Development of radical synthetic methodology using solid-phase organic synthesis

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DEVELOPMENT OF RADICAL SYNTHETIC METHODOLOGY USING SOLID-PHASE ORGANIC SYNTHESIS

By

Rehana Karim

A Doctoral Thesis

Submitted in partial fulfilment of the requirements for the award of PhD of Loughborough University

March 2003

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# ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Expansion</th>
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<tbody>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>AIBN</td>
<td>Azobisisobutyronitrile</td>
</tr>
<tr>
<td>Ar</td>
<td>Aryl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butoxycarbonyl</td>
</tr>
<tr>
<td>bp</td>
<td>Boiling Point</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DIC</td>
<td>Diisopropylcarbodiimide</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-Dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide</td>
</tr>
<tr>
<td>EPR</td>
<td>Electron Paramagnetic Resonance</td>
</tr>
<tr>
<td>Equiv.</td>
<td>Equivalent</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>GC-MS</td>
<td>Gas Chromatography Mass Spectroscopy</td>
</tr>
<tr>
<td>HOAT</td>
<td>1-Hydroxyazabenzotriazole</td>
</tr>
<tr>
<td>HOBT</td>
<td>1-Hydroxybenzotriazole</td>
</tr>
<tr>
<td>IR</td>
<td>Infra-Red</td>
</tr>
<tr>
<td>Lit.</td>
<td>Literature</td>
</tr>
<tr>
<td>Mes</td>
<td>Mesyl</td>
</tr>
<tr>
<td>mp</td>
<td>Melting Point</td>
</tr>
<tr>
<td>MS</td>
<td>Mass Spectroscopy</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>SET</td>
<td>Single electron transfer</td>
</tr>
<tr>
<td>TBDMS</td>
<td>t-butyldimethylsilyl</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin Layer Chromatography</td>
</tr>
<tr>
<td>TTMSS</td>
<td>tris(trimethylsilyl)silane</td>
</tr>
<tr>
<td>TMEDA</td>
<td>N,N,N',N'-tetramethylethylethylenediamine</td>
</tr>
<tr>
<td>Ts</td>
<td>Tosyl</td>
</tr>
<tr>
<td>UV</td>
<td>Ultra-Violet</td>
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ABSTRACT

Development of Radical Synthetic Methodology Using Solid-Phase Organic Synthesis

Rehana Karim
PhD 2003

The synthesis of heterocycles using radical intermediates has become an important area of research in recent years. The aim of our research was to develop radical methodologies to construct heterocycles on solid-support. Tri-cyclic benzimidazole derivatives are desirable synthetic targets with a range of biological activity and are part of certain antitumour agents. Solid-supported radical reactions with substituted benzimidazoles were performed under different experimental conditions, including different solvents, three different resins (Wang, Merrifield and Rink) and different radical reagents. 4-Mercaptobenzoic acid moiety served as a traceless linker in radical ipso-substitution reactions of benzimidazole precursors attached to solid-support to construct tri-cyclic and tetra-cyclic benzimidazole adducts. The solution-phase radical ipso-substitution protocol was quite successfully translated onto solid-support.

Microwave irradiation has also been used on resin-bound benzimidazole derivatives to construct tri-cyclic systems. It gave successful results compatible with thermal solid-supported radical reactions. The advantage of microwave is that the system is automated and takes a very short time (ca. 10-20 min) for reactions to go to completion. To our knowledge, this is the first use of microwave irradiation for solid-phase radical reactions.

Imidazoles, indole, pyrrole and pyrazole derivatives were synthesised successfully, by radical ‘oxidative’ methodology, using various radical mediators. Tributylgermanium hydride mediated radical cyclisations onto the above mentioned heteroarenes gave excellent results. The presence of electron withdrawing group (ester functionality) on these heterocycles promoted cyclisation. One of the objectives was to synthesise heterocycles on solid-support using radical ‘oxidative’ methodology. For that purpose we used a template heterocycle with an electron withdrawing ester functionality which can be hydrolysed and resulting acid coupled to resin (Wang, Rink or Quadrage or tentage!). We established solution-phase radical ‘oxidative’ cyclisation protocol and successfully applied it to solid-supported pyrazole moiety.
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GENERAL INTRODUCTION

1.1 Solid-Phase Organic Synthesis

The techniques for solid-phase synthesis are based on the pioneering work of Merrifield who used solid-phase to synthesise peptides. The revolution in the synthesis of peptides has lead to generation of synthetic enzymes, vaccines and antibiotics. Since then it has increasingly been explored for the synthesis of polypeptides and oligonucleotides. The field was extensively investigated during 1970’s, and interest in the field has re-emerged with the advent of combinatorial chemistry. Reactions on solid-supports will be significant in the future for the fast, simultaneous, and multiple synthesis of several new compounds if required in the search of lead structures and their optimisation for preparation of novel pharmaceutical targets. Recently there has been greater focus on the adaptations of other organic reactions to solid-phase.

1.1.1 Advantages of Solid-Phase Organic Synthesis

a) Supported synthesis can be automated; this is significant in multiple parallel synthesis.
b) Purification and isolation steps are eliminated by the covalent binding of the substrate and product to the support. Furthermore, purification is simplified to washing the support with an appropriate set of solvents.
c) The use of support allows the easy handling of toxic compounds.
d) The properties of the support can be used to modify the reactivity of the functional groups of the pendant molecule.
e) Many supports can be regenerated and reused.
f) Excess reagents can be employed to drive the reaction to completion without complicating purification procedure.
g) Principle of high dilution; undesired side reactions such as cross-linking and multiple couplings can be suppressed by using supports with low loading.

The common polymer backbone is polystyrene, crosslinked with 1% or 2% divinylbenzene. The latter is the preferred one for reactions at higher temperatures or for reactions with organometallic
reagents. These resins are compatible with a wide range of reaction conditions;
i. They are compatible with a range of polar and apolar solvents such as DMF, NMP, alcohols, THF, acetonitrile and DCM.
ii. Mixing is attained by: vortexing by employing orbital shakers, ultrasonic or magnetic stirrers or by bubbling gas through suspensions.

1.1.2 Disadvantages of Solid-Phase Organic Synthesis

A. Use of supports makes separation of two different supported compounds impossible in most cases.
B. Supported reactions are usually slower than the reactions of solution-phase analogues reactions.
C. The support can adversely affect the reactivity of the functional groups of the pendant molecule.
D. Prolonged use of mechanical stirring can give rise to mechanical damage of the resins.
E. The temperature range for reactions is about $-78^\circ$C to $155^\circ$C.

Solid-phase synthesis is performed by immobilizing a starting material to the solid support as shown in (Figure 1).

![Figure 1](image)

1.1.3 Types of Support

There are different types of support on which chemistry has been performed, these are generally categorised as inorganic supports and polymeric supports. Inorganic supports are silica based whereas polymeric supports include soluble polymer supports and cross linked polymers. The common polymer backbone is polystyrene, crosslinked with 1% or 2% divinylbenzene. The most widely used class of support in supported organic chemistry is cross-linked polymer supports.4
1.1.4 Linkers

Solid-phase syntheses require a covalent linker group to attach the small molecule onto the polymeric resin. A linker has been described as a bifunctional protecting group which is attached to the molecule being synthesised through a bond labile to the cleavage conditions and is attached to the solid-support through a more stable bond, but needs to be cleaved selectively at the end of the synthesis releasing the desired product from the resin into solution. The selection of a suitable linker for a particular class of target molecules is crucial in designing solid-phase synthesis. As there are a wide range of protecting groups in solution-phase organic chemistry, capable of protecting many functional groups, hence, there is a wide repertoire of polymer linking groups (Figure 2).

![Figure 2](image)

Early linkers drew simply on protecting groups such as Ellman’s polymer bound THP protecting group \(1^5\) (Figure 2) and the polymer-bound trityl group \(2, 6\) both draw directly on commonly used solution-phase protecting groups. The commonly used linkers include acid labile, base labile, photolabile, traceless and safety catch linkers.

Acid Labile Linkers

Strong acid is one of commonly employed cleavage conditions in solid-phase synthesis. The lability of an acid labile linker is dependent on the relative stability of the protonated linker versus the cation formed upon cleavage. Hence, the more stable the cation formed, the more labile the linker is to acid (Figure 3). The stability of the cations (Figure 3) increases from left to right as the number of electron donating groups increases. The same trend can be seen when comparing the ester linker \(3\), derived from hydroxymethylpolystyrene, which requires HF for cleavage. The Wang linker \(4\) requires 50% TFA/DCM to promote cleavage, and the Sasrin linker \(5\) requires 1-3% TFA/DCM.

Several linkers have been reported for the solid-phase synthesis of hydroxamic acids. In one case the acid labile 2-chlorotrityl functionalised polystyrene was converted to the corresponding \(N\)-Fmoc-
aminooxy-2-chlorotrityl resin 6 (Scheme 1); subsequent synthetic steps and acidolysis with 5% TFA/DCM released the desired hydroxamic acid from resin.

![Scheme 1](image)

**Figure 3**

Scheme 1. **Reagents and conditions:** i, 2-chlorotrityl polystyrene, (i-Pr)$_2$NEt; ii, Fmoc peptide synthesis; iii, DBU, Ph(CH$_2$)$_3$Br; iv, 5% TFA/DCM.

**Base Labile Linkers**

Two types of cleavage are included under this heading; the more common type involves nucleophilic substitution, usually on an ester; the other type involves a base catalysed reaction, for instance, elimination or cyclisation. The nucleophilic labile linker can be exemplified by the hydroxymethylpolystyrene derived ester 3 (Scheme 2). The true base labile linker is exemplified by the tertiary amine linker 8 (Scheme 3).
The use of photolabile linkers in solid-phase synthesis is an attractive strategy as photolysis can provide an orthogonal non-invasive method of cleavage. The most common type of photolabile linkers are based on o-nitrobenzyl linkers. Routledge has studied the utility and scope of thiohydroxamic acid as a photolabile 'traceless linker' for solid-phase synthesis. The linker is immobilised onto the resin (Scheme 4). It is also an efficient traceless linker revealing an aliphatic CH bond on photolysis at 350 nm.

Traceless Linkers

Traceless linkers, which enable the attachment of arenes and alkanes to a polymeric support, are becoming increasingly popular. These anchoring groups allow chemical transformations on the polymer-bound molecules, which can be cleaved from the resin leaving no residual functionality to bias a library. A traceless linker can be defined as a linker which upon cleavage leads to the formation of a C-H bond on the seceding molecule. The first traceless linkers for arenes were described independently by Ellman and Veber. The silicon traceless linker developed by Veber
(Scheme 5) allows the introduction of a proton on the binding site of the silicon moiety by *ipso* substitution on the arenes.

![Scheme 5](image)

**Scheme 4.** *Reagents and conditions:* i, Chloromethyl-polystyrene (0.8 mmol/g), NaH (3 equiv.), DMF, 60 °C, 18 h, 98%; ii, TFA/DCM/Et3SiH (9:10:1), rt, 1 h; iii, 1,1-thiocarbonyldiimidazole (3 equiv.), DCM, rt, 18 h, 78%; iv, N-methylhydroxylamine hydrochloride (3 equiv.), triethylamine (6 equiv.), DCM, rt, 18 h, 73%; v, N-methylindole-3-acetic acid (2 equiv.), DIC (2 equiv.), HOBT (2 equiv.), DMAP (0.2 equiv.), DCM, DMF, 85%; vi, Bu3SnH/THF (1:40), 30 min, 350 nm, 55%.

![Scheme 5](image)

**Scheme 5.** *Reagents and conditions:* i, TFA, 25 °C.
Safety Catch Linkers

Safety catch linkers rely on a two step cleavage. The first step involves activation of the linker, the second step involves the cleavage. This is demonstrated by Kenner's safety catch linker 13 (Scheme 6).\textsuperscript{13,14} It is stable to both acidic and basic conditions until the nitrogen is alkylated either by diazomethane or iodoacetonitrile. Once activated by alkylation, cleavage proceeds under nucleophilic conditions.

\begin{center}
\begin{tikzpicture}
  \node[shape=circle,draw,fill=black!10] (a) at (1,0) {13};
  \node[shape=circle,draw,fill=black!10] (b) at (3,0) {14};
  \draw[->,above] (a) -- node[above]{activation} (b);
  \draw[->,below] (b) -- node[below]{cleavage} (b);
  \node at (2,-0.5) {R\textsuperscript{2} = Me, CH\textsubscript{2}CN};
\end{tikzpicture}
\end{center}

\textbf{Scheme 6}

Once the resin and synthetic route has been chosen, the next problem is how to monitor solid-phase reactions and for this, there are number of methods available, which are listed below;

A. FT-IR and FT-Raman spectroscopy.
B. Elemental analysis.
C. Photometry (\textit{e.g.} -NH\textsubscript{2} monitored by photometric Fmoc determination).
D. Solid-state and gel-phase \textsuperscript{13}C NMR spectroscopy, as well as \textsuperscript{1}H and \textsuperscript{13}C correlation NMR spectroscopy.
E. Titration of reactive groups (\textit{e.g.} -NH\textsubscript{2}, -COOH, ArOH, -SH).
F. High resolution \textsuperscript{1}H MAS and MAS-CH correlation in the gel phase.

However, analysis of solid-supported substrates is still not accurate enough due to the interference of the polymer backbone and the low loadings generally employed.

1.1.5 Combinatorial Chemistry

Combinatorial chemistry is a method for the rapid generation of large numbers of compounds. Solid-phase is highly suitable to combinatorial chemistry for the following reasons: easy work-up
procedures; high yield by using excess reagents and its amenability to multiple and automated synthesis. The area can be split into three main methods:

1. **Split and Mix Synthesis.** To generate a very large number of products by combinatorial synthesis on the solid-support, the 'split and mix' method has been widely used (Figure 4).

   The synthesis is performed by taking a large number of beads and splitting them into equal groups. To each is then added a different substrate. The chemistry is performed, and the beads combined, mixed and then split again. Ellman has provided an example of combinatorial benzodiazepine synthesis (Scheme 7) using 'split and mix' method. One major advantage of this method is to build large libraries relatively easily involving few synthetic steps. The major limitation of the 'split and mix' synthesis method is the problem of screening and deconvolution.

2. **Multiple Parallel Synthesis:** In multiple parallel synthesis, the individual compounds are kept separate throughout the synthesis. Such procedures are commonly carried out in multi-well microtitre plates. The main advantage is that the position on the plate, provides the chemical history of the beads, therefore removing any problem of deconvolution. The other advantage is that screening can be both on and off bead without loss of information. These factors allow the synthesis and screening of discrete quantities of large numbers of compounds. The
disadvantage of this method is that the library size is relatively small, therefore, the possibility of finding a hit is lowered.

Scheme 7. Reagents and conditions: i, Fmoc protected amino acid fluorides, 4-methyl-2,6-di-tert-butylpyridine; ii, 20% piperidine in DMF; iii, HOAc/DMF (5/95), 60 °C; iv, lithiated 5-(phenylmethyl)-2-oxazolidinone in THF, -78 °C, followed by alkyl iodides R\textsubscript{3}I, DMF; v, TFA/H\textsubscript{2}O/Me\textsubscript{2}S (95:5:10).

3. Spatially Addressable Synthesis: This technique is based on identifying compounds by location. One example of this method is light-directed synthesis. A sequence of photodeprotection, and coupling are performed, allowing the synthesis of large number of peptides whose identity can be determined by their position on the slide.
1.2 Radical Methodology

Russian-born chemist Moses Gomberg provided the first example of a free radical in 1900, in the form of trivalent compound triphenylmethyl radical which was generated when triphenylmethyl bromide was treated with silver metal (Scheme 8).¹⁹

\[
(C_6H_5)_3CBR + Ag \rightarrow (C_6H_5)_3C^* + AgBr
\]

Scheme 8

He demonstrated that in oxygen-free solution of benzene the triphenyl methyl radical is in equilibrium with its dimer. Although triphenylmethyl radical was observable only because it was stabilized by resonance unlike other typical free radical, its chemical properties showed what kind of behaviour to expect of free radicals in general and most important of all it showed that such species as free radicals could exist.
However, the beginnings of synthesis involving radical methodology did not appear until 1937 with Hey and Waters and the homolytic phenylation of aromatic substrates, as well as with Kharasch and the regioselectivity of HBr addition to alkenes, called the peroxide effect or the Kharasch effect or anti-Markovinkov. The importance of radical-mediated processes in production of synthetic polymers, especially synthetic rubber, gave a major impetus to radical chemistry during the Second World War.

Many biological, combustion and auto-oxidation reactions involve radical processes. Radical reactions are important in living systems since they are involved in normal biological processes and energy production. They are also induced by external factors such as radiation, medicines and foodstuffs. Some biochemical reactions are explained by the formation of free radicals: lipid peroxidation, isomerisation by coenzyme B12, etc. EPR spectroscopy and the spin-trapping techniques contribute greatly to the detection and identification of the free radical intermediates in this field. A radical has been defined as a molecular entity containing one or more unpaired electrons, in practice, some limitations are imposed on this definition. Thus transition metal ions, or atoms of the alkali metals would not be referred to as radicals. This definition also includes species formed from familiar organic molecules by the loss or gain of a single electron. Examples are the amine radical cation \( \text{Me}_2\text{N}^+ \) and naphthalene radical anion \( \text{naph}^- \).

![Radical Examples](image)

The presence of unpaired electrons gives radicals the property of paramagnetism. Information about the structure of radicals is provided by physical methods (e.g. IR and EPR spectroscopy), by calculation and by chemical methods. EPR spectroscopy is the most appropriate and the most powerful method for studying species containing one or more unpaired electrons. This method is quite sensitive, being capable of detecting free radicals at concentrations of the order of \( 10^{-8} \text{ M} \). It provides information about both the nature of the radical and its structure (conformation, configuration, delocalization of the unpaired electron).
1.2.1 Characteristics of Free Radicals

Free radicals are generated in a number of general ways, *e.g.*

A) Through homolytic cleavage of bonds,

\[ \text{A-B} \rightarrow \text{A}^* + \text{B}^* \]

*Scheme 9*

B) By reaction of molecules with other free radicals,

\[ \text{A-B} + \text{X} \rightarrow \text{A}^* + \text{B-X} \]

*Scheme 10*

These procedures are called the initiation step, the second step involves the disappearance of radicals, and it is termed as termination. Radical reactions can involve addition, elimination, oxidation, reduction and cyclisation.

\[ \text{A}^* + \text{B}^* \rightarrow \text{A-B} \]

*Scheme 11*

1.2.2 Chemoselectivity of Radicals

Radical reactions can be performed under mild, neutral conditions. Due to the high chemoselectivity of radical reactions, many functional groups will survive radical reaction conditions and therefore, protection is unnecessary. Commonly used substrates in radical reactions are alkyl iodides and bromides due to ease of fission of C-X bond. The approximate order of reactivity for certain leaving groups to generate radicals is as follows, R-Cl < R-SPh < R-NO₂ < R-SePh < R-Br < R-I.

1.2.3 Regioselectivity and Stereoselectivity of Radical Cyclisations

Radical cyclisation normally consists of intramolecular additions to double or triple bonds. They are of great interest as they allow the synthesis of a wide variety of 5- and 6- membered cyclic compounds with high regioselectivity and often very good stereoselectivity. For example, the
cyclisation of the hex-5-en-1-yl radical 22, is irreversible and forms the primary radical 23, derived from 5-exo cyclisation, in preference to the thermodynamically more stable secondary radical 24 (Scheme 12).  

\[
\begin{align*}
&\text{Br} \quad \text{\( \rightarrow \)} \\
&\text{\( \rightarrow \)} \\
&\text{\( \rightarrow \)} \\
&\text{\( \rightarrow \)} \\
&\text{\( \rightarrow \)}
\end{align*}
\]

\[ k = 2.3 \times 10^6 \text{ s}^{-1} \]

\[ k = 4.1 \times 10^3 \text{ s}^{-1} \]

\[
\begin{align*}
&\text{22} \\
&\text{23} \\
&\text{24} \\
&\text{25} \\
&\text{26}
\end{align*}
\]

\[ \text{64\%} \]

\[ \text{1\%} \]

**Scheme 12.** *Reagents and conditions:* i, Bu\(_3\)SnH, AIBN, benzene.

In both instances, the reaction leads to the formation of a C-C σ-bond at the expense of a much weaker C=C π-bond. At 25 °C, the rate of 5-exo cyclisation is 2.3 x 10^6 s\(^{-1}\) compared to a much slower rate of 4.1 x 10^3 s\(^{-1}\) for 6-endo cyclisation. The preference for 5-exo cyclisation has been explained on the basis of stereoelectronic effects favouring a chair-like transition state (which is known as the Beckwith model). Following cyclisation, the cyclic radicals 23 and 24 abstract a hydrogen atom from tributyltin hydride (at approximately the same rate) to form cyclised adducts 25 and 26, respectively together with Bu\(_3\)Sn• which re-enters the chain reaction. Baldwin has outlined the rules for ring-closure reactions which describe the size of the ring, the hybridisation state of the atom under attack and the resulting regioselectivity of radical cyclisation.

In the above mentioned example of the hexenyl radical cyclisation, the 1,5-cyclisation observed is a 5-exo-trig process and the 1,6 cyclisation is termed as a 6-endo-trig process. Factors determining the regio- and stereoselectivity include chain length and chain substituents.
1.2.4 Synthesis of Heterocycles by Radical Cyclisation Methodology

1.2.5 Oxidative Radical Cyclisations

Radical cyclisation for the synthesis of heterocycles is a well documented methodology in the literature. Many new methods are being developed to synthesise the wide range of novel natural products. The majority of radical cyclisations are carried out using tributyltin hydride but other radical generating procedures are becoming increasingly popular. Amongst the huge variety of radical cyclisation reactions those with oxidative rearomatisation have been extensively studied.21,22 The conditions employed in most cases were oxidative, which is important in regenerating the final aromaticity of the desired target. Overall these reactions give cyclisation by loss of HX.

In order to explain these oxidative cyclisation reactions, Bowman proposed the first pseudo $S_{RN1}$ mechanism-pseudo substitution radical nucleophilic unimolecular, for radical cyclisation of aryl radicals onto thioamides (Scheme 13).23

\[
\text{Scheme 13. Reagents and conditions: i, Bu}_3\text{SnH, AIBN, toluene, 24 h, 69%}.
\]

The generated aryl radical cyclises onto the sulfur of the carbon-sulfur double bond to produce a delocalised radical. The pseudo $S_{RN1}$ mechanism relies upon the fact that tributyltin hydride acts as a base and liberates hydrogen gas. It was proposed that the tributyltin hydride removes the proton bound to the nitrogen to generate the intermediate radical anion 29 (Scheme 14). The delocalised radical anion intermediate 29 then undergoes single electron transfer with a molecule of starting material to generate the cyclised adduct 28 and a molecule of starting material as delocalised radical anion 30 (Scheme 15). The radical anion 30 undergoes dissociation to an anion (I') and the initial aryl radical. Prior to dissociation, the radical anion is localised on the
carbon-iodine bond and the $\sigma$-bond is composed of three electrons with the unpaired electron residing in the $\sigma^*$-molecular orbital.

Scheme 14. Formation of the radical anion.

These types of oxidative radical cyclisation reactions require more than one equivalent of tributyltin hydride. Support for the "pseudo $S_{RN1}$ mechanism" has been offered by Beckwith and Storey. The mechanism has not been solved and a common view is abstraction of hydrogen hydrogen by a radical in the reaction. For example, Curran findings are in contradiction with the "pseudo $S_{RN1}$ mechanism". Curran proposes that it is the 2-cyanoprop-2-yl radical (from AIBN) that acts as an oxidant (Scheme 16). For these oxidative radical cyclisations an excess of AIBN is required.

Cyclisation of $N$-(o-alkyl) radicals onto heteroarenes has been used to annulate pyrrole, imidazole and indole. An example of these oxidative radical cyclisations using tributyltin hydride is shown in Scheme 17 for the synthesis of [1,2-$\alpha$]fused pyrroles. Treatment of the precursors 33 with tributyltin hydride yield $N$-(o-alkyl)pyrrole radicals 34 which cyclise onto the pyrrole rings to form the cyclised $\pi$ radicals 35. In an oxidative step a hydrogen atom is lost to yield the [1,2-$\alpha$]fused pyrroles 36. [1,2-$\alpha$]Fused imidazoles have also been synthesised by the oxidative radical cyclisation methodology.
Scheme 15. Single electron transfer and radical anion dissociation.

Scheme 16. Oxidative rearomatisation.
Scheme 17. *Reagents and conditions:* i, Bu$_3$SnH (syringe pump addition), AIBN, CH$_3$CN, reflux, 36 (n = 1, 28%; n = 2, 55%; n = 3, 40%).

Tributyltin hydride mediated 'oxidative' cyclisation protocol has successfully been used for the short synthesis of withasomnine 38, one of the few pyrazole natural products (Scheme 18).

Scheme 18. *Reagents and conditions:* i, Bu$_3$SnH (syringe pump addition), ACCN, toluene, reflux, 38 (n = 1, 38%; n = 2, 63%).

In this example a side chain alkyl radical generated from the precursor selanide 37 cyclises onto the pyrazole ring with subsequent loss of hydrogen atoms. There have been a large number of reports of aryl or heteroaryl radical cyclisation onto pendant arenes/heteroarenes. A good example is the cyclisation of indol-2-yl radicals onto phenyl rings as illustrated in Scheme 19. The precursors 39 (n = 1-3) initially give reactive indolyl radicals 40 which cyclise to yield the π radicals 41 and after loss of a hydrogen atom yield the tetracyclic isoindolo-[1,2-a]indoles 42.
Scheme 19. *Reagents and conditions:* i, Bu$_3$SnH (syringe pump addition), AIBN, CH$_3$CN, reflux, 40 (n = 1, 25%; n = 2, 65%; n = 3, 37%).

1.2.6 Tandem or Cascade Radical Cyclisations

The majority of radical cyclisations used for the syntheses of heterocycles proceed via 5-exo-trig regioselectivity. The tandem or cascade radical cyclisation approach has been widely used for natural product synthesis containing heterocyclic rings. For example, Curran and co-workers have developed a novel radical methodology for the synthesis of the important anticancer alkaloid camptothecin 46 (Scheme 20)$^{30,31}$ and analogues such as mappicine.$^{32}$
Scheme 20. Reagents and conditions: i, PhNC, (Me$_3$Sn)$_2$, PhH, sunlamp, 70 °C, 8 h, 63 %.

1.2.7 Ipso-Substitutions

Intramolecular nucleophilic and electrophilic ipso-substitution reactions are typical aromatic substitution processes. Ipso-substitution is substitution at a position already carrying a substituent. One possibility is to introduce a group which will participate in ipso-substitution. The use of sulfur-based groups has served this purpose and appears to offer a general protocol which is distinct from the oxidative radical cyclisations and it may offer possibilities for regiocontrolled cyclisation. [1,2-α]-Fused benzimidazoles, imidazoles, and indoles have been synthesised using regioselective (ipso) aromatic homolytic substitution. The [1,2-α]fused imidazoles were synthesised from $N$-(ω-phenylselanyl)alkyl-$N$-(phenylsulfonyl)-imidazoles by cyclisation of intermediate $N$-(ω-alkyl) radicals, generated using Bu$_3$SnH, with displacement of the phenylsulfonyl groups. Similarly, the [1,2-α]fused benzimidazoles were synthesised from
N-(o-phenylselanyl)alkyl-2-(phenylsulfanyl)benzimidazoles with displacement of phenylsulfanyl leaving groups. Caddick has successfully demonstrated that a tosyl radical catalysed isomerisation can provide an effective route to biologically valuable fused[1,2-α]indole ring system. An example of the protocol is shown in Scheme 21 for the conversion of the alkynyl precursor 47 to the cyclised indole 50.

![Scheme 21](image)

**Scheme 21.** Reagents and conditions: i, TsSePh (0.25 equiv.), AIBN, benzene, reflux, 72-89%.

Motherwell reported examples of a number of heterocyclic compounds (Scheme 22). Tricyclic 52 is a product of the oxidative cyclisation from an initial aryl radical, while biphenyl 53 is the product of ipso-substitution-sulfur dioxide is eliminated. The tricyclic adduct 55 is the result of an aryl radical undergoing intramolecular radical cyclisation onto a pyridine ring.

![Scheme 22](image)

**Scheme 22.** Reagents and conditions: i, Bu₃SnH, AIBN, 52 (33%), 53 (10%), 55 (43%).
Coumarins are naturally occurring lactones which possess valuable pharmaceutical properties along with crop protection and analytical utilities. A highly efficient route to azacoumarins with an unusual mechanism of double *ipso*-substitutions has been reported by Zhang. A radical precursor aryl benzoate 57 (Scheme 23) is prepared by O-acylation of 3-methoxy-2-(1H)-pyridone 56 with 2-bromobenzoyl chloride in the presence of $K_2CO_3$ and tetrabutylammonium bromide. This intermediate is then treated with TTMSS to afford azacoumarin 58 in 75% yield.

Scheme 23. Reagents and conditions: i, 2-bromobenzoyl chloride, $K_2CO_3$, TBAB; ii, TTMSS, AIBN, benzene, 80 °C, 75%.

The anticipated direct 1,6-*ipso*-substitution product 59 is not observed at all. The proposed mechanism is illustrated in Scheme 24.

Scheme 24. A double *ipso* substitution mechanism.
Further support for *ipso* substitution of aromatic carbonyloxy radicals comes from a study by Togo and Yokoyama in oxidative cyclisation of *o*-aryl aromatic acids.\(^{37}\)

### 1.2.8 Reagents for Radical Reactions

Group 14 metal-hydrogen and metal-metal compounds have been successfully used to mediate a wide range of radical transformations such as cyclisations, intermolecular additions, radical rearrangements and cascade reactions. Few examples of tributyltin hydride mediated reactions have been covered in previous section. Tributyltin hydride and related group 14 hydrides readily act as hydrogen atom donors in free radical reactions. The tributyltin hydride radical \( \text{Bu}_3\text{Sn}^- \) can be easily prepared, photochemically or thermally from reaction of \( \text{Bu}_3\text{SnH} \) with peroxides or azo compounds (Scheme 25).

\[
\begin{align*}
\text{O}^- + \text{H-SnBu}_3 & \rightarrow \text{OH} + \text{SnBu}_3 \text{·} \\
\text{CN}^- + \text{H-SnBu}_3 & \rightarrow \text{CN} + \text{SnBu}_3 \text{·}
\end{align*}
\]

Scheme 25

Silicon and germanium hydrides undergo related hydrogen atom transfer reaction (Table 1).\(^{38}\)

**Table 1.** Absolute rate constants \( (k) \) for reaction of group 14 hydrides with the *tert*-butoxyl radical at 25 °C.

<table>
<thead>
<tr>
<th>Metal hydride</th>
<th>( k/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-SnPh(_3)</td>
<td>4.3 x 10(^8)</td>
</tr>
<tr>
<td>H-SnBu(_3)</td>
<td>1.9 x 10(^8)</td>
</tr>
<tr>
<td>H-Si(SiMe(_3))(_3)</td>
<td>1.1 x 10(^8)</td>
</tr>
<tr>
<td>H-GeBu(_3)</td>
<td>9.2 x 10(^7)</td>
</tr>
<tr>
<td>H-GePh(_3)</td>
<td>9.2 x 10(^7)</td>
</tr>
<tr>
<td>H-Si(SMe(_3))(_3)</td>
<td>4.4 x 10(^7)</td>
</tr>
<tr>
<td>H-SiPh(_3)</td>
<td>1.1 x 10(^7)</td>
</tr>
<tr>
<td>H-SiEt(_3)</td>
<td>5.7 x 10(^6)</td>
</tr>
</tbody>
</table>
The stronger Ge-H bond (\(-370 \text{kJ mol}^{-1}\) for \(\text{Bu}_3\text{GeH}\)) and the Si-H bond (\(-398 \text{kJ mol}^{-1}\) for \(\text{Et}_3\text{SiH}\)) ensures that these reactions proceed at lower rates than the corresponding tributyltin hydride reactions.

Trialkyltin radicals react in bimolecular homolytic substitution (S\(_\text{N}2\)) reactions with a huge variety of organohalides, selenides, sulfides or xanthates to form carbon centred radicals (Scheme 26). The rate of reaction of a tin-centred radical with an organohalide depends on both the nature of the halogen group and to a lesser extent, the alkyl or aryl group. In general the weaker the carbon-halogen bond the faster the rate of halogen-atom abstraction. Similar reactions are observed for related germanium- and silicon-centred radicals (Table 2). 39

![Scheme 26](image)

**Table 2.** Absolute rate constants (\(k\)) for reaction between organohalides with \(\text{Bu}_3\text{sn}^*\), \(\text{Bu}_3\text{Ge}^*\) and silicon radical, \(\text{Et}_3\text{Si}^*\) and \((\text{Me}_3\text{Si})_3\text{Si}^*\) radicals at 25 °C.

<table>
<thead>
<tr>
<th>Compound</th>
<th>(\text{Bu}_3\text{sn}^*) (k/\text{dm}^3 \text{mol}^{-1} \text{s}^{-1})</th>
<th>(\text{Bu}_3\text{Ge}^*) (k/\text{dm}^3 \text{mol}^{-1} \text{s}^{-1})</th>
<th>(\text{Et}_3\text{Si}^*) (k/\text{dm}^3 \text{mol}^{-1} \text{s}^{-1})</th>
<th>((\text{Me}_3\text{Si})_3\text{Si}^*) (k/\text{dm}^3 \text{mol}^{-1} \text{s}^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{Br-CH}_2\text{Ph})</td>
<td>(1.5 \times 10^7)</td>
<td>(8 \times 10^9)</td>
<td>(2.4 \times 10^9)</td>
<td>(9.6 \times 10^8)</td>
</tr>
<tr>
<td>(\text{Br-C(CH}_3)_3)</td>
<td>(1.7-1.4 \times 10^8)</td>
<td>(8.6 \times 10^7)</td>
<td>(1.1 \times 10^9)</td>
<td>(1.2 \times 10^8)</td>
</tr>
<tr>
<td>(\text{Cl-CH}_2\text{Ph})</td>
<td>(1.1 \times 10^8)</td>
<td>(1.9 \times 10^6)</td>
<td>(2.0 \times 10^7)</td>
<td>(4.6 \times 10^6)</td>
</tr>
</tbody>
</table>

The most commonly used reagent is \(\text{Bu}_3\text{SnH}\) but it is toxic and there are problems associated with the purification of desired targets. The purification can be made easier by using \(\text{Bu}_3\text{SnH}\) catalytically. In this methodology \(\text{Bu}_3\text{SnCl}\) is reduced *in situ* with sodium cyanoborohydride or sodium borohydride; this has an added advantage of keeping the concentration of \(\text{Bu}_3\text{SnH}\) low to facilitate cyclisation instead of reduction. One of the attractive alternatives to toxic tin-centred radicals are non-toxic triorganosilanes. The most successful tin hydride substitute to date is tris(trimethylsilyl)silane. 40

An example of a TTMSS mediated cyclisation has been shown in Equation 1 (Scheme 27). 41 Moreover, Giese-type reductive addition reactions of alkyl halides onto activated olefins were successfully performed with \((\text{TMS})_3\text{SiH}\) Equation 2 (Scheme 27). 42 The ease of separating the
Silane byproducts \((\text{TMS})_3\text{SiX}\) from organic products is an attractive feature of it. Unfortunately, it is more air-sensitive and expensive than tributyltin hydride.

![Scheme 27](image)

\textbf{Scheme 27. Reagents and conditions:} i, \((\text{TMS})_3\text{SiH}, \text{AIBN}, \text{benzene, 16 h}; \) ii, \(\text{POCl}_3, \text{NaBH}_3\text{CN}, \text{NaOMe}; \) iii, \((\text{TMS})_3\text{SiH}, \text{AIBN}, 90\%\).

Triorganogermanium hydrides can also be used as triorganotin hydride substitutes. The use of trialkylgermanium hydrides, including \(\text{Bu}_3\text{GeH}\) and \((\text{TMS})_3\text{GeH}\), as potential contenders for \(\text{Bu}_3\text{SnH}\) has also been investigated. These hydrides react less rapidly with carbon-centred radicals than tributyltin hydride hence competitive simple reduction is observed to a lesser extent. As an example, the addition of 1-iodoundecane to acrylonitrile using \((\text{TMS})_3\text{GeH}\) is shown in Equation 3 (Scheme 28).\textsuperscript{43} Radical cyclisation reactions can also be carried out with tri-2-furylgermane as a triorganotin hydride substitute.\textsuperscript{44} The reactions are generally carried out in THF using \(\text{Et}_3\text{B}\) and \(\mathrm{O}_2\) as an initiator.

![Scheme 28](image)

\textbf{Scheme 28. Reagents and conditions:} i, \((\text{TMS})_3\text{GeH}, \text{AIBN}, 80 \, ^\circ\text{C, 71\%}; \) ii, tri-2-furylgermane, \(\text{V-70, H}_2\text{O}, 80 \, ^\circ\text{C, 75\%}.\)
Furthermore, the tri-2-furylgermane reactions can be carried out using catalytic amounts of the germe and water is tolerated as a solvent in these reductive radical chain reactions. V-70 was used as a water soluble radical initiator in these reactions, as shown for a typical 5-exo-cyclisation in Equation 4 (Scheme 28). Organogermanium hydrides are expensive and another disadvantage is that germanium-centred radicals generally react less readily with alkyl halides than Bu$_3$Sn• or (TMS)$_3$Si• radicals.

Metal centred radicals can be prepared by homolysis of weak metal-metal bonds in metal dimers of the type R$_n$M-MR$_n$. Tin-centred radicals can be generated from hexaalkylditin or hexaarylditin compounds as the weakest bond in these compounds is the tin-tin bond and this can be homolytically cleaved by heating above 100 °C or by photolysis (Scheme 29). Dimers of other group 14 elements also undergo homolysis to give radicals. In hexamethyl compounds of the type Me$_6$M$_2$, where M is a group 14 element, the strength of the M-M bond decreases as the size of the element increases and so lead-centred radicals are generally more easily formed than silicon-centred radicals.

Bowman has reported a cascade radical synthesis of heteroarenes via iminyl radicals using hexamethylditin Equations 5 and 6 (Scheme 30).  

Scheme 29

![Scheme 29](image)

Scheme 30. Reagents and conditions: i, (Me$_3$Sn)$_2$, t-BuPh, sunlamp irradiation (2 x 150 W), 150 °C, 48 h, 73%; ii, (Me$_3$Sn)$_2$, t-BuPh, sunlamp irradiation (2 x 150 W), 150 °C, 48 h, 60%.
Similar reactions can be mediated using polymer-supported distannanes.  

Other metals have also been used for radical reactions. For example, Parsons has investigated some interesting atom transfer radical cyclisations using dimanganese decacarbonyl \([\text{Mn}_2(\text{CO})_{10}]\).  
The photolysis of this dimer using visible light generates the manganese pentacarbonyl radical which reacts with organohalides to form carbon-centred radicals (Scheme 31). The advantages of the use of dimanganese decacarbonyl include mild reaction conditions, clean and efficient cyclisation-trapping sequences and simple removal of manganese halide by-products (on DBU work-up). The use of copper complexes in mediating atom transfer radical cyclisation reactions have also been reported. 

\[
\text{Scheme 31. Reagents and conditions: i, 10\% Mn}_2(\text{CO})_{10}, \text{hv, DCM, 1 h, 78\%.}
\]

Non-metal hydrides, bearing a weak non-metal–hydrogen bond can also replace \(\text{Bu}_3\text{SnH}\) in radical reactions. Suitable non-metal hydrogen bonds include sulfur hydrogen, phosphorus-hydrogen or boron-hydrogen.

Polarity reversal catalysis using thiols as catalysts has been intensively investigated. The concept has successfully been applied in reductive radical chain reactions using stoichiometric amounts of trialkylsilanes in the presence of a thiol as a catalyst. Halogen abstractions with thiyl radicals are not favourable. The important H-transfer reactions in these chain processes benefit from favourable polar effects in their transition states. The concept is outlined briefly in Scheme 32.

Thiols can be used in cyclisation reactions. Thiyl radical addition/cyclisation reactions have been summarized thoroughly. For example, the reaction of the carbamate 80 with thiophenol under radical conditions affords the cyclised compound 81 in 85\% yield (Scheme 33).
Scheme 32. Polarity reversal catalysis using thiols and trialkylsilanes in radical reductions.

Scheme 33. Reagents and conditions: i, PhSH, AIBN, 85%, dr = 3:1.

A variety of organophosphorous compounds bearing weak phosphorus–hydrogen bonds can act as effective hydrogen-atom donors. For example, two alternative phosphorous compounds of particular significance in radical chemistry are hypophosphorous acid (H₃PO₂) and its N-ethylpiperidine salt (EPHP). These compounds, which contain weak P-H bonds, can replace Bu₃SnH in many cyclisation reactions and have the added advantage that they allow us to carry out radical reactions in aqueous media. Murphy has reported the use of hypophosphorous acid and its corresponding salt (EPHP) to mediate radical cyclisations in both aqueous and organic media. For example, EPHP was used to mediate a key 5-exo-trig cyclisation reaction leading to the synthesis of the natural product alboatrin (Scheme 34).
Scheme 34. Reagents and conditions: i, EPHP, AIBN, 77%.

Phosphorous based radical reagents are an attractive alternative to organotins because these reagents are inexpensive, easily handled, and the phosphorous halide by-products are readily removed. Although, in some cases, the phosphonyl radicals can add to double bonds rather than react with the alkyl halides. The phosphonyl radicals are also less reactive than tin- or silicon-centred radicals so alkyl halides with weak carbon-halogen bonds are required, this can be an advantage because the lower reactivity of phosphonyl radicals can ensure that the weakest bond within a polyhalogenated precursor is selectively broken.

Other radical reagents, which can act as hydrogen donors are continually being developed. Roberts showed that phosphine ligated boranes can be used as radical reducing reagents. New hydrides of gallium and indium have been introduced to act as radical reducing reagents in reductive chain reactions. Other transition metal based hydrides such as Schwartz reagent $\text{[Cp}_2\text{Zr(H)Cl]}$ are promising alternatives to the tin hydrides. Another major advance in the area of radical chemistry is the use of solid-supports to perform radical reactions.

1.2.9 Solid-Phase Radical Reactions

The construction of libraries of compounds using combinatorial and parallel synthesis has witnessed a great deal of development in recent years. The need for fast delivery of large number of diverse compounds for high throughput screening assays has initiated a huge effort in industry and academia aimed at designing and adapting reactions for solid-phase synthesis. As a result many solution-phase reactions have been adapted to solid-supported substrates. The execution of radical reactions on solid-supports would be very valuable for combinatorial chemistry. When we started our studies, only two applications had been reported. In 1997, Balasubramanian reported the first example of solid-supported synthesis of dihydrobenzofurans from aryl halide precursors (Scheme 35), the first carbon-carbon bond-forming reactions on solid-phase using radical methodology.
Scheme 35. Reagents and conditions: i, Bu$_3$SnH (4.7 equiv.), AIBN, t-BuOH, toluene, 100 °C; ii, NaOMe, MeOH, rt, 24 h; iii, Bu$_3$SnH (20-25 equiv.), 5 mol% AIBN, toluene, 70-80 °C, 4 examples, 63-80%.

Aryl halide cyclisations onto unsaturated bonds have also been investigated by Du and Armstrong (Scheme 36).^59

Scheme 36. Reagents and conditions: i, HMPA (40 equiv.), SmI$_2$ (10 equiv.), THF, rt, 1 h; ii, 20% TFA/DCM, 63%; iii, (40 equiv.) HMPA, 3-pentanone (20 equiv.), SmI$_2$ (10 equiv.), THF, rt, 2 h; iv, 20% TFA/DCM, 33%.
Successful intramolecular radical cyclisations from aryl iodides precursors on polystyrene–Rink resin and TentaGel-Wang resin show that these resins are compatible with radical conditions. Furthermore, TentaGel resin allowed polymer swelling in aqueous solvents. α-Amino esters have successfully been synthesised on solid-support (Scheme 37) using a radical protocol.⁶⁰

![Scheme 37](image)

**Scheme 37.** *Reagents and conditions:* i, DEAD, PPh₃, THF, rt; ii, RI, (Me₃Sn)₂, benzene, hv; iii, 1 M HCl/Et₂O, MeOH/DCM; iv, 10% Pd/C, EtOH/AcOH/H₂O.

The oxime acid 92 was attached to the Wang resin employing Mitsunobu esterification method to give the resin-bound phenylsulfonyl oxime ether 93. The attachment of 92 to the resin proceeded well. Treatment of 93 with alkyl iodides and hexamethylditin in benzene and irradiation at 30 nm for 24 h at 35 °C afforded 94 as shown in Scheme 37. Compound 94 was cleaved from solid-support by treatment with HCl/Et₂O (1-N) in MeOH/DCM for 48 h at room temperature to give the product 95 in high yield based on the initial loading of the Wang resin. Then the successful reduction of compound 95 gave final product 96 in good yields.

These early results demonstrated that radical reactions on solid-support have great synthetic potential as new carbon-carbon bond forming methods for combinatorial chemistry. Solid-phase intramolecular reactions⁶⁰ have indicated that intermolecular reactions are also possible using similar approaches. Caddick demonstrated successful examples of addition of toluenesulfonyl radicals to isolated alkenes and alkynes on solid-support. Excellent yields of addition to both alkenes and
alkynes were observed in certain cases (Scheme 38). Success of intermolecular radical reactions on solid-support shows its potential applications.

Scheme 38. Reagents and conditions: i, 5-Hexynoic acid, DIPEA, HATU, DMF; ii, 5-Hexenoic acid, DIPEA, HATU, DMF; iii, TsBr, AIBN, toluene, 65-70 °C; iv, 95% TFA (aq.).

Synthesis of substituted indolines on solid-support, via radical methodology has also been reported (Scheme 39).

Scheme 39. Reagents and conditions: i, R₂NH₂ (10 equiv.), Et₃N (27 equiv.), DCM, 25 °C, 12 h; ii, Bu₃SnH (4 equiv.), AIBN (1.3 equiv.), toluene, 90 °C, 2-4 h.
These results show that solid-phase synthesis of substituted indolines can be achieved and tracelessly cleaved giving access to the medicinally important 1-methylindolines. Furthermore, radical cyclisation reaction itself results in a cyclizing cleavage from the resin, instead of requiring a separate step for target release.

Solid-phase radical reactions are not only limited to tributyltin hydride which is most widely used as the radical mediator. There are reports of supported radical reactions which have demonstrated the successful generation of radicals using other radical mediators. Recent studies within our group by William Barton have shown that the Quadragel alkylselenides and Quadragel acyl selenides can facilitate a traceless cleavage protocol whereby the radical chain propagating entity is tethered to the resin and the newly generated radical centre is released into solution. A successful application of this protocol is illustrated in Scheme 40. The homolytic cleavage of the pyrazole precursor 111 was carried out using TTMSS/AIBN. The radical cyclisation afforded the withasomnmine analogue 112 in 61% yield. This methodology has been extended to other interesting heterocycles.

Scheme 40. Reagents and conditions: i, NaBH₄, I(CH₂)₄Cl, EtOH, 38%; ii, Quadragel-Ms, K₂CO₃, DMF, 80%; iii, TTMSS, ACCN, toluene, 61%.

Functionalised pyrrolidines have been synthesised by radical cyclisation of oxime ethers attached to a polymer support by use of triethylborane as the radical initiator. Stereocontrol in free radical mediated reactions is of great significance in organic synthesis.
In recent years, a high degree of stereocontrol in solution-phase radical reactions has been achieved at low temperature by using triethylborane as the radical initiator. A high degree of stereocontrol in solid-phase radical reactions has also been achieved by using triethylborane and diethylzinc as the radical initiators at low reaction temperature (Scheme 41).

Scheme 41. Reagents and conditions: i, Et₃B, DCM, -78 °C, K₂CO₃, THF, MeOH, 20 °C.

Scheme 42. Reagents and conditions: i, RI, Et₃B in hexane, toluene, 100 °C; ii, NaOMe, MeOH, THF, H₂O, 20 °C.
Tandem radical reactions are an excellent method for the stereoselective construction of multiple bonds on solid-support. The Naito group has investigated the simple solid-phase tandem radical addition-cyclisation reaction of aldoxime ethers onto α,β-unsaturated carbonyl groups (Scheme 42).66

The synthesis of benzofurans using tetrathiafulvalene (TTF) as an oxidant to generate aryl radicals from arenediazonium fluoborates has successfully been carried out in solution-phase. The synthesis of benzofurans has also successfully been performed on resin.67 The polymer-supported tetrathiafulvalene approach gives easily isolated products from radical-polar crossover reactions and the support is regenerated and hence can be reused.

The use of solid-supported organotin hydride has been reported by Neumann and others.68 Solid-supported organotin reagents have a great potential for synthetic organic chemistry as polymer-supported tin hydride allows easy separation of the supported tin by-products by simple filtration. Barton-McCombie deoxygenation of secondary alcohols has successfully been carried out using catalytic amounts of supported tin hydride in the presence of trimethoxysilane.69 The results show that the catalytic use of supported organotin hydride is non-polluting; the solid-phase approach to Barton-McCombie deoxygenation of secondary alcohols seems especially suitable for applications in the synthesis of bioactive compounds. The Barton radical decarboxylation on solid-phase has also been reported by Tadei.70

Scheme 43. Reagents and conditions: i, 25% Piperidine in DMF, 25 min followed by succinic anhydride, DMF (3 equiv.), 70 °C, 3 h; ii, 1-hydroxy-2-pyridinethione (3 equiv.), DIPEA (4 equiv.), DMF, rt, 4 h; iii, hv (200 W lamp), CBrCl3 (50 equiv.), DMF, 20 min; iv, hv (200 W lamp), THF, 20 min; v, TFA/DCM/Et3SiH (1/1/0.1), rt, 1 h.
A Wang type resin was loaded with Fmoc-Gly-OH and after deprotection of the nitrogen, reacted with succinic anhydride to give product 119 (Scheme 43). The Barton ester 120 was synthesised by reaction of 119 with 1-hydroxy-2-pyridinethione using HBTU (2-(1H-benzo-triazole-1-yl)-1,1,3,3-tetramethyluronium hexafluoro-phosphate) in the presence of DIPEA in DMF. Irradiation of 120 in benzene or THF followed by acid cleavage afforded product 121 in 76% isolated yield. The irradiation of Barton ester 120 in DMF in the presence of at least 50 equiv. of CBrCl₃, gave compound 122 exclusively in 72% yield. The reaction was employed to generate peptides containing novel amino acids on solid-phase (Scheme 43). The authors have demonstrated that the photochemical fragmentation of the Barton ester can be successfully employed to generate radicals on solid-phase.

A new polymer-supported radical source has been developed by Taddei for a solid-phase version of the Hunsdiecker reaction or to liberate free alkoxy radicals that undergo cyclisations under mild conditions (Scheme 44).

Scheme 44. Reagents and conditions: i, BrCH₂CO₂H, NaOH, MeOCOCl, Et₃N, DMAP, DCM, rt, 12 h; ii, Br₂, dry MeOH; iii, EtOCSSK, acetone, 0 °C, 5 h, rt, 12 h, NH₂OH.HCl, pyridine, MeOH, 0 °C; iv, ZnCl₂ (5 M in Et₂O), LiOH, MeOH/THF; v, N-Fmoc-Gly-Wang resin, piperidine, DMF,
HBTU, DIPEA, NMP, rt, 6 h; vi, KOH, HOCH₂CH₂OH; vii, pyridine, rt, 3 days; viii, benzene, 200 W lamp, t-BuSH, rt, 4 h.

A Wang resin carrying N-Fmoc-Gly was deprotected under standard conditions and acid 125 was coupled with the supported glycine under classical peptide coupling conditions to afford 126. The alkylation procedure is long but provided the desired hydroxamate 128. The radical cyclisation of compound 128 was carried out in benzene by irradiating the mixture with a tungsten lamp (200 W) in the presence of t-BuSH as radical trap. The reaction gave the expected 5-exo-trig cyclised product 129.

Solid-supported organotin reagents have been shown to mediate efficient radical cyclisation reactions but the reductive nature of these cyclisations is a major disadvantage. Therefore, the growth of transition-metal mediated radical reactions has gained importance. Clark has shown that efficient 5-exo and 5-endo atom transfer radical cyclisations can be mediated by solid-supported Schiff base copper complexes and these catalysts can be reused (Scheme 45).  

![Scheme 45.](image)

**Scheme 45. Reagents and conditions:** i, CuCl, MeCN; ii, DCM, 80 °C, 1 h, 93%.

Reaction of the solid-supported catalyst 131 with N-allyl-N-benzyl-2,2,2-trichloro precursor 132 proceeded well to give 133 in 93% yield. From the above mentioned solid-supported reactions it can be concluded that there are no inherent difficulties in performing radical reactions on solid-phase.

In the beginning, there were doubts about benzylic hydrogen abstraction from the polystyrene matrix, but success of radical reactions on solid-phase contradicts these unfounded doubts. A unique feature of solid-supported reactions is the loading of polymeric resins, typically ≤ 1 mmol/g.
of beads, hence effectively placing an upper limit for the maximum concentration attainable for solid-phase reactions. This high dilution facilitated by the solid-support can be useful for radical reactions. Another important feature of solid-supported reactions is the introduction of linkers which serve as spacers between the substrate and the matrix. The linker can influence the chain mobility to a great extent as well as the polymer microenvironment where the reaction is taking place. Solid-phase protocols offer advantages in terms of easy reaction workup. Development of efficient and novel radical protocols on solid-support would be very valuable for combinatorial chemistry.

1.3 Aims and Objectives of the project

The synthesis of interesting heterocyclic compounds using radical protocols continues to grow in importance and is finding increasing application in pharmaceutical synthesis. The aim of our research is to develop radical methodologies to construct heterocycles (benzimidazoles, imidazoles, indoles and pyrroles) on solid-support. The solution-phase protocol has already been developed; it involves radical ipso substitution as shown in Scheme 46.

Scheme 46. Radical cyclisation via ipso-substitution.

In translating the radical synthetic methodology onto solid-phase suitable plans are required for attachment of radical precursors to the resin. Again the incorporated carboxyl or alcohol functionality in radical precursors (136-138 and 141) provide useful handles for attachment as
shown in Scheme 47. Carboxylic acid groups are excellent for developing ‘lead’ optimisation due to the wide range of functional group transformations to aldehydes, ketones, amides and nitriles.

Scheme 47. Solid-phase radical cyclisation via ipso-substitution and potential precursors.

The attachment handle could be placed on the benzo ring 138, theazole ring 134 and 137 or on the side chain 141. Two different radical protocols, *i.e.* radical cyclisations involving *ipso*-substitution (Scheme 47) and radical oxidative cyclisations (Scheme 48), would be investigated and optimised, using a variety of radical reagents, for the construction of heterocycles onto solid-support. Another objective of the project was to study aryl radical cyclisations to construct novel heterocycles in solution-phase and then extend those protocols on solid-phase and build a library of biologically active compounds by cleaving the desired targets using a variety of amines to give diversity to the desired heterocycles 144 and 146 as depicted in Scheme 48.
Scheme 48. Solid-phase radical cyclisations via oxidative methodology.
CHAPTER 2

Intramolecular Alkyl Radical Cyclisations by “ipso” Substitution at the C-2 Position of Benzimidazoles and Imidazoles in Solution-Phase

2.1 Introduction

Synthesis of benzimidazole and imidazole analogues is becoming increasingly important. Several functionalised benzimidazoles and imidazoles exhibit biological properties. The benzimidazole is an important heterocyclic nucleus which has seen extensive use in medicinal chemistry. Benzimidazole derivatives have shown such a diverse biological activities as inhibition of phosphodiesterase IV. The benzimidazole ring occurs in vitamin B12 and in many biological active compounds. The imidazole ring occurs in many naturally occurring compounds such as histidine.

The aim of our research is to synthesise an array of functionalised benzimidazoles and imidazoles via radical methodology as described in Chapter 1, Section 1.3. Caddick initially developed a novel protocol to [1,2-α]fused indoles based on intramolecular aromatic “ipso” substitution. Bowman and co-workers advanced these studies with cyclisations onto imidazoles and benzimidazoles. Our initial studies set out to copy the previous study in the research group by Aldabbagh and Bowman. We decided to adapt this protocol to provide a facile route to a number of [1,2-α]fused benzimidazole and imidazole systems in solution-phase and then translate the synthetic sequence onto solid-support. The free radical route selected to synthesise [1,2-α]fused benzimidazoles and imidazoles is shown in Scheme 49.
2.1.1 Preparation of N-(ω-Phenylselanyl)alkyl-2-(phenylsulfanyl)benzimidazoles

Radical Precursors

Prior to introducing the phenylsulfanyl group (a radical leaving group necessary for ipso-substitution) at the C-2 position of benzimidazole it is necessary to protect N-1, as the use of organolithium reagent would deprotonate C-2 as well as N-1 position and generate a dianion which would complicate the synthesis. The trityl group was selected for the protection of benzimidazole; it is a cheap commercially available reagent. The protection of benzimidazole with trityl chloride gave compound 149 in 78% yield. It has long been recognised that the C-2 position on the N-protected benzimidazole is the most acidic. Hence, the lithiated C-2 anion of 1-(triphenylmethyl)-1H-benzo[d]imidazole 150 was formed using n-BuLi in dry THF at −78 °C, and this was quenched using diphenyl disulfide at 0 °C (Scheme 50).

Scheme 49. Reagents and conditions: i, N-protection; ii, substitution at C-2; iii, N-deprotection; iv, N-alkylation; v, radical cyclisation.

Scheme 50. Reagents and conditions: i, trityl chloride, Et₃N, DCM, rt, 78%; ii, n-BuLi, THF; iii, diphenyl disulfide; iv, conc. HCl, MeOH, reflux, 80%.
The trityl group was hydrolytically cleaved by refluxing compound 151 in acidic aqueous methanol over 3 h to afford 1H-benzo[d]imidazol-2-yl phenyl sulfide 152 in 80% yield. The phenylselanyl alkyl precursors were prepared for subsequent intramolecular alkyl radical cyclisation reactions. The phenylselanyl (PhSe) group is an excellent leaving group in radical reactions but a poor leaving group in S_N2 substitutions. The 1-iodo-ω-(phenylselanyl)alkanes (156-158) were synthesised using methodology previously developed by the Bowman group. The iodine atom in 1-chloro-ω-iodoalkanes was displaced by phenylselanide anion (PhSe⁻), which was generated by reduction of diphenyl diselenide with sodium borohydride as shown in Equation 7 (Scheme 51).

\[
\begin{align*}
X & \quad Cl & \quad \text{(i)} & \quad PhSe & \quad Cl \\
X = I, n = 1 & \quad 153, n = 1 & \quad 154, n = 2 & \quad 155, n = 3 \\
X = Br, n = 2 & \\
\end{align*}
\]

Scheme 51. Reagents and conditions: i, diphenyl diselenide, NaBH₄, MeOH, rt, 153 (86%), 154 (69%), 155 (99%); ii, sodium iodide, acetone, reflux, 156 (82%), 157 (65%), 158 (89%).

The chlorides (153-155) were converted to the iodides as shown in Equation 8 (Scheme 51) by S_N2 displacement using an excess of sodium iodide in acetone. The yields were satisfactory in all cases. The 1-[(ω-phenylselanyl)alkyl]benzimidazole precursors (159-160) were synthesised in moderate to good yields using sodium hydride in dry THF and 1-iodo-ω-(phenylselanyl)alkanes (156-158) as shown in Scheme 52.

\[
\begin{align*}
\text{152} & \quad \text{(i)} & \quad \text{159, n = 1} & \quad \text{160, n = 2} \\
\end{align*}
\]

Scheme 52. Reagents and conditions: i, sodium hydride, ICH₂(CH₂)_nCH₂SePh, THF, reflux, 159 (77%), 160 (54%).
2.1.2 Radical Cyclisations of 1-[(o-Phenylselanyl)alkyl]-2-(phenylsulfanyl)-1H-benzimidazole Radical Precursors (159-160)

1-[3-(Phenylselanyl)propyl]-2-(phenylsulfanyl)-1H-benzo[d]imidazole 159 (Scheme 53) was treated with Bu$_3$SnH under standard radical cyclisation conditions (slow addition of tributyltin hydride, using syringe pump). The work up procedure involved extraction of the benzimidazole compounds into acidic solution, washing with light petroleum in order to remove tributyltin residues and subsequent basification of the aqueous layer afforded 2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole 161 in a 29% yield. Analysis of the petroleum layer showed the presence of tin residues and unidentifiable material. Decomposition must have occurred which accounts for the low yield of the cyclised product 161. The reaction has been previously studied in our group and the proposed mechanism has been outlined in Chapter 1, Section 1.3, Scheme 46.

Scheme 53. Reagents and conditions: i, Bu$_3$SnH, AIBN, toluene, reflux, 29%.

The earlier studies of 5-membered ring cyclisation onto heteroarenes has been shown to be slow due to ring strain. In an attempt to overcome the slow rate of cyclisation of precursor 159, a non-reductive radical reagent was used. In the absence of a H-donating radical source we hoped that a better yield would be obtained.

2.1.3 Use of Hexamethylditin

Hexamethylditin was used in place of Bu$_3$SnH in a photolysis reaction (Chapter 1, Section 1.2.8, Scheme 29) with 1-[3-(phenylselanyl)propyl]-2-(phenylsulfanyl)-1H-benzo[d]imidazole 159 (Scheme 54). We tried to optimise the yield of 2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole.
161, using hexamethylditin and UV lamp irradiation to generate the alkyl radicals for radical cyclisations. We only obtained the cyclised product 161 in 26% yield. The rest of the mixture contained unidentifiable material. We did not observe the reduced product since hexamethylditin was used in place of tributyltin hydride, i.e. there is no source of hydrogen to reduce the intermediate alkyl radical. The reaction was repeated twice using exactly the same conditions without improvement in the yield.

Scheme 54. Reagents and conditions: i, hexamethylditin, t-butylbenzene, hv, 30 h, 85 °C, 26%.

When the same reaction was repeated in toluene we observed the reduced product and the cyclised product in 1:1 ratio. The yield of the cyclised product 161 was more or less the same as it was in the two previous attempts. Therefore, we concluded that toluene is a source of hydrogen which is capable of reducing the intermediate alkyl radical, therefore, we observed the reduced product. We did not observe any reduction when tert-butylbenzene was employed as a solvent as it has a tertiary centre adjacent to the benzene ring. Theoretically, the lack of a hydrogen source should encourage cyclisation over reduction. The low yields of the cyclised product 161 indicate that some kind of decomposition occurs under the conditions employed.

The radical cyclisations of 1-[4-(phenylselanyl)butyl]-2-(phenylsulfanyl)-1H-benzo[d]imidazole 160, to construct 1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine 162, were carried out as illustrated in Scheme 55. The reaction was carried out under different experimental conditions and the results have been summarised in Table 3.

When the radical cyclisation was performed in acetonitrile, a high yield of the cyclised product was obtained. It can be concluded that the best solvent choice is acetonitrile for the synthesis of 1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine 162. The 61% yield compares favourably with the yield previously obtained (54%) in the research group.33
Scheme 55. Reagents and conditions: i, Bu$_3$SnH, radical initiator (AIBN or AMBN), solvent (toluene, cyclohexane or acetonitrile), reflux.

Table 3. Reaction conditions for the synthesis of 1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine 162.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bu$_3$SnH, AIBN, toluene, reflux, 8 h.</td>
<td>25%</td>
</tr>
<tr>
<td>2</td>
<td>Bu$_3$SnH, AIBN, cyclohexane, reflux, 8 h.</td>
<td>23%</td>
</tr>
<tr>
<td>3</td>
<td>Bu$_3$SnH, AMBN, acetonitrile, reflux, 8 h.</td>
<td>61%</td>
</tr>
</tbody>
</table>

Comparison of these radical cyclisation reactions shows that the formation of the six membered ring may be more favourable than the formation of the five membered ring. Although the radical cyclisation of 1-[3-(phenylselanyl)propyl]-2-(phenylsulfanyl)-1H-benzo[d]imidazole 159 proceeds by way of a 5-exo route, and the cyclisation of 1-[4-(phenylselanyl)butyl]-2-(phenylsulfanyl)-1H-benzo[d]imidazole 160 proceeds by way of a 6-exo route, the synthesis of a tricyclic 6,5,5-benzimidazole goes through a very strained transition state. The transition state is much less strained in the formation of the six-membered ring in the cyclisation of the intermediate radical 160a to 1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine 162. This provides evidence that cyclohexane ring formation is more favourable than cyclopentane ring formation when cyclising onto a 5-membered ring heteroarene. It also suggests that the cyclisation rate of the alkyl radical generated from 1-[4-(phenylselanyl)butyl]-2-(phenylsulfanyl)-1H-benzo[d]imidazole 160 is very high. Cyclisation occurs before the alkyl radical can be intercepted and reduced by any source of hydrogen.
2.1.4 Preparation of 2-Chloro-1-[(o-Phenylselanyl)alkyl]-1H-benzimidazole Radical Precursors (164-166)

One of the objectives was to optimise the conditions for radical cyclisations in solution-phase before translating the reaction sequence onto solid-phase. For that purpose, the benzimidazole precursors (164-166) with a chloro substituent at C-2 position were synthesised successfully (Scheme 56). The aim was to compare the reactivity of leaving groups as a result of ipso-substitution.

![Scheme 56](image)

Scheme 56. Reagents and conditions: i, sodium hydride, ICH\(_2\)\((\text{CH}_2)\_n\text{CH}_2\text{SePh}, \text{THF, reflux, 3 h, 164 (61%), 165 (42%), 166 (51%)}.\)

2.1.5 Radical Cyclisation of 2-Chloro-1-[(3-phenylselanyl)propyl]-1H-benzo[d]imidazole 164

The radical precursor 164 was treated with Bu\(_3\)SnH under standard radical cyclisation conditions (slow addition of tributyltin hydride, using syringe pump) (Scheme 57). 2,3-Dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole 161 was afforded in 10% yield. From our studies with the 2-phenylsulfanyl analogue, we expected that the synthesis of 2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole 161 would be difficult due to the strain caused by the formation of two five membered rings. Again, we suggest that the intermediate alkyl radical is quenched by H-transfer from Bu\(_3\)SnH. We observed the reduced product 167 as the major product and the yield of the cyclised product 161 was worse than the yield obtained with the corresponding 2-phenylsulfanyl analogue 159.

From the previous radical cyclisations with the 2-phenylsulfanyl analogues it can be concluded that the formation of tricyclic 6,5,6-benzimidazole is less strained and consequently the degree of cyclisation is greater. All the above mentioned alkyations and cyclisations were performed using the selanide radical precursors. The effect of a different radical precursor was also investigated, bromine instead of a phenylselanyl group.
At that stage we started working on the synthesis of tributylgermanium hydride so that we could test the efficiency of different radical reagents in radical cyclisation reactions.

2.2 Synthesis of Tributylgermanium Hydride

The majority of radical reactions are carried out using tributylin hydride. The synthesis of complex natural products can be handled with ease using key radical transformations. However, it is difficult to remove toxic organotin compounds from desired targets in purification procedures. Organotin compounds are neurotoxic and any food or medicines containing these compounds are unfit for human consumption. For this reason, the use of triorganotin hydrides for the synthesis of medicines, drugs, and food additives is avoided, and non-toxic alternatives to tin hydride have been investigated. Researchers have investigated trialkylgermanium hydrides, including Bu$_3$GeH and (Me$_3$Si)$_3$GeH as potential replacements for tributyltin hydride. Several advantages of Bu$_3$GeH over Bu$_3$SnH have been well documented, tributylgermanium hydride is quite stable. These hydrides generally react less readily with carbon-centred radicals and so have the advantage that simple reduction is less of a problem than for Bu$_3$SnH cyclisations. Studies of the use of triorganogermaanium hydrides as alternatives to Bu$_3$SnH had also been initiated in the research group by Sussie Krintel. Hence we decided to use tributylgermanium hydride; the synthesis and the proposed mechanism for the Cp$_2$TiCl$_2$ catalyzed reaction of GeCl$_4$ with n-BuMgCl to produce Bu$_3$GeH is shown in Scheme 58. The synthesis was very successful and we isolated Bu$_3$GeH in 95% yield.
GeCl₄ + 5 n-BuMgCl $\xrightarrow{\text{Cp₂TiCl₂}}$ n-Bu₃GeH + n-Bu₄Ge

Proposed Mechanism

\[ \text{GeCl}_4 + 3\text{ n-BuMgCl} \rightarrow \text{Bu}_3\text{GeCl} \]

\[
\begin{align*}
\text{GeCl}_4 + 3\text{ n-BuMgCl} & \rightarrow \text{Bu}_3\text{GeCl} \\
\text{Cp}_2\text{TiCl}_2 & \rightarrow \text{Bu}_3\text{GeH} + \text{n-Bu}_2\text{GeH}_2 + \text{Bu}_2\text{GeCl}_2 + \text{Bu}_2\text{GeClH}
\end{align*}
\]

Scheme 58. Synthesis of tributylgermanium hydride.

The experiment was repeated with an excess of germanium tetrachloride and the rest of the conditions were kept identical. This led to incomplete butylation of the GeCl₄ and the reaction afforded a mixture of products which were non-separable. LC-MS analysis of the mixture confirmed the products as shown in Scheme 59. The product mixture was reduced using an excess of LiAlH₄ in dry ether. The reduction step proceeded very efficiently and resulted in the formation of Bu₃GeH and Bu₂GeH₂. Distillation under reduced pressure yielded Bu₃GeH (21%) and Bu₂GeH₂ (28%).

\[
\begin{align*}
\text{GeCl}_4 + \text{BuMgCl} & \xrightarrow{(i)} \text{Bu}_2\text{GeH}_2 + \text{Bu}_3\text{GeH} + \text{Bu}_2\text{GeCl}_2 + \text{Bu}_2\text{GeClH} \\
& \xrightarrow{(ii)} \text{Bu}_2\text{GeH}_2 + \text{Bu}_3\text{GeH}
\end{align*}
\]

Scheme 59. Reagents and conditions: i, cat. Cp₂TiCl₂, ether; ii, LiAlH₄, ether, 0 °C, 20 h.

The efficient separation of Bu₂GeH₂ and Bu₃GeH by distillation under reduced pressure was an interesting improvement of the published protocol in which the mixture of Bu₃GeH and Bu₄Ge had to be distilled two or three times to get clean separation. This different set of conditions needs to be optimised and will possibly lead to an improved synthesis. Bu₂GeH₂ may also prove a useful reagent. Direct reduction of commercially available Bu₃GeCl with LiAlH₄ in dry ether is another option which involves less synthetic steps and relatively less expensive route to the desired radical reagent.
2.2.1 Radical Cyclisation of 1-(4-Bromobutyl)-2-chloro-1H-benzo[d]imidazole 168

1-(4-Bromobutyl)-2-chloro-1H-benzo[d]imidazole 168 was successfully prepared by alkylation of 2-chlorobenzimidazole 163 with 1,4-dibromobutane and the radical cyclisation was carried out using tributylgermanium hydride (one pot addition) as shown in Scheme 60.

Scheme 60. Reagents and conditions: i, sodium hydride, 1,4-dibromobutane, DMF, 20 h, 168 (95%); ii, Bu₃GeH, AIBN, toluene, reflux, 12 h, 162 (54%).

The work up procedure involved extraction of the cyclised adduct 162 into acidic solution and washing with light petroleum in order to remove tributylgermanium residues. Subsequent basification of the aqueous layer gave 1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine 162 in a yield of 54%. Tributylgermanium hydride was used as an alternative to tributyltin hydride to increase and optimise the yield of the cyclised material. The advantages of germanium hydride include an easy work up procedure and it also eliminates the use of syringe pump (slow addition of a radical reagent).

2.3 Preparation of Imidazole Radical Precursors

A large number of imidazole derivatives show biological activity, e.g. nitroimidazoles, which are used as antibiotics and anticancer agents. The radical cyclisation onto imidazoles has been documented by Bowman et al. These cyclisations involved an intramolecular ipso-substitution protocol. One of the objectives of our project was to synthesise imidazole moieties using radical methodology on solid-support to avoid purification problems and to test various radical reagents to promote cyclisation onto imidazoles tethered to the resin. For that purpose, we decided to construct a solution-phase model to determine the efficiency of radical cyclisation and then translate it onto resin.
Earlier studies in the group had shown that *ipso*-substitution could be carried out on 2-(phenylsulfonyl)imidazoles (Scheme 61).  

![Scheme 61](image)

**radical precursor** | **product (% yield)**
---|---
169a, $Z = Ts, \quad n = 1$ | 172a, 52%  
169b, $Z = Ts, \quad n = 2$ | 172b, 48%  
169c, $Z = Ts, \quad n = 3$ | 172c, 63%  
170, $Z = SPh, \quad n = 1$ | 172a, 16%  
171, $Z = PhSO_2, \quad n = 1$ | 172a, 51%

**Scheme 61.** *Reagents and conditions:* i, $Bu_3SnH$, AIBN, toluene, reflux.

This work reported that the yields of cyclisation were moderate to good when PhSO$_2$ was the leaving group but when phenylsulfanyl (PhS) was used as the leaving group the yield of cyclisation was low with a slightly higher yield of reduced product (18%). The authors suggested that the stronger electron withdrawing group (PhSO$_2$) was required to facilitate the cyclisation step. PhSO$_2$ makes the ring more electron deficient and accelerates attack by the nucleophilic alkyl radical. Therefore, when imidazoles are used a more electron withdrawing group (or better leaving group) is required. The imidazole ring in benzimidazole is less aromatic and hence, addition of the intermediate radical in cyclisation is more facile and the more weakly electron withdrawing 2-(phenylsulfanyl) group is sufficient to facilitate cyclisation over reduction. Caddick *et al.* in their studies on 2-substituted indoles had shown that PhSO$_2$ was best but that PhSO and PhS also worked but the yields of the desired cyclised adducts were less satisfactory than those obtained with the corresponding sulfones.

We therefore considered that a more electron withdrawing arylsulfanyl group may prove useful. We also sought an easier route to introduce the Z-leaving group. In order to test this hypothesis 1H-imidazole-2-yl pyridin-2-yl sulfide 174 was synthesised by substitution of 2-chloropyridine with commercially available 2-mercaptoimidazole 173 and subsequent alkylation reaction afforded 1-[4-(phenylselanyl)butyl]-1H-imidazole-2-yl pyridin-2-yl sulfide 175 in excellent yield (99%) (Scheme 62). Thiopyridine was chosen as a possible radical leaving group for *ipso* substitution because of its electron withdrawing nature.
Scheme 62. Reagents and conditions: i, potassium carbonate, 2-chloropyridine, DMF, reflux, 174 (95%); ii, sodium hydride, ICH₂(CH₂)₂CH₂SePh, THF, reflux, 175 (99%).

The thiopyridine moiety should be a good radical leaving group due to its electron withdrawing nature and we assumed that it would result in higher cyclisation yields to give the desired bi-cyclic imidazole adducts. Furthermore, for solid-phase radical reactions, pyridine could be used as a linker with a handle which could either be hydroxy or carboxy functionality to be attached to the solid-support. We also synthesised 1H-benzo[d]imidazole-2-yl pyridin-2-yl sulfide 177 (Scheme 63) to investigate the radical cyclisations on benzimidazole moiety with a more electron withdrawing radical leaving group. The yield was not optimised.

Scheme 63. Reagents and conditions: i, potassium carbonate, 2-chloropyridine, DMF, reflux, 40%.

2.3.1 Radical Cyclisations of 1-[4-(Phenylselanyl)butyl]-1H-imidazole-2-yl pyridin-2-yl sulfide 175

The radical methodology was applied to 1-[4-(phenylselanyl)butyl]-1H-imidazole-2-yl pyridin-2-yl sulfide 175 as shown in Scheme 64. Radical cyclisations were attempted under various experimental conditions as summarized in Table 4. In most attempts the cyclised product was not observed except when we performed reaction at room temperature using triethylborane as an initiator and tris-(trimethylsilyl)silane as a radical generating reagent (Entry 4). The reaction resulted in the formation of 5,6,7,8-tetrahydroimidazo[1,2-a]pyridine 180 in 9% yield. We also observed the formation of 1-butyl-1H-imidazol-2-yl pyridin-2-yl sulfide 179 in 16% yield. Entries 1 and 2 show the formation of 1-[but-3-enyl]-1H-imidazole-2-yl pyridin-2-yl sulfide 178. The reason
for the formation of 1-[but-3-enyl]-1H-imidazole-2-yl pyridin-2-yl sulfide 178 is unknown but this kind of alkene by-product has also been observed in other radical cyclisation reactions in our group which involve cyclisations onto azoles.

\[
\begin{array}{c}
\text{175} \\
\text{SePh} \\
\end{array} \rightarrow 
\begin{array}{c}
\text{178} \\
\text{179} \\
\text{180} \\
\text{175} \\
\end{array}
\]

Scheme 64. Radical cyclisation of 1-[4-(phenylselanyl)butyl]-1H-imidazole-2-yl pyridin-2-yl sulfide 175.

Table 4. Reaction conditions for the synthesis of 5,6,7,8-tetrahydroimidazo[1,2-a]pyridine 180.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bu$_3$SnH (slow addition), AIBN, toluene, reflux, 10 h.</td>
<td>Alkene by-product 178 (60%) and starting material 175 (20%)</td>
</tr>
<tr>
<td>2</td>
<td>Bu$_3$GeH, AIBN, toluene, reflux, 14 h.</td>
<td>Alkene by-product 178 (12%) and starting material 175 (30%)</td>
</tr>
<tr>
<td>3</td>
<td>TTMSS, BE$_3$, acetonitrile/cyclohexane, 24 h.</td>
<td>All starting material 175</td>
</tr>
<tr>
<td>4</td>
<td>TTMSS, BE$_3$, benzene, 24 h.</td>
<td>Reduced product 179 (16%) and cyclised product 180 (9%)</td>
</tr>
</tbody>
</table>

The results of these radical cyclisations indicate that it is not feasible to translate the synthetic sequence onto solid-support as thiopyridine is apparently not an efficient radical leaving group or facilitator of the cyclisation step. Therefore, we decided to adopt other strategies, i.e. to find other suitable linkers which can serve as an efficient leaving group during ipso-substitution processes.

In the next chapter we describe our studies of solid-supported benzimidazole precursors and corresponding radical cyclisations.
CHAPTER 3

Intramolecular Radical Cyclisations, by "ipso" Substitution, of Solid-Supported Benzimidazoles

3.1 Synthesis of Solid-Supported Benzimidazole Derivatives

In adapting our solution-phase ipso-substitution methodology to solid-phase, suitable precursors were required for attachment to the resin. There were several approaches under consideration for solid-supported radical reactions as shown in Chapter 1, Section 1.3, Scheme 47. We decided to study several different benzimidazole derivatives having a carboxyl functionality to provide the useful handle for attachment to solid-phase. Initially we investigated benzimidazole derivatives with the carboxylic acid on the leaving group. Methyl 2-((H-benzo[d]imidazol-2-ylsulfanyl)ethanoate 181 was selected as a solution-phase mimic for potential solid-phase work, as it has the handle to be attached to the resin. A putative synthesis for radical precursors and radical cyclisation is shown in Scheme 65.

Scheme 65. Reagents and conditions: i, NaH, ICH$_2$(CH$_2$)$_n$CH$_2$SePh, THF, reflux; ii, 2 M NaOH, methanol, reflux; iii, Wang resin, DMAP, DIC, DCM; iv, Bu$_3$SnH, AIBN, toluene, reflux.
This route does leave both the product and the Bu$_3$Sn-moieties in solution, therefore requiring separation after the solid-phase reaction. The advantages would be the ability to recycle the thiol and that unreacted starting material and uncyclised reduced material would be left attached to the resin. The latter should greatly assist purification of cyclised products. In the benzimidazole studies the cyclised products are easily separated from Bu$_3$Sn-residues by extraction in acidic solution.

As a first stage in our synthetic endeavours, we decided to perform the esterification of 2-benzimidazolylsulfanyl)acetic acid. The esterification of (2-benzimidazolylsulfanyl)acetic acid 187 gave the desired methyl 2-(1H-benzo[d]imidazol-2-ylsulfanyl)ethanoate 181 in 89% yield as illustrated in Scheme 66.

![Scheme 66](image)

Scheme 66. Reagents and conditions: i, acetyl chloride, MeOH, reflux, 89%.

The alkylation of methyl 2-(1H-benzo[d]imidazol-2-ylsulfanyl)ethanoate 181 was investigated. Simple methylation was attempted to synthesise methyl 2-[(1-methyl-1H-benzo[d]imidazol-2-yl)sulfanyl]ethanoate 188 (Scheme 67). The reaction resulted in the formation of a complex product mixture. Further alkylation attempts were also not fruitful, probably due to the molecule having more than one reactive site for deprotonation. Hence, due to complexities that arose as a result of alkylation, we considered that another route had to be investigated.

![Scheme 67](image)

Scheme 67. Reagents and conditions: i, sodium hydride, MeI, THF, reflux.
3.1.1 Studies Using Mercaptobenzoic Acid as a Linker and a Leaving Group

We decided to look at other alternative approaches such as developing a synthetic sequence which involved less synthetic steps towards the synthesis of solid-supported benzimidazole precursors (Scheme 68). It is highly desirable to minimise demanding synthetic steps when planning a solid-phase synthesis and therefore it is easier to adapt established solution-phase precedents to polymer supported reaction. We also needed compounds which contained less reactive sites. The use of cheap and readily available 2-chlorobenzimidazole 163 appeared a good route to test the homolytic aromatic substitution protocol on solid-phase. Possible routes to the required radical precursors attached to solid-support are shown in Scheme 68.

Scheme 68. Putative syntheses of solid-supported benzimidazole precursors and radical cyclisations.

The solid-supports which we employed for radical reactions are shown in Scheme 69.
Scheme 69. Common solid-supports for organic reactions.

Primarily, we decided to synthesise simple precursors to check the feasibility of further application and S$_N$Ar reactions at the C-2 position of 2-chlorobenzimidazole 163 with thiolates (Scheme 70). The synthesis of 2-chloro-1-(triphenylmethyl)-1H-benzo[d]imidazole 193 and 2-chloro-1-methyl-1H-benzo[d]imidazole 195 proceeded well (Scheme 70). Therefore C-2 substitutions on 2-chloro-1-(triphenylmethyl)-1H-benzo[d]imidazole 193 and 2-chloro-1-methyl-1H-benzo[d]imidazole 195 were performed under different experimental conditions. The initial attempts were not successful, but after a few attempts, the difficulties were overcome and we managed to get satisfactory substitutions. The results are summarized in Table 5.

Scheme 70. Reagents and conditions: i, trityl chloride, Et$_3$N, DCM, 193 (30%); ii, NaH, MeI, THF, reflux 195 (64%); iii, PhSH, bases (NaH or KOH), solvents (THF or ethanol) 196 (85%).
Table 5. Reaction conditions for the synthesis of benzimidazole derivatives 194 and 196.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Compound 193, NaH, PhSH, THF, reflux overnight.</td>
<td>Unsuccessful</td>
</tr>
<tr>
<td>2</td>
<td>Compound 193, PhSH, EtOH, KOH, 16 h reflux.</td>
<td>Unsuccessful</td>
</tr>
<tr>
<td>3</td>
<td>Compound 195, NaH, PhSH, THF, reflux overnight.</td>
<td>70%</td>
</tr>
<tr>
<td>4</td>
<td>Compound 195, PhSH, EtOH, KOH, 16 h reflux.</td>
<td>85%</td>
</tr>
</tbody>
</table>

The failure of C-2 substitution, in the case of 2-chloro-1-(triphenylmethyl)-1H-benzo[d]imidazole 193, is associated with the steric hindrance of bulky trityl group. Substitution with the less sterically hindered 2-chloro-1-methyl-1H-benzo[d]imidazole 195 proceeded without difficulty. The next substitution we studied was between 2-chlorobenzimidazole 163 and benzenethiol prior to protection or alkylation reactions (Scheme 71). The substitution reaction was carried out under different experimental conditions (Table 6). The substitution reaction afforded 1H-benzo[d]imidazol-2-yl phenyl sulfide 152 in 66% yield (Entry 4).

Scheme 71. Reagents and conditions: i, PhSH, EtOH, KOH, reflux, 66%.

Table 6. Reaction conditions for the synthesis of 1H-benzo[d]imidazol-2-yl phenyl sulfide 152.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K₂CO₃, PhSH, acetone, rt.</td>
<td>Unsuccessful</td>
</tr>
<tr>
<td>2</td>
<td>Et₃N, PhSH, DCM, rt.</td>
<td>Unsuccessful</td>
</tr>
<tr>
<td>3</td>
<td>NaH, PhSH, THF, reflux, overnight.</td>
<td>Unsuccessful</td>
</tr>
<tr>
<td>4</td>
<td>PhSH, EtOH, KOH, reflux, 6 h.</td>
<td>66%</td>
</tr>
</tbody>
</table>
After establishing the correct conditions for the substitution at the C-2 position of 2-chlorobenzimidazole 163, the next step was the introduction of 4-mercaptobenzoic acid 189 (a linker) via ipso-substitution as shown in Scheme 72. The ipso-substitution of chlorine at the C-2 position of 2-chlorobenzimidazole 163 with 4-mercaptobenzoic acid 189 was successful and 4-(1H-benzo[d]imidazol-2-ylsulfanyl)benzene-1-carboxylic acid 190 was afforded in a 68% yield. To optimise the yield, varying equivalents of potassium hydroxide were used and the rest of the parameters were kept identical. No significant change was observed. An excess of potassium hydroxide could result in substitution to yield 2-hydroxybenzimidazole and then tautomerism to 1,3-dihydrobenzimidazole-2-one. Further hydrolysis could open the 5-membered ring.

Scheme 72. Reagents and conditions: i, 4-mercaptobenzoic acid 189, EtOH, KOH, reflux, 68%.

Alkylation of 4-[(1H-benzo[d]imidazol-2-yl)sulfanyl]benzene-1-carboxylic acid 190 to synthesise 4-{1-[3-(phenylselanyl)propyl]-1H-benzo[d]imidazol-2-yl}sulfanyl]benzene-1-carboxylic acid 197 was also attempted, but under the conditions employed, the lack of protection of carboxy proton resulted in complications (Scheme 73).

Scheme 73. Reagents and conditions: i, sodium hydride, 1-iodo-3-(phenylselanyl)propane, THF, reflux.

After considering the difficulties involved in the alkylation of 4-(1H-benzo[d]imidazol-2-ylsulfanyl)benzene-1-carboxylic acid 190, we decided that the best choice was to perform substitution reactions on previously alkylated 2-chlorobenzimidazole precursors (164-166) (Chapter 2, Section 2.1.4, Scheme 56). The S_vAr reactions on these alkylated 2-chlorobenzimidazoles were very successful (Scheme 74).
Scheme 74. Reagents and conditions: i, 4-mercaptobenzoic acid 189, potassium tert-butoxide, ethanol, reflux, 18 h, 197 (90%), 198 (quantitative), 199 (quantitative).

3.1.2 Synthesis of 4-Mercapto-N-(4-methylbenzyl)-benzamide 200 for S_N Ar Substitution Reactions

The other alternative approach under investigation towards the solid-supported benzimidazole precursors was the attachment of the linker to the desired solid-support (resin) followed by subsequent S_N Ar substitution. First of all, we decided to develop a solution-phase protocol as a guide for solid-phase procedures. The carboxyl group on the linker can be attached either as an ester (Wang, Merrifield) or by an amide (Rink, Amino Merrifield). We decided to initially investigate the possibility of amide attachment.

Our initial work involved a sample coupling reaction between 4-mercaptobenzoic acid 189 and 4-methylbenzylamine to synthesise 4-mercaptopo-N-(4-methyl-benzyl)-benzamide 200 as a mimic of the solid-phase system (Scheme 75). The conditions would subsequently be employed for the substitution of 2-chlorobenzimidazole163 on solid-phase. Unfortunately all the attempts to synthesise 4-mercaptopo-N-(4-methylbenzyl)-benzamide 200 failed (Table 7).

Scheme 75. Reagents and conditions: i, 4-methylbenzylamine, DIC, DMAP, DCM, rt.
Table 7. Reaction conditions for the synthesis of 4-mercapto-N-(4-methylbenzyl)-benzamide 200.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DIC, DMAP (cat.), 4-methylbenzylamine, DCM, rt, 18 h.</td>
<td>Unsuccessful</td>
</tr>
<tr>
<td>2</td>
<td>EDCI, NMM, 4-methylbenzylamine, DCM, -15 °C, 3 h.</td>
<td>Unsuccessful</td>
</tr>
<tr>
<td>3</td>
<td>EDCI, Et₃N, 4-methylbenzylamine, DCM, rt, 18 h.</td>
<td>Unsuccessful</td>
</tr>
<tr>
<td>4</td>
<td>DIC, DMAP (cat.), 4-methylbenzylamine, DCM, reflux, 18 h.</td>
<td>Unsuccessful</td>
</tr>
</tbody>
</table>

References in the literature⁹⁹ provided an insight into the failure of desired coupling, i.e. the unprotected thiol functionality of 4-mercaptobenzoic acid 189 is very reactive towards the intermediate carbodiimide complexes and hence, resulted in the formation of thioester. Therefore, it was decided to investigate other methods for solution-phase reactions, e.g. to form mixed anhydrides using chlorosulfonyl isocyanate⁹⁰ or isobutyl chloroformate⁹¹ and then react it with 4-methylbenzylamine to form an amide linkage. We decided to protect the 4-mercaptobenzoic acid 189 with a triphenylmethyl group prior to performing coupling reaction with 4-methylbenzylamine. The subsequent cleavage of the trityl group would result in the formation of the 4-mercapto-N-(4-methylbenzyl)-benzamide 200 and allow substitution reactions to be carried out on 2-chlorobenzimidazole derivatives. The protection of the 4-mercaptobenzoic acid 189 with a trityl group was performed as shown in Scheme 76. The reaction was carried out under two different sets of experimental conditions (Table 8). The use of triphenylmethanol proved more successful than the use of triphenylmethyl chloride.
Table 8. Reaction conditions for the synthesis of 4-(tritylsulfanyl)-benzoic acid 201.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-mercaptobenzoic acid 189, trityl chloride, Et₃N, DCM.</td>
<td>12%</td>
</tr>
<tr>
<td>2</td>
<td>4-mercaptobenzoic acid 189, triphenylmethanol, TFA, Et₃N, DCM.</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Scheme 76. Reagents and conditions:** i, triphenylmethanol, TFA, reflux, 100%.

4-(Tritylsulfanyl)-benzoic acid 201 was coupled with 4-methylbenzylamine as illustrated in Scheme 77. However the reaction afforded two products that co-eluted on column chromatography which made the purification difficult and furthermore cleavage of S-trityl under different experimental conditions also failed (Table 9). As the deprotection of S-trityl protected 202 proved difficult so we decided to look at another protecting group. 4-(Acetylsulfanyl)-benzoic acid 203 was synthesised in excellent yield (Scheme 78).

**Scheme 77. Reagents and conditions:** i, ClSO₂-NCO, Et₃N, 4-methylbenzylamine, DCM; ii, acidic conditions.
Table 9. Attempted synthesis of 4-mercaptop-N-(4-methylbenzyl)-benzamide 200.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TFA, DCM, reflux.</td>
<td>Unsuccessful</td>
</tr>
<tr>
<td>2</td>
<td>1 M HCl, MeOH, reflux.</td>
<td>Unsuccessful</td>
</tr>
<tr>
<td>3</td>
<td>HBr/acetic acid 30 % wt.</td>
<td>Unsuccessful</td>
</tr>
</tbody>
</table>

Scheme 78. Reagents and conditions: i, acetic anhydride, pyridine, rt, 100%.

Coupling reactions using 203 were performed to afford 4-mercaptop-N-(4-methylbenzyl)-benzamide 200 under different experimental conditions (Scheme 79). The results are summarised in Table 10. The major product of the coupling reactions was an undesired by-product 204 as shown in Scheme 79. The undesired reaction pathway led to in-situ transfer of the acetyl group from sulfur to nitrogen. The S-acetyl group is very labile under the reaction conditions employed and therefore we decided to abandon this methodology and continue work on S-trityl precursor 201.

Scheme 79. Attempted synthesis of 4-mercaptop-N-(4-methylbenzyl)-benzamide 200.

Table 10. Synthesis of 4-mercaptop-N-(4-methylbenzyl)-benzamide 200.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-methylbenzylamine, NMM, EDCI, DCM&lt;sup&gt;94&lt;/sup&gt;</td>
<td>15 %</td>
</tr>
<tr>
<td>2</td>
<td>4-methylbenzylamine, CISO&lt;sub&gt;2&lt;/sub&gt;NCO, Et&lt;sub&gt;3&lt;/sub&gt;N, DCM&lt;sup&gt;90&lt;/sup&gt;</td>
<td>Poor yield</td>
</tr>
</tbody>
</table>
Further study of the coupling reaction between 4-(tritylsulfanyl)-benzoic acid 201 and 4-methylbenzylamine gave better yields and when HOAT was employed as the coupling agent with EDCI, a high yield (86%) of amide 202 was obtained. Cleavage of the S-trityl group was also accomplished by a literature procedure.\(^{95}\)

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{S} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\text{COOH} & \quad \text{CO} \\
\hline
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

\[\text{(i)}\]

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{S} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\text{HN} & \quad \text{Q} \\
\hline
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

\[\text{(ii)}\]

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{S} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\text{HN} & \quad \text{Q} \\
\hline
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

#### Scheme 80. Reagents and conditions:
- i, 4-methylbenzylamine, HOAT, EDCI, DCM, 86%;
- ii, TFA/DCM/Et\(_3\)SiH (9:10:1), rt, 17%.

### 3.1.3 Coupling Reactions

Our first solid-phase studies were conducted with Wang resin (Section 3.1.1, Scheme 69). The efficient preparation of benzimidazole derivatives on solid-support in high yield and purity is illustrated in Scheme 81. The coupling reactions of benzimidazole acid derivatives (197-199) were carried out using corresponding diisopropylcarbodiimide (DIC), with DMAP added to catalyse the esterification of Wang resin. The results of the coupling reactions showed that for complete immobilisation (loading) of the benzimidazole acid precursors (197-199) onto Wang resin, it was necessary to perform double coupling (to attain a high loading of 205-207).

In order to monitor the outcome of a reaction carried out on the solid-support we found that FT-IR spectroscopy using samples of the resin prepared as a KBr disk to be a suitable and informative method for identification of polymer-supported organic compounds. IR spectra for the benzimidazole precursors (205-207) show the formation of ester band and (MAS) \(^1\)H NMR spectra show complete immobilisation (attachment) of benzimidazole precursors onto resin. The loadings were assessed by cleavage and analysis of a portion of the resin-bound precursors (205-207) prior to
performing the cyclisation reactions.

Scheme 81. Reagents and conditions: i, NaH, THF, ICH₂(CH₂)ₙCH₂SePh, reflux; ii, 4-mercaptobenzoic acid, potassium tert-butoxide, ethanol, reflux; iii, Wang resin, DIC, DMAP, DCM, DMF; iv, radical mediators (tributyltin hydride, TTMSS, tributylgermanium hydride), radical initiators (AIBN, AMBN) and common solvents as described in tables 11, 12, 13, 14.

We also used Rink resin and amino Merrifield resin (Section 3.1.1, Scheme 69) for coupling reactions (Scheme 82). The objective was to compare the compatibility of these resins with radical cyclisation conditions.

Scheme 82. Reagents and conditions: i, amino Merrifield resin or Rink resin, DIC, DMAP or HOAT, DCM, DMF; ii, radical mediators (tributyltin hydride, TTMSS, tributylgermanium hydride), radical initiators (AIBN, AMBN) and common solvents as described in tables 11 and 12.
We continued our efforts to develop different routes towards solid-supported benzimidazole precursors. One of the routes involved the attachment of 4-tritylsulfanyl-benzoic acid 201 to the resin. The coupling reaction was carried out using amino Merrifield resin (Scheme 83). The IR spectrum of the resin-bound moiety 210 showed the amide band at 1718 cm\(^{-1}\) and 1654 cm\(^{-1}\), and thereby confirmed the successful attachment of the 4-(tritylsulfanyl)-benzoic acid 201 to the resin. Elemental analysis was not conclusive hence quantitative loading was not determined.

![Scheme 83. Reagents and conditions: i, 4-(tritylsulfanyl)-benzoic acid 201, DIC, HOAT, DCM.](image)

This alternative putative synthesis of solid-supported benzimidazole precursors is illustrated in Scheme 84. The idea was to develop a traceless linker for radical ipso-substitution reactions on resin and regenerate the linker at the end of the reaction and re-use it. This protocol could allow the same resin-linker to be used for a variety of different heterocycles to be loaded via S\(_x\)Ar reaction. Due to lack of time this protocol was not further studied but provides another potential route for radical synthesis on solid-phase.

![Scheme 84. Reagents and conditions: i, TFA/DCM/Et\(_3\)Si, rt; ii, 2-chlorobenzimidazole derivatives (164-166), KOH, a suitable solvent for solid-phase reaction; iii, Bu\(_3\)SnH, AIBN, toluene, reflux.](image)
3.1.4 Radical Cyclisations of Solid-Supported Benzimidazole Precursors

The solid-supported benzimidazole precursors (205-207) were subjected to radical cyclisations under various experimental conditions. The idea was to optimise the conditions required for radical reactions, e.g. the use of several radical reagents, amounts of initiators, reaction times, temperature, loading levels on the resins and attachment and cleavage conditions. Success of these solid-supported radical cyclisations would enable us to extend the study to more complicated and novel reactions to show that solid phase synthesis can be applied to new radical syntheses as a common synthetic tool.

Synthesis of 2,3-Dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole 161 on Solid-Phase

We performed the radical cyclisations on Wang resin-bound benzimidazole 205 as shown in Scheme 85. The results are summarised in Table 11. In all these radical cyclisation reactions the product was easily separated by filtration from the resin and the Bu₃Sn-residues separated by extraction of cyclised product 161 into dilute acid. Unreacted starting material and reduced product were cleaved off the resin using TFA/DCM (9:1). The LC/MS analysis of the cleaved material confirmed the presence of reduced product and starting material (Entries 4 and 6). We did not determine the yields of the reduced product 212 and starting material 197 in all these instances as the cleaved sample was contaminated with tin residues and other by-products hence we submitted the crude sample for purification (using automated Flex HPLC, reversed phase column chromatography). We managed to get pure reduced product 212 but loss of material occurs during this automated purification process.

![Scheme 85. Synthesis of 2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole 161 on solid-phase.](image-url)
Table 11. Reaction conditions for the synthesis of 2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole 161.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Resin 208, Bu₃SnH, AIBN, benzene, reflux, 18 h, one pot addition.</td>
<td>161 (trace)</td>
</tr>
<tr>
<td>2</td>
<td>Resin 205, Bu₃SnH, AIBN, benzene, reflux, 24 h, one pot addition.</td>
<td>161 (trace), 212 also observed</td>
</tr>
<tr>
<td>3</td>
<td>Resin 205, Bu₃SnH, AIBN, benzene, reflux, 48 h, one pot addition.</td>
<td>161 (trace), 212 also observed</td>
</tr>
<tr>
<td>4</td>
<td>Resin 205, Bu₃SnH, AIBN, benzene, slow addition over 7 h. Overall reflux 8 h.</td>
<td>161 (3 %), 212 (10%) and 197 (41%)</td>
</tr>
<tr>
<td>5</td>
<td>Resin 205, Bu₃SnH, AIBN, benzene, slow addition over 5 h. The addition of reagents was repeated over 5 h. Overall reflux 10 h.</td>
<td>161 (5 %), 212 also observed</td>
</tr>
<tr>
<td>6</td>
<td>Resin 205, Bu₃SnH, AIBN, toluene, slow addition over 26 min, reflux. Further Bu₃SnH/AIBN was added after 3 h. Overall reflux 5 h.</td>
<td>161 (11 %), 212 and 197 also observed</td>
</tr>
<tr>
<td>7</td>
<td>Resin 205, Bu₃SnH, AIBN, benzene, slow addition over 2 h, reflux. Further Bu₃SnH/AIBN was added after 3 h. Overall reflux 5 h.</td>
<td>161 (5 % ), 212 also observed</td>
</tr>
</tbody>
</table>

We obtained all the spectroscopic data to confirm the structure of the reduced product 212. None of the above mentioned reaction conditions led to a significant improvement in the yield of 2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole 161 and this poor yield could be associated with the ring strain which in turn favours reduced product 212 over cyclised product 161. Synthesis of 2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole 161 in solution-phase also gave poor yields. These results indicate that solid-phase synthesis provides similar results to solution-phase, i.e. no real advantage.

Therefore, we decided to work on other resin-bound benzimidazole moieties to construct tricyclic 6,5,6-fused and 6,5,7-fused benzimidazole derivatives. The first studies were on the Wang resin-bound precursor 206 as shown in Scheme 86 and Table 12. The analogous reaction in solution-phase proceeded in high yield. The synthesis of 1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine 162 on solid-phase was performed under different experimental conditions. Entries 4 and 8 showed the best results achieved so far and in both instances the yields were comparable with solution-phase
reactions. In all these radical cyclisation reactions unreacted starting material \textit{198}, reduced product \textit{213} and alkene-by product \textit{214} were cleaved off the resin using TFA/DCM (9:1). The LC/MS analysis was carried out on cleaved material to confirm the products. We did not determine the yields of the reduced product \textit{213}, alkene by-product \textit{214} and unreacted starting material \textit{198} in all these instances as the cleaved samples were contaminated with tin residues and other by-products. Hence we submitted the crude sample for purification using automated Flex HPLC, reversed phase column chromatography.

We managed to get pure reduced product \textit{213}, alkene by-product \textit{214} and unreacted starting material \textit{198} but loss of material occurs during this automated purification process. We obtained all the spectroscopic data to confirm the structure of the reduced product \textit{213} and the alkene by-product \textit{214}. Also, as expected, slow addition of Bu$_3$SnH gave better yields of cyclisation and less of uncyclised reduced product \textit{213}. The dilution effect of the sites on the resin does not overcome one-pot addition and dilution of Bu$_3$SnH is still required by using syringe pump addition.

![Scheme 86. Synthesis of 1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine 162 on solid-phase.](image)

The results also show that both Rink resin \textit{209} (Entry 7) and Wang resin \textit{206} are quite compatible for radical reactions. When TTMSS (Entries 9 and 10) and tributylgermanium hydride (Entry 13) were used as radical mediators, the yields of the cyclised product \textit{162} are not as good as with tributyltin hydride.
Table 12. Reaction conditions for the synthesis of 1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine 162.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Resin 206, Bu$_3$SnH, AIBN, benzene, slow addition over 12 h, reflux.</td>
<td>162 (14 %), 213, 198 and 214 were also isolated</td>
</tr>
<tr>
<td>2</td>
<td>Resin 206, Bu$_3$SnH, AIBN, benzene, slow addition over 12 h, overall reflux 48 h.</td>
<td>162 (trace), 198 and 214 were also isolated</td>
</tr>
<tr>
<td>3</td>
<td>Resin 206, Bu$_3$SnH, AIBN, benzene, one pot addition, overall reflux 48 h.</td>
<td>162 (3 %), 198 and 214 were also isolated</td>
</tr>
<tr>
<td>4</td>
<td>Resin 206, Bu$_3$SnH, AIBN, benzene, slow addition over 7 h, then filtration followed by washing, addition of equimolar reagents over 7 h, reflux.</td>
<td>162 (60 %), 213 and 214 were also isolated</td>
</tr>
<tr>
<td>5</td>
<td>Resin 206, Bu$_3$SnH, AIBN, benzene, slow addition over 7 h, reflux.</td>
<td>162 (49 %)</td>
</tr>
<tr>
<td>6</td>
<td>Resin 206, Bu$_3$SnH, AIBN, DMF/benzene (6/5 mL), slow addition over 4.5 h, overall reflux 7 h.</td>
<td>162 (9 %), 198 and 214 were also isolated</td>
</tr>
<tr>
<td>7</td>
<td>Rink resin 209, Bu$_3$SnH, AIBN, benzene, slow addition over 6 h, overall reflux 7 h.</td>
<td>162 (44 %), 213 and 198 were also isolated</td>
</tr>
<tr>
<td>8</td>
<td>Resin 206, Bu$_3$SnH, AIBN, benzene, slow addition over 7 h, overall reflux 8 h.</td>
<td>162 (57 %), 213 was also isolated</td>
</tr>
<tr>
<td>9</td>
<td>Resin 206, TTMSS, AIBN, benzene, one pot addition, reflux 10 h.</td>
<td>162 (20 %), 213 was also isolated</td>
</tr>
<tr>
<td>10</td>
<td>Resin 206, TTMSS, AIBN, benzene, slow addition over 5 h, overall reflux 8 h.</td>
<td>162 (16 %), 213 was also isolated</td>
</tr>
<tr>
<td>11</td>
<td>Resin 206, Bu$_3$SnH, AIBN, toluene, slow addition over 2 h, then 3 h further reflux. Another addition of Bu$_3$SnH/AIBN. A further 1.5 h reflux.</td>
<td>162 (49 %), 213 and 214 were also isolated</td>
</tr>
<tr>
<td>12</td>
<td>Resin 206, Bu$_3$SnH, AIBN, benzene, slow addition over 2 h, then 3 h further reflux. Another addition of Bu$_3$SnH/AIBN. A further 1.5 h reflux.</td>
<td>162 (58 %), 213 and 214 were also isolated</td>
</tr>
<tr>
<td>13</td>
<td>Resin 206, Bu$_3$GeH, AIBN, toluene, one pot addition, overall reflux 8 h.</td>
<td>162 (22 %), 198 was also isolated</td>
</tr>
</tbody>
</table>

Tributylgermanium hydride did not work efficiently with the phenylselenyl system. Bu$_3$GeH has a stronger Ge-H bond than the Sn-H bond in Bu$_3$SnH and reacts ca. 20 x slower. Therefore, to
achieve higher yields with Bu₃GeH longer reaction times will be required. Another reason could be associated with phenylselanyl formation which can inhibit radical reactions. A lot of unreacted material was observed which may suggest that inhibition is a problem. However, the results still prove that TTMSS and tributylgermanium hydride can be used as an alternative to tributyltin hydride for solid-phase radical reactions, but obviously the conditions have to be optimised for these radical mediators.

**Synthesis of 7,8,9,10-Tetrahydro-6H-benzo[4,5]imidazo[1,2-a]azepine 215 on Solid-Phase**

In order to complete our studies on solid-phase we needed to carry out 5-, 6- and 7-membered ring cyclisations. The 5-membered ring cyclisations were as disappointing as the solution-phase whereas 6-membered ring cyclisations were optimised to similar yields as solution-phase. 7-Membered ring cyclisations suffer from an unfavourable entropy barrier, and very low yield of 7,8,9,10-tetrahydro-6H-benzo[4,5]imidazo[1,2-a]azepine 215 was achieved in solution-phase (17%). We performed 7-membered ring radical cyclisations on Wang resin-bound benzimidazole 207 as shown in Scheme 87. The results are summarised in Table 13. The yield of the seven membered [1,2-a]fused benzimidazole 215 was poor in both instances; more work needs to be carried out to maximise the yield. The factor behind the poor yield could be the entropy barrier which disfavours the radical cyclisation which results from a large ring size.

![Scheme 87](image)

Table 13. Reaction conditions for the synthesis of 7,8,9,10-tetrahydro-6H-benzo[4,5]imidazo[1,2-a]azepine 215.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bu₃SnH, AIBN, benzene, slow addition over 5 h, then 5 h further reflux.</td>
<td>215 (2 %), 216 also isolated</td>
</tr>
<tr>
<td>2</td>
<td>Bu₃SnH, AIBN, tert-butylbenzene, slow addition over 2.5 h, then 9 h further heating at 130 °C.</td>
<td>215 (4 %), 216 (72%)</td>
</tr>
</tbody>
</table>

3.1.5 Radical Cyclisation Reactions Using Microwave Irradiation

Radical reactions were performed on Wang resin-bound benzimidazole derivatives (205-207) using "Smiths Personnel Chemistry synthesiser" a source of microwave irradiation. This synthesiser has an integrated liquid handler which allows automated microwave reactions of up to 96 separate reaction vessels. The conditions for each reaction can be individually programmed. The reactions are carried out in sealed tubes with working volumes of up to ~3 mL. The results of these reactions are summarised in Table 14. The yields were determined by ¹H NMR spectroscopy using the internal standard.

Scheme 88. Synthesis of 1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine 162 on solid-phase using microwave irradiation.
Table 14. Radical cyclisations of Wang resin-bound benzimidazole precursor 206 for the synthesis of 1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine 162.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Time: 10 + 10 min (double addition); Temp.: 100 °C; Solvents: DMF/benzene (1.25/1.25 mL); Conditions: Bu₃SnH, AMBN.</td>
<td>162 (14 %), 213 was observed</td>
</tr>
<tr>
<td>2</td>
<td>Time: 10 + 10 min (double addition); Temp.: 100 °C; Solvents: Propan-1-ol/benzene (1/1mL); Conditions: Bu₃SnH, AMBN.</td>
<td>162 (52 %), 213 was observed</td>
</tr>
<tr>
<td>3</td>
<td>Time: 10 min; Temp.: 130 °C; Solvents: Propan-1-ol (2.5 mL); Conditions: Bu₃SnH, AMBN.</td>
<td>162 (20 %), 213 was observed</td>
</tr>
<tr>
<td>4</td>
<td>Time: 10 + 10 min (double addition); Temp.: 100 °C; Solvents: t-Butanol/benzene (1.25/1.25 mL); Conditions: Bu₃SnH, AMBN.</td>
<td>162 (36 %), 213 was observed</td>
</tr>
<tr>
<td>5</td>
<td>Time: 10 min; Temp.: 135 °C; Solvents: Propan-1-ol/benzene (1.25/1.25 mL); Conditions: Bu₃SnH, AMBN.</td>
<td>162 (44 %), 213 was observed</td>
</tr>
<tr>
<td>6</td>
<td>Time: 10 + 10 min (double addition); Temp.: 100 °C; Solvents: CH₃CN/benzene (1.25/1.25 mL); Conditions: Bu₃SnH, AMBN.</td>
<td>162 (17 %), 213 was observed</td>
</tr>
<tr>
<td>7</td>
<td>Time: 10 + 10 min (double addition); Temp.: 135 °C; Solvents: Propan-1-ol/benzene (1.25/1.25 mL); Conditions: Bu₃SnH, AMBN.</td>
<td>162 (44 %), 213 was observed</td>
</tr>
</tbody>
</table>

The cyclised product 162 was obtained by filtration of resin followed by washing of resin with appropriate set of solvents. As all these experiments were conducted on a small portion of resin 206 (20 ~ 25 mgs) hence, we only conducted LC/MS analysis of the filtrate containing cyclised product 162 and tin residues to confirm the structures. We determined the yields of cyclised product 162 by 1H NMR spectroscopy using the internal standard. Unreacted starting material and reduced product were cleaved off the resin using TFA/DCM (9:1). The LC/MS analysis of the cleaved material confirmed the benzimidazole products.

We did not determine the yields of the reduced product 213 and unreacted starting material 198 in all these instances. We believe the results to be very novel. To our knowledge, these results are the first report of radical reactions on solid-phase using microwave irradiation. The cost of the apparatus will be a limiting factor, but where available, provide a new method for dramatically
cutting the time of reactions. The main advantage of this technique is the short reaction time. In the case of the tricyclic 6,5,6-fused benzimidazole 162, the highest yield is 52% (Entry 7) and the reaction is complete within 20 min. This time is short for radical reactions but considerably longer than the normal time of 1-5 min required for most reactions using this technique of focussed microwave irradiation. The optimum yield is similar to that of solution-phase and that of solid-phase without irradiation but with shorter reaction times. Propan-1-ol was found to be the most suitable solvent for microwave radical reactions as it is quite polar and generally, for reactions carried out using microwave, polar solvents give best results. The solvent optimisation indicates the importance of the correct solvent for use of combined solid-phase and microwave irradiation together.

With the success of the cyclisation of resin-bound benzimidazole precursor 206 to 162, we investigated the 5-membered ring cyclisation using the same optimal conditions (Scheme 89).

Unfortunately, the results of microwave irradiation parallel those for solution-phase and solid-phase. Again the yield was determined by $^1$H NMR spectroscopy using the internal standard.

![Scheme 89](image)

**Scheme 89.** Reagents and conditions: i, Bu$_3$SnH, AMBN, 20 min, 135 °C, propan-1-ol/benzene (1.25/1.25 mL), 3%.

Solution-phase radical reactions to synthesise 1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine 162 using the microwave methodology were also performed (Scheme 90) but the yields are not impressive. The results of these reactions have been summarised in Table 15. These solution-phase reactions were not optimised due to time constraints but results conclusively provide evidence that microwave radical reactions are feasible and take a lot less time then under normal conditions. Again the yields were determined by $^1$H NMR spectroscopy using the internal standard.

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Scheme 90. Synthesis of 1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine 162 in solution-phase using microwave irradiation.

Table 15. Reaction conditions for the synthesis of 1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine 162 using microwave irradiation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Time: 10 min; Temp.: 135 °C; Solvents: Propan-1-ol/benzene (1.25/1.25 mL); Conditions: Bu₃SnH, AIBN.</td>
<td>162 (11 %)</td>
</tr>
<tr>
<td>2</td>
<td>Time: 10 min; Temp.: 100 °C; Solvents: Propan-1-ol/benzene (1.25/1.25 mL); Conditions: Bu₃SnH, AMBN.</td>
<td>162 (20 %)</td>
</tr>
</tbody>
</table>

Further studies are required to fully determine the conditions for radical reactions on solid-phase using ‘focused’ microwave irradiation. In conclusion, we have demonstrated that intramolecular alkyl radical cyclisations, by ipso-substitution, onto solid-supported benzimidazole precursors are facile processes.
As discussed at the beginning of this chapter, there are several possibilities for attaching the benzimidazoles to solid-supports. The advantage of attachment via the benzene ring of the benzimidazole is that the radical cyclisation via ipso-substitution results in the formation of the cyclised product which remains tethered to the resin. After the completion of radical reaction, the resin would be washed with appropriate set of solvents to remove all the excess of reagents which would eliminate traces of toxic tin-residues. The products could subsequently be cleaved off the resin using 95% TFA/DCM. Obviously the disadvantages of this route would be the separation of the cyclised product from other by-products. Purification would need to be achieved using conventional chromatographic methods. A putative synthesis of the solid-supported benzimidazole precursors is shown in Scheme 91.

Scheme 91. Reagents and conditions: i, Wang resin, DMAP, DIC, DCM; ii, Bu₃SnH, AIBN, toluene, reflux; iii, TFA/DCM.

The construction of a solution-phase model to mimic the solid-phase system was proposed. Both the acid and 1-NH need to be protected to facilitate phenylsulfanylation at C-2. Synthesis of the methyl 1H-benzo[d]imidazole-5-carboxylate 222 was successful and the pure product was obtained at the end of the reaction (Scheme 92). We also prepared the benzyl ester, phenylmethyl 1H-benzo[d]imidazole-5-carboxylate 223, for comparative studies (Scheme 92). Tritylation of the methyl 1H-benzo[d]imidazole-5-carboxylate 222 was almost quantitative (Scheme 93).
Scheme 92. Reagents and conditions: i, acetyl chloride, MeOH, reflux, 222 92%; ii, DEAD, PPh₃, benzyl alcohol, THF, rt, 223 8%.

Scheme 93. Reagents and conditions: i, trityl chloride, Et₃N, DCM, rt, 93%; ii, n-BuLi, diphenyl disulfide, THF; iii, Hydrolysis under acidic conditions.

Protection of N-1 of precursor 222 with the trityl group was carried out to avoid the problems as described earlier. Unfortunately, tritylation gave the 5- and 6- isomers as protection can occur onto N-3 as well as onto N-1. The separation of these regioisomers was attempted using conventional flash chromatographic methods but the mixture of regioisomers proved to be inseparable. Therefore, we attempted the synthesis of the 2-(phenylsulfanyl)-1-(triphenylmethyl)benzimidazole ester 226 on a mixture of non-separable regioisomers 224 and 225 (Scheme 93). Attempts all failed, possibly due to steric hindrance from the trityl group. We came to the conclusion that it was best to reduce the methyl 1-(triphenylmethyl)-1H-benzo[d]imidazole-5-carboxylate 224 and methyl 1-(triphenylmethyl)-1H-benzo[d]imidazole-6-carboxylate 225 to corresponding alcohols.

The advantage of the hydroxy analogue is that the zwitterionic character is removed making subsequent (solution-phase) reactions easy. Methyl 1-(triphenylmethyl)-1H-benzo[d]imidazole-5-carboxylate 224 and methyl 1-(triphenylmethyl)-1H-benzo[d]imidazole-6-carboxylate 225 were
reduced to two regio-isomers [1-(triphenylmethyl)-1H-benzo[d]imidazol-6-yl]-methanol 227 and [1-(triphenylmethyl)-1H-benzo[d]imidazol-5-yl]-methanol 228 (Scheme 94) in good yield. The protection of the benzimidazole alcohol precursors 227 and 228 was carried out using tert-butyldimethylsilyl chloride, which proceeded satisfactorily.

![Reaction Scheme](image)

**Scheme 94.** Reagents and conditions: i, LiAlH₄, Et₂O, 68%; ii, TBDMSCl, imidazole, DMF, 50%.

Considerable difficulty was encountered with the Zwitterionic nature of the benzimidazole carboxylic acid. The formation of regioisomers was also a major problem in most of the synthetic steps. Separation of these regioisomers proved more difficult than expected due to co-elution in column chromatography. Attempts to separate the regioisomers have so far not proved successful which hampers further research into continuation of SPOS. At this point we decided to concentrate our studies on the ipso-substitution route and no further work was carried out.

The next chapter describes the intramolecular aryl radical cyclisations onto benzimidazole moieties in solution-phase and on solid-phase.
CHAPTER 4

Intramolecular Aryl Radical Cyclisations, by “ipso” Substitution, at the C-2 Position of Benzimidazoles and Imidazoles

4.1 Introduction

Aryl radical cyclisations are now widely used in organic synthesis for the construction of fused aromatic systems. The intramolecular addition of aryl radicals to multiple bonds is well documented in the literature. The number of aryl radical cyclisations onto arenes and heteroarenes is less well investigated. Some examples are detailed here. Harrowven et al. has reported a total synthesis of the alkaloid toddaquinoine in which an intramolecular addition of an aryl radical to a pyridine ring featured as the key step. Caddick et al. has shown that ipso-substitution by vinyl and aryl radical cyclisations onto indole moiety are viable processes but are moderate yielding (Scheme 95).

\[ \text{Scheme 95. Reagents and conditions: i, Bu}_3\text{SnH, AIBN, toluene, reflux, 31%}. \]

Aryl radical cyclisations have been used for the syntheses of the Amaryllidaceae alkaloids, vasconine, assoanine, oxoassinine and pratosine. The Jones group has also investigated the intramolecular cyclisation of aryl radicals onto pyrrole. One of the these successful additions of aryl radicals onto heteroarenes is shown in Scheme 96. Radical cyclisation of the \( N\)-(2-iodophenyl)pyrrole-3-carboxamide 233 gave the tricyclic pyrrolo[3,2-c]quinolone 234, the ring system found in the recently isolated alkaloid martinelline.
Scheme 96. **Reagents and conditions:** i, Bu$_3$SnH, AIBN, toluene, reflux, 52%.

### 4.1.1 Intramolecular Aryl Radical Cyclisations onto Benzimidazoles in Solution-Phase

The examples in the literature suggested that cyclisation of aryl radicals onto pendant arenes/heteroarenes provides a useful method of constructing biologically interesting fused heterocycles as outlined in the introductory section. The objective of our research was to study the reactions of benzimidazoles with alkyl and aryl radicals. Our studies of the cyclisation of alkyl radicals onto benzimidazoles is reported in Chapter 2 and 3. Our aim was to develop a simple protocol for aryl radical cyclisation onto heteroarene using o-(halogenophenyl)alkyl building blocks. For instance, aryl radical cyclisations onto benzimidazoles would result in the formation of tetracycles (Scheme 97). There has been considerable interest in tetracycles of this kind as they exhibit biological activity.$^{102}$

![Scheme 96](image)

**Scheme 96.** **Reagents and conditions:** i, Bu$_3$SnH, AIBN, toluene, reflux, 52%.

![Scheme 97](image)

**Scheme 97.** **Reagents and conditions:** i, KOH, DMF, rt; ii, 4-mercaptobenzoic acid, potassium tert-butoxide, ethanol, reflux; iii, acetyl chloride, methanol, reflux; iv, radical reagents (*i.e.* TTMSS, ...
Bu$_3$SnH or Bu$_3$GeH), radical initiators (AIBN or AMBN) and common solvents (toluene, benzene, hexane or acetonitrile).

4.1.2 Preparation of Aryl Radical Precursors

After the successful synthesis of tricyclic benzimidazole derivatives on solid-phase we decided to investigate tetracyclic systems first in solution-phase and then translate these synthetic sequences onto solid-phase. To construct 6,5,5,6-fused benzimidazole derivatives via aryl radical cyclisation methodology we synthesised versatile aryl precursors to meet the requirements necessary for the system. 1-Iodo-2-(iodomethyl)benzene 241 was prepared as shown in Scheme 98. The chloride 240 was stirred under reflux with sodium iodide in a Finkelstein reaction to afford the 1-iodo-2-(iodomethyl)benzene 241 quantitatively. It is imperative that Finkelstein reaction is carried out in the dark environment as decomposition of the benzylic iodide occurs in the light. We also prepared another aryl precursor which involved activation of commercially available 2-iodobenzyl alcohol 242 with methanesulfonyl chloride to form a mesylate derivative 243. The mesyl group is a good leaving group in S$_2$N$_2$ reactions and can be easily displaced by nucleophiles. We synthesised (2-iodophenyl)methyl methanesulfonate 243 in a 60% yield (Scheme 99).

![Scheme 98](image1)

**Scheme 98. Reagents and conditions: i, sodium iodide, acetonitrile, reflux, 100%.

![Scheme 99](image2)

**Scheme 99. Reagents and conditions: i, methanesulfonyl chloride, triethylamine, DCM, rt, 60%.

In order to construct 6,5,6,6-fused benzimidazole derivatives via our proposed aryl radical cyclisation methodology, we also synthesised corresponding aryl precursors to meet the
requirements necessary for the system. We decided to use identical strategy as applied to 2-iodobenzyl alcohol 242. The treatment of 2-bromophenylethyl alcohol 244 with methanesulfonyl chloride afforded 2-(2-bromophenyl)ethyl methanesulfonate 245 in a yield of 99% (Scheme 100). The synthesis of 1-bromo-2-(2-chloroethyl)benzene 246 also proceeded successfully in a moderate yield (66%); the aim was to carry out the displacement reaction with sodium iodide because iodide is a good leaving group in $S_N2$ reactions (Scheme 101).

![Scheme 100. Reagents and conditions: i, methanesulfonyl chloride, triethylamine, toluene, rt, 18 h, 99%.](image)

![Scheme 101. Reagents and conditions: i, conc. HCl, 115 °C, 18 h, 66%.](image)

4.1.3 Synthesis of Methyl 4-((1-[(2-iodophenyl)methyl]-1H-benzo[d]imidazol-2-yl)sulfanyl)benzene-1-carboxylate 249

The alkylation of 2-chlorobenzimidazole 163 was readily achieved using the KOH/DMF conditions. The substitution of 2-chloro-1-[(2-iodophenyl)methyl]-1H-benzo[d]imidazole 247 resulted in the quantitative formation of 4-((1-[(2-iodophenyl)methyl]-1H-benzo[d]imidazol-2-yl)sulfanyl)benzene-1-carboxylic acid 248 (Scheme 102). Esterification of 4-((1-[(2-iodophenyl)methyl]-1H-benzo[d]imidazol-2-yl)sulfanyl)benzene-1-carboxylic acid 248 gave methyl 4-((1-[(2-iodophenyl)methyl]-1H-benzo[d]imidazol-2-yl)sulfanyl)benzene-1-carboxylate 249 in a 78% yield. We synthesised the ester with the aim of solution-phase studies of aryl radical cyclisation as a model for later studies on solid-phase.
Scheme 102. **Reagents and conditions:** i, potassium hydroxide, 1-iodo-2-(iodomethyl)benzene 241, DMF, rt, 95%; ii, 4-mercaptobenzoic acid, potassium tert-butoxide, ethanol, reflux, 18 h, 100%; iii, acetyl chloride, methanol, reflux, 18 h, 78%.

### 4.1.4 Radical Cyclisation Reactions of Methyl 4-{{1-[(2-iodophenyl)methyl]-1H-benzo[d]imidazol-2-yl}sulfanyl}benzene-1-carboxylate 249

Methyl 4-{{1-[(2-iodophenyl)methyl]-1H-benzo[d]imidazol-2-yl}sulfanyl}benzene-1-carboxylate 249 was subjected to free radical conditions (TTMSS, slow syringe pump addition) and afforded 11H-benzo[4,5]imidazo[1,2-a]isoindole 250 (20%) as the minor product (Scheme 103). The reduced product methyl 4-{{1-(phenylmethyl)-1H-benzo[d]imidazole-2-yl}sulfanyl}benzene-1-carboxylate 251 was unfortunately the major product, obtained in a 40% yield. When the radical cyclisation of precursor 249 was repeated using tributylgermanium hydride (one pot addition), the reduced compound 251 was afforded as the sole product (60%). The results suggest that the formation of 5-membered ring is hindered due to the strain in the transition state, hence, we observed the reduced 251 as the predominant product in both instances. The result with Bu₃GeH is unusual in that the slower rate of H-abstraction from Bu₃GeH should allow more time for cyclisation to take place, as had been observed for alkyl radical cyclisations.
Scheme 103. Reagents and conditions: i, TTMSS, AIBN, toluene, reflux, 5 h, 250 (20%), 251 (40%).

The precursor 248 was also coupled with Wang resin to give a resin-bound benzimidazole moiety 252 as shown in Scheme 104. The loading of the resin was found to be 0.60 mmol/g by cleaving a portion of resin with TFA/DCM (9/1).

Scheme 104. Reagents and conditions: i, Wang resin, DMAP, DIC, DCM/DMF, rt.

4.2 Synthesis of 1-[2-(2-Bromophenyl)ethyl]-2-chloro-1H-benzo[d]imidazole 253

We extended our work to include the synthesis of 6,5,6,6-fused benzimidazole derivatives. From our previous studies it was apparent that the formation of 6-membered ring is a more facile reaction. The first step of the synthesis of radical precursor involved alkylation of 2-chlorobenzimidazole 163 (Scheme 105). We synthesised 1-[2-(2-bromophenyl)ethyl]-2-chloro-1H-benzo[d]imidazole 253 using Mitsonobu conditions. The reaction gave a mixture of the product 253 and a non-isolable DEAD by-product (1:1). Therefore, this route was not deemed suitable for the synthesis of 1-[2-(2-bromophenyl)ethyl]-2-chloro-1H-benzo[d]imidazole 253 due to the problems associated with purification. Therefore, an alternative route was employed and 1-[2-(2-bromophenyl)ethyl]-2-chloro-1H-benzo[d]imidazole 253 was prepared in 98% yield by alkylation of 2-chlorobenzimidazole 163 using sodium hydride in dry THF, and 2-(2-bromophenyl)ethyl methanesulfonate 245, as shown in Scheme 105.
Scheme 105. *Reagents and conditions:* i, triphenylphosphine, DEAD, 2-bromophenylethyl alcohol, DCM, rt, 24 h; ii, sodium hydride, THF, 2-(2-bromophenyl)ethyl methanesulfonate, reflux, 3 h, 98%.

4.2.1 Synthesis of Methyl 4-([1-[2-(2-bromophenyl)ethyl]-1H-benzo[d]imidazol-2-yl)sulfanyl] benzene-1-carboxylate 255

The substitution of 1-[2-(2-bromophenyl)ethyl]-2-chloro-1H-benzo[d]imidazole 253 with 4-mercaptobenzoic acid 189 resulted in the quantitative formation of 4-([1-[2-(2-bromophenyl)ethyl]-1H-benzo[d]imidazol-2-yl)sulfanyl]benzene-1-carboxylic acid 254 (Scheme 106). Esterification of the benzimidazole acid precursor 254 gave methyl 4-([1-[2-(2-bromophenyl)ethyl]-1H-benzo[d]imidazol-2-yl)sulfanyl]benzene-1-carboxylate 255 in a 76% yield.

Scheme 106. *Reagents and conditions:* i, 4-mercaptobenzoic acid, potassium tert-butoxide, ethanol, reflux, 18 h, 99%; ii, acetyl chloride, methanol, reflux, 18 h, 76%.
4.2.2 Radical Cyclisation Reactions to Synthesise 5,6-Dihydrobenzo[4,5]imidazo[2,1-a]isoquinoline 256

The radical cyclisation reaction was carried out using tributyltin hydride (slow addition over 5 h using a syringe pump). 4-{1-[2-(2-Bromophenyl)ethyl]-1H-benzo[d]imidazole-2-yl}sulfanylbenzene-1-carboxylic acid 254 was treated with Bu3SnH, prior to performing the radical reaction on precursor 255. The radical cyclisation reaction gave 5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinoline 256 (11 %, determined by 1H NMR spectroscopy using an internal standard). GC/MS analysis also confirmed the formation of 5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinoline 256. The poor yield of the cyclised product 256, in this instance, is due to poor solubility of precursor 254 in toluene. No solubility problems were encountered with the methyl ester and radical cyclisation of methyl 4-{1-[2-(2-bromophenyl)ethyl]-1H-benzo[d]imidazol-2-yl}sulfanylbenzene-1-carboxylate 255 afforded cyclised product 256 (60%).

Scheme 107. Reagents and conditions: i, tributyltin hydride, AIBN, toluene, reflux, 8 h, 60%.

The results indicate that in the radical cyclisation of 255 which proceeds via a 6-exo route, the transition state is much less strained in the formation of 6-membered ring in 256. These results are in good agreement with our previous alkyl radical cyclisations onto benzimidazole to construct the 6,5,6-fused benzimidazole adduct 162. As a part of our continuing efforts to adapt radical cyclisation methodology to polymer supported reactions we also investigated a solid-phase synthesis of 5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinoline 256.

4.2.3 Synthesis of Solid-Supported Benzimidazole Precursor 257

The preparation of the benzimidazole derivative 257 on solid-support was achieved in high yield as illustrated in Scheme 108. The coupling reaction of 4-{1-[2-(2-bromophenyl)ethyl]-1H-
benzo[d]imidazole-2-yl)sulfanyl)benzene-1-carboxylic acid 254 was performed using corresponding diisopropylcarbodiimide (DIC), with DMAP added to catalyse the esterification of the Wang resin. The results of the coupling reactions showed that for complete immobilisation of benzimidazole acid precursor 254 onto Wang resin, it is necessary to perform double coupling to attain a high loading of 257. The IR spectrum of the solid-supported benzimidazole precursor 257 shows the formation of ester band at 1713 cm\(^{-1}\) and the (MAS) \(^1\)H NMR spectrum shows complete immobilisation (attachment) of benzimidazole precursor onto resin. The loading was assessed by cleavage and analysis of a portion of the resin-bound precursor 257 prior to performing the cyclisation reactions.

Scheme 108. Reagents and conditions: i, Wang resin, DMAP, DIC, DCM/DMF, rt.

4.2.4 Radical Cyclisations of Solid-Supported Benzimidazole Precursor 257

Previously established solution-phase radical methodology was applied to the solid-supported benzimidazole derivative 257 (Scheme 109). The results of radical cyclisation reactions of resin-bound benzimidazole adduct 257 are outlined in Table 16.


<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bu₃SnH, AIBN, benzene, reflux, 8 h.</td>
<td>256 (44%), 254 and 258 were also observed</td>
</tr>
<tr>
<td>2</td>
<td>Bu₃GeH, AIBN, toluene, reflux, 8 h.</td>
<td>256 (71%), 254 and 258 were also observed</td>
</tr>
</tbody>
</table>

At the end of the radical reactions, the resin was filtered and the filtrate collected. The filtrate was analysed by MS, HPLC and ¹H NMR spectroscopy. The analysis indicated that the cyclised product 256 was formed predominantly in both instances. The optimum result was attained when the solid-supported precursor 257 was reacted with tributylgermanium hydride (a non-toxic radical mediator). The yield of cyclised product 256 is very impressive (71%) especially as the reaction has not yet been optimised. The use of tributylgermanium hydride also eliminated the use of slow syringe pump addition. The cyclised product 256 was contaminated with tributylgermanium residues and was purified using flash chromatography to obtain pure cyclised adduct 256. Purification proved to be much easier when tributylgermanium hydride was employed in radical reactions. The by-products were cleaved from the resin using standard cleavage conditions. GC-MS analysis of cleaved sample shows the presence of the reduced product and the starting material. The % yield was not determined because the attempts to separate the reduced product and the starting material failed due to co-elution in column chromatography. Interestingly, tributylgermanium hydride did not work as efficiently with the phenylselenyl system in our previous studies (Chapter 2 and 3) as with the aromatic bromide.

In summary, we have demonstrated the successful cyclisation of aryl radicals by ipso-substitution onto benzimidazole in solution-phase and on solid-phase. In order to create chemical diversity in the cyclised product 256, we plan to utilise commercially available substituted benzimidazole derivatives.
4.3 Preparation of Imidazole Radical Precursors

One of the objectives of our project was to extend the aryl radical cyclisation methodology to imidazoles with the aim of constructing interesting biologically active imidazole moieties. We began our model studies to determine the efficiency of intramolecular aryl radical cyclisation onto C-2 position of imidazole in solution-phase. Solid-phase approaches have been widely used in the generation of libraries for lead discovery; the ultimate aim is to examine the solid-phase synthesis of imidazole analogues using radical ipso-substitution strategy.

The first step towards the synthesis of an imidazole radical precursor involved reaction between commercially available 2-mercaptoimidazole 259 and commercially available 6-chloronicotinic acid ethyl ester. This moiety behaves as a traceless linker as a result of radical ipso-substitution reaction. It is also strongly electron withdrawing and should favour intramolecular radical ipso-substitution process (Scheme 110). Preparation of the desired intermediate ethyl 6-(1H-imidazol-2-ylsulfanyl)pyridine-3-carboxylate 260 was achieved in a reasonable yield (50%). The treatment of precursor 257 with 2-(2-bromophenyl)ethyl methanesulfonate 245 under NaH/DMF conditions afforded ethyl 6-({1-[2-(2-bromophenyl)ethyl]-1H-imidazol-2-yl}sulfanyl)pyridine-3-carboxylate 261 in a 75% yield.

![Scheme 110](image)

**Scheme 110.** *Reagents and conditions*: i, sodium hydride, 6-chloronicotinic acid ethyl ester, DMF, 80 °C, 12 h, 50%; ii, sodium hydride, 2-(2-bromophenyl)ethyl methanesulfonate 245, DMF, rt, 25 h, 75%.
4.3.1 Radical Cyclisations of Ethyl 6-\{(1-[2-(2-bromophenyl)ethyl]-1H-imidazol-2-yl)sulfanyl\}pyridine-3-carboxylate 261

The radical methodology was applied to ethyl 6-\{(1-[2-(2-bromophenyl)ethyl]-1H-imidazol-2-yl)sulfanyl\}pyridine-3-carboxylate 261 as depicted in Scheme 111 and Table 17.

![Scheme 111. Synthesis of 5,6-dihydroimidazo[2,1-\(a\)]isoquinoline 262.](image)

**Table 17. Reaction conditions for the synthesis of 5,6-dihydroimidazo[2,1-\(a\)]isoquinoline 262.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bu(_3)SnH (slow addition), AIBN, toluene, reflux, 10 h.</td>
<td>262 (37%), 261 (19%) and 263 (32%)</td>
</tr>
<tr>
<td>2</td>
<td>TTMSS, AIBN, toluene, reflux, 12 h.</td>
<td>262 (45%) and 263 (45%)</td>
</tr>
<tr>
<td>3</td>
<td>Bu(_3)GeH, AIBN, toluene, reflux, 8 h.</td>
<td>262 (20%) and 263 (56%)</td>
</tr>
</tbody>
</table>

The intramolecular aryl radical cyclisations onto imidazole were successful. All these experimental conditions led to the formation of the cyclised product 262 in moderate yield as well as the reduced uncyclised product 263. However, the reaction conditions have not yet been optimised and higher yields of cyclisation could possibly be achieved. Due to time restraints we decided to investigate aryl radical cyclisations via 'oxidative' methodology to construct heterocycles on solid-support as a priority, and if time permitted we would explore this area further.
CHAPTER 5

Synthesis of Novel Heterocycles by Oxidative Radical Cyclisation Methodology

5.1 Introduction

Radical oxidative cyclisation reactions have extensively been reviewed in Chapter 1, Section 1.2.5. Imidazole, indole and pyrrole subunits are widely distributed in nature. The oxidative radical cyclisations have been reported for several nitrogen containing heteroarenes, and several literature precedents show that imidazoles, indoles, pyrroles and pyrazoles with an electron withdrawing group can be successfully employed to synthesise a range of polycyclic nitrogen heterocycles that may exhibit biological activity.

Moody has successfully investigated alkyl radical cyclisations onto substituted indoles as depicted in Scheme 112. Indole cyclisation studies by Muchowski are quite similar to those of Moody. Muchowski also investigated aryl radical cyclisations onto a substituted pyrrole core (Scheme 113). Kraus carried out aryl radical conditions onto substituted indoles with a carbonyl link between the indole and aryl groups. 6-Oxo-6H-isoindolo[2,1-a]indole-11-carbaldehyde was obtained as a sole product (Scheme 114). It is notable that Moody, Muchowski and Kraus all observe only the oxidized products after radical cyclisation, and that the presence of an electron withdrawing group is required on the radical accepting ring system.

\[
\text{CHO} \quad \text{CHO} \\
\text{(i)} \quad \text{(i)} \\
\text{N} \quad \text{N} \\
\text{Cl}  \\
\text{264} 
\]

Scheme 112. Reagents and conditions: i, Bu₂SnH, AIBN, toluene, reflux, 3 h, 264 n = 1 (64%), n = 2 (75%), n = 3 (43%).
Scheme 113. Reagents and conditions: i, Bu₃SnH, AIBN, benzene, reflux, hv, 24 h, 266 (43%), 267 (<10%).

Scheme 114. Reagents and conditions: i, Bu₃SnH, AIBN, benzene, reflux, hv, 4 h, 35%.

Our aim in these studies was to develop aryl radical cyclisations, via ‘oxidative’ methodology, onto imidazole, indole, pyrrole and pyrazole rings to get access to novel heterocycles. The presence of electron withdrawing functionality on these templates is known to assist cyclisation. We decided to utilise commercially available ester containing imidazole, indole, pyrrole and pyrazole moieties. The ultimate aim was to construct heterocycles on solid-support using the radical ‘oxidative’ methodology. For that purpose we needed a template heterocycle with a functionality (e.g. ester/carboxylic acid) which could be coupled to the resin (Wang, Rink or Tentagel) followed by radical cyclisation to attain our targets. In this way we could build a library of biologically active compounds. We planned to cleave the desired targets from the resins using a variety of amines to give diversity to the desired heterocycles.

5.1.1 Synthesis of Imidazole Analogues Using the ‘Oxidative’ Radical Methodology

Our initial work involved synthesis of imidazole moieties via oxidative radical methodology. The alkylation of substituted imidazoles can be problematic because there are two reactive nitrogen atoms, hence it is possible for alkylation to occur on either nitrogen and give two regioisomers. Alkylation can also occur on both nitrogen atoms resulting in salt formation. Therefore, the control of the regiochemistry of the alkylation is very important. The imidazole-4(5)-carboxylate exists as a
mixture of tautomers with the 4-tautomer being predominant. The anion generated is ambident and has two canonical forms with negative charge, either on N-1 or N-3. Under basic conditions the alkylation occurs at N-1 as the base deprotonates the imidazole ring and the most nucleophilic of the ambident nitrogen anion centre reacts. The N-1 anion of methyl 4-imidazole-carboxylate 270 is the most nucleophilic because it is the least affected by the electron withdrawing properties of the ester group, e.g. Scheme 115. In neutral conditions, alkylation will occur on N-3. The lone pair of electrons on N-3 makes it the more nucleophilic of the two nitrogen atoms. Alkylation followed by loss of a proton from N-1 would form the isomeric product.

Alkylation of methyl 4-imidazole-carboxylate 270 afforded methyl 1-[(2-iodophenyl)methyl]-1H-imidazole-4-carboxylate 271 in a modest yield (43%). The other regioisomer 272 was not observed. The result suggest that dialkylation may have occurred and the imidazole is lost as the salt at filtration (Scheme 115).

Scheme 115. Reagents and conditions: i, sodium hydride, 1-iodo-2-(iodomethyl)benzene, DMF, 80 °C, 13 h, 271 (43%), 272 (0%).

Radical cyclisation reactions of precursor 271 gave methyl 1-(phenylmethyl)-1H-imidazole-4-carboxylate 274 as a sole product. The cyclised product 273 was not obtained at all. Formation of the 5-membered ring in 273 is more difficult because the 5,5,6-fused system is more strained (Scheme 116). The results of these cyclisations are identical to our previous findings (Chapter 4, Section 4.1.4).

Table 18. Reaction conditions for the synthesis of the cyclised product 273.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bu₃SnH, AIBN, toluene, reflux, 13 h.</td>
<td>274 (33%)</td>
</tr>
<tr>
<td>2</td>
<td>Bu₃GeH, AIBN, toluene, reflux, 10 h.</td>
<td>274 (56%)</td>
</tr>
</tbody>
</table>

Alkylation of methyl 4-imidazole-carboxylate 270 with 2-(2-bromophenyl)ethyl methanesulfonate 245 gave two regioisomers methyl 1-[2-(2-bromophenyl)ethyl]-1H-imidazole-4-carboxylate 275 and methyl 1-[2-(2-bromophenyl)ethyl]-1H-imidazole-5-carboxylate 276. The two regioisomers were easily separated by column chromatography and were identified by ¹H NMR spectroscopy. The yields of these regioisomers are comparable. The reason for the lack of regioselectivity towards the 4-isomer is not clear.

Scheme 117. Reagents and conditions: i, sodium hydride, 2-(2-bromophenyl)ethyl methanesulfonate 245, DMF, 80 °C, 13 h, 275 (50%), 276 (48%).
Radical cyclisation reactions of methyl 1-[2-(2-bromophenyl)ethyl]-1H-imidazole-4-carboxylate 275 were carried out under different experimental conditions (Scheme 118). The results have been summarised (Table 19). When the radical cyclisation reaction was performed using Bu3SnH, low yields of the methyl 5,6-dihydroimidazo[5,1-a]isoquinoline-1-carboxylate 277 (16%) and methyl 5,6-dihydroimidazo[2,1-a]isoquinoline-2-carboxylate 278 (4%) were observed (Entry 1). The formation of methyl 5,6-dihydroimidazo[2,1-a]isoquinoline-2-carboxylate 278 was unexpected, but upon careful consideration it appeared that both modes of cyclisation are viable processes. The electron withdrawing effect of ester group at C-4 position can induce cyclisation onto C-2 position (by making it more electrophilic) as well as C-5 position of imidazole. We did not observe the reduced product or the starting material. The structure of methyl 5,6-dihydroimidazo[5,1-a]isoquinoline-1-carboxylate 277 was confirmed using X-ray crystallography, as shown in Figure 6. A 90° rotation of the molecule is also shown, which illustrated the planarity of the molecule.


<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bu3SnH, AIBN, toluene, reflux, 10 h.</td>
<td>277 (16%) and 278 (4%)</td>
</tr>
<tr>
<td>2</td>
<td>Bu3GeH, PhSH, AIBN, toluene, reflux, 10 h.</td>
<td>277 (44%)</td>
</tr>
<tr>
<td>3</td>
<td>Bu3GeH, AIBN, toluene, reflux, 10 h.</td>
<td>277 (38%) and 278 (19%)</td>
</tr>
<tr>
<td>4</td>
<td>TTMSS, AIBN, toluene, reflux, 12 h.</td>
<td>277 (30%) and 278 (30%)</td>
</tr>
</tbody>
</table>
Figure 6. X-ray crystal structures of methyl 5,6-dihydroimidazo[5,1-$\alpha$]isoquinoline-1-carboxylate 277.
The amount of cyclisation was much greater when Bu$_3$GeH, was employed (Entry 2). Methyl 5,6-
dihydroimidazo[5,1-a]isoquinoline-1-carboxylate 277 was obtained in a moderate yield of 44% as a
sole product. The results demonstrate that some kind of decomposition also occurred which
prevented the efficiency of radical cyclisation reaction. The radical cyclisation of methyl 1-[2-(2-
bromophenyl)ethyl]-1H-imidazole-4-carboxylate 275 was repeated with Bu$_3$GeH but without
addition of catalytic amount of thiol to assist cyclisation. The cyclisation reaction was successful
and afforded methyl 5,6-dihydroimidazo[5,1-a]isoquinoline-1-carboxylate 277 in a 38% yield and
methyl 5,6-dihydroimidazo[2,1-a]isoquinoline-2-carboxylate 278 in a 19% yield (Entry 3). It is
noteworthy that in all the above results, the uncyclised compounds are not observed at all. The
reaction of methyl 1-[2-(2-bromophenyl)ethyl]-1H-imidazole-4-carboxylate 275 with TTMSS and
AIBN gave the methyl 5,6-dihydroimidazo[5,1-a]isoquinoline-1-carboxylate 277 in a 30% yield and
methyl 5,6-dihydroimidazo[2,1-a]isoquinoline-2-carboxylate 278 in a 30% yield. The separation of
these cyclised products 277 and 278 was readily achieved by column chromatography in all these
instances. There are not obvious reasons for the different regioselectivities between the formation of
the 2-isomer 278 and the 5-isomer 277.

The analysis of the results show that aryl radical cyclisation onto imidazole can be best attained by
using Bu$_3$GeH. We have already listed the advantages of using Bu$_3$GeH in radical reactions over
triorganotin radical mediators. The results also suggest that Bu$_3$GeH is an efficient reagent in
radical cyclisation reactions and provided first successful example of intramolecular aryl radical
cyclisations onto imidazole. Success of TTMSS mediated intramolecular aryl radical cyclisation
onto imidazole shows that it is also an attractive non-toxic alternative to toxic triorganotin hydride.

In all these radical cyclisation reactions we used AIBN in excess because the evidence suggests that
AIBN is the oxidising agent and plays a part in oxidation step. The postulated mechanisms are
outlined in Scheme 119. The intermediate π-radical 280 is stable and reacts slowly if at all with
radical mediator Bu$_3$SnH or Bu$_3$GeH, otherwise the reduced product would be formed. It is clear
that in all of the above results, the reduced product is not afforded at all. Only the cyclisation
products are obtained. Disproportionation would involve the aryl radical 279 abstracting hydrogen
from the intermediate cyclised radical 280 to give a molecule of cyclised product and a molecule of
the reduced product 281(Scheme 120) in a chain inhibition step. The formation of the π-radical 280
inhibits the reduction of the aryl radical 280. Therefore, we assume that the π-radical 280 must have
been intercepted by AIBN or a break down product from AIBN.
The assumption that AIBN acts as the oxidant needs further investigation. Routes A and B (Scheme 119) result in the formation of 2-cyanopropane which was not detected in our studies. 2-Cyanopropane is very volatile compound and could be lost either from the reaction vessel during reflux or during evaporation of solvent in work up. There is no concrete evidence of what is involved in rearomatisation step.

**Scheme 119.** Possible role of AIBN in the oxidative step of the radical cyclisation.
Scheme 120. Putative disproportionation between the aryl radical and the intermediate cyclised radical.

The unusual formation of the regioisomer 278 via cyclisation onto the 2-position of the imidazole 275 suggested that better cyclisation might be obtained using the imidazole 5-ester 276. The other regioisomer, methyl 1-[2-(2-bromophenyl)ethyl]-1H-imidazole-5-carboxylate 276 was subjected to the radical conditions as detailed in Table 20. Our surmise proved to be correct and methyl 5,6-dihydroimidazo[2,1-a]isoquinoline-3-carboxylate 282 was obtained in 71% yield (Entry 1). No unreacted material was recovered. Repeating the reaction using Bu₃GeH also afforded cyclised product 282 in a yield of 54%. We expected a higher yield of cyclised product 282 in the case of Bu₃GeH. No other by-products were observed in either of these reactions. We conclude that cyclisation occurs before the aryl radical can be intercepted and reduced by any source of hydrogen. The structure of methyl 5,6-dihydroimidazo[2,1-a]isoquinoline-3-carboxylate 282 was confirmed using X-ray crystallography as shown in Figure 7.

Table 20. Reaction conditions for the synthesis of methyl 5,6-dihydroimidazo[2,1-a]isoquinoline-3-carboxylate 282.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bu₂SnH, AIBN, toluene, reflux, 13 h.</td>
<td>282 (71%)</td>
</tr>
<tr>
<td>2</td>
<td>Bu₂GeH, AIBN, toluene, reflux, 12 h.</td>
<td>282 (54%)</td>
</tr>
</tbody>
</table>

Figure 7. X-ray crystal structure of methyl 5,6-dihydroimidazo[2,1-a]isoquinoline-3-carboxylate 282.
5.1.2 Synthesis of Methyl 5,6-dihydroindolo[2,1-a]isoquinoline-12-carboxylate 285 by Oxidative Radical Cyclisation

The first step in the synthesis involved the alkylation of methyl indole-3-carboxylate 283 (Scheme 122). Alkylation under basic conditions gave methyl 1-[2-(2-bromophenyl)ethyl]-1H-indole-3-carboxylate in a moderate yield of 40%. The synthesis required improvement but was not further optimised.

![Scheme 122](image)

**Scheme 122.** Reagents and conditions: i, sodium hydride, 2-(2-bromophenyl)ethyl methanesulphonate 245, DMF, 21 h, 40%.

Treatment of methyl 1-[2-(2-bromophenyl)ethyl]-1H-indole-3-carboxylate 284 with Bu₃GeH (one pot addition) led to the isolation of methyl 5,6-dihydroindolo[2,1-a]isoquinoline-12-carboxylate 285 in 68% yield as shown in Scheme 123. The intramolecular radical cyclisation onto the substituted indole ring was achieved successfully. No unreacted starting material, other by-products or reduced products were recovered.

![Scheme 123](image)

**Scheme 123.** Reagents and conditions: i, Bu₃GeH, AIBN, toluene, reflux, 12 h, 68%.
We have shown that aryl radical cyclisation onto indole substituted with an electron withdrawing group occurs readily. When the electron withdrawing group is at the C-3 position of the indole ring, cyclisation occurs onto C-2 position. This is due to the fact that the cyclisation is occurring onto an α,β-unsaturated position and the intermediate radical is extensively delocalised and therefore has increased stability.

5.1.3 Synthesis of Ethyl 5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate 288 by Oxidative Radical Cyclisation

The same alkylation procedure as that used for the alkylation of methyl 4-imidazole-carboxylate 271 was followed utilising 2-(2-bromophenyl)ethyl methanesulfonate 245. Since the radical cyclisation of the six-membered ring was proven to be the most successful in all the previous examples, then ethyl 1-[2-(2-bromophenyl)ethyl]-1H-pyrrole-2-carboxylate 287 was synthesised by alkylation of ethyl pyrrolo-2-carboxylate 286 (Scheme 124).

\[
\text{Scheme 124. Reagents and conditions: i, sodium hydride, 2-(2-bromophenyl)ethyl methanesulfonate 245, DMF, 80 °C, 97%}
\]

The radical cyclisation of ethyl 1-[2-(2-bromophenyl)ethyl]-1H-pyrrole-2-carboxylate 287 was performed using Bu₃GeH (one pot addition) as illustrated in Scheme 125. The only compound isolated from the reaction under these conditions was the desired cyclisation to yield ethyl 5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate 288 in 82% yield. The successful intramolecular radical cyclisation onto substituted pyrrole at C-5 position provides evidence that 6-exo mode of cyclisation is very favourable though it is very unusual not to observe any reduced product.
Scheme 125. Reagents and conditions: i, Bu3GeH, AIBN, toluene, reflux, 12 h, 82%.

5.1.4 Synthesis of Ethyl 2-(trifluoromethyl)-5,6-dihydropyrazolo[5,1-a]isoquinoline-1-carboxylate 293 by Oxidative Radical Cyclisation

There are very few natural products containing pyrazole rings compared to other nitrogen containing heteroarenes. Withasomnine 289 (Figure 8) was first isolated from *Withania somnifera* 26 years ago. Withasomnine 289 and analogues contain a [1,2-b]-fused bicyclic pyrazole structural motif.108

Will Barton, one of our group members has successfully employed a radical protocol to construct withasomnine 289 analogues as shown in Chapter 1, Section 1.2.5, Scheme 18.

![Scheme 125](image)

Figure 8. Withasomnine.

We also wanted to utilize the aryl radical cyclisation protocol to synthesise pyrazole analogues. The commercially available ethyl 3-(trifluoromethyl)pyrazole-4-carboxylate 290 was considered as a potential substrate for intramolecular aryl radical cyclisations to be studied in detail. The regioselective alkylation of ethyl 3-(trifluoromethyl)pyrazole-4-carboxylate 290 proved difficult and afforded two regioisomers (Scheme 126). The desired regioisomer 291 was formed predominantly. The separation of these regioisomers was not very efficient because the ethyl 1-[2-(2-bromophenyl)ethyl]-3-(trifluoromethyl)-1H-pyrazole-4-carboxylate 291, at the end of the purification, was still found to be contaminated with compound 292.
Scheme 126. Reagents and conditions: i, sodium hydride, DMF, 80 °C, 291 (85%).

Intramolecular aryl oxidative radical cyclisation of ethyl 1-[2-(2-bromophenyl)ethyl]-3-(trifluoromethyl)-1H-pyrazole-4-carboxylate 291 at the C-5 position was achieved in moderate yield using Bu₃GeH (one pot addition) and AIBN in excess (Scheme 127). The ethyl 2-(trifluoromethyl)-5,6-dihydropyrazolo[5,1-a]isoquinoline-1-carboxylate 293 was identified as the main reaction product. No unreacted starting material was recovered. The putative rearomatisation mechanism has already been described.

Scheme 127. Reagents and conditions: i, Bu₃GeH, AIBN, toluene, reflux, 12 h, 57%.

5.1.5 Synthesis of Solid-Supported Pyrrole 295 and Pyrazole 297

Success of intramolecular aryl radical cyclisations via ‘oxidative’ methodology in solution-phase enabled us to adapt the protocol for solid-supported synthesis of these interesting heteroarenes. The first step towards the synthesis of solid-supported pyrrole precursor 295 involved the hydrolysis of previously synthesised ethyl 1-[2-(2-bromophenyl)ethyl]-1H-pyrrole-2-carboxylate 287 as depicted
in Scheme 128. The hydrolysis of the pyrrole precursor 287 furnished the desired acid precursor 294 under standard conditions in excellent yield. Our past experience has shown that the Wang resin is highly compatible with the radical reaction conditions. Hence, 1-[2-(2-bromophenyl)ethyl]-1H-pyrrole-2-carboxylic acid 294 was tethered to the Wang resin using DIC and catalytic DMAP. The IR spectrum of the solid-supported pyrrole precursor 295 showed the formation of an ester band at 1702 cm\(^{-1}\). Attempts to cleave the material from a portion of resin proved futile. Therefore, we did not attempt the radical cyclisation reaction on pyrrole 295 as the cleavage of cyclised material would suffer the same fate so we decided to look for alternative approaches to solve the problem.

\[ \text{Scheme 128. Reagents and conditions: i, 2 M sodium hydroxide, ethanol, reflux, 8 h, 98%; ii, Wang resin, DMAP, DIC, DCM/DMF, rt.} \]

At the same time we started working on solid-supported pyrazole derivative 297. The hydrolysis of ethyl 1-[2-(2-bromophenyl)ethyl]-3-(trifluoromethyl)-1H-pyrazole-4-carboxylate 291 afforded pyrazole acid precursor 296 in a yield of 97% as shown in Scheme 129. The coupling reaction of pyrazole acid derivative 296 was carried out using the corresponding diisopropylcarbodiimide (DIC), with DMAP added to catalyse the esterification of Wang resin.

\[ \text{Scheme 129. Reagents and conditions: i, 2 M sodium hydroxide, ethanol, reflux, 8 h, 97%; ii, Wang resin, DMAP, DIC, DCM/DMF, rt.} \]
The results of the coupling reactions showed that for complete immobilisation of pyrazole acid precursor 296 onto Wang resin, it was necessary to perform double coupling to attain a high loading of 297. The IR spectrum for the resin-bound pyrazole 297 showed the formation of an ester band at 1723 cm$^{-1}$. The loading was assessed by cleavage and analysis of a portion of the resin-bound precursor 297 (TFA/DCM 9:1) prior to performing the cyclisation reactions.

5.2 Radical Cyclisation Reactions of Solid-Supported Pyrazole 297

Radical cyclisation reactions were performed on resin-bound pyrazole 297 under various experimental conditions to test the efficiency of intramolecular aryl cyclisations (Scheme 130). The results have been summarized in Table 21.

![Scheme 130. Synthesis of 2-(trifluoromethyl)-5,6-dihydropyrazolo[5,1-a]isoquinoline-1-carboxylic acid 298.](image)

**Table 21. Reaction conditions for the synthesis of 2-(trifluoromethyl)-5,6-dihydropyrazolo[5,1-a]isoquinoline-1-carboxylic acid 298.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bu$_3$GeH, AIBN, toluene, reflux, 30 h.</td>
<td>298 (20%), 296 (70%)</td>
</tr>
<tr>
<td>2</td>
<td>TTMSS, AIBN, toluene, reflux, 24 h.</td>
<td>298 (53%), 299 (27%)</td>
</tr>
</tbody>
</table>
The treatment of resin-bound pyrazole 297 with Bu₃GeH was carried out (Entry 1). After the radical cyclisation reaction, the resin was filtered and washed with an appropriate set of solvents to eliminate the traces of the excess of reagents. The tethered products on the resin were cleaved using TFA/DCM (9/1) and a crystalline material was recovered. The LC-MS analysis of the cleaved sample from the resin confirmed the presence of cyclised adduct 2-(trifluoromethyl)-5,6-dihydropyrazolo[5,1-a]isoquinoline-1-carboxylic acid 298, unaltered starting material 296 and reduced product 299. The 'H NMR spectrum of the cleaved sample was very clean and also showed the cyclised product 298 and the starting material 296 (1:1). The separation of these compounds by column chromatography was unsuccessful due to co-elution. The radical cyclisation reaction of resin-bound pyrazole 297 was repeated using TTMSS (Entry 2). Again we observed the 2-(trifluoromethyl)-5,6-dihydropyrazolo[5,1-a]isoquinoline-1-carboxylic acid 298 and the reduced product 299. The % yield has been determined by the weight of the material recovered at the end of these reactions. Careful manipulation of radical mediator resulted in the higher ratio of cyclised product 298. Time constraints did not permit us to examine the synthesis in more detail and extend it to other interesting heteroarenes. The results of the solid-supported aryl cyclisations onto pyrazole show its future potential. Separation of resulting polar compounds can be resolved by derivatising the products. Modification in cleavage conditions could lead us to synthesise a small library of novel compounds which may have pharmacological activities.

5.2.1 Conclusions

- Tributylgermanium hydride and TTMSS have shown great potential for solid-phase radical reactions.
- The mercaptobenzoic acid linker which we introduced at C-2 position of 2-chloro benzimidazole derivatives is a novel traceless linker and can be used for combinatorial synthesis.
- Other interesting heterocyclic analogues have been synthesised in solution-phase via the oxidative radical approach. Successful synthesis of the pyrazole 298 via the oxidative methodology using the solid-phase shows its potential for combinatorial synthesis.
EXPERIMENTAL

General

IR spectra were recorded on a Perkin-Elmer FT-IR Paragon 1000 spectrometer. The IR spectra were carried out on neat samples unless otherwise stated. $^1$H NMR spectra were recorded using a Bruker AC 250 spectrometer at 250 MHz unless otherwise stated and $J$ values are given in Hz. $^{13}$C NMR spectra were recorded using 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 an internal reference unless otherwise stated. 1,4-Dimethoxybenzene was used as an internal standard where indicated. Chemical shifts are reported in δ units. Elemental analysis was carried out on a Perkin Elmer 2400 CHN Elemental Analyser. Mass spectra were recorded using a Kratos MS 80 instrument. The GC-MS used was the Fisons GC 8000 series (AS 800) spectrometer.

TLC using silica gel as the absorbent was performed with aluminium backed plates 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 60 F$_{254}$). TLC plates were viewed under UV, with iodine or by immersing the plate in either of the solutions of KMnO$_4$ or phosphomolybdic acid. 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.

All the alkylations, substitutions and radical reactions were carried out under an atmosphere of nitrogen, using dry glassware. Anhydrous solvents such as THF, DMF, acetonitrile, benzene and toluene were obtained commercially. Other solvents such as DCM, ethyl acetate, light petroleum and methanol were distilled before use. Sodium hydride was obtained as a 60 % dispersion in mineral oil and was washed with light petroleum. Analytical grade diethyl ether and acetone were obtained commercially.
EXPERIMENTAL FOR CHAPTER TWO

1-(Triphenylmethyl)-1H-benzo[d]imidazole 149

![Chemical Structure](image)

Benzimidazole 148 (9.48 g, 80.2 mmol) was dissolved in DCM (500 mL). Triphenylmethyl chloride (30.0 g, 107.5 mmol) was added over 20 min and the mixture stirred until the solution was complete. Triethylamine (34 mL, 243.9 mmol) 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-(triphenylmethyl)-1H-benzo[d]imidazole 149 as cream coloured needles (22.53 g, 62.6 mmol, 78 %); mp 180-182 °C (lit.\(^\text{199}\) mp 180-181 °C); (Found: M\(^+\), 360.1624. C\(_{26}\)H\(_{20}\)N\(_2\) requires 360.1626); \(\delta\)\(_{\text{H}}\) 6.50 (1 H, ddd, \(J = 8.3, 0.9, 0.9, 7\)-H), 6.88 (1 H, ddd, \(J = 8.9, 7.2, 1.2, 5\)-H), 7.15-7.32 (16 H, m, ArH), 7.77 (1 H, ddd, \(J = 8.3, 0.9, 0.9, 4\)-H) and 7.87 (1 H, s, 2'-H); \(\delta\)\(_{\text{c}}\) 75.41 (C\(_q\)), 115.38 (benzimidazole ArCH), 120.28 (benzimidazole ArCH), 122.02 (benzimidazole ArCH), 122.30 (benzimidazole ArCH), 128.00 (3 x ArCH), 128.13 (6 x ArCH), 130.16 (6 x ArCH), 134.78 (ArC), 141.35 (3 x ArC), 144.13 (ArC) and 144.65 (2-C); m/z El 360 (M\(^+\), 2 %), 243 (100) and 165 (100).

1-[(3-Chloropropyl)selanyl]benzene 153\(^{33}\)

![Chemical Structure](image)

Diphenyl diselenide (5.0 g, 16.0 mmol) was dissolved in absolute ethanol (810 mL) at ambient temperature. Sodium borohydride (1.34 g, 35.5 mmol) was added slowly to the stirred solution at 0 °C. After 30 min, 1-chloro-3-iodopropane (3.43 g, 31.9 mmol) was added dropwise and the mixture was stirred at ambient temperature overnight. The solution was evaporated to dryness and 2 M hydrochloric acid (75 mL) was added and the solution extracted with diethyl ether (8 x 50 mL). The combined organic extracts were washed with sodium carbonate (3 x 50 mL) and brine (2 x 50 mL) and dried (MgSO\(_4\)). The crude product was purified by column chromatography using silica gel as
absorbent with light petroleum/DCM (4:1) as eluents to yield 1-[(3-chloropropyl)selanyl]benzene 153 as a pale yellow oil (6.42 g, 27.4 mmol, 86%); (Found: M+, 233.9714. C9H11SeCl requires 233.9715); \( \nu_{\text{max}} \)(neat)/cm\(^{-1}\) 3071, 2954, 1578, 1477, 1437, 1262, 1072, 1022, 735 and 691; \( \delta_{\text{H}} \) 2.10 (2 H, quintet, \( J = 7.0, 2\)-H), 3.00 (2 H, t, \( J = 7.0, \text{CH}_2\text{SePh} \)), 3.62 (2 H, t, \( J = 7.0, \text{ClCH}_2 \)), 7.23-7.28 (3 H, m, ArH) and 7.47-7.51 (2 H, m, ArH); \( \delta_{\text{C}} \) 24.42 (2-C), 32.52 (1-C), 44.22 (3-C), 126.97 (ArCH), 129.06 (ArCH), 131.00 (ArC) and 132.67 (ArCH); \( m/z \) El 234 (M+, 90%), 171 (17), 158 (100), 91 (35), 78 (65), 51 (25) and 41 (22).

1-[(4-Chlorobutyl)selanyl]benzene 154

Diphenyl diselenide (10.0 g, 32.0 mmol) was dissolved in methanol (1 L) at room temperature. Sodium borohydride (3.05 g, 80.0 mmol) was added slowly to the stirred solution at 0 °C. After 30 min, 4-bromo-1-chlorobutane (8.11 mL, 70.4 mmol) was added dropwise and the mixture was stirred at ambient temperature overnight. The solution was evaporated to dryness and 2 M hydrochloric acid (75 mL) was added and the solution extracted with diethyl ether (8 x 50 mL). The combined organic extracts were washed with sodium carbonate (3 x 50 mL) and brine (3 x 50 mL) and dried (MgSO\(_4\)). The crude product was purified by column chromatography using silica gel as absorbent and light petroleum/DCM (9:1) as eluents to yield 1-[(4-chlorobutyl)selanyl]benzene 154 as a colourless oil (12.0 g, 48.39 mmol, 69%); (Found: M+, 247.9873. C\(_{10}\)H\(_{13}\)ClSe requires 247.9871); \( \nu_{\text{max}} \)(neat)/cm\(^{-1}\) 3070, 2935, 1578, 1477, 1437, 1312, 1299, 1280, 1073, 1022 and 736; \( \delta_{\text{H}} \) (1.83-1.94 (4 H, m, 2-H, 3-H), 2.92 (2 H, t, \( J = 7.0, \text{CH}_2\text{SePh} \)), 3.53 (2 H, t, \( J = 6.0, \text{ClCH}_2 \)), 7.22-7.28 (3 H, m, ArH) and 7.48-7.50 (2 H, m, ArH); \( \delta_{\text{C}} \) 26.66 (3-C), 26.97 (2-C), 32.40 (CH\(_2\)SePh), 44.33 (ClCH\(_2\)), 126.91 (ArCH), 129.07 (ArCH), 130.04 (ArC) and 132.71 (ArCH); \( m/z \) El 248 (M+, 44%), 158 (45), 91 (100), 78 (43) and 55 (55).

1-[(5-Chloropentyl)selanyl]benzene 155

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Diphenyl diselenide (9.48 g, 30.4 mmol) was dissolved in absolute ethanol (600 mL) at ambient temperature. Sodium borohydride (2.30 g, 60.8 mmol) was added slowly to stirred solution at 0 °C. After 30 min, 1-bromo-5-chloropentane (8.0 mL, 60.7 mmol) was added dropwise and the mixture was stirred at ambient temperature overnight. The solution was evaporated to dryness and 2 M hydrochloric acid (75 mL) was added and the solution extracted with diethyl ether (8 x 50 mL). The combined organic extracts were washed with sodium carbonate (3 x 50 mL) and brine (2 x 50 mL) and dried (MgSO₄). The crude product was purified by column chromatography using silica gel as absorbent with light petroleurn/DCM (4:1) as eluents to yield 1-[(5-chloropentyl)selanyl]benzene 155 as a clear oil (15.90 g, 60.68 mmol, 99 %); (Found: M⁺, 262.0029. C₁₁H₁₅SeCl requires 262.0028); νmax (neat)/cm⁻¹ 3050, 1578, 1437, 1300, 1234, 1073, 1022, 736 and 699; δH 1.51-1.59 (2 H, m, 3-H), 1.69-1.80 (4 H, m, 4-H, 2-H), 2.90 (2 H, t, J = 7.3, 1-H), 3.51 (2 H, t, J = 6.6, 5-H), 7.21-7.28 (3 H, m, ArH) and 7.45-7.50 (2 H, m, ArH); δC 27.05 (3-C), 27.58 (2-C), 29.43 (4-C), 32.05 (1-C), 44.79 (5-C), 126.80 (ArCH), 129.04 (2 x ArCH), 130.31 (ArC) and 132.61 (2 x ArCH); m/z El (262 (M⁺, 50%), 181 (14), 158 (65), 77 (88), and 69 (100).

1-[(3-Iodopropyl)selanyl]benzene 156

1-[(3-Chloropropyl)selanyl]benzene 153 (2.88 g, 12.3 mmol) and sodium iodide (24.0 g, 160.1 mmol) were added to dry acetone (250 mL) and stirred in the dark 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 afford 1-[(3-iodopropyl)selanyl]benzene 156 as a yellow oil (3.3 g, 10.1 mmol, 82 %); (Found: M⁺, 325.9070. C₉H₁₁SeI requires 325.9071); νmax (neat)/cm⁻¹ 3054, 2969, 1578, 1477, 1436, 1203, 1022, 735 and 691; δH 2.15 (2 H, quintet, J = 7.0, 2-H), 2.98 (2 H, t, J = 7.0, CH₂SePh), 3.28 (2 H, t, J = 7.0, ICH₂), 7.25-7.28 (3 H, m, ArH) and 7.49-7.52 (2 H, m, ArH); δC (6.50 (CH₂SePh), 28.54 (CH₂), 33.66 (ICH₂), 127.55 (ArCH), 129.57 (ArCH), 129.85 (ArC) and 133.35 (ArCH); m/z FAB 326 (M⁺, 100 %), 199 (60) and 169 (25).
1-[(4-Iodobutyl)selanyl]benzene 157

1-[(4-Chlorobutyl)selanyl]benzene 154 (3.60 g, 14.6 mmol) and sodium iodide (26.98 g, 180.0 mmol) 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 afford 1-[(4-iodobutyl)selanyl]benzene 157 as yellow-orange oil (3.2 g, 9.5 mmol, 65 %); (Found: M+, 339.9227. C_{10}H_{13}Se requires 247.9227); δ_H 1.77-1.82 (2 H, m, 2-H), 1.90-1.95 (2 H, m, 3-H), 2.89 (2 H, t, J = 7.1, CH_2SePh), 3.18 (2 H, t, J = 6.7, ClCH_2), 7.25-7.27 (3 H, m, ArH) and 7.45-7.52 (2 H, m, ArH); m/z El 339 (M+, 11 %), 213 (100), 183 (57), 157 (50) 91 (28) 77 (36) and 55 (81). The oil darkened on standing at ambient temperature.

1-[(5-Iodopentyl)selanyl]benzene 158

1-[(5-Chloropentyl)selanyl]benzene 155 (5.00 g, 19.1 mmol) and sodium iodide (17.17 g, 114.5 mmol) 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 afford 1-[(5-iodopentyl)selanyl]benzene 158 as a brown oil (6.01 g, 17.0 mmol, 89 %); (Found: M+, 353.9388. C_{11}H_{15}Sel requires 353.9384); ν_max (neat)/cm\(^{-1}\) 3069, 2930, 1578, 1477, 1436, 1296, 1266, 1196, 1072, 1022, 874, 735 and 690; δ_H 1.50-1.56 (2 H, m, 3-H), 1.70-1.87 (4 H, m, 4-H, 2-H), 2.90 (2 H, t, J = 7.36, 1-H), 3.16 (2 H, t, J = 6.96, 5-H), 7.23-7.28 (3 H, m, ArH) and 7.46-7.50 (2 H, m, ArH); m/z El 354 (M+, 14 %), 323 (20), 227 (27), 197 (66), 155 (42), and 69 (100).
1-(Triphenylmethyl)-1H-benzo[d]imidazole 149 (6.00 g, 16.7 mmol) was dissolved in THF (185 mL) and the mixture was stirred at ambient temperature. The temperature of the stirred solution was lowered to −78 °C and a solution of n-butyllithium added dropwise (15.0 mL, 24.0 mmol). The solution turned pink and was stirred at 0 °C for a further 20 min. A solution of diphenyl disulfide (5.45 g, 25.0 mmol) in THF (15.0 mL) was added dropwise and the stirring was continued overnight. The solution was evaporated to give the crude product as a yellow oil which was dissolved in methanol (100 mL) and concentrated hydrochloric acid (10.0 mL, 31-34 % w/w solution) was added. The reaction mixture was heated under reflux for 4 h. The reaction mixture was reduced to approximately 20 mL in vacuo and extracted with light petroleum to remove by-products. The aqueous layer, containing the protonated benzimidazole compounds, was basified to pH 14 with sodium carbonate and 1 M sodium hydroxide (few drops). The basic solution was extracted with DCM (3 x 20 mL). The combined organic extracts were dried (MgSO₄) and evaporated to dryness to yield a crude solid. The residue was purified by column chromatography using neutral alumina as absorbent with DCM and diethyl ether (1:1) as eluents to afford 1H-benzo[d]imidazol-2-yl phenyl sulfide 152 as white crystals (3.00 g, 13.3 mmol, 80 %), mp 202-205 °C (lit.¹¹⁰ mp 201.5-202.5 °C); (Found: M⁺, 226.0559. C₉₅H₇₁N₂S requires 226.0565); νmax (nujol)/cm⁻¹ 1617, 1510, 1412, 1348, 1265, 1233, 977, 739 and 686; δH 7.15-7.51 (9 H, m, ArH); m/z El 226 (M⁺ 60 %), 225 (100), 192 (10), 167 (5), 77 (8).

1-[3-(Phenylselanyl)propyl]-2-(phenylsulfanyl)-1H-benzo[d]imidazole 159³³

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1H-Benz[o][d]imidazol-2-yl phenyl sulfide 152 (0.65 g, 3.0 mmol) was added slowly to NaH (90 mg, 3.8 mmol) in dry THF (200 mL). The mixture was stirred and heated under reflux for 1 h and 1-[(3-iodopropyl)selanyl]benzene 156 (0.73 g, 2.2 mmol) in THF (10 mL) was added dropwise to the reaction mixture. 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 DCM followed by diethyl ether as eluent to afford 1-[(3-phenylselanyl)propyl]-2-(phenylsulfanyl)-1H-benzo[d]imidazole 159 as a pale yellow oil (0.99 g, 2.3 mmol, 77 %); (Found: M⁺, 424.0504. C₂₂H₂₀N₂SSe requires 424.0512); νmax (neat)/cm⁻¹: 3056, 2930, 1579, 1478, 1423, 1354, 1248, 1023, 908, 740 and 690; δH (ppm): 2.02-2.15 (2 H, m, 2-H), 2.81 (2 H, t, J = 7.0, 3-H), 4.31 (2 H, t, J = 7.0, 1-H), 7.19-7.28 (9 H, m, ArH), 7.37-7.46 (4 H, m, ArH) and 7.71-7.75 (1 H, m, ArH); δC: 24.80 (2-C), 30.10 (3-C), 44.60 (1-C), 110.05 (ArCH), 120.32 (ArCH), 122.85 (ArCH), 123.68 (ArCH), 127.65 (ArCH), 128.32 (ArCH), 129.76 (2 x ArCH), 129.87 (2 x ArCH), 131.07 (2 x ArCH), 133.37 (2 x ArCH), 129.81 (ArC), 132.27 (ArC), 136.18 (ArC), 143.75 (ArC) and 148.03 (ArC); m/z: El 424 (M⁺, 10 %), 356 (35), 225 (43), 199 (100).

1-[4-(Phenylselanyl)butyl]-2-(phenylsulfanyl)-1H-benzo[d]imidazole 160

1H-benzo[d]imidazol-2-yl phenyl sulfide 152 (0.96 g, 4.3 mmol) was added slowly to a suspension of NaH (0.12 g, 5.0 mmol) in dry THF (190 mL). The mixture was stirred and heated under reflux for 1 h and 1-[(4-iodobutyl)selanyl]benzene 157 (1.44 g, 4.3 mmol) in THF (10 mL) was added dropwise to the reaction mixture. 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 brown oil, which was purified by column chromatography using neutral alumina as absorbent and light petroleum/ethyl acetate (4:1) as eluents to afford 1-[4-(phenylselanyl)butyl]-2-(phenylsulfanyl)-1H-benzo[d]imidazole 160 as a pale yellow oil (1.0 g, 2.3 mmol, 54 %); (Found: M⁺, 438.0664. C₂₃H₂₂N₂SSe requires 438.0669); νmax (neat)/cm⁻¹: 3056, 2934, 1579, 1477, 1461, 1437, 1422, 1355, 1278, 1023, 1023, 909 and 739; δH (ppm): 1.66-1.69 (2 H, m, 3-H), 1.81-1.84 (2 H, m,
2-H), 2.84 (2 H, t, J = 7.0, 4-H), 4.23 (2 H, t, J = 7.0, 1-H), 7.22-7.26 (9 H, m, ArH), 7.27-7.43 (4 H, m, ArH) and 7.70-7.80 (1 H, m, ArH); δC 27.16 (3-C), 27.23 (2-C), 29.51 (4-C), 44.19 (1-C), 109.66 (benzimidazole 4-C), 120.04 (benzimidazole 7-C), 122.38 (benzimidazole 6-C), 123.24 (benzimidazole 5-C), 127.08 (ArCH), 127.80 (ArCH), 129.09 (2 x ArCH), 129.45 (2 x ArCH), 129.71 (ArC), 130.49 (2 x ArCH), 132.18 (ArC), 133.01 (2 x ArCH), 135.73 (ArC), 143.41 (ArC) and 147.40 (benzimidazole 2-C); m/z El 438 (M+, 80 %), 281 (100), 239 (25), 172 (22), 109 (13) and 77 (27).

2,3-Dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole 161

Method A (thermal method, using tributyltin hydride and toluene)

A solution of tri-n-butyltin hydride (0.83 mL, 3.1 mmol) in toluene (50 mL) was added to 1-[3-(phenylselanyl)propyl]-2-(phenylsulfanyl)-1H-benzo[d]imidazole 159 (0.60 g, 1.4 mmol) in toluene (150 mL) at reflux over 5 h using a syringe pump. AIBN (0.16 g, 1.4 mmol) was added to the refluxing reaction mixture at equal intervals. The solution was stirred and heated under reflux for a further 1 h. Dilute hydrochloric acid was added to the cooled reaction mixture to extract the protonated benzimidazole compounds into the aqueous layer and washed with light petroleum to remove Bu3Sn-residues. The acidic aqueous layer was basified with sodium carbonate and then aqueous sodium hydroxide (few drops) to pH 14. The basic solution was extracted with DCM (3 x 20 mL). The combined organic extracts were dried (MgSO4) and evaporated to dryness to give a pale yellow oil crude product (0.20 g). The crude product was purified by column chromatography using silica gel as absorbent with light petroleum and ethyl acetate as eluents to give 2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole 161 as white crystals (57 mg, 0.36 mmol, 25 %), mp 105-107 °C (lit.111 mp 114-115 °C); δH 2.70 (2 H, quintet, J = 7.4, 2-H), 3.05 (2 H, t, J = 7.2, 1-C), 7.25-7.40 (3 H, m, ArH) and 7.67-7.73 (1 H, m, ArH).
Method B (uv irradiation, hexamethylditin and \textit{tert}-butylbenzene)

The reaction mixture of 1-[3-(phenylselanyl)propyl]-2-(phenylsulfanyl)-1\textit{H}-benzo[d]imidazole 159 (89 mg, 0.21 mmol) and hexamethylditin (114 mg, 0.35 mmol) in \textit{tert}-butylbenzene (10.0 mL) was irradiated with UV lamp at 85 °C for 30 h. Dil. hydrochloric acid was added to the cooled reaction mixture to extract the protonated benzimidazole compounds into the aqueous layer and washed with light petroleum to remove Bu$_3$Sn-residues. The acidic aqueous layer was basified with sodium carbonate and aqueous sodium hydroxide (few drops) to pH 14. The basic solution was extracted with DCM (3 x 20 mL). The combined organic extracts were dried (MgSO$_4$) and evaporated to dryness. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum and ethyl acetate as eluents to give 2,3-dihydro-1\textit{H}-benzo[d]pyrrolo[1,2-a]imidazole 161 as white crystals (9 mg, 0.06 mmol, 26%). The spectral data were identical to those of an authentic material.

1,2,3,4-Tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine 162

\[\text{\begin{tikzpicture} \node [regular polygon, regular polygon sides=8, draw, minimum size=1.5cm] (p) {}; \node at (p.corner 1) (8a) {}; \node at (p.corner 2) (9a) {}; \node at (p.corner 3) (1) {}; \node at (p.corner 4) (2) {}; \node at (p.corner 5) (3) {}; \node at (p.corner 6) (4) {}; \node at (p.corner 7) (5) {}; \node at (p.corner 8) (7) {}; \draw (8a) -- (9a) -- (1) -- (2) -- (3) -- (4) -- (5) -- (7); \draw (8a) -- (4); \draw (9a) -- (5); \draw (1) -- (2); \draw (3) -- (4); \draw (5) -- (7); \end{tikzpicture}} \]

A solution of tri-\textit{n}-butyltin hydride (0.68 mL, 2.5 mmol) in acetonitrile (50 mL) was added to 1-[4-(phenylselanyl)butyl]-2-(phenylsulfanyl)-1\textit{H}-benzo[d]imidazole 160 (0.50 g, 1.2 mmol) in acetonitrile (500 mL) at reflux over 5 h using a syringe pump. AMBN (0.24 g, 1.3 mmol) was added to refluxing reaction mixture at equal intervals. The solution was stirred and heated under reflux for a further 1 h. Dilute hydrochloric acid was added to the cooled reaction mixture to extract the protonated benzimidazole compounds into the aqueous layer and washed with light petroleum to remove Bu$_3$Sn-residues. The acidic aqueous layer was basified with sodium carbonate and aqueous sodium hydroxide (few drops) to pH 14. The basic solution was extracted with DCM (3 x 20 mL). The combined organic extracts were dried (MgSO$_4$) and evaporated to dryness to yield white crystalline solid. The $^1$H NMR spectrum of the crude product showed the presence of cyclised product and traces of other impurities. The crude product was purified by column chromatography using neutral alumina as absorbent with light petroleum and ethyl acetate as eluents to give 1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine 162 as white crystals (121 mg, 0.70 mmol, 61%), mp
2-Chloro-1-[(3-phenylselanyl)propyl]-1H-benzo[d]imidazole 164

2-Chlorobenzimidazole 163 (2.00 g, 13.1 mmol) was added slowly to NaH (0.33 g, 15.7 mmol) in dry THF (240 mL). The mixture was stirred and heated under reflux for 1 h and 1-[(3-iodopropyl)selanyl]benzene (4.28 g, 13.1 mmol) in THF (10.0 mL) was added dropwise to the reaction mixture. 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. The residue was purified by column chromatography using neutral alumina as absorbent and light petroleum/ethyl acetate (9:1) as eluents to afford 2-chloro-1-[(3-phenylselanyl)propyl]-1H-benzo[d]imidazole 164 as a pale yellow oil (2.79 g, 8.0 mmol, 61%); (Found: M+, 350.0091. C_{16}H_{15}ClN_{2}Se requires 350.0089); (Found: C, 55.38; H, 4.40; N, 7.94. requires C, 54.95; H, 4.32; N, 8.01 %); \( \nu_{\text{max}} \) (neat)/cm\(^{-1}\) 2930, 1615, 1578, 1469, 1450, 1375, 1329, 1247, 1154, 1022, 761, 740 and 691; \( \delta_{\text{H}} \) 2.12-2.33 (2 H, m, 2-H), 2.88 (2 H, t, \( J = 6.9, 3\)-H), 4.28 (2 H, t, \( J = 7.1, 1\)-H), 7.20-7.23 (6 H, m, ArH), 7.43-7.45 (2 H, m, ArH) and 7.65-7.68 (1 H, m, ArH); \( \delta_{\text{C}} \) 24.10 (2-C), 29.30 (3-C), 43.81 (1-C), 109.36 (benzimidazole 4/7-C), 119.46 (benzimidazole 4/7-C), 122.67 (benzimidazole 5/6-C), 123.17 (benzimidazole 5/6-C), 127.32 (ArCH), 129.09 (ArC), 129.22 (2 x ArCH), 132.97 (2 x ArCH), 134.99 (ArC), 140.35 (ArC) and 141.71 (benzimidazole 2-C); \( m/z \) El 350 (M+, 43 %), 315 (55), 165 (62), 91 (100) and 77 (29).
2-Chloro-1-[(4-phenylselanyl)butyl]-1H-benzo[d]imidazole 165

![Chemical Structure](image)

2-Chlorobenzimidazole 163 (2.50 g, 16.4 mmol) was added slowly to NaH (0.47 g, 19.7 mmol) in dry THF (240 mL). The mixture was stirred and heated under reflux for 1 h, and 1-[(4-iodobutyl)selanyl]benzene (6.22 g, 13.1 mmol) in THF (10.0 mL) was added dropwise to the reaction mixture. 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. The solid was purified by column chromatography using neutral alumina as absorbent and light petroleum/ethyl acetate (9:1) as eluents to afford 2-chloro-1-[(4-phenylselanyl)butyl]-1H-benzo[d]imidazole 165 as a pale yellow oil (2.5 g, 6.87 mmol, 42 %); (Found: M', 364.0250. C₁₇H₁₇ClN₂Se requires 364.0246); \( \nu_{\text{max}} \, (\text{neat})/\text{cm}^{-1} \) 3033, 2936, 2860, 1615, 1579, 1469, 1446, 1379, 1279, 1242, 1154, 1073, 1022, 911 and 739; \( \delta_{\text{H}} \) 1.70-1.76 (2 H, m, 3-H), 1.94-2.00 (2 H, m, 2-H), 2.90 (2 H, t, \( J = 7.1 \), 4-H), 4.18 (2 H, t, \( J = 7.1 \), 1-H), 7.23-7.28 (6 H, m, ArH), 7.41-7.46 (2 H, m, ArH) and 7.67-7.71 (1 H, m, ArH); \( \delta_{\text{C}} \) 27.01 (3-C), 27.20 (2-C), 29.16 (4-C), 43.94 (1-C), 109.38 (benzimidazole 4/7-C), 119.55 (benzimidazole 4/7-C), 122.66 (benzimidazole 5/6-C), 123.14 (benzimidazole 5/6-C), 127.16 (ArCH), 129.11 (2 x ArCH), 129.53 (ArC), 133.05 (2 x ArCH), 134.94 (ArC, 3a), 140.43 (ArC, 7a) and 141.79 (benzimidazole 2-C); \( m/z \) El 364 (M', 50 %), 205 (100), 165 (90), 129 (30) and 77 (28).

2-Chloro-1-[(5-phenylselanyl)pentyl]-1H-benzo[d]imidazole 166

![Chemical Structure](image)

2-Chlorobenzimidazole 163 (2.77 g, 18.2 mmol) was added slowly to a suspension of NaH (0.87 g, 36.4 mmol) in dry THF (250 mL). The mixture was stirred and heated under reflux for 1 h and 1-
[(5-iodopentyl)selanyl]benzene 158 (6.42 g, 18.2 mmol) in THF (10 mL) was added dropwise to the reaction mixture. 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. The solid was purified by column chromatography using neutral alumina as absorbent and light petroleum/ethyl acetate (9:1) as eluents to afford 2-chloro-1-[5-(phenylselanyl)pentyl]-1H-benzo[d]imidazole 166 as a pale yellow oil (3.53 g, 9.3 mmol, 51%); (Found: M", 378.0405. C\textsubscript{18}H\textsubscript{19}ClN\textsubscript{2}Se requires 378.0402); ν\textsubscript{max} (neat)/cm\textsuperscript{-1} 3054, 2934, 1615, 1578, 1469, 1447, 1379, 1352, 1272, 1235, 1022 and 741; δ\textsubscript{H} 1.35-1.42 (2 H, m, 3-H), 1.62-1.78 (4 H, m, 2-H and 4-H), 2.91 (2 H, t, J = 7.4, 5-H), 4.23 (2 H, t, J = 7.0, 1-H), 7.23-7.30 (6 H, m, ArH and 6-H), 7.41-7.44 (2 H, m, 5-H and 7-H) and 7.58-7.60 (1 H, m, 4-H); δ\textsubscript{C} 26.77 (4-C), 27.43 (3-C), 28.83 (2-C), 29.75 (5-C), 44.29 (1-C), 109.37 (benzimidazole 4/7-C), 119.54 (benzimidazole 4/7-C), 122.63 (benzimidazole 5/6-C), 123.10 (benzimidazole 5/6-C), 126.91 (ArCH), 129.08 (2 x ArCH), 130.13 (ArC), 132.70 (2 x ArCH), 134.99 (7a-C), 140.50 (3a-C) and 141.80 (benzimidazole 2-C); m/z El 378 (M\textsuperscript{+}, 20%), 343 (8), 262 (48), 158 (68), 77 (48) and 69 (100).

Radical cyclisation of 2-chloro-1-[((3-phenylselanyl)propyl]-1H-benzo[d]imidazole 164

![Radical cyclisation of 2-chloro-1-[(3-phenylselanyl)propyl]-1H-benzo[d]imidazole 164](image)

A solution of tributyltin hydride (0.74 mL, 2.8 mmol) in toluene (50 mL) was added to 2-chloro-1-[(3-phenylselanyl)propyl]-1H-benzo[d]imidazole 164 (0.64 g, 1.8 mmol) in toluene (150 mL) at reflux over 7 h using a syringe pump. AIBN (149 mg, 0.92 mmol) was added to refluxing reaction mixture at equal intervals. The solution was stirred and heated under reflux for a further 1 h. Dil. hydrochloric acid was added to the cooled reaction mixture to extract the protonated benzimidazole compounds into the aqueous layer and washed with light petroleum to remove Bu\textsubscript{3}Sn-residues. The acidic aqueous layer was basified with sodium carbonate and aqueous sodium hydroxide (few drops) to pH 14. The basic solution was extracted with DCM (3 x 20 mL). The combined organic extracts were dried (MgSO\textsubscript{4}) and evaporated to dryness to give a pale yellow oil. The \textsuperscript{1}H NMR spectrum of the crude product showed the presence of reduced and the cyclised products (8:1) ratio. The crude mixture was purified by column chromatography using neutral alumina as absorbent and light
petroleum/EtOAc (9:1) as eluents to yield 2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole 161 as pure white crystals (28 mg, 0.18 mmol, 10 %); \( \delta_H \) 2.70 (2 H, quintet, \( J = 7.4 \), 2-H), 3.05 (2 H, t, \( J = 7.6 \), 3-H), 4.1 (2 H, t, \( J = 7.2 \), 1-C), 7.25-7.40 (3 H, m, ArH) and 7.67-7.73 (1 H, m, ArH). And 2-chloro-1-propyl-1H-benzo[d]imidazole 167 was obtained as a pale yellow oil (0.18 g, 0.93 mmol, 51 %); (Found: M+, 194.0611. C\(_{10}\)H\(_{11}\)N\(_2\)Cl requires 194.0607); \( \nu_{\text{max}} \) (neat)/cm\(^{-1}\) 3057, 2967, 2879, 1616, 1469, 1445, 1375, 1330, 1281, 1244, 1216, 1131, 1008, 762 and 742; \( \delta_H \) 0.96 (3 H, t, \( J = 7.5 \), CH\(_3\)), 1.85 (2 H, septet, \( J = 7.4 \), 2-H), 4.12 (2 H, t, \( J = 7.2 \), 1-H), 7.23-7.30 (3 H, m, ArH) and 7.66-7.70 (1 H, m, ArH); \( \delta_C \) 1.21 (CH\(_3\)), 22.66 (CH\(_2\)), 45.95 (NCH\(_2\)), 109.49 (ArCH), 119.41 (ArCH), 122.51 (ArCH), 123.19 (ArCH), 135.04 (ArC, 7a/3a), 140.58 (ArC, 3a/7a) and 141.70 (ArC, 2-C); m/z El 194 (M+, 67 %), 165 (100), 152 (24), 129 (22), 90 (10) and 77 (9).

**Tributylgermanium hydride**

\( \text{Bu}_3\text{GeH} \)

Tetrachlorogeranium (5.00 g, 23.3 mmol) and butylmagnesium chloride (2 M solution in diethyl ether, 57 mL) were dropwise added to a solution of \( \text{C}_{27}\text{TiCl}_2 \) (0.43 g, 1.7 mmol) in freshly distilled diethyl ether (140 mL) at \(-78 \) °C over 45 min. The mixture was allowed to warm up to rt over 45 min during which period a colour change from milky red to green was observed and thereafter refluxed for 15 h. After cooling to \( 0 \) °C aqueous hydrochloric acid (2 M, 57 mL) was added over 1 h and a colour change to red was observed. The organic layer was separated and the aqueous phase was extracted with ether. The combined organic layer was dried (MgSO\(_4\)) and evaporated to dryness to give a liquid which was filtered through celite to remove a red solid. Distillation under reduced pressure gave tributylgermanium hydride as a colourless oil (5.41 g, 22.1 mmol, 95 %). The spectral data corresponds to that stated in literature; \( \delta_H \) 0.82-0.92 (15 H, m, 1-H and 4-H), 1.34-1.43 (12 H, m, 2-H and 3-H) and 3.68 (1 H, sep, \( J = 2.8 \), GeH).

**1-(4-Bromobutyl)-2-chloro-1H-benzo[d]imidazole 168**

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2-Chlorobenzimidazole 163 (2.00 g, 13.1 mmol) was added slowly to a suspension of sodium hydride (0.47 g, 19.6 mol) in dry DMF (20 mL). The mixture was stirred for 1 h and 1,4-dibromobutane (3.57 mL, 26.2 mmol) in DMF (10 mL) was added dropwise to the reaction mixture and it was stirred for 20 h. The reaction mixture was evaporated to dryness. The solid was purified by column chromatography using neutral alumina as absorbent and light petroleum/ethyl acetate (9:1) as eluents to afford 1-(4-bromobutyl)-2-chloro-1\textit{H}-benzo[\textit{d}]imidazole 168 as a pale yellow oil (3.60 g, 12.5 mmol, 95\%); (Found: MH+, 286.9946. C\textsubscript{11}H\textsubscript{12}BrClN\textsubscript{2} requires 286.9950); \(\nu_{\max} \) (neat)/cm\textsuperscript{-1} 2950, 2369, 1705, 1614, 1469, 1446, 1376, 1279, 1243, 1152, 1143, 1008 and 743; \(\delta_{\text{H}} \) 1.90-1.95 (2 H, m, CH\textsubscript{2}), 2.01-2.05 (2 H, m, CH\textsubscript{2}), 3.42 (2 H, t, \(J = 8.0, \text{BrCH}_2\)), 4.24 (2 H, t, \(J = 8.0, \text{NCH}_2\)), 7.27-7.32 (3 H, m, ArH) and 7.70-7.71 (1 H, m, ArH); \(\delta_{\text{C}} \) 27.92 (CH\textsubscript{2}), 29.54 (CH\textsubscript{2}), 32.55 (BrCH\textsubscript{2}), 43.63 (NCH\textsubscript{2}), 109.35 (benzimidazole 4/7-C), 119.60 (benzimidazole 4/7-C), 122.79 (benzimidazole 5/6-C), 123.28 (benzimidazole 5/6-C), 134.86 (ArC), 140.38 (ArC) and 141.73 (ArC); \(m/z \) El 286 (M\textsuperscript{+}, 35\%), 209 (18), 165 (100), 129 (54), 102 (48), 90 (52), 77 (34) and 55 (45).

**Radical cyclisation of 1-(4-bromobutyl)-2-chloro-1\textit{H}-benzo[\textit{d}]imidazole 168**

Tributylgermanium hydride (0.56 mL, 2.16 mmol) was added to 1-(4-bromobutyl)-2-chloro-1\textit{H}-benzo[\textit{d}]imidazole 168 (0.31 g, 1.1 mmol) in toluene (100 mL), followed by portion wise addition of AIBN (0.35 g, 2.2 mmol) to the refluxing reaction mixture at equal intervals. The solution was stirred and heated under reflux for 12 h. The reaction mixture was evaporated to dryness. The crude product was purified by column chromatography using neutral alumina as absorbent with light petroleum and ethyl acetate as eluents to give 1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-\textit{a}]pyridine 162 as white crystals (0.10 g, 0.58 mmol, 54\%); \(\nu_{\max} \) (KBr)/cm\textsuperscript{-1} 1610, 1505, 1425, 1397, 1328, 1278, and 745; \(\delta_{\text{H}} \) 1.98-2.09 (2 H, m, 3-H), 2.10-2.13 (2 H, m, 2-H), 3.09 (2 H, t, \(J = 7.0, 4\text{-H}\)), 4.06 (2 H, t, \(J = 7.0, 1\text{-H}\)), 7.21-7.30 (3 H, m, ArH) and 7.66-7.69 (1 H, m, ArH).
1H-Imidazole-2-yl pyridin-2-yl sulfide 174

A mixture of 2-mercaptoimidazole 173 (2.00 g, 20.0 mmol), 2-chloropyridine (1.89 mL, 20.0 mmol) and anhydrous K₂CO₃ (7.00 g, 50.7 mmol) in DMF (70 mL) was heated at reflux for 12 h. The reaction mixture was evaporated to dryness and the crude product was purified by column chromatography using neutral alumina as absorbent and light petroleum/ethyl acetate (1:1) as eluents to afford 1H-imidazole-2-yl pyridin-2-yl sulfide 174 as white crystals (3.36 g, 19.0 mmol, 95%), mp 97.8-99.5 °C; (Found: M⁺, 177.0361. C₈H₇N₃S requires 177.0361); νmax (KBr)/cm⁻¹: 3000, 2994, 2374, 1849, 1560, 1419, 1330, 1122, 966, 756 and 720; δH (7.8, 3-H), 6.93 (1 H, d, J = 7.8, 5-H), 7.11 (2 H, s, imidazole 5-H and 4-H), 7.38 (1 H, d, J = 7.8, 1.6, 4-H) and 8.29 (1 H, d, J = 4.8, 6-H); δC 120.48 (3-C), 121.41 (5-C), 125.05 (4-C), 134.46 (imidazole 2-C), 137.13 (imidazole 4-C), 148.94 (imidazole 6-C) and 159.06 (2-C); m/z El 177 (M⁺, 100 %), 167 (8), 145 (9), 133 (13), 119 (42), 110 (25), 84 (25) and 78 (57).

1-[4-(Phenylselanyl)butyl]-1H-imidazole-2-yl pyridin-2-yl sulfide 175

1H-Imidazole-2-yl pyridin-2-yl sulfide 174 (0.45 g, 2.5 mmol) was added slowly to NaH (0.12 g, 5.1 mmol) in dry THF (90 mL). The mixture was stirred and heated under reflux for 1 h and 1-[4-iodobutyl]selanyl]benzene 157 (0.86 g, 2.5 mmol) in THF (10.0 mL) was added dropwise to the reaction mixture. The mixture was heated under reflux for a further 24 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 residue was purified by column chromatography using neutral alumina as absorbent and light
petroleum/ethyl acetate (3:1) and (1:1) as eluents to afford 1-[4-(phenylselanyl)butyl]-1H-imidazole-2-yl pyridin-2-yl sulfide 175 as a dark brown oil (0.98 g, 2.51 mmol, 99 %); (Found: M+, 389.0465. C_{18}H_{19}N_{3}S requires 389.0455); \nu_{\text{max}} (\text{neat})/\text{cm}^{-1} 2934, 2101, 1606, 1574, 1477, 1449, 1418, 1277, 1120, 916, 760, 738 and 692; \delta_{l} 1.57-1.64 (2 \text{ H, m, } \text{CH}_2), 1.78-1.86 (2 \text{ H, m, } \text{CH}_2), 2.79 (2 \text{ H, t, } J = 7.2, \text{PhSeCH}_2), 4.02 (2 \text{ H, t, } J = 7.2, \text{NCH}_2), 6.84 (1 \text{ H, d, } J = 8.4, 3-\text{H}), 6.99 (1 \text{ H, ddd, } J = 7.5, 7.5 \text{ and } 0.8, 5-\text{H}), 7.12 (1 \text{ H, d, } J = 1.2, \text{imidazole 4-H or 5-H}), 7.22-7.25 (4 \text{ H, m, ArH}), 7.39-7.47 (3 \text{ H, m, ArH}) \text{ and } 8.36 (1 \text{ H, dd, } J = 4.8 \text{ and } 1.2, 6-\text{H}); \delta_{c} 26.80 (\text{CH}_2), 27.01 (\text{PhSeCH}_2), 30.70 (\text{CH}_2), 46.57 (\text{NCH}_2), 120.55 (\text{pyridine 3-C}), 121.12 (\text{pyridine 5-C}), 122.78 (\text{imidazole 4-C}), 126.96 (\text{ArCH}), 128.98 (\text{ArCH}), 129.06 (\text{ArCH}), 129.78 (\text{ArC}), 130.95 (\text{imidazole 5-C}), 133.47 (2 \times \text{ArCH}), 135.45 (\text{imidazole 2-C}), 137.03 (\text{pyridine 4-C}), 149.66 (\text{pyridine 6-C}) \text{ and } 159.12 (\text{pyridine 2-C}); \text{m/z } \text{El } 389 (M^+, 3 \%), 370 (5), 312 (12), 279 (65), 254 (15), 232 (32), 213 (28), 177 (45), 157 (32), 122 (85), 91 (45) \text{ and } 73 (100).

1H-Benz[\text{d}]imidazole-2-yl pyridin-2-yl sulfide 177

![Structure of 1H-Benz[\text{d}]imidazole-2-yl pyridin-2-yl sulfide 177](image)

A mixture of 2-mercaptobenzimidazole 176 (2.0 g, 13.3 mmol), 2-chloropyridine (1.26 mL, 13.3 mmol) and anhydrous K$_2$CO$_3$ (10.0 g, 72.4 mmol) in DMF (70 mL) was heated at reflux for 12 h. The reaction mixture was evaporated to dryness and the crude product was purified by column chromatography using neutral alumina as absorbent and light petroleum/ethyl acetate (1:1) as eluents to afford 1H-benz[\text{d}]imidazole-2-yl pyridin-2-yl sulfide 177 as white crystals (1.21 g, 5.3 mmol, 40 %), mp 145-147 °C; (Found: M^+, 227.0519. C$_{12}$H$_{9}$N$_{3}$S requires 227.0517); \nu_{\text{max}} (\text{KBr})/\text{cm}^{-1} 3057, 2951, 2773, 2593, 2372, 1847, 1567, 1413, 1274, 1117, 984 and 748; \delta_{l} 7.07 (1 \text{ H, dd, } J = 6.7 \text{ and } 6.7, \text{pyridine 5-H}), 7.20-7.26 (3 \text{ H, m, ArH}), 7.52 (1\text{H, dd, } J = 6.7 \text{ and } 6.7, \text{pyridine 4-H}), 7.58-7.60 (2 \text{ H, m, ArH}) \text{ and } 8.46 (1 \text{ H, d, } J = 4.15, \text{pyridine 6-H}); \delta_{c} 114.75 (\text{pyridine 3-C}), 121.46 (4/7-C), 122.51 (\text{pyridine 5-C}), 123.33 (5/6-C), 137.32 (\text{pyridine 4-C}), 138.50 (3a-C and 7a-C), 146.20 (2-C), 149.17 (\text{pyridine 6-C}) \text{ and } 155.47 (\text{pyridine 2-C}); \text{m/z } \text{El } 227 (M^+, 100 \%), 194 (6), 169 (94), 149 (11), 122 (24), 91 (13) \text{ and } 78 (42).
A solution of tributyltin hydride (0.12 mL, 0.45 mmol) in toluene (50 mL) was added to 1-[4-(phenylselanyl)butyl]-1H-imidazole-2-yl pyridin-2-yl sulfide 175 (116 mg, 0.29 mmol) in toluene (200 mL) at reflux over 10 h using a syringe pump. AIBN (48 mg, 0.3 mmol) was added to refluxing reaction mixture at equal intervals. The solution was stirred and heated under reflux for a further 1 h. Dil. hydrochloric acid was added to the cooled reaction mixture to extract the protonated imidazole compounds into the aqueous layer and washed with light petroleum to remove Bu₂Sn-residues. The acidic aqueous layer was basified with sodium carbonate and then sodium hydroxide (few drops) to pH 14. The basic solution was extracted with DCM (3 x 20 mL). The combined organic extracts were dried (MgSO₄) and evaporated to dryness to afford 1-[4-(phenylselanyl)butyl]-1H-imidazole-2-yl pyridin-2-yl sulfide 175 as a dark brown oil (23 mg, 0.06 mmol, 20 %) and 1-(but-3-enyl)-1H-imidazole-2-yl pyridin-2-yl sulfide 178 as a dark brown oil (39 mg, 0.17 mmol, 60 %); (Found: M⁺, 231.0835. C₁₂H₁₃N₃S requires 231.0830); \( \nu_{\text{max}} \) (neat)/cm⁻¹ 3468, 3106, 2977, 2932, 1682, 1574, 1561, 1449, 1418, 1278, 1119, 978, 917, 761, 721 and 618; \( \delta_H \) 2.44 (2 H, q, \( J = 7.1 \), CH₂), 4.13 (2 H, t, \( J = 7.1 \), NCH₂), 4.99 (2 H, m, 4-H), 5.68 (1 H, m, 3-H), 6.86 (1 H, d, \( J = 8.1 \), pyridine 3-H), 7.03 (1 H, dd, \( J = 6.82 \) and 6.82, pyridine 5-H), 7.17 (1 H, s, imidazole 4-H), 7.26 (1 H, s, imidazole 5-H), 7.45 (1 H, ddd, \( J = 7.8, 7.8 \) and 2.1, pyridine 4-H) and 8.39 (1 H, d, \( J = 4.6 \), pyridine 6-H); \( \delta_C \) 35.21 (CH₂), 46.73 (NCH₂), 118.20 (4-C), 120.77 (imidazole 4-C), 121.22 (imidazole 5-C), 123.23 (pyridine 3-C), 130.95 (pyridine 5-C), 133.48 (3-C), 135.52 (imidazole 2-C), 137.07 (pyridine 4-C), 149.71 (pyridine 6-C) and 159.10 (pyridine 2-C); \( m/z \) El 231 (M⁺, 32 %), 198 (16), 177 (100), 153 (25), 121 (82), 78 (88) and 59 (57).
To a solution of 1-[(4-(phenylselanyl)butyl]-1H-imidazole-2-yl pyridin-2-yl sulfide 175 (59 mg, 0.15 mmol) in anhydrous benzene (25 mL), TTMSS (0.06 mL, 0.2 mmol) and Et₃B (1.0 M in cyclohexane, 0.3 mmol) were added dropwise. The flask was fitted with a rubber septum and air was introduced through a needle during stirring at rt for 5 h. Further addition of TTMSS (0.06 mL, 0.2 mmol) and Et₃B (1.0 M in hexane, 0.3 mmol) were carried out and the reaction mixture was stirred for another 10 h. Dilute hydrochloric acid was added to the cooled reaction mixture to extract the protonated imidazole compounds into the aqueous layer and washed with light petroleum to remove Bu₃Sn-residues. The acidic aqueous layer was basified with sodium carbonate and aqueous sodium hydroxide (few drops) to pH 14. The basic solution was extracted with DCM (3 x 20 mL). The combined organic extracts were dried (MgSO₄) and evaporated to dryness to afford 5,6,7,8-tetrahydroimidazo[1,2-α]pyridine 180 (0.014 mmol, 9 %). The yield was determined by ¹H NMR spectroscopy using the internal standard.
Acetyl chloride (12.0 mL, 168.8 mmol) was added dropwise over 10 min to MeOH (50 mL) cooled in ice. The solution was stirred for 5 min, (2-benzimidazolylsulfanyl)acetic acid 187 (2.0 g, 9.6 mmol) was added in one portion and the solution slowly heated to reflux. Heating under reflux was continued overnight. The reaction mixture was cooled and evaporated to dryness to give the crude methyl ester. Distilled water (50 mL) was added to the crude methyl ester hydrochloride and the acidic solution was washed with DCM (2 x 50 mL). The aqueous layer contained benzimidazole compounds and was basified to pH 14 with sodium carbonate and 1 M sodium hydroxide (few drops). The basic solution was extracted with DCM (3 x 50 mL). The combined organic extracts were dried (MgSO₄) and evaporated to dryness to afford methyl 2-(1H-benzo[d]imidazol-2-ylsulfanyl)ethanoate 181 as off white crystals (1.86 g, 8.4 mmol, 87%), mp 114-117 °C; (Found: M⁺, 222.0467, CIHN₂O₂S requires 222.0463); νmax (Nujol)/cm⁻¹ 2923, 2853, 1743, 1459, 1376 and 1165; δH 3.78 (3 H, s, OCH₃), 4.01 (2 H, s, CH₂), 7.19-7.26 (2 H, m, ArH) and 7.51-7.53 (2 H, m, ArH); δC 34.30 (CH₂), 53.20 (OCH₃), 114.48 (2 x ArCH), 122.29 (ArCH), 122.60 (ArCH), 139.19 (2 x ArC), 148.31 (ArC 2-C) and 170.90 (C=O); m/z El 222 (M⁺, 54 %), 221 (58), 190 (50), 163 (100), 149 (32) and 118 (38).

Attempted synthesis of methyl 2-[(1-methyl-1H-benzo[d]imidazol-2-yl)sulfanyl]ethanoate 188

Methyl 2-(1H-benzo[d]imidazol-2-ylsulfanyl)ethanoate 181 (0.20 g, 0.9 mmol) was added slowly to a suspension of NaH (26 mg, 1.08 mmol) in dry THF (60 mL), followed by dropwise addition of MeI (0.06 mL, 0.9 mmol). The mixture was stirred and heated under reflux for 3 h. The salts
formed were removed by filtration on a celite bed and the solution was evaporated to dryness to yield a colourless oil, crude product contained non-isolable species by chromatography.

2-Chloro-1-(triphenylmethyl)-1H-benzo[d]imidazole 193

2-Chlorobenzimidazole 163 (1.96 g, 12.9 mmol) was dissolved in DCM (200 mL). Triphenylmethyl chloride (4.30 g, 15.4 mmol) was added over 20 min and the mixture stirred until the solution was complete. Triethylamine (2.58 mL, 18.5 mmol) was added slowly to the stirred solution and the stirring was continued overnight at ambient temperature. The solution was evaporated to dryness to give the crude product. The crude product was purified by column chromatography using neutral silica as absorbent with light petroleum and EtOAc as eluents to afford 2-chloro-1-(triphenylmethyl)-1H-benzo[d]imidazole 193 as white needles (1.50 g, 3.9 mmol, 30%), mp 157-160 °C; (Found: M+, 395.1315. C_{25}H_{19}ClN_{2} requires 395.1315); (Found: C, 79.25; H, 4.91; N, 6.48. C_{25}H_{19}ClN_{2} requires C, 79.08; H, 4.85; N, 7.09 %); \nu_{max} (KBr)/cm^{-1} 3061, 2369, 1482, 1442, 1274, 1023, 749 and 701; \delta_{H} 5.70 (1 H, d, J = 8.8, 4/7-H), 6.85 (1 H, dd, J = 7.9 and 7.9, 5/6-H), 7.15 (1 H, dd, J = 7.6 and 7.6, 5/6-H), 7.26-7.36 (15 H, ArH) and 7.66 (1 H, d, J = 8.1, 4/7-H); \delta_{C} 114.61(benzimidazole 4/7-C), 119.36 (benzimidazole 4/7-C), 122.27 (benzimidazole 5/6-C), 122.55 (benzimidazole 5/6-C), 127.83 (3 x ArCH), 127.93 (6 x ArCH), 130.22 (6 x ArCH), 136.75 (ArC), 141.76 (3 x ArC), 142.07 (ArC) and 142.97 (benzimidazole 2-C); m/z FAB 395 (M+, 12 %), 243 (*CPh_{3}, 100), 165 (20) and 136 (17).

2-Chloro-1-methyl-1H-benzo[d]imidazole 195

2-Chlorobenzimidazole 163 (2.0 g, 13.1 mmol) was added slowly to NaH (0.47 g, 19.7 mmol) in dry THF (150 mL). The mixture was stirred and heated under reflux for 1 h and methyl iodide (0.82
mL, 13.1 mmol) in THF (10.0 mL) was added dropwise to the reaction mixture. 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 white solid. The solid was purified by column chromatography using neutral alumina as absorbent with light petroleum and EtOAc as eluent to afford 2-chloro-1-methyl-1H-benzimidazole 195 as white crystals (1.40 g, 8.4 mmol, 64 %), mp 114-117 °C (lit.5 mp 114-116 °C); (Found: M⁺, 166.0297. C₈H₇ClN₂ requires 166.0298); (Found: C, 58.04; H, 4.41; N, 16.22. C₈H₇ClN₂ requires C, 57.67; H, 4.23; N, 16.81 %); νmax (KBr)/cm⁻¹: 3054, 2928, 1616, 1474, 1428, 1368, 1349, 1330, 1115, 1006 and 735; δH 3.78 (3 H, s, CH₃), 7.26-7.31 (3 H, m, ArH) and 7.68-7.70 (1 H, d, J = 8.4, ArH); δc 30.50 (CH₃), 109.23 (benzimidazole 4/7-C), 119.43 (benzimidazole 4/7-C), 122.70 (benzimidazole 5/6-C), 123.13 (benzimidazole 5/6-C), 135.67 (3a/7a-C), 140.97 (3a/7a-C), 141.70 (2-C); m/z El 166 (M⁺, 100 %), 129 (15), 90 (14) and 77 (19).

1-Methyl-1H-benzimidazol-2-yl phenyl sulfide 196

Benzenesulfanyll (0.31 mL, 3.0 mmol) was dissolved in EtOH (30 mL) containing KOH (0.17 g, 3.0 mmol) and the mixture was left stirring for 5 min. 2-Chloro-1-methyl-1H-benzimidazole 195 (0.50 g, 3.0 mmol) was added to the reaction mixture and the reaction mixture was heated under reflux for 18 h. The reaction mixture was filtered and evaporated to dryness to give 1-methyl-1H-benzimidazol-2-yl phenyl sulfide 196 as white crystals (0.62 g, 2.6 mmol, 85 %), mp 66-69 °C; (Found: M⁺, 240.0726. C₁₄H₁₂N₂S requires 240.0721); νmax (KBr)/cm⁻¹: 2373, 1577, 1441, 1409, 1324, 1276, 1078 and 739; δH 3.69 (3 H, m, CH₃), 7.20-7.29 (6 H, m, ArH), 7.34 (2 H, dd, J = 8.2 and 1.1, ArH) and 7.75-7.77 (1 H, m, ArH); δc 30.72 (CH₃), 109.45 (benzimidazole 4/7-C), 119.83 (benzimidazole 4/7-C), 122.38 (benzimidazole 5/6-C), 123.23 (benzimidazole 5/6-C), 127.62 (ArCH), 129.43 (2 x ArCH), 130.17 (2 x ArCH), 132.15 (benzimidazole 3a/7a-C), 136.47 (benzimidazole 3a/7a-C), 143.12 (ArC) and 147.58 (benzimidazole 2-C); m/z El 239 (M⁺, 100 %), 224 (11), 207 (14), 91 (14) and 77 (15).
1H-Benzo[d]imidazol-2-yl phenyl sulfide 152

\[
\begin{align*}
\text{PhSH (0.61 mL, 6.8 mmol) was dissolved in EtOH (18 mL) followed by KOH (0.35 g, 6.2 mmol) and the mixture was stirred for 5 min. 2-Chlorobenzimidazole 163 (1.0 g, 6.6 mmol) was added to the reaction mixture which was heated at reflux for 6 h. The reaction mixture was filtered and evaporated to give the crude product as a pale yellow crystalline powder. The crude product was purified by column chromatography using alumina as absorbent with light petroleum and ethyl acetate (4:1) as eluents to afford 1H-benzo[d]imidazol-2-yl phenyl sulfide 152 as white crystals (0.98 g, 4.3 mmol, 66%), mp 202-205 °C (lit.1, mp 201.5-202.5 °C); (Found: M+, 226.0559. } \\
C_{13}H_{10}N_2S \text{ requires 226.0565); } \\
\nu_{\text{max}} \text{(KBr)/cm}^{-1} 1617, 1510, 1412, 1348, 1265, 1233, 977, 739 \text{ and 686; } \\
\delta_{\text{H(DMSO)}} 7.15-7.51 (9 \text{ H, m, ArH}); \\
\text{m/z El 226 (M+ 60%), 225 (100), 192 (10), 167 (5), 77 (8).}
\end{align*}
\]

4-(1H-Benzo[d]imidazol-2-ylsulfanyl)benzene-1-carboxylic acid 190

\[
\begin{align*}
\text{4-Mercaptobenzoic acid 189 (1.05 mL, 6.8 mmol) was dissolved in EtOH (30 mL) followed by KOH (0.35 g, 6.2 mmol) and the mixture was stirred for 5 min. 2-Chlorobenzimidazole 163 (1.00 g, 6.6 mmol) was added to the reaction mixture and the reaction mixture was heated under reflux overnight. The reaction mixture was filtered and evaporated to dryness to give the crude product as a pale yellow crystalline powder which was recrystallised from methanol to give 4-(1H-benzo[d]imidazol-2-ylsulfanyl)benzene-1-carboxylic acid 190 as off-white crystals (1.20 g, 4.4 mmol, 68%), mp 270-275 °C; (Found: MH+, 271.0541. } \\
C_{14}H_{10}N_2O_2S \text{ requires 271.0544); } \\
\nu_{\text{max}} \text{(DCM slurry)/cm}^{-1} 3500, 3054, 2987, 1690, 1593, 1567, 1506, 1423 \text{ and 1265; } \\
\delta_{\text{H(DMSO)}} 7.23-7.26 (2 \text{ H, m, benzimidazole 5-H and 6-H}), 7.50-7.53 (2 \text{ H, d, } J = 8.2, 3\text{-H and 5-H}), 7.50-7.70 (2 \text{ H, m, benzimidazole, 4-H, 7-H}) \text{ and } 7.93-7.96 (2 \text{ H, d, } J = 8.3, 2\text{-H and 6-H}); \\
\delta_{\text{C(DMSO)}} 122.0
\end{align*}
\]

128
4-((1-[3-Phenylselanyl)propyl]-1H-benzo[d]imidazol-2-yl)sulfanyl)benzene-1-carboxylic acid

4-Mercaptobenzoic acid 189 (0.34 g, 2.2 mmol) was dissolved in EtOH (25 mL) followed by KOH (0.11 g, 2.03 mmol) and the mixture was stirred for 5 min. 2-Chloro-1-[(3-phenylselanyl)propyl]-1H-benzo[d]imidazole 164 (0.74 g, 2.1 mmol) was added to the reaction mixture and the reaction mixture was heated under reflux 18 h. The reaction mixture was filtered and evaporated to dryness to give the crude product as a pale yellow crystalline powder. The solid was recrystallised from methanol to give 4-((1-[3-phenylselanyl)propyl]-1H-benzo[d]imidazol-2-yl)sulfanyl)benzene-1-carboxylic acid 197 as off-white crystals (0.60 g, 1.3 mmol, 61 %), mp 158.5-159.9 °C; (Found: M⁺, 468.0416. C₂₃H₂₀N₂O₂Se requires 468.0411); (Found: C, 58.79; H, 4.28; N, 6.00.

C₂₃H₂₀N₂O₂Se requires C, 59.10; H, 4.31; N, 5.99 %); νmax (KBr)/cm⁻¹ 3200, 3000, 2472, 2346, 1924, 1701, 1654, 1594, 1560, 1476, 1465, 1420, 1382, 1270, 1251, 1169, 1016, 860, 764 and 747; δH 2.19-2.25 (2 H, m, CH₂), 2.94 (2 H, t, J = 6.8, PhSeCH₂), 4.37 (2 H, t, J = 7.1, NCH₂), 7.24-7.33 (6 H, m, ArH), 7.48-7.52 (2 H, m, ArH), 7.55 (2 H, dd, J = 7.2, 1.2, 3-H and 5-H), 7.72-7.76 (1H, m, ArH) and 7.90 (2 H, dd, J = 7.2, 1.2, 2-H and 6-H); δC 24.38 (CH₂), 29.71 (PhSeCH₂), 44.12 (NCH₂), 109.27 (benzimidazole 4/-7-C), 118.65 (benzimidazole 4/-7-C), 122.94 (benzimidazole 5/-6-C), 123.23 (benzimidazole 5/-6-C), 127.44 (ArCH), 129.15 (ArC), 129.31 (2 x ArCH), 131.13 (2 x ArCH), 131.97 (ArC), 133.13 (2 x ArCH), 133.38 (2 x ArCH), 133.46 (ArC), 135.39 (ArC), 142.22 (ArC), 149.63 (ArC) and 167.81 (C=O); m/z FAB 468 (M⁺, 8 %), 329 (11), 307 (45), 289 (35), 176 (48), 154 (100) and 107 (85).
4-\((1\text{-}[4\text{-phenylselanyl})\text{butyl}]\text{-}1H\text{-benzo}\text{[d]imidazol-2-yl}\text{sulfanyl})\text{benzene-1-carboxylic acid}\)

\[
\text{C}_{24}\text{H}_{22}\text{N}_{2}\text{O}_{2}\text{Se}
\]

4-Mercaptobenzoic acid 189 (0.33 g, 2.1 mmol) was dissolved in EtOH (30 mL) followed by KOH (0.37 g, 3.3 mmol) and the mixture was stirred for 5 min. 2-Chloro-1-\((1\text{-}[4\text{-phenylselanyl})\text{butyl}]\text{-}1H\text{-benzo}\text{[d]imidazole}\) 165 (0.79 g, 2.2 mmol) was added to the reaction mixture and the reaction mixture was heated under reflux overnight. The reaction mixture was filtered and evaporated to dryness to give the crude product as a pale yellow crystalline powder which was recrystallised from methanol to give 4-\((1\text{-}[4\text{-phenylselanyl})\text{butyl}]\text{-}1H\text{-benzo}\text{[d]imidazol-2-yl}\text{sulfanyl})\text{benzene-1-carboxylic acid}\) 198 as off-white crystals (1.00 g, 2.1 mmol, 98 %), mp 104-108 °C; (Found: M⁺, 482.0578. C_{24}H_{22}N_{2}O_{2}Se requires 482.0568); \(\nu_{\text{max}}\) (KBr)/cm\(^{-1}\) 3448, 3055, 2930, 2479, 2374, 1896, 1701, 1461, 1385, 1263, 1170, 1015, 747 and 693; \(\delta_{\text{H}}\) (DMSO) 1.53-1.61 (2 H, m, CH₂), 1.75-1.83 (2 H, m, CH₂), 2.88 (H, t, \(J = 7.2\), PhSeCH₂), 4.29 (2 H, t, \(J = 7.0\), NCH₂), 7.22-7.36 (8 H, m, ArH), 7.39 (2 H, d, \(J = 8.4\), 3-H and 5-H), 7.61-7.68 (1 H, m, ArH) and 7.90 (2 H, d, \(J = 8.4\), 2-H and 6-H); \(\delta_{\text{C}}\) (DMSO) 26.51 (CH₂), 26.91 (CH₂), 29.56 (PhSeCH₂), 44.03 (NCH₂), 111.19 (benzimidazole 4/7-C), 119.50 (benzimidazole 4/7-C), 122.62 (benzimidazole 5/6-C), 123.57 (benzimidazole 5/6-C), 126.93 (ArCH), 129.29 (2 x ArCH), 129.51 (2 x ArCH), 130.08 (ArC), 130.59 (2 x ArCH), 131.93 (ArCH), 131.98 (ArCH), 135.98 (ArC), 137.34 (ArC), 143.17 (ArC), 145.78 (ArC) and 167.35 (C=O); \(m/z\) FAB 482 (M⁺, 10 %), 393 (10), 322 (22), 281 (12), 213 (24), 192 (20), 154 (75) and 136 (100).

4-\((1\text{-}[5\text{-phenylselanyl})\text{pentyl}]\text{-}1H\text{-benzo}\text{[d]imidazol-2-yl}\text{sulfanyl})\text{benzene-1-carboxylic acid}\)

\[
\text{C}_{28}\text{H}_{28}\text{N}_{2}\text{O}_{2}\text{Se}
\]
4-Mercaptobenzoic acid 189 (1.27 g, 8.2 mmol) was dissolved in EtOH (40 mL) followed by potassium tert-butoxide (1.39 g, 12.4 mmol) and the mixture was stirred for 5 min. 2-Chloro-1-[5-(phenylselanyl)pentyl]-1H-benzo[d]imidazole 166 (3.12 g, 8.3 mmol) was added to the reaction mixture and the reaction mixture was heated under reflux overnight. The reaction mixture was filtered and evaporated to dryness to give 4-([1-[5-phenylselanyl)pentyl]-1H-benzo[d]imidazole-2-yl)sulfanyl]benzene-1-carboxylic acid 199 as off-white sticky gum (4.00 g, 8.1 mmol, 98 %); (Found: M+, 496.0716. C_{25}H_{24}N_{2}O_{2}SSe requires 496.0724); \nu_{\text{max}} (KBr)/cm^{-1} 3379, 3047, 2922, 1693, 1590, 1546, 1383, 1012, 839 and 739; \delta_{\text{H}}(\text{DMSO}) 1.29-1.37 (2 H, m, CH$_2$), 1.55-1.70 (4 H, m, CH$_2$CH$_2$), 2.86 (2 H, t, J = 7.2, PhSeCH$_2$), 4.24 (2 H, t, J = 7.2, NCH$_2$), 7.21-7.28 (5 H, m, ArH), 7.32 (2 H, d, J = 8.4, 3-H and 5-H), 7.41 (2 H, d, J = 8.0, ArH), 7.57 (1 H, d, J = 7.9, benzimidazole 7-H), 7.63 (1 H, d, J = 7.4, benzimidazole 4-H) and 7.84 (2 H, d, J = 8.4, 2-H and 6-H); \delta_{\text{C}}(\text{DMSO}) 26.49 (CH$_2$), 26.75 (CH$_2$), 28.99 (PhSeCH$_2$), 29.45 (CH$_2$), 44.33 (NCH$_2$), 111.04 (benzimidazole 4/7-C), 119.35 (benzimidazole 4/7-C), 122.45 (benzimidazole 5/6-C), 123.33 (benzimidazole 5/6-C), 126.80 (ArCH), 129.45 (2 x ArCH), 129.55 (2 x ArCH), 130.00 (ArC), 130.46 (2 x ArCH), 131.75 (2 x ArCH), 135.99 (3a-C and 7a-C), 143.16 (ArC), 145.00 (ArC) and 167.54 (C=O); m/z El 496 (M+, 19 %), 388 (42), 322 (62), 203 (100), 131 (58), 91 (39) and 69 (68).

4-(Tritylsulfanyl)-benzoic acid 201

4-Mercaptobenzoic acid 189 (2.00 g, 13.0 mmol) and triphenylmethanol (3.37 g, 13.0 mmol) were dissolved by gentle shaking in TFA (20 mL). The reaction mixture was heated under reflux for 2 h. Then the mixture was evaporated to dryness to afford pure 4-(tritylsulfanyl)-benzoic acid 201 as light brown crystals (2.57 g, 6.5 mmol, 100 %); (Found: M', 396.1179. C$_{26}$H$_{20}$O$_{2}$S requires 396.1184); \nu_{\text{max}} (KBr)/cm^{-1} 3017, 2546, 1685, 1654, 1592, 1489, 1443, 1426, 1292, 1130, 935, 853, 810, 763 and 698; \delta_{\text{H}}(\text{DMSO}) 6.99 (2 H, d, J = 8.1, 3-H and 5-H), 7.29-7.34 (15 H, m, ArH) and 7.58 (2 H, d, J = 8.1, 2-H and 6-H); \delta_{\text{C}}(\text{DMSO}) 127.13 (3 x ArCH), 128.05 (6 x ArCH), 128.92 (2 x ArCH), 129.44 (6 x ArCH), 131.33 (2 x ArCH), 143.53 (ArC) and 167.04 (C=O); m/z El 396 (M', 4 %), 243 (100), 228 (12), 165 (95), 154 (22), 142 (27), 91 (18) and 44 (30).
**N-(4-Methylbenzyl)-4-(tritylsulfanyl)benzamide 202**

![Chemical Structure](image)

4-(Tritylsulfanyl)-benzoic acid 201 (1.00 g, 2.5 mmol) was dissolved in DCM (50 mL) and cooled to –15 °C followed by addition of HOAT (0.34 g, 2.5 mmol), EDCI (0.48, 2.5 mmol) and then 4-methylbenzylamine (0.32 mL, 2.5 mmol). The reaction mixture was stirred for 4 h at the same temperature and then left stirring for 2 h at rt. Ice cooled 1 M HCl (30 mL) was added and the aqueous layer was extracted with DCM (3 X 30 mL). The combined organic layers were extracted with saturated sodium bicarbonate (30 mL). The aqueous layer was washed again with DCM (3 X 30 mL) and the combined organics were dried and the solution was evaporated to dryness to afford N-[(4-methylbenzyl)-4-(tritylsulfanyl)benzamide 202 as off white crystals (1.08 g, 2.2 mmol, 86 %), mp 174-177 °C; (Found: M+, 500.2054. C_{34}H_{29}NOS requires 500.2048); ν_{max} (KBr)/cm^{-1} 3299, 3054, 3023, 2921, 1718, 1652, 1635, 1593, 1539, 1443, 1317, 1298, 1181, 1154, 1034, 1015, 741 and 699; δ_{H} 2.34 (3 H, m, CH\textsubscript{3}), 4.53 (2 H, d, J = 5.5, CH\textsubscript{2}), 6.21 (1 H, s, NH), 6.92 (2 H, d, J = 8.3, ArH), 7.17-7.28 (15 H, m, ArH) and 7.36-7.39 (6 H, m, ArH); δ_{C} 21.10 (CH\textsubscript{3}), 43.91 (CH\textsubscript{2}), 70.88 (C\textsubscript{q}), 126.51 (2 x ArCH), 126.99 (3 x ArCH), 128.09 (2 x ArCH), 128.29 (6 x ArCH), 129.44 (2 x ArCH), 129.95 (6 x ArCH), 132.20 (2 x ArCH), 134.98 (ArC), 137.40 (ArC), 140.17 (ArC), 144.03 (3 x ArC), 146.88 (ArC) and 166.67 (C=O); m/z FAB 500 (M\textsuperscript{+}, 12 %), 243 (*CPh\textsubscript{3}, 100), 165 (17), 136 (9) and 105 (13).

**4-(Acetylsulfanyl)benzene-1-carboxylic acid 203**

![Chemical Structure](image)

4-Mercaptobenzoic acid 189 (2.0 g, 13.0 mmol) was treated with acetic anhydride (2.0 mL, 21.4 mmol) in pyridine (2.3 mL) overnight. The reaction mixture was evaporated to dryness and then the
residue was dissolved in EtOAc, washed with 2 M HCl (30 mL) and then with brine (30 mL). The organic layer was dried (MgSO₄), and the solution was evaporated to dryness to give 4-(acetylthiophenyl)benzene-1-carboxylic acid 203 as white crystals (2.54 g, 13.0 mmol, 100%), mp 194-200 °C (lit. mp 200.2-203.5 °C); (Found: M⁺, 196.0197. C₉H₈O₃S requires 196.0194); \( \nu_{\text{max}} \) (KBr/cm⁻¹) 3200, 2844, 2669, 2551, 1703, 1690, 1674, 1593, 1565, 1426, 1398, 1317, 1292, 1180, 1120, 936, 858 and 764; \( \delta_{\text{H}} \) 2.46 (3 H, s, CH₃), 7.54 (2 H, d, \( J = 8.4 \), 3-H and 5-H) and 8.14 (2 H, d, \( J = 8.4 \), 2-H and 6-H); \( \delta_{\text{C}} \) 30.49 (CH₃), 129.86 (ArC), 130.72 (2 x ArCH), 134.05 (2 x ArCH), 134.72 (ArC), 170.78 (C=O) and 192.51 (C=O); \( m/z \) Ei 196 (M⁺, 7 %), 154 (56), 136 (71), 109 (16) and 43 (100).

4-Mercapto-1-(4-methylbenzyl)benzamide 200

\[
\begin{array}{c}
\text{H}_2\text{S} \quad \text{O} \\
\text{N} \quad \text{CH}_3 \\
\end{array}
\]

N-(4-Methylbenzyl)-4-(tritylsulfanyl)benzamide 202 (0.23 g, 0.5 mmol) was dissolved in DCM/TFA/Et₃SiH (4.5/5/0.5 mL) and the reaction mixture was stirred for 2 h at rt. The reaction mixture was evaporated to dryness to give crude product. The residue was dissolved in 1 M sodium hydroxide (20 mL) and washed with light petroleum (3 x 20 mL). Then the aqueous layer was acidified with 1 M hydrochloric acid and extracted with ethyl acetate (3 x 30 mL). The combined organics were dried and the solution was evaporated to dryness to afford 4-mercapto-1-(4-methylbenzyl)benzamide 200 as light brown crystals (22 mg, 0.09 mmol, 17%), mp 163-165 °C; (Found: M⁺, 258.0946. C₁₅H₁₅NOS requires 258.0953); \( \nu_{\text{max}} \) (KBr/cm⁻¹) 3321, 1652, 1637, 1594, 1539, 1487, 1319, 1301, 1099, 842 and 789; \( \delta_{\text{H}} \) 2.35 (3 H, m, CH₃), 3.57 (1 H, s, SH), 4.59 (2 H, s, CH₂), 6.35 (1 H, s, NH), 7.18-7.29 (6 H, m, ArH) and 764 (2 H, d, \( J = 7.4 \), ArH); \( \delta_{\text{C}} \) 21.11 (CH₃), 43.94 (CH₂), 127.61 (2 x ArCH), 127.97 (2 x ArCH), 128.56 (2 x ArCH), 129.47 (2 x ArCH), 131.38 (ArC), 134.95 (ArC), 135.05 (ArC), 136.21 (ArC) and 166.58 (C=O); \( m/z \) FAB 258 (M⁺, 100 %), 176 (20), 154 (82), 136 (70), 120 (13) and 105 (80).
To a portion of Wang resin (1.0 g, 1.7 mmol) was added DCM (20 mL). The resin was left to swell for 1 h under N₂. 4-((1-[3-Phenylselanyl)propyl]-1H-benzo[d]imidazol-2-yl)sulfanyl)benzene-1-carboxylic acid 197 (0.55 g, 1.2 mmol), DMAP (0.36 g, 2.9 mmol) and DIC (1.0 mL, 5.8 mmol) were added sequentially. The suspension was shaken for 48 h at rt. The reaction mixture was filtered and washed with DCM, MeOH, DMF, MeOH and DCM (20 mL each). The resin was dried at 40 °C under vacuum for 24 h. The coupling reaction was repeated.

The (MAS) magic angle ¹H NMR (see appendix) spectrum showed complete immobilisation of the compound onto the Wang resin.

IR ν max (KBr)/cm⁻¹ 3025, 2920, 1713, 1591, 1511, 1447, 1265, 1173, 1097, 1010, 822, 738 and 693.

To a portion of Wang resin (1.0 g, 1.7 mmol) was added DCM (20 mL). The resin was left to swell for 1 h under N₂. 4-((1-[4-Phenylselanyl)butyl]-1H-benzo[d]imidazol-2-yl)sulfanyl)-benzene-1-carboxylic acid 198 (1.21 g, 2.5 mmol), DMAP (0.62 g, 5.1 mmol) and DIC (1.1 mL, 6.8 mmol) were added sequentially. The suspension was shaken for 48 h at rt. The reaction mixture was filtered and washed with DCM, MeOH, DMF, MeOH and DCM (20 mL each). The resin was dried at 40 °C under vacuum for 24 h. The coupling reaction was repeated with equimolar reagents.

The (MAS) magic angle ¹H NMR spectrum (see appendix) showed complete immobilisation of the compound onto the Wang resin.
IR \( \nu_{\text{max}} \) (KBr)/cm\(^{-1}\): 3026, 2921, 2363, 1713, 1591, 1512, 1447, 1356, 1265, 1173, 1097, 1011, 822, 739 and 694.

**Wang resin-bound benzoimidazole derivative 207**

![Chemical Structure](image)

To a portion of Wang resin (2.00 g, 3.4 mmol) was added DCM (20 mL). The resin was left to swell for 1 h under N\(_2\). 4-({1-[5-(Phenylselanyl)pentyl]-1H-benzo[d]imidazole-2-yl}sulfanyl)-benzene-1-carboxylic acid 199 (2.00 g, 4.0 mmol), DMAP (2.45 g, 20.1 mmol) and DIC (4.26 mL, 27.2 mmol) were added sequentially. The suspension was shaken for 48 h at rt. The reaction mixture was filtered and washed with DCM, MeOH, DMF, MeOH and DCM (20 mL each). The resin was dried at 40 °C under vacuum for 24 h. The coupling reaction was repeated under similar conditions.

The (MAS) magic angle \(^1\)H NMR spectrum (see appendix) showed complete immobilisation of the compound onto the Wang resin.

IR \( \nu_{\text{max}} \) (KBr)/cm\(^{-1}\): 3024, 2921, 2851, 1943, 1717, 1592, 1511, 1451, 1421, 1374, 1353, 1266, 1238, 1173, 1098, 1013, 824, 758, 738 and 697.

**Amino-Merrifield resin-bound benzimidazole derivative 208**

![Chemical Structure](image)

To a portion of amino-Merrifield resin (0.40 g, 0.48 mmol) was added DCM (15 mL). The resin was left to swell for 1 h under N\(_2\). 4-({1-[3-(Phenylselanyl)propyl]-1H-benzoimidazol-2-yl}sulfanyl)-benzene-1-carboxylic acid 197 (0.5 g, 1.1 mmol), DMAP (0.12 g, 1.0 mmol) and DIC (0.23 mL, 1.4 mmol) were added sequentially. The suspension was shaken for 72 h at rt. The
reaction mixture was filtered and washed with DCM, MeOH, DMF, MeOH and DCM (20 mL each). The resin was dried at 40 °C under vacuum for 24 h.

IR \nu_{\text{max}} (\text{KBr})/\text{cm}^{-1} 3424, 3024, 2923, 1655, 1594, 1511, 1478, 1422, 1245, 1014, 838, 736 and 691.

**Rink resin-bound benzoimidazole derivative 209**

![Diagram of Rink resin-bound benzoimidazole derivative 209]

To a portion of Rink resin (0.62 g, 0.5 mmol) was added DCM (15 mL). The resin was left to swell for 1 h under N₂. 4-({1-[4-Phenylselenyl]butyl}-1H-benzo[d]imidazol-2-yl)sulfanyl)-benzene-1-carboxylic acid 198 (0.3 g, 0.6 mmol), HOAT (0.25 g, 1.8 mmol) and DIC (0.5 mL, 3.15 mmol) were added sequentially. The suspension was shaken for 48 h at rt. The reaction mixture was filtered and washed with DCM, MeOH, DMF, MeOH and DCM (20 mL each). The resin was dried at 40 °C under vacuum for 24 h. The coupling reaction was repeated with equimolar reagents. The (MAS) magic angle ¹H NMR spectrum (see appendix) showed immobilisation of the compound onto the Rink resin.

IR \nu_{\text{max}} (\text{KBr})/\text{cm}^{-1} 3413, 2921, 1659, 1503, 1349, 1207,1026, 827, 742 and 695.

**Resin-bound 4-(tritylsulfanyl)-benzoic acid moiety 210**

![Diagram of Resin-bound 4-(tritylsulfanyl)-benzoic acid moiety 210]

To a portion of Amino-Merrifield resin (0.50 g, 0.6 mmol) was added DCM (15 mL). The resin was left to swell for 1 h under N₂. 4-(Tritylsulfanyl)-benzoic acid 201 (0.71 g, 1.8 mmol), HOAT (0.24 g, 1.8 mmol) and DIC (0.28 mL, 1.8 mmol) were added sequentially. The suspension was shaken for 48 h at rt. The reaction mixture was filtered and washed with DCM, MeOH, H₂O, MeOH and DCM (30 mL each). The resin was dried at 53 °C under vacuum for 12 h.
IR $\nu_{\text{max}}$(KBr)/cm$^{-1}$ 3421, 3056, 2917, 1719, 1654, 1595, 1509, 1490, 1448, 1151, 1015 and 753.

Radical cyclisations of resin-bound benzimidazole 205

\[ \text{Method A (thermal method, Bu}_3\text{SnH and toluene)} \]

A solution of tributyltin hydride (0.10 mL, 0.4 mmol) and AIBN (26 mg, 0.16 mmol) in toluene (2.0 mL) was added to refluxing suspension of resin-bound benzimidazole moiety 205 (170 mg, 0.16 mmol) in toluene (4.0 mL) over 26 min using a syringe pump. The reaction was stirred at reflux for 3 h and then a further portion of tributyltin hydride/AIBN (0.008 mL/5 mg) in toluene (1 mL) was added over 5 min and the reaction mixture was heated at reflux for a further 1.5 h. Then the reaction mixture was filtered and washed with toluene, DCM and MeOH (20 mL each). The resin was dried at 40 °C under vacuum for 24 h. The LC-MS analysis of the filtrate showed cyclised product 161 (3 mg, 0.018 mmol, 11 %). The remaining products were cleaved from the resin using TFA/DCM (9/1). The LC-MS analysis of the cleaved sample from the resin showed the reduced product 212 mainly.

Data for the cyclised product 161 was recorded; $\delta_H$ 2.70 (2 H, quintet, $J = 7.4$, 2-H), 3.05 (2 H, t, $J = 7.6$, 3-C), 4.1 (2 H, t, $J = 7.2$, 1-C), 7.25-7.40 (3 H, m, ArH) and 7.67-7.73 (1 H, m, ArH).

Spectral data for the reduced product 4-[(1-propyl-1H-benzo[d]imidazol-2-yl)sulfanyl]benzene-1-carboxylic acid 212 was recorded; (Found: M*, 313.1010. C$_{17}$H$_{16}$N$_2$O$_2$S requires 313.1011); $\nu_{\text{max}}$(KBr)/cm$^{-1}$ 3400, 3065, 2973, 2877, 2465, 2345, 1918, 1701, 1654, 1594, 1460, 1429, 1389, 1254, 1182, 1135 and 1015; $\delta_H$(DMSO) 0.82 (3 H, t, $J = 7.4$, CH$_3$), 1.66-1.75 (2 H, m, ArH), 4.26 (2 H, t, $J = 7.2$, NCH$_2$), 7.26-7.33 (2 H, m, ArH), 7.46 (2 H, d, $J = 6.6$, 3-H and 5-H), 7.65-7.68 (2 H, m, ArH) and 7.91 (2 H, d, $J = 6.6$, 2-H and 6-H); $\delta_C$(DMSO) 10.9 (CH$_3$), 22.6 (CH$_2$), 45.6 (NCH$_2$), 110.9 (benzimidazole 4′/7-C), 119.0 (benzimidazole 4′/7-C), 122.20 (benzimidazole 5′/6-C), 123.20 (benzimidazole 5′/6-C), 128.8 (2 × ArCH), 129.6 (1-C), 130.20 (2 × ArCH), 135.6 (7a-C), 138.10 (4a-C), 142.17 (3a-C), 145.1 (benzimidazole 2-C) and 166.6 (C=O); m/z FAB 313 (M*, 90 %), 176 (39), 154 (100) and 136 (85).
Method B (thermal method, Bu₃SnH and benzene)
A solution of tributyltin hydride (0.12 mL, 0.43 mmol) and AIBN (42 mg, 0.26 mmol) in benzene (7 mL) was added to refluxing suspension of resin-bound benzimidazole moiety 205 (100 mg, 0.097 mmol) in benzene (8 mL) over 7 h using a syringe pump. After that the reaction mixture was heated at reflux for a further 1 h. Then the reaction mixture was cooled to room temperature, filtered and washed with toluene, DCM and MeOH (20 mL each). The resin was dried at 40 °C under vacuum for 24 h. The LC-MS analysis of the filtrate only had tributyltin impurities and cyclised product 161 (3%). The yield was determined by ¹H NMR spectroscopy using the internal standard.

The remaining products were cleaved from the resin using TFA/DCM (9/1). The LC-MS analysis of the cleaved sample from the resin showed the reduced product 212 (4 mg, 0.01 mmol, 10 %) and the starting material 197 (18 mg, 0.04 mmol, 41 %).

Radical cyclisations of resin-bound benzimidazole moiety 206

Method A (thermal method, Bu₃SnH and benzene)
A solution of tributyltin hydride (0.06 mL, 0.23 mmol) and AIBN (16 mg, 0.095 mmol) in benzene (3.0 mL) was added to refluxing suspension of resin-bound benzimidazole moiety 206 (100 mg, 0.095 mmol) in benzene (3.0 mL) over 2 h using a syringe pump. After 3 h reflux, a further portion of tributyltin hydride/AIBN (0.008 mL/5 mg) in toluene (1.0 mL) was added over 5 min and the reaction mixture was heated at reflux for a further 1.5 h. Then the reaction mixture was cooled to room temperature, filtered and washed with toluene (3 x 10 mL). The filtrate only had tributyltin
impurities and cyclised product (which were removed using Flex HPLC system) to afford 1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine 162 as white crystals (9.3 mg, 0.054 mmol, 57%), mp 96-100 °C (lit.11 mp, 99.8-100.1 °C); (Found: M⁺, 172.1003. C₁₁H₁₂N₂ requires 172.1001); ν max (KBr)/cm⁻¹ 1610, 1505, 1425, 1397, 1328, 1278, and 745; δ₁H 1.98-2.09 (2 H, m, 3-H), 4.06 (2 H, t, J = 7.0, 1-H), 7.21-7.30 (3 H, m, ArH) and 7.66-7.69 (1 H, m, ArH); δ₁C 20.73 (3-C), 22.65 (2-C), 25.39 (4-C), 42.43 (1-C), 108.71 (6/9-C), 118.82 (6/9-C), 121.67 (7/8-C), 122.10 (7/8-C), 134.51 (7a-C), 142.65 (3a-C) and 151.71 (4a-C); m/z FAB 172 (M⁺, 100 %), 144 (28), 117 (10) and 77 (8).

The resin was dried at 40 °C under vacuum for 24 h. The remaining products were cleaved from the resin using TFA/DCM (9/1). The LC-MS analysis of the cleaved sample from the resin showed the reduced product 213 and the by-product (which were purified using Flex HPLC system).

Data for 4-[(1-butyl-1H-benzo[d]imidazol-2-yl)sulfanyl]benzene-1-carboxylic acid 213 was recorded; (Found: MH⁺, 327.1170. C₁₈H₁₆N₂O₂S requires 327.1167); ν max (KBr)/cm⁻¹ 3490, 2934, 2363, 1700, 1594, 1420, 1364, 1258, 1199, 1179, 1122 and 1017; δ₁H(DMSO) 0.78 (3 H, t, J = 7.4, CH₃), 1.16-1.25 (2 H, m, CH₂), 1.56-1.63 (2 H, m, CH₂), 4.27 (2 H, t, J = 7.3, NCH₂), 7.23-7.31 (2 H, m, ArH), 7.43 (2 H, d, J = 6.6, 3-H and 5-H), 7.62-7.65 (2 H, m, ArH) and 7.88 (2 H, d, J = 6.4, 2-H and 6-H); δ₁C(DMSO) 13.44 (CH₃), 19.33 (CH₂), 31.35 (CH₂), 44.04 (NCH₂), 110.92 (benzimidazole 4/7-C), 119.03 (benzimidazole 4/7-C), 122.37 (benzimidazole 5/6-C), 123.33 (benzimidazole 5/6-C), 128.94 (2 x ArCH), 129.68 (1-C), 130.27 (2 x ArCH), 135.58 (7a-C), 138.08 (4-C),142.51 (3a-C), 145.12 (2-C) and 166.63 (C=O); m/z FAB 327 (MH⁺, 100 %), 271 (12), 176 (12), 154 (33) and 136 (31).

Data for 4-[(1-but-3-enyl-1H-benzo[d]imidazol-2-yl)sulfanyl]benzene-1-carboxylic acid 214 was recorded; (Found: MH⁺, 325.1005. C₁₈H₁₆N₂O₂S requires 325.1011); ν max (KBr)/cm⁻¹ 3447, 2458, 2368, 1936, 1686, 1592, 1467, 1430, 1387, 1262, 1204, 1167, 1137, 1015 and 922; δ₁H(DMSO) 2.42-2.44 (2 H, m, CH₂), 4.38 (2 H, t, J = 7.04, NCH₂), 4.88-4.92 (2 H, m, CH₂), 5.70-5.82 (1 H, m, CH), 7.26-7.33 (2 H, m, ArH), 7.44 (2 H, d, J = 6.7, 3-H and 5-H), 7.67 (2 H, d, J = 6.9, ArH) and 7.91 (2 H, d, J = 6.7, 2-H and 6-H); δ₁C(DMSO) 33.55 (CH₂), 43.55 (NCH₂), 110.95 (benzimidazole 4/7-C), 117.71 (=CH₂), 119.10 (benzimidazole 4/7-C), 122.22 (benzimidazole 5/6-C), 123.20 (benzimidazole 5/6-C), 128.69 (2 x ArCH), 129.52 (1-C), 130.18 (2 x ArCH), 134.25 (-CH=), 135.47 (3a/7a-C), 138.31 (4-C), 142.70 (3a/7a-C), 145.03 (2-C) and 166.57 (C=O); m/z FAB 325 (MH⁺, 100 %), 271 (14), 176 (46), 154 (76) and 136 (80).
Method B (thermal method, Bu$_3$SnH and toluene)
A solution of tributyltin hydride (0.06 mL, 0.23 mmol) and AIBN (16 mg, 0.095 mmol) in toluene (3.0 mL) was added to refluxing suspension of resin-bound benzimidazole moiety 206 (100 mg, 0.095 mmol) in toluene (3.0 mL) over 2 h using a syringe pump. After 3 h reflux, a further portion of tributyltin hydride/AIBN (0.008 mL/5 mg) in toluene (1.0 mL) was added over 5 min and the reaction mixture was heated at reflux for a further 1.5 h. The reaction mixture was cooled to room temperature, filtered and washed with toluene (3 x 10 mL). The filtrate only had tributyltin impurities and cyclised product (which were removed using Flex HPLC system) to afford 1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine 162 as white crystals (8 mg, 0.047 mmol, 49 %).

The resin was dried at 40 °C under vacuum for 24 h. The LC-MS analysis of the cleaved sample from the resin showed the reduced product 213 mainly.

Method C (thermal method, TTMSS and benzene)
To refluxing suspension of resin-bound benzimidazole moiety 206 (55 mg, 0.052 mmol) in benzene (10 mL) was added TTMSS (65 µL, 0.21 mmol) followed by portion wise addition of AIBN (34 mg, 0.2 mmol). The reaction mixture was heated at reflux for 10 h. Then the reaction mixture was cooled to room temperature, filtered and washed with toluene, DCM and MeOH (20 mL each). The LC-MS analysis of the filtrate only had TTMSS impurities and cyclised product (which were removed using Flex HPLC system) to afford 1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine 162 as white crystals (1.8 mg, 0.01 mmol, 20 %).

The resin was dried at 40 °C under vacuum for 24 h. The LC-MS analysis of the cleaved sample from the resin showed the reduced product 213.

Method D (thermal method, Bu$_3$GeH and toluene)
To refluxing suspension of resin-bound benzimidazole 206 (100 mg, 0.095 mmol) in toluene (15mL) was added Bu$_3$GeH (0.11 mL, 0.43 mmol) followed by portion wise addition of AIBN (43 mg, 0.26 mmol). The reaction mixture was heated at reflux for 8 h. Then the reaction mixture was cooled to room temperature, filtered and washed with toluene, DCM and MeOH (20 mL each). The filtrate only had germanium based impurities and cyclised product (which were removed using acid extraction method) to afford 1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine 162 as white crystals (4 mg, 0.021 mmol, 22 %).
The resin was dried at 40 °C under vacuum for 24 h. The remaining products were cleaved from the resin using TFA/DCM (9/1). The LC-MS analysis of the cleaved sample from the resin showed the starting material 198.

**Method E (thermal method, using Rink resin 209, Bu₃SnH and benzene)**

A solution of tributyltin hydride (0.12 mL, 0.43 mmol) and AIBN (42 mg, 0.26 mmol) in toluene (7 mL) was added to refluxing suspension of resin-bound benzimidazole 209 (200 mg, 0.12 mmol) in benzene (7 mL) over 6 h using a syringe pump. After that the reaction mixture was heated at reflux for a further 1 h. Then the reaction mixture was cooled to room temperature, filtered and washed with toluene, DCM and MeOH (20 mL each). The resin was dried at 40 °C under vacuum for 24 h. The LC-MS analysis of the filtrate only had tin impurities and cyclised product (which were removed using Flex HPLC system) to afford 1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine 162 as white crystals (8.6 mg, 0.05 mmol, 44%).

The remaining products were cleaved from the resin using TFA/DCM (9/1). The LC-MS analysis of the cleaved sample from the resin showed the reduced product 213.

**Method F (Microwave irradiation, using Wang resin-bound benzimidazole 206)**

**General method:** A suspension of resin was prepared in various solvents in a microwave pyrex tube, followed by addition of the radical reagent and the initiator, the pyrex tube was then sealed and placed in an automated microwave.

(i) Time: 10 + 10 min (double addition of reagents); Temperature: 100 °C; Solvents: Propan-1-ol/benzene (1.25/1.25 mL); Reagents: Wang resin (22 mg, 0.021 mmol), Bu₃SnH (2 x 3.57 eq.) and AIBN (2 x 3.57 eq.). After 20 min the reaction vessel was removed from the microwave, cooled to room temperature and unsealed. The reaction mixture was filtered and washed with toluene, DCM and MeOH (20 mL each). The LC-MS analysis of the filtrate showed the presence of the cyclised product. The filtrate only had tin based impurities and 1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine 162 (52%). The yield was determined by ¹H NMR spectroscopy using the internal standard.

(ii) Time: 10 + 10 min (double addition of reagents); Temperature: 100 °C; Solvents: t-Butanol/benzene (1.25/1.25 mL); Reagents: Wang resin (25 mg, 0.024 mmol), Bu₃SnH (2 x 3.58
eq.) and AMBN (2 x 3.58 eq.). After 20 min the reaction vessel was removed from the microwave, cooled to room temperature and unsealed. The reaction mixture was filtered and washed with toluene, DCM and MeOH (20 mL each). The resin was dried at 40 °C under vacuum for 24 h. The LC-MS analysis of the filtrate showed the presence of the cyclised product. The filtrate only had tin based impurities and 1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine 162 (36 %). The yield was determined by 1H NMR spectroscopy using the internal standard.

(iii) Time: 10 min; Temperature: 135 °C; Solvents: Propan-1-ol/benzene (1.25/1.25 mL); Reagents: Wang resin (25 mg, 0.024 mmol), Bu3SnH (2 x 3.58 eq.) and AMBN (2 x 3.58 eq.). After 20 min the reaction vessel was removed from the microwave, cooled to room temperature and unsealed. The reaction mixture was filtered and washed with toluene, DCM and MeOH (20 mL each). The resin was dried at 40 °C under vacuum for 24 h. The LC-MS analysis of the filtrate showed the presence of the cyclised product. The filtrate only had tin based impurities and 1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine 162 (44 %). The yield was determined by 1H NMR spectroscopy using the internal standard.

Radical cyclisations of resin-bound benzimidazole moiety 207

A solution of tributyltin hydride (0.14 mL, 0.50 mmol) and AIBN (28 mg, 0.17 mmol) in tert-butylbenzene (2.0 mL) was added to a suspension of refluxing resin-bound benzimidazole adduct 207 (125 mg, 0.11 mmol) in tert-butylbenzene (3.0 mL) over 2.25 h using a syringe pump. Then the reaction mixture was heated at 130 °C for a further 9 h. The reaction mixture was filtered and washed with toluene, DCM and MeOH (20 mL each). The LC/MS analysis of the filtrate showed the 7,8,9,10-tetrahydro-6H-benzo[4,5]imidazo[1,2-a]azepine 215 (1 mg, 0.004 mmol, 4 %). The yield was determined by 1H NMR spectroscopy using the internal standard.

The 1H NMR data for the cyclised product 215 is as follows; δH 1.73-1.95 (6 H, m, 7-H, 8-H and 9-H), 3.07-3.11 (2 H, m, 6-H), 4.14-4.18 (2 H, m, 10-H), 7.18-7.28 (3 H, m, ArH) and 7.65-7.69 (1 H, m, ArH). The resin was dried at 40 °C under vacuum for 24 h. The remaining products were
cleaved from the resin using TFA/DCM (9/1). The LC-MS analysis of the cleaved sample from the resin showed the pure reduced product 216 (27 mg, 0.08 mmol, 72%).

Spectral data for 4-[(1-pentyl-1H-benzo[d]imidazol-2-yl)sulfanyl]benzene-1-carboxylic acid 216 was recorded; (Found: M⁺, 340.1242. C₁₉H₂₀N₂O₂S requires 340.1246); νmax (KBr)/cm⁻¹ 3056, 2928, 2477, 1910, 1689, 1596, 1463, 1385, 1272, 1115, 1007, 836 and 742; δH(DMSO) 0.76 (3 H, t, J = 6.9, CH₃), 1.15-1.24 (4 H, m, CH₂CH₂), 1.62-1.68 (2 H, m, CH₂), 4.28 (2 H, t, J = 7.3, NCH₂), 7.26 (1 H, t, J = 8.1, ArH), 7.31 (1 H, t, J = 7.9, ArH), 7.44 (2 H, d, J = 7.7, 3-H and 5-H), 7.64 (1 H, d, J = 8.0, benzimidazole 7-H), 7.67 (1 H, d, J = 7.9, benzimidazole 4-H) and 7.91 (2 H, d, J = 6.7, 2-H and 6-H); δc(DMSO) 13.56 (CH₃), 21.56 (CH₂), 28.09 (CH₂), 28.83 (CH₂), 44.14 (NCH₂), 110.81 (benzimidazole 4/7-C), 119.12 (benzimidazole 4/7-C), 122.19 (benzimidazole 5/6-C), 123.20 (benzimidazole 5/6-C), 128.70 (2 x ArCH), 130.0 (1-C), 130.18 (2 x ArCH), 135.56 (3a/7a-C), 138.23 (3a/7a-C), 142.72 (4-C), 144.93 (benzimidazole 2-C) and 166.55 (C=O); m/z El 339 (M⁺, 100 %), 307 (14), 297 (34), 269 (86), 225 (26), 187 (28), 150 (30), 131 (24) and 73 (28).

Methyl 1H-benzo[d]imidazole-5-carboxylate 222

Acetyl chloride (7.0 mL, 98.4 mmol) was added dropwise over 10 min to MeOH (100 mL) cooled in ice. The solution was stirred for 5 min and solid 5-benzimidazole carboxylic acid 221 (5.00 g, 30.8 mmol) was added in one portion and the solution slowly heated to reflux. Heating under reflux was continued overnight. The solution was cooled and evaporated to dryness to give the crude methyl ester. Distilled water (50 mL) was added to the crude methyl ester hydrochloride and the aqueous layer basified to pH 14 with sodium carbonate and 1 M sodium hydroxide (few drops). The basic solution was extracted with DCM (3 x 50 mL). The combined organic extracts were dried (MgSO₄) and evaporated to dryness to afford methyl 1H-benzo[d]imidazole-5-carboxylate 222 as light brown coloured crystals (5.00 g, 28.4 mmol, 92 %), mp 134-137 °C (lit.112 mp 134-136 °C); (Found: M⁺, 176.0585. C₉H₉N₂O₂ requires 176.0586); (Found: C, 60.86; H, 4.66; N, 15.57. requires C, 61.35; H, 4.58; N, 15.90 %); νmax (Nujol)/cm⁻¹ 2922, 1725, 1713, 1462, 1377, 1296 and 746; δH(DMSO) 3.89
A solution of PPh$_3$ (0.81 g, 3.1 mmol) and benzyl alcohol (0.48 g, 4.6 mmol) in THF (10 mL) was added dropwise to a solution of DEAD (0.49 mL, 3.1 mmol) and 5-benzimidazole carboxylic acid 221 (0.50 g, 3.1 mmol) in THF (10 mL) at room temperature. The mixture was stirred overnight at room temperature. The solution was evaporated to dryness, 2 M aqueous HCl (50 mL) was added and the acidic solution was washed with DCM (2 x 50 mL). The aqueous layer contained benzimidazole compounds and was basified to pH 14 with sodium carbonate and 1 M sodium hydroxide (few drops). The basic solution was extracted with DCM (3 x 50 mL). The combined organic extracts were dried (MgSO$_4$) and evaporated to dryness to afford phenylmethyl 1H-benzo[d]imidazole-5-carboxylate 223 as a pale yellow oil (60 mg, 0.24 mmol, 8 %); (Found: M$^+$, 252.0898. C$_{15}$H$_{12}$N$_2$O$_2$ requires 252.0899); $\nu$ max (DCM slurry)/cm$^{-1}$ 1711, 1624, 1297, 1227, 1084 and 749; $\delta$H 5.38 (2 H, s, OCH$_2$Ph), 7.25-7.44 (5 H, m, ArH), 7.65 (1 H, d, J = 8.0, benzimidazole 7-H), 8.03 (1 H, d, J = 8.0, benzimidazole 6-H), 8.23 (1 H, s, benzimidazole 4-H) and 8.46 (1 H, s, benzimidazole 2-H); $\delta$C 66.79 (OCH$_2$Ph), 115.03 (benzimidazole 7-C), 118.40 (benzimidazole 4-C), 124.52 (benzimidazole 6-C), 124.89 (ArC, 5-C), 128.04 (2 x ArCH), 128.24 (ArCH), 128.62 (2 x ArCH), 136.12 (ArC), 137.79 (ArC, 3a), 140.91 (ArC, 7a), 143.09 (ArCH, 2-C) and 167.03 (C=O); m/z El 252 (M$^+$, 40 %), 207 (12) and 145 (92).
Methyl 1-(triphenylmethyl)-1H-benzo[d]imidazole-5-carboxylate 224 and methyl 1-
(triphenylmethyl)-1H-benzo[d]imidazole-6-carboxylate 225

Methyl 1H-benzo[d]imidazole-5-carboxylate 222 (7.25 g, 41.2 mmol) was dissolved in DCM (600 mL). Triphenylmethyl chloride (13.43, 49.3 mmol) was added over 20 min and the mixture stirred until dissolution was complete. Triethylamine (9.32 mL, 66.9 mmol) was added slowly to the stirred solution and heated at reflux overnight. The solution was evaporated to dryness and purified by column chromatography using neutral alumina as absorbent and light petroleum/EtOAc (9:1) as eluents to yield a non-separable mixture of methyl 1-(triphenylmethyl)-1H-benzo[d]imidazole-5-
carboxylate 224 and methyl 1-(triphenylmethyl)-1H-benzo[d]imidazole-6-carboxylate 225 as cream coloured crystals (16.0 g, 38.3 mmol, 93 %), mp 154-160 °C; (Found: M⁺, 418.1682. C25H22N2O2 requires 418.1681); (Found: C, 76.87; H, 5.06; N, 6.38. requires C, 77.04; H, 5.08; N, 6.42 %); νmax (Nujol)/cm⁻¹ 2922, 2853, 1713, 1459, 1376, 752 and 701; δH 3.75 (3 Hs, s, OMe), 3.89 (3 Hs, s, OMe), 6.50 (1 Hs, dd, J = 8.7, 0.5, 7-H), 7.17 (16 Hs, m, ArH), 7.33 (15 Hs, m, ArH), 7.62 (1 Hs, dd, J = 8.7, 1.6, 6-H), 7.78 (1 Hs, dd, J = 8.6, 0.6, 4-H), 7.87 (1 Hs, dd, J = 8.6, 1.5, 5-H), 7.96 (1 Hs, s, 2-H), 8.03 (1 Hs, s, 2-H) and 8.50 (1 Hs, dd, J = 1.6, 0.6, 4-H); δC 51.91 (CH₃), 52.01 (CH₃), 75.78 (Cq), 75.84 (Cq), 115.05 (ArCH), 117.62 (ArCH), 119.96 (ArCH), 122.15 (ArCH), 123.45 (ArCH), 123.66 (ArCH), 124.38 (ArC), 124.44 (ArC), 128.27 (ArCH), 128.29 (ArCH), 129.91 (ArCH), 129.93 (ArCH), 134.51 (ArC), 138.05 (ArC), 140.99 (ArC, CPh₃), 141.03 (ArC, CPh₃), 144.36 (ArC), 145.69 (ArCH, 2-C), 146.61 (ArCH, 2-C), 148.04 (ArC), 167.16 (C=O) and 167.44 (C=O); m/z El 418 (M⁺, 15 %), 387 (M⁺, 12), 359 (6) and 243 (100).
Methyl 2-(phenylsulfanyl)-1H-benzo[d]imidazole 226

Methyl 1-(triphenylmethyl)-1H-benzo[d]imidazole-5-carboxylate 224 and methyl 1-(triphenylmethyl)-1H-benzo[d]imidazole-6-carboxylate 225 (4.0 g, 9.6 mmol) were dissolved in THF (150 mL) and the mixture was stirred at ambient temperature. The temperature of the stirred solution was lowered to -78 °C and a solution of n-butyllithium added dropwise (12.0 mL, 18.0 mmol). The solution turned brown and was stirred at 0 °C for a further 20 min. A solution of diphenyl disulfide (3.14 g, 14.4 mmol) in THF (50 mL) was added dropwise and the stirring was continued for a further 3 h. The solution was evaporated to give the crude sticky brown oil, hydrolysis performed using 99% TFA in DCM cleaved trityl group. Deionised water (50 mL) was added to the crude product which was extracted with light petroleum to remove by-products. The aqueous layer contained the protonated benzimidazole compounds and was basified to pH 14 with sodium carbonate and 1 M aqueous sodium hydroxide solution (few drops). The basic solution was extracted with DCM (3 x 40 mL). The combined organic extracts were dried (MgSO₄) and evaporated to dryness to yield a crude oil. The oil was purified by column chromatography using alumina as absorbent and light petroleum/ethyl acetate (9:1) as eluents to afford methyl 2-(phenylsulfanyl)-1H-benzo[d]imidazole 226 which still does not seem to be pure and it has been submitted for GC-MS analysis.

[1-(Triphenylmethyl)-1H-benzo[d]imidazol-5-yl]-methanol 228 and [1-(triphenylmethyl)-1H-benzo[d]imidazol-6-yl]-methanol 227

An isomeric mixture of methyl 1-(triphenylmethyl)-1H-benzo[d]imidazole-5-carboxylate 224 and methyl 1-(triphenylmethyl)-1H-benzo[d]imidazole-6-carboxylate 225 (6.0 g, 14.4 mmol) in THF (100 mL) was added dropwise to a suspension of LiAlH₄ (0.41 g, 10.8 mmol) in THF (150 mL) at 0
°C (ice bath). After stirring for 6 h at rt, the mixture was carefully hydrolysed by addition of H₂O (1 mL) and 20% NaOH (0.80 mL). The reaction mixture was dried (MgSO₄) and evaporated to give pure pale yellow powder containing two isomers [1-(triphenylmethyl)-1H-benzo[d]imidazol-5-yl]-methanol 228 and [1-(triphenylmethyl)-1H-benzo[d]imidazol-6-yl]-methanol 227 (3.8 g, 9.72 mmol, 68%), mp 100-105 °C; (Found: MH⁺, 391.1802. C₂₇H₂₂N₂O requires 391.1810); (Found: C, 82.55; H, 5.58; N, 7.06. requires C, 83.05; H, 5.68; N, 7.17 %); νₘₚ (Nujol)/cm⁻¹ 3384, 3054, 2924, 1445, 1265, 1114, 895 and 739; δₚ 4.45 (2 Hₚ, s, CH₂), 4.71 (2 Hₚ, s, CH₂), 6.45 (1 Hₚ, d, J = 8.3, 7-H), 6.93 (1 Hₚ, dd, J = 8.6, 1.6, 6-H), 7.15-7.34 (33 H, m, ArH), 7.72 (1 Hₚ, d, J = 7.4, 4-H), 7.74 (1 Hₚ, s, 2-H) and 7.88 (1 Hₚ, s, 2-H); δc 65.61 (2 x CH₂), 75.49 (2 x Cq), 113.87 (ArCH), 115.48 (ArCH), 118.88 (ArCH), 120.28 (ArCH), 121.70 (ArCH), 122.11 (ArCH), 128.06 (6 x ArCH), 128.17 (12 x ArCH), 129.98 (12 x ArCH), 134.35 (ArC), 134.90 (ArC), 135.07 (ArC), 135.52 (ArC), 141.26 (ArC), 144.25 (ArC), 144.58 (2 x 2-C) and 144.69 (ArC); m/z El 390 (M⁺, 1 %), 243 (100) and 165 (88).

1-(1,1-dimethylethyl)-1, 1-dimethylsilyl[[1-(triphenylmethyl)-1H-benzo[d]imidazol-5-yl]methyl] ether 230 and 1-(1,1-dimethylethyl)-1, 1-dimethylsilyl[[1-(triphenylmethyl)-1H-benzo[d]imidazol-6-yl]methyl] ether 229

[1-(Triphenylmethyl)-1H-benzo[d]imidazol-5-yl]-methanol 228 and 1-(triphenylmethyl)-1H-benzo[d]imidazol-6-yl]-methanol 227 (1.6 g, 4.1 mmol), tert-butyldimethylsilyl chloride (1.79 g, 11.9 mmol) and imidazole (0.22 g, 3.2 mmol) were dissolved in DMF (25 mL) and the solution was stirred overnight. Saturated sodium chloride (75 mL) was added and the solution extracted with DCM (2 x 75 mL). The combined organic extracts were combined and dried (MgSO₄). The crude product was purified by column chromatography using neutral alumina as absorbent with light petroleum/EtOAc (9:1) as eluents to yield 1-(1,1-dimethylethyl)-1,1-dimethylsilyl{[1-(triphenylmethyl)-1H-benzo[d]imidazol-5-yl]methyl} ether 230 and 1-(1,1-dimethylethyl)-1,1-dimethylsilyl{[1-(triphenylmethyl)-1H-benzo[d]imidazol-6-yl]methyl} ether 229 as a brown oil (1.00 g, 2.0 mmol, 50%); (Found: [MH⁺], 505.2674. C₃₃H₃₆N₂OSi requires 505.2675); νₘₚ
(neat)/cm⁻¹ 3058, 2955, 2856, 1735, 1695, 1598, 1493, 1446, 1265, 1087, 839; δH 0.12 (9 Hb, s, CH₃), 0.09 (6 Hb, s, CH₃), 0.78 (9 Hb, s, CH₃), 0.93 (6 Hb, s, CH₃), 4.54 (2 Hb, s, CH₂), 4.78 (2 Hb, s, CH₂), 6.42 (1 Hb, d, J = 8.6, 7-H), 6.53 (1 Hb, s, 4-H), 6.88 (1 Hb, d, J = 8.6, 6-H), 7.10 (1 Hb, d, J = 8.3, 5-H), 7.16-7.32 (30 H, m, ArH), 7.70 (1 Hb, d, J = 8.3, 4-H), 7.74 (1 Hb, d, J = 0.7, 7-H), 7.85 (1 Hb, s, 2-H) and 7.86 (1 Hb, s, 2-H); δC 5.32 (2 x CH₃), 5.22 (2 x CH₃), 25.94 (3 x CH₃), 26.01 (3 x CH₃), 65.05 (CH₂), 65.19 (CH₂), 113.08 (ArCH), 115.06 (ArCH), 117.67 (ArCH), 119.68 (ArCH), 120.83 (ArCH), 121.13 (ArCH), 127.12 (ArCH), 128.12 (ArCH), 129.94 (ArCH), 133.00 (ArC), 134.74 (ArC), 135.50 (ArC), 135.97 (ArC), 141.28, (ArC), 141.31 (ArC), 144.10 (2 x 2-C) and 147.09 (ArC); m/z El 505 (MH⁺, 1 %), 447 (5), 243 (100), 165 (65) and 131 (28).
1-Iodo-2-(iodomethyl)benzene 241

![Image of 1-Iodo-2-(iodomethyl)benzene 241]

1-Iodo-2-(chloromethyl)benzene 240 (10.0 g, 39.6 mmol) and sodium iodide (30.0 g, 200 mmol) were added to dry acetonitrile (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 afford 1-iodo-2-(iodomethyl)benzene 241 as a dark brown oil (13.48 g, 39.2 mmol, 99 %); (Found: M+, 343.8552. C_{7}H_{6}I_{2} requires 343.8559); \( \nu_{\text{max}} \) (neat)/cm\(^{-1}\) 2360, 2342, 1580, 1464, 1433, 1424, 1273, 1212, 1152, 1012, 827, 757 and 644; \( \delta_{\text{H}} \) 4.54 (2 H, s, CH\(_{2}\)), 6.92 (1 H, dd, \( J = 7.6 \) and 7.6, 5-H), 7.28 (1 H, dd, \( J = 7.6 \) and 7.6, 4-H), 7.47 (1 H, d, \( J = 8.0 \), 3-H), 7.80 (1 H, d, \( J = 8.0 \), 6-H); \( \delta_{\text{C}} \) 12.17 (CH\(_{2}\)), 99.74 (1-C), 129.32 (4-C), 129.51 (5-C), 129.76 (3-C), 140.23 (6-C) and 141.43 (2-C); \( m/z \) El 344 (MH\(^{+}\), 5 %), 254 (12), 217 (100) and 90 (47).

(2-Iodophenyl)methyl methanesulfonate 243

![Image of (2-Iodophenyl)methyl methanesulfonate 243]

To a flask containing 2-iodobenzyl alcohol 242 (10.0 g, 42.7 mmol) was added DCM (80 mL) and triethylamine (17.86 mL, 128.2 mmol). The solution was cooled to 0 °C in an ice bath and methanesulfonyl chloride (4.97 mL, 64.1 mmol) was added. The reaction mixture was stirred at rt for 18 h. The reaction mixture was extracted into water and DCM. The DCM layers were collected and dried (MgSO\(_{4}\)) and evaporated to afford (2-iodophenyl)methyl methanesulfonate 243 as a pale yellow oil (8.0 g, 25.6 mmol, 60 %); \( \nu_{\text{max}} \) (neat)/cm\(^{-1}\) 3031, 2932, 1575, 1443, 1367, 1173, 1014,
966, 815, 745 and 668; \( \delta_H \) 3.65 (3 H, s, CH\(_3\)), 4.67 (2 H, s, CH\(_2\)), 6.99 (1 H, ddd, \( J = 8.3, 8.3 \) and 1.6, 4-H), 7.34 (1 H, ddd, \( J = 7.6, 7.6 \) and 0.8, 5-H), 7.47 (1 H, dd, \( J = 7.6 \) and 1.6, 6-H) and 7.85 (1 H, d, \( J = 7.9, 3\)-H); \( \delta_C \) 51.66 (CH\(_3\)), 53.10 (CH\(_2\)), 100.19 (2-C), 129.37 (5-C), 130.73 (4-C), 130.85 (6-C), 140.26 (1-C) and 140.30 (3-C); m/z El 252 (100 %), 217 (100) and 90 (51).

2-(2-Bromophenyl)ethyl methanesulfonate 245

![Structure of 2-(2-Bromophenyl)ethyl methanesulfonate](image)

To a flask containing 2-bromophenylethyl alcohol 244 (0.5 mL, 3.7 mmol) was added toluene (30 mL) and triethylamine (1.54 mL, 11.1 mmol). The solution was cooled to 0 °C in an ice bath and methanesulfonyl chloride (0.43 mL, 5.6 mmol) was added. The reaction mixture was stirred at rt for 18 h. The reaction mixture was extracted into water and DCM. The DCM layers were collected and dried (MgSO\(_4\)) and evaporated to afford 2-(2-bromophenyl)ethyl methanesulfonate 245 as a pale yellow oil (1.0 g, 3.7 mmol, 99 %); (Found: M\(^+\), 277.9611. C\(_{11}\)H\(_{11}\)BrO\(_2\)S requires 277.9612); \( \nu_{\text{max}} \) (neat)/cm\(^{-1}\) 3057, 3024, 2939, 1594, 1568, 1473, 1442, 1353, 1173, 1038, 1022, 958, 905, 858, 805, 755 and 657; \( \delta_H \) 2.88 (3 H, s, CH\(_3\)), 3.21 (2 H, t, \( J = 6.8, \) CH\(_2\)), 4.45 (2 H, t, \( J = 6.8, \) OCH\(_2\)), 7.11-7.15 (1 H, m, ArH), 7.28-7.29 (2 H, m, ArH) and 7.55 (1 H, d, \( J = 8.1, 3\)-H); \( \delta_C \) 35.86 (CH\(_2\)Ph), 37.22 (CH\(_3\)), 68.51 (OCH\(_2\)), 124.41 (ArC), 127.72 (ArCH), 128.93 (ArCH), 131.53 (ArCH), 132.93 (ArCH) and 135.60 (ArC); m/z El 278 (M\(^+\), 3 %), 220 (26), 182 (68), 169 (100), 103 (38), 90 (40) and 77 (34).

1-Bromo-2-(2-chloroethyl)benzene 246

![Structure of 1-Bromo-2-(2-chloroethyl)benzene](image)
A mixture of 2-bromophenylethyl alcohol 244 (0.7 mL, 5.2 mmol) and concentrated hydrochloric acid (5 mL) was heated in a Reacti-Vial at 115 °C for 18 h. After cooling to rt the mixture was poured into water and extracted with diethyl ether. The organic layers were dried (MgSO₄) and evaporated to dryness to give 1-bromo-2-(2-chloroethyl)benzene 246 as a clear oil (0.75 g, 3.41 mmol, 66 %); (Found: M⁺, 217.9498. C₈H₆BrCl requires 217.9498); νmax (neat)/cm⁻¹ 3058, 2959, 1590, 1568, 1471, 1440, 1329, 1304, 1280, 1248, 1109, 1026, 944, 901, 754, 699 and 659; δH 3.15 (2H, t, J = 7.4, PhCH₂), 3.69 (2 H, t, J = 7.3, ClCH₂), 7.03-7.09 (1 H, m, ArH), 7.20-7.22 (2 H, m, ArH) and 7.50 (1 H, d, J = 8.1, 6-H); δC 39.23 (PhCH₂), 43.07 (CH₂Cl), 124.34 (ArC), 127.48 (ArCH), 128.59 (ArCH), 131.27 (ArCH), 132.86 (ArCH) and 137.16 (ArC); m/z El 218 (M⁺, 33 %), 169 (100), 103 (25), 90 (32), 77 (35) and 49 (49).

2-Chloro-1-[(2-iodophenyl)methyl]-1H-benzo[d]imidazole 247

2-Chlorobenzimidazole 163 (3.00 g, 19.7 mmol) was added to a vigorously stirred suspension of ground potassium hydroxide (3.30 g, 59.0 mmol) in dry DMF (80 mL) and stirred for 30 min. 1-Iodo-2-(iodomethyl)benzene 241 (13.53 g, 39.3 mmol) was added in one portion. The reaction was stirred for 24 h, partitioned between ethyl acetate and water and the organic layer was removed. The organic extract was washed with water followed by brine, dried (MgSO₄) and evaporated to dryness. The residue was purified by column chromatography using neutral alumina as absorbent and light petroleum/ethyl acetate (4:1) as eluents to afford 2-chloro-1-[(2-iodophenyl)methyl]-1H-benzo[d]imidazole 247 as cream coloured crystals (6.87 g, 18.7 mmol, 95 %), mp 106.2-109.3 °C; (Found: M⁺, 367.9573. C₁₄H₁₀ClN₂ requires 367.9577); νmax (KBr)/cm⁻¹ 3059, 2920, 1700, 1615, 1455, 1428, 1329, 1282, 1240, 1198, 1013, 986, 749 and 650; δH 5.38 (2 H, s, CH₂), 6.48 (1 H, d, J = 8.0, 6-H), 7.00 (1 H, dd, J = 8.0 and 8.0, 4-H), 7.08-7.34 (4 H, m, ArH), 7.75 (1 H, d, J = 8.0, ArH) and 7.91 (1 H, d, J = 8.0, 3-H); δC 52.93 (CH₂), 96.74 (Ar 2-C), 109.88 (benzimidazole 4/7-C), 119.66 (benzimidazole 4/7-C), 123.13 (benzimidazole 5/6-C), 123.62 (benzimidazole 5/6-C), 126.61 (ArCH), 128.88 (ArCH), 130.08 (ArCH), 135.04 (3a-C), 136.84 (7a-C), 139.74 (ArCH),
141.04 (benzimidazole 2-C) and 141.83 (Ar 1-C); m/z El 368 (M⁺, 62 %), 241 (35), 217 (100), 205 (13), 152 (19) and 90 (47).

4-((1-[(2-Iodophenyl)methyl]-1H-benzo[d]imidazol-2-yl)sulfanyl)benzene-1-carboxylic acid 248

4-Mercaptobenzoic acid 189 (1.54 g, 10.0 mmol) was dissolved in EtOH (60 mL) followed by potassium tert-butoxide (1.70 g, 15.2 mmol) and the mixture was stirred for 5 min. 2-Chloro-1-[(2-iodophenyl)methyl]-1H-benzo[d]imidazole 247 (3.74 g, 10.1 mmol) was added to the reaction mixture and heated under reflux overnight. The reaction mixture was filtered and evaporated to dryness to give the crude product. The residue was purified by column chromatography using silica gel as absorbent and light petroleum/ethyl acetate (1:1) as eluents to afford 4-((1-[(2-iodophenyl)methyl]-1H-benzo[d]imidazol-2-yl)sulfanyl)benzene-1-carboxylic acid 248 as a pale yellow crystalline powder (4.88 g, 10.0 mmol, 99 %), mp 98.2-103.5 °C; (Found: M⁺, 485.9915. C₂₇H₁₆IN₂O₂S requires 485.9905); νmax (KBr)/cm⁻¹ 3382, 3056, 2964, 1924, 1695, 1591, 1544, 1434, 1385, 1271, 1185, 838 and 734; δH 5.49 (2 H, s, CH₂), 6.31 (1 H, dd, J = 7.6, 1.2, 6-H), 7.02 (1 H, ddd, J = 7.6, 7.6, 1.6, 4-H), 7.19 (1 H, ddd, J = 7.6, 7.6, 0.8, 5-H), 7.25-7.28 (2 H, m, ArH), 7.34 (2 H, dd, J = 6.6, 1.8, 3-H and 5-H), 7.40-7.44 (1 H, m, ArH), 7.69-7.73 (1 H, m, ArH), 7.81 (2 H, dd, J = 6.6, 1.6, 2-H and 6-H), and 7.91 (1 H, dd, J = 7.8, 1.0, 3-H); δc 52.81 (CH₂), 97.96 (2-C), 111.07 (benzimidazole 4/7-C), 119.55 (benzimidazole 4/7-C), 122.85 (benzimidazole 5/6-C), 123.77 (benzimidazole 5/6-C), 126.83 (4-C), 129.03 (5-C), 129.89 (6-C), 129.95 (2 x ArCH), 130.39 (2 x ArCH), 133.03 (1-C), 136.28 (3a-C), 137.81 (4-C), 138.26 (7a-C), 139.73 (3-C), 143.21 (benzimidazole 2-C), 147.88 (1-C) and 167.92 (C=O); m/z El 486 (M⁺, 4 %), 465 (48), 431 (8), 378 (7), 262 (22), 217 (100), 178 (20), 154 (50), 90 (61) and 73 (58).
Methyl 4-{{1-[(2-iodophenyl)methyl]-1H-benzo[d]imidazol-2-yl}sulfanyl}benzene-1-carboxylate 249

Acetyl chloride (2.0 mL, 28.0 mmol) was added dropwise over 10 min to MeOH (25 mL) cooled in an ice bath. The solution was stirred for 5 min and 4-{{1-[(2-iodophenyl)methyl]-1H-benzo[d]imidazol-2-yl}sulfanyl}benzene-1-carboxylic acid 248 (0.62 g, 1.3 mmol) was added in one portion and the solution slowly heated to reflux. Heating under reflux was continued overnight. The solution was cooled and evaporated to dryness to give the crude methyl ester. Distilled water (10 mL) was added to the crude methyl ester hydrochloride and the aqueous layer was basified to pH 14 with sodium carbonate and 1 M aqueous sodium hydroxide solution (few drops). The basic solution was extracted with DCM (3 x 25 mL). The combined organic extracts were dried (MgSO4) and evaporated to dryness. The residue was purified by column chromatography using neutral alumina as absorbent and light petroleum/ethyl acetate (1:1) as eluents to afford methyl 4-{{1-[(2-iodophenyl)methyl]-1H-benzo[d]imidazol-2-yl}sulfanyl}benzene-1-carboxylate 249 as white crystals (0.5 g, 1.0 mmol, 78 %), mp 179.1-181.2 °C; (Found: MH+, 501.0131. C22H17IN2O2S requires 501.0134); νmax (KBr)/cm⁻¹ 2940, 1713, 1589, 1544, 1428, 1351, 1277, 1107, 1012, 841, 824, 748 and 689; δH 3.79 (3 H, s, CH₃), 5.33 (2 H, s, CH₂), 6.19 (1 H, d, J = 7.2, 6-H), 6.81 (1 H, dd, J = 7.6, 1.0, 4-H), 6.94 (1 H, dd, J = 7.6, 1.0, 5-H), 7.07 (1 H, d, J = 7.6, ArH), 7.17-7.27 (2 H, m, ArH), 7.30 (2 H, d, J = 8.8, 3-H and 5-H), 7.72-7.74 (2 H, m, ArH) and 7.76 (2 H, d, J = 8.4, 2-H and 6-H); δC 51.18 (CH₃), 52.30 (CH₂), 95.79 (C-2), 109.22 (benzimidazole 4/7-C), 119.29 (benzimidazole 4/7-C), 122.08 (benzimidazole 5/6-C), 123.14 (benzimidazole 5/6-C), 125.60 (4-C), 127.58 (5-C), 128.14 (1-C), 128.35 (6-C), 128.45 (2 x ArCH), 129.31 (2 x ArCH), 134.84 (4-C), 136.20 (3a-C), 136.98 (7a-C), 138.51 (3-C), 142.35 (benzimidazole 2-C), 145.55 (1-C) and 165.24 (C=O); m/z FAB 501 (MH⁺, 32 %), 327 (19), 281 (22), 217 (40), 147 (54) and 136 (100).
Method A (TTMSS, AIBN and toluene)

TTMSS (0.68 mL, 2.2 mmol) in toluene (20 mL) was added to methyl 4-[[1-(2-iodophenyl)methyl]-1H-benzo[d]imidazole-2-yl]sulfanyl]benzene-1-carboxylate 249 (0.55 g, 1.1 mmol) in toluene (480 mL) at reflux over 5 h using a syringe pump. AIBN (0.27 g, 1.7 mmol) was added to the refluxing reaction mixture at equal intervals. The crude mixture was evaporated to dryness and purified by column chromatography using neutral alumina as absorbent and light petroleum/ethyl acetate (9:1) as eluents to afford 11H-benzo[4,5]imidazo[1,2-a]isoindole 250 as a crystalline white solid (45 mg, 0.22 mmol, 20%), mp 144.0-149.0 °C; (Found: M⁺, 206.0841. C₁₄H₁₀N₂ requires 206.0844); νmax (KBr)/cm⁻¹ 2927, 2367, 1657, 1433, 1399, 1269 and 740; δH 5.27 (2 H, s, CH₂), 7.26-7.42 (7 H, m, ArH) and 7.70-7.72 (1 H, m, ArH); δc 46.18 (CH₂), 108.29 (benzimidazole 6/9-C), 118.90 (benzimidazole 6/9-C), 122.12 (benzimidazole 7/8-C), 122.62 (benzimidazole 7/8-C), 123.44 (11a-C), 127.09 (3-C), 127.47 (4-C), 127.81 (2-C), 128.38 (1-C), 129.07 (4a-C), 134.69 (5a and 9a) and 134.89 (4b-C); m/z El 206 (M⁺, 46 %), 149 (17), 119 (8), 91 (16) and 77 (18). We also isolated methyl 4-[[1-(phenylmethyl)-1H-benzo[d]imidazole-2-yl]sulfanyl]benzene-1-carboxylate 251 as a pale yellow oil (165 mg, 0.44 mmol, 40 %); (Found: M⁺, 375.1167. C₂₂H₁₈N₂O₂S requires 375.1167); νmax (KBr)/cm⁻¹ 2950, 1721, 1594, 1434, 1350, 1276, 1181, 1108, 1016, 824 and 760; δH 3.89 (3 H, s, CH₃), 5.45 (2 H, s, CH₂), 7.06-7.08 (2 H, m, ArH), 7.23-7.34 (8 H, m, ArH), 7.88 (1 H, d, J = 7.6, ArH) and 7.90 (2 H, d, J = 7.9, 2-H and 6-H); δc 48.34 (CH₃), 52.21 (CH₂), 110.42 (benzimidazole 4/7-C), 120.28 (benzimidazole 4/7-C), 122.90 (benzimidazole 5/6-C), 123.95 (benzimidazole 5/6-C), 126.72 (ArCH), 127.98 (ArCH), 128.74 (ArCH), 128.87 (ArCH), 130.39 (ArCH), 128.95 (ArC), 135.51 (ArC), 135.98 (ArC), 138.85 (ArC), 143.51 (ArC), 145.96 (2-C) and 166.40 (C=O); m/z FAB 375 (M⁺, 74 %), 322 (20), 243 (43), 167 (87), 154 (100) and 136 (74).
Method B (tributylgermanium hydride, AIBN and toluene)

Tributylgermanium hydride (0.09 mL, 0.36 mmol) was added to methyl 4-((1-[2-iodophenyl)methyl]-1H-benzo[d]imidazol-2-yl)sulfanyl)benzene-1-carboxylate 249 (0.13 g, 0.25 mmol) in toluene (40 mL) followed by portion wise addition of ACCN (excess) to the refluxing reaction mixture at equal intervals. The solution was stirred and heated under reflux for 9 h. The crude product was purified by column chromatography using neutral alumina as absorbent and light petroleum/ethyl acetate (9:1) as eluents to afford the reduced product methyl 4-[(1-(phenylmethyl)-1H-benzo[d]imidazole-2-yl)sulfanyl]benzene-1-carboxylate 251 as a pale yellow oil (68 mg, 0.18 mmol, 60%) exclusively. The TLC and ¹H-NMR and IR spectra were identical to those of an authentic sample.

Synthesis of resin-bound benzimidazole moiety 252

To a portion of Wang resin (1.0 g, 1.7 mmol) was added DCM (20 mL). The resin was left to swell for 1 h under N₂. 4-((1-[2-Iodophenyl)methyl]-1H-benzo[d]imidazol-2-yl)sulfanyl)benzene-1-carboxylic acid 248 (1.40 g, 3.9 mmol), DMAP (0.62 g, 5.1 mmol) and DIC (1.33 mL, 8.5 mmol) were added sequentially. The suspension was shaken for 48 h at rt. The reaction mixture was filtered and washed with DCM, MeOH, DMF, MeOH and DCM (20 mL each). The resin was dried at 40 °C under vacuum for 24 h. The coupling reaction was repeated under similar conditions. The loading on the resin was determined by cleaving a known amount of resin using [TFA/DCM (9/1)](0.60 mmol/g).

IR ν max (KBr)/cm⁻¹: 3424, 3058, 3024, 2919, 2365, 1944, 1717, 1596, 1510, 1492, 1445, 1371, 1266, 1239, 1173, 1099, 1011, 822, 743 and 696.
2-Chlorobenzimidazole 163 (0.35 g, 2.3 mmol) was added slowly to a suspension of NaH (0.12 g, 5.0 mmol) in dry THF (60 mL). The mixture was stirred and heated under reflux for 1 h and 2-(2-bromophenyl)ethyl methanesulfonate 245 (0.49 g, 1.8 mmol) in THF (10 mL) was added dropwise to the reaction mixture. 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. The solid was purified by column chromatography using silica gel as absorbent and light petroleum/ethyl acetate (9:1) as eluents to afford 1-[2-(2-bromophenyl)ethyl]-2-chloro-1H-benzo[d]imidazole 253 as cream coloured crystals (0.58 g, 1.7 mmol, 98 %), mp 73.5-75.4 °C; (Found: M⁺, 333.9871. C₁₅H₁₂N₂BrCl requires 333.9872); νmax (KBr)/cm⁻¹ 3042, 2932, 1614, 1473, 1452, 1378, 1357, 1329, 1263, 1170, 1032, 1004, 758, 746, 729 and 655; δH 3.20 (2 H, t, J = 7.3, CH₂), 4.40 (2 H, t, J = 7.3, NCH₂), 6.89 (1 H, t, J = 6.5, ArH), 7.05-7.10 (2 H, m, ArH), 7.22-7.23 (3 H, m, ArH), 7.51-7.54 (1 H, t, J = 8.0, ArH) and 7.64-7.68 (1 H, m, ArH); δC 35.93 (CH₂), 43.84 (NCH₂), 109.30 (benzimidazole 4/7-C), 119.37 (benzimidazole 4/7-C), 122.60 (benzimidazole 5/6-C), 123.12 (benzimidazole 5/6-C), 124.40 (2-C), 127.84 (ArCH), 128.93 (ArCH), 131.06 (ArCH), 132.99 (ArCH), 134.88 (ArC), 136.37 (ArC), 140.42 (ArC) and 141.58 (benzimidazole 2-C); m/z El 334 (M⁺, 22 %), 255 (11), 182 (45), 165 (100), 129 (27), 90 (34) and 70 (32).
4-({1-[2-(2-Bromophenyl)ethyl]-1H-benzo[d]imidazole-2-yl}sulfanyl)benzene-1-carboxylic acid 254

4-Mercaptobenzoic acid 189 (2.06 g, 13.4 mmol) was dissolved in EtOH (60 mL) followed by potassium tert-butoxide (2.25 g, 20.1 mmol) and the mixture was left stirring for 5 min. 1-[2-(2-Bromophenyl)ethyl]-2-chloro-1H-benzo[d]imidazole 253 (4.50 g, 13.4 mmol) was added to the reaction mixture and the reaction mixture was heated under reflux overnight. The reaction mixture was filtered and evaporated to dryness to give the crude product. The crude product was purified by column chromatography using silica gel as absorbent and light petroleum/ethyl acetate (1:1) as eluents to afford 4-({1-[2-(2-bromophenyl)ethyl]-1H-benzo[d]imidazole-2-yl}sulfanyl)benzene-1-carboxylic acid 254 as white crystals (6.0 g, 13.4 mmol, 99 %), mp 203-207 °C; (Found: MH+, 453.0279. C22H17BrN2O2S requires 453.0273); \( \nu_{\text{max}} \) (KBr)/cm\(^{-1}\) 3423, 3054, 2372, 1699, 1592, 1539, 1413, 1259, 1170, 1017, 851 and 746; \( \delta_d\) (DMSO) 3.14 (2 H, t, \( J = 7.0, \) CH\(_2\)), 4.53 (2 H, t, \( J = 7.0, \) NCH\(_2\)), 7.02 (1 H, d, \( J = 7.2, \) ArH), 7.20-7.29 (4 H, m, ArH), 7.33 (2 H, d, \( J = 8.4, \) 3-H and 5-H), 7.53-7.57 (2 H, m, ArH), 7.64 (1 H, d, \( J = 7.6, \) ArH) and 7.89 (2 H, d, \( J = 8.8, \) 2-H and 6-H); \( \delta_c\) (DMSO) 35.81 (CH\(_2\)), 44.28 (NCH\(_2\)), 110.94 (benzimidazole 4/7-C), 119.47 (benzimidazole 4/7-C), 122.64 (benzimidazole 5/6-C), 123.55 (benzimidazole 5/6-C), 124.39 (1-C), 128.28 (ArCH), 129.27 (2 x ArCH), 129.40 (ArCH), 130.58 (2 x ArCH), 131.70 (ArCH), 132.94 (ArCH), 135.80 (4-C), 137.09 (3a-C and 7a-C), 143.17 (ArC), 146.32 (benzimidazole 2-C) and 168.56 (C=O); \( m/z \) FAB 453 (MH\(^+\), 25 %), 373 (4), 307 (10), 289 (80), 154 (100) and 136 (83).
Acetyl chloride (0.46 mL, 6.6 mmol) was added dropwise over 10 min to MeOH (25 mL) cooled in an ice bath. The solution was stirred for 5 min and 4-({1-[2-(2-bromophenyl)ethyl]-1H-benzo[d]imidazol-2-yl}sulfanyl)benzene-1-carboxylic acid 254 (0.30 g, 0.7 mmol) was added in one portion and the solution slowly heated to reflux. Heating under reflux was continued overnight. The solution was cooled and evaporated to dryness to yield the crude methyl ester. Distilled water (10 mL) was added to the crude methyl ester hydrochloride and the aqueous layer basified to pH 14 with sodium carbonate and 1 M aqueous sodium hydroxide solution (few drops). The basic solution was extracted with DCM (3 × 25 mL). The combined organic extracts were dried (MgSO₄) and evaporated to dryness to afford methyl 4-({1-[2-(2-bromophenyl)ethyl]-1H-benzo[d]imidazol-2-yl}sulfanyl)benzene-1-carboxylate 255 as light brown crystals (0.23 g, 0.5 mmol, 76 %), mp 102.5-103.5 °C; (Found: M⁺, 466.0353. C₂₃H₁₇BrN₂O₂S requires 466.0351); ν max (KBr)/cm⁻¹ 3037, 2948, 1724, 1594, 1475, 1456, 1428, 1352, 1284, 1272, 1182, 1168, 1108, 1012, 851, 822, 768, 764, 750 and 691; δH 3.14 (2 H, t, J = 7.3, CH₂), 4.48 (2 H, t, J = 7.2, NCH₂), 3.87 (3 H, s, OCH₃), 6.79 (1 H, d, J = 6.2, ArH), 7.07-7.10 (2 H, m, ArH), 7.31-7.37 (5 H, m, ArH), 7.52 (1 H, d, J = 7.2, ArH), 7.78-7.80 (1 H, m, ArH) and 7.92 (2 H, d, J = 8.3, 2-H and 6-H); δc 36.45 (CH₂), 44.29 (NCH₂), 52.18 (OCH₃), 109.94 (benzimidazole 4/-7-C), 120.23 (benzimidazole 4/-7-C), 122.73 (benzimidazole 5/-6-C), 123.78 (benzimidazole 5/-6-C), 124.51 (2-C), 127.83 (ArCH), 128.43 (ArCH), 128.89 (ArCH), 130.40 (ArCH), 131.04 (ArCH), 133.02 (ArCH), 135.64 (ArC), 136.59 (ArC), 139.25 (ArC), 143.37 (1-C), 145.42 (ArC) and 166.35 (C=O); m/z El 466 (M⁺, 100 %), 387 (97), 322 (10), 297 (22), 284 (45), 253 (38), 238 (45), 220 (33), 169 (27), 103 (39) and 77 (55).
A solution of tributyltin hydride (0.19 mL, 0.7 mmol) in toluene (20 mL) was added to methyl 4-({1-[2-(2-bromophenyl)ethyl]-1H-benzo[d]imidazol-2-yl}sulfanyl)benzene-1-carboxylate 255 (0.13 g, 0.28 mmol) in toluene (150 mL) at reflux over 5 h using a syringe pump. AIBN (69 mg, 0.42 mmol) was added portion wise to the refluxing reaction mixture at equal intervals. The solution was stirred and heated under reflux for a further 3 h. The reaction mixture was evaporated to dryness and then purified by column chromatography using silica gel as absorbent with light petroleum and ethyl acetate as eluents to give product which still had traces of tin impurity. Dil. hydrochloric acid was added to the cooled reaction mixture to extract the protonated benzimidazole compounds into the aqueous layer and washed with light petroleum to remove Bu₃Sn-residues. The acidic aqueous layer was basified with sodium carbonate and aqueous sodium hydroxide (few drops) to pH 14. The basic solution was extracted with DCM (3 x 20 mL). The combined organic extracts were dried (MgSO₄) and evaporated to dryness to give 5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinoline 256 as off-white crystals (31 mg, 0.14 mmol, 50%), mp 125.0-130.0 °C; (Found: M⁺, 220.1000. C₁₅H₁₂N₂ requires 220.1001); νmax (KBr)/cm⁻¹ 2922, 2370, 2344, 1480, 1458, 1406, 1325, 1171 and 736; δH 3.30 (2 H, t, J = 6.9, 5-H), 4.35 (2 H, t, J = 6.9, 6-H), 7.26-7.43 (6 H, m, ArH), 7.81-7.85 (1 H, m, ArH) and 8.29-8.32 (1 H, m, ArH); δC 28.26 (5-C), 40.42 (6-C), 109.05 (benzimidazole 8/11-C), 119.76 (benzimidazole 8/11-C), 122.5 (benzimidazole 9/10-C), 122.71 (benzimidazole 9/10-C), 125.70 (ArCH), 126.64 (12b-C), 127.76 (ArCH), 128.08 (ArCH), 130.18 (ArCH), 134.27 (11a-C), 134.65 (7a-C), 143.86 (4a-C) and 149.10 (12a-C); m/z El 220 (M⁺, 100%), 109 (9), 86 (10) and 77 (9).
Synthesis of solid-supported benzimidazole adduct 257

To a portion of Wang resin (0.6 g, 1.0 mmol) was added DCM/DMF (15/5 mL). The resin was left to swell for 1 h under N₂. 4-((1-[2-(2-Bromophenyl)ethyl]-1H-benzo[d]imidazole-2-yl)sulfanyl)benzene-1-carboxylic acid 254 (0.6 g, 1.3 mmol), DMAP (0.48 g, 3.9 mmol) and DIC (1.03 mL, 6.6 mmol) were added sequentially. The suspension was shaken for 48 h at rt. The reaction mixture was filtered and washed with DCM, MeOH, DMF, MeOH and DCM (20 mL each). The resin was dried at 40 °C under vacuum for 24 h. The coupling reaction was repeated under similar conditions.

The loading on the resin was determined by cleaving a known amount of resin using [TFA/DCM (9/1)](0.98 mmol/g).

IR ν<sub>max</sub> (KBr)/cm<sup>-1</sup> 3023, 2919, 1713, 1590, 1441, 1263, 1170, 1095, 1090, 1010, 821, 742 and 694.

Radical cyclisation of resin-bound benzimidazole moiety 256

Method A (thermal, tributylgermanium hydride and toluene)

To refluxing suspension of the resin-bound benzimidazole 257 (140 mg, 0.14 mmol) in toluene (15 mL) was added tributylgermanium hydride (0.11 mL, 0.4 mmol), followed by portion wise addition of AIBN (43 mg, 0.26 mmol). The mixture was heated at reflux for 8 h, followed by another addition of tributylgermanium hydride (0.11 mL, 0.43 mmol) and AIBN (43 mg, 0.26 mmol). The reaction mixture was heated at reflux for another 8 h. The reaction mixture was filtered and washed.
with toluene (20 mL), DCM (20 mL) and MeOH (20 mL) to give 5,6-
dihydrobenzo[4,5]imidazo[2,1-a]isoquinoline 256 as off-white crystals (20 mg, 0.1 mmol, 71 % ),
mp 125.0-130.0 °C; (Found: M⁺, 220.1000. C₁₅H₁₂N₂ requires 220.1001); νmax (KBr)/cm⁻¹ 2922,
2370, 2344, 1480, 1458, 1406, 1325, 1171 and 736; δH 3.30 (2 H, t, J = 6.9, 5-H), 4.35 (2 H, t, J =
6.9, 6-H), 7.26-7.43 (6 H, m, ArH), 7.81-7.85 (1 H, m, ArH) and 8.29-8.32 (1 H, m, ArH); δC 28.26
(5-C), 40.42 (6-C), 109.05 (benzimidazole 8/11-C), 119.76 (benzimidazole 8/11-C), 122.5
(benzimidazole 9/10-C), 122.71 (benzimidazole 9/10-C), 125.70 (ArCH), 126.64 (12b-C), 127.76
(ArCH), 128.08 (ArCH), 130.18 (ArCH), 134.27 (11a-C), 134.65 (7a-C), 143.86 (4a-C) and
149.10 (12a-C); m/z El 220 (M⁺, 100 %), 109 (9), 86 (10) and 77 (9).

Method B (thermal, tributyltin hydride and toluene)
A solution of tributyltin hydride (0.12 mL, 0.44 mmol) and AIBN (43 mg, 0.26 mmol) in toluene (5
mL) was added to refluxing suspension of the resin-bound benzimidazole 257 (100 mg, 0.098
mmol) in toluene (10 mL) over 7 h using a syringe pump. The reaction mixture was cooled, filtered
and washed with toluene (20 mL), DCM (20 ml) and MeOH (20 mL) to give 5,6-
dihydrobenzo[4,5]imidazo[2,1-a]isoquinoline 256 as off-white crystals (10 mg, 0.04 mmol, 44 % ),
mp 125.0-130.0 °C; (Found: M⁺, 220.1000. C₁₅H₁₂N₂ requires 220.1001); νmax (KBr)/cm⁻¹ 2922,
2370, 2344, 1480, 1458, 1406, 1325, 1171 and 736; δH 3.30 (2 H, t, J = 6.9, 5-H), 4.35 (2 H, t, J =
6.9, 6-H), 7.26-7.43 (6 H, m, ArH), 7.81-7.85 (1 H, m, ArH) and 8.29-8.32 (1 H, m, ArH).

Method C (TTMSS, BE₃ and toluene)
To a suspension of the resin-bound benzimidazole 257 (111 mg, 0.11 mmol) in toluene (15 mL),
TTMSS (0.06 mL, 0.19 mmol) and Et₃B (1.0 M in cyclohexane, 0.2 mmol) were added dropwise.
The flask was fitted with a rubber septum and air was introduced through a needle during stirring at
rt for 5 h. Further addition of TTMSS (0.12 mL, 0.38 mmol) and Et₃B (1.0 M in hexane, 0.3 mmol)
were carried out at equal intervals and the reaction mixture was stirred for another 10 h. The
reaction mixture was filtered and washed with toluene (20 mL), DCM (20 ml) and MeOH (20 mL)
to give 5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinoline 256 as off-white crystals (7 mg, 0.03
mmol, 29 % ). The TLC, ¹H-NMR and IR spectra for the cyclised product were identical to an
authentic sample.
Ethyl 6-[(1H-imidazol-2-yl)sulfanyl]pyridine-3-carboxylate 260

![Diagram of 260]

2-Mercaptoimidazole 259 (2.00 g, 20.0 mmol) was added slowly to a suspension of NaH (0.58 g, 24.2 mmol) in dry DMF (40 mL). The mixture was stirred and heated at 80 °C for 1 h, followed by addition of ethyl 6-chloronicotinate (3.71 g, 20.0 mmol) in DMF (10 mL) and the reaction mixture was heated at 80 °C for 12 h. The reaction mixture was evaporated to dryness and the crude product was purified by column chromatography using silica gel as absorbent and light petroleum/ethyl acetate (1:1) as eluents to afford ethyl 6-[(1H-imidazol-2-yl)sulfanyl]pyridine-3-carboxylate 260 as white crystals (2.49 g, 10.0 mmol, 50 %), mp 145.7-146.9 °C; (Found: M⁺, 249.0573 C₁₁H₁₁N₃O₂S requires 249.0572); ν_max (KBr)/cm⁻¹ 3079, 2986, 2745, 2502, 1866, 1715, 1574, 1444, 1275, 1113, 1011, 965, 851 and 767; δₜ 1.40 (3 H, t, J = 7.2, CH₃), 4.40 (2 H, q, J = 7.2, CH₂), 7.12 (1 H, d, J = 8.6, 5-H), 7.23-7.26 (2 H, s, imidazole 5-H and 4-H), 8.10 (1 H, d, J = 8.6, 4-H) and 9.02 (1 H, s, 2-H); δ_c 14.25 (CH₃), 61.55 (CH₂), 121.31 (5-C), 123.31 (imidazole 4-C and 5-C), 133.18 (ArC), 135.09 (imidazole 2-C), 137.58 (4-C), 150.48 (2-C), 162.62 (C=O) and 164.77 (6-C); m/z El 250 (MH⁺, 100 %), 232 (33), 221 (7), 163 (11), 130 (12), 103 (21), 91 (10) and 77 (11).

Ethyl 6-[(1-[2-(2-bromophenyl)ethyl]-1H-imidazol-2-yl)sulfanyl]pyridine-3-carboxylate 261

![Diagram of 261]

Ethyl 6-[(1H-imidazol-2-yl)sulfanyl]pyridine-3-carboxylate 260 (0.90 g, 3.6 mmol) was added slowly to a suspension of NaH (0.22 g, 9.2 mmol) in dry DMF (30 mL). The mixture was stirred for 1 h and 2-(2-bromophenyl)ethyl methanesulfonate 245 (1.30 g, 4.7 mmol) in DMF (10 mL) was added dropwise to the reaction mixture. The mixture was stirred at rt for a further 24 h. The salts
formed were removed by filtration on a celite bed and the solution was evaporated to dryness to yield a brown solid. The crude product was purified by column chromatography using neutral alumina as absorbent and light petroleum/ethyl acetate (1:1) as eluents to afford ethyl 6-({1-[2-(2-bromophenyl)ethyl]-1H-imidazol-2-yl}sulfanyl)pyridine-3-carboxylate 261 as a pale yellow oil (1.16 g, 2.70 mmol, 75 %); (Found: M+, 431.0312. C$_{19}$H$_{16}$BrN$_3$S$_2$O$_2$ requires 431.0303); $\nu_{max}$ (neat)/cm$^{-1}$ 3105, 3056, 2981, 1716, 1584, 1472, 1456, 1429, 1366, 1283, 1269, 1173, 1128, 1025, 854 and 766; $\delta$H 1.38 (3 H, t, J = 7.2, CH$_3$), 3.13 (2 H, t, J = 7.2, CH$_2$), 4.31-4.39 (4 H, m, NCH$_2$, OCH$_2$), 6.88 (1 H, dd, J = 8.4, 0.4, 5-H), 6.96 (1 H, dd, J = 7.6, 1.6, Ar 6-H), 7.08 (1 H,ddd, J = 7.4, 7.4 and 1.2, Ar 5-H), 7.10 (1 H, s, imidazole 4-H or 5-H), 7.16 (1 H, ddd, J = 7.4, 7.4 and 1.2, Ar 4-H), 7.27 (1 H, s, imidazole 4-H/5-H), 7.49 (1 H, dd, J = 8.0 and 1.2, Ar 3-H), 8.04 (1 H, dd, J = 8.4 and 2.0, 4-H) and 8.96 (1 H, s, 2-H); $\delta$C 14.23 (CH$_3$), 37.88 (CH$_2$), 46.73 (NCH$_2$), 61.36 (OCH$_2$), 120.40 (5-C), 123.15 (Ar 2-C), 123.41 (imidazole 4-C), 124.39 (3-C), 127.75 (imidazole 5-C), 128.86 (Ar 5-C), 131.04 (Ar 6-C), 131.19 (Ar 4-C), 132.99 (Ar 3-C), 134.43 (Ar 1-C), 136.32 (imidazole 2-C), 137.67 (4-C), 150.86 (2-C), 164.40 (C=O) and 164.89 (6-C); m/z El 431 (M+, 4 %), 352 (11), 249 (46), 181 (100), 153 (64), 84 (45) and 49 (39).

5,6-Dihydroimidazo[2,1-a]isoquinoline 262

Method A (tributyltin hydride, AIBN and toluene)

A solution of tributyltin hydride (0.26 mL, 1.0 mmol) in toluene (40 mL) was added to ethyl 6-({1-[2-(2-bromophenyl)ethyl]-1H-imidazol-2-yl}sulfanyl)pyridine-3-carboxylate 261 (0.15 g, 0.4 mmol) in toluene (210 mL) at reflux over 7 h using a syringe pump. AIBN (0.14 g, 0.85 mmol) was added to the refluxing reaction mixture at equal intervals. The solution was stirred and heated under reflux for a further 3 h. Dil. hydrochloric acid was added to the cooled reaction mixture to extract the protonated imidazole compounds into the aqueous layer and washed with light petroleum to remove Bu$_3$Sn-residues. The acidic aqueous layer was basified with sodium carbonate and aqueous sodium hydroxide (few drops) to pH 14. The basic solution was extracted with DCM (3 x 20 mL). The combined organic extracts were dried (MgSO$_4$) and evaporated to dryness. The crude product was
purified by column chromatography using neutral alumina as absorbent and light petroleum/ethyl acetate (7:3) as eluents to afford 5,6-dihydroimidazo[2,1-a]isoquinoline 262 as a clear oil (22 mg, 0.13 mmol, 37%); (Found: M+, 170.0847. C_{11}H_{10}N_{2} requires 170.0844); ν_{max} (neat)/cm^{-1} 3171, 2923, 1708, 1499, 1466, 1329, 1250, 1195, 1099, 911, 772, 738 and 714; δ_{H} 3.16 (2 H, t, J = 6.8, CH_{2}), 4.17 (2 H, t, J = 6.8, NCH_{2}), 6.94 (1 H, s, 2/3-H), 7.15 (1 H, s, 2/3-H), 7.26-7.27 (3 H, m, ArH) and 8.02 (1 H, d, J = 8.0, 10-H); δ_{C} 28.59 (6-C), 43.33 (5-C), 119.12 (2-C), 123.57 (3-C), 127.62 (9-C), 127.76 (10-C), 128.35 (8/7-C), 129.08 (8/7-C), 132.35 (10a-C and 6a-C) and 142.92 (10b-C); m/z El 170 (M+, 4 %), 149 (5), 128 (16), 115 (16), 77 (21), and 57 (23). Unreacted starting material 261 was also recovered (28 mg, 0.07 mmol, 19%).

**Method B (TTMSS, AIBN and toluene)**

A solution of TTMSS (0.41 mL, 1.33 mmol) in toluene (30 mL) was added to ethyl 6-{{1-[2-(2-bromophenyl)ethyl]-1H-imidazol-2-yl}sulfanyl}pyridine-3-carboxylate 261 (0.23 g, 0.5 mmol) in toluene (220 mL) at reflux over 8 h using a syringe pump. AIBN (0.16 g, 1.00 mmol) was added to the refluxing reaction mixture at equal intervals. The solution was stirred and heated under reflux for a further 4 h. Dil. hydrochloric acid was added to the cooled reaction mixture to extract the protonated imidazole compounds into the aqueous layer and washed with light petroleum to remove TTMSS-residues. The acidic aqueous layer was basified with sodium carbonate and aqueous sodium hydroxide (few drops) to pH 14. The basic solution was extracted with DCM (3 x 20 mL). The combined organic extracts were dried (MgSO_{4}) and evaporated to dryness. The residue was purified by column chromatography using neutral alumina as absorbent and light petroleum/ethyl acetate (7:3) as eluents to afford 5,6-dihydroimidazo[2,1-a]isoquinoline 262 as a clear oil (41 mg, 0.24 mmol, 45%). The TLC and ^{1}H-NMR and IR spectra were identical to those of an authentic sample.

**Method C (tributylgermanium hydride, AIBN and toluene)**

Tributylgermanium hydride (0.12 mL, 0.46 mmol) was added to ethyl 6-{{1-[2-(2-bromophenyl)ethyl]-1H-imidazol-2-yl}sulfanyl}pyridine-3-carboxylate 261 (0.23 g, 0.5 mmol) in toluene (30 mL) followed by portion wise addition of AIBN (75 mg, 0.46 mmol) to the refluxing reaction mixture at equal intervals. The solution was stirred and heated under reflux for a further 8 h. Dil. hydrochloric acid was added to the cooled reaction mixture to extract the protonated imidazole compounds into the aqueous layer and washed with light petroleum to remove Bu_{3}Ge-residues. The acidic aqueous layer was basified with sodium carbonate and aqueous sodium...
hydroxide (few drops) to pH 14. The basic solution was extracted with DCM (3 x 20 mL). The combined organic extracts were dried (MgSO₄) and evaporated to dryness. The crude product was purified by column chromatography using neutral alumina as absorbent and light petroleum/ethyl acetate (7:3) as eluents to afford 5,6-dihydroimidazo[2,1-α]isoquinoline 262 as a clear oil (7 mg, 0.04 mmol, 20%). The TLC and ¹H-NMR and IR spectra were identical to those of an authentic sample.
Methyl 1[(2-iodophenyl)methyl]-1H-imidazole-4-carboxylate 271

Methyl 4-imidazole-carboxylate 270 (0.50 g, 4.0 mmol) was added slowly to a suspension of NaH (0.29 g, 11.9 mmol) in dry DMF (40 mL). The mixture was stirred and heated under reflux for 1 h and (2-iodophenyl)methyl methanesulfonate 241 (2.47 g, 7.9 mmol) in DMF (10 mL) was added dropwise to the reaction mixture. The mixture was heated under reflux for a further 12 h. The salts formed were removed by filtration on a celite bed and the solution was evaporated to dryness to yield a pale yellow oil. The oil was purified by column chromatography using neutral alumina as absorbent and light petroleum/ethyl acetate (1:4) as eluents to afford methyl 1-[(2-iodophenyl)methyl]-1H-imidazol-4-carboxylate 271 as a clear oil (0.58 g, 1.7 mmol, 43%); (Found: M⁺, 341.9860. C₁₂H₁₁N₂O₂ requires 341.9865); ν max (neat)/cm⁻¹ 2947, 1718, 1545, 1437, 1380, 1224, 1204, 1119, 1014, 765, 742 and 660; δH 3.88 (3 H, s, CH₃), 5.20 (2 H, s, CH₂), 7.02 (1 H, dd, J = 7.6, 1.2, 6-H), 7.07 (1 H, ddd, J = 7.6, 7.6 and 1.6, 4-H), 7.36 (1 H, ddd, J = 7.6, 7.6 and 1.2, 5-H), 7.59 (1 H, s, imidazole 5-H), 7.60 (1 H, s, imidazole 2-H) and 7.89 (1 H, dd, J = 8.0, 1.2, 3-H); δC 51.71 (CH₃), 55.86 (CH₂), 98.62 (2-C), 125.38 (imidazole 2-C), 129.12 (4-C), 129.18 (5-C), 130.52 (6-C), 134.15 (imidazole 4-C), 137.37 (1-C), 138.41 (imidazole 2-C), 140.15 (Ar 3-C) and 163.16 (C=O); m/z El 342 (M⁺, 27 %), 311 (12), 284 (13), 217 (100), 183 (46), 121(15) and 90 (43).
Attempted radical cyclisation of methyl 1[(2-iodophenyl)methyl]-1H-imidazole-4-carboxylate 271

Method A (tributyltin hydride, AIBN and toluene)

A solution of tributyltin hydride (0.39 mL, 1.5 mmol) in toluene (40 mL) was added to methyl 1-[(2-iodophenyl)methyl]-1H-imidazol-4-carboxylate 271 (0.20 g, 0.6 mmol) in toluene (120 mL) at reflux over 7 h using a syringe pump. AIBN (0.12 g, 0.7 mmol) was added to the refluxing reaction mixture at equal intervals. The solution was stirred and heated under reflux for a further 5 h. Dil. hydrochloric acid was added to the cooled reaction mixture to extract the protonated imidazole compounds into the aqueous layer and washed with light petroleum to remove Bu₃Sn-residues. The acidic aqueous layer was basified with sodium carbonate and aqueous sodium hydroxide (few drops) to pH 14. The basic solution was extracted with DCM (3 x 20 mL). The combined organic extracts were dried (MgSO₄) and evaporated to dryness. The residue was purified by column chromatography using neutral alumina as absorbent and light petroleum/ethyl acetate (1:1) as eluents to afford methyl 1-(phenylmethyl)-1H-imidazole-4-carboxylate 274 as a colourless oil (41 mg, 0.19 mmol, 33 %); (Found: MH⁺, 217.0976. C₁₂H₁₂N₂O₂ requires 217.0977); \( \nu_{\text{max}} \) (neat)/cm⁻¹ 2363, 1720, 1545, 1440, 1380, 1224, 1119, 997 and 713; \( \delta_\text{H} \) 3.88 (3 H, s, OCH₃), 5.14 (2 H, s, CH₂), 7.17-7.20 (2 H, m, ArH), 7.25-7.26 (1 H, m, ArH), 7.37-7.41 (2 H, m, ArH), 7.56 (1 H, s, imidazole 5-H) and 7.60 (1 H, m, imidazole 2-H); \( \delta_\text{C} \) 51.39 (CH₂), 51.73 (OCH₃), 118.58 (imidazole 4-C), 125.40 (imidazole 5-C), 127.58 (ArCH), 128.78 (ArCH), 129.24 (ArCH), 138.07 (imidazole 2-C), 142.92 (1-C) and 163.23 (C=O); m/z El 216 (M⁺, 10 %), 185 (5), 158 (8), 128 (4), 91 (100), 77 (8) and 65 (18).
Method B (tributylgermanium hydride, AIBN and toluene)

Tributylgermanium hydride (0.16 mL, 0.6 mmol) was added to methyl 1-[(2-iodophenyl)methyl]-1H-imidazol-4-carboxylate 271 (86 mg, 0.25 mmol) in toluene (30 mL) followed by portion wise addition of AIBN (102 mg, 0.63 mmol) to the refluxing reaction mixture at equal intervals. The solution was stirred and heated under reflux for 10 h. Dil. hydrochloric acid was added to the cooled reaction mixture to extract the protonated imidazole compounds into the aqueous layer and washed with light petroleum to remove Bu₃Ge-residues. The acidic aqueous layer was basified with sodium carbonate and aqueous sodium hydroxide (few drops) to pH 14. The basic solution was extracted with DCM (3 x 20 mL). The combined organic extracts were dried (MgSO₄) and evaporated to dryness. The crude oil was purified by column chromatography using neutral alumina as absorbent and light petroleum/ethyl acetate (1:1) as eluents to afford methyl 1-(phenylmethyl)-1H-imidazole-4-carboxylate 274 as a colourless oil (30 mg, 0.14 mmol, 56%). The TLC and ¹H-NMR and IR spectra for the reduced product were identical to an authentic sample.

Methyl 1-[2-(2-bromophenyl)ethyl]-1H-imidazole-4-carboxylate 275 and methyl 1-[2-(2-bromophenyl)ethyl]-1H-imidazole-5-carboxylate 276

Methyl 4-imidazole-carboxylate 270 (0.50 g, 4.0 mmol) was added slowly to a suspension of sodium hydride (0.30 g, 12.5 mol) in dry DMF (40 mL). The mixture was stirred and heated at 80 °C for 1 h and 2-(2-bromophenyl)ethyl methanesulfonylate 245 (2.00 g, 7.2 mmol) in DMF (10 mL) was added dropwise to the reaction mixture and it was heated at 80 °C for 12 h. The reaction mixture was evaporated to dryness and the crude product was purified by column chromatography using silica gel as absorbent and light petroleum/ethyl acetate (1:1) and ethyl acetate as eluents to afford methyl 1-[2-(2-bromophenyl)ethyl]-1H-imidazole-4-carboxylate 275 as a pale yellow oil (0.61 g, 1.98 mmol, 50%); (Found: M⁺, 308.0157. C₁₃H₁₃BrN₂O₂ requires 308.0160); νₒₓ
(neat)/cm⁻¹ 2948, 1724, 1472, 1382, 1225, 1197, 1120, 1029, 997, 757 and 660; δH 3.10 (2 H, t, J = 7.2, CH₂), 3.79 (3 H, s, OCH₃), 4.16 (2 H, t, J = 7.2, NCH₂), 6.88 (1 H, dd, J = 7.2 and 1.6, Ar 6-H), 7.04 (1 H, ddd, J = 7.6, 7.6 and 1.6, Ar 4-H), 7.11 (1 H, ddd, J = 7.6, 7.6 and 1.6, Ar 5-H), 7.24 (1 H, s, imidazole 5-H) and 7.47-7.50 (2 H, m, imidazole 2-H and Ar 3-H); δC 37.04 (CH₂), 45.95 (NCH₂), 50.61 (OCH₃), 123.16 (Ar 2-C), 124.11 (imidazole 5-C), 126.98 (ArCH), 128.14 (ArCH), 129.97 (ArCH), 132.18 (imidazole 4-C), 134.93 (Ar 1-C), 136.89 (imidazole 2-C) and 162.19 (C=O); m/z El 309 (MH⁺, 1 %), 229 (34), 197 (95), 169 (52), 115 (53), 108 (100), 89 (68), 77 (69) and 53 (77). The column chromatography also yielded the other regioisomer methyl 1-[2-(2-bromophenyl)ethyl]-1H-imidazole-5-carboxylate 276 as a white crystalline powder (0.59 g, 1.90 mmol, 48 %), mp 92.0-95.9 °C; (Found: MH⁺, 309.0239. C₁₉H₁₃BrN₂O₂ requires 309.0238); (Found: C, 50.29; H, 4.05; N, 8.25. requires C, 50.50; H, 4.24; N, 9.06 %); νmax (KBr)/cm⁻¹ 3079, 1715, 1539, 1475, 1437, 1362, 1236, 1162, 1108, 1025, 947, 867, 761 and 660; δH 3.22 (2 H, t, J = 7.0, CH₂), 3.89 (3 H, s, OCH₃), 4.55 (2 H, t, J = 7.0, NCH₂), 6.98 (1 H, d, J = 7.4, Ar 6-H), 7.10 (1 H, ddd, J = 7.4, 7.4 and 1.9, Ar 4-H), 7.17 (1 H, ddd, J = 7.4, 7.4 and 1.9, Ar 5-H), 7.28 (1 H, s, imidazole 4-H), 7.56 (1 H, d, J = 7.4, Ar 3-H) and 7.73 (1 H, s, imidazole 2-H); δC 37.65 (CH₂), 46.42 (NCH₂), 51.55 (OCH₃), 122.09 (imidazole 5-C), 124.40 (Ar 2-C), 127.81 (ArCH), 128.70 (ArCH), 131.13 (ArCH), 132.99 (ArCH), 136.76 (Ar 1-C), 138.05 (imidazole 4-C), 142.15 (imidazole 2-C) and 160.72 (C=O); m/z El 309 (MH⁺, 1 %), 277 (2), 229 (100), 197 (15), 182 (8), 169 (25), 103 (18), 89 (13) and 77 (29).

Methyl 5,6-dihydroimidazo[5,1-a]isoquinoline-1-carboxylate 277 and methyl 5,6-dihydroimidazo[2,1-a]isoquinoline-2-carboxylate 278

Method A (tributyltin hydride, AIBN and toluene)

A solution of tributyltin hydride (0.31 mL, 1.1 mmol) in toluene (20 mL) was added to methyl 1-[2-(2-bromophenyl)ethyl]-1H-imidazole-4-carboxylate 275 (0.14 g, 0.5 mmol) in toluene (120 mL) at reflux over 5 h using a syringe pump. AIBN (0.11 g, 0.68 mmol) was added to the refluxing
reaction mixture at equal intervals. The solution was stirred and heated under reflux for a further 5 h. Dil. hydrochloric acid was added to the cooled reaction mixture to extract the protonated imidazole compounds into the aqueous layer and washed with light petroleum to remove Bu₃Sn-residues. The acidic aqueous layer was basified with sodium carbonate and aqueous sodium hydroxide (few drops) to pH 14. The basic solution was extracted with DCM (3 x 20 mL). The combined organic extracts were dried (MgSO₄) and evaporated to dryness. The crude product was purified by column chromatography using neutral alumina as absorbent and light petroleum/ethyl acetate (1:1) and ethyl acetate as eluents to afford methyl 5,6-dihydroimidazo[5,1-a]isoquinoline-1-carboxylate 277 as a crystalline white needles (16 mg, 0.07 mmol, 16 %), mp 179.0-182.9 °C; (Found: M⁺, 228.0900. C₁₃H₁₂N₂O₂ requires 228.0900); v_max (KBr)/cm⁻¹ 3118, 2951, 2368, 1689, 1546, 1469, 1432, 1347, 1217, 1182, 1164, 1107, 939, 769 and 655; δH 3.10 (2 H, t, J = 6.5, CH₂), 3.96 (3 H, s, OCH₃), 4.17 (2 H, t, J = 6.5, NCH₂), 7.27 (1 H, dd, J = 8.0 and 1.0, 7-H), 7.32 (1 H, ddd, J = 8.0, 8.0 and 1.0, 9-H), 7.38 (1 H, ddd, J = 8.0, 8.0 and 1.0, 8-H), 7.54 (1 H, s, 3-H) and 8.74 (1 H, dd, J = 8.0 and 1.0, 10-H); δC 29.60 (5-C), 42.47 (6-C), 51.91 (OCH₃), 125.93 (1-C), 127.65 (9-C), 127.80 (10-C), 128.23 (10b-C), 128.37 (8/7-C), 129.07 (7/8-C), 133.01 (10a-C), 133.80 (6a-C), 135.51 (3-C) and 164.17 (C=O); m/z EI 228 (M⁺, 74 %), 197(100), 170 (54), 140 (13) and 115 (25). The X-Ray crystallography also confirmed the structure of methyl 5,6-dihydroimidazo[5,1-a]isoquinoline-1-carboxylate. Further elution yielded the other cyclised product, methyl 5,6-dihydroimidazo[2,1-a]isoquinoline-2-carboxylate 278 as a pale yellow oil (11 mg, 0.05 mmol, 4 %); (Found: M⁺, 228.0900. C₁₃H₁₂N₂O₂ requires 228.0900); v_max (neat)/cm⁻¹ 3134, 2953, 2925, 2359, 1723, 1542, 1461, 1437, 1349, 1326, 1258, 1225, 1199, 1181, 1124, 1103, 1006, 808, 777, 737 and 718; δH 3.11 (2 H, t, J = 7.2, CH₂), 3.84 (3 H, s, OCH₃), 4.15 (2 H, t, J = 7.20, NCH₂), 7.17 (1 H, dd, J = 6.8 and 2.0, 7-H), 7.23-7.30 (2 H, m, ArH), 7.58 (1 H, s, 3-H) and 8.10 (1 H, dd, J = 7.6 and 2.0, 10-H); δC 27.24 (6-C), 42.73 (5-C), 50.79 (OCH₃), 123.55 (ArCH), 124.40 (ArCH), 125.15 (2-C), 126.70 (ArCH), 126.81 (ArCH), 127.29 (10a-C), 128.34 (3-C), 131.68 (6a-C), 144.02 (10b-C) and 162.52 (C=O); m/z EI 228 (M⁺, 100 %), 197 (92), 170 (75), 140 (12), 115 (28) and 77 (10).

**Method B (tributylgermanium hydride, benzenethiol, AIBN and toluene)**

Tributylgermanium hydride (0.12 mL, 0.46 mmol) was added to methyl 1-[2-(2-bromophenyl)ethyl]-1H-imidazole-4-carboxylate 275 (0.13 g, 0.41 mmol) and benzenethiol (4 μL, 10 mol%) in toluene (55mL), followed by portion wise addition of AIBN (102 mg, 0.62 mmol) to the refluxing reaction mixture at equal intervals. The solution was stirred and heated under reflux for 10 h. Dil. hydrochloric acid was added to the cooled reaction mixture to extract the protonated
imidazole compounds into the aqueous layer and washed with light petroleum to remove Bu₃Ge-residues. The acidic aqueous layer was basified with sodium carbonate and aqueous sodium hydroxide (few drops) to pH 14. The basic solution was extracted with DCM (3 x 20 mL). The combined organic extracts were dried (MgSO₄) and evaporated to dryness. The residue was purified by column chromatography using neutral alumina as absorbent and light petroleum/ethyl acetate (7:3) as eluents to afford methyl 5,6-dihydroimidazo[5,1-a]isoquinoline-1-carboxylate 277 as a crystalline white solid (41 mg, 0.18 mmol, 44%), mp 179.0-182.9 °C. The TLC and ¹H-NMR and IR spectra were identical to those of an authentic sample. The ¹H-NMR spectrum of the crude product showed the presence of starting material and traces of other unidentifiable materials. The % recovery of unaltered starting material was not recorded.

Method C (tributylgermanium hydride, AIBN and toluene)
Tributylgermanium hydride (0.20 mL, 0.8 mmol) was added to methyl 1-[2-(2-bromophenyl)ethyl]-1H-imidazole-4-carboxylate 275 (98 mg, 0.32 mmol) in toluene (40 mL), followed by portion wise addition of AIBN (130 mg, 0.8 mmol) to the refluxing reaction mixture at equal intervals. The solution was stirred and heated under reflux for 10 h. Dil. hydrochloric acid was added to the cooled reaction mixture to extract the protonated imidazole compounds into the aqueous layer and washed with light petroleum to remove Bu₃Ge-residues. The acidic aqueous layer was basified with sodium carbonate and aqueous sodium hydroxide (few drops) to pH 14. The basic solution was extracted with DCM (3 x 20 mL). The combined organic extracts were dried (MgSO₄) and evaporated to dryness. The crude product was purified by column chromatography using neutral alumina as absorbent and light petroleum/ethyl acetate (1:1) and ethyl acetate as eluents to afford methyl 5,6-dihydroimidazo[5,1-a]isoquinoline-1-carboxylate 277 as a crystalline white solid (27 mg, 0.12 mmol, 38%), mp 179.0-182.9 °C. Further elution yielded the other product, methyl 5,6-dihydroimidazo[2,1-a]isoquinoline-2-carboxylate 278 as a pale yellow oil (14 mg, 0.06 mmol, 19%). The TLC and ¹H-NMR and IR spectra for products were identical to authentic samples. The ¹H-NMR spectrum of the crude product showed the presence of starting material only.

Method D (TTMSS, AIBN and toluene)
A solution of TTMSS (0.48 mL, 1.54 mmol) in toluene (30 mL) was added to methyl 1-[2-(2-bromophenyl)ethyl]-1H-imidazole-4-carboxylate 275 (0.19 g, 0.62 mmol) in toluene (170 mL) at reflux over 8 h using a syringe pump. AIBN (0.25 g, 1.54 mmol) was added to the refluxing reaction mixture at equal intervals. The solution was stirred and heated under reflux for a further 4
Dil. hydrochloric acid was added to the cooled reaction mixture to extract the protonated imidazole compounds into the aqueous layer and washed with light petroleum to remove TTMSS-residues. The acidic aqueous layer was basified with sodium carbonate and aqueous sodium hydroxide (few drops) to pH 14. The basic solution was extracted with DCM (3 x 20 mL). The combined organic extracts were dried (MgSO₄) and evaporated to dryness. The residue was purified by column chromatography using neutral alumina as absorbent and light petroleum/ethyl acetate (1:1) and ethyl acetate as eluents to afford methyl 5,6-dihydroimidazo[5,1-α]isoquinoline-1-carboxylate 277 as a crystalline white solid (43 mg, 0.19 mmol, 30 %), mp 179.0-182.9 °C. Further elution yielded the other product, methyl 5,6-dihydroimidazo[2,1-α]isoquinoline-2-carboxylate 278 as a pale yellow oil (42 mg, 0.19 mmol, 30 %). The TLC and ¹H-NMR and IR spectra for the products were identical to authentic samples.

Methyl 5,6-dihydroimidazo[2,1-α]isoquinoline-3-carboxylate 282

Method A (tributyltin hydride, AIBN and toluene)

A solution of tributyltin hydride (0.40 mL, 1.5 mmol) in toluene (20 mL) was added to methyl 1-[2-(2-bromophenyl)ethyl]-1H-imidazole-5-carboxylate 276 (0.18 g, 0.6 mmol) in toluene (180 mL) at reflux over 5 h using a syringe pump. AIBN (0.23 g, 1.40 mmol) was added to the refluxing reaction mixture at equal intervals. The solution was stirred and heated under reflux for a further 7 h. Dil. hydrochloric acid was added to the cooled reaction mixture to extract the protonated imidazole compounds into the aqueous layer and washed with light petroleum to remove Bu₃Sn-residues. The acidic aqueous layer was basified with sodium carbonate and aqueous sodium hydroxide (few drops) to pH 14. The basic solution was extracted with DCM (3 x 20 mL). The combined organic extracts were dried (MgSO₄) and evaporated to dryness. The residue was purified by column chromatography using neutral alumina as absorbent and light petroleum/ethyl acetate (1:1) as eluents to afford methyl 5,6-dihydroimidazo[2,1-α]isoquinoline-3-carboxylate 282 as a crystalline white solid (95 mg, 0.42 mmol, 71 %), mp 122.0-124.9 °C; (Found: MH⁺, 229.0981.
C₁₃H₁₃N₂O₂ requires 229.0977); νₑₑₓ (KBr/cm⁻¹) 2372, 1710, 1509, 1387, 1337, 1252, 1184, 1108, 1072 and 980; δₜ 3.17 (2 H, t, J = 7.2, CH₂), 3.88 (3 H, s, OCH₃), 4.62 (2 H, t, J = 7.2, NCH₂), 7.26-7.28 (1 H, m, 9-H), 7.33-7.39 (2 H, m, 8-H and 7-H), 7.83 (1 H, s, imidazole 2-H) and 8.07 (1 H, m, 10-H); δₑ 28.14 (6-C), 42.17 (5-C), 51.48 (OCH₃), 122.14 (3-C), 124.68 (ArCH), 126.23 (10a-C), 127.65 (ArCH), 127.75 (ArCH), 129.80 (ArCH), 133.19 (6a-C), 137.87 (imidazole 2-C), 148.34 (10b-C) and 161.01 (C=O); m/z El 228 (M⁺, 100 %), 213 (8), 197 (42), 183 (7), 169 (17), 140 (13), 128 (17), 115 (35) and 84 (29).

Method B (tributylgermanium hydride, AIBN and toluene)
Tributylgermanium hydride (0.15 mL, 0.59 mmol) was added to methyl 1-[2-(2-bromophenyl)ethyl]-1H-imidazole-5-carboxylate 276 (0.12 g, 0.39 mmol) in toluene (55 mL), followed by portion wise addition of AIBN (149 mg, 0.91 mmol) to the refluxing reaction mixture at equal intervals. The solution was stirred and heated under reflux for 12 h. Dil. hydrochloric acid was added to the cooled reaction mixture to extract the protonated imidazole compounds into the aqueous layer and washed with light petroleum to remove Bu₃Ge-residues. The acidic aqueous layer was basified with sodium carbonate and aqueous sodium hydroxide (few drops) to pH 14. The basic solution was extracted with DCM (3 x 20 mL). The combined organic extracts were dried (MgSO₄) and evaporated to dryness. The residue was purified by column chromatography using neutral alumina as absorbent and light petroleum/ethyl acetate (1:1) as eluents to afford methyl 5,6-dihydroimidazo[2,1-a]isoquinoline-3-carboxylate 282 as a crystalline white solid (48 mg, 0.21 mmol, 54%), mp 122.0-124.9 °C. The TLC and ¹H-NMR and IR spectra were identical to an authentic sample. X-Ray crystallography confirmed the structure of methyl 5,6-dihydroimidazo[2,1-a]isoquinoline-3-carboxylate. The ¹H-NMR spectrum of the crude product showed the starting material (24 mg, 0.08 mmol, 20 %).

Methyl 1-[2-(2-bromophenyl)ethyl]-1H-indole-3-carboxylate 284
Methyl indole-3-carboxylate 283 (1.50 g, 8.6 mmol) was added slowly to a suspension of sodium hydride (0.31 g, 12.84 mol) in dry DMF (20 mL). The mixture was stirred for 1 h and 2-(2-bromophenyl)ethyl methanesulfonate 245 (3.57 g, 12.8 mmol) in DMF (10 mL) was added dropwise to the reaction mixture and it was stirred for 20 h. The reaction mixture was evaporated to dryness and the crude product was purified by column chromatography using neutral alumina as absorbent and toluene as eluent to afford methyl 1-[2-(2-bromophenyl)ethyl]-1H-indole-3-carboxylate 284 as white crystals (1.20 g, 3.4 mmol, 40 %), mp 111.7-112.8 °C; (Found: M+, 357.0371. C_{18}H_{16}BrNO_{2} requires 357.0364); ν_{max} (KBr)/cm^{-1} 2946, 1696, 1534, 1470, 1442, 1267, 1224, 1162, 1116, 1093, 1026 and 747; δ_{H} 3.27 (2 H, t, J = 7.6, CH_{2}), 3.90 (3 H, s, OCH_{3}), 4.40 (2 H, t, J = 7.6, NCH_{2}), 6.93 (1 H, dd, J = 7.2 and 2.0, 6-H), 7.08-7.16 (1 H, m, ArH), 7.25-7.30 (1 H, m, ArH), 7.40-7.42 (1 H, m, ArH), 7.57 (1 H, dd, J = 7.2 and 2.0, Ar 3-H), 7.70 (1 H, s, indole 2-H) and 8.15-8.19 (1 H, m, indole 4-H); δ_{C} 37.10 (CH_{2}), 46.60 (NCH_{2}), 51.00 (OCH_{3}), 107.17 (indole 3-C), 109.89 (ArCH), 121.76 (ArCH), 121.88 (ArCH), 122.81 (ArCH), 124.24 (Ar 2-C), 126.63 (indole 3a-C), 127.82 (ArCH), 128.88 (ArCH), 131.07 (ArCH), 133.08 (ArCH), 134.23 (ArCH), 136.36 (indole 7a-C), 136.84 (Ar 1-C) and 165.48 (C=O); m/z El 357 (M+, 14 %), 278 (8), 138 (100), 129 (10) and 77 (8).

Methyl 5,6-dihydroindolo[2,1-a]isoquinoline-12-carboxylate 285

![Diagram 285](image)

Tributylgermanium hydride (0.16 mL, 0.63 mmol) was added to methyl 1-[2-(2-bromophenyl)ethyl]-1H-indole-3-carboxylate 284 (0.15 g, 0.4 mmol) in toluene (55 mL), followed by portion wise addition of AIBN (150 mg, 0.91 mmol) to the refluxing reaction mixture at equal intervals. The solution was stirred and heated under reflux for 12 h. The reaction mixture was evaporated to dryness. The residue was purified by column chromatography using silica gel as absorbent, hexane/toluene (1:1) and toluene as eluents to afford methyl 5,6-dihydroindolo[2,1-a]isoquinoline-12-carboxylate 285 as a clear oil (80 mg, 0.29 mmol, 68%); (Found: M+, 277.1104. C_{18}H_{13}NO_{2} requires 277.1103); ν_{max} (neat)/cm^{-1} 2947, 1698, 1530, 1468, 1455, 1404, 1282, 1224,
1188, 1154, 1110, 1022, 768 and 747; δ_H 3.15 (2 H, t, J = 6.5, CH_2), 3.99 (3 H, s, OCH_3), 4.24 (2 H, t, J = 6.5, NCH_2), 7.25-7.40 (6 H, m, ArH), 8.19 (1 H, m, 11-H) and 8.53 (1 H, dd, J = 7.2 and 1.8, 1-H); δ_C 29.75 (5-C), 40.36 (6-C), 51.12 (OCH_3), 103.02 (12-C), 109.13 (indole 8-C), 122.04 (indole 11/10/9-C), 122.40 (indole 11/10/9-C), 122.91 (indole 11/10/9-C), 126.67 (ArCH), 127.66 (ArCH), 129.28 (ArCH), 129.73 (ArCH), 133.18 (11a-C), 134.76 (12b-C), 135.31 (4a-C), 138.05 (12a-C), 139.96 (7a-C) and 166.38 (C=O); m/z El 277 (M⁺, 100 %), 246 (92), 217 (38), 188 (30), 108 (14) and 77 (9).

Ethyl 1-[2-(2-bromophenyl)ethyl]-1H-pyrrole-2-carboxylate 287

Ethyl pyrrolo-2-carboxylate 286 (2.50 g, 18.0 mmol) was added slowly to a suspension of NaH (1.72 g, 71.7 mmol) in dry DMF (45 mL). The mixture was stirred and heated at 80 °C for 1 h and 2-(2-bromophenyl)ethyl methanesulphonate 245 (6.0 g, 21.59 mmol) in DMF (10 mL) was added drop wise to the reaction mixture. The mixture was stirred and heated at 80 °C overnight. The salts formed were removed by filtration on a celite bed and the solution was evaporated to dryness to yield a pale yellow oil. The oil was purified by column chromatography using silica gel as absorbent and toluene as eluent to afford ethyl 1-[2-(2-bromophenyl)ethyl]-1H-pyrrole-2-carboxylate 287 as a pale yellow oil (5.59 g, 17.4 mmol, 97 %); (Found: M⁺, 321.0367. C_{16}H_{16}BrNO_2 requires 321.0364); ν_max (neat)/cm⁻¹ 3109, 3056, 2979, 2869, 1694, 1567, 1531, 1470, 1415, 1325, 1241, 1171, 1101, 1077, 1027, 917, 738 and 657; δ_H 1.36 (3 H, t, J = 7.2, CH_3), 3.20 (2 H, q, J = 7.1, OCH_3), 4.52 (2 H, t, J = 7.3, NCH_2), 6.02 (1 H, dd, J = 3.9 and 2.5, pyrrole 4-H), 6.59 (1 H, dd, J = 2.5 and 1.9, pyrrole 5-H), 6.95 (1 H, dd, J = 3.9 and 1.9, pyrrole 3-H), 7.02-7.16 (3 H, m, ArH) and 7.53 (1 H, dd, J = 7.9 and 1.2, Ar 3-H); δ_C 14.48 (CH_3), 37.23 (CH_2), 48.73 (NCH_3), 59.78 (OCH_3), 107.76 (pyrrole 4-C), 118.23 (pyrrole 3-C), 121.63 (pyrrole 2-C), 124.45 (Ar 2-C), 126.75 (ArCH), 127.53 (ArCH), 128.30 (pyrrole 5-C), 131.27
Tributylgermanium hydride (0.19 mL, 0.8 mmol) was added to ethyl 1-[2-(2-bromophenyl)ethyl]-1H-pyrrole-2-carboxylate 287 (0.16 g, 0.5 mmol) in toluene (40 mL), followed by portion wise addition of AIBN (246 mg, 1.5 mmol) to the refluxing reaction mixture at equal intervals. The solution was stirred and heated under reflux for 12 h. The reaction mixture was evaporated to dryness. The residue was purified by column chromatography using silica gel as absorbent, hexane/toluene (1:1) as eluents to afford ethyl 5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate 288 as a clear oil (99 mg, 0.41 mmol, 82%); (Found: M+, 241.1103. C_{19}H_{15}NO_2 requires 241.1103); \nu_{\text{max}}\ (\text{neat})/\text{cm}^{-1} 2928, 1694, 1489, 1446, 1260, 1224, 1150, 1105, 1068 and 749; \delta_{\text{H}} 1.37 (3 \text{ H, } t, J = 7.2, \text{ CH}_3), 3.08 (2 \text{ H, } t, J = 6.8, \text{ CH}_2), 4.31 (2 \text{ H, } q, J = 7.0, \text{ OCH}_2), 4.64 (2 \text{ H, } t, J = 6.8, \text{ NCH}_2), 6.52 (1 \text{ H, } d, J = 4.0, \text{ pyrrole 1-H}), 7.02 (1 \text{ H, } d, J = 4.0, \text{ pyrrole 2-H}), 7.20-7.28 (3 \text{ H, } m, \text{ ArH}) and 7.56 (1 \text{ H, } d, J = 7.6, \text{ Ar 10-H}); \delta_{\text{C}} 14.49 (\text{ CH}_3), 28.94 (\text{ CH}_2), 42.18 (\text{ NCH}_2), 59.85 (\text{ OCH}_2), 104.40 (\text{ pyrrole 1-C}), 113.71 (\text{ pyrrole 3-C/10b-C}), 118.22 (\text{ pyrrole 2-C}), 122.12 (\text{ pyrrole 3-C/10b-C}), 123.62 (\text{ ArCH}), 127.15 (\text{ ArCH}), 127.39 (\text{ ArCH}), 128.39 (\text{ ArCH}), 131.74 (\text{ Ar 10a-C}), 136.04 (\text{ Ar 6a-C}) and 161.43 (\text{ C=O}); m/z \text{ El 241 (M+, 100 %), 213 (39), 196 (28), 168 (32), 139 (11), 115 (11) and 77 (3).}
Ethyl 1-[2-(2-bromophenyl)ethyl]-3-(trifluoromethyl)-1H-pyrazole-4-carboxylate 291

Ethyl 3-(trifluoromethyl)pyrazole-4-carboxylate 290 (2.0 g, 9.6 mmol) was added slowly to a suspension of NaH (0.96 g, 40 mmol) in dry DMF (30 mL). The mixture was stirred and heated at 80 °C for 1 h and 2-(2-bromophenyl)ethyl methanesulphonate 245 (5.34 g, 19.2 mmol) in DMF (5 mL) was added drop wise to the reaction mixture. The mixture was heated at 80 °C overnight. The salts formed were removed by filtration on a celite bed and the solution was evaporated to dryness to yield a pale yellow oil. The oil was purified by column chromatography using silica gel as absorbent and light petroleum/ethyl acetate (2:1) and (1:1) as eluents to afford ethyl 1-[2-(2-bromophenyl)ethyl]-3-(trifluoromethyl)-1H-pyrazole-4-carboxylate 291 as a pale yellow oil (3.69 g, 9.45 mmol, 85 %); (Found: MH+, 391.0269. C_{15}H_{14}BrF_{3}N_{2}O_{2} requires 391.0269); ν_{max} (neat)/cm^{-1} 3135, 3070, 2984, 1732, 1543, 1474, 1443, 1368, 1303, 1223, 1143, 1054, 847, 776 and 752; δ_{ii} 1.33 (3 H, t, J = 7.2, CH₃), 3.32 (2 H, t, J = 7.2, CH₂), 4.30 (2 H, q, J = 7.2, OCH₂), 4.42 (2 H, t, J = 7.2, NCH₂), 6.99 (1 H, dd, J = 7.4 and 1.8, ArH), 7.12 (1 H, ddd, J = 7.4, 7.4 and 1.2, ArH), 7.20 (1 H, ddd, J = 7.6, 7.6 and 1.6, ArH), 7.58 (1 H, dd, J = 8.0 and 1.2, ArH) and 7.74 (1 H, s, pyrazole 5-H); δ_{c} 14.08 (CH₃), 36.78 (CH₂), 52.36 (NCH₂), 60.88 (OCH₂), 112.97 (CF₃), 119.07 (pyrazole 4-C), 121.75 (pyrazole 3-C), 124.26 (Ar 2-C), 127.91 (ArCH), 129.08 (ArCH), 131.08 (ArCH), 133.16 (ArCH), 135.80 (pyrazole 5-C), 136.07 (Ar 1-C) and 160.80 (C=O); m/z El 391 (M⁺, 1 %), 345 (10), 311 (100), 283 (29), 265 (18), 182(100), 169 (48), 103 (78) and 77 (51).
Ethyl 2-(trifluoromethyl)-5,6-dihydropyrazolo[5,1-a]isoquinoline-1-carboxylate 293

![Chemical structure of ethyl 2-(trifluoromethyl)-5,6-dihydropyrazolo[5,1-a]isoquinoline-1-carboxylate 293](image)

Tributylgermanium hydride (0.21 mL, 0.8 mmol) was added to ethyl 1-[2-(2-bromophenyl)ethyl]-3-(trifluoromethyl)-1H-pyrazole-4-carboxylate 291 (0.16 g, 0.4 mmol) in toluene (35 mL), followed by portion wise addition of AIBN (167 mg, 1.02 mmol) to the refluxing reaction mixture at equal intervals. The solution was stirred and heated under reflux for 12 h. The reaction mixture was evaporated to dryness. The residue was purified by column chromatography using silica gel as absorbent, hexane/toluene (1:1) as eluents to afford ethyl 2-(trifluoromethyl)-5,6-dihydropyrazolo[5,1-a]isoquinoline-1-carboxylate 293 as a clear oil (72 mg, 0.23 mmol, 57%); (Found: M⁺, 310.0926. C₁₅H₁₃F₃N₂O₂ requires 310.0929); νₚₐₛₑₓ (neat)/cm⁻¹ 2928, 2369, 1717, 1473, 1199, 1142 and 1042; δₜₚ 1.39 (3 H, t, J = 7.2, CH₃), 3.19 (2 H, t, J = 6.8, 6-H), 4.36-4.42 (4 H, m, 5-H and OCH₂), 7.30-7.40 (3 H, m, ArH) and 8.30-8.32 (1 H, m, 10-H); δₑ 13.82 (CH₃), 29.31 (6-C), 47.15 (5-C), 61.37 (OCH₂), 109.00 (CF₃), 119.46 (pyrazole 1-C), 122.13 (pyrazole 2-C), 125.00 (Ar 10a-C), 127.60 (ArCH), 127.83 (ArCH), 128.07 (ArCH), 130.23 (10-C), 133.34 (6a-C), 141.54 (10b-C) and 162.56 (C=O); m/z El 310 (M⁺, 43 %), 282 (10), 265 (100), 238 (14), 140 (5), 104(38), 91 (10), and 77 (6).

1-[2-(2-Bromophenyl)ethyl]-1H-pyrrole-2-carboxylic acid 294

![Chemical structure of 1-[2-(2-Bromophenyl)ethyl]-1H-pyrrole-2-carboxylic acid 294](image)

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Ethyl 1-[2-(2-bromophenyl)ethyl]-1H-pyrrole-2-carboxylate (0.1 g, 0.31 mmol) was dissolved in ethanol (2.5 mL) followed by addition of aqueous sodium hydroxide (2 M, 5.0 mL). The reaction mixture was heated under reflux for 8 h and followed by TLC. Then the reaction mixture was cooled and washed with diethyl ether (3 x 20 mL). The aqueous layer was acidified to pH 3 with hydrochloric acid and thoroughly extracted with dichloromethane (3 x 30 mL). The organic layers were washed with water, dried (MgSO₄) and evaporated to dryness to afford 1-[2-(2-bromophenyl)ethyl]-1H-pyrrole-2-carboxylic acid (89 mg, 0.30 mmol, 98%), mp 158-163 °C; (Found: M⁺, 293.0057. C₁₉H₁₂BrN₂O₂ requires 293.0051); νmax (KBr)/cm⁻¹ 3448, 2925, 2629, 2371, 1672, 1534, 1438, 1332, 1264, 1116, 1027, 924 and 741; δH 3.23 (2 H, t, J = 7.2, CH₂), 4.56 (2 H, t, J = 7.2, NCH₂), 6.08 (1 H, dd, J = 4.0 and 2.4, pyrrole 4-H), 6.66 (1 H, dd, J = 4.0 and 2.4, pyrrole 5-H), 7.01 (1 H, dd, J = 7.6 and 2.0, Ar 6-H), 7.09 (1 H, ddd, J = 7.6, 7.6 and 1.7, ArH), 7.11 (1 H, dd, J = 4.0 and 2.0, pyrrole 3-H), 7.19 (1 H, ddd, J = 7.6, 7.6 and 1.2, ArH) and 7.55 (1 H, dd, J = 7.6 and 1.2, Ar 3-H); δc 38.22 (CH₂), 48.93 (NCH₂), 108.34 (pyrrole 4-C), 120.45 (pyrrole 2-C), 120.49 (pyrrole 3-C), 124.49 (Ar 2-C), 127.60 (ArCH), 128.41 (ArCH), 130.30 (pyrrole 5-C), 131.27 (ArCH), 132.76 (ArCH), 137.59 (Ar 1-C) and 164.96 (C=O); m/z El 293 (M⁺, 1 %), 265 (4), 214 (100), 170 (60), 124 (87), 94 (46) and 77 (23).

1-[2-(2-bromophenyl)ethyl]-3-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (1.20 g, 3.1 mmol) was dissolved in ethanol (10 mL) followed by addition of aqueous sodium hydroxide (2 M, 15 mL). The reaction mixture was heated under reflux for 8 h and followed by TLC. Then the reaction mixture was cooled and washed with ethyl acetate (3 x 20 mL). The aqueous layer was acidified to pH 3 with hydrochloric acid and thoroughly extracted with dichloromethane (3 x 30 mL).
mL). The organic layers were washed with water, dried (MgSO₄) and evaporated to dryness to afford 1-[2-(2-bromophenyl)ethyl]-3-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid 296 as light brown crystals (1.10 g, 3.0 mmol, 97%); (Found: MH⁺, 362.9956. C₁₃H₁₀BrF₃N₂O₂ requires 362.9961); νₘₐₓ (KBr)/cm⁻¹ 3300, 2953, 2683, 2600, 1697, 1547, 1499, 1438, 1309, 1236, 1191, 1145, 1048, 945 and 754; δH 3.34 (2 H, t, J = 7.2, CH₂), 4.45 (2 H, t, J = 7.2, NCH₂), 6.97 (1 H, dd, J = 7.6 and 1.6, Ar 6-H), 7.12-7.22 (2 H, m, ArH), 7.15 (1 H, ddd, J = 7.6, 7.6 and 1.6, Ar 4-H), 7.20 (1 H, ddd, J = 7.6, 7.6 and 1.6, Ar 5-H), 7.58(1 H, dd, J = 7.6 and 1.6, Ar 3-H) and 7.75 (1 H, s, pyrazole 5-H); δC 36.72 (CH₂), 52.67 (NCH₂), 111.63 (CF₃), 118.82 (pyrazole 4-C), 121.50 (pyrazole 3-C), 124.22 (Ar 2-C), 127.92 (ArCH), 129.18 (ArCH), 131.06 (ArCH), 133.21 (ArCH), 135.91 (Ar 1-C), 136.76 (pyrazole 5-C) and 165.57 (C=O); m/z El 283 (95%), 182 (100), 169 (60), 103 (62), 90 (52), 77(45) and 69 (32).

Synthesis of solid-supported pyrrole moiety 295

To a portion of Wang resin (0.25 g, 0.43 mmol) was added DCM (8.0 mL). The resin was left to swell for 1/2 h under N₂. 1-[2-(2-Bromophenyl)ethyl]-1H-pyrrole-2-carboxylic acid 294 (0.25 g, 0.9 mmol) in DMF (8.0 mL), DMAP (0.16 g, 1.3 mmol) and DIC (0.4 mL, 2.6 mmol) were added sequentially. The suspension was shaken for 48 h at rt. The reaction mixture was filtered and washed with DCM, MeOH, DMF, MeOH and DCM (20 mL each). The resin was dried at 40 °C under vacuum for 24 h. The coupling reaction was repeated with equimolar reagents. IR νₘₐₓ (KBr)/cm⁻¹ 3455, 3042, 2916, 2366, 1702, 1597, 1517, 1449, 1222, 1084, 1010, 751 and 683.
Synthesis of solid-supported pyrazole moiety 297

To a portion of Wang resin (0.40 g, 0.7 mmol) was added DCM (8.0 mL). The resin was left to swell for 1/2 h under N₂. 1-[2-(2-Bromophenyl)ethyl]-3-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid 296 (0.62 g, 1.7 mmol) in DMF (8.0 mL), DMAP (0.25 g, 2.1 mmol) and DIC (0.64 mL, 4.1 mmol) were added sequentially. The suspension was shaken for 48 h at rt. The reaction mixture was filtered and washed with DCM, MeOH, DMF, MeOH and DCM (20 mL each). The resin was dried at 40 °C under vacuum for 24 h. The coupling reaction was repeated with equimolar reagents. IR \( \nu_{\text{max}} \) (KBr)/\( cm^{-1} \) 3458, 3026, 2922, 2370, 1723, 1602, 1508, 1370, 1290, 1211, 1138, 1037, 815, 747 and 693.

Radical cyclisations of resin-bound pyrazole adduct 297

Method A (thermal method, Bu₃GeH and toluene)
To refluxing resin-bound pyrazole 297 (140 mg, 0.11 mmol) in toluene (10 mL) was added Bu₃GeH (0.55 mL, 2.1 mmol) followed by portion wise addition of AIBN (0.25 g, 1.5 mmol) to the refluxing
reaction mixture at equal intervals. The reaction mixture was heated at reflux for 30 h. Then the reaction mixture was cooled to room temperature, filtered and washed with toluene, DCM and MeOH (20 mL each). The resin was dried at 40 °C under vacuum for 24 h. The tethered products on the resin were cleaved using TFA/DCM (9/1) and a crystalline material was recovered (44 mg). The LC-MS of the cleaved sample from the resin confirmed the presence of cyclised adduct 2-(trifluoromethyl)-5,6-dihydropyrazolo[5,1-a]isoquinoline-1-carboxylic acid 298 and the starting material 296. The 1H NMR spectrum of the cleaved sample was very clean and showed the cyclised product 298 (20%) and the unreacted starting material 296 (70%)(1:3.5). The separation of these compounds by column chromatography due to co-elution was unsuccessful.

The 1H NMR data for the cyclised product 298 has been recorded; \( \delta_{\text{H}} \) 3.20 (2 H, t, \( J = 6.8, 6\)-H), 4.40 (2 H, t, \( J = 6.8, 5\)-H), 7.16-7.34 (3 H, m, ArH) and 8.33-8.35 (1 H, m, 10-H); \( \delta_{\text{C}} \) 29.35 (pyrazole 6-C), 47.25 (pyrazole 5-C), 108.00 (CF\(_3\)), 119.25 (pyrazole 1-C), 121.94 (pyrazole 2-C), 124.75 (Ar 10a-C), 127.71 (ArCH), 128.09 (ArCH), 128.36 (ArCH), 130.55 (Ar 10-C), 133.68 (Ar 6a-C), 142.73 (pyrazole 10b-C) and 166.91 (C=O).

**Method B (thermal method, TTMSS and toluene)**

TTMSS (1.3 mL, 4.2 mmol) and AIBN (0.20 g, 1.2 mmol) were added to refluxing resin-bound pyrazole moiety 297 (111 mg, 0.09 mmol) in toluene (15 mL) at equal intervals. The reaction mixture was heated at reflux for 30 h. Then the reaction mixture was cooled to room temperature, filtered and washed with toluene, DCM and MeOH (20 mL each). The resin was dried at 40 °C under vacuum for 24 h. The tethered products on the resin were cleaved using TFA/DCM (9/1) and red brown oil was recovered (30 mg). The LC-MS of the cleaved sample from the resin confirmed the presence of cyclised adduct 2-(trifluoromethyl)-5,6-dihydropyrazolo[5,1-a]isoquinoline-1-carboxylic acid 298 and the reduced product 299. The 1H NMR spectrum of the cleaved sample was very clean and showed the cyclised product 298 (53%) and the reduced product 299 (27%). The separation of these compounds by column chromatography due to co-elution was unsuccessful.

The 1H NMR data for the cyclised product 298 has been recorded; \( \delta_{\text{H}} \) 3.20 (2 H, t, \( J = 6.8, 6\)-H), 4.40 (2 H, t, \( J = 6.8, 5\)-H), 7.16-7.34 (3 H, m, ArH) and 8.33-8.35 (1 H, m, 10-H); \( \delta_{\text{C}} \) 29.35 (pyrazole 6-C), 47.25 (pyrazole 5-C), 108.00 (CF\(_3\)), 119.25 (pyrazole 1-C), 121.94 (pyrazole 2-C), 124.75 (Ar 10a-C), 127.71 (ArCH), 128.09 (ArCH), 128.36 (ArCH), 130.55 (Ar 10-C), 133.68 (Ar 6a-C), 142.73 (pyrazole 10b-C) and 166.91 (C=O). The 1H NMR data for the reduced product 299
has also been recorded; \( \delta_{H} 3.20 \) (2 H, t, \( J = 6.8 \), CH\(_2\)), 4.40 (2 H, m, NCH\(_2\)), 7.08 (1 H, d, \( J = 7.6 \), ArH), 7.16-7.34 (1 H, m, ArH), 7.39-7.42 (3 H, m, ArH) and 7.75 (1 H, s, 5-H); \( \delta_{C} 36.25 \) (CH\(_2\)), 54.77 (NCH\(_2\)), 111.70 (CF\(_3\)), 118.90 (pyrazole 4-C), 121.58 (pyrazole 3-C), 127.27 (ArCH), 128.60 (ArCH), 128.94 (ArCH), 136.67 (pyrazole 5-C) and 165.37 (C=O).
REFERENCES


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63 W. R. S. Barton and W. R. Bowman, unpublished results.


84 S. Krintel and W. R. Bowman, unpublished results.


112 Patent; Rhein-Chemie; DE 1948795; 1971; *Chem. Abstr.*, EN 75; 129812.
**APPENDIX: X-RAY CRYSTALLOGRAPHY DATA**

Table 1: Crystal data and structure refinement for methyl 5,6-dihydroimidazo[5,1-a]isoquinoline-1-carboxylate

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Table 2. Atomic coordinates and equivalent isotropic displacement parameters (Å\(^2\))
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Table 3. Bond lengths [Å] and angles [°] for rbl.

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<th>Length [Å]</th>
<th>Angle [°]</th>
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<td>C(3)-N(4)</td>
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<td>1.463(4)</td>
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<td>C(6)-C(6A)</td>
<td>1.511(4)</td>
<td>C(6A)-C(7)</td>
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<td>C(6A)-C(10A)</td>
<td>1.409(4)</td>
<td>C(7)-C(8)</td>
</tr>
<tr>
<td>C(8)-C(9)</td>
<td>1.386(5)</td>
<td>C(9)-C(10)</td>
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<tr>
<td>C(10)-C(10A)</td>
<td>1.396(4)</td>
<td>C(10A)-C(10B)</td>
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<tr>
<td>O(13)-C(14)</td>
<td>1.445(4)</td>
<td></td>
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Table 4. Anisotropic displacement parameters (Å²) for rb1. The anisotropic displacement factor exponent takes the form: $-2\pi h^2\alpha^2U_{11}^* + ...
+ 2h\kappa a^* b^* U_{12}^*
$

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<th></th>
<th>$U_{11}$</th>
<th>$U_{22}$</th>
<th>$U_{33}$</th>
<th>$U_{12}$</th>
<th>$U_{13}$</th>
<th>$U_{23}$</th>
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<td>C(1)</td>
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<tr>
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<tr>
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<td>0.0038(11)</td>
<td>0.0018(10)</td>
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<tr>
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<td>0.0058(9)</td>
<td>0.0031(9)</td>
<td>0.0029(8)</td>
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<tr>
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<td>0.0139(13)</td>
<td>0.0279(15)</td>
<td>0.0042(11)</td>
<td>0.0035(12)</td>
<td>0.0044(11)</td>
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<tr>
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<td>0.0188(14)</td>
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<td>0.0003(11)</td>
<td>0.0003(11)</td>
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<tr>
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<td>0.0238(14)</td>
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<td>0.0044(10)</td>
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<tr>
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<td>0.0270(15)</td>
<td>0.0222(14)</td>
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<td>0.0020(11)</td>
<td>0.0046(12)</td>
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<tr>
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<td>0.0339(17)</td>
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<td>0.0068(11)</td>
<td>0.0059(12)</td>
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<tr>
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<td>0.0229(14)</td>
<td>0.0314(16)</td>
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<td>0.0034(11)</td>
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<tr>
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<td>0.0207(14)</td>
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<td>0.0054(10)</td>
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<tr>
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<td>0.0197(13)</td>
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<td>0.0079(10)</td>
<td>0.0039(10)</td>
<td>0.0050(9)</td>
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<tr>
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<td>0.0268(14)</td>
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<tr>
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<td>0.0055(10)</td>
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<tr>
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<td>0.0300(11)</td>
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<tr>
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Table 5. Hydrogen coordinates and isotropic displacement parameters (Å²) for rb1.

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<th>U</th>
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<tr>
<td>H(5B)</td>
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<tr>
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<td>H(7)</td>
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Table 6. Torsion angles [°] for rbl.

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<tr>
<td>C(1)-N(2)-C(3)-N(4)</td>
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</tr>
<tr>
<td>N(2)-C(3)-N(4)-C(5)</td>
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</tr>
<tr>
<td>C(10B)-N(4)-C(5)-C(6)</td>
<td>-37.8(4)</td>
</tr>
<tr>
<td>C(5)-C(6)-C(6A)-C(7)</td>
<td>144.4(3)</td>
</tr>
<tr>
<td>C(10A)-C(6A)-C(7)-C(8)</td>
<td>1.2(4)</td>
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<td>C(6A)-C(7)-C(8)-C(9)</td>
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<td>C(8)-C(9)-C(10)-C(10A)</td>
<td>-1.0(4)</td>
</tr>
<tr>
<td>C(9)-C(10)-C(10A)-C(10B)</td>
<td>-177.2(2)</td>
</tr>
<tr>
<td>C(6)-C(6A)-C(10A)-C(10)</td>
<td>177.6(2)</td>
</tr>
<tr>
<td>C(6)-C(6A)-C(10A)-C(10B)</td>
<td>-2.1(4)</td>
</tr>
<tr>
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<td>176.4(2)</td>
</tr>
<tr>
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</tr>
<tr>
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</tr>
<tr>
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<td>C(10B)-C(1)-C(11)-O(13)</td>
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</tr>
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<td>O(12)-C(11)-O(13)-C(14)</td>
<td>2.8(4)</td>
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Table 1: Crystal data and structure refinement for methyl 5,6-dihydroimidazo[2,1-a]isoquinoline-3-carboxylate 282

<table>
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<th>Property</th>
<th>Value</th>
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<tr>
<td>Wavelength</td>
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<td>Space group</td>
<td>P2(1)/c</td>
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<tr>
<td>b</td>
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<tr>
<td>c</td>
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<tr>
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<tr>
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<tr>
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<tr>
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<tr>
<td>Refinement method</td>
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<td>Data / restraints / parameters</td>
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<tr>
<td>R indices (all data)</td>
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</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.177 and -0.213 e.Å⁻³</td>
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Table 2. Atomic coordinates ($\times 10^3$) and equivalent isotropic displacement parameters ($\text{Å}^2 \times 10^3$). $U(\text{eq})$ is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

<table>
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Table 3. Bond lengths [Å] and angles [°].

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Table 4. Anisotropic displacement parameters (Å² x 10³). The anisotropic displacement factor exponent takes the form: 

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Proton NMR spectrum of CDCl3-swollen gel

Pulse Sequence: s2pul

Amino Merrifield resin
Proton NMR spectrum of CDCl3-swollen gel

Wang resin
Proton NMR spectrum of CDC13-swollen gel

Pulse Sequence: s2pu1

Rink resin
Resin-bound benzoimidazole derivative 207

![Resin-bound benzoimidazole derivative 207](image_url)
Proton NMR spectrum of Cbets-SepTent gel

Pulse Sequence: s2pul

![Chemical Structure: Cbets-SepTent](image)
Ex Fluka (o8564)
Proton NMR spectrum of CDC13-swollen gel

Pulse Sequence: s2pu1
Pulse Sequence: s2pul

Proton NMR Spectrum of CbCl3-solution gel

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