products. Unlike imidazoles, pyrroles cannot undergo an acidic extraction to remove tin residues, and so column chromatography had to be used in order to obtain pure samples of cyclised products. The oxidative Fentons conditions have also been used by Muchowski et al\textsuperscript{40} to synthesise 2,3-dihydro-1\textit{H}-pyrrolizinecarbaldehyde (368), and 5,6,7,8-tetrahydro-3-indolizinecarbaldehyde (369) in 50, and 58\% yield respectively, as shown in scheme 141.

Scheme 139. Radical cyclisations onto 3-acetylpyrroles using Bu$_3$SnH

Scheme 140. Radical cyclisations onto pyrrole-2-carbaldehydes using Bu$_3$SnH

Scheme 141. Radical cyclisations onto pyrrole-2-carbaldehydes using Fenton's conditions
4.6 Conclusions and Future Work

We have thus reported the synthesis of novel bicyclic [1,2-α] and [1,2-c] fused imidazoles, and pyrrolizidines using radical cyclisation reactions. These can now be added to the growing list of reported oxidative radical cyclisation reactions using Bu₃SnH, which were reviewed in section 1.3.3. The regioselectivity of radical cyclisations onto imidazole-4-carbaldehydes, and 3-acetylpyrroles were determined by the addition of the nucleophilic alkyl radicals onto the β-position of α,β-unsaturated aldehydes or ketones in a Michael type manner. Aromatic conjugation present in the imidazole and pyrrole heterocycles, allows the aldehyde group to direct the addition of the nucleophilic alkyl radical onto the C-2 position in cyclisations onto imidazole-5-carbaldehyde, and onto the C-5 position in cyclisations of pyrrole-2-carbaldehydes.

The regioselectivity of radical cyclisations was reduced in 4-phenyl substituted imidazoles, and in the formation of five and seven membered fused imidazoles and pyrroles. Work must now be carried out to determine the mechanism of these radical cyclisation reactions.

The putative synthesis of the tricyclic imidazole (372) is shown in scheme 142, and may now be possible using the synthetic methodology described in this chapter. The biggest problem in this synthesis will probably be the preparation of the cyclopropane (371). Two literature routes to cyclopropane (371) are outlined in schemes 143 and 144. Both these routes involve the initial generation of the dibromocarbene from bromoform, and it’s 1,2-dipolar addition onto a double bond to form the cyclopropane ring. However, both these initial reactions have only been reported in poor yields, e.g. cyclopropane (373) was reported in 4% yield. The longer synthesis shown in scheme 144 is necessary because the addition of dihalocarbenes to α,β-unsaturated aldehydes is known not to be a feasible process, thus the acid (374) had to be made.

Scheme 142. A possible synthesis of tricyclic imidazole (372)
Scheme 143. A two step synthesis of 1,1-dibromo-2-bromomethylcyclopropane (371)

Scheme 144. A longer synthesis of 1,1-dibromo-2-bromomethylcyclopropane (370)
5.0 Experimental

5.1 General

5.2 Experimental for Chapter 2
1) Preparation of 2-(5-nitro-1H-imidazolyl)-1-ethanol (175)
2) Preparation of 1-(2-chloroethyl)-5-nitro-1H-imidazole (172)
3) Preparation of 2(4)-chloro-1-(2-chloroethyl)-5-nitro-1H-imidazole (176)
4) Attempted synthesis of 5H-pyrrolo[1,2-a]imidazole (182) by an intramolecular Schewizer-Light reaction
5) Preparation of allyl 4-methyl-1-benzenesulfonate [allyl tosylate, 193]
6) Preparation of 1-allyl-5-nitro-1H-imidazole (190) (using allyl tosylate)
7) Preparation of 1-allyl-5-nitro-1H-imidazole (190) (using allyl bromide)
8) Preparation of (1-allyl-5-nitro-1H-imidazolyl)methanol (198)
9) Preparation of 1-allyl-5-nitro-1H-imidazolecarbaldehyde (191)

5.3 Experimental for Chapter 3
10) Preparation of 1-(triphenylmethyl)imidazole [1-(trityl)imidazole, 217]
11) Preparation of 2-[(4-methylphenyl)sulfonyl]-1-(triphenylmethyl)-1H-imidazole (218)
12) Preparation of 2-(phenylsulfanyl)-1-(triphenylmethyl)-1H-imidazole (219)
13) Preparation of 2-chloro-1-(triphenylmethyl)-1H-imidazole (220)
14) Preparation of 2-[(4-methylphenyl)sulfonyl]-1H-imidazole [2-tosylimidazole, 221]
15) Preparation of 2-(phenylsulfanyl)-1H-imidazole (222)
16) Preparation of 1-(3-bromo-2-propenyl)-2-[(4-methylphenyl)sulfonyl]-1H-imidazole (223)
17) Attempted radical cyclisation of 1-(3-bromo-2-propenyl)-2-[(4-methylphenyl)sulfonyl]-1H-imidazole (223)
18) Preparation of 1-(3-chloropropyl)-2-[(4-methylphenyl)sulfonyl]-1H-imidazole (224) (using 1-chloro-3-iodopropane)
19) Preparation of 1-(3-chloropropyl)-2-[(4-methylphenyl)sulfonyl]-1H-imidazole (224) (using 1-bromo-3-chloropropane)
20) Preparation of 1-(3-iodopropyl)-2-[(4-methylphenyl)sulfonyl]-1H-imidazole (226)
21) Preparation of 2-[(4-methylphenyl)sulfonyl]-1-[3-phenylselanyl)propyl]-1H-imidazole (227)
22) Preparation of 2-[(4-methylphenyl)sulfonyl]-1-[4-phenylselanyl)butyl]-1H-imidazole (228)
23) Preparation of 2-[(4-methylphenyl)sulfonyl]-1-[5-phenylselanyl)penty]-1H-imidazole (229)
24) Preparation of 3-chloro-1-(phenylselanyl)propane (230)
25) Preparation of 4-chloro-1-(phenylselanyl)butane (231)
26) Preparation of 5-chloro-1-(phenylselanyl)pentane (232)
27) Preparation of 3-iodo-1-(phenylselanyl)propane (233)
28) Preparation of 4-iodo-1-(phenylselanyl)butane (234)
29) Preparation of 5-iodo-1-(phenylselanyl)pentane (235)
30) Preparation of 6,7-dihydro-5H-pyrrolo[1,2-a]imidazole (183) (from the tosylate 227)
31) Preparation of 5,6,7,8-tetrahydroimidazo[1,2-a]pyridine (211)
32) Preparation of 6,7,8,9-tetrahydro-5H-imidazo[1,2-a]azepine (212)
33) Preparation of 2-(phenylsulfonyl)-1H-imidazole (239)
34) Preparation of 1-[(3-phenylselanyl)propyl]-2-(phenylsulfanyl)-1H-imidazole (241)
35) Radical cyclisation of 1-[(3-phenylselanyl)propyl]-2-(phenylsulfanyl)-1H-imidazole (241)
36) Preparation of 1-[(3-phenylselanyl)propyl]-2-(phenylsulfanyl)-1H-imidazole (243)
37) Preparation of 6,7-dihydro-5H-pyrrolo[1,2-a]imidazole (183) (from the phenylsulfonate 243)
38) Preparation of 1-(triphenylmethyl)benzimidazole [1-(trityl)benzimidazole, 258]
39) Preparation of 2-[(4-methylphenyl)sulfonyl]-1-(triphenylmethyl)benzimidazole (259)
40) Preparation of 2-(phenylsulfanyl)-1-(triphenylmethyl)benzimidazole (260)
41) Preparation of 2-(phenylsulfonyl)-1H-benzimidazole (261)
42) Preparation of 1-[3-(1H-benzoimidazol-1-yl)propyl]-1H-benzoimidazole (263)
43) Preparation of 1,3-di(3-bromopropyl)-3H-benzoimidazol-1-ium bromide (264)
44) Preparation of 1-(3-chloropropyl)-2-(phenylsulfanyl)-1H-benzimidazole (265)
45) Attempted preparation of 1-(3-bromopropyl)-2-(phenylsulfanyl)-1H-benzimidazole (266)
using sodium bromide in acetone (Finkelstein conditions)
46) Preparation of 1-(3-bromopropyl)-2-(phenylsulfanyl)-1H-benzimidazole (266)
47) Preparation of 1-[3-(phenylselanyl)propyl]-2-(phenylsulfanyl)-1H-benzimidazole (267)
48) Preparation of 1-[4-(phenylselanyl)butyl]-2-(phenylsulfanyl)-1H-benzimidazole (268)
49) Preparation of 1-[5-(phenylselanyl)pentyl]-2-(phenylsulfanyl)-1H-benzimidazole (269)
50) Preparation of 2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole (252)
51) Preparation of 1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine (253)
52) Preparation of 7,8,9,10-tetrahydro-6H-benzo[4,5]imidazo[1,2-a]azepine (254)
53) Preparation of 1-(3-chloropropyl)-1H-benzimidazole (270)
54) Preparation of 1-[3-(phenylselanyl)propyl]-1H-benzimidazole (271)
55) Attempted radical cyclisation of 1-[3-(phenylselanyl)propyl]-1H-benzimidazole (271)
56) Preparation of 2-deuterio-1-[3-(phenylselanyl)propyl]-1H-benzimidazole (275)
57) Radical cyclisation of 2-deuterio-1-[3-(phenylselanyl)propyl]-1H-benzimidazole (275)
58) Radical cyclisation of 1-[3-(phenylselanyl)propyl]-1H-benzimidazole (271) using Bu3SnD

5.4 Experimental for Chapter 4

59) Preparation of 1-(3-chloropropyl)-1H-4-imidazolecarbaldehyde (288)
60) Preparation of 1-(3-bromopropyl)-1H-4-imidazolecarbaldehyde (290)
61) Preparation of 1-(4-bromobutyl)-1H-4-imidazolecarbaldehyde (292)
62) Preparation of 1-(5-bromopentyl)-1H-4-imidazolecarbaldehyde (294)
63) Preparation of 1-(6-bromohexyl)-1H-4-imidazolecarbaldehyde (296)
64) Preparation of 1-(12-bromododecyl)-1H-4-imidazolecarbaldehyde (298)
65) Preparation of 1-(4-chlorobutyl)-1H-5-imidazolecarbaldehyde (301)
66) Preparation of 1-[(3-phenylselanyl)propyl]-1H-5-imidazolecarbaldehyde (303)
67) Preparation of 1-[(4-phenylselanyl)butyl]-1H-5-imidazolecarbaldehyde (305)
68) Preparation of 1-(3-iodopropyl)-1H-4-imidazolecarbaldehyde (306)
69) Preparation of 6,7-dihydro-5H-pyrrolo[1,2-c]imidazole-1-carbaldehyde (307) (from the in situ formation of the iodide 306)
70) Preparation of 1-[(3-phenylselanyl)propyl]-1H-4-imidazolyl)methanol (309)
71) Preparation of 1-[(3-phenylselanyl)propyl]-1H-4-imidazolecarbaldehyde (302)
72) Preparation of 6,7-dihydro-5H-pyrrolo[1,2-c]imidazole-1-carbaldehyde (307) (from the selenide 302)
73) Preparation of 6,7-dihydro-5H-pyrrolo[1,2-c]imidazole-1-carbaldehyde (307) (from the bromide 290)
74) Preparation of 5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-1-carbaldehyde (310)
75) Preparation of 5,6,7,8-tetrahydro-5H-imidazo[1,5-a]azepine-1-carbaldehyde (312)
76) Attempted radical cyclisation of 1-(6-bromohexyl)-1H-4-imidazolecarbaldehyde (296)
77) Attempted radical cyclisation of 1-(12-bromododecyl)-1H-4-imidazolecarbaldehyde (298)
78) Preparation of 1-(3-bromopropyl)-5-methyl-1H-4-imidazolecarbaldehyde (318)
79) Attempted radical cyclisation of 1-(3-bromopropyl)-5-methyl-1H-4-imidazolecarbaldehyde (318)
80) Preparation of 1-(3-bromopropyl)-2-methyl-1H-4-imidazolecarbaldehyde (320)
81) Preparation of (E)-4-(3-methyl-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-3-buten-2-one (322)
82) Preparation of 1-(2-bromobenzyl)-1H-4-imidazolecarbaldehyde (323)
83) Attempted radical cyclisation of 1-(2-bromobenzyl)-1H-4-imidazolecarbaldehyde (323)
84) Attempted radical cyclisation of 1-[(3-phenylselanyl)propyl]-1H-5-imidazolecarbaldehyde (303)
85) Preparation of 5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-3-carbaldehyde (332)
86) Preparation of 1-(triphenylmethyl)-1H-2-imidazolecarbaldehyde (335)
87) Preparation of imidazole-1H-2-carbaldehyde (181)
88) Attempted alkylation of imidazole-1H-2-carbaldehyde (181)
89) Preparation of 1-[(3-phenylselanyl)propyl]imidazole (339)
90) Preparation of 1,3-di[3-(phenylselanyl)propyl]-1H-imidazol-3-ium iodide (340)
91) Attempted preparation of 1-[(3-phenylselanyl)propyl]-1H-2-imidazolecarbaldehyde (338) (from 1-[(3-phenylselanyl)propyl]imidazole 339)
92) Preparation of 2-(diethoxymethyl)imidazole (181)
93) Preparation of 2-(diethoxymethyl)-1-[(3-phenylselanyl)propyl]-1H-imidazole (342)
94) Preparation of 1-[(3-phenylselanyl)propyl]-2-imidazolecarbaldehyde (338)
95) Attempted radical cyclisation of 1-[3-(phenylselenyl)propyl]-2-imidazolecarbaldehyde (338)
96) Preparation of 1-(3-bromopropyl)-4-phenyl-1H-imidazole (344)
97) Preparation of 1-(4-bromobutyl)-4-phenyl-1H-imidazole (345)
98) Preparation of 1-(4-bromobutyl)-4-nitro-1H-imidazole (346)
99) Preparation of 1-phenyl-6,7-dihydro-5H-pyrrolo[1,2-c]imidazole (347)
100) Radical cyclisation of 1-(4-bromobutyl)-4-phenyl-1H-imidazole (345)
101) Attempted radical cyclisation of 1-(4-bromobutyl)-4-nitro-1H-imidazole (346)
102) Preparation of 1-(phenylsulfonyl)-1H-pyrrole (352)
103) Preparation of 1-(1H-3-pyrrolyl)1-ethanone [3-acetylpyrrole, 353]
104) Preparation of 1-[1-(3-bromopropyl)-1H-3-pyrrolyl]-1-ethanone (356)
105) Preparation of 1-[1-(4-bromobutyl)-1H-3-pyrrolyl]-1-ethanone (357)
106) Preparation of 1-[1-(5-bromopentyl)-1H-3-pyrrolyl]-1-ethanone (358)
107) Preparation of 1-(3-bromopropyl)-1H-pyrrolecarbaldehyde (359)
108) Preparation of 1-(4-bromobutyl)-1H-pyrrolecarbaldehyde (360)
109) Preparation of 1-(5-bromopentyl)-1H-pyrrolecarbaldehyde (361)
110) Preparation of 1-(2,3-dihydro-1H-7-pyrroloizinyl)-1-ethanone (362)
111) Preparation of 1-(5,6,7,8-tetrahydro-1-indolizinyl)-1-ethanone (364)
112) Preparation of 6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-3-carbaldehyde (366)
113) Preparation of 2,3-dihydro-1H-5-pyrrolizinecarbaldehyde (368)
114) Preparation of 5,6,7,8-tetrahydro-3-indolizinecarbaldehyde (369)
115) Preparation of 6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-3-carbaldehyde (370)
5.0 Experimental

5.1 General

IR spectra were determined using a Nicolet 205 FT-IR spectrometer and Perkin Elmer FT-IR Paragon 1000 spectrometer as KBr discs for solids and as thin films for liquids. $^1$H NMR spectra were measured using the Bruker AC 250 spectrometer at 250.0 MHz unless otherwise stated. J values are given in Hz. $^{13}$C NMR spectra were measured using the Bruker DPX 400 MHz spectrometer at 100.6 MHz unless otherwise stated. NMR spectra were recorded with CDCl$_3$ as solvent and tetramethylsilane (TMS) as internal reference unless otherwise stated. Mass spectra were recorded using a Kratos MS 80 instrument, and EPSRC Mass Spectrometry Service, Swansea University. Elemental analysis was carried out on a Perkin Elmer 2400 CHN Elemental Analyser. The GC-MS used was the Fisons GC 8000 series (AS 800). Melting points were carried out using Leica Galen Melting Point Apparatus, and are uncorrected.

TLC using silica gel as absorbent was carried out with aluminium backed plates coated with silica gel (Merck Kieselgel 60 F$_{254}$), and TLC using alumina as absorbent was carried out with aluminium backed plates coated with neutral aluminium oxide (Merck 150 F$_{254}$, Type T). Column chromatography using silica gel was carried out with Merck Kieselgel 60 H silica and column chromatography using alumina was carried out with Aldrich aluminium oxide, activated neutral, Brockmann 1, STD Grade, 150 mesh size. Prep-TLC was carried out using aluminium oxide (Merck 60 PF$_{254}$, Type E).

All of the following alkylation and radical cyclisation reactions of imidazoles, benzimidazoles and pyrroles were carried out using dry glassware and under an atmosphere of nitrogen. Anhydrous acetonitrile, THF and toluene were obtained commercially, and were used as reaction solvents in all the stated cases. Sodium hydride was obtained as 60% dispersion in oil, and was washed with light petroleum and 2.5 M solution of n-butyl lithium in hexane was used in all stated cases.

The work up of reactions and column chromatography were carried out using light petroleum (refers to the bp 40-60 °C fraction), ethyl acetate, dichloromethane, diethyl ether and methanol. Light petroleum and ethyl acetate were distilled from calcium chloride and dichloromethane was distilled over phosphorus pentoxide. Analytical grade diethyl ether and methanol were obtained commercially.
5.2 Experimental for Chapter 2

1) 2-(5-Nitro-1H-1-imidazolyl)-1-ethanol (175)\(^{94}\)

\[
\begin{align*}
\text{O}_2\text{N} & \\
& \text{N} \\
& \text{H} \\
& \text{171} \\
& \rightarrow \\
& \text{O}_2\text{N} \\
& \text{N} \\
& \text{H} \\
& \text{HO} \\
& \text{175}
\end{align*}
\]

4(5)-Nitroimidazole 171 (12.50 g, 0.111 mol) and potassium iodide (5.00 g, 30.1 mmol) were added to 2-chloroethanol (250 ml) and heated under reflux for 18 h. The solution was evaporated to dryness to yield a tan residue, which was added to water (200 ml). The solution was gravity filtered to remove the unreacted nitroimidazole and the filtrate basified to pH 8 with saturated sodium carbonate solution. The solution was extracted into ethyl acetate (2 x 100 ml) and evaporated to dryness to yield a brown residue, which was recrystallised from absolute ethanol to yield pale brown crystals of 2-(5-nitro-1H-1-imidazolyl)-1-ethanol 175 (3.82 g, 22%), mp 99-100 °C (lit.\(^{94}\) mp 96-97 °C); (Found: C, 38.2; H, 4.1; N, 26.8. C\(_5\)H\(_7\)N\(_3\)O\(_3\) requires C, 38.2; H, 4.4; N, 26.8%); \(\delta_H\) 2.06 (1 H, s, OH), 3.99-4.02 (2 H, t, J 4.8, 2'-CH\(_2\)), 4.52-4.56 (2 H, t, J 4.8, NCH\(_2\)), 7.66 (1 H, s, Im-2-H) and 8.00 (1 H, s, Im-4-H).

2) 1-(2-Chloroethyl)-5-nitro-1H-imidazole (172)\(^{82}\)

\[
\begin{align*}
\text{O}_2\text{N} & \\
& \text{N} \\
& \text{HO} \\
& \text{175} \\
& \rightarrow \\
& \text{O}_2\text{N} \\
& \text{N} \\
& \text{Cl} \\
& \text{172}
\end{align*}
\]

2-(5-Nitro-1H-1-imidazolyl)-1-ethanol 175 (2.00 g, 12.7 mmol) was added to thionyl chloride (50 ml) and heated under reflux for 3 h. The excess thionyl chloride was evaporated to leave a tan residue, which was added to water (100 ml). The aqueous solution was basified to pH 8 with saturated sodium carbonate solution and extracted into ethyl acetate (2 x 100 ml). The solution was evaporated to dryness to yield a brown residue, which was purified by column chromatography using neutral alumina as absorbent with dichloromethane as eluent to yield pale yellow needles of 1-(2-chloroethyl)-5-nitro-1H-imidazole 172 (0.78 g, 35%), mp 49-50 °C (lit.\(^{82}\) mp 49-51 °C); \(\delta_H\) 3.87-3.90 (2 H, t, J 5.4, 2'-CH\(_2\)), 4.66-4.70 (2 H, t, J 5.4, NCH\(_2\)), 7.67 (1 H, s, Im-2-H) and 8.04 (1 H, s, Im-4-H); \(\delta_C\) (62.5 MHz) 42.50 (2'-CH\(_2\)), 49.51 (NCH\(_2\)), 134.04 (Im-4-CH) and 142.51 (Im-2-CH); \(m/z\) 175 (M\(^+\), 35%), 158 (9), 140 (25), 129 (9), 67 (39), 63 (60) and 28 (100).
3) 2(4)-Chloro-1-(2-chloroethyl)-5-nitro-1H-imidazole (176)

![Chemical structure](image)

2-(5-Nitro-1H-1-imidazolyl)-1-ethanol 175 (2.00 g, 12.7 mmol) was added to thionyl chloride (50 ml) and heated under reflux for 54 h. The excess thionyl chloride was evaporated to leave a tan residue, which was added to water (100 ml). The aqueous solution was basified to pH 8 with saturated sodium carbonate solution and extracted into ethyl acetate (2 x 100 ml). The solution was evaporated to dryness to yield a brown residue, which was purified by column chromatography using neutral alumina as absorbent with dichloromethane as eluent to yield cream coloured crystals of 2(4)-chloro-1-(2-chloroethyl)-5-nitro-1H-imidazole 176 (1.2 g, 45%), mp 92-93 °C (Found: M+, 208.9759. C$_5$H$_5$N$_3$Cl$_2$O$_2$ requires M, 208.9757); $\nu_{\text{max}}$/cm$^{-1}$ 3107, 1538 (NO$_2$), 1506, 1390, 1360 (NO$_2$), 1340 and 827; $\delta_H$ 3.82-3.87 (2 H, t, $J$ 5.7, 2'-CH$_2$), 4.37-4.41 (2 H, t, $J$ 5.7, NCH$_2$) and 7.87 (1 H, s, Im-2(4)-H); $\delta_C$ 42.02 (2'-CH$_2$), 49.61 (NCH$_2$), 121.73 (Im-CH), 132.68 (Im-CH) and 146.14 (q-C, Im-5-C); m/z 209 (M+, 28%), 90 (66), 63 (100) and 27 (53).

4) Attempted synthesis of 5H-pyrrolo[1,2-a]imidazole (182) by an intramolecular Schewizer-Light reaction

![Chemical structure](image)

Imidazole-2-carbaldehyde (0.27 g, 2.8 mmol) was added to sodium hydride (0.08 g, 3.4 mmol) in THF (100 ml), and the mixture was stirred and heated under reflux for 2 h. Vinyltriphenylphosphonium bromide (Schweizer reagent, 1.14 g, 3.1 mmol) was added, and the mixture was stirred and heated under reflux for a further 5 h. The salts formed were removed by filtration on a celite bed and the solution was evaporated to dryness to give a tan residue, which rapidly darkened to yield unidentifiable products.
5) Allyl 4-methyl-1-benzenesulfonate [allyl tosylate, 193]

25% Aqueous sodium hydroxide solution (70 ml, 0.4 mol) was added dropwise to a solution of allyl alcohol (51.2 g, 0.9 mol) and p-toluenesulfonyl chloride (76.4 g, 0.4 mol) at 0-10 °C. The reaction mixture was allowed to stand at ambient temperature for 18 h and was poured onto iced-water (400 ml). The aqueous solution was extracted with dichloromethane (2 x 200 ml), and the combined organic extracts dried (MgSO4) and evaporated to dryness to yield allyl 4-methyl-1-benzenesulfonate 193 (56.0 g, 66%) as a colourless oil; δH 2.42 (3 H, s, CH3), 4.48-4.51 (2 H, m, 1'-CH2), 5.20-5.24 (1 H, m, 3'-cis-H), 5.24-5.32 (1 H, m, 3'-trans-H), 5.73-5.84 (1 H, m, 2'-CH), 7.31-7.34 (2 H, d, J 7.5, ArH) and 7.75-7.78 (2 H, d, J 7.5, ArH).

6) 1-Allyl-5-nitro-1H-imidazole (190) (using allyl tosylate)

![Chemical Reaction Diagram]

4(5)-Nitroimidazole 171 (15.0 g, 0.133 mol), allyl 4-methyl-1-benzenesulfonate 193 (32.0 g, 0.150 mol) and 4-methyl-1-benzenesulfonic acid monohydrate [p-toluenesulfonic acid monohydrate] (1.0 g, 5 mmol) were heated at 130 °C for 18 h. Sodium carbonate solution (300 ml, 1.0 M) was added to the cooled melt, and stirred for 10 min. The mixture was gravity filtered to remove unreacted nitroimidazole and the filtrate extracted with dichloromethane (2 x 150 ml). The combined organic extracts were dried (MgSO4) and evaporated to dryness to give a brown oil containing 1-allyl-5-nitro-1H-imidazole 190; δH 4.97-5.00 (2 H, m, NCH2), 5.15-5.22 (1 H, dd, J 1.5 and J 17.1, 3'-trans-H), 5.32-5.36 (1 H, d, J 9.6, 3'-cis-H), 5.94-6.09 (1 H, m, 2'-H), 7.60 (1H, s, Im-2-H) and 8.02 (1H, s, Im-4-H) and 1-allyl-4-nitro-1H-imidazole 194 (4.0 g, 18% and 2% yield respectively by 1H NMR spectroscopic analysis of reaction mixture using a known amount of 1,4-dimethoxybenzene as internal standard).

7) 1-Allyl-5-nitro-1H-imidazole (190) (using allyl bromide)

![Chemical Reaction Diagram]
4(5)-Nitroimidazole 171 (2.00 g, 18 mmol) and allyl bromide (1.5 ml, 18 mmol) were added to DMF (75 ml). The mixture was stirred and heated under reflux at 50-75 °C for 96 h. The solution was evaporated to dryness to yield a tan residue, which was added to sodium carbonate solution (100 ml) and the mixture gravity filtered to remove unreacted nitroimidazole. The filtrate was extracted with dichloromethane (2 x 50 ml), the combined organic extracts washed with brine (3 x 50 ml), dried (MgSO₄) and evaporated to dryness to give a tan oil containing 1-allyl-5-nitro-1H-imidazole 190 and 1-allyl-4-nitro-1H-imidazole 194 (0.17 g, 3% and 3% yield respectively by ¹H NMR spectroscopic analysis of reaction mixture using a known amount of 1,4-dimethoxybenzene as internal standard).

8) (1-Allyl-5-nitro-1H-2-imidazolyl)methanol (198)

A crude mixture of 1-allyl-5-nitro-1H-imidazole 190 and 1-allyl-4-nitro-1H-imidazole 194 (2.55 g, 9/1 respectively by ¹H NMR spectroscopic analysis), paraformaldehyde (3.09 g, 0.102 mol) and DMSO (150 ml) were introduced into a Carius tube and sealed. The sealed tube was heated at 120 °C for 54 h, and the contents of the tube were allowed to cool to room temperature. The tube was opened and the solution was evaporated to dryness to yield a brown residue, which was purified by column chromatography using neutral alumina as absorbent with dichloromethane followed by 5% methanol / dichloromethane as eluent to yield unreacted yellow needles of 1-allyl-4-nitro-1H-imidazole 194 (0.14 g), mp 44-46 °C (Found: M⁺, 153.0537. C₆H₇N₃O₂ requires M⁺, 153.0538); νmax /cm⁻¹ 3426, 3078, 1545 (NO₂), 1525, 1345 (NO₂) and 1294; δH 4.63-4.65 (2 H, m, NCH₂), 5.32-5.36 (1 H, d, 16.8 Hz, 3'-trans-H), 5.42-5.46 (1 H, d, J 10.3, 3'-cis-H), 5.91-6.07 (1 H, m, 2'-H), 7.45 (1 H, s, Im-2-H), and 7.77 (1 H, s, Im-5-H); δC 50.54 (NCH₂), 119.20 (3'-CH₂), 120.94 (CH), 130.57 (CH) and 135.83 (CH); m/z 153 (M⁺, 61%), 137 (32), 107 (60) and 41 (100); Further elution yielded a brown oil of (1-allyl-5-nitro-1H-2-imidazolyl)methanol 198 (1.11 g, 40%), containing a residual amounts of DMSO; (Found: M⁺, 183.0624. C₇H₉N₃O₃ requires M⁺, 183.0644); νmax /cm⁻¹ 2878, 1537 (NO₂), 1467, 1382 and 1359 (NO₂); δH 3.34-3.39 (1 H, t, J 6.2, OH), 4.73-4.77 (2 H, m, CH₂OH), 5.01-5.09 (1 H, dd, J 1.9 and J 17.5, 3'-trans-H), 5.10-5.12 (2 H, m, NCH₂), 5.25-5.30 (1 H, dd, J 1.4 and J 10.4, 3'-cis-H), 5.92-6.05 (1 H, m, 2'-H) and 7.96 (1 H, s, Im-4-H); δC 47.96 (NCH₂), 56.41 (CH₂OH), 118.16 (3'-CH₂), 131.31 (CH), 133.33 (CH) and 151.56 (Im-2-C); m/z 183 (M⁺, 7%), 152 (12), 142 (8), 41 (100), 31 (27) and 29 (50).
9) 1- Allyl-5- nitro-1H- imidazolecarbaldehyde (191)

\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{CH}_2\text{OH} \\
\text{198} & \\
\text{O}_2\text{N} & \quad \text{CHO} \\
\text{191}
\end{align*}
\]

(1- Allyl-5- nitro-1H-2- imidazolyl)methanol 198 (0.300 g, 1.64 mmol) and activated manganese dioxide (0.712 g, 8.2 mmol) were heated under reflux in dry dichloromethane (150 ml) for 18 h. The mixture was cooled, filtered on a celite bed and the residue washed with dichloromethane (3 x 50 ml). The combined filtrate washings were evaporated to give a brown oil of 1- allyl-5- nitro-1H- imidazolecarbaldehyde 191; \(\delta_H\) 5.13-5.20 (1 H, dd, \(J = 1.9\) and \(J = 17.1\), 3'-trans-H), 5.25-5.30 (1 H, d, \(J = 12.4\), 3'-cis-H), 5.51-5.54 (2 H, m, NCH\(_2\)), 5.90-6.04 (1 H, m, 2'-H), 8.14 (1 H, s, Im-4-H) and 9.94 (1 H, s, CHO) and recovered (1- allyl-5- nitro-1H-2- imidazolyl)methanol 198 (0.183 g, 64% and 1% yield respectively by 1H NMR spectroscopic analysis of reaction mixture using a known amount of 1,4-dimethoxybenzene as internal standard).

5.3 Experimental for Chapter 3

10) 1-(Triphenylmethyl)imidazole [1-(Trityl)imidazole, 217]

\[
\begin{align*}
\text{204} & \\
\text{217}
\end{align*}
\]

Imidazole 204 (10.2 g, 0.150 mol) was dissolved in dichloromethane (200 ml). Triphenylmethyl chloride (46.0 g, 0.165 mol) was added over 20 min and the mixture stirred until the solution was complete. Triethylamine (42 ml, 0.300 mol) was added slowly to the stirred solution and the stirring was continued overnight at ambient temperature. The solution was evaporated to dryness and the residue was recrystallised from absolute ethanol and dried to give 1-(tri phenylmethyl)imidazole 217 as pale white needles (42.0 g, 90%), mp 229-230 °C (lit.\(^{108}\) mp 229-230 °C).
11) 2-[(4-Methylphenyl)sulfonyl]-1-(triphenylmethyl)-1H-imidazole (218)

\[
\begin{align*}
\text{N} & \quad \text{CPh}_3 \\
\text{217} & \quad \text{N} \quad \text{SO}_2\text{Tol} \\
\text{218}
\end{align*}
\]

1-(Trityl)imidazole 217 (9.0 g, 27 mmol) was dissolved in THF (300 ml) and TMEDA (12 ml, 81 mmol) was added to the stirred solution at ambient temperature. The temperature of the stirred solution was lowered to -78 °C, and a solution of n-butyllithium (13 ml, 32 mmol) added dropwise. The solution turned red and was stirred at 0 °C for a further 20 min. A solution of p-toluenesulfonyl fluoride (14.1 g, 81 mmol) in THF (50 ml) was added dropwise and the stirring was continued at ambient temperature for a further 2 h. The solution was evaporated to dryness and saturated ammonium chloride (50 ml) and water (100 ml) was added to the residue. The aqueous mixture was extracted with dichloromethane (3 x 50 ml), the organic extracts dried (MgSO₄), and the solution evaporated to dryness. The crude solid was purified by column chromatography using silica gel as absorbent with light petroleum and dichloromethane as eluent. Evaporation of the eluates containing the second component gave white crystals of 2-[(4-methylphenyl)sulfonyl]-1-(triphenylmethyl)-1H-imidazole 218 (4.1 g, 33%), mp 175 -176 °C (Found: C, 75.3; H, 5.4; N, 5.4. C₂₉H₂₅N₂O₂S requires C, 75.0; H, 5.2; N, 5.6%); \( \nu_{\text{max}} \text{ cm}^{-1} \) 1594, 1493, 1447, 1337 (SO₂), 1233, 1174 and 1148 (SO₂); \( m/z \) 464 (M⁺, 85%), 387 (100), 188 (40), 105 (100), 91 (27), 77 (53) and 28 (27).

12) 2-(Phenylsulfanyl)-1-(triphenylmethyl)-1H-imidazole (219)

\[
\begin{align*}
\text{N} & \quad \text{CPh}_3 \\
\text{217} & \quad \text{N} \quad \text{SPh} \\
\text{219}
\end{align*}
\]

1-(Trityl)imidazole 217 (8.0 g, 25.8 mmol) was dissolved in THF (300 ml), the temperature of this stirred solution was lowered to -78 °C, and a solution of n-butyllithium (13 ml, 31.0 mmol) added dropwise. The solution turned red and was stirred at 0 °C for a further 20 min. A solution of diphenyl disulfide (16.9 g, 77.4 mmol) in THF (100 ml) was added dropwise and the stirring was continued at ambient temperature for a further 2 h. The solution was evaporated to dryness and saturated ammonium chloride (50 ml) and water (100 ml) was added to the residue. The aqueous mixture was extracted with dichloromethane (3 x 50 ml), the organic extracts dried (MgSO₄) and evaporated to dryness. The crude solid was purified by column chromatography using silica gel as absorbent with light petroleum / dichloromethane and then diethyl ether as
eluent. Evaporation of the eluates containing the second component gave white crystals of 2-(phenylsulfonyl)-1-(triphenylmethyl)-1H-imidazole 219 (5.0 g, 46%), mp 172-174 °C, (Found: C, 80.2; H, 5.2; N, 6.3. C_{28}H_{22}N_{2}S requires C, 80.4; H, 5.3; N, 6.7%); \nu_{\text{max}} /\text{cm}^{-1} 1580, 1492, 1479, 1446, 1415, 1233, 753, 705, 689 and 640.

13) 2-Chloro-1-(triphenylmethyl)-1H-imidazole (220)

\[
\begin{align*}
\text{1-(Trityl)imidazole 217 (2.00 g, 6 mmol) was dissolved in THF (100 ml) and the temperature of} \\
\text{the stirred solution was lowered to -78 °C, and a solution of } n\text{-butyllithium (3 ml, 7 mmol)} \\
\text{added dropwise. The solution turned red and was stirred at } 0 \degree \text{C for a further 20 min. A solution} \\
\text{of p-toluenesulfonyl chloride (3.7 g, 18 mmol) in THF (50 ml) was added dropwise and the} \\
\text{stirring was continued at ambient temperature for a further 2 h. The solution was evaporated to} \\
\text{dryness and saturated ammonium chloride (50 ml) and water (100 ml) was added to the residue.} \\
\text{The aqueous mixture was extracted with dichloromethane (3 x 50 ml), the organic extracts dried} \\
\text{(MgSO}_{4}\text{), and the solution evaporated to dryness. The crude solid was purified by column} \\
\text{chromatography using silica gel with light petroleum and dichloromethane as eluent.} \\
\text{Evaporation of the eluates containing the second component gave yellow crystals of 2-chloro-1-} \\
\text{(triphenylmethyl)-1H-imidazole 220, (0.29 g, 14%), mp 225-227 °C.}
\end{align*}
\]

General procedure for the removal of the trityl protective group
14) 2-[(4-Methylphenyl)sulfonyl]-1H-imidazole [2-tosylimidazole, 221]

\[
\begin{align*}
\text{2-[(4-Methylphenyl)sulfonyl]-1-(triphenylmethyl)-1H-imidazole 218 (3.00 g, 6.5 mmol) was} \\
\text{dissolved in methanol (100 ml) and concentrated hydrochloric acid (10 ml, 31-34% w/w} \\
\text{solution) added. The solution was heated under reflux for 2 h. After cooling the solution to} \\
\text{ambient temperature, most of the solvent was evaporated and the residue added to water} \\
\text{(100 ml). The acidic aqueous mixture was extracted with dichloromethane (2 x 50 ml), which} \\
\text{removed the hydrolysis product, triphenylmethyl alcohol. The acidic aqueous layer was} \\
\text{evaporated to leave approximately 30-40 ml of a solution containing the salt of the imidazole}
\end{align*}
\]
compound, which was precipitated as the free base from the saturated aqueous acidic solution using solid sodium carbonate until foaming ceased. The precipitate was filtered, dried (MgSO₄) and recrystallised with absolute ethanol to yield white needles of 2-[(4-methylphenyl)sulfonyl]-IH-imidazole 221 (0.63 g, 44%), mp 200-202 °C (Found: C, 53.7; H, 4.1; N, 12.4. C₁₀H₁₀N₂O₂S requires C, 54.0; H, 4.5; N, 12.6%); νmax /cm⁻¹ 1333 (SO₂), 1152 (SO₂), 1107 and 1082; δH ([²H₆] Me₂SO) 2.36 (3 H, s, CH₃), 7.22 (2 H, bs, Im-4, 5-H), 7.40-7.43 (2 H, d, J 7.5, Ar-H) and 7.77-7.80 (2 H, d, J 7.5, Ar-H); δC ([²H₆] Me₂SO) 22.96 (CH₃), 129.27, 132.02, 139.06 (q-C), 145.34 (q-C) and 46.69 (q-C); m/z 158 (M⁺, 100%), 131(31), 91(48), 77(5), 65(24) and 39 (12).

15) 2-(Phenylsulfanyl)-IH-imidazole (222)

The general procedure for the removal of the trityl protective group was followed. 2-(Phenylsulfanyl)-1-(triphenylmethyl)-IH-imidazole 219 (4.67 g, 11.2 mmol) gave white needles of 2-(phenylsulfanyl)-IH-imidazole 222 (1.61 g, 85%), mp 175-176 °C, (Found: MH⁺, 177.0486. C₀H₈N₂S + H requires M, 177.0486); νmax /cm⁻¹ 2625, 1582, 1479, 1441, 1416, 1326, 1100, 964, 751 and 739; δH ([²H₆] Me₂SO) 7.10-7.35 (7 H, m, Im-4(5)-H and Ar-H) and 12.81 (1 H, bs, NH); δC ([²H₆] Me₂SO) 124.54, 125.40, 126.38, 128.30, 133.65 (q-C) and 134.96 (q-C); m/z 176 (M⁺, 43%), 175 (92), 175 (92), 77 (88), 72 (73), 69 (35), 65 (48) and 51 (100).

General procedure for the alkylation of imidazoles

16) 1-(3-Bromo-2-propenyl)-2-[(4-methylphenyl)sulfonyl]-IH-imidazole (223)

2-[(4-Methylphenyl)sulfonyl]-IH-imidazole 221 (0.600 g, 2.7 mmol) was added to sodium hydride (70 mg, 3 mmol) in acetonitrile (100 ml). The mixture was stirred and heated under reflux for 1 h, and 1,2-dibromopropene (mixture of cis and trans isomers, 1.620 g, 8.1 mmol) was added. The mixture was stirred and heated under reflux for a further 2 h. The salts formed were removed by filtration on a celite bed and the solution was evaporated to dryness to yield a
tan solid. The crude product was purified by column chromatography using silica gel with 60% diethyl ether / light petroleum as eluent to yield yellow crystals of 1-(3-bromo-2-propenyl)-2-[(4-methylphenyl)sulfonyl]-1H-imidazole 223 (0.920 g, 77%), as a mixture of cis and trans isomers in a ratio approximately to that of the the starting dibromopropene, mp 99-100 °C (Found: M⁺, 340.9825. C_{13}H_{13}N_{2}BrO_{2}S requires M, 340.9825); v_{max} /cm⁻¹ 1624, 1594, 1329 (SO₂), 1152, 1147 (SO₂) and 782; δ_{H} 2.40 (3 H, s, CH₃), 4.92-4.94 (2 H, d, J 5.0, 1'-cis CH₂), 5.09-5.12 (2 H, dd, J 1.5 Hz and J 6.5, 1'-trans-CH₂), 6.24-6.33 (1 H, m, 2'-cis and trans-H), 6.43-6.47 (1 H, m, 3'-cis and trans-H), 7.04 (1 H, d, J 0.8, Im-4(5)-H), 7.10 (1 H, d, J 0.8, Im-4(5)H), 7.31-7.35 (2H, d, J 7.5, Ar-H) and 7.87-7.90 (2 H, d, J 7.5, Ar-H); δ_{C} 22.08 (CH₃), 47.30 (1'-cis -CH₂), 49.56 (1'-trans-CH₂), 111.57, 112.96, 124.18-124.37 (Im-CH), 128.71, 129.48 (2'-cis and trans-H), 130.37 and 130.47; m/z 341 (M⁺, 5%), 277 (77), 197 (100), 155 (5), 119 (12), 106 (46), 65 (20) and 39 (33).

General procedure for the radical cyclisation of imidazoles and benzimidazoles

17) Attempted radical cyclisation of 1-(3-bromo-2-propenyl)-2-[(4-methylphenyl)sulfonyl]-1H-imidazole (223)

![Imidazole 223](image)

A solution of tri-n-butyltin hydride (0.5 ml, 1.89 mmol) and AIBN (0.160 g, 0.95 mmol) in toluene (50 ml) was added to 1-(3-bromo-2-propenyl)-2-[(4-methylphenyl)sulfonyl]-1H-imidazole 233 (0.427 g, 1.26 mmol) in toluene (200 ml) at reflux over 5 h. The solution was stirred and heated under reflux for a further 1 h. After cooling to room temperature, the solution was evaporated to dryness, and 2 M hydrochloric acid solution (50 ml) was immediately added, and the acidic solution was washed with light petroleum (12 x 50 ml). The solution was basified to pH 8 with saturated sodium carbonate solution followed by the addition of 2 M sodium hydroxide solution until the aqueous solution was at pH 14. The hydroxide solution was extracted into dichloromethane (2 x 100 ml), and the combined organic extracts dried (MgSO₄) and evaporated to dryness to yield a brown oil residue, which was placed under an atmosphere of nitrogen. TLC and ¹H NMR spectroscopic analysis showed a complete conversion of the starting bromide to unidentifiable products.
18) 1-[3-Chloropropyl]-2-[(4-methylphenyl)sulfonyl]-1H-imidazole (224) (using 1-chloro-3-iodopropane)

The general procedure for the alkylation of imidazoles in acetonitrile was followed.

2-[(4-Methylphenyl)sulfonyl]-1H-imidazole 221 (0.160 g, 0.72 mmol), sodium hydride (26 mg, 1.08 mmol) and 1-chloro-3-iodopropane (0.23 ml, 2.16 mmol) in acetonitrile (100 ml) gave a tan residue, which was purified by column chromatography using silica gel as absorbent with light petroleum and ethyl acetate as the eluent to yield 1-[3-chloropropyl]-2-[(4-methylphenyl)sulfonyl]-1H-imidazole as yellow needles 224 (0.114 g, 53%), mp 68-69 °C (Found : M⁺, 298.0543. C₁₃H₁₅N₂ClO₂S requires M⁺, 298.0543); \( \delta_{\text{H}} \) 2.32-2.39 (2 H, m, 2'-CH₂), 2.44 (3 H, s, CH₃), 3.51-3.58 (2 H, t, \( J \) 6.3, CH₂Cl), 4.51-4.56 (2 H, t, J 6.3, NCH₂), 7.07 (1 H, s, Im-4(5)-H), 7.12 (1 H, s, Im-4(5)-H), 7.34-7.37 (2 H, d, J 7.5, Ar-H) and 7.90-7.93 (2 H, d, J 7.5, Ar-H); \( \delta_{\text{C}} \) 20.15 (CH₃), 32.07 (2'-CH₂), 39.75 (CH₂Cl), 43.72 (NCH₂), 123.08 (Im-CH), 126.81 (Im-CH), 128.18, 128.23, 135.25 (q-C), 141.79 (q-C) and 143.81 (q-C); m/z 299 (MH⁺, 3%), 249 (3), 199 (34), 172 (100), 152 (15), 91 (94), 77 (13), 65 (48) and 41 (39). Evaporation of the eluates containing the second component gave 2-[(4-methylphenyl)sulfonyl]-1-(3-2-[(4-methylphenyl)sulfonyl]-1H-imidazolyl)propyl]-1H-imidazole [1,3-bis(2-tosylimidazolyl)propane, 225], as white needles (0.143 g, 40%); \( \delta_{\text{H}} \) 2.44 (6 H, s, CH₃), 2.47-2.50 (2 H, m, 2'-CH₂), 4.41-4.47 (4 H, t, J 7.5, NCH₂), 7.04 (2 H, s, Im-4(5)-H), 7.14 (2 H, s, Im-4(5)-H), 7.35-7.38 (4 H, d, J 7.5, ArH) and 7.88-7.91 (4 H, d, J 7.5, ArH).

19) 1-[3-Chloropropyl]-2-[(4-methylphenyl)sulfonyl]-1H-imidazole (224) (using 1-bromo-3-chloropropane)

2-[(4-Methylphenyl)sulfonyl]-1H-imidazole 221 (0.260 g, 1.17 mmol), sodium hydride (42 mg, 1.75 mmol) and 1-bromo-3-chloropropane (0.35 ml, 3.51 mmol) in acetonitrile (100 ml) gave a tan residue, which was purified by column chromatography using silica gel as absorbent with light petroleum and ethyl acetate as the eluent to yield 1-[3-chloropropyl]-2-[(4-methylphenyl)sulfonyl]-1H-imidazole 224, as a yellow needles (0.348 g, 68%) and 2-[(4-methylphenyl)sulfonyl]-1-(3-2-[(4-methylphenyl)sulfonyl]-1H-imidazolyl)propyl]-1H-imidazole 225, as white needles (87 mg, 15%).
20) 1-(3-Iodopropyl)-2-[(4-methylphenyl)sulfonyl]-1H-imidazole (226)

1-[3-Chloropropyl]-2-[(4-methylphenyl)sulfonyl]-1H-imidazole 224 (0.110 g, 0.36 mmol), and sodium iodide (0.270 g, 1.80 mmol) were added to dry acetonitrile (50 ml), and heated under reflux for 6 h. The precipitated sodium chloride was removed by filtration on a celite bed, and the solution was evaporated to dryness. The residue was added to saturated sodium sulfite solution (100 ml) and extracted with dichloromethane (2 x 50 ml). The combined organic extracts dried (MgSO₄) and evaporated to dryness to yield a tan residue, which was purified by column chromatography using silica gel as absorbent with 25% ethyl acetate / light petroleum as eluent to yield colourless needles of 1-(3-iodopropyl)-2-[(4-methylphenyl)sulfonyl]-1H-imidazole 226 (42 mg, 30%), (Found : MH⁺ 390.9977. C₁₃H₁₅N₂I0₂S + H requires M, 389.9979); νmax /cm⁻¹ 3111, 2925, 1596, 1330 (S02), 1293, 1186, 1147 and 1082; δH 2.34-2.42 (2 H, m, 2'-CH₂), 2.45 (3 H, s, CH₃), 3.12-3.17 (2 H, t, J 6.3, CH₂), 4.45-4.51 (2 H, t, J 7.5, NCH₂), 7.09 (1 H, s, Im-4(5)-H), 7.12 (1 H, s, Im-4(5)-H), 7.36-7.39 (2 H, d, J 7.5, Ar-H) and 7.91-7.94 (2 H, d, J 7.5, Ar-H); δC 0.00 (CH₂), 20.03 (CH₃), 32.62 (2'-CH₂), 46.67 (NCH₂), 122.66 (Im-CH), 126.69 (Im-CH), 128.06 (Ar-CH), 128.27 (Ar-CH), 141.63 (q-C) and 143.69 (q-C); m/z 391 (MH₂⁺, 38%), 265 (8), 223 (9), 111 (16), 109 (100) and 69 (8), which rapidly darken to unidentifiable products on standing at ambient temperature.

21) 2-[(4-Methylphenyl)sulfonyl]-1-[3-(phenylselanyl)propyl]-1H-imidazole (227)

The general procedure for the alkylation of imidazoles in acetonitrile was followed.

2-[(4-Methylphenyl)sulfonyl]-1H-imidazole 221 (0.121 g, 0.55 mmol), sodium hydride (16 mg, 0.66 mmol) and 3-iodo-1-(phenylselanyl)propane 233 (0.180 g, 0.55 mmol) in acetonitrile (150 ml) gave a tan residue, which was purified by column chromatography using silica gel as absorbent with light petroleum and diethyl ether as eluent to yield 2-[(4-methylphenyl)sulfonyl]-1-[3-(phenylselanyl)propyl]-1H-imidazole 227, as a yellow oil
(0.110 g, 48%); (Found: M⁺, 420.0413. C₁₉H₂₀N₂O₂S₂Se requires M, 420.0410); υmax /cm⁻¹
1596, 1579, 1478, 1438, 1332, 1293, 1266, 1148 (SO₂), 736 and 658; δH 2.13-2.24 (2 H, m, 2'-CH₂), 2.40 (3 H, s, CH₃), 2.82-2.88 (2 H, t, J 7.1, CH₂SePh), 4.41-4.47 (2 H, t, J 7.1, NCH₂), 6.94 (1 H, s, Im-4(5)-H), 7.08 (1 H, s, Im-4(5)-H), 7.25-7.28 (3 H, m, SePh-H), 7.30-7.33 (2 H, d, J 7.5, Ar-H), 7.46-7.50 (2 H, m, SePh-H) and 7.87-7.90 (2 H, d, J 7.5, Ar-H); δC (62.5 MHz) 21.63 (CH₃), 23.84 (2'-CH₂), 31.35 (PhSeCH₂), 47.49 (PhSeCH₂), 124.15, 127.25, 128.19, 129.21, 129.66, 129.87, 132.87, 136.67 (q-C), 143.33 (q-C) and 146.00 (q-C); m/z 265 (100%), 155 (13), 108 (17), 91 (72), 41 (21) and 65 (66).

22) 2-[(4-Methylphenyl)sulfonyl]-1-[4-(phenylselanyl)butyl]-1H-imidazole (228)

![Diagram](image)

The general procedure for the alkylation of imidazoles in acetonitrile was followed. 2-[(4-Methylphenyl)sulfonyl]-1H-imidazole 221 (0.195 g, 0.88 mmol), sodium hydride (25 mg, 1.06 mmol) and 4-iodo-1-(phenylselanyl)butane 234 (0.289 g, 0.88 mmol) in acetonitrile (150 ml) gave a tan residue, which was purified by column chromatography using silica gel as absorbent with light petroleum and diethyl ether as eluent to yield 2-[(4-methylphenyl)sulfonyl]-1-[4-(phenylselanyl)butyl]-1H-imidazole as 228 cream coloured crystals (0.156 g, 41%), mp 105-107 °C (Found: M⁺, 434.0567. C₂₀H₂₂N₂O₂S₂Se requires M, 434.0567); υmax /cm⁻¹ 2915, 1598, 1478, 1463, 1430, 1330 (SO₂), 1296, 1148 and 788; δH 1.67-1.74 (2 H, m, 3'-CH₂), 1.91-1.98 (2 H, m, 2'-CH₂), 2.43 (3 H, s, CH₃), 2.86-2.92 (2 H, t, J 7.1, CH₂SePh), 4.30-4.36 (2 H, t, J 7.3, NCH₂), 6.95 (1 H, s, Im-4(5)-H), 7.11 (1 H, s, Im-4(5)-H), 7.25-7.28 (3 H, m, SePh-H), 7.33-7.36 (2 H, d, J 7.5, Ar-H), 7.46-7.50 (2 H, m, SePh-H) and 7.89-7.92 (2 H, d, J 7.5, Ar-H); δC (62.5 MHz) 21.63 (CH₃), 26.81 (3'-CH₂), 26.95 (2'-CH₂), 31.09 (PhSeCH₂), 47.44 (N-CH₂), 123.93, 126.98, 127.97, 128.13, 129.62, 129.87, 132.76, 132.79, 136.80 (q-C), 143.33 (q-C) and 145.14 (q-C); m/z 434 (M⁺, 4%), 279 (30), 223 (12), 157 (20), 122 (21) and 91 (100).

23) 2-(4-Methylphenyl)sulfonyl]-1-[5-(phenylselanyl)pentyl]-1H-imidazole (229)

![Diagram](image)
The general procedure for the alkylation of imidazoles in acetonitrile was followed.

2-[(4-Methylphenyl)sulfonyl]-1H-imidazole 221 (0.130 g, 0.59 mmol), sodium hydride (21 mg, 88 mmol) and 5-iodo-1-(phenylselanyl)pentane 235 (0.208 g, 0.59 mmol) in acetonitrile (100 ml) gave a tan residue, which was purified by column chromatography using silica gel as absorbent with light petroleum and dichloromethane as eluent to yield 2-[(4-methylphenyl)sulfonyl]-1-[5-(phenylselanyl)pentyl]-1H-imidazole, as 229 white crystals (0.132 g, 50%), mp 83-85 °C (Found: M+, 448.0724. C21H2N2O2SSe requires M, 448.0723);

$\nu_{\text{max}}/\text{cm}^{-1}$ 2937, 1578, 1476, 1432, 1326 (SO2), 1174 (SO2), 1074, 813 and 796; $\delta_H$ 1.32-1.45 (2 H, m, 3'-CH2), 1.68-1.81 (4 H, m, 2' and 4'-CH2), 2.38 (3 H, s, CH3), 2.85-2.88 (2 H, t, J 7.3, CH2SePh), 4.27-4.31 (2 H, t, J 7.4, NCH2), 6.95 (1 H, s, Im-4(5)-H), 7.10 (1 H, s, Im-4(5)-H), 7.22-7.27 (3 H, m, SePh-H), 7.30-7.32 (2 H, d, J 7.5, Ar-H), 7.46-7.48 (2 H, m, SePh-H) and 7.88-7.90 (2 H, d, J 7.5, Ar-H); $\delta_C$ 21.93 (CH3), 26.93 (3'-CH2), 27.67 (4'-CH2), 30.21, 31.15, 48.37 (N-CH2), 124.50, 127.23, 128.44, 129.24, 130.30, 130.64, 132.41, 137.44 (q-C), 143.49 (q-C), 145.52 (q-C) and 153.18 (q-C); m/z 448 (M+, 16%), 293 (29), 223 (49), 157 (30), 136 (28) and 91 (100).

General procedure for the introduction of the phenylselanyl group

24) 3-Chloro-1-(phenylselanyl)propane (230)$^{112}$

Diphenyl diselenide (3.70 g, 11.9 mmol) was dissolved in absolute ethanol (600 ml) at ambient temperature. Sodium borohydride (1.00 g, 26.4 mmol) was added slowly to the stirred solution at 0 °C. After 30 mins, 1-chloro-3-iodopropane (4.85 g, 23.7 mmol) was added dropwise and the mixture was stirred at ambient temperature for 16 h. The solution was evaporated to dryness and 2 M hydrochloric acid (50 ml) was added and the solution extracted with diethyl ether (6 x 50 ml). The combined organic extracts were washed with sodium carbonate (2 x 50 ml) and brine (50 ml) and dried (MgSO4). The crude product was purified by column chromatography using silica gel as absorbent with 80% light petroleum / dichloromethane as eluent to yield 3-chloro-1-(phenylselanyl)propane 230, as a yellow oil (4.77 g, 88%); $\delta_H$ 2.07-2.18 (2 H, m, 2'-CH2), 3.02-3.07 (2 H, t, J 7.1, CH2SePh), 3.63-3.68 (2 H, t, J 6.3, CH2Cl), 7.26-7.30 (3 H, m, Ph-H) and 7.49-7.53 (2 H, m, Ph-H); $\delta_C$ 24.16 (2'-CH2), 32.24 (PhSeCH2), 43.88 (ClCH2), 126.72 (Ph-CH), 128.76 (Ph-CH) 129.13 (q-C) and 132.48 (Ph-CH).

25) 4-Chloro-1-(phenylselanyl)butane (231)$^{112}$

115
The general procedure for the introduction of the phenylselanyl group was followed. Diphenyl diselenide (2.00 g, 6.4 mmol), sodium borohydride (0.61 g, 16.0 mmol) and 1-chloro-4-iodobutane (2.79 g, 12.8 mmol) gave a crude yellow oil, which was purified by column chromatography using silica gel as absorbent with 80% light petroleum / dichloromethane as eluent. 4-Chloro-1-(phenylselanyl)butane 231 was given as a yellow oil (1.97 g, 63%); $\delta_H$ 1.82-1.94 (4 H, m, 2' and 3'-CH$_2$), 2.91-2.96 (2H, t, $J$ 6.8, CH$_2$SePh), 3.51-3.56 (2 H, t, $J$ 6.2, CH$_2$Cl), 7.24-7.30 (3 H, m, Ph-H) and 7.46-7.52 (2 H, m, Ph-H); $\delta_C$ (62.5 MHz) 26.91, 27.19, 32.34 (PhSeCH$_2$), 44.27 (ClCH$_2$), 126.86 (Ph-CH), 127.66 (q-C), 129.02 (Ph-CH) 129.13 (Ph-CH), 131.46 (Ph-CH) and 132.65 (Ph-CH).

26) 5-Chloro-1-(phenylselanyl)pentane (232)

The general procedure for the introduction of the phenylselanyl group was followed. Diphenyl diselenide (2.00 g, 6.4 mmol), sodium borohydride (0.61 g, 16.0 mmol) and 1-chloro-5-iodopentane (2.98 g, 12.6 mmol) gave 5-chloro-1-(phenylselanyl)pentane 232, as a yellow oil (2.94 g, 89%), which required no further purification; $\nu_{\text{max}}$ / cm$^{-1}$ 1579, 1477, 1436, 1300, 1073, 1022, 735 and 691; $\delta_H$ 1.61-1.64 (2 H, m, 3'-CH$_2$), 1.75-1.83 (4 H, m, 2'- and 4'-CH$_2$), 2.94-2.97 (2 H, t, $J$ 7.3, CH$_2$SePh), 3.53-3.56 (2 H, t, $J$ 6.5, CH$_2$Cl), 7.27-7.32 (3 H, m, Ph-H) and 7.52-7.55 (2 H, m, Ph-H); $\delta_C$ 27.26 (3'-CH$_2$), 27.68, 28.29, 32.54 (PhSeCH$_2$), 45.17 (ClCH$_2$), 127.11 (Ph-CH), 129.17 (Ph-CH), 129.43 (Ph-CH), 130.74 (q-C) and 133.01 (Ph-CH).

General procedure for iodide formation

27) 3-Iodo-1-(phenylselanyl)propane (233)

3-Chloro-1-(phenylselanyl)propane 230 (2.50 g, 10.7 mmol) and sodium iodide (16.00 g, 0.107 mol) were added to dry acetone (250 ml) and heated under reflux for 18 h. The precipitated sodium chloride was removed by filtration on a celite bed and the solution was evaporated to dryness. The solid residue was triturated with diethyl ether and the solution filtered a second time. The ether solution was evaporated to dryness to yield 3-iodo-1-(phenylselanyl)propane 233, as a yellow-orange oil (2.69 g, 77%), which required no further purification; $\delta_H$ 2.09-2.20 (2 H, m, 2'-CH$_2$), 2.95-3.01 (2 H, t, $J$ 7.1, CH$_2$SePh), 3.26-3.31 (2 H, t, $J$ 6.8, CH$_2$I), 7.26-7.28 (3 H, m, Ph-H) and 7.49-7.51 (2H, m, Ph-H); $\delta_C$ 4.83 (CH$_2$I), 27.07 (2'-CH$_2$), 32.22 (PhSeCH$_2$), 126.08 (Ph-CH), 127.99 (Ph-CH) 128.39 (q-C) and 131.96 (Ph-CH).
28) 4-Iodo-1-(phenylselanyl)butane (234)\(^{112}\)

\[
\begin{array}{c}
\text{PhSe} & \text{Cl} \\
231 & \rightarrow \\
\text{PhSe} & \text{I} \\
234
\end{array}
\]

4-Chloro-1-(phenylselanyl)butane 231 (1.80 g, 7.3 mmol) and sodium iodide (10.87 g, 72.6 mmol) were added to dry acetone (250 ml) and heated under reflux for 18 h. The standard work up procedure for the formation of iodides was followed to give 4-iodo-1-(phenylselanyl)butane 234, as a yellow-orange oil (1.92 g, 78%); \(\delta_H 1.78-1.84 (2 \text{ H, m, 2'} (3')-\text{CH}_2), 1.93-1.99 (2 \text{ H, m, 2'} (3')-\text{CH}_2), 2.89-2.95 (2 \text{ H, t, } J 7.2, \text{CH}_2\text{SePh}), 3.15-3.21 (2 \text{ H, t, } J 6.8, \text{CH}_2\text{I}), 7.26-7.30 (3 \text{ H, m, Ph-H}) \text{ and } 7.49-7.52 (2 \text{ H, m, Ph-CH}; \delta_C (62.5 \text{ MHz}) 6.44 (\text{CH}_2\text{I}), 27.41, 31.67, 34.09 (\text{PhSeCH}_2), 127.76 (\text{Ph-CH}), 129.84 (\text{Ph-CH}) 129.90 (\text{Ph-CH}), 130.89 (q-C) \text{ and } 133.66 (\text{Ph-CH}). \) The oil rapidly darkens and solidifies on standing at ambient temperature.

29) 5-Iodo-1-(phenylselanyl)pentane (235)

\[
\begin{array}{c}
\text{PhSe} & \text{Cl} \\
232 & \rightarrow \\
\text{PhSe} & \text{I} \\
235
\end{array}
\]

5-Chloro-1-(phenylselanyl)pentane 232 (1.80 g, 6.9 mmol) and sodium iodide (10.30 g, 68.7 mmol) were added to dry acetone (250 ml) and were heated under reflux for 18 h. The standard work up procedure for the formation of iodides was followed to give 5-iodo-1-(phenylselanyl)pentane 235 as a yellow-orange oil (1.56 g, 64%); (Found: M\(^+\), 353.9384. \(\text{Cl}_1\text{H}_{15}\text{Se} \text{requires } M, 353.9385\)); \(\nu_{\text{max}} / \text{cm}^{-1} 2253, 1478, 1438, 1199, 1023, 909, 733, 692 \text{ and } 650; \delta_H 1.49-1.58 (2 \text{ H, m, 3'-CH}_2), 1.67-1.86 (4 \text{ H, m, 2' and 4'-CH}_2), 2.88-2.94 (2 \text{ H, t, } J 7.3, \text{CH}_2\text{SePh}), 3.14-3.19 (2 \text{ H, t, } J 7.0, \text{CH}_2\text{I}), 7.25-7.31 (3 \text{ H, m, Ph-H}) \text{ and } 7.48-7.52 (2 \text{ H, m, Ph-H); } \delta_C 7.42 (\text{CH}_2\text{I}), 28.55, 30.09, 31.65, 33.95 (\text{PhSeCH}_2), 127.76 (\text{Ph-CH}), 130.05 (\text{Ph-CH}) 132.52 (q-C), 133.55 (\text{Ph-CH}) \text{ and } 133.59 (\text{Ph-CH}); m/z 354 (M\(^+\), 6%), 227 (37), 171 (18), 157 (87), 91 (48), 77 (76), 69 (97) \text{ and } 41 (100).\)

30) 6, 7-Dihydro-5H-pyrrolo[1, 2-\alpha]imidazole (183)\(^{105}\) (from the tosylate 227)

\[
\begin{array}{c}
\text{SO}_2\text{ToI} \\
227 & \rightarrow \\
\text{SePh} \\
183
\end{array}
\]

A solution of tri-\(n\)-butyltin hydride (0.1 ml, 0.35 mmol) and AIBN (30 mg, 0.18 mmol) in
toluene (30 ml) was added to 2-[(4-methylphenyl)sulfonyl]-1-[3-(phenylselanyl)propane]-1H-imidazole 227 (95 mg, 0.23 mmol) in toluene (100 ml) at reflux over 5 h. The solution was stirred and heated under reflux for a further 1 h. After cooling to room temperature, the standard work up procedure for the radical cyclisation of imidazoles and benzimidazoles was followed to yield white crystals of 6,7-dihydro-5H-pyrrolo[1,2-alimidazole 183 (13 mg, 52 %), mp 72 °C (lit. 105 72.5-75.5 °C), which required no further purification; δH 2.57-2.68 (2 H, m, 6-CH2), 2.83-2.89 (2 H, t, J 7.7, 7-CH2), 3.94-3.99 (2 H, t, J 7.0, NCH2), 6.87 (1 H, s, Im-2(3)-H) and 7.04 (1 H, s, Im-2(3)-H); δC 23.41 (6-CH2), 26.77 (7-CH2), 45.00 (NCH2), 114.88 (Im-CH), 133.41 (Im-CH) and 155.10 (q-C, Im-7a-C).

31) 5, 6, 7, 8-Tetrahydroimidazo[1,2-alpyridine (211)105

A solution of tri-n-butyltin hydride (0.39 ml, 1.48 mmol) and AIBN (70 mg, 0.49 mmol) in toluene (50 ml) was added to 2-[(4-methylphenyl)sulfonyl]-1-[3-(phenylselanyl)butane]-1H-imidazole 228 (0.427 g, 0.98 mmol) in toluene (200 ml) at reflux over 10 h. The solution was stirred and heated under reflux for a further 1 h. After cooling to room temperature, the standard work up procedure for the radical cyclisation of imidazoles and benzimidazoles was followed to yield 5,6,7,8-tetrahydroimidazo[1,2-alpyridine 211 (57 mg, 48%), as a colourless sticky oil, which required no further purification; δH 1.89-1.97 (4 H, m, 6 and 7-CH2), 2.82-2.87 (2 H, t, J 6.0, 8-CH2), 3.90-3.95 (2 H, t, J 5.6, NCH2), 6.75 (1 H, s, Im-2(3)-H) and 6.94 (1 H, s, Im-2(3)-H); δC 21.21 (7-CH2), 23.54 (6-CH2), 24.95 (8-CH2), 45.09 (NCH2), 118.27 (Im-CH), 135.57 (Im-CH) and 145.21 (q-C, Im-8a-C).

32) 6, 7, 8, 9-Tetrahydro-5H-imidazo[1,2-alazepine (212)105

A solution of tri-n-butyltin hydride (0.11 ml, 0.42 mmol) and AIBN (23 mg, 0.14 mmol) in toluene (50 ml) was added to 2-[(4-methylphenyl)sulfonyl]-1-[5-(phenylselanyl)penty]-1H-imidazole 229 (0.125 g, 0.28 mmol) in toluene (200 ml) at reflux over 10 h. The solution was

118
stirred and heated under reflux for a further 1 h. After cooling to room temperature, the standard work up procedure for the radical cyclisation of imidazoles and benzimidazoles was followed to yield the 6, 7, 8, 9-tetrahydro-5H-imidazo[1,2-a]azepine 212 (32 mg, 63%), as a colourless sticky oil, which required no further purification; δH 1.64-1.80 (6 H, m, 6, 7, 8-CH2), 2.87-2.92 (2 H, m, 9-CH2), 3.90-3.94 (2 H, m, NCH2), 6.74 (lH, s, Im-2(3)-H) and 6.79 (1 H, s, Im-2(3)-H); δC 22.56 (7-CH2), 26.11 (8-CH2), 29.40 (6-CH2), 30.11 (9-CH2), 48.77 (NCH2), 119.22 (Im-CH), 126.21 (Im-CH) and 150.90 (q-C, Im-9a-C).

33) 2-(Phenylsulfonyl)-1H-imidazole (239)

\[
\begin{align*}
\text{N} & \quad \text{SPh} \\
\text{H} & \\
\begin{array}{c}
\text{222} \\
\rightarrow \\
\text{S(O)Ph} \\
\end{array} \\
& \\
\begin{array}{c}
\text{N} & \quad \text{SO_2Ph} \\
\text{H} & \\
\text{238} & \quad \text{239} \\
\end{array}
\end{align*}
\]

A solution of 2-(phenylsulfanyl)-1H-imidazole 222 (0.440 g, 2.5 mmol) in THF-methanol (25 ml, 1:1) was added dropwise to a solution of oxone™ (3.380 g, 5.5 mmol) at 0 °C in THF-methanol (25 ml, 1:1) and the solution was stirred at ambient temperature for a further 48 h. The solution was filtered on a celite bed, the filtrate added to water (100 ml) and extracted with dichloromethane (3 x 50 ml). The combined organic extracts dried (MgSO4) and evaporated to dryness to yield a white solid. The residue was purified by column chromatography using silica gel as absorbent with ethyl acetate as eluent to yield white needles of 2-(phenylsulfanyl)-1H-imidazole 239 (0.302 g, 58%); mp 188-190 °C, (Found: C, 51.3; H, 3.8; N, 12.9. CgHgN2O2S requires C, 51.9; H, 3.9; N, 13.5%); νmax /cm⁻¹ 2764, 1446, 1330 (SO₂), 1155 (SO₂) and 1107; δH ([²H₆]Me₂SO) 7.33 (2 H, m, Im-4(5)-H), 7.64-7.68 (2 H, m, Ar-H), 7.72-7.75 (1 H, m, Ar-H) and 7.94-7.97 (2 H, m, Ar-H); δC ([²H₆]Me₂SO) 134.14, 136.56, 140.94, 146.84 (q-C) and 149.92 (q-C); m/z 208 (M⁺, 8%), 144 (88), 117 (76), 90 (21), 77(100) and 51 (57). Further elution with ethyl acetate / methanol yielded white needles of 2-(phenylsulfanyl)-1H-imidazole 238 (0.101 g, 21%); mp 160-161°C, (Found: M⁺, 192.0357. CgHgN2OS requires M, 192.0357); νmax /cm⁻¹ 2628, 1441, 1330, 1086 and 1054; δH 7.19-7.20 (2 H, m, Im-4(5)-H), 7.46-7.49 (3 H, m, Ar-H) and 7.71-7.75 (2 H, m, Ar-H); δC 120.20, 125.35, 129.96, 132.24, 142.79 (q-C) and 146.55 (q-C). m/z 192 (M⁺, 8%), 175 (62), 144 (100), 125 (12), 117 (39), 77 (72) and 51 (61).

34) 1-[3-(Phenylselanyl)propyl]-2-(phenylsulfanyl)-1H-imidazole (241)

\[
\begin{align*}
\begin{array}{c}
\text{N} \\
\text{H} & \\
\text{SPh} \\
\text{H} & \\
\text{222} \\
\rightarrow \\
\begin{array}{c}
\text{SPh} \\
\text{241} \\
\end{array}
\end{array}
\end{align*}
\]
The general procedure for the alkylation of imidazoles in acetonitrile was followed. 2-(Phenylsulfanyl)-1H-imidazole 222 (0.470 g, 2.67 mmol), sodium hydride (0.160 g, 6.68 mmol) and 3-iodo-1-(phenylselanyl)propane 233 (0.870 g, 2.67 mmol) in acetonitrile (150 ml) gave a tan residue, which was purified by column chromatography using silica gel as absorbent with light petroleum and diethyl ether as eluent to yield 1-[3-(phenylselanyl)propyl]-2-(phenylsulfanyl)-1H-imidazole 241 as a yellow oil (0.555 g, 56%); \( \nu_{\text{max}} \text{ cm}^{-1} \) 2940, 1580, 1478, 1458, 1438, 1027, 1023, 690; \( \delta_H \) 1.95-2.06 (2 H, m, 2'-CH\text{2}), 2.71-2.76 (2 H, t, J 7.0, CH\text{2}SePh), 4.09-4.14 (2 H, t, J 7.0, NCH\text{2}), 7.04 (2 H, m, Im-4(5)-H), 7.14-7.29 (8 H, m, Ar-H) and 7.42-7.46 (2 H, m, Ar-H); \( \delta_C \) 23.98 (2'-CH\text{2}), 30.80 (PhSeCH\text{2}), 46.36 (NCH\text{2}), 122.43, 126.61, 127.22, 128.03, 129.16, 130.52 and 132.97.

35) Radical cyclisation of 1-[3-(phenylselanyl)propyl]-2-(phenylsulfanyl)-1H-imidazole (241)

\[
\begin{align*}
\text{N} & \quad \text{SPh} \\
\text{N} & \quad \text{SePh}
\end{align*}
\]

A solution of tri-n-butyltin hydride (0.59 ml, 2.19 mmol) and AIBN (0.120 g, 0.73 mmol) in toluene (50 ml) was added to 1-[3-(phenylselanyl)propyl]-2-(phenylsulfanyl)-1H-imidazole 241 (0.547 g, 1.46 mmol) in toluene (200 ml) at reflux over 5 h. The solution was stirred and heated under reflux for a further 1 h. After cooling to room temperature, the standard work up procedure for the radical cyclisation of imidazoles and benzimidazoles was followed to yield a tan oil containing 6,7-dihydro-5H-pyrrolo[1,2-a]imidazole 183 and 1-propyl-1H-imidazole 242; \( \delta_H \) 0.80-0.86 (3 H, t, J 7.4, CH\text{3}), 1.62-1.70 (2 H, m, 2'-CH\text{2}), 3.92-3.96 (2 H, t, J 6.8, NCH\text{2}) and 7.02-7.56 (7 H, m, Im-H, and Ar-H); (82 mg, 16% and 18% yield respectively by \( ^1\text{H} \) NMR spectroscopic analysis of reaction mixture using a known amount of 1,4-dimethoxybenzene as internal standard).

36) 1-[3-(Phenylselanyl)propyl]-2-(phenylsulfonyl)-1H-imidazole (243)

\[
\begin{align*}
\text{N} & \quad \text{SO_2 Ph} \\
\text{N} & \quad \text{SePh}
\end{align*}
\]

The general procedure for the alkylation of imidazoles in acetonitrile was followed.
2-(Phenylsulfonyl)-1H-imidazole 239 (0.136 g, 0.65 mmol), sodium hydride (24 mg, 0.98 mmol) and 3-iodo-1-(phenylselanyl)propane 233 (0.212 g, 0.65 mmol) in acetonitrile (100 ml) gave a tan residue, which was purified by column chromatography using silica gel as absorbent with light petroleum and diethyl ether as eluent to yield 1-[3-(phenylselanyl)propyl]-2-(phenylsulfonyl)-1H-imidazole 243, as a yellow oil (0.214 g, 81%). (Found: M+, 406.0254. C_{18}H_{18}N_{2}O_{2}SSe requires M, 406.0254; δ_H 2.10-2.21 (2 H, m, 2'-CH_2), 2.80-2.86 (2 H, t, J 7.1, CH_2SePh), 4.40-4.46 (2 H, t, J 7.1, NCH_2), 6.95 (1 H, m, Im-4(5)-H), 7.09 (1 H, m, Im-4(5)-H), 7.25-7.27 (3 H, m, SePh-H), 7.45-7.49 (2 H, m, SePh-H), 7.50-7.53 (2 H, d, J 7.5, Ar-H), 7.57-7.63 (1 H, m, Ar-H) and 7.97-8.00 (2 H, d, J 7.5, Ar-H); δ_C (62.5 MHz) 23.92 (2'-CH_2), 31.50 (PhSeCH_2), 47.68 (NCH_2), 124.55, 127.38, 128.14, 129.22, 129.35, 130.00, 132.99, 134.10, 139.93 (q-C) and 142.79 (q-C); m/z 406 (M+, 100%), 376 (30), 329 (14), 305 (41), 284 (45), 265 (100), 157 (23) and 77 (66).

37) 6, 7-Dihydro-5H-pyrrolo[1,2-a]imidazole (183) (from the phenylsulfonate 243)

![Diagram](image)

A solution of tri-n-butyltin hydride (0.16 ml, 0.54 mmol) and AIBN (30 mg, 0.18 mmol) in toluene (50 ml) was added to 1-[3-(phenylselanyl)propyl]-2-(phenylsulfonyl)imidazole 243 (0.146 g, 0.36 mmol) in toluene (100 ml) at reflux over 5 h. The solution was stirred and heated under reflux for a further 1 h. After cooling to room temperature, the standard work up procedure for the radical cyclisation of imidazoles and benzimidazoles was followed to yield 6, 7-dihydro-5H-pyrrolo[1,2-a]imidazole 183 (19 mg, 51%), as a colourless sticky oil, which required no further purification.

38) 1-(Triphenylmethyl)benzimidazole [1-(Trityl)benzimidazole, 258]

![Diagram](image)

1-(Trityl)benzimidazole 257 was prepared by the same method as used for the tritylation of imidazole. Triphenylmethyl chloride (39 g, 0.140 mol), benzimidazole (15 g, 0.128 mol) and
triethylamine (35 ml, 0.250 mol) gave a residue, which was recrystallised twice with absolute ethanol and dried to give cream coloured needles of 1-(triphenylmethyl)benzimidazole 258 (31 g, 67%), mp 181-182 °C (lit. 147 mp 180-181 °C), (Found: M+, 360.1620. C26H2oN2 requires M, 360.1626); $\nu_{\text{max}}$ / cm$^{-1}$ 1609, 1478, 1443, 1274, 1224, 781, 748 and 700; m/z 360 (M+, 6%), 243 (100), 165 (53), 118 (24) and 91 (12).

39) 2-[(4-Methylphenyl)sulfonyl]-1-(triphenylmethyl)benzimidazole (259)

![Diagram](source)

1-(Trityl)benzimidazole 258 (1.00 g, 2.75 mmol) was dissolved in THF (100 ml) and TMEDA (1.2 ml, 8.25 mmol) added to the stirred solution at ambient temperature. The temperature of the stirred solution was lowered to -78 °C and a solution of n-butyllithium added dropwise (1.6 ml, 4.12 mmol). The solution turned pink and was stirred at 0 °C for a further 20 min. A solution of p-toluenesulfonyl fluoride (1.44 g, 8.45 mmol) in THF (10 ml) was added dropwise and the stirring was continued for a further 3 h. The solution was evaporated and saturated ammonium chloride (50 ml) and water (100 ml) added to the residue. The aqueous mixture was extracted with dichloromethane (3 x 50 ml), the organic extracts dried (MgSO$_4$) and the solution evaporated to dryness to yield a crude solid, which was purified by column chromatography using silica gel with light petroleum and dichloromethane as eluent. Evaporation of the eluates containing the second component gave white crystals of 2-[(4-methylphenyl)sulfonyl]-1-(triphenylmethyl)benzimidazole 259 (0.16 g, 11%), mp 86-87 °C; m/z  517 (MH+, 100%), 162 (90), 138 (95), 90 (98) and 65 (55).

40) 2-(Phenylsulfanyl)-1-(triphenylmethyl)benzimidazole (260)

![Diagram](source)

1-(Trityl)benzimidazole 258 (4.0 g, 11 mmol) was dissolved in THF (200 ml) and TMEDA (5.0 ml, 34 mmol) added to the stirred solution at ambient temperature. The temperature of the stirred solution was lowered to -78 °C and a solution of n-butyllithium added dropwise (5.2 ml, 13 mmol). The solution turned pink and was stirred at 0 °C for a further 20 min. A solution of
diphenyl disulfide (7.3 g, 34 mmol) in THF (30 ml) was added dropwise and the stirring was continued for a further 3 h. The solution was evaporated and saturated ammonium chloride (50 ml) and water (100 ml) added to the residue. The aqueous mixture was extracted with dichloromethane (3 x 50 ml), the organic extracts dried (MgSO₄), and the solution evaporated to dryness to yield a crude solid, which was purified by column chromatography using silica gel as absorbent with light petroleum and dichloromethane as eluent. Evaporation of the eluates containing the second component gave white crystals of 2-(phenylsulfanyl)-1-(triphenylmethyl)benzimidazole 260 (3.5 g, 68%), mp 182-184 °C (Found: M⁺ 469.1734, C₃₂H₂₅N₂S requires M⁺, 469.1738); νmax 1581, 1492, 1440, 1267 and 745 cm⁻¹; m/z 469 (M⁺, 31%), 243 (100), 225 (33), 165 (37) and 31 (27).

41) 2-(Phenylsulfanyl)-1H-benzimidazole (261)

The general procedure for the removal of the trityl protective group was followed. 2-(Phenylsulfanyl)-1-(triphenylmethyl)benzimidazole 260 (0.95 g, 2 mmol) gave white needles of 2-(phenylsulfanyl)-1H-benzimidazole 261 (0.32 g, 70%), mp 201-203 °C (lit.¹⁴⁸, mp 201.5-202.5 °C), (Found: C, 68.7; H, 4.3; N, 12.4. C₁₃H₁₀N₂S requires C, 69.0; H, 4.5; N, 12.4%); νmax / cm⁻¹ 1618, 1477, 1442, 1413, 1349, 1266, 1235, 978, 740 and 686; m/z 226 (60%), 225 (100), 167 (5), 155 (8), 90 (5), 77 (8) and 51 (10).

42) 1-[3-(1H-Benzimidazol-1-yl)propyl]-1H-benzoimidazole (263)

Benzimidazole 257 (5.00 g, 42.3 mmol) was added slowly to sodium hydride (1.22 g, 50.8 mmol) in THF (350 ml). The mixture was stirred and heated under reflux for 1 h, and 1,3-dibromopropane (2.1 ml, 21.1 mmol) was added dropwise. The mixture was heated under reflux for a further 2 h. The salts formed were removed by filtration on a celite bed and the
solution was evaporated to dryness to yield a tan solid, which was purified by column chromatography using neutral alumina as absorbent with ethyl acetate / methanol as eluent to yield 1-[3-(1H-benzoimidazol-1-yl)propyl]-1H-benimidazole 263, as a white solid (5.14 g, 44%); mp 119-121°C (lit.123, mp 120-121°C); δ H 2.50-2.59 (2 H, m, 2'-CH2), 4.18-4.24 (4 H, t, J 6.9, NCH2), 7.28-7.35 (4 H, m, Ar-H), 7.84-7.88 (4 H, m, Ar-H) and 8.10 (2 H, s, Im-2-H).

43) 1,3-Di(3-bromopropyl)-3H-benzoimidazol-1-ium bromide (264)

![Chemical Structure](image)

Benzimidazole 257 (1.00 g, 8.5 mmol) was added slowly to sodium hydride (0.25 g, 10.2 mmol) in THF (200 ml). The mixture was stirred and heated under reflux for 1 h, and 1,3-dibromopropene (8.6 ml, 84.6 mmol) was added dropwise. The mixture was heated under reflux for a further 2 h. The salts formed were removed by filtration on a celite bed and the solution was evaporated to dryness to yield a tan residue, which was purified by column chromatography using neutral alumina as absorbent with ethyl acetate / methanol as eluent to yield 1,3-di(3-bromopropyl)-3H-benzoimidazol-1-ium bromide 264, as a white solid (0.31 g, 10%); mp >300 °C (Found: M+, 358.9758. C13H17N2Br2 requires M, 358.9758); δ H 2.53-2.71 (4 H, m, 2'-CH2), 3.50-3.54 (2 H, t, J 6.0, CH2Br), 3.65-3.70 (2 H, t, J 5.8, CH2Br) 4.67-4.84 (4 H, t, J 7.0, NCH2), 7.57-7.64 (2 H, m, Ar-H), 7.81-7.88 (2 H, m, Ar-H) and 11.15 (1 H, s, Im-2-H); δ C 29.94 (2'-CH2), 30.21(2'-CH2), 32.35 (CH2Br), 32.41 (CH2Br), 42.05 (NCH2), 45.33 (NCH2), 113.57 (Ar-H), 113.62 (Ar-H), 127.68 (Ar-H), 127.83 (Ar-H), 131.73 (q-C), 131.86 (q-C) and 143.42 (q-C, Im-2-C); m/z 361 (M, 37%), 317 (100), 271 (87), 235 (23), 208 (9) and 131 (11).

44) 1-(3-Chloropropyl)-2-(phenylsulfanyl)-1H-benimidazole (265)

![Chemical Structure](image)

2-(Phenylsulfanyl)-1H-benimidazole 261 (0.657 g, 2.9 mmol) was added slowly to sodium hydride (86 mg, 3.6 mmol) in THF (200 ml), and heated under reflux for 1 h, and 1-bromo-3-
chlopropane (0.2 ml, 2.2 mmol) was added dropwise. The mixture was heated under reflux for a further 2 h. The salts formed were removed by filtration on a celite bed and the solution was evaporated to dryness to yield a tan solid, which was purified by column chromatography using neutral alumina as absorbent with light petroleum and dichloromethane followed by diethyl ether as eluent to give 1-(3-chloropropyl)-2-(phenylsulfanyl)-1H-benzimidazole 265 as a cream coloured needles (0.342 g, 39%); δH (400 MHz) 2.14-2.21 (2 H, m, 2'-CH2), 3.49-3.52 (2 H, t, J 6.1, CH2Cl), 4.39-4.43 (2 H, t, J 7.0, NCH2), 7.28-7.33 (5 H, m, Ar-H), 7.43-7.45 (3 H, m, Ar-H) and 7.77-7.79 (1 H, m, Ar-H); δC 32.80 (2'-CH2), 42.11 (CH2Cl), 42.20 (NCH2), 109.92, 120.46, 122.96, 123.86, 128.34, 129.61, 131.03, 132.25 (q-C), 136.31 (q-C), 143.74 (q-C) and 147.88 (q-C).

45) Attempted preparation of 1-(3-bromopropyl)-2-(phenylsulfanyl)-1H-benzimidazole (266) using sodium bromide in acetone (Finkelstein conditions)

\[
\begin{align*}
\text{N} & \text{N} \quad \text{Cl} \\
\text{SPh} & \text{265} \quad \text{NaBr, acetone} \\
\text{Br} & \text{266}
\end{align*}
\]

1-(3-Chloropropyl)-2-(phenylsulfanyl)-1H-benzimidazole 265 (0.291 g, 0.96 mmol) and sodium bromide (0.99 g, 9.63 mmol) were added to dry acetone (100 ml), and heated under reflux for 18 h. The solution was evaporated to dryness and the solid residue was triturated with diethyl ether and the solution filtered a second time. The ether solution was evaporated to dryness, but only the 1-(3-chloropropyl)-2-(phenylsulfanyl)-1H-benzimidazole 265 was isolated.

46) 1-(3-Bromopropyl)-2-(phenylsulfanyl)-1H-benzimidazole (266)

\[
\begin{align*}
\text{N} & \text{N} \quad \text{Cl} \\
\text{SPh} & \text{265} \quad \text{CH}_3\text{CH}_2\text{Br, NaBr (cat.)} \\
\text{Br} & \text{266}
\end{align*}
\]

1-(3-Chloropropyl)-2-(phenylsulfanyl)-1H-benzimidazole 265 (0.171 g, 0.56 mmol), bromoethane (1.25 ml, 16.8 mmol), and sodium bromide (30 mg, 0.29 mmol) were added to dry N-methyl-2-pyrrolidinone (50 ml) and heated at 65 °C for 36 h. The mixture was added to brine (50 ml) and extracted with diethyl ether (3 x 50 ml), and the organic extracts dried (MgSO4). The solution was evaporated to dryness to yield a white solid containing 1-(3-bromopropyl)-2-(phenylsulfanyl)-1H-benzimidazole 266; δH 2.23-2.31 (2 H, m, 2'-CH2), 3.33-3.38 (2 H, t, J 6.2,
CH$_2$Br), 4.37-4.42 (2 H, t, J 7.1, NCH$_2$), 7.28-7.37 (5 H, m, Ar-H), 7.42-7.46 (3 H, m, Ar-H) and 7.77-7.80 (1 H, m, Ar-H); $\delta$C 18.06 (CH$_2$Br), 32.89 (2'-CH$_2$), 42.11 (NCH$_2$), 110.02, 120.45, 122.99, 123.87, 128.36, 129.88, 130.15, 132.21 (q-C), 136.28 (q-C), 143.71 (q-C), and 147.90 (q-C) and 1-(3-chloropropyl)-2-(phenylsulfanyl)-1H-benzimidazole 265 (47 mg, 22% and 2% yield respectively by $^1$H NMR spectroscopic analysis using a known amount of 1,4-dimethoxybenzene as internal standard).

General procedure for the alkylation of benzimidazoles

47) 1-[3-(Phenylselanyl)propyl]-2-(phenylsulfanyl)-1H-benzimidazole (267)

![Diagram](https://via.placeholder.com/150)

2-(Phenylsulfanyl)-1H-benzimidazole 261 (0.650 g, 3.0 mmol) was added slowly to sodium hydride (86 mg, 3.6 mmol) in THF (200 ml). The mixture was stirred and heated under reflux for 1 h, and 3-iodo-1-(phenylselanyl)propane 233 (0.730 g, 2.3 mmol) in THF (200 ml) was added dropwise. The mixture was heated under reflux for a further 2 h. The salts formed were removed by filtration on a celite bed and the solution was evaporated to dryness to yield a tan solid, which was purified by column chromatography using neutral alumina as absorbent with light petroleum and dichloromethane followed by diethyl ether as eluent to give 1-[3-(phenylselanyl)propyl]-2-(phenylsulfanyl)-1H-benzimidazole 267 as a yellow oil (0.560 g, 44%) (Found: M$,^+$, 424.0525. C$_{22}$H$_{20}$N$_2$Se requires M$,^+$, 424.0525); $\nu_{\text{max}}$ / cm$^{-1}$ 1579, 1478, 1423, 1355, 1248, 1023, 909, 739 and 690; $\delta$H 2.04-2.15 (2 H, m, 2'-CH$_2$), 2.81-2.86 (2 H, t, J 6.9, CH$_2$SePh), 4.31-4.37 (2 H, t, J 7.1, NCH$_2$), 7.24-7.33 (8 H, m, Ar-H), 7.41-7.49 (4 H, m, Ar-H) and 7.77-7.81 (2 H, m, Ar-H); $\delta$C 23.48 (2'-CH$_2$), 28.79 (PhSeCH$_2$), 43.27 (NCH$_2$), 108.68, 119.07, 121.49, 122.33, 126.31, 129.94, 128.36, 129.66, 131.07 (q-C), 132.04, 134.86 (q-C), 144.48 (q-C) and 146.61 (q-C); m/z 424 (M$,^+$, 34%), 315 (43), 267 (88), 239 (50), 157 (26), 129 (33), 109 (48), 77 (100) and 51 (75).

48) 1-[4-(Phenylselanyl)butyl]-2-(phenylsulfenyl)-1H-benzimidazole (268)

![Diagram](https://via.placeholder.com/150)
The general procedure for the alkylation of benzimidazoles in THF was followed.

2-(Phenylsulfanyl)-1H-benzimidazole 261 (0.265 g, 1.17 mmol), sodium hydride (42 mg, 1.76 mmol) and 4-iodo-1-(phenylselanyl)butane 234 (0.300 g, 0.88 mmol) in THF (150 ml) gave a tan residue. The residue was purified by column chromatography using neutral alumina as absorbent with light petroleum and dichloromethane followed by diethyl ether as eluent to give 1-[4-(phenylselanyl)butyl]-2-(phenylsulfenyl)-1H-benzimidazole 268, as a yellow oil (0.228 g, 44%); (Found: M⁺, 438.0669. C₂₃H₂₂N₂SSe requires M⁺, 438.0668); v max / cm⁻¹ 1581, 1479, 1462, 1438, 1424, 1360, 1279, 1024, 907 and 733; δH 1.24-1.57 (2 H, m, 3'-CH₂), 1.60-1.75 (2 H, m, 2'-CH₂), 2.68-2.74 (2 H, t, J 7.1, CH₂SePh), 4.06-4.11 (2 H, t, J 7.2, NCH₂), 7.11-7.21 (8 H, m, Ar-H), 7.27-7.33 (4 H, m, Ar-H) and 7.65-7.69 (2 H, m, Ar-H); δC (62.5 MHz) 27.08 (3'-CH₂), 27.16 (2'-CH₂), 30.35 (PhSeCH₂), 44.11 (NCH₂), 109.66, 119.94, 122.33, 123.19, 127.01, 129.39, 129.67, 130.43 (q-C), 132.91, 135.67 (q-C) and 143.40 (q-C); m/z 438 (M⁺, 54%), 281 (100), 239 (46), 225 (70), 171 (50), 157 (43), 109 (48), 91 (58), 77 (94) and 51 (47).

49) 1-[5-(Phenylselanyl)penty1]-2-(phenylsulfanyl)-1H-benzimidazole (269)

The general procedure for the alkylation of benzimidazoles in THF was followed.

2-(Phenylsulfanyl)-1H-benzimidazole 261 (0.661 g, 2.92 mmol), sodium hydride (0.105 g, 4.39 mmol) and 5-iodo-1-(phenylselanyl)pentane 235 (1.034 g, 2.92 mmol) in THF (200 ml) gave a tan residue. The residue was purified by column chromatography using neutral alumina as absorbent with light petroleum and dichloromethane followed by diethyl ether as eluent to give 1-[5-(phenylselanyl)penty1]-2-(phenylsulfenyl)-1H-benzimidazole 269 as a yellow oil (0.992 g, 75%); (Found: M⁺, 452.0825. C₂₄H₂₄N₂SSe requires M⁺, 452.0825); v max / cm⁻¹ 1579, 1478, 1422, 1355, 1266, 1023, 738 and 690; δH 1.41-1.44 (2 H, m, 3'-CH₂), 1.65-1.71 (4 H, m, 2' and 4'-CH₂), 2.80-2.86 (2 H, t, J 7.3, CH₂SePh), 4.18-4.24 (2 H, t, J 7.4, NCH₂), 7.25-7.31 (8 H, m, Ar-H), 7.39-7.49 (4 H, m, Ar-H) and 7.77-7.79 (2 H, m, Ar-H); δC (62.5 MHz) 26.84 (3'-CH₂), 27.34 (4'-CH₂), 29.00 (2'-CH₂), 29.64 (PhSeCH₂), 44.53 (NCH₂), 109.70, 119.85, 122.29, 123.19, 126.79, 129.03, 130.52, 132.52, 135.70 (q-C), 143.25 (q-C) and 147.43 (q-C); m/z 452 (M⁺, 6%), 295 (16), 225 (28), 206 (12), 158 (35), 157 (35), 91 (43), 78 (100) and 51 (64).
50) 2,3-Dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole (252)$^{121}$

A solution of tri-\textit{n}-butyltin hydride (0.42 ml, 1.59 mmol) and AIBN (90 mg, 0.80 mmol) in toluene (50 ml) was added to 1-[3-(phenylselanyl)propyl]-2-(phenylsulfanyl)-1H-benzimidazole 267 (0.450 g, 1.06 mmol) in toluene (150 ml) at reflux over 5 h. The solution was stirred and heated under reflux for a further 1 h. The standard work up procedure for the radical cyclisation of imidazoles and benzimidazoles was followed. The crude white product was purified by column chromatography using silica gel as absorbent with light petroleum and ethyl acetate as eluent to give 2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole 252 as white crystals (83 mg, 49%), mp 105-107 °C (lit.$^{121}$, mp 114-115 °C) (Found: M+, 158.0844. C$_{10}$H$_{10}$N$_2$ requires M, 158.0844); $\delta$H 2.66-2.78 (2 H, m, 2'-CH$_2$), 3.04-3.10 (2 H, t, J 7.5, CCH$_2$), 4.08-4.14 (2 H, t, J 7.0, NCH$_2$), 7.17-7.33 (3 H, m, Ar-H) and 7.68-7.72 (1 H, m, Ar-H); $\delta$C 23.89 (3'-CH$_2$), 26.48 (2'-CH$_2$), 43.12 (NCH$_2$), 109.86, 119.99, 122.05, 122.14, 132.79 (q-C), 149.30 (q-C) and 161.55 (q-C); m/z 158 (M+, 96%), 157 (100), 130 (16), 129 (14), 103 (24), 102 (15), 86 (25), 84 (38) and 51 (31).

51) 1,2,3,4-Tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine (253)$^{121}$

A solution of tri-\textit{n}-butyltin hydride (0.17 ml, 0.63 mmol) and AIBN (34 mg, 0.21 mmol) in toluene (50 ml) was added to 1-[4-(phenylselanyl)butyl]-2-(phenylsulfanyl)-1H-benzimidazole 268 (0.184 g, 0.42 mmol) in toluene (150 ml) at reflux over 5 h. The solution was stirred and heated under reflux for a further 1 h. After cooling to room temperature, the standard work up procedure for the radical cyclisation of imidazoles and benzimidazoles was followed to yield white crystals of 1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine 253 (39 mg, 54%), mp 98-100 °C (lit.$^{121}$ mp, 99.8-100.1°C), which required no further purification; (Found: M+, 172.1000. C$_{11}$H$_{12}$N$_2$ requires M, 172.1000); $\nu_{\text{max}}$/cm$^{-1}$ 1615, 1509, 1483, 1458, 1416, 1320, 1286, 1274, 1228, 1158, 1006, 769 and 756; $\delta$H 2.01-2.10 (2 H, m, 3'-CH$_2$), 2.12-2.18 (2 H, m, 2'-CH$_2$),
3.08-3.13 (2 H, t, J 6.5, CCH₂), 4.07-4.11 (2 H, t, J 6.0, NCH₂), 7.22-7.32 (3 H, m, Ar-H) and 7.68-7.72 (1 H, m, Ar-H); δC 20.28 (3'-CH₂), 22.18 (2'-CH₂), 24.95 (CCH₂), 41.94 (NCH₂), 108.19, 118.37, 121.15, 121.57, 134.10 (q-C), 142.32 (q-C) and 151.18 (q-C); m/z 172 (M⁺, 100), 144 (54), 117 (51), 102 (38), 90 (45), 77 (53) and 51 (51).

52) 7,8,9,10-Tetrahydro-6H-benzo[4,5]imidazo[1,2-a]azepine (254)²¹

A solution of tri-n-butyltin hydride (0.41 ml, 1.54 mmol) and AIBN (85 mg, 0.52 mmol) in toluene (50 ml) was added to 1-[5-(phenylselanyl)pentyl]-2-(phenylsulfanyl)-IH-benzimidazole 269 (0.465 g, 1.03 mmol) in toluene (250 ml) at reflux over 10 h. The solution was stirred and heated under reflux for a further 1 h. After cooling to room temperature, the standard work up procedure for the radical cyclisation of imidazoles and benzimidazoles was followed to yield white crystals of 7,8,9,10-tetrahydro-6H-benzo[4,5]imidazo[1,2-a]azepine 254 (31 mg, 17%), mp 124 °C (lit.²¹ mp, 124-125 °C); δH 1.73-1.95 (6 H, m, 2', 3', 4'-CH₂), 3.07-3.11 (2 H, m, CCH₂), 4.14-4.18 (2 H, m, NCH₂), 7.18-7.28 (3 H, m, Ar-H) and 7.65-7.69 (1 H, m, Ar-H); δC 27.53, 30.71, 31.85, 32.87, 46.51(NCH₂), 110.66, 121.17, 124.08, 124.47, 137.76 (q-C), 144.21 (q-C) and 150.29 (q-C)

53) 1-(3-Chloropropyl)-1H-benzimidazole (270)

Benzimidazole 257 (2.00 g, 16.9 mmol) was added slowly to sodium hydride (0.48 g, 20.3 mmol) in THF (200 ml). The mixture was stirred, and heated under reflux for 1 h and 1-bromo-3-chloropropane (1.3 ml, 13.0 mmol) was added dropwise. The mixture was heated under reflux for a further 2 h. The salts formed were removed by filtration on a celite bed and the solution was evaporated to dryness to yield a tan solid, which was purified by column chromatography using neutral alumina as absorbent with ethyl acetate / methanol as eluent to yield 1-(3-chloropropyl)-1H-benzimidazole 270, as a brown oil (1.80 g, 55%), (Found: M⁺, 194.0614. C₁₀H₁₁N₂Cl requires M, 194.0611); νmax / cm⁻¹ 1614, 1496, 1459, 1384, 1366, 1331,
1286, 1246, 1203, 767 and 745; \( \delta_H \): 2.28-2.38 (2 H, m, 2'-CH₂), 3.46-3.51 (2 H, t, \( J = 5.9 \), CH₂Cl), 4.40-4.45 (2 H, t, \( J = 6.5 \), NCH₂), 7.27-7.36 (2 H, m, Ar-H), 7.43-7.47 (1 H, m, Ar-H), 7.82-7.85 (1 H, m, Ar-H) and 7.95 (1 H, s, Im-2-H); \( \delta_C \): 32.50 (2'-CH₂), 41.60 (CH₂Cl), 41.96 (NCH₂), 109.86, 120.91, 122.75, 123.55, 134.00 (q-C), 143.46 (2-C) and 144.21 (q-C); \( m/z \): 194 (M⁺, 37%), 131 (100), 104 (14), 77 (23), 51 (9) and 39 (11).

54) 1-[3-(Phenylselanyl)propyl]-1H-benzimidazole (271)

![Chemical Structure](image)

Diphenyl diselenide (0.500 g, 1.6 mmol) was dissolved in absolute ethanol (300 ml) at ambient temperature. Sodium borohydride (0.132 g, 3.5 mmol) was added slowly to the stirred solution at 0 °C. The solution was stirred for a further 10 min at ambient temperature, and a solution of 1-(3-chloropropyl)benzimidazole 270 (0.623 g, 3.2 mmol) in absolute ethanol (50 ml) added. After stirring for 3 h at ambient temperature, the solution was evaporated to dryness, and 2 M hydrochloric acid solution (100 ml) added, and the acidic solution washed with light petroleum (5 x 100 ml). The solution was basified to pH 8 with saturated sodium carbonate solution followed by the addition of 2 M sodium hydroxide solution until the aqueous solution was at pH 14. The hydroxide solution was extracted with dichloromethane (2 x 100 ml), and the combined organic extracts dried (MgSO₄), and evaporated to dryness to yield 1-[3-(phenylselanyl)propyl]-1H-benzimidazole 271, as a viscous yellow oil (0.617 g, 61%) which required no purification; (Found: M⁺, 316.0481. C₁₆H₁₆N₂Se requires M⁺, 316.0478); \( \nu_{\text{max}} \) / cm⁻¹: 1615, 1579, 1495, 1478, 1459, 1438, 1367, 1287, 1260, 1228 and 741; \( \delta_H \): 2.17-2.29 (2 H, m, 2'-CH₂), 2.81-2.87 (2 H, t, \( J = 6.8 \), PhSeCH₂), 4.29-4.35 (2 H, t, \( J = 6.8 \), NCH₂), 7.28-7.39 (5 H, m, Ar-H), 7.47-7.49 (3 H, m, Ar-H), 7.79-7.81 (1 H, m, Ar-H) and 7.84 (1 H, m, Im-2-H); \( \delta_C \): 23.24, 28.62 (SeCH₂), 43.10 (NCH₂), 108.58, 119.47, 121.94, 121.16, 121.94, 128.00, 128.28, 131.86, 132.65 (q-C), 141.95 and 142.92 (q-C); \( m/z \): 316 (M⁺, 8%), 160 (38), 131 (100), 104 (7), 77 (25) and 51 (20).

55) Attempted radical cyclisation of 1-(3-phenylselanylpropyl)-1H-benzimidazole (271)

![Chemical Structure](image)
A solution of tri-n-butyltin hydride (0.77 ml, 2.85 mmol) and AIBN (0.160 g, 0.95 mmol) in toluene (50 ml) was added to 1-[3-(phenylselanyl)propyl]-1H-benzimidazole 271 (0.600 g, 1.89 mmol) in toluene (200 ml) at reflux over 5 h. The solution was stirred and heated under reflux for a further 1 h. The standard work up procedure for the radical cyclisation of imidazoles and benzimidazoles was followed to yield a brown oil of 1-propyl-1H-benzimidazole 273 (0.294 g, 98%), which was not further purified; (Found: M⁺, 160.1000. C₁₀H₁₂N₂ requires M, 160.1000); vₓ max/cm⁻¹ 1615, 1498, 1384, 1287, 1259, 1213 and 743; δH 0.86-0.92 (3 H, t, CH₃), 1.77-1.92 (2 H, m, 2'-CH₂), 4.02-4.07 (2 H, t, NCH₂), 7.21-7.29 (2 H, m, Ar-H), 7.32-7.37 (1 H, m, Ar-H), 7.77-7.81 (1 H, s, Im-2-H); δC 11.67 (CH₃), 23.47 (2'-CH₂), 47.03 (NCH₂), 109.89, 118.89, 120.67, 122.33, 123.90, 134.23 (q-C) and 143.36, 144.28 (q-C); m/z 160 (M⁺, 66%), 131 (100), 118 (10), 104 (10) and 77 (22). There was a trace of 2, 3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole 252 (5%, by ¹H NMR spectroscopic analysis of reaction mixture using a known amount of 1,4-dimethoxybenzene as internal standard).

56) 2-Deuterio-1-[3-(Phenylselanyl)propyl]-1H-benzimidazole (275)

1-(Trityl)benzimidazole 258 (6.00 g, 16.5 mmol) was dissolved in THF (350 ml) and TMEDA (7.3 ml, 49.5 mmol) was added to the stirred solution at ambient temperature. The temperature of the stirred solution was lowered to -78 °C and a solution of n-butyllithium (7.2 ml, 18.1 mmol) added dropwise. The solution turned pink and was stirred at 0 °C for a further 20 min. A solution of deuterium oxide (1.0 ml, 50.0 mmol) in THF (30 ml) added dropwise, and the stirring was continued for a further 3 h. The solution was evaporated and saturated ammonium chloride (50 ml) and water (100 ml) added to the residue. The aqueous mixture was extracted with dichloromethane (3 x 50 ml), and evaporated to dryness to yield a crude white solid, which was dissolved in methanol (250 ml). Concentrated hydrochloric acid (10 ml, 31-34% w/w solution) was added, and the solution was heated under reflux for 2 h. After cooling the solution to ambient temperature, most of the solvent was evaporated and the residue added to water (100 ml). The acidic aqueous mixture was extracted with dichloromethane (2 x 50 ml), which removed the hydrolysis product, triphenylmethanol. The acidic aqueous layer was evaporated to leave approximately 30-40 ml of a solution containing the salt of benzimidazole. The benzimidazole was precipitated from the saturated aqueous acidic solution using solid sodium carbonate until effervescence ceased. The precipitate was filtered and dried to yield crude 2-deuterio-1H-benzimidazole 274 (1.19 g, 61%), as white crystals. The general
procedure for the alkylation of benzimidazoles in THF was followed. 2-Deuterio-1H-benzimidazole 274 (1.19 g, 10.0 mmol), sodium hydride (0.29 g, 12.0 mmol) and 3-iodo-1-(phenylselanyl)propane 233 (2.43 g, 7.5 mmol) gave a tan residue. The residue was purified by column chromatography using neutral alumina as absorbent with light petroleum and dichloromethane followed by diethyl ether as eluent to give a mixture

2-deuterio-1-[3-(phenylselanyl)propyl]-1H-benzimidazole 275, and

1-[3-(phenylselanyl)propyl]-1H-benzimidazole 271, as a yellow oil (1.49 g, 1.6 / 1.0 respectively by GC-MS analysis); 275 (Found: M+, 317.0541. C_{16}H_{15}N_{2}DSe requires M, 317.0540); δH 2.17-2.29 (2 H, m, 2'-CH2), 2.81-2.87 (2 H, t, J 6.8, PhSeCH2), 4.29-4.35 (2 H, t, J 6.8, NCH2), 7.28-7.39 (5 H, m, Ar-H), 7.47-7.49 (3 H, m, Ar-H) and 7.79-7.81 (1 H, m, Ar-H); δC 23.24, 28.62 (SeCH2), 43.10 (NCH2), 108.58, 119.47, 121.94, 121.16, 121.94, 128.00, 128.28, 131.86, 132.65 (q-C), 141.95 and 142.92 (q-C); m/z 317 (M+, 17%), 160 (30), 157 (27), 132 (100), 131 (42), 78 (31), 77 (79) and 51 (31).

57) Radical cyclisation of 2-deuterio-1-[3-(phenylselanyl)propyl]-1H-benzimidazole (275)

A solution of tri-n-butyltin hydride (0.57 ml, 2.16 mmol) and AIBN (0.118 g, 0.72 mmol) in toluene (50 ml) was added to the mixture of 2-deuterio-1-[3-(phenylselanyl)propyl]-1H-benzimidazole 275, and 1-[3-(phenylselanyl)propyl]-1H-benzimidazole 271 (0.455 g, ratio 1.6 / 1 respectively by GC-MS analysis) in toluene (250 ml) at reflux over 5 h. The solution was stirred and heated under reflux for a further 1 h. The standard work up procedure for the radical cyclisation of imidazoles and benzimidazoles was followed to yield a mixture of 2-deuterio-3-propylbenzimidazole 276; m/z 161 (M+, 89%), 160 (35), 132 (100), 131 (45) and 77 (42) and 2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole 252, as a brown oil (0.189 g, 4.0 / 1.0 respectively by GC-MS analysis).

58) Radical cyclisation of 1-[3-(phenylselanyl)propyl]-1H-benzimidazole (271) using tri-n-butyltin deuteride
A solution of tri-\(n\)-butyltin deuteride (1.04 ml, 3.91 mmol) and AIBN (0.268 g, 1.63 mmol) in toluene (50 ml) was added to the mixture of 1-[3-(phenylselanyl)propyl]-1\(H\)-benzimidazole 271 (1.030 g, 3.26 mmol) in toluene (350 ml) at reflux over 5 h. The solution was stirred and heated under reflux for a further 1 h. The standard work up procedure for the radical cyclisation of imidazoles and benzimidazoles was followed to yield a mixture of 1-(3-deuteropropyl)-1\(H\)-benzimidazole 277; \(m/z\) 161 (\(M^+\), 54%), 160 (96), 132 (25), 131 (100), 77 (57) and 2,3-dihydro-1\(H\)-benzo[d]pyrrolo[1,2-\(a\)]imidazole 252, as a brown oil (0.389 g, 3.3 / 1.0 respectively by GC-MS analysis).

5.4 Experimental for Chapter 4

59) 1-(3-Chloropropyl)-1\(H\)-4-imidazolecarbaldehyde (288)

![Chemical structure of Imidazole-4(5)-carbaldehyde 278, 1-(3-Chloropropyl)-1\(H\)-4-imidazolecarbaldehyde 288, and 1-(3-Chloropropyl)-1\(H\)-5-imidazolecarbaldehyde 289]

Imidazole-4(5)-carbaldehyde 278 (5.40 g, 56.2 mmol) was added to sodium hydride (2.02 g, 84.3 mmol) in THF (400 ml). The mixture was stirred and heated under reflux for 1 h, and 1-bromo-3-chloropropane (22.2 ml, 0.225 mol) was added. The mixture was stirred and heated under reflux for a further 2 h. The salts formed and unreacted imidazole were removed by filtration on a celite bed. The solution was evaporated to yield a crude slurry, which was purified by column chromatography using neutral alumina as absorbent with light petroleum / dichloromethane followed by ethyl acetate / methanol as eluent to yield 1-(3-chloropropyl)-1\(H\)-5-imidazolecarbaldehyde 289, as a yellow oil (0.34 g, 4%). Further elution using ethyl acetate / methanol yielded 1-(3-chloropropyl)-1\(H\)-4-imidazolecarbaldehyde 288, as a fluorescent yellow oil (5.55 g, 58%); \(\nu_{\text{max}}\) / cm\(^{-1}\) 2960, 2751, 1690 (C=O), 1539, 1497, 1452, 1349, 1327, 1163 and 1148; \(\delta_{\text{H}}\) (360.1 MHz) 2.18-2.29 (2 H, m, 2'-CH\(_2\)), 3.47-3.51 (2 H, t, \(J\) 5.9, CH\(_2\)Cl), 4.22-4.26 (2 H, t, \(J\) 6.6, NCH\(_2\)), 7.60 (1 H, s, Im-2-H), 7.65 (1 H, s, Im-5-H) and 9.87 (1 H, s, CHO); \(\delta_{\text{C}}\) 33.45 (2'-CH\(_2\)), 40.99 (CH\(_2\)Cl), 44.51 (NCH\(_2\)), 124.51 (Im-2-CH), 139.27 (Im-5-CH) and 186.67 (CHO).

60) 1-(3-Bromopropyl)-1\(H\)-4-imidazolecarbaldehyde (290)

![Chemical structure of Imidazole-4(5)-carbaldehyde 278, 1-(3-Bromopropyl)-1\(H\)-4-imidazolecarbaldehyde 290]

133
Imidazole-4(5)-carbaldehyde 278 (4.00 g, 41.6 mmol) was added to sodium hydride (1.50 g, 62.4 mmol) in THF (300 ml). The mixture was stirred and heated under reflux for 1 h, and 1,3-dibromopropane (43.0 ml, 0.424 mol) was added. The mixture was stirred and heated under reflux for a further 2 h. The salts formed and unreacted imidazole were removed by filtration on a celite bed. The solution was evaporated to yield a crude slurry, which was purified by column chromatography using neutral alumina as absorbent with light petroleum / dichloromethane followed by ethyl acetate / methanol as eluent to yield 1-(3-bromopropyl)-IH-4-imidazolecarbaldehyde 290, as a yellow gummy oil (3.58 g, 40%); (Found: M+, 215.9901. C7H9N2BrO requires M, 215.9899); νmax / cm⁻¹ 3110, 2961, 2824, 1682 (C=O), 1538, 1497, 1454, 1381, 1327, 1249, 1162, 1046, 979, 855, 780 and 627; δH 2.27-2.37 (2 H, m, 2'-CH₂), 3.30-3.36 (2 H, t, J 7.5, CH₂Br), 4.20-4.26 (2 H, t, J 7.5, NCH₂), 7.61 (1 H, s, Im-2-H), 7.64 (1 H, s, Im-5-H) and 9.87 (1H, s, CHO); δC 29.13 (2'-CH₂), 32.44 (CH₂Br), 45.60 (NCH₂), 124.35 (Im-2-CH), 139.21 (Im-5-CH) and 186.58 (CHO); m/z 234 (M+, 36%), 158 (47), 91 (27), 78 (70), 51 (45) and 41 (100).

61) 1-(4-Bromobutyl)-IH-4-imidazolecarbaldehyde (292)

Imidazole-4(5)-carbaldehyde 278 (2.000 g, 21.0 mmol) was added to sodium hydride (0.374 g, 31.5 mmol) in THF (300 ml). The mixture was stirred and heated under reflux for 1 h, and 1,4-bromobutane (25.1 ml, 0.210 mol) was added. The mixture was stirred and heated under reflux for a further 2 h. The salts formed and unreacted imidazole were removed by filtration on a celite bed. The solution was evaporated to yield a crude slurry, which was purified by column chromatography using neutral alumina as absorbent with light petroleum / dichloromethane followed by ethyl acetate / methanol as eluent to yield 1-(4-bromobutyl)-IH-5-imidazolecarbaldehyde 293, as a yellow oil (0.290 g, 6%), (Found: M⁺, 230.0055 C₈H₁₁N₂Br requires M, 230.0055); νmax / cm⁻¹ 2196, 1668 (C=O), 1536, 1489, 1348 and 1124; δH 1.84-2.00 (4 H, m, 2' and 3'-CH₂), 3.38-3.43 (2 H, t, J 6.2, CH₂Br), 4.31-4.36 (2 H, t, J 7.0, NCH₂), 7.68 (1 H, s, Im-2-H), 7.81 (1 H, s, Im-5-H) and 9.75 (1 H, s, CHO); δC 29.32 (3'-CH₂), 29.44 (2'-CH₂), 32.32 (CH₂Br), 46.25 (NCH₂), 143.43 (Im-CH), 144.05 (Im-CH) and 179.10 (CHO); Further elution with ethyl acetate / methanol yielded 1-(4-bromobutyl)-IH-4-imidazolecarbaldehyde 292, as a yellow oil (2.70 g, 56%); νmax / cm⁻¹ 2945, 1686 (C=O), 1541, 1497, 1450, 1349 and 1160; δH 1.82-1.93 (2 H, m, 3'-CH₂), 2.00-2.09 (2 H, m, 2'-CH₂), 3.39-3.44 (2 H, t, J 6.2, CH₂Br), 4.03-4.09 (2 H, t, J 7.0, NCH₂), 7.58 (1 H, s, Im-2-H), 7.64 (1 H, s,
62) 1-(5-Bromopentyl)-1H-4-imidazolecarbaldehyde (294)

Imidazole-4(5)-carbaldehyde 278 (1.417 g, 14.7 mmol) was added to sodium hydride (0.530 g, 22.1 mmol) in THF (300 ml). The mixture was stirred and heated under reflux for 1 h and 1,5-dibromopentane (20.0 ml, 0.147 mol) was added. The mixture was stirred and heated under reflux for a further 2 h. The salts formed and unreacted imidazole were removed by filtration on a celite bed. The solution was evaporated to yield a crude slurry, which was purified by column chromatography using neutral alumina as absorbent with light petroleum / dichloromethane followed by ethyl acetate / methanol as eluent to yield 1-(5-bromopentyl)-1H-4-imidazolecarbaldehyde 294, as a tan oil (2.241 g, 63%) (Found: MH+, 245.0289. C9H13N2BrO + H requires M, 244.0290); νmax / cm⁻¹ 2862, 1683 (C=O), 1539, 1497, 1356, 1144, 1048 and 979; δH 1.43-1.55 (2 H, m, 3'-CH₂), 1.80-2.08 (4 H, m, 2' and 4'-CH₂), 3.40-3.45 (2 H, t, J 5.8, CH₂Br), 4.00-4.06 (2 H, t, J 7.1, NCH₂), 7.57 (1 H, s, Im-2-H), 7.64 (1 H, s, Im-5-H) and 9.88 (1 H, s, CHO); δC 24.95 (3'-CH₂), 29.99 (4'-CH₂), 31.78 (2'-CH₂), 32.85 (CH₂Br), 47.43 (NCH₂), 124.07 (Im-2-CH), 138.57 (Im-5-CH) and 186.19 (CHO); m/z 247 (83), 245 (MH+, 82%), 219 (38), 217 (37), 165 (100), 137 (94) and 86 (15).

63) 1-(6-Bromohexyl)-1H-4-imidazolecarbaldehyde (296)

Imidazole-4(5)-carbaldehyde 278 (2.018 g, 21.0 mmol) was added to sodium hydride (0.756 g, 31.5 mmol) in THF (400 ml). The mixture was stirred and heated under reflux for 1 h and 1,6-dibromohexane (10.2 ml, 63.0 mmol) was added. The mixture was stirred and heated under reflux for a further 2 h. The salts formed and unreacted imidazole were removed by filtration on
a celite bed. The solution was evaporated to yield a crude slurry, which was purified by column chromatography using neutral alumina as absorbent with light petroleum / dichloromethane followed by ethyl acetate / methanol as eluent to yield 1-(6-bromohexyl)-1H-4-imidazolecarbaldehyde 296, as a yellow oil (4.877 g, 60%); δH 1.34-1.56 (4 H, m, 3' and 4'-CH2), 1.80-1.91 (4 H, m, 2' and 5'-CH2), 3.38-3.43 (2 H, t, J 6.5, CH2Br), 3.99-4.04 (2 H, t, J 7.1, NCH2), 7.56 (1 H, s, Im-2-H), 7.63 (1 H, s, Im-5-H) and 9.88 (1 H, s, CHO); δC 25.99 (4'-CH2), 27.71, 31.05, 32.58, 34.08 (CH2Br), 47.94 (NCH2), 124.56 (Im-2-CH), 139.04 (Im-5-CH), 142.94 (q-C, Im-4-C) and 185.60 (CHO).

64) 1-(12-bromododecyl)-1H-4-imidazolecarbaldehyde (298)

Imidazole-4(5)-carbaldehyde 278 (1.5 g, 15.6 mmol) was added to sodium hydride (0.6 g, 23.4 mmol) in THF (300 ml). The mixture was stirred and heated under reflux for 1 h and 1,12-dodecane (51.1 g, 0.156 mol) in THF (100 ml) was added. The mixture was stirred and heated under reflux for a further 2 h. The salts formed and unreacted imidazole were removed by filtration on a celite bed. The solution was evaporated to yield a tan solid, which was purified by column chromatography using neutral alumina as absorbent with light petroleum / dichloromethane followed by ethyl acetate as eluent to yield 1-(12-bromododecyl)-1H-4-imidazolecarbaldehyde 298, as cream coloured needles (6.2 g, 77%), mp 41-43 °C (Found: M+, 342.1307. C16H27N2BrO requires M+, 342.1307); δH 1.26 (16 H, m, 3'-10'-CH2), 1.80-1.88 (4 H, m, 2' and 11'-CH2), 3.38-3.44 (2 H, m, CH2Br), 3.96-4.02 (2 H, t, J 7.1, NCH2), 7.54 (1 H, s, Im-2-H), 7.62 (1 H, s, Im-5-H) and 9.88 (1 H, s, CHO); δC (62.5 MHz) 26.31, 28.02, 28.60, 28.85, 29.21, 29.24, 29.29, 30.71, 32.68, 34.00 (CH2Br), 47.63 (NCH2), 124.20 (Im-2-CH), 138.61 (Im-5-CH), 143.33 (q-C, Im-4-C) and 186.15 (CHO); m/z 342 (M+, >1%), 263 (34), 137 (13), 110 (23), 69 (28) and 55 (100).

65) 1-(4-Chlorobutyl)-1H-5-imidazolecarbaldehyde (301)
Imidazole-4(5)-carbaldehyde 278 (0.500 g, 5.2 mmol) and 1-chloro-4-iodobutane (6.4 ml, 52 mmol) were heated under reflux in acetonitrile (200 ml) for 18 h. The solution was evaporated to dryness to yield a tan residue, which was purified by column chromatography using neutral alumina as absorbent with light petroleum / dichloromethane followed by ethyl acetate / methanol as eluent to yield 1-(4-chlorobutyl)-1H-5-imidazolecarbaldehyde 300, as a yellow oil (0.144 g, 15%) (Found: M+, 186.0561. C₈H₁₁N₂ClO requires M, 186.0561); νₒₓ / cm⁻¹ 2958, 2854, 1676 (C=O), 1535, 1487, 1348 and 1125; δH (360.1 MHz) 1.76-1.82 (2 H, m, 3'-CH₂), 1.93-1.99 (2 H, m, 2'-CH₂), 3.56-3.62 (2 H, t, J 6.4, CH₂Cl), 4.32-4.36 (2 H, t, J 7.1, NCH₂), 7.68 (1 H, s, Im-2(4)-H), 7.81 (1 H, s, Im-2(4)-H) and 9.75 (1 H, s, CHO); δC (125.1 MHz) 28.23 (3'-CH₂), 29.19 (2'-CH₂), 43.95 (CH₂Cl), 46.37 (NCH₂), 143.45 (Im-CH), 144.07 (Im-CH) and 179.10 (CHO); m/z 187 (MH⁺, 100%), 157 (100), 151 (63), 123 (88), 109 (88), 95 (55), 55 (97) and 27 (100).

66) 1-[3-(Phenylselanyl)propyl]-1H-5-imidazolecarbaldehyde (303)

Imidazole-4(5)-carbaldehyde 278 (1.230 g, 12.8 mmol) was added to 3-iodo-1-(phenylselanyl)propane 233 (4.168 g, 12.8 mmol) in THF (200 ml) and the mixture was stirred and heated under reflux for 54 h. The solution was evaporated to yield a crude slurry, which was purified by column chromatography using neutral alumina as absorbent with light petroleum / dichloromethane followed by ethyl acetate / methanol as eluent to yield a yellow gummy oil of 1-[3-(phenylselanyl)propyl]-1H-5-imidazolecarbaldehyde 303 (0.414 g, 11%) (Found: M⁺, 294.0268. C₁₃H₁₄N₂OSe requires M, 294.0271); νₒₓ / cm⁻¹ 3054, 1670 (C=O), 1579, 1537, 1479, 1436, 1346, 1207, 1123 and 1022; δH 2.01-2.20 (2 H, m, 2'-CH₂), 2.79-2.84 (2 H, t, J 6.8, CH₂SePh), 4.37-4.42 (2 H, t, J 6.8, NCH₂), 7.26-7.29 (3 H, m, Ph-H), 7.47-7.50 (2 H, m, Ph-H), 7.61 (1 H, s, Im-2-H), 7.79 (1 H, s, Im-4-H) and 9.72 (1H, s, CHO); δC 22.81 (2'-CH₂), 28.81 (CH₂SePh), 44.73 (NCH₂), 125.69, 127.44 (q-C) 127.59, 129.29 (q-C), 131.40, 142.14, 142.50 and 177.42 (CHO); m/z 294 (M+, 17%), 157 (10), 137 (100), 109 (13) and 100 (21). Further elution with ethyl acetate / methanol yielded a yellow gummy oil of 1-[3-(phenylselanyl)propyl]-1H-4-imidazolecarbaldehyde 302 (0.188 g, 5%).
67) 1-[4-(Phenylselanyl)butyl]-1H-5-imidazolecarbaldehyde (305)

Imidazole-4(5)-carbaldehyde 278 (0.744 g, 8.06 mmol) was added to 4-iodo-1-(phenylselanyl)butane 234 (2.740 g, 8.06 mmol) in THF (200 ml), and the mixture was stirred and heated under reflux for 54 h. The solution was evaporated to yield a crude slurry, which was purified by column chromatography using neutral alumina as absorbent with light petroleum / dichloromethane followed by ethyl acetate / methanol as eluent to yield a yellow gummy oil of 1-[4-(phenylselanyl)butyl]-1H-5-imidazolecarbaldehyde 305 (0.323 g, 13%); ν<sub>max</sub> / cm<sup>-1</sup> 2253, 1675 (C=O), 1644, 1536, 1478, 1347 and 1126; δ<sub>H</sub> (400 MHz) 1.69-1.76 (2 H, m, 3'-CH<sub>2</sub>), 1.91-1.98 (2 H, m, 2'-CH<sub>2</sub>), 2.90-2.93 (2 H, t, J 6.0, CH<sub>2</sub>SePh), 4.30-4.33 (2 H, t, J 7.2, NCH<sub>2</sub>), 7.27-7.31 (3 H, m, Ph-H), 7.48-7.51 (2 H, m, Ph-H), 7.60 (1 H, s, Im-2-H), 7.82 (1 H, s, Im-4-H) and 9.76 (1H, s, CHO); δ<sub>C</sub> 27.24 (3'-CH<sub>2</sub>), 27.46 (2'-CH<sub>2</sub>), 31.11 (CH<sub>2</sub>SePh), 47.03 (NCH<sub>2</sub>), 127.49, 129.53, 130.16 (q-C), 133.28, 133.39, 144.31 and 179.52 (CHO).

68) 1-(3-Iodopropyl)-1H-4-imidazolecarbaldehyde (306)

1-(3-Chloropropyl)-1H-4-imidazolecarbaldehyde 288 (3.0 g, 17.4 mmol) and sodium iodide (26.1 g, 0.174 mol) were added to dry acetone (250 ml) and heated under reflux for 18 h. The standard work up procedure for the formation of iodides was followed to give 1-(3-iodopropyl)-1H-4-imidazolecarbaldehyde 306, as a yellow-orange solid (4.1 g, 89%); δ<sub>H</sub> (360.1 MHz) 2.23-2.30 (2 H, m, 2'-CH<sub>2</sub>), 3.07-3.10 (2 H, t, J 6.5, CH<sub>2</sub>I), 4.16-4.20 (2 H, t, J 6.3, NCH<sub>2</sub>), 7.62 (1 H, s, Im-2-H), 7.66 (1 H, s, Im-5-H) and 9.80 (1 H, s, CHO); δ<sub>C</sub> 0.00 (2'-CH<sub>2</sub>I), 32.69 (2'-CH<sub>2</sub>), 46.54 (NCH<sub>2</sub>), 122.91 (Im-2-CH), 137.90 (Im-5-CH) and 185.42 (CHO). The product rapidly decomposed in the dark and under inert atmospheres to give an intractable brown solid.
69) 6,7-Dihydro-5H-pyrrolo[1,2-c]imidazole-1-carbaldehyde (307)
(from the \textit{in situ} formation of iodide 306)

\[
\begin{align*}
\text{OHC} & \quad \text{N} \\
\text{Cl} & \quad \text{HN} \quad \text{I}
\end{align*}
\]

1-(3-Chloropropyl)imidazole-4-carbaldehyde 288 (0.300 g, 1.74 mmol) and sodium iodide (2.600 g, 17.00 mmol) were added to dry acetonitrile (250 ml) and heated under reflux for 18 h. The precipitated sodium chloride was removed in darkness by filtration on a celite bed and the 1-(3-iodopropyl)imidazole-4-carbaldehyde 306, which was formed \textit{in situ}. A solution of tri-\textit{n}-butyltin hydride (0.69 ml, 2.62 mmol) and AIBN (0.140 g, 0.86 mmol) in toluene (50 ml) was immediately added to the solution of 1-(3-iodopropyl)-1H-4-imidazolecarbaldehyde 306 at reflux over 5 h. The solution was stirred and heated under reflux for a further 1 h. The standard work up procedure for the radical cyclisation of imidazoles and benzimidazoles was followed to yield a tan solid, which was purified by prep-TLC using neutral alumina as absorbent with ethyl acetate / methanol as eluent to yield 6,7-dihydro-5H-pyrrolo[1,2-c]imidazole-1-carbaldehyde 307, as white needles (7 mg, 3%) and 1-propyl-1H-4-imidazolecarbaldehyde 308, as a colourless oil (12 mg, 7%).

70) \{1-[3-(Phenylselanyl)propyl]-1H-4-imidazolyl\}methanol (309)

Diphenyl diselenide (2.53 g, 8.1 mmol) was dissolved in absolute ethanol (600 ml) at ambient temperature. Sodium borohydride (0.67 g, 17.7 mmol) was added slowly to the stirred solution at 0 °C. After 30 min, 1-(3-bromopropyl)-1H-4-imidazolecarbaldehyde 290 (1.92 g, 8.89 mmol) in absolute ethanol (100 ml) was added and the mixture was stirred at ambient temperature for 16 h. The solution was evaporated to dryness and 2 M hydrochloric acid (100 ml) added and the acidic solution was washed with light petroleum (3 x 100 ml) to remove selenide residues. The solution was basified to pH 8 with saturated sodium carbonate solution followed by the addition of 2 M sodium hydroxide solution until the aqueous solution was at pH 14. The hydroxide solution was extracted into dichloromethane (2 x 100 ml), and the combined
organic extracts dried (MgSO₄) and evaporated to dryness to yield a brown solid, which was recrystallised with ethyl acetate to yield the [1-[3-(phenylselanyl)propyl]-1H-4-imidazolyl]methanol 309, as yellow-orange crystals (1.08 g, 41%) (Found: M⁺, 296.0437. C₁₃H₁₆N₂SeO requires M, 296.0428); ν max / cm⁻¹ 3054, 1709, 1579, 1478, 1438, 1265 and 1161; δ H 2.08-2.15 (2 H, m, 2'-CH₂), 2.78-2.84 (2 H, t, J 6.8, CH₂SePh), 4.00-4.05 (2 H, t, J 6.6, NCH₂), 6.80 (1 H, s, Im-5-H), 7.24-7.29 (3 H, m, Ph-H), 7.37 (1 H, s, Im-2-H) and 7.47-7.51 (2 H, m, Ph-H); δ C 24.41 (2'-CH₂), 31.28 (CH₂SePh), 46.49 (NCH₂), 58.34 (CH₂OH), 116.47 (Im-5-CH), 127.74, 129.66, 133.57, 137.33 (Im-2-CH), 143.27 and (q-C, Im-4-C); m/z 296 (M⁺, 98%), 157 (49), 138 (62), 121 (72), 109 (100), 82 (97) and 41 (81).

71) 1-[3-(Phenylselanyl)propyl]-1H-4-imidazolecarbaldehyde (302)

{1-[3-(Phenylselanyl)propyl]-1H-4-imidazolyl}methanol 309 (0.879 g, 3.0 mmol) and activated manganese dioxide (2.700 g, 31.1 mmol) were stirred at ambient temperature in dry dichloromethane (200 ml) for 48 h. The mixture was filtered on a celite bed and the residue washed with dichloromethane (3 x 50 ml). The combined filtrate washings were evaporated to an oil, which was purified by column chromatography using neutral alumina as absorbent with ethyl acetate / methanol as eluent to yield 1-[3-(phenylselanyl)propyl]-1H-4-imidazolecarbaldehyde 302, as a yellow gummy oil (0.635 g, 72%) (Found: M⁺, 294.0236. C₁₃H₁₄N₂OSe requires M, 294.0271); ν max / cm⁻¹ 3054, 1684 (C=O), 1539, 1478, 1438, 1266, 1160, 1022 and 910; δ H 2.10-2.21 (2 H, m, 2'-CH₂), 2.79-2.85 (2 H, t, J 6.8, CH₂SePh), 4.11-4.16 (2 H, t, J 6.8, NCH₂), 7.26-7.31 (3 H, m, Ph-H), 7.48-7.52 (3 H, m, Ph-H and Im-2-H), 7.55 (1 H, s, Im-5-H) and 9.86 (1 H, s, CHO); δ C 25.40 (2'-CH₂), 32.33 (CH₂SePh), 48.21 (NCH₂), 125.30, 131.02, 134.94, 140.43, 145.78 and 187.73 (CHO); m/z 294 (M⁺, 100%), 157 (48), 137 (38), 109 (56), 84 (67), 77 (57), 49 (65) and 41 (62).

72) 6,7-Dihydro-5H-pyrrolo[1,2-c]imidazole-1-carbaldehyde (307) (from the selenide 302)
A solution of tri-n-butyltin hydride (1.0 ml, 3.72 mmol) and AIBN (0.213 g, 1.30 mmol) in toluene (50 ml) was added to 1-[3-(phenylselanyl)propyl]-1H-4-imidazolecarbaldehyde 302 (0.730 g, 2.48 mmol) in acetonitrile (750 ml) at reflux over 5 h. The solution was stirred and heated under reflux for a further 1 h. The standard work up procedure for the radical cyclisation of imidazoles and benzimidazoles was followed to yield a tan solid, which was purified by column chromatography using neutral alumina as absorbent with ethyl acetate/methanol as eluent to yield 6,7-dihydro-5H-pyrrolo[1,2-c]imidazole-1-carbaldehyde 307, as white needles (92 mg, 27%) and 1-propyl-1H-4-imidazolecarbaldehyde 308, as a colourless oil (38 mg, 11%).

73) 6,7-Dihydro-5H-pyrrolo[1,2-c]imidazole-1-carbaldehyde (307) (from the bromide 290)

A solution of tri-n-butyltin hydride (4.3 ml, 5.4 mmol) and AIBN (0.593 g, 3.6 mmol) in toluene (50 ml) was added to 1-(3-bromopropyl)-1H-4-imidazolecarbaldehyde 290 (1.560 g, 7.2 mmol) in acetonitrile (750 ml) at reflux over 5 h. The solution was stirred and heated under reflux for a further 1 h. The standard work up procedure for the radical cyclisation of imidazoles and benzimidazoles was followed to yield a tan solid, which was purified by column chromatography using neutral alumina as absorbent with ethyl acetate/methanol as eluent to yield 6,7-dihydro-5H-pyrrolo[1,2-c]imidazole-1-carbaldehyde 307, as white needles (0.411 g, 42%), mp 137-139 °C (Found: M+, 136.0637. C7H8N2O requires M, 136.0637); νmax/cm⁻¹ 3223, 1672 (C=O), 1618, 1471, 1446, 1345, 1300, 1281, 1134 and 744; δH 2.66-2.80 (2 H, m, 6-CH₂), 3.07-3.13 (2 H, t, J 7.5, 7-CH₂), 4.03-4.09 (2 H, t, J 7.2, NCH₂), 7.48 (1 H, s, Im-3-H), and 9.83 (1H, s, CHO); δC 23.43 (6-CH₂), 29.22 (7-CH₂), 45.09 (NCH₂), 132.21 (Im-3-CH), 133.52 (q-C, Im-7a-C), 145.05 (q-C, Im-1-C) and 186.95 (CHO); m/z 136 (M+, 40%), 135 (39), 108 (36), 107 (52), 81(29), 80 (100), 79 (27), 53 (84), 52 (82), 41 (36) and 39 (42). Further elution with ethyl acetate/methanol yielded 1-propyl-1H-4-imidazolecarbaldehyde 308, as a colourless oil (0.100 g, 10%) (Found: M+, 138.0795. C7H10N2O requires M, 138.0793); δH 0.93-0.99 (3 H, t, J 7.4, CH₃), 1.81-1.93 (2 H, m, 2'-CH₂), 3.94-3.99 (2 H, t, J 7.1, NCH₂), 7.55 (1 H, s, Im-2-H), 7.62 (1 H, s, Im-5-H) and 9.87 (1H, s, CHO); δC 11.40 (CH₃), 24.59 (2'-CH₂), 49.75 (NCH₂), 124.49 (Im-2-CH), 139.07 (Im-5-CH), 142.92 and 186.77 (CHO); m/z 138 (M⁺, 100%), 121 (12), 110 (46), 95 (61), 81 (13), 68 (25) and 43 (47).
74) 5,6,7,8-Tetrahydroimidazo[1,5-a]pyridine-1-carbaldehyde (310)

A solution of tri-n-butyltin hydride (1.9 ml, 7.16 mmol) and AIBN (0.378 g, 2.30 mmol) in toluene (50 ml) was added to 1-(4-bromobutyl)-1H-4-imidazolecarbaldehyde 292 (1.078 g, 4.69 mmol) in acetonitrile (750 ml) at reflux over 5 h. The solution was stirred and heated under reflux for a further 1 h. The standard work up procedure for the radical cyclisation of imidazoles and benzimidazoles was followed to yield a tan solid, which was purified by column chromatography using neutral alumina as absorbent with ethyl acetate / methanol as eluent to yield 5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-1-carbaldehyde 310, as yellow needles (0.344 g, 49%) mp 51-53 °C, (Found: M⁺, 150.0793. C₉H₁₀N₂O requires M⁺, 150.0793); νmax / cm⁻¹ 2957, 1672 (C=O), 1553, 1514, 1266 and 1151; δH 1.86-2.05 (4 H, m, 6 and 7-CH₂), 3.07-3.12 (2 H, t, J 6.4, 8-CH₂), 4.00-4.05 (2 H, t, J 6.0, NCH₂), 7.42 (1 H, s, Im-3-H) and 9.89 (1H, s, CHO); δC (62.5 MHz) 20.35, 22.67, 23.18 (8-CH₂), 44.18 (NCH₂), 137.29 (Im-3-CH) and 187.90 (CHO); m/z 151 (MH⁺, 100%), 150 (M⁺, 69), 149 (56), 121 (19), 94 (9) and 67 (31).

75) 6,7,8,9-Tetrahydro-5H-imidazo[1,5-a]azepine-1-carbaldehyde (312)

A solution of tri-n-butyltin hydride (1.20 ml, 4.50 mmol) and AIBN (0.246 g, 1.50 mmol) in toluene (50 ml) was added to 1-(5-bromopentyl)-1H-4-imidazolecarbaldehyde 294, (0.726 g, 3.00 mmol) in acetonitrile (350 ml) at reflux over 10 h. The solution was stirred and heated under reflux for a further 1 h. The standard work up procedure for the radical cyclisation of imidazoles and benzimidazoles was followed to yield a tan solid, which was purified by column chromatography using neutral alumina as absorbent with ethyl acetate / methanol as eluent to yield 6,7,8,9-tetrahydro-5H-imidazo[1,5-a]azepine-1-carbaldehyde 312, as white needles (69 mg, 14%) mp 86-88 °C, (Found: M⁺, 164.0950. C₉H₁₂N₂O requires M⁺, 164.0950); νmax / cm⁻¹ 2857, 1666 (C=O), 1555, 1524, 1392 and 1353; δH 1.65-1.89 (6 H, m, 6, 7 and
8-CH₂), 3.20-3.22 (2 H, m, 9-CH₂), 4.01-4.05 (2 H, m, NCH₂), 7.39 (1 H, s, Im-3-H) and 9.92 (1H, s, CHO); δC 24.52, 26.76, 29.07, 30.89, 48.38 (NCH₂), 137.80 (q-C, Im-9a-C), 138.19 (Im-3-CH), 141.76 (q-C, Im-1-C) and 187.95 (CHO); m/z 165 (MH⁺, 24%), 164 (M⁺, 100), 163 (45), 149 (18), 135 (91), 121 (34), 107 (43) and 81 (31). Further elution with ethyl acetate / methanol yielded 1-pentyl-1H-4-imidazolecarbaldehyde 313, as a colourless oil (40 mg, 8%), (Found: M⁺, 166.1106. C₉H₁₄N₂O requires M, 166.1106); δH 0.88-0.93 (3 H, t, J 6.9, CH₃), 1.25-1.40 (4 H, m, 7 and 8-CH₂), 1.77-1.88 (2 H, m, 6-CH₂), 3.96-4.02 (2 H, t, 17.1, NCH₂), 7.62 (1 H, s, Im-2-H), 7.63 (1 H, s, Im-5-H) and 9.88 (1H, s, CHO); δC 14.17 (CH₃), 22.45 (4'-CH₂), 28.98, 30.89, 48.12 (NCH₂), 124.39 (Im-2-CH), 139.00 (Im-5-CH), 142.96 (q-C, Im-4-C) and 186.77 (CHO); m/z 166 (M⁺, 24%), 137 (61), 110 (25), 109 (20), 95 (26), 81 (34), 68 (16), 55 (28) and 41 (100).

76) Attempted radical cyclisation of 1-(6-bromohexyl)-1H-4-imidazolecarbaldehyde (296)

A solution of tri-n-butyltin hydride (0.53 ml, 2.01 mmol) and AIBN (0.110 g, 0.67 mmol) in toluene (50 ml) was added to 1-(6-bromohexyl)-1H-4-imidazolecarbaldehyde 296, (0.346 g, 1.34 mmol) in acetonitrile (350 ml) at reflux over 10 h. The solution was stirred and heated under reflux for a further 1 h. The standard work up procedure for the radical cyclisation of imidazoles and benzimidazoles was followed to yield a tan solid, which was purified by prep-TLC using neutral alumina as absorbent with ethyl acetate / methanol as eluent to yield 1-hexyl-1H-4-imidazolecarbaldehyde 315, as a colourless oil (0.136 g, 56%); δH 0.86-0.91 (3 H, t, J 6.5, CH₃), 1.28-1.31 (6 H, m, 3', 4', and 5'-CH₂), 1.79-1.84 (2 H, m, 2'-CH₂), 3.96-4.02 (2 H, t, J 7.2, NCH₂), 7.55 (1 H, s, Im-2-H), 7.63 (1 H, s, Im-5-H) and 9.87 (1H, s, CHO); δC 14.26 (CH₃), 22.76, 26.48, 31.08, 31.06, 48.14 (NCH₂), 124.48 (Im-2-CH), 139.01 (Im-5-CH), 142.89 (q-C, Im-4-C) and 186.72 (CHO).

77) Attempted radical cyclisation of 1-(12-bromododecyl)-1H-4-imidazolecarbaldehyde (298)
A solution of tri-n-butyltin hydride (0.58 ml, 2.19 mmol) and AIBN (0.120 g, 0.73 mmol) in toluene (50 ml) was added to 1-(12-bromodecyl)-1H-4-imidazolecarbaldehyde 298, (0.500 g, 1.46 mmol) in toluene (350 ml) at reflux over 10 h. The solution was stirred and heated under reflux for a further 1 h. The standard work up procedure for the radical cyclisation of imidazoles and benzimidazoles was followed to yield a yellow oil of 1-dodecyl-1H-4-imidazolecarbaldehyde 317, as an oil (0.269 g, 70%); (Found: M+, 264.2202. C_{16}H_{28}N_{2}O requires M, 264.2202); ν_{max} / cm^{-1} 2854, 1689 (C=O), 1540, 1466, 1378, 1158 and 910; δ_{H} 0.85-0.91 (3 H, t, J 6.6, CH_{3}), 1.25-1.38 (18 H, m, 3'-11'-CH_{2}), 1.79-1.82 (2 H, m, 2'-CH_{2}), 3.96-4.02 (2 H, t, J 7.1, NCH_{2}), 7.54-7.55 (1 H, d, J 0.9, Im-2-H), 7.63 (1 H, d, J 0.9, Im-5-H) and 9.88 (1H, s, CHO); δ_{C} 14.45 (CH_{3}), 23.02, 26.80, 29.32, 29.66, 29.77, 29.83, 29.92, 31.18, 31.31, 32.24, 48.10 (NCH_{2}), 124.52 (Im-2-CH), 139.03 (Im-5-CH), 142.88 (q-C, Im-4-C) and 186.65 (CHO); m/z 264 (M^+, 57%), 235 (44), 221 (23), 207 (29), 151 (36), 137 (37), 110 (81), 97 (48), 55 (73), 55 (73) and 41 (100) [which required no further purification].

78) 1-(3-Bromopropyl)-5-methyl-1H-4-imidazolecarbaldehyde (318)

4-Methylimidazole-4-carbaldehyde (2.000 g, 18.2 mmol) was added to sodium hydride (0.655 g, 27.3 mmol) in THF (300 ml). The mixture was stirred and heated under reflux for 1 h and 1,3-dibromopropane (18.5 ml, 0.182 mol) was added. The mixture was stirred and heated under reflux for a further 2 h. The salts formed and unreacted imidazole were removed by filtration on a celite bed. The solution was evaporated to yield a crude slurry, which was purified by column chromatography using neutral alumina as absorbent with light petroleum / dichloromethane followed by ethyl acetate / methanol as eluent to yield 1-(3-bromopropyl)-5-methyl-1H-4-imidazolecarbaldehyde 318, as a yellow gummy oil (1.428 g, 34%); (Found: M^+, 230.0062. C_{8}H_{11}N_{2}BrO requires M, 230.0055); ν_{max} / cm^{-1} 3081, 1668 (C=O), 1556, 1510, 1407, 1382, 1310, 1272, 1234, 1213, 1102 and 806; δ_{H} 2.24-2.35 (2 H, m, 2'-CH_{2}), 2.58 (3 H, s, CH_{3}), 3.35-3.39 (2 H, t, J 6.0, CH_{2}Br), 4.11-4.17 (2 H, t, J 6.8, NCH_{2}), 7.59 (1 H, s, Im-2-H) and 9.96 (1H, s, CHO); δ_{C} 9.75 (CH_{3}), 29.23 (2'-CH_{2}), 32.98 (CH_{2}Br), 42.77 (NCH_{2}), 135.25 (q-C, Im-5-C), 137.95 (Im-2-CH), 138.42 (q-C, Im-4-C) and 187.88 (CHO); m/z 232 (27), 230 (M^+, 27%), 151 (100), 124 (35), 109 (14), 96 (24) and 41 (54).
79) Attempted radical cyclisation of 1-(3-Bromopropyl)-5-methyl-1H-4-imidazolecarbaldehyde (318)

A solution of tri-n-butyltin hydride (0.88 ml, 3.32 mmol) and AIBN (0.181 g, 1.10 mmol) in toluene (50 ml) was added to 1-(3-bromopropyl)-5-methyl-1H-4-imidazolecarbaldehyde 318 (0.540 g, 2.35 mmol) in acetonitrile (350 ml) at reflux over 5 h. The solution was stirred and heated under reflux for a further 1 h. The standard work up procedure for the radical cyclisation of imidazoles and benzimidazoles was followed to yield a yellow-orange oil of 5-methyl-1-propyl-1H-4-imidazolecarbaldehyde 319 (0.154 g, 46%); \( \nu_{\text{max}} / \text{cm}^{-1} 3111, 2876, 1674 \) (C=O), 1557, 1510, 1456, 1381, 1259, 1209, 1170 and 1109; \( \delta_{H} 0.90-0.99 \) (3 H, t, J 7.4, CH3), 1.74-1.83 (2 H, m, 2'-CH2), 2.53 (3 H, s, Im-CH3), 3.82-3.88 (2 H, t, J 7.2, NCH2), 7.44 (1 H, s, Im-2-H) and 9.92 (1H, s, CHO); \( \delta_{C} \) (62.5 MHz) 9.34 (Im-CH3), 11.06 (CH3), 23.72 (2'-CH2), 46.24 (NCH2), 137.53 (Im-2-CH) and 187.54 (CHO) [which required no further purification].

80) 1-(3-Bromopropyl)-2-methyl-1H-4-imidazolecarbaldehyde (320)

2-Methylimidazole-4-carbaldehyde (1.000 g, 9.08 mmol) was added to sodium hydride (0.327 g, 13.63 mmol) in THF (150 ml). The mixture was stirred and heated under reflux for 1 h and 1,3-dibromopropane (9.2 ml, 90.80 mmol) was added. The mixture was stirred and heated under reflux for a further 2 h. The salts formed and unreacted imidazole were removed by filtration on a celite bed. The solution was evaporated to yield a crude slurry, which was purified by column chromatography using neutral alumina as absorbent with light petroleum / dichloromethane followed by ethyl acetate / methanol as eluent to yield 1-(3-bromopropyl)-2-methyl-1H-4-imidazolecarbaldehyde 320, as a yellow gummy oil (0.948 g, 45%) (Found: M+, 230.0055. \( \text{C}_{9}\text{H}_{11}\text{N}_{2}\text{BrO} \text{requires M, 230.0055}; \nu_{\text{max}} / \text{cm}^{-1} 3125, 1678 \) (C=O), 1547, 1418, 1351, 1254, 1163, 1102, 991 and 812; \( \delta_{H} 2.28-2.33 \) (2 H, m, 2'-CH2), 2.48 (3 H, s, CH3), 3.35-3.39 (2 H, t,
J 6.0, CH₂Br), 4.11-4.17 (2 H, t, J 6.7, NCH₂), 7.59 (1 H, s, Im-5-H) and 9.81 (1H, s, CHO); δC 13.53 (CH₃), 29.21 (2'-CH₂), 33.05 (CH₂Br), 44.83 (NCH₂), 125.81 (Im-5-CH), 141.13 (q-C, Im-2-C), 147.34 (q-C, Im-4-C) and 185.94 (CHO); m/z 232 (30), 231 (19), 230 (M⁺, 23%), 150 (48), 149 (48), 121 (44), 81 (35), 79 (28) and 41 (100).

81) (E)-4-(3-methyl-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-3-buten-2-one (322)

A solution of tri-n-butyltin hydride (1.04 ml, 3.9 mmol) and AIBN (0.213 g, 1.3 mmol) in toluene (50 ml) was added to 1-(3-bromopropyl)-2-methyl-1H-4-imidazolecarbaldehyde 320 (0.600 g, 2.6 mmol) in acetonitrile (350 ml) at reflux over 5 h. The solution was stirred and heated under reflux for a further 1 h. After cooling to room temperature, the solution was evaporated to dryness, 2 M hydrochloric acid solution (50 ml), and a trace of acetone was added, and the acidic solution was washed with light petroleum (12 x 50 ml). The solution was basified to pH 8 with saturated sodium carbonate solution followed by the addition of 2 M sodium hydroxide solution until the aqueous solution was at pH 14. The hydroxide solution was extracted into dichloromethane (2 x 100 ml) and the combined organic extracts dried (MgSO₄), and evaporated to dryness to yield a tan solid, which was purified by column chromatography using neutral alumina as absorbent with ethyl acetate / methanol as eluent to yield (E)-4-(3-methyl-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-3-buten-2-one 322, as yellow oil (0.494 g, 75%) (Found: M⁺, 190.1106. C₁₁H₁₄N₂O requires M, 190.1106); ν max / cm⁻¹ 2961, 1661 (C=O), 1422, 1363 and 1254; δH (400 MHz) 2.28 (3 H, s, CH₃), 2.88 (3 H, s, Im-CH₃), 2.64-2.69 (2 H, m, 6-CH₂), 2.91-2.94 (2 H, t, J 7.4, 7-CH₂), 3.86-3.89 (2 H, t, J 7.1, NCH₂), 6.58-6.62 (1 H, d, δ J 15.8, 1'-trans-H) and 7.36-7.40 (1 H, d, δ J 15.8, 2'-trans-H); δC 13.51 (Im-CH₃), 23.32 (6-CH₂), 28.28 (CH₃), 29.58 (7-CH₂), 44.28 (NCH₂), 123.02 (1'-CH), 127.81 (q-C), 135.83 (2'-CH), 141.32 (q-C, Im-3-C) and 198.92 (CHO); m/z 190 (M⁺, 86%), 175 (100), 147 (88), 106 (34) and 77 (59).
82) 1-(2-Bromobenzyl)-IH-4-imidazolecarbaldehyde (323)

![Chemical Structure]

Imidazole-4(5)-carbaldehyde 278 (0.600 g, 6.24 mmol) was added to sodium hydride (0.225 g, 9.36 mmol) in THF (300 ml). The mixture was stirred and heated under reflux for 1 h, and 2-bromobenzyl bromide (5.23 ml, 28.70 mmol) was added. The mixture was stirred and heated under reflux for a further 2 h. The salts formed and unreacted imidazole were removed by filtration on a celite bed. The solution was evaporated to yield a brown slurry, which was purified by column chromatography using neutral alumina as absorbent with light petroleum / dichloromethane followed by ethyl acetate as eluent to yield 1-(2-bromobenzyl)-IH-4-imidazolecarbaldehyde 323, as a yellow oil (0.739 g, 45%); (Found: M+, 263.9898. Cl1H9N2BrO requires M, 263.9899); \( \nu_{\text{max}} / \text{cm}^{-1} \) 2251, 2229, 1688 (C=O), 1539, 1442, 1152, 1030 and 909; \( \delta_{\text{H}} \) 5.26 (2 H, s, NCH2), 7.09-7.12 (1 H, m, Ar-CH), 7.22-7.37 (2 H, m, Ar-CH), 7.60-7.62 (1 H, m, Ar-CH), 7.64 (1 H, s, Im-2(5)-H), 7.65 (1 H, s, Im-2(5)-H) and 9.85 (1 H, s, CHO); \( \delta_{\text{C}} \) (62.5 MHz) 51.37 (NCH2), 123.59 (q-C, Ar-CBr), 124.68, 128.27, 129.88, 130.58, 133.43, 134.00 (q-C), 139.04, 142.39 (q-C, Im-2-C) and 186.04 (CHO); \( m/z \) 266 (13%), 264 (M+, 13%), 263 (6), 185 (34), 171 (100), 169 (98), 157 (46), 90 (73), 89 (76) and 63 (32).

83) Attempted radical cyclisation of 1-(2-bromobenzyl)-IH-4-imidazolecarbaldehyde (323)

![Chemical Structure]

A solution of tri-\( n \)-butyltin hydride (0.57 ml, 2.14 mmol) and AIBN (0.117 g, 0.72 mmol) in toluene (50 ml) was added to 1-(2-bromobenzyl)-IH-4-imidazolecarbaldehyde 323 (0.377 g, 1.43 mmol) in toluene (350 ml) at reflux over 5 h. The solution was stirred and heated under reflux for a further 1 h. The standard work up procedure for the radical cyclisation of imidazoles and benzimidazoles was followed to yield a brown oil, which was purified by prep-TLC using neutral alumina as absorbent with ethyl acetate / methanol as eluent to yield

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1-(2-bromobenzyl)-1H-4-imidazolecarbaldehyde 324, as a yellow oil (0.136 g, 51%); (Found: M+, 186.0793. C_{11}H_{10}N_{2}BrO requires M, 186.0793); δH 5.17 (2 H, s, NCH2), 7.19-7.22 (2 H, m, Ar-CH), 7.38-7.41 (3 H, m, Ar-CH), 7.61-7.62 (2 H, m, Im-2(5)-H) and 9.88 (1 H, s, CHO); δC (62.5 MHz) 51.96 (NCH2), 124.75, 128.09, 129.35, 129.73, 134.92 (q,C), 139.15, 134.00 (q,C), and 186.04 (CHO); mlz 186 (100%), 149 (38), 91 (38) and 65 (59).

84) Attempted radical cyclisation of 1-[3-(Phenylselanyl)propyl]-1H-5-imidazolecarbaldehyde (303)

![Diagram](image)

A solution of tri-n-butyltin hydride (0.18 ml, 0.68 mmol) and AIBN (37 mg, 0.23 mmol) in toluene (50 ml) was added to 1-[3-(phenylselanyl)propyl]-1H-5-imidazolecarbaldehyde 303 (0.140 g, 0.45 mmol) in acetonitrile (100 ml) at reflux over 5 h. The solution was stirred and heated under reflux for a further 1 h. The standard work up procedure for the radical cyclisation of imidazoles and benzimidazoles was followed to yield a tan solid, which was purified by prep-TLC using neutral alumina as absorbent with ethyl acetate / methanol as eluent to yield 1-propyl-1H-5-imidazolecarbaldehyde 331, as a yellow oil (45 mg, 73%); (Found: M+, 138.0793. C_{7}H_{10}N_{2}O requires M, 138.0793); ν_max / cm⁻¹ 1676 (C=O), 1466, 1383, 1347 and 1214; δH 0.89-0.96 (3 H, t, CH3), 1.76-1.82 (2 H, m, 2'-CH2), 4.23-4.29 (2 H, t, J 7.2, NCH2), 7.79 (1 H, s, Im-2(4)-H), 7.80 (1 H, s, Im-2(4)-H) and 9.87 (1H, s, CHO); mlz 139 (MH+, 100%), 121 (30), 97 (34) and 41 (38).

85) 5,6,7,8-Tetrahydroimidazo[1,2-a]pyridine-3-carbaldehyde (332)

![Diagram](image)

A solution of tri-n-butyltin hydride (0.38 ml, 1.44 mmol) and AIBN (79 mg, 0.48 mmol) in toluene (50 ml) was added to 1-[4-(phenylselanyl)butyl]-1H-5-imidazolecarbaldehyde 305 (0.295 g, 0.96 mmol) in acetonitrile (150 ml) at reflux over 5 h. The solution was stirred and heated under reflux for a further 1 h. The standard work up procedure for the radical cyclisation of imidazoles and benzimidazoles was followed to yield a tan solid, which was purified by...
column chromatography using neutral alumina as absorbent with ethyl acetate / methanol as eluent to yield 5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-3-carbaldehyde 332, as yellow oil (76 mg, 53%) (Found: M+, 150.0793. C8H10N2O requires M, 150.0793); νmax / cm⁻¹ 1686 (C=O), 1637, 1489, 1406, 1364, 1265; δH 1.92-2.03 (4 H, m, 6 and 7-CH2), 2.95-3.00 (2 H, t, J 6.2, CCH2), 4.31-4.35 (2 H, t, J 5.7, NCH2), 7.75 (1 H, s, Im-2-H) and 9.66 (1H, s, CHO); δC 20.04 (7-CH2), 22.76 (6-CH2), 25.20 (CCH2), 46.08 (NCH2), 142.62 (Im-2-H) and 179.11 (CHO); m/z 150 (M+, 100), 149 (60), 135 (16), 122 (25) and 84 (62)

86) 1-(Triphenylmethyl)-1H-2-imidazolecarbaldehyde (335)¹⁰⁷

![Chemical structure](image)

1-(Trityl)imidazole 217 (10.0 g, 32.2 mmol) was dissolved in THF (200 ml) and a solution of n-butyllithium (14 ml, 35.2 mmol) added dropwise to the stirred solution at -78 °C. The solution which gradually turned red was stirred at 0 °C for a further 20 min and DMF (5.4 ml, 64.4 mmol) added dropwise. The solution was stirred overnight at ambient temperature and evaporated to dryness. Saturated ammonium chloride (50 ml) and water (100 ml) was added to the residue. The aqueous mixture was extracted with dichloromethane (3 x 50 ml) and the organic extracts were washed with brine (2 x 100 ml). The organic extracts were evaporated to dryness to yield yellow crystals, which were recrystallised with ethyl acetate to give pale yellow needles of the 1-(triphenylmethyl)-1H-2-imidazolecarbaldehyde 335 (8.0 g, 74%), mp 184 °C (lit.¹⁰⁷, mp 189-190 °C); (Found: C, 81.9; H, 5.1; N, 8.3. C23H18N2O requires C, 81.7; H, 5.3; N, 8.3%).

87) Imidazole-1H-2-carbaldehyde (181)¹³⁵

![Chemical structure](image)

The general procedure for the removal of the protective trityl group was followed. 1-(Trityl)-1H-2-imidazolecarbaldehyde 335 (8.00 g, 23.6 mmol) gave a cream coloured precipitate of imidazole-1H-2-carbaldehyde 181 (0.58 g, 26%), mp 208-212 °C (lit.¹³⁵, mp 204-205 °C); νmax / cm⁻¹ 1692 (C=O), 1424, 1411, 1342 and 1136; δH ([1H₆]Me₂SO) 7.44 (2 H, bs, Im-4(5)-H) and 9.66 (1 H, s, CHO).

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88) Attempted alkylation of imidazole-1\(H\)-2-carbaldehyde (181)

![Chemical structure of imidazole-1\(H\)-2-carbaldehyde (181) and product (338)]

Imidazole-1\(H\)-2-carbaldehyde 181 (0.500 g, 20.3 mmol) was added to sodium hydride (0.732 g, 30.5 mmol) in THF (300 ml). The mixture was stirred and heated under reflux for 1 h and 3-iodo-1-(3-phenylselanyl)propane 233 (9.914 g, 30.4 mmol) was added. The mixture was stirred and heated under reflux for a further 2 h. The salts formed were removed by filtration on a celite bed and the solution was evaporated to dryness to yield an intractable mixture of unidentified products.

89) 1-[(3-(Phenylselanyl)propyl]imidazole (339)

![Chemical structure of imidazole 204 and product (339)]

Imidazole 204 (0.500 g, 7.34 mmol) was added to sodium hydride (0.260 g, 11.02 mmol) in THF (300 ml). The mixture was stirred and heated under reflux for 1 h and 3-iodo-1-(3-phenylselanyl)propane 233 (2.390 g, 7.34 mmol) was added. The mixture was stirred and heated under reflux for a further 2 h. The salts formed were removed by filtration on a celite bed and the solution was evaporated to dryness to yield a tan solid. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum / dichloromethane followed by ethyl acetate / methanol as eluent to yield 1-[(3-(phenylselanyl)propyl]imidazole 339, as a yellow oil (0.787 g, 41%), (Found: M\(^+\), 266.0328. C\(_{12}\)H\(_{14}\)N\(_2\)Se requires M\(^+\), 266.0322); \(\nu\) max / cm\(^{-1}\) 3424, 2089, 1644, 1579, 1509, 1478, 1438, 1229 and 1080; \(\delta\)\(_H\) 2.04-2.13 (2 H, m, 2'-CH\(_2\)), 2.76-2.82 (2 H, t, J 6.9, CH\(_2\)SePh), 4.02-4.08 (2 H, t, J 6.8, NCH\(_2\)), 6.86 (1 H, s, Im-5-H), 7.06 (1 H, s, Im-4-H), 7.25-7.29 (3 H, m, Ph-H), 7.44-7.48 (2 H, m, Ph-H) and 7.49 (1 H, s, Im-2-H); \(\delta\)\(_C\) (62.5 MHz) 23.93 (2'-CH\(_2\)), 30.90 (CH\(_2\)SePh), 45.97 (NCH\(_2\)), 127.34 (Ar-CH), 129.21 (Ar-CH), 129.47 (Ar-CH) and 133.06 (Ar-CH); \(m/\ell\) 266 (M\(^+\), 89%), 185 (26), 157 (28), 109 (72) and 81 (100).
90) 1,3-Di[3-(phenylselanyl)propyl]-IH-imidazol-3-ium iodide (340)

Imidazole 204 (0.716 g, 10.52 mmol) was added to sodium hydride (0.379 g, 15.78 mmol) in THF (300 ml). The mixture was stirred and heated under reflux for 1 h and 3-iodo-1-(3-phenylselanyl)-propane 233 (6.853 g, 21.03 mmol) was added. The mixture was stirred and heated under reflux for a further 2 h. The salts formed were removed by filtration on a celite bed and the solution was evaporated to dryness to yield a tan residue, which was purified by column chromatography using neutral alumina as absorbent with light petroleum / dichloromethane followed by ethyl acetate / methanol as eluent to yield 1,3-di[3-(phenylselanyl)propyl]-IH-imidazol-3-ium iodide 340, as a yellow oil (0.973 g, 20%); \( \nu_{\text{max}} / \text{cm}^{-1} \) 3071, 1578, 1561, 1478, 1437, 1166 and 918; \( \delta_H \) 2.27-2.32 (4 H, m, 2'-CH\(_2\)), 2.89-2.95 (4 H, t, J 6.8, CH\(_2\)SePh), 4.43-4.49 (4 H, t, J 7.0, NCH\(_2\)), 6.89 (1 H, s, Im-4(5)-H), 7.10 (1 H, s, Im-4(5)-H), 7.25-7.29 (6 H, m, Ph-H), 7.47-7.50 (4 H, m, Ph-H) and 10.08 (1 H, s, Im-2-H); \( \delta_C \) 23.98 (2'-CH\(_2\)), 30.50 (CH\(_2\)SePh), 49.87 (NCH\(_2\)), 122.67, 127.97, 129.17 (q-C), 129.72, 129.87 and 137.27.

91) Attempted preparation of 1-[3-(Phenylselanyl)propyl]-1H-2-imidazolcarbaldehyde (338) (from 1-[3-(phenylselanyl)propyl]imidazole 339)

1-[3-(Phenylselanyl)propyl]imidazole 339 (0.309 g, 1.16 mmol) was dissolved in THF (100 ml) and a solution of n-butyllithium (0.70 ml, 1.76 mmol) added dropwise to the stirred solution at -78 °C. The solution was stirred at 0 °C for a further 40 min and DMF (0.23 ml, 3.48 mmol) added dropwise. The solution was stirred overnight at ambient temperature and evaporated to dryness. Saturated ammonium chloride (50 ml) and water (100 ml) was added to the residue. The aqueous mixture was extracted with dichloromethane (3 x 50 ml) and the organic extracts washed with brine (2 x 50 ml). The organic extracts were evaporated to dryness, but only the starting 1-[3-(phenylselanyl)propyl]imidazole 339 was recovered.
92) 2-(Diethoxymethyl)imidazole (181)

\[
\begin{align*}
&\text{N} \quad \text{CHO} \\
&\text{H} \\
&\text{181}
\end{align*}
\]

\[
\begin{align*}
&\text{N} \quad \text{CH(OEt)₂} \\
&\text{H} \\
&\text{341}
\end{align*}
\]

Imidazole-1H-2-carbaldehyde 181 (0.80 g, 3.7 mmol) was dissolved in dry ethanol (150 ml), and concentrated sulfuric acid (0.5 ml, H₂SO₄ > 96%) added. The solution was stirred and heated under reflux for 4 h. The solution was cooled and neutralised with solid sodium carbonate and filtered. The filtrate was evaporated to dryness and the crude product purified by column chromatography using neutral alumina as absorbent with ethyl acetate as the eluent to yield white needles of 2-(diethoxymethyl)imidazole 341 (1.22 g, 86%); mp 114-116 °C (lit. 137, mp 115-116 °C); δH 1.22-1.28 (6 H, t, J 17.5, CH₃), 3.58-3.73 (4 H, m, CH₂), 5.61 (1 H, s, CH(OEt)₂) and 7.05 (2 H, brs, Im-H); δC 15.10 (CH₃), 62.00 (CH₂), 96.71 (CH(OEt)₂), 115.22 (Im-CH), 128.94 (Im-CH) and 145.80 (2-C).

93) 2-Diethoxymethyl-1-[3-(phenylselanyl)propyl]-1H-imidazole (342)

\[
\begin{align*}
&\text{N} \quad \text{CH(OEt)₂} \\
&\text{H} \\
&\text{341}
\end{align*}
\]

\[
\begin{align*}
&\text{N} \quad \text{CH(OEt)₂} \\
&\text{H} \\
&\text{342}
\end{align*}
\]

2-(Diethoxymethyl)imidazole 341 (0.781 g, 2.1 mmol) was added to sodium hydride (78 mg, 3.2 mmol) in THF (200 ml). The mixture was stirred and heated under reflux for 1 h and 3-iodo-1-(3-phenylselanyl)-propane 233 (0.711 g, 2.1 mmol) was added. The mixture was stirred and heated under reflux for a further 2 h. The salts formed were removed by filtration on a celite bed and the solution was evaporated to dryness to yield a tan solid. The crude product was purified by column chromatography using neutral alumina as absorbent with dichloromethane/light petroleum followed by ethyl acetate as eluent to give 2-diethoxymethyl-1-[3-(phenylselanyl)propyl]-1H-imidazole 342, as a colourless oil (0.498 g, 64%), (Found: M⁺, 368.1003. C₁₇H₂₄N₂O₂Se requires M, 368.1002); νmax / cm⁻¹ 2978, 2246, 1579, 1498, 1478, 1438, 1105, 1060, 910 and 732; δH 1.17-1.23 (6 H, t, J 7.0, CH₃), 2.11-2.23 (2 H, m, 2'-CH₂), 2.85-2.90 (2 H, t, J 7.3, CH₂SePh), 3.46-3.58 (2 H, m, diastereotopic-CH₂CH₃), 3.68-3.77 (2 H, m, diastereotopic-CH₂CH₃), 4.23-4.29 (2 H, t, J 7.0, NCH₂), 5.57 [1 H, s, CH(OEt)₂], 6.68 (1 H, s, Im-H), 6.97 (1 H, s, Im-H), 7.26-7.28 (3 H, m, Ph-H) and 7.47-7.51 (2 H, m, Ph-H); δC 15.39 (CH₃), 24.65 (2'-CH₂), 31.64 (CH₂SePh), 46.12 (NCH₂), 63.55
(CH₂CH₃), 99.29 (CH(OEt)₂), 121.22, 127.45, 127.63, 129.49, 129.90 (q-C), 133.28 (Ph-CH) and 145.10 (q-C); m/z 368 (M⁺, 7%), 295 (21), 199 (60), 157 (68), 137 (54), 121 (100), 109 (59), 77 (71), 47 (70) and 41 (61).

94) 1-[3-(Phenylselanyl)propyl]-1H-2-imidazolcarbaldehyde (338)

\[
\begin{align*}
\text{342} & \quad \rightarrow \quad \text{338} \\
\end{align*}
\]

2-(Diethoxymethyl)-1-[3-(phenylselanyl)propyl]-1H-imidazole 342 (0.444 g, 1.21 mmol) was dissolved in ethanol (300 ml), concentrated hydrochloric acid (5 ml, 31-34% w/w solution) and water (100 ml) added. The solution was heated under reflux for 2 h. The solution was cooled, and neutralised with solid sodium carbonate and filtered. The filtrate was evaporated to leave approximately 100 ml of solution, which was extracted with dichloromethane (2 x 50 ml). The combined organic extracts dried (MgSO₄), and evaporated to dryness to yield 1-[3-(phenylselanyl)propyl]-1H-2-imidazolcarbaldehyde 338, as a yellow oil (0.207 g, 58%), (Found: M⁺, 294.0271. C₁₃H₁₄N₂OSe requires M⁺, 294.0271); v max cm⁻¹: 2936, 1684 (C=O), 1475, 1437, 1335, 1157, 771 and 737; δH 2.03-2.11 (2 H, m, 2'-CH₂), 2.72-2.77 (2 H, t, J 7.1, CH₂SePh), 4.37-4.43 (2 H, t, J 6.9, NCH₂), 7.05 (1 H, s, Im-H), 7.17-7.19 (4 H, m, Im-H and Ph-H) and 7.37-7.41 (2 H, m, Ph-H); δC (62.5 MHz) 23.73 (2'-CH₂), 30.80 (CH₂SePh), 47.01 (NCH₂), 126.47, 127.19, 129.13, 131.50, 132.93, 137.08 (q-C) 143.14 (q-C) and 181.75 (CHO); m/z 294 (M⁺, 16%), 265 (5), 157 (29), 137 (100), 109 (39) and 77 (66).

95) Attempted radical cyclisation of 1-[3-(phenylselanyl)propyl]-1H-2-imidazolcarbaldehyde (338)

\[
\begin{align*}
\text{338} & \quad \rightarrow \quad \text{339} \\
\end{align*}
\]

A solution of tri-n-butyltin hydride (0.23 ml, 0.87 mmol) and AIBN (47 mg, 0.29 mmol) in toluene (50 ml) was added to 1-[3-(phenylselanyl)propyl]-1H-2-imidazolcarbaldehyde 338 (0.170 g, 0.58 mmol) in acetonitrile (100 ml) at reflux over 5 h. The solution was stirred and heated under reflux for a further 1 h. The standard work up procedure for the radical cyclisation
of imidazoles and benzimidazoles was followed to yield a tan solid, which was purified by prep-TLC using neutral alumina as absorbent with ethyl acetate as eluent to yield 1-[3-(phenylselanyl)propyl]imidazole 339, as a yellow oil (34 mg, 22%). Spectra identical with that previously recorded.

96) 1-(3-Bromopropyl)-4-phenyl-1H-imidazole (344)

\[
\begin{align*}
\text{Ph} & \quad \text{N} \\
\text{343} & \quad \text{344} \\
\end{align*}
\]

4-Phenyl-1H-imidazole 343 (1.500 g, 10.40 mmol) was added to sodium hydride (0.374 g, 15.6 mmol) in THF (300 ml). The mixture was stirred and heated under reflux for 1 h and 1,3-dibromopropane (10.6 ml, 0.104 mol) was added. The mixture was stirred and heated under reflux for a further 2 h. The salts formed and unreacted imidazole were removed by filtration on a celite bed. The solution was evaporated to yield a crude oil, which was purified by column chromatography using neutral alumina with light petroleum / dichloromethane followed by ethyl acetate as eluent to yield 1-(3-bromopropyl)-4-phenyl-1H-imidazole 344, as a colourless oil (1.350 g, 49%); (Found: M⁺, 264.0262. C₁₂H₁₃N₂Br requires M, 264.0263); \(\nu_{\text{max}} / \text{cm}^{-1}\) 1605, 1482, 1368, 1280, 1195, 1067, 1046 and 941; \(\delta_H\) 2.26-2.37 (2H, m, \(2'\)-CH₂), 3.33-3.38 (2H, t, J 6.1, CH₂Br), 4.14-4.20 (2H, t, J 6.5, NCH₂), 7.22 (1H, s, Im-5-H), 7.23-7.27 (1H, m, Ph-H), 7.35-7.41 (2H, m, Ph-H), 7.56 (1H, s, Im-2-H) and 7.76-7.79 (2H, m, Ph-H); \(\delta_C\) (62.5 MHz) 29.36 (2'-CH₂), 33.28 (CH₂Br), 44.67 (NCH₂), 114.47, 124.70, 126.70, 126.83, 128.55 and 137.44; \(m/z\) 266 (22%), 264 (M⁺, 23), 184 (10), 158 (32), 157 (50), 143 (33), 130 (97), 103 (93), 102 (70), 89 (100), 77 (35), 51 (45) and 41 (100).

97) 1-(4-Bromobutyl)-4-phenyl-1H-imidazole (345)

\[
\begin{align*}
\text{Ph} & \quad \text{N} \\
\text{343} & \quad \text{345} \\
\end{align*}
\]

4-Phenyl-1H-imidazole 343 (1.838 g, 12.74 mmol) was added to sodium hydride (0.459 g, 19.11 mmol) in THF (300 ml). The mixture was stirred and heated under reflux for 1 h, and 1,4-dibromobutane (15.2 ml, 0.127 mol) was added. The mixture was stirred and heated under reflux for a further 2 h. The salts formed and unreacted imidazole were removed by filtration on a celite bed. The solution was evaporated to yield a crude slurry, which was purified by column
chromatography using neutral alumina as absorbent with light petroleum / dichloromethane followed by ethyl acetate as eluent to yield 1-(4-bromobutyl)-4-phenyl-1H-imidazole 345, as a colourless oil (1.417 g, 40%); (Found: M+, 278.0419. C_{13}H_{15}N_{2}Br requires M, 278.0419); \nu_{\text{max}} / \text{cm}^{-1} 1606, 1554, 1501, 1483, 1444, 1195 and 1068; \delta_{H} 1.81-1.88 (2 H, m, 2'(3')-CH_{2}), 1.94-2.01 (2 H, m, 2'(3')-CH_{2}), 3.36-3.41 (2 H, t, J 6.2, CH_{2}Br), 3.93-3.99 (2 H, t, J 6.7, NCH_{2}), 7.19-7.21 (1 H, m, Im-5-H), 7.24-7.28 (1 H, m, Ph-H), 7.34-7.41 (2 H, m, Ph-H), 7.48-7.49 (1H, m, Im-2-H) and 7.75-7.79 (2 H, m, Ph-H); \delta_{C} 28.97, 29.92, 32.92 (CH_{2}Br), 48.68 (NCH_{2}), 116.81, 127.02, 129.13, 130.93, 131.58, 131.90, 136.37 (q-C), 139.55 and 144.69 (q-C); m/z 280 (47%), 278 (M+, 42), 199 (100), 145 (39), 133 (33), 89 (88), 77 (31) and 55 (78).

98) 1-(4-Bromobutyl)-4-nitro-1H-imidazole (346)

4 (5)-Nitro-1H-imidazole 171 (1.622 g, 14.3 mmol) was added to sodium hydride (0.528 g, 22.0 mmol) in THF (300 ml). The mixture was stirred and heated under reflux for 1 h and 1,4-dibromobutane (17.0 ml, 0.143 mmol) was added. The mixture was stirred and heated under reflux for a further 2 h. The salts formed and unreacted imidazole were removed by filtration on a celite bed. The solution was evaporated to yield a crude slurry, which was purified by column chromatography using silica gel as absorbent with light petroleum / dichloromethane followed by ethyl acetate as eluent to yield brown needles of 1-(4-bromobutyl)-4-nitro-1H-imidazole 346 (1.55 g, 44%), mp 34-35 °C (Found: M+, 246.9957. C_{7}H_{10}N_{2}BrO_{2} requires M, 246.9957); \nu_{\text{max}} / \text{cm}^{-1} 2949, 1638, 1544 (NO_{2}), 1490, 1403, 1383 and 1335; \delta_{H} 1.87-1.95 (2 H, m, 3'-CH_{2}), 2.00-2.09 (2 H, m, 2'-CH_{2}), 3.41-3.46 (2 H, t, J 6.1, CH_{2}Br), 4.06-4.12 (2 H, t, J 7.0, NCH_{2}), 7.45-7.46 (1 H, d, J 1.6, Im-2-H) and 7.79-7.80 (1H, d, J 1.6, Im-5-H); \delta_{C} 29.54, 29.68, 32.48 (CH_{2}Br), 47.99 (NCH_{2}), 119.49 (2-CH), 136.32 (5-CH) and 148.64 (q-C, 4-C); m/z 248 (M+, 9%), 168 (100), 137 (14), 135 (13), 122 (36) and 55 (91).

99) 1-Phenyl-6,7-dihydro-5H-pyrrolo[1,2-c]imidazole (347)
A solution of tri-n-butyltin hydride (0.66 ml, 2.50 mmol) and AIBN (0.137 g, 0.84 mmol) in toluene (50 ml) was added to 1-(3-bromopropyl)-4-phenyl-1H-imidazole 344 (0.440 g, 1.67 mmol) in toluene (350 ml) at reflux over 5 h. The solution was stirred and heated under reflux for a further 1 h. The standard work up procedure for the radical cyclisation of imidazoles and benzimidazoles was followed to yield a mixture of 1-phenyl-6,7-dihydro-5H-pyrrolo[1,2-c]imidazole 347 and 1-propyl-4-phenylimidazole 348, as a tan solid (0.169 g, 1.0 / 1.1 respectively by 1H NMR spectroscopic analysis of relative peak areas); 347: δH 2.71-2.79 (2 H, m, 6-CH2), 3.06-3.12 (2 H, t, 17.2, CCH2), 4.05-4.10 (2 H, t, 17.2, NCH2), 7.18-7.21 (1 H, m, Ph-H), 7.36-7.42 (2 H, m, Ph-H) and 7.73-7.76 (2 H, m, Ph-H); 348: δH 0.95-1.01 (3 H, t, 17.4, CH3), 1.83-1.91 (2 H, m, 2'-CH2), 3.92-3.97 (2 H, t, 17.0, NCH2), 7.21 (1H, s, Im-5-H), 7.25-7.27 (1 H, m, Ph-H), 7.35-7.41 (2 H, m, Ph-H), 7.60 (1H, s, Im-2-H) and 7.77-7.80 (2 H, m, Ph-H).

100) Radical Cyclisation of 1-(4-bromobutyl)-4-phenyl-1H-imidazole (345)

A solution of tri-n-butyltin hydride (0.76 ml, 2.85 mmol) and AIBN (0.156 g, 0.95 mmol) in toluene (50 ml) was added to 1-(4-bromobutyl)-4-phenyl-1H-imidazole 345 (0.530 g, 1.90 mmol) in toluene (350 ml) at reflux over 5 h. The solution was stirred and heated under reflux for a further 1 h. The standard work up procedure for the radical cyclisation of imidazoles and benzimidazoles was followed to yield a yellow oil mixture of 1-phenyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine 349 and 2-phenyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine 350 (0.185 g, 2.5 / 1.0 respectively by GC-MS analysis); 349: δH 1.92-2.01 (4 H, m, 6 and 7-CH2), 2.98-3.03 (2 H, t, J 6.4, CCH2), 4.01-4.06 (2 H, t, J 5.6, NCH2), 7.24-7.76 (5 H, m, Ph-H) and 7.48 (1 H, s, Im-3-H); m/z 198 (M+, 74%), 197 (100), 170 (34), 169 (58), 157 (22), 115 (31), 103 (24) and 77 (22); 350: δH 1.87-1.90 (4 H, m, 6 and 7-CH2), 2.93-2.98 (2 H, t, J 5.7, CCH2), 3.95-4.01 (2 H, t, J 6.1, NCH2), 7.06 (1 H, s, Im-3-H) and 7.24-7.76 (5 H, m, Ph-H); m/z 198 (M+, 100%), 197 (39), 170 (20), 169 (20), 130 (24), 104 (26) and 77 (27); (Found: M+, 198.1157. C13H14N2 requires M, 198.1157).
101) Attempted radical cyclisation of 1-(4-Bromobutyl)-4-nitro-1H-imidazole (346)

A solution of tri-n-butyltin hydride (0.45 ml, 1.68 mmol) and AIBN (92 mg, 0.56 mmol) in toluene (50 ml) was added to 1-(4-bromobutyl)-4-nitro-1H-imidazole 346 (0.259 g, 1.12 mmol) in toluene (250 ml) at reflux over 5 h. The solution was stirred and heated under reflux for a further 1 h. The reaction solution was cooled to ambient temperature and the solvent was evaporated to dryness to yield a tan residue. Ethyl acetate (50 ml) and saturated potassium fluoride solution (50 ml) were added and the mixture agitated vigorously for 2 h. The organic phase was extracted, dried (MgSO₄), and evaporated to dryness to yield a yellow residue, which was purified by column chromatography using silica gel as absorbent with light petroleum followed by ethyl acetate as eluent, but only unidentifiable products were isolated.

102) 1-(Phenylsulfonyl)-1H-pyrrole (352)

![Diagram of 1-(Phenylsulfonyl)-1H-pyrrole]

Pyrrole 351 (9.02 ml, 0.13 mol) and sodium hydride (4.68 g, 0.195 mol) in THF (450 ml) were stirred, and heated under reflux 3.5 h. Benzenesulfonyl chloride (34.24 ml, 0.27 mol) was added dropwise, and the mixture heated under reflux for a further 2 h. The residual salts were removed by filtration on a celite bed, and the solution was evaporated to dryness to yield a black residue, which was purified by column chromatography using silica gel as absorbent with light petroleum / dichloromethane as eluent to yield 1-(phenylsulphonyl)-1H-pyrrole 352, as colourless needles (18.43 g, 66%), mp 88-90 °C (lit.141, mp 89-89.5 °C); δH 6.30-6.32 (2 H, m, pyrrole-H), 7.16-7.18 (2 H, m, pyrrole-H), 7.48-7.61 (3 H, m, Ph-H) and 7.84-7.88 (2 H, m, Ph-H).

103) 1-(1H-3-Pyrrolyl)-1-ethanone [3-acetylpyrrole, 353]

![Diagram of 1-(1H-3-Pyrrolyl)-1-ethanone]

Acetic anhydride (7 ml) was added to a suspension of anhydrous aluminium chloride (20.00 g, 0.150 mol) in 1,2-dichloroethane (50 ml). The mixture was stirred at ambient temperature for 10 min and a solution of 1-(phenylsulfonyl)-1H-pyrrole 352 (4.91 g, 22.2 mmol) in
1,2-dichloroethane (50 ml) added. The reaction mixture was stirred for 2 h, quenched with water (50 ml) and extracted with dichloromethane (2 x 50 ml). The combined organic extracts were evaporated to dryness to yield red-brown crystals of 1-[1-(phenylsulfonyl)-1H-3-pyrrolyl]-1-ethanone 354 (4.52 g, 17.2 mmol), which were added to dioxane (75 ml). Sodium hydroxide solution (75 ml, 5 M) was added, and the solution stirred for 36 h. The hydroxide solution was extracted with ethyl acetate (3 x 50 ml), and the combined organic extracts dried (MgSO4) and evaporated to dryness to yield brown crystals of 3-acetylpyrrole (1.99 g, 82%), mp 106-107 °C (lit. 141, mp 105-107 °C); δH 2.36 (3 H, s, CH3), 6.59-6.60 (1 H, m, pyrrole-5-H), 6.70-6.73 (1 H, m, pyrrole-4-H) and 7.35-7.37 (1 H, m, pyrrole-2-H); δC 28.99 (CH3), 110.67 (pyrrole-5-CH), 121.25 (pyrrole-4-CH), 125.20 (pyrrole-2-CH), 128.08 (pyrrole-3-C) and 195.82 (CO).

General Procedure for the alkylation of pyrroles

1-(3-Bromopropyl)-1H-3-pyrrolyl]-1-ethanone 356

3-Acetylpyrrole 353 (0.310 g, 2.84 mmol) was added to sodium hydride (0.136 mg, 5.68 mmol) in THF (150 ml). The mixture was stirred for 30 min at ambient temperature and 1,3-dibromopropane (2.89 ml, 28.40 mol) was added. The mixture was stirred and refluxed for 2 h. The residual salts formed were removed by filtration on a celite bed and the solution was evaporated to dryness to yield a brown slurry, which was purified by column chromatography using silica gel as absorbent with light petroleum / dichloromethane as eluent to yield 1-[1-(3-bromopropyl)-1H-3-pyrrolyl]-1-ethanone 356, as a yellow oil (0.332 g, 51%); (Found: M+, 229.0103. C9H12NBrO requires M, 229.0103); νmax / cm⁻¹ 1652 (C=O), 1530 and 1255; δH 2.23-2.33 (2 H, m, 2'-CH2), 2.40 (3 H, s, CH3), 3.29-3.34 (2 H, t, J 6.1, CH2Br), 4.08-4.13 (2 H, t, J 6.4, CH2N), 6.58-6.60 (1 H, m, pyrrole-4,5-H), 6.64-6.66 (1 H, m, pyrrole-2-H) and 7.29-7.31(1 H, m, pyrrole-H); δC 27.45 (CH3), 29.93 (2'-CH2), 33.99 (CH2Br), 48.00 (NCH2), 110.11 (pyrrole-CH), 122.73 (pyrrole-CH), 126.13 (pyrrole-CH), 126.77 (pyrrole-3-C) and 193.75 (CO); m/z 232 (MH2+, 96%), 217 (100), 150 (97), 135 (98), 121 (19), 106 (54), 94 (72) and 80 (21).
105) 1-[1-(4-Bromobutyl)-1H-3-pyrrolyl]-1-ethanone (357)

\[
\begin{array}{c}
\text{COCH}_3 \\
\text{353}\end{array} \longrightarrow \begin{array}{c}
\text{COCH}_3 \\
\text{357}\end{array}
\]

The general procedure for the alkylation of pyrroles was followed. 3-Acetylpyrrole 353 (0.620 g, 5.69 mmol), sodium hydride (0.273 mg, 11.38 mmol) and 1,4-dibromobutane (6.75 ml, 56.90 mol) in THF (150 ml) gave a tan residue, which was purified by column chromatography using silica gel as absorbent with light petroleum / dichloromethane as eluent to yield 1-[1-(4-bromobutyl)-1H-3-pyrrolyl]-1-ethanone 357, as a yellow oil (0.744 g, 56%); (Found: M$, C_{10}H_{14}NBrO requires M, 243.0259); $\nu_{\text{max}}/\text{cm}^{-1}$ 1654 (C=O), 1530, 1201 and 933; $\delta_{H}$ 1.81–1.86 (2 H, m, 3’-CH$_2$), 1.94–2.00 (2 H, m, 2’-CH$_2$), 2.39 (3 H, s, CH$_3$), 3.37–3.42 (2 H, t, $J_{6.6}$, CH$_2$Br), 3.90–3.96 (2 H, t, $J_{6.7}$, CH$_2$N), 6.58–6.62 (2 H, m, pyrrole-4,5-H) and 7.26-7.28 (1 H, m, pyrrole-2-H); $\delta_C$ (62.5 MHz) 28.98 (CH$_3$), 29.41 (3’-CH$_2$), 29.54 (2’-CH$_2$), 32.01 (CH$_2$Br), 49.19 (NCH$_2$), 109.31 (pyrrole-CH), 121.98 (pyrrole-CH) and 125.44 (pyrrole-CH); m/z 245 (MH$_2^+$, 39%), 228 (88), 164 (100), 135 (25), 122 (57), 109 (14), 94 (75) and 80 (23).

106) 1-[1-(5-Bromopentyl)-1H-3-pyrrolyl]-1-ethanone (358)

\[
\begin{array}{c}
\text{COCH}_3 \\
\text{353}\end{array} \longrightarrow \begin{array}{c}
\text{COCH}_3 \\
\text{358}\end{array}
\]

The general procedure for the alkylation of pyrroles was followed. 3-Acetylpyrrole 353 (0.500 g, 4.59 mmol), sodium hydride (0.220 mg, 9.17 mmol) and 1,5-dibromopentane (6.25 ml, 45.90 mol) in THF (150 ml) gave a tan residue, which was purified by column chromatography using silica gel as absorbent with light petroleum / dichloromethane as eluent to yield 1-[1-(5-bromopentyl)-1H-3-pyrrolyl]-1-ethanone 358, as a yellow oil (0.743 g, 63%); $\nu_{\text{max}}/\text{cm}^{-1}$ 1652 (C=O), 1531, 1453, 1386, 1251, 1103 and 933; $\delta_{H}$ 1.45–1.50 (2 H, m, 3’-CH$_2$), 1.79–1.91 (4 H, m, 2’ and 4’-CH$_2$), 2.39 (3 H, s, CH$_3$), 3.37-3.42 (2 H, t, $J_{6.6}$, CH$_2$Br), 3.88-3.93 (2 H, t, $J_{7.0}$, CH$_2$N), 6.57-6.62 (2 H, m, pyrrole-4,5-H) and 7.26-7.28 (1 H, m, pyrrole-2-H); $\delta_C$ (62.5 MHz) 25.09, 26.98 (CH$_3$), 30.25, 32.01 (2’-CH$_2$), 33.10 (CH$_2$Br), 49.81 (NCH$_2$), 109.31 (pyrrole-CH), 122.02 (pyrrole-CH), 125.48 (pyrrole-CH) and 193.35 (CO).
107) 1-((3-Bromopropyl)-1H-2-pyrrolecarbaldehyde (359)

The general procedure for the alkylation of pyrroles was followed.
Pyrrole-2-carbaldehyde 177 (1.50 g, 15.8 mmol), sodium hydride (0.76 g, 31.7 mmol) and 1,3-dibromopropane (16.0 ml, 0.16 mol) in THF (150 ml) gave a brown slurry, which was purified by column chromatography using silica gel as absorbent with light petroleum / dichloromethane as eluent to yield 1-((3-bromopropyl)-1H-2-pyrrolecarbaldehyde 359, as a yellow oil (2.43 g, 71%), (Found: M+ 214.9946. C8H10NBrO requires M, 214.9946); \( \nu_{\text{max}} \) / cm\(^{-1} \) 2805, 1526, 1661 (C=O), 1369 and 885; \( \delta_{\text{H}} \) 2.19-2.29 (2 H, m, 2'-CH\(_2\)), 3.20-3.25 (2 H, t, \( J \) 6.2, CH\(_2\)Br), 4.37-4.42 (2 H, t, \( J \) 6.4, NCH\(_2\)), 6.15-6.18 (1 H, m, pyrrole-4-H), 6.68-6.90 (1 H, m, pyrrole-5-H), 6.97 (1 H, m, pyrrole-3-H) and 9.45 (1 H, s, CHO); \( \delta_{\text{C}} \) 29.33 (2'-CH\(_2\)), 29.37 (3'-CH\(_2\)), 47.45 (NCH\(_2\)), 110.09 (pyrrole-5-CH), 125.66 (pyrrole-4-CH), 131.56 (pyrrole-3-CH), 132.38 (pyrrole-2-C) and 179.63 (CHO); \( m/z \) 215 (M+, 18%), 186 (11), 136 (100), 108(92), 94 (89) and 80 (100).

108) 1-((4-Bromobutyl)-1H-2-pyrrolecarbaldehyde (360)

The general procedure for the alkylation of pyrroles was followed.
Pyrrole-2-carbaldehyde 177 (1.65 g, 17.3 mmol), sodium hydride (0.83 g, 34.6 mmol) and 1,4-dibromobutane (19.1 ml, 0.16 mol) in THF (150 ml) gave a tan residue, which was purified by column chromatography using silica gel as absorbent with light petroleum / dichloromethane as eluent to yield 1-((4-bromobutyl)-1H-2-pyrrolecarbaldehyde 360, as a yellow oil (2.46 g, 62%); (Found: M+, 228.9991. C\(_9\)H\(_{12}\)NBrO requires M, 229.0103); \( \nu_{\text{max}} \) / cm\(^{-1} \) 2800, 1603 (C=O), 1525, 1444, and 609; \( \delta_{\text{H}} \) 1.85-1.92 (4 H, m, 2' and 3'-CH\(_2\)), 3.37-3.42 (2 H, t, \( J \) 6.2, CH\(_2\)Br), 4.33-4.38 (2 H, t, \( J \) 6.6, CH\(_2\)N), 6.22-6.25 (1 H, m, pyrrole-4-H), 6.93-6.95 (2 H, m, pyrrole-3 and 5-H) and 9.53 (1 H, s, CHO); \( \delta_{\text{C}} \) 29.33 (3'-CH\(_2\)), 29.37 (2'-CH\(_2\)), 32.58 (CH\(_2\)Br), 47.82 (NCH\(_2\)), 109.52 (pyrrole-5-CH), 124.71 (pyrrole-4-CH), 130 87 (pyrrole-3-CH), 131.08
109) 1-(5-Bromopentyl)-1H-2-pyrrolecarbaldehyde (361)

\[
\begin{array}{c}
\text{CHO} \\
\uparrow \\
\text{Br}
\end{array}
\]

\[
\begin{array}{c}
\text{CHO} \\
\downarrow \\
\text{COCH}_3
\end{array}
\]

The general procedure for the alkylation of pyrroles was followed. Pyrrole-2-carbaldehyde 177 (1.67 g, 17.6 mmol), sodium hydride (0.84 g, 35.2 mmol) and 1,5-dibromopentane (21.5 ml, 0.16 mol) in THF (150 ml) gave a tan residue, which was purified by column chromatography using silica gel as absorbent with light petroleum / dichloromethane as eluent to yield 1-(5-bromopentyl)-1H-2-pyrrolecarbaldehyde 361, as a yellow oil (2.11 g, 45%); \( \nu \text{max} \ cm^{-1} 2805, 1660 (\text{C}=\text{O}), 1572, 1321, 885, 838 \) and 763; \( \delta_H 1.38-1.48 (2 \ H, m, 3'\text{-CH}_2), 1.72-1.93 (4 \ H, m, 2' \text{ and } 4'\text{-CH}_2), 3.36-3.42 (2 \ H, t, J 6.7, \text{CH}_2\text{Br}), 4.28-4.43 (2 \ H, t, J 7.2, \text{NCH}_2), 6.21-6.23 (1 \ H, m, \text{pyrrole-4-H}), 6.92-6.94 (2 \ H, m, \text{pyrrole-3 and 5-H}) \) and 9.52 (1 H, s, CHO); \( \delta_C 24.25 (3'\text{-CH}_2), 30.49 (4'\text{-CH}_2), 32.13 (2'\text{-CH}_2), 33.52 (\text{CH}_2\text{Br}), 48.24 (\text{NCH}_2), 109.36 (\text{pyrrole-5-CH}), 109.93 (\text{pyrrole-4-CH}), 124.95 (\text{pyrrole-3-CH}), 131.31 (\text{q-C, pyrrole-2-C}) \) and 179.28 (CHO); \( m/z 245 (M^+, 89\%), 229 (17), 217 (22), 165 (60), 137 (100), 123 (38), 109 (59), 95 (32) \) and 81 (52).

General procedure for the radical cyclisation of pyrroles. 

110) 1-(2,3-Dihydro-1H-7-pyrrolizinyl)-1-ethanone (362)

A solution of tri-n-butyltin hydride (0.45 ml, 1.68 mmol) and AIBN (63 mg, 0.38 mmol) in toluene (50 ml) was added to 1-[1-(3-bromopropyl)-1H-3-pyrrolyl]-1-ethanone 356 (0.175 g, 0.76 mmol) in toluene (200 ml) at reflux over 5 h. The reaction solution was cooled to ambient temperature and the solvent was evaporated to dryness to yield a tan residue. Ethyl acetate (50 ml) and saturated potassium fluoride solution (50 ml) were added and the mixture agitated.
vigorously for 2 h. The organic phase was extracted, dried (MgSO₄) and evaporated to dryness to yield a yellow residue, which was purified by column chromatography using silica gel as absorbent with light petroleum / dichloromethane as eluent to yield 1-propyl-1H-3-pyrrolyl-1-ethanone 363, as a yellow oil (12 mg, 10%); (Found: M⁺, 151.0995. C₉H₁₃NO requires M⁺, 151.0997); νmax / cm⁻¹ 1651 (C=O), 1531, 1199 and 1102; δH 0.90-0.95 (3 H, t, J 7.4, CH₃), 1.77-1.86 (2 H, m, 2-CH₂), 2.40 (3 H, s, COCH₃), 3.82-3.88 (2 H, t, J 7.1, NCH₂), 6.57-6.62 (2 H, m, pyrrole-H) and 7.27-7.28 (1 H, m, pyrrole-H); δC (62.5 MHz) 11.05 (CH₃), 24.37 (2'-CH₂), 26.98 (COCH₃), 51.76 (NCH₂), 109.17 (pyrrole-CH), 122.07 (pyrrole-CH) and 125.59 (pyrrole-CH); m/z 151 (M⁺, 45%), 136 (100), 94 (48) and 43 (21). Further elution with light petroleum / dichloromethane yielded 1-(2,3-dihydro-1H-7-pyrrolizinyl)-1-ethanone 362, as a yellow oil (52 mg, 46%); (Found: M⁺, 149.0841. C₉H₁₁NO requires M⁺, 149.0841); νmax / cm⁻¹ 1646 (C=O), 1535, 1430, 1371, 1294, 1245 and 1206; δH 2.37 (3 H, s, COCH₃), 2.48-2.62 (2 H, m, 2-CH₂), 3.07-3.13 (2 H, t, J 6.4, 8-CH₂), 3.95-4.00 (2 H, t, J 7.2, NCH₂), 6.55-6.56 (1 H, m, pyrrole-5-H) and 6.61-6.62 (1 H, s, pyrrole-6-H); δC (62.5 MHz) 23.55 (2-CH₂), 26.09 (1-CH₂), 27.08 (COCH₃), 46.63 (NCH₂), 113.29 (pyrrole-5-CH) and 114.82 (pyrrole-6-CH); m/z 149 (M⁺, 43%), 134 (100), 106 (15), 77 (7), 51 (7) and 43 (9).

111) 1-(5,6,7,8-Tetrahydro-1-indolizinyl)-1-ethanone (364)

A solution of tri-n-butyltin hydride (0.74 ml, 2.78 mmol) and AIBN (0.114 mg, 0.69 mmol) in toluene (50 ml) was added to 1-[1-(4-bromobutyl)-1H-3-pyrrolyl]-1-ethanone 357 (0.338 g, 1.39 mmol) in toluene (350 ml) at reflux over 5 h. The standard work up procedure for the radical cyclisation of pyrroles was followed to yield a yellow residue, which was purified by column chromatography using silica gel as absorbent with light petroleum / dichloromethane as eluent to yield 1-(5,6,7,8-tetrahydro-1-indolizinyl)-1-ethanone 364, as a yellow oil (0.102 g, 45%); (Found: M⁺, 163.0997. C₁₀H₁₃NO requires M⁺, 163.1000); νmax / cm⁻¹ 1647 (C=O), 1535, 1504, 1319, 1228 and 1206; δH 1.78-1.88 (2 H, m, 7-CH₂), 1.86-1.99 (2 H, m, 6-CH₂), 2.37 (3 H, s, COCH₃), 3.07-3.12 (2 H, t, J 6.4, 8-CH₂), 3.91-3.95 (2 H, t, J 5.9, NCH₂), 6.43-6.44 (1 H, d, J 3.1, pyrrole-3-H) and 6.49-6.50 (1 H, d, J 3.1, pyrrole-2-H); δC 20.53, 23.88, 24.66 (8-CH₂), 28.46 (COCH₃), 46.02 (NCH₂), 110.43 (pyrrole-3-CH), 119.56 (pyrrole-2-CH), 120.47 (pyrrole-8a-C), 136.74 (pyrrole-1-C) and 194.63 (CO); m/z 164 (M⁺, 17%), 163 (48), 149 (21), 148 (100), 122 (22), 120 (30) and 43 (39).
A solution of tri-n-butyltin hydride (0.45 ml, 1.68 mmol) and AIBN (64 mg, 0.39 mmol) in toluene (50 ml) was added to 1-[1-(5-bromopentyl)-1H-3-pyrrolyl]-1-ethanone 358 (0.200 g, 0.78 mmol) in toluene (300 ml) at reflux over 7 h. The standard work up procedure for the radical cyclisation of pyrroles was followed to yield a yellow residue, which was purified by column chromatography using silica gel as absorbent with light petroleum / dichloromethane as eluent to yield 1-pentyl-1H-3-pyrrolyl-1-ethanone 367, as a yellow oil (25 mg, 18%); (Found: M+, 179.1310. C11H17NO requires M, 179.1310); \( \nu \text{max} / \text{cm}^{-1} \) 1652 (C=O), 1531, 1454, 1439, 1386, 1348 and 1251; \( \delta \text{H} \) 0.87-0.92 (3 H, t, J 6.2, CH3), 1.23-1.36 (4 H, m, 7 and 8-CH2), 1.72-1.84 (2 H, m, 6-CH2), 2.39 (3 H, s, COCH3), 3.84-3.90 (2 H, t, J 7.1, NCH2), 6.56-6.58 (1 H, m, pyrrole-H), 6.59-6.61 (1 H, m, pyrrole-H) and 7.25-7.27 (1 H, m, pyrrole-H); \( \delta \text{C} \) 14.27 (CH3), 22.99 (4'-CH2), 27.85 (COCH3), 29.06 (3'-CH2), 31.23 (2'-CH2), 50.75 (NCH2), 109.57 (pyrrole-CH), 122.53 (pyrrole-CH), 126.25 (pyrrole-CH) and 193.92 (CO); \( m/z \) 179 (M+, 19%), 164 (49), 136 (15), 134 (10), 94 (36), 80 (28) and 43 (100). Further elution with light petroleum / dichloromethane yielded 6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-3-carbaldehyde 366, as a yellow oil (75 mg, 54%); (Found: M+, 177.1154. C10H15NO requires M, 177.1154); \( \nu \text{max} / \text{cm}^{-1} \) 1648 (C=O), 1535, 1501, 1438, 1347, 1260, 1251 and 1221; \( \delta \text{H} \) 1.55-1.85 (6 H, m, 6, 7 and 8-CH2), 2.40 (3 H, s, COCH3), 3.28-3.32 (2 H, m, 9-CH2), 3.91-3.95 (2 H, m, NCH2), 6.38-6.39 (1 H, d, J 3.0, pyrrole-3-H) and 6.42-6.43 (1 H, J 3.0, pyrrole-2-H); \( \delta \text{C} \) 22.79, 24.54, 25.87 (COCH3), 28.02 (6-CH2), 30.42 (9-CH2), 46.02 (NCH2), 108.50 (pyrrole-3-CH), 119.86 (pyrrole-2-CH), 120.11 (pyrrole-9a-C) and 194.80 (CO); \( m/z \) 177 (M+, 14%), 162 (26), 134 (15), 55 (16) and 43 (100).

A solution of tri-n-butyltin hydride (1.21 ml, 4.56 mmol) and AIBN (0.188 g, 1.14 mmol) in
toluene (50 ml) was added to 1-(3-bromopropyl)-1H-2-pyrrolecarbaldehyde 359 (0.491 g, 2.28 mmol) in toluene (300 ml) at reflux over 5 h. The standard work up procedure for the radical cyclisation of pyrroles was followed to yield a yellow residue, which was purified by column chromatography using silica gel as absorbent with light petroleum / dichloromethane as eluent to yield a 2,3-dihydro-1H-5-pyrrolizinecarbaldehyde 368, as a yellow oil, (86 mg, 28%); (Found: M⁺, 135.0683. C₉H₉NO requires M, 135.0684; νmax / cm⁻¹ 1652 (C=O), 1472 and 804; δH 2.24-2.60 (2 H, m, 2-CH₂), 2.82-2.88 (2 H, t, J 7.4, 1-CH₂), 4.26-4.32 (2 H, t, J 7.2, NCH₂), 5.97-5.98 (1 H, d, J 3.8, pyrrole-7-H), 6.93-6.94 (1 H, d, J 3.8, pyrrole-6-H) and 9.40 (1 H, s, CHO); δC (62.5 MHz) 24.43 (2-CH₂), 27.54 (1-CH₂), 47.90 (NCH₂), 103.50 (pyrrole-7-CH), 128.68 (pyrrole-6-CH) and 178.49 (CHO); m/z 135 (M⁺, 100%), 120 (17), 106 (55), 79 (51) and 65 (16).

114) 5,6,7,8-Tetrahydro-3-indolizinecarbaldehyde (369)

A solution of tri-n-butyltin hydride (1.15 ml, 4.34 mmol) and AIBN (0.178 g, 1.09 mmol) in toluene (50 ml) was added to 1-(4-bromobutyl)-1H-2-pyrrolecarbaldehyde 360 (0.494 g, 2.17 mmol) in toluene (350 ml) at reflux over 5 h. The standard work up procedure for the radical cyclisation of pyrroles was followed to yield a yellow residue, which was purified by column chromatography using silica gel as absorbent with light petroleum / dichloromethane as eluent to yield 5,6,7,8-tetrahydro-3-indolizinecarbaldehyde 369, as a yellow oil (0.178 g, 55%); (Found: M⁺, 149.0841. C₉H₁₁NO requires M, 149.0841; νmax / cm⁻¹ 1652 (C=O), 1573 and 1301; δH 1.63-1.85 (2 H, m, 7-CH₂), 1.95-1.97 (2 H, m, 6-CH₂), 2.81-2.86 (2 H, t, J 6.3, 8-CH₂), 4.35-4.40 (2 H, t, J 6.1, NCH₂), 5.97-5.98 (1 H, d, J 3.8, pyrrole-1-H), 6.86-6.88 (1 H, d, J 3.8, pyrrole-2-H) and 9.41 (1 H, s, CHO); δC 19.77 (7-CH₂), 22.92 (6-CH₂), 23.75 (8-CH₂), 45.60 (NCH₂), 107.93 (pyrrole-1-CH), 124.01 (pyrrole-2-CH), 131.13 (pyrrole-8a-C), 133.40 (pyrrole-3-C) and 178.17 (CHO); m/z 149 (M⁺, 100%), 134 (18), 120 (52), 108 (34), 93 (24), 80 (10) and 65 (12).
A solution of tri-n-butyltin hydride (1.28 ml, 4.84 mmol) and AIBN (0.178 g, 1.21 mmol) in toluene (50 ml) was added to 1-(5-bromopentyl)-1H-2-pyrrolecarbaldehyde (0.591 g, 2.42 mmol) in toluene (400 ml) at reflux over 5 h. The standard work up procedure for the radical cyclisation of pyrroles was followed to yield a yellow residue, which was purified by column chromatography using silica gel as absorbent with light petroleum / dichloromethane as eluent to yield 6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-3-carbaldehyde 370, as a yellow oil (0.157 g, 40%); (Found: M⁺, 163.0997. C₁₀H₁₃NO requires M, 163.0994); νmax / cm⁻¹ 1649 (C=O), 1573 and 1472; δH 1.62-1.83 (6 H, m, 6, 7 and 8-CH₂), 2.73-2.78 (2 H, m, 9-CH₂), 4.66 (2 H, m, NCH₂), 5.98-5.99 (1 H, d, J 3.9, pyrrole-1-H), 6.75-6.77 (1 H, d, J 3.9, pyrrole-2-H) and 9.39 (1 H, s, CHO); δC 27.28 (7-CH₂), 28.58 (8-CH₂), 29.00 (6-CH₂), 31.48 (9-CH₂), 46.73 (NCH₂), 109.66 (pyrrole-1-CH), 125.46 (pyrrole-2-CH), 131.77 (pyrrole-9a-C), 148.01 (pyrrole-3-C) and 179.32 (CHO); m/z 163 (M⁺, 100%), 155 (6), 146 (20), 135 (61), 120 (11), 106 (25), 93 (9) and 80 (9).
REFERENCES


35. For a review, see F. Minisci, E. Vismara, F. Fontana, Heterocycles, 1989, 28, 489.


44. F. Coppa, F. Fontana and F. Minisci, Tetrahedron Lett., 1992, 33, 687, (includes "the Barton mechanism").


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APPENDIX

X-ray Crystallography Data for 6,7-Dihydro-5H-pyrrolo[1,2-c]imidazole carbaldehyde (307)
Experimental Details

A. Crystal Data

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B. Intensity Measurements

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No. of Reflections Measured: Total: 610
Corrections

Lorentz-polarization
Absorption
(trans. factor: 0.7686 - 1.0000)
Decay (0.09% decline)
Secondary Extinction
(coefficient: 5.10 : 5.1048e-05)

C. Structure Solution and Refinement

Structure Solution: Direct Methods (SIR92)
Refinement: Full-matrix least-squares
Function Minimized: \( \Sigma \omega (|F_o| - |F_c|)^2 \)
p-factor: 0.0040
Anomalous Dispersion: All non-hydrogen atoms
No. Observations (I>3.00\(\sigma\)(I)): 393
No. Variables: 62
Reflection/Parameter: 6.34
Residual R; Rw: 0.039 ; 0.038
Godness of fit: 3.03
Max Shift / Error in Final Cycle: 0.23
Maximum in Final Diff. Map: 0.15 e^-/\(\circ\)A³
Minimum peak in final Diff. Map: -0.13 e^-/\(\circ\)A³