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Radical aromatic cyclisation and substitution reactions

By

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A thesis submitted in partial fulfillment of the requirement for the degree of Doctor of Philosophy in Chemistry

University of Warwick, Department of Chemistry

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| Abbreviation | Definition |
|--------------|------------|
| [O]          | Oxidation  |
| AIBN         | Azobisisobutyrylnitrile |
| Anh.         | Anhydrous |
| App.         | Apparent (doublet, etc) |
| Ar           | Aryl group |
| ATRC         | Atom Transfer Radical Cyclisation |
| bd           | Broad doublet |
| BMIM BF$_4$  | 1-Butyl-3-methylimidazolium tetrafluoroborate |
| Bn           | Benzyl group |
| bs           | Broad singlet |
| CI           | Chemical Ionization |
| COSY         | Correlation Spectroscopy |
| CV           | Cyclic Voltammetry |
| D            | Deuterium atom |
| d            | Doublet |
| d            | Doublet (in $^{13}$C NMR (DEPT)-a methide carbon = CH) |
| dd           | Doublet of doublets |
| dt           | Doublet of triplets |
| DCE          | Dichloroethane |
| DCM          | Dichloromethane |
| DEPT         | Distortionless Enhancement through Polarization Transfer |
| DLP          | Dilauroyl peroxide |
| Acronym   | Description                                      |
|-----------|--------------------------------------------------|
| DPDC      | Di-isopropyl peroxydicarbonate                    |
| $dr$      | Diastereoisomeric ratio                          |
| $E^+$     | Electrophile                                     |
| EI        | Electron Impact                                  |
| ESI       | Electrospray Ionisation                          |
| FAB       | Fast Atom Bombardment                            |
| GLC       | Gas Liquid Chromatography                        |
| HETCOR    | Heteronuclear Correlated Spectroscopy            |
| HMBC      | Heteronuclear Multiple Bond Connectivity          |
| HOMO      | Higher Occupied Molecular Orbital                |
| HPLC      | High Performance Liquid Chromatography           |
| HRMS      | High Resolution Mass Spectrometry               |
| $hv$      | Irradiation by light                             |
| ICP-Emission | Inductively Coupled Plasma-Emission             |
| ICP-MS    | Inductively Coupled Plasma-Mass Spectrometry     |
| INADEQUATE | Incredible Natural Abundance Double Quantum Transfer Experiment |
| INEPT     | Insensitive Nuclei Enhancement by Population Transfer |
| $J$       | Coupling constant in hertz                       |
| L         | Copper-Ligand                                    |
| LSIMS     | Liquid Secondary Ion Mass Spectrometry           |
| LRMS      | Low Resolution Mass Spectrometry                |
| LUMO      | Lowest Unoccupied Molecular Orbital              |
| $m$       | Multiplet                                        |
| Abbreviation | Description |
|--------------|-------------|
| m/z          | Mass/charge ratio |
| MPLC         | Medium Pressure Liquid Chromatography |
| NCS          | N-Chlorosuccinimide |
| NOE          | Nuclear Overhauser Effect |
| Nu⁻          | Nucleophile |
| oct.         | Octet |
| q            | Quartet |
| q            | Quartet (in $^{13}$C NMR- a methyl carbon = CH$_3$) |
| quin.        | Quintet |
| R            | General alkyl group |
| Rf           | Retention factor |
| RMM          | Relative Molecular Mass |
| rt           | Room Temperature |
| S            | Sinister (Latin for left) |
| s            | Singlet |
| s            | Singlet (in $^{13}$C NMR- a quaternary carbon = C) |
| SET          | Single Electron Transfer |
| SOMO         | Singly Occupied Molecular Orbital |
| Spt.         | Septet |
| Sext.        | Sextet |
| t            | Triplet |
| t            | Triplet (in $^{13}$C NMR- a methylene carbon = CH$_2$) |
| t.t          | triplet of triplets |
| Abbreviation | Description |
|--------------|-------------|
| TBTH         | Tributyltin hydride |
| TEA          | Triethylamine |
| TPA          | Tris (2-pyridylmethyl)amine |
| TTMSS        | Tris (trimethylsilyl)silane |
| WAS          | Warwick Analytical Service |
| Z            | Zusammen (German for together) Notation used in alkenes |
| Δ            | Chemical Shift in Parts Per Million |
0.3 Acknowledgements

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0.4 Declaration

The work described in this thesis is the original work of the author, except where acknowledgement has been made to results and ideas previously reported. The work was carried out in the department of chemistry, University of Warwick between August 1st 2003 and September 4th 2006 and has not been previously submitted for a degree at any other institution.
0.5 Abstract

This dissertation is divided into five chapters. Chapter One consists of an introduction to radical cyclisation and rearrangement reactions. Chapter Two investigates the reactions of substituted arylsulfonamides 278a-l with copper bromide and an amine ligand-TPA. This reaction involves an alkyl radical generated from the copper (I) bromide/TPA complex, which can then undergo a 1,5- ipso attack onto the sulfonamide leading to a cyclohexadienyl radical intermediate. Re-aromatisation and extrusion of sulfur dioxide leads to an amidyl radical intermediate. This can undergo either cyclisation back onto the aromatic ring to give the 6-substituted oxindole 336, or reduction from H-atom abstraction by the solvent leading to rearranged amides. A minor product identified as a 5-substituted oxindole 333 may be formed from direct radical cyclisation onto the sulfonamide followed by extrusion of sulfur dioxide. An unambiguous synthesis of 333 was obtained through the Stollé method in order to rigorously identify this product. For completion, the rearranged amide 280e was also unambiguously synthesised from known literature sources. It has been shown that the selectivity towards either rearrangement or cyclisation is dependent upon the solvent used and temperature. For example, toluene induces excellent selectivity towards cyclisation (to furnish oxindoles), while using dichloromethane (DCM) induces a greater selectivity towards rearranged amides. Chapter Three explores the effects of varying the alkyl chain length on the nitrogen atom on selectivity, while keeping both the aryl group and initiator the same. It has been shown that selectivity towards the rearrangement (or decrease in cyclisation) occurred when the alkyl chain was increased from N-butyl to N-dodecyl. In addition a similar solvent effect on selectivity was observed as discussed in Chapter 3, notably relatively more rearranged amide was produced with DCM and oxindoles with toluene.
Chapter four involves investigating the copper-mediated radical cyclisation of halo-amides to give oxindoles directly. The final chapter consists of the experimental.
Chapter One

1.0 Introduction to radical chemistry

Radicals are defined as chemical species that contain one or more unpaired electrons. Amongst the several types of radicals known to the chemist, it is the carbon-centred radical, which has received the most attention. This has been particularly the case in reactions involving the formation of new C—C bonds, such as polymerisation reactions,\(^1\) and the construction of cyclic compounds.\(^2-4\) The use of nitrogen,\(^5\) phosphorus\(^6\) or sulfur-based\(^7-8\) radicals are less common in synthesis, yet there has been extensive research in these areas.

The majority of carbon based alkyl radicals (eg. •CH\(_3\)) are trigonal planar in structure (similar to carbocations), although some exceptions are possible. When hydrogen atoms on a methyl radical are replaced by an \(\sigma\)-attractor, \(\pi\)-donor component or group (halogen, OH, NH\(_2\)) this leads to pyramidalization of the radical. In the case of •CF\(_3\), this results in a tetrahedral structure.\(^9\) The \(sp^2\)-hybridized atom is electron deficient, and as such, the stability of the radical is increased with substitution of alkyl groups, hence tertiary alkyl radicals are stabilized more than secondary ones. Resonance is also a contributing factor in radical stability.\(^2\)

1.1 Classes of radical reactions

Radicals can undergo a range of reactions, for example abstraction (eq. \(D\)^10\), intermolecular addition (eq. \(2\)^11 intramolecular addition (eq. \(2\)^12 rearrangement (eq. \(4\)^13 and radical-radical reaction (eq. \(5\)^14 as outlined in Scheme 1.
1.2 Radical abstraction reactions

An early example of radical abstraction reactions were those involving the reaction between an alkyl radical and an alkyl halide. Much work was done during the 1960’s on these types of reactions. King and Swinbourne\textsuperscript{15} investigated the abstraction of halogen atoms by methyl radicals. Thermal homolytic dissociation of \( \text{di-}\text{tert}-\text{butylperoxide} \) \( \text{1} \) gives two molecules of \( \text{tert}-\text{butyl peroxide radical} \) \( \text{2} \).\textsuperscript{16} The \( \text{tert}-\text{butyl peroxide radical} \) \( \text{2} \) formed can then undergo a \( \beta \)-fragmentation to give a methyl radical \( \text{3} \) and acetone. A high temperature (>150\(^\circ\text{C}\)) is required to produce the methyl radical \( \text{3} \), since the activation energy is between 6-8 kcal/mol higher for \( \beta \)-fragmentation than that of hydrogen abstraction by \( \text{tert}-\text{butyl peroxide radical} \) \( \text{2} \). Reaction of a methyl radical \( \text{3} \) and ethyl chloride \( \text{4} \) yield both methane \( \text{5} \) and the 1-chloroethyl radical \( \text{6} \) as shown in Scheme 2.
Whilst the majority of reactions involve abstraction of hydrogen atoms from alkanes, it is also possible to get abstraction of other atoms attached to an alkyl group. These include radical leaving groups such as PhS, PhSe, Barton esters, and xanthates (which are popular ways to achieve de-oxygenation of alcohols). Abstraction of atoms other than hydrogen (e.g. halogens) have also been reported. In this case tributyltin radical abstracts an iodine atom from iodobenzene to give an aryl radical and tributyltin iodide as depicted inScheme 3.

### Scheme 3 Halogen abstraction from an aromatic ring

#### 1.3 Radical addition reactions

Radicals can add to unsaturated substrates, (such as alkenes, alkynes and aromatic groups) in an inter- and intramolecular fashion.

#### 1.3.1 Intermolecular addition

In 1933 a series of reactions by Kharasch, McCabe and Mayo on the addition of hydrogen bromide to propylene were studied. Homolytic dissociation of dibenzoyl peroxide at room temperature gave two molecules of benzoyl peroxide radical. In the presence of a benzoyl peroxide radical, rapid abstraction of the hydrogen...
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atom from hydrogen bromide 11 led to the bromine radical, which could then add to propylene 12. This was followed by formation of a secondary alkyl radical intermediate 13, which underwent hydrogen atom transfer to furnish the anti-Markovikov product 1-bromopropane 14 in 87% at room temperature, as illustrated in Scheme 4. The regiochemistry of addition in the presence of anti-oxidants was reversed and the Markovnikov product, (iso-propyl bromide, not shown) formed via an ionic (electrophilic) addition resulted.

![Scheme 4 Radical bromination of an alkene](image)

1.4 Intramolecular addition reactions (cyclisations)\textsuperscript{23-26}

With the exception of radical polymerisation reactions, intramolecular radical reactions have probably received the most attention. Baldwin’s rules\textsuperscript{27} generally govern the regiochemical outcomes of these cyclisations, hence, the 5-hexenyl radical 15 preferentially cyclises to give the 5-exo product 16 via a chair-like transition state.\textsuperscript{28} The reactions are normally under kinetic control and as such the major product is the five membered ring in the ratio of 98:2 (16:17) at room temperature for the all carbon case as illustrated in Scheme 5. Cyclisation onto alkynes\textsuperscript{29} and aromatics are also possible (see Section 2.0).
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Scheme 5  5-Hexenyl radical cyclisation

1.5 Radical rearrangements

A range of radical rearrangement (or migration) reactions has been reported where either atoms or groups of atoms, can undergo migration. A classic example is the 1,2-phenyl migration\(^\text{30}\) of radical 18 (Scheme 6). The migration is thought to occur via 3-ipso-exo cyclisation onto the aromatic ring to furnish the spirocyclised radical intermediate 19 followed by reversible ring opening via cleavage of the alternative C/C bond to yield the iso-butyl benzyl radical 20.

Scheme 6  Possible radical rearrangement reaction

1.5.1 Group transfer reactions

Urry and Kharasch explored neophyl rearrangements in 1944.\(^\text{31}\) These are 1,2-migrations\(^\text{32}\) typified by the reaction shown in Scheme 7. Groups that undergo this type of migration include nitrates\(^\text{33}\) 22, phosphate,\(^\text{34}\) ester\(^\text{35}\) and sulfonate derivatives.\(^\text{33}\) The driving force for such reactions is often the formation of a more stable radical (i.e. the primary radical 21 was transformed to the secondary benzylic radical 22 as depicted in
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Scheme 7. O-Neophyl rearrangement of 1,1-diarylalkoxyl radicals have also been reported. These sorts of migration can also occur in vivo, normally mediated by vitamin B\textsubscript{12} and cobalt dependent enzymes.

![Scheme 7 An 1,2-aryl migration]

1.5.2 Hydrogen abstraction reaction

Other rearrangement can occur via hydrogen abstractions. A range of H-abstraction reactions have been reported (eg. 1,2-;\textsuperscript{38} 1,4-;\textsuperscript{38} 1,5-;\textsuperscript{39} 1,6-,\textsuperscript{40} 1,7-)\textsuperscript{41} However the commonest are 1,5-H abstraction which occur via a chair-like transition state. For example, peroxide-initiated radical abstraction of the iodo compound 23 (Scheme 8) yielded the alkyl radical intermediate 24. This then underwent a 1,5-H abstraction, to give 25 which was terminated by abstraction of an iodine atom to furnish the iodosulfone 26 in 94% yield.

![Scheme 8 An 1,5-H abstraction from alkyl iodide]

Hydrogen abstractions can also occur from aromatics.\textsuperscript{42} Irradiation of an iodobenzophenone 27 (Scheme 9) in tert-butanol furnished the aryl radical intermediate 28, which then underwent 1,5-hydrogen abstraction to give the new radical 29.
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Scheme 9  An 1,5-H abstraction from an iodo aromatic compound

In another example, Curran\textsuperscript{43} has treated an \textit{ortho}-halo-aromatic \textbf{30} (\textbf{Scheme 10}) with tributyltin hydride/AIBN to form the aryl radical intermediate \textbf{31}, which underwent an 1,5-H atom abstraction to furnish the alkyl radical intermediate \textbf{32}.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme10}
\caption{An 1,5-H abstraction from an aryl radical to form an alkyl radical}
\end{figure}

\section{Radical-radical reactions\textsuperscript{3, 9}}

The process in which two radical species interact to form non-radical products is called chain termination. Two processes are possible: (1) radical coupling and (2) disproportionation. In the following example, the methyl radical \textbf{3} and ethyl radical \textbf{33} re-combine to give the radical coupled product propane \textbf{34} or through disproportionation to furnish methane \textbf{5} and ethylene \textbf{35} as depicted in \textbf{Scheme 11} When two of the same radical fragments re-combine, this is called dimerisation. A classic example is the Kolbe\textsuperscript{44} anodic oxidation of carboxylic acid salts.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme11}
\caption{Possible radical coupling and disproportionation reaction}
\end{figure}
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2.0 Aromatic radical reactions-Addition to aromatic ring.

Intermolecular addition onto an aromatic ring can go through three possible mechanistic pathways. These include; (1) aromatic nucleophilic substitution-an attack by a nucleophile (Nu\(^-\)), giving an anionic σ-complex, and loss of an anion; (2) aromatic electrophilic substitution—an attack by an electrophile (E\(^+\)), giving a cationic σ-complex, and loss of a cation; and (3) aromatic homolytic substitution—an attack by a radical (R\(^-\)), giving a radical σ-complex and loss of a leaving group (which is normally hydrogen, H\(^+\)). An early example of an intramolecular homolytic aromatic substitution involves the Pschorr reaction as illustrated in Scheme 12. In this example, the radical precursor when treated with copper (I) chloride furnished the aryl radical through loss of nitrogen gas. This aryl radical can then add into the aromatic ring to give the cyclohexadienyl radical intermediate followed by re-aromatisation to the tetracyclic product.

![Scheme 12](image)

2.1 Introduction

The primary objectives of this thesis were to investigate the cyclisation of radicals into aryl rings. Due to the nature of the cyclisation systems involved (discussed in Chapters 2-4) rearrangement reactions compete with the desired cyclisations. Therefore, the remainder of the introduction will focus both on radical cyclisation into aryl rings and radical rearrangement reactions.
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2.2 Mechanistic aspects of aromatic homolytic substitution reactions

Historically, homolytic aromatic substitutions have resulted in poor yields and product mixtures. A prime example of this is the Gomberg reaction,\textsuperscript{56} that not only gives every possible regioisomer, but also radical-radical coupling by-products as shown in Scheme 13. In this example, the aryl diazonium salt 40 when treated with a base (\textsuperscript{-}OH), furnishes the aryl radical 41 through loss of nitrogen gas and the generation of a hydroxide radical. The aryl radical 41 can then add into another aromatic ring 42, which if substituted (Z) could lead to several regioisomers-namely para 43, meta 44 and ortho 45 radical intermediates, followed by re-aromatisation to give para 46, meta 47 and ortho 48 biaryls. The aryl radical 41 could also recombine with another aryl radical 41 to give the dimerised product 49.

\begin{center}
\includegraphics[width=\textwidth]{scheme13.png}
\end{center}

Scheme 13 The Gomberg reaction
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A far more useful variant of this reaction involves intramolecular homolytic aromatic substitution, which will be illustrated later in the thesis. The mechanism of re-aromatisation (oxidation) in these substitution reactions is somewhat curious. The first step of the reaction appears logical and straightforward, in that a radical $R^\bullet$ attacks the aryl ring (see Scheme 14) to produce a sigma complex (or cyclohexadienyl radical when the aryl ring is benzene). This intermediate then has to undergo what is formally an oxidation reaction to give the fully aromatic product. The strange feature of the mechanism lies in this re-aromatisation step, since typically these reactions are conducted using Bu$_3$SnH as the radical mediator (see Scheme 15), formally a reducing agent. Therefore, it would appear that oxidation is taking place in the presence of a redundant! Several hypotheses have been forwarded to explain this dichotomy over the years.

This process has been extensively reviewed by Bowman and Storey. The intermolecular reaction proceeds via a sigma ($\sigma$) complex intermediate 50 as illustrated in Scheme 14, followed by extraction of the leaving group and re-aromatisation. The mechanism for the re-aromatisation will depend upon the reaction conditions employed, and the leaving group X.

![Diagram](image_url)

Scheme 14  Homolytic aromatic substitution-mechanistic outline
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Intermolecular addition reactions of the type outlined in Scheme 14 have been previously investigated. Traynham\textsuperscript{58} has conducted mechanistic studies on the effects of substituents on the aromatic ring (ipso substitution).

2.3 Alkyl radical cyclisation onto aromatics

While cyclisation of alkyl radicals onto unsaturated systems (e.g. alkenes, see Section 1.4), abound in the literature, there are relatively few examples of cyclisation of such radicals onto aromatic rings (Scheme 15). In these reactions, there is direct attack onto the aromatic ring, from the nucleophilic alkyl radical followed by re-aromatisation. The mechanism of this re-aromatisation will depend upon the reaction conditions.

The uses of aryl halides\textsuperscript{59-60} as substrates to initiate cyclisations onto monoaromatics have also been investigated. Beckwith and Storey\textsuperscript{60} has shown that the precursor 51 when treated with tributyltin hydride and AIBN in toluene led to the aryl radical 52 that could undergo an 1,5-hydrogen atom transfer to furnish the newly stabilised tertiary radical 53. This was followed by aromatic homolytic substitution leading to the cyclohexadienyl radical intermediate 54 to give the oxindole 55 in 81% yield as depicted in Scheme 16.
Scheme 16  Synthesis of a spirocyclic oxindole\textsuperscript{60}

Three possible mechanisms for re-aromatisation have been postulated; (1) oxidation of 54 by AIBN as mentioned by Curran.\textsuperscript{61} (2) disproportionation of 56 followed by oxidation of the cyclohexadienyl radical intermediate during work-up. In this illustrative example (Scheme 17); the re-aromatisation process occurs as follows; one molecule of the aryl radical intermediate 56 abstracts a hydrogen atom from another molecule of the aryl radical intermediate 56 leading to the re-aromatised product 58 and the cyclohexadienyl radical intermediate 57, which upon oxidation would furnish the bicyclic product 58.

Scheme 17  Disproportion reaction
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The third possibility invokes a mechanism involving the intervention of the initiator fragments, and later proven by Beckwith, Storey and Bowman as illustrated in Scheme 18. By using the fully deuterated aromatic substrate 59 the production of the deuterated initiator fragment 60 was proven. However, it would appear, at least in the system investigated that other mechanistic pathways were operating at the same time.

Scheme 18  Investigation of re-aromatisation using deuterated arenes.

Until recently the mechanism proposed by Bowman\(^6\)\(^2\) was generally accepted as an adequate explanation for oxidation in \(\text{Bu}_3\text{SnH}\) mediated reactions. This involved \(\text{Bu}_3\text{SnH}\) acting as a hydride donor and radical 61 acting as a protic acid to give the arene radical anion 62. This is then postulated to undergo a single electron transfer (SET) to the starting halide to maintain the chain process as shown in Scheme 19.

Scheme 19  Bowman’s hypothetic mechanism for re-aromatisation
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More recently a thorough investigation of the mechanism of general re-aromatisation under different conditions has been published. Each mechanistic possibility has been investigated and it would appear that the radical initiator is the key to determining the mechanism.

Two parallel mechanistic pathways were proposed. The first, involving an initiator fragment (resulting from AIBN homolysis) as outlined below. Under the conditions of the reaction investigated this would appear to be the minor mechanism. The major mechanism appears to involve the initiator acting as an oxidising agent prior to homolysis. These two competing mechanistic pathways are illustrated in Scheme 20. It would appear from the results presented that the postulation of each pathway is highly dependent upon the substrate, initiator, radical mediator and other reaction conditions.

Scheme 20 Bowman and Storey proposed mechanism for re-aromatisation
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Storey has applied this methodology to the synthesis of aza-oxindoles. In addition to tributyltin hydride as a radical carrier or radical mediator, other reagents have also been employed to furnish carbocyclic and heterocyclic compounds. These cyclisations can be carried out with a combination of TTMSS/AIBN. Further evidence suggesting the role of the initiators involvement in re-aromatisation can be seen in the synthesis of methoxybenzene derivatives as well as with other reagents.

2.3.1 Cyclisation of xanthates

(S)-Aryl ether xanthates was treated with dilauroyl peroxide, and the alkyl radical was produced (Scheme 21). This then cyclised to give a mixture of products. Interestingly, radical cyclisation via path A predominates leading to the (S) 3-aminochromane with the substituent in the 5-position. Radical cyclisation via the cyclohexadienyl radical intermediate (path B) led to the (S) 3-aminochromane with the ketone substituent in the 7-position. Re-aromatisation under these xanthate-mediated conditions was postulated to go through a single electron transfer-SET process as described by Zard, however, it would seem feasible, that the lauroyl radical could abstract the hydrogen atom from intermediate or to produce re-aromatisation.
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Scheme 21  Guillaumet synthesis of aminochromane\textsuperscript{65}

However, several inconsistencies in this work were observed. It was stated that the iodo compound 63a gave the best overall yield (37\% for 66); yet, it is evident that it is the xanthate compound 63b that has the highest yields (69\%) for the aminochromanes 66.

Similarly, \(\alpha\)-tetralone derivative 73 have also been synthesised using an alkyl radical cyclisation (48\%). Zard\textsuperscript{67} investigated the radical addition of acetophenone xanthate 69 onto vinyl pivalate 70 in the presence of dilauroyl peroxide (DLP) to give the radical adduct 71 (scheme 22). This alkyl radical 71 then underwent cyclisation onto the aromatic ring leading to 73 (48\%), after re-aromatisation of 72.\textsuperscript{68-70} No mechanistic hypothesis was presented for re-aromatisation, but again, the initiator, dilauroyl peroxide is required in stoichiometric quantities in order to obtain reasonable yields of product. This would strongly suggest that the initiator is involved with the re-aromatisation process as previously discussed.
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Scheme 22  Zard’s synthesis of α-tetralone$^{67}$

2.4 Sequential intermolecular/intramolecular radical cyclisation onto aromatics

The use of an initial intermolecular addition to generate a new radical that is suitable for cyclisation into aromatics has been achieved. This methodology has been used in the synthesis of heterocycles and provides an elegant method for the generation of a cyclisation precursor radical. $N$-allyl-anilides 74 were treated with the ‘Tordo alkoxyamine’ 75.$^{71-73}$ Thermal homolysis of 75 led to the formation of an alkyl radical 76 and a nitroxyl radical (“SG1”) 77. Radical addition of 76 to the alkene generated the more stable radical intermediate 78, followed by intramolecular addition onto the aromatic ring to furnish the cyclohexadienyl radical intermediate 79, which upon re-aromatisation furnished the indole product 80 in 63% yield as shown in Scheme 23. No evidence of products produced from the trapping of the radical intermediate 79 was observed. It was assumed that re-aromatisation arose either from H-atom abstraction by the nitrooxide radical or because of its initial re-combination with SG1 77 followed by elimination to furnish 80. No mechanistic evidence is presented for either pathway.
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Scheme 23  Tordo’s synthesis of indole

The same method was used in synthesising oxindole \(82\). The nitroxide radical\(^ {74}\) ("SG1")-tethered substrate \(81\) underwent aromatic homolytic substitution and re- aromatisation to furnish \(82\) in 63% yield as depicted in Scheme 24.

Scheme 24  Synthesis of \(N\)-methyl-3,3-dimethyloxindole

Carbocycles can also be produced via intramolecular addition (Scheme 25). Addition of a tosyl radical \(84\) onto the terminal alkene \(83\) furnished the more stable secondary alkyl radical intermediate \(85\), which could undergo cyclisation onto the aromatic ring leading to the cyclohexadienyl radical intermediate \(86\). Oxidation of \(86\) by subsequent reaction with copper acetate furnished the tetrahydronaphthalene \(87\) in 90% yield.\(^ {75}\) In this case the oxidation by \(\text{Cu}^{2+}\) gives the cyclohexadienyl cation (not shown), which loses a proton generating acetic acid and \(\text{Cu}^{1}\). When the reactions were carried out under acidic
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conditions (acetic acid), high yields were obtained (90%, 48h), when formic acid was used, the reaction was accelerated 82%, (9h).

\[
\begin{align*}
\text{E} = & \text{COOCH(CH}_3\text{)}_2 \\
\end{align*}
\]

Scheme 25  Synthesis of carbo cyclics \(^7\)

A less common sequential approach to heteroaromatics via cyclisation onto an aryl group is the intermolecular-intramolecular reactions of benzylideneamines. Thermal homolytic dissociation of diisopropyl peroxydicarbonate (DPDC) \(^9\) (2 equivalents) \(88\) in benzene at 60 °C gave the isopropyloxycarbonyl radical \(89\) which could then abstract a hydrogen atom from \(N\)-benzylideneamine \(90\). \(^24\) Addition of this radical to the alkyne, \(91\) was maintained until complete consumption of the radical initiator \(89\). This then gave the vinyl radical intermediate \(93\) which subsequently underwent cyclisation into the aryl ring to yield the quinoline derivatives \(94\) as depicted in Scheme 26. Similar approaches to \(Luotenin A\) \(^47\) have shown that re-aromatisation occurred from hydrogen abstraction of the intermediate cyclohexadienyl radical intermediate by a methyl radical generated from the breakdown of \(\text{Me}_3\text{Sn}^\bullet\) radicals or \(\text{tert}-\text{butoxyl radicals. In this example, a high concentration of hexamethyliditin was required (14 equivalents) to furnish the product. This could explain how the step from \(93\) to \(94\) was achieved. In that case it would be from the homolysis of DPDC and subsequent hydrogen abstraction during the re-aromatisation stage.
A similar class of reactions were used by Bowman in the synthesis of Camptothecin,\textsuperscript{76-80} mappicine, luotonin\textsuperscript{76} and Zanardi’s synthesis of phenanthridine \textsuperscript{98} (Scheme 27).\textsuperscript{77} The key step in these reactions was a 6-\textit{endo} attack of an aryl radical \textsuperscript{96} onto the imine, to give the aminyl radical intermediate \textsuperscript{97}. This was followed by re-aromatisation to furnish phenanthridine \textsuperscript{98} in 19\% yield. The mechanism of re-aromatisation for this reaction involves extrusion of the \textit{tert}-Bu group.\textsuperscript{77} Reactions involving re-aromatisation from extrusion of an alkyl group have been reviewed by Bowman \textit{et al.}\textsuperscript{78-79}
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Scheme 27  Zanardi’s synthesis of phenanthridine$^{77}$

2.5  Aromatic radical cyclisation onto aromatics

Over the last decade, the synthesis of polyaromatics by cyclisation of aryl radicals onto aromatic rings has become popular. The synthesis of phenanthrene derivatives from cis-stilbenes have recently been used in the synthesis of steganone.$^{81}$ The aryl radical 99 generated from homolysis of the corresponding bromo aromatic compound with Bu$_3$SnH (not shown) cyclised onto the second aromatic ring leading to intermediate 100. Re-aromatisation presumably occurs by hydrogen abstraction of the cyclohexadienyl intermediate by the initiator (AIBN) as discussed previously, no evidence to the contrary has been presented by Harrowven et al.$^{82}$ Phenanthrene 101 was furnished in 32%, which showed that disproportionation may possibly be responsible for the oxidation process (Scheme 28).$^{81}$
In addition to the above example, this methodology has been used to synthesise a range of polyaromatic natural products e.g. \( \beta \)-copaena, \( \beta \)-ylangene, lemmalonol,\(^{83-84} \) seychellene,\(^{85} \) and towards the synthesis of vitamin \( D_3 \).\(^{86} \) In a related reaction, Harrowven,\(^{82} \) used cis-stilbene (Scheme 29). In this case, the accepting aromatic ring was not electron rich but electron poor. Cis-4-cyano stilbene 102 was treated under classical radical conditions (tributyltin hydride, AIBN) to generate the aryl radical intermediate 103, which could add via an intramolecular exo/endo-trig cyclisation to give the cyclohexadienyl radical intermediate 104. Re-aromatisation of the radical intermediate 105 probably occurs as described above, involving the initiator either homolysed or intact to give phenanthrene in 85% yield. Disproportionation can be ruled out as a mechanistic possibility. This reaction was repeated for the electron rich cis-3-methoxy stilbene 106, under similar conditions to furnish regioisomers 107 and 108 in high yield (82%). This should be compared to results from cis-3-cyano stilbene that gave similar regioisomers at slightly lower yields (78%) (not shown).
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Scheme 29  Harrowven’s synthesis of phenanthridines\textsuperscript{87}

Harrowven\textsuperscript{87} has also shown that the cis stilbene \textbf{109} (Scheme 30) when treated with tributyltin hydride furnished the aryl radical intermediate \textbf{110}. This radical then added onto to the aromatic ring to give the cyclohexadienyl radical intermediate \textbf{111}. Re-aromatisation furnished the helicene \textbf{112} in 52\% yield. Alternatively, the radical intermediate \textbf{110} can undergo addition onto C-7, leading through re-aromatisation to furnish dibenzo[\(a,h\)]anthracene \textbf{113} in 17\% yield. Preference for the C-5 over C-7 attack was evident. The reason for this selectivity is not clear, but is most likely to occur because of a more favourable SOMO-LUMO interaction with C-5. Possible re-aromatisation mechanisms were not mentioned.
An alternative approach by Harrowven$^{88}$ to furnish [5]-helicene 112 is the use of (Z,Z)-1,4-bis-iodo stilbenes. Treatment of the bis-iodo substrate (not shown) under classical radical conditions (tributyltin hydride, AIBN) furnished the di-radical intermediate 114, which underwent radical coupling to furnish the [5]-helicene 112 in 35% yield and the by-product dibenzo[a,h]anthracene 113 in 27% yield (Scheme 31). Since aryl radical formation is relatively fast compared to homolytic aromatic substitution it is indeed likely that a biaryl intermediate like 114 actually is formed, rather than the formation of one radical followed by the formation of another. There is however no evidence for radical-radical coupling, which is a fast process. In this reaction a fourfold excess of tributyltin hydride was used to push the reaction towards bicyclisation. Harrowven stated that the driving force for re-aromatisation overcame the energy barrier caused by the lack of planarity on helicene.
2.6 Alkyl radical cyclisation onto heteroaromatics

Cyclisation of radicals into heteroaromatics is a relatively new process. The first example of this involves cyclisation of an alkyl radical into a protonated pyridinium salt.\textsuperscript{89} Intermolecular and intramolecular aromatic homolytic substitutions into heterocycles are relatively well researched. An example of an intermolecular addition into an heteroaromatic was first demonstrated by Minisci,\textsuperscript{90} whereby the nucleophilic alkyl radical ($R\cdot$) can add intermolecularly into the protonated pyridinium salt 115 to give the radical cationic species 116. Loss of a proton yields the radical $\alpha$ to the nitrogen atom 117. Re-aromatisation under oxidative conditions leads to the fully aromatic product 118 as depicted in Scheme 32.

Scheme 31 Harrowven’s synthesis of helicene and phenanthrene\textsuperscript{88}

Scheme 32 Murphy’s reaction of protonated pyridinium salts
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An intramolecular version of this reaction was accomplished by Murphy.\textsuperscript{91-92} In this example (Scheme 33), treatment of the 2-iodoalkyl pyridinium salt 119 with tributyltin hydride (1.3 eq.) and AIBN (1.2 eq.) gave the nucleophilic alkyl radical 120 which could add into the pyridinium ring to furnish the tetrahydroquinolizinium salt 121 in 60% yield.

![Scheme 33 Murphy’s intramolecular addition into pyridinium salt](image)

2.6.1 Radical cyclisation onto pyrazoles

Intramolecular cyclisation onto pyrazoles have been accomplished to give 4-phenyl pyrazole derivatives 125.\textsuperscript{93} Reaction of a 4-phenylpyrazole phenylselenyl precursor 122 with tributyltin hydride (1.3 eq.) and ACCN (1.5 eq.) gave the alkyl radical intermediate 123 (Scheme 34), which underwent a 6-\textit{exo} cyclisation to give the intermediate \( \pi \)-radical 124 followed by oxidation to furnish 4-phenylpyrazole 125 in 63% yield. For cyclisations involving a 5-\textit{exo} or 7-\textit{exo} cyclisation, there was a considerable amount of reduced product 126 formed. There was no product pertaining to the other regioisomer 127.
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Scheme 34  Intramolecular cyclisation of pyrazine\(^{93}\)

The reaction was repeated using the ester\(^{93}\) [COOEt] on C-3 of the pyrazole (Scheme 35). Treatment of the radical precursor 128 with tris(trimethylsilyl)silane (1.3 eq.) and triethylborane (Et\(_3\)B) (1.5 eq.) as the radical initiator in refluxing toluene under an aerial atmosphere furnished the alkyl radical 129 which underwent 6-exo cyclisation to furnish the cyclic radical intermediate 130 followed by oxidation to give the bicyclic product 131 in 36% yield. Both 5-exo and 7-exo cyclisations were disfavoured, and only the reduced product 132 was isolated, due to faster H-abstraction of hydrogen by the intermediate radical 129. In addition, none of the regioisomeric cyclised product 133 was observed, which indicated the regioselectivity was more favourable towards C-5 than C-2 (the nitrogen atom adjacent to the alkyl chain).
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The mechanism for the oxidative step 130 to 131 is not clear, but it is reported that the stability of the $\pi$-radical intermediate 131 is crucial (to aromatisation).\textsuperscript{94-98} The re-aromatisation could occur from H-abstraction by the ethyl radical formed during the oxygen-generated breakdown of Et$_3$B that was used as the initiator. With ACCN as initiator, more than one equivalent of initiator was required, which indicated that involvement of ACCN or its breakdown products (1-cyanocyclohex-1-yl radical) was involved in re-aromatisation.\textsuperscript{57, 94-103}

2.6.2 Radical cyclisation onto imidazoles

Further studies were conducted involving cyclisation onto imidazoles\textsuperscript{94} (Scheme 36). In these reactions the alkyl bromide radical precursor 134 when treated with tributyltin hydride (1.5 eq.) and AIBN (0.25 eq.) generated the nucleophilic alkyl radical intermediate 135, which underwent cyclisation at the electrophilic C-2 position of the imidazole, leading to the $\pi$-radical intermediate 136 followed by oxidation to the product 137. Again, it was observed that 6-exo cyclisation was more selective (no reduced product) than that concerning the 5-exo and 7-exo cyclisation (both generating the
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reduced product 138). There was no regioisomer 139 resulting from cyclisation onto the C-5 position.

![Chemical structure](image)

Key: a) \( n = 1, 137 = 42\% \); b) \( n = 2, 137 = 49\% \); c) \( n = 3, 137 = 14\%; 138 = 8\% \).

**Scheme 36  Intramolecular cyclisation of imidazole**

In order to explore the regioselectivity of this reaction, the reaction was repeated, blocking the C-5 of the imidazole with a methyl group 140 (Scheme 37). The result was complete selectivity towards C-2 cyclisation leading to the bicyclic product 141 in 75% yield. Furthermore, regioselectivity was investigated, whereby C-2 of the imidazole was blocked with a methyl group 142. This resulted in only reduced product 143 being isolated in 46% yield. The regioselectivity would appear to be determined by nucleophilic alkyl radical addition onto the electrophilic \( \beta \)-position of the imidazole. This reaction was also investigated with tributylgeranium hydride.

![Chemical structure](image)

**Scheme 37  Blocking of the C-2 and C-5 with methyl group**
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In addition, a carbaldehyde in the α-position of the imidazole 144 gave good yields of the 6-membered ring product 145 in 53% yield (Scheme 38). However, attempts to mediate 5-exo cyclisation from the radical precursor 146 failed leading to the reduced product 147.

Scheme 38  Intramolecular cyclisation of pyrrole and imidazole

In this paper, there is no specific proposed mechanism to explain the oxidative radical cyclisation of these substrates with Bu$_3$SnH. There are three putative mechanisms proposed in the earlier papers: (1) formation of a dihydro product and subsequent air oxidation to achieve re-aromatisation. However this is unlikely since reactions are performed under an inert atmosphere; (2) H-abstraction by AIBN and/or 2-cyanoprop-2-yl radicals;$^{105}$ although Lobo, Prabhaker et.al.$^{106}$ conducted experimental work on similar oxidative cyclisation, which showed that the hydrogen that is lost, is not abstracted by 2-cyanoprop-2-yl radicals. (3) a pseudo-$S_{RN1}$ mechanism.$^{94}$

2.7  *Ipso*-substitution and extrusion of a good radical leaving groups

The reaction of radical precursor 148 (Scheme 39)$^{107}$ when treated with tributyltin hydride and AIBN led to the alkyl radical intermediate 149. The intermediate radical is weakly nucleophilic and adds to the electrophilic C-2 carbon leading to the π-radical intermediate 150. Elimination of the leaving group furnished the product 151. In the previous section cyclisation occurred at sites substituted by an H-atom and not at sites blocked by substituents (e.g. COOEt). However, if the substituent (e.g. Z, 148) is a good
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radical leaving group, ipso substitution with loss of this group can occur. Caddick has used this methodology to furnish [1,2-α] indoles using sulfone, sulfide and sulfoxide groups as leaving groups in substituted indoles.\textsuperscript{108} Highest yields were obtained from 6-exo attack onto sulfoxides (tosyl group).

\begin{center}
\begin{align*}
\text{Scheme 39 Intramolecular ipso cyclisation of imidazoles}\textsuperscript{107}
\end{align*}
\end{center}

There was no noticeable change in yield for \( n = 1 \) on varying the tosyl leaving group \textbf{151a} in 52\% yield and the phenylsulfonyl leaving group \textbf{151a} in 51\% yield. The low yield for the phenylsulfanyl group \textbf{151a} (16\%) is attributed to this leaving group not being sufficiently electron withdrawing to facilitate complete attack at C-2 by the weakly nucleophilic alkyl radical. The same approach can be used to prepare [1,2-α]-fused benzimidazole \textbf{152} as depicted in Scheme 40.\textsuperscript{108-110} The radical precursor \textbf{152} was treated with tributyltin hydride and AIBN to give the alkyl radical intermediate \textbf{153}. This underwent an attack on the electrophilic C-2 carbon of the benzimidazole to give the \( \pi \)-radical intermediate \textbf{154}, and elimination of the phenylsulfanyl group to give the product \textbf{155}.
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Scheme 40  Intramolecular ipso cyclisation of benzimidazole\textsuperscript{10}

The 5-exo cyclisation to 155a (n=1) proceeded in a higher yield to that of the analogous imidazole reaction in 16% yield as depicted in Scheme 39. The yields for the benzimidazole were reasonably good, with the 6-exo cyclisation providing higher yields (54%) than the 5- and 7-exo cyclisations. This was explained because the imidazole ring in benzimidazole has less aromatic character than in imidazole, and that addition of the alkyl radical was more facile, and also because the weakly electron withdrawing (phenylsulfanyl) group facilitates cyclisation over reduction.

2.8  Cyclisation of pyrroles

Related work by Bowman\textsuperscript{94} on pyrroles has shown similar selectivities with respect to the 6-exo cyclisation (no reduced product observed). In this case the bromo alkyl radical precursor 156 was treated with tributyltin hydride (1.5 eq.) and AIBN (0.25%), which generated the alkyl radical intermediate 157 followed by addition onto the electrophilic C-2 to yield the \( \pi \)-radical intermediate 158, which after oxidation furnished the product 159 as depicted in Scheme 41. Again, both the 5-exo and 7-exo cyclisations were accompanied by small amounts of reduced products 160.
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Several cyclisations onto the C-2 position of imidazoles proceed by reductive cyclisation and not aromatic homolytic substitution\(^\text{48}\) that indicates that reduction of the intermediate radical by \(\text{Bu}_3\text{SnH}\) is faster than re-aromatisation. However, when an electron-withdrawing group is present in the C-3 position, normal aromatic homolytic substitution is largely favoured.\(^\text{111-116}\)

### 2.9 Acyl radical cyclisation on pyrroles

Acyl radicals also undergo addition reactions.\(^\text{97}\) In this example, treatment of the phenylselenyl radical precursor 161 with tributyltin hydride and AIBN furnished the acyl radical intermediate 162 as illustrated in Scheme 42. This was followed by *exo* attack onto the pyrrole to give the \(\pi\)-radical intermediate 163, followed by oxidation to the product 164\(_a\) (n = 1) in 31% yield and 164\(_b\) (n = 2) in 20% yield. No reduced product 165 was isolated. An alternative product can be formed from the intermediate 166. Decarbonylation gave the alkyl radical 166 that could add in an *exo*-fashion onto the pyrrole to give the \(\pi\)-radical intermediate 167, followed by oxidation to the product 168\(_a\) (n = 1) in 0% yield and 168\(_b\) (n = 2) in 13%. Only the reduced product 169\(_a\) (n = 1) was isolated in 34% yield.
It should be noted that decarbonylation is an exothermic process. The rate of CO loss (approximately $2 \times 10^2$ M$^{-1}$ s$^{-1}$) at 80 °C to generate a primary alkyl radical, is much slower than CO addition ($6.3 \times 10^5$ M$^{-1}$ s$^{-1}$) at 80 °C for primary alkyl radicals.\textsuperscript{117} In order to facilitate the synthesis of 164 this reaction was conducted under a CO atmosphere. Furthermore, this methodology has been applied towards tetracyclic heterocycles\textsuperscript{119} from 2-indolylacyl radicals. The mechanism for re-aromatisation\textsuperscript{98} in this reaction is still unclear. In the Bu$_3$SnH mediated oxidative cyclisation, more than one equivalent of AIBN is required, which would suggest that AIBN is involved in an H-abstraction mechanism for this step (see Scheme 20).

Azo compounds can act as oxidants, and as such would give dihydro-AIBN 172 (Scheme 43) as the expected product. Subsequently, experimental studies using AIBMe 170 as the radical initiator with radical precursor 161b furnished the cyclised product
164b and dihydro-AIBN 171 indicating that AIBMe 170 was responsible for the oxidative step.

Scheme 43  Mechanism indicating AIBN involvement in re-aromatisation

2.10  Aryl radical cyclisation onto heteroaromatics

A popular approach to polyheteroaromatics is the addition of an aryl radical onto another heteroaromatic such as quinoline (Scheme 44). Radical intermediates 173a and 173b are produced from homolysis of the corresponding C-X bonds with Bu3SnH (not shown). The use of iodo aromatics is superior in terms of yield to the bromo analogues. The stilbene radical intermediate 173a, underwent 6-exo/endo-trig cyclisation to furnish the two regioisomers resulting from attack at C-2, 174a in 57% yield and C-4, 175a in 38% yield. When the reaction was repeated without the alkene bridge (e.g. an ethyl bridge between the aromatic and the quinoline 173b), yields were slightly less for the C-2 analogue 174b in 51% yield and C-4, 175b in 23% yield. The low yield from the bromo precursor was due to several intractable products. The use of the iodide precursor proved more effective. Again, it was shown that the product from C-4 addition occurred in higher yields. The mechanism for re-aromatisation was postulated to go through two mechanistic pathways as described by Harrowven et al. Similar methodology using cobalt (II)-salophen was used in the synthesis of Toddaquinoline. 121
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Key: Bromo precursor Bu$_3$SnH, 0.9 eq. AIBN, PhMe, 80°C; $174a = 24\%$, $175a = 46\%$; $174b = 18\%$, $175b = 15\%$; Iodo precursor Bu$_3$SnH, 0.1 eq. AIBN, PhMe, 80°C; $174a = 38\%$, $175a = 57\%$; $174b = 23\%$, $175b = 51\%$.

**Scheme 44** Harrowven’s synthesis of polyheteroaromatics$^{119}$

Cyclisations onto indoles have been explored by Harrowven$^{122}$ using halo $N$-benzyl indoles derivative $176$. In this case the aryl radical $177$ generated from tributyltin hydride mediated homolysis of the aryl iodide underwent a 5-exo trig cyclisation to furnish the radical intermediate $178$. Hydrogen abstraction from another molecule of tributyltin hydride furnished the tetracycle $179$ in 80% yield and the reduced product $180$ in <5% yields as depicted in **Scheme 45**.

**Scheme 45** Intramolecular cyclisation of indoles
Further developments of this reaction were employed in the synthesis of several heterocycles namely-deoxyvascinone, mackinazoline, luotinin A, tryptanthrin.\textsuperscript{123} 

The Jones’ group has developed cyclisation onto pyrroles further.\textsuperscript{124-126} An ortho bromo anilide derivative \textsuperscript{181} when treated with tributyltin hydride (0.02M) and sub-stoichiometric amount of AIBN furnished the aryl radical intermediate \textsuperscript{182} as illustrated in Scheme 46. This could undergo three reactive pathways. The radical intermediate \textsuperscript{182} could undergo 6-endo cyclisation via the radical intermediate \textsuperscript{183} onto the pyrrole to furnish the product \textsuperscript{186}. It could undergo 6-exo cyclisation via the radical intermediate \textsuperscript{184}onto the pyrrole to give the regioisomeric product \textsuperscript{187}. Finally, it could undergo 5-exo cyclisation via the radical intermediate \textsuperscript{185} to furnish the spirocyclised product \textsuperscript{188}. 

It is important to note the effects of substituents on the nitrogen atom of the pyrrole ring in controlling the reaction. If unsubstituted groups (R\textsubscript{2} = H), then regioisomeric products \textsuperscript{186a} (R\textsubscript{1} = Me, R\textsubscript{2} = H, 37\%) and \textsuperscript{187a} (R\textsubscript{1} = Me, R\textsubscript{2} = H, 15\%) dominated. Conversely, cyclisation using N-t-Boc group led predominately to the spirocyclised product \textsuperscript{188b} (R\textsubscript{1} = Me, R\textsubscript{2} = Boc) in 31\% yield, with the regioisomers as minor products (\textsuperscript{186b}/\textsuperscript{187b} = 18%/1\%). If an electron-withdrawing group was attached to the nitrogen atom of the pyrrole, only \textsuperscript{186c} (R\textsubscript{1} = SEM, R\textsubscript{2} = Me) was furnished in 43\% yield. The regioselectivity was unaffected when substituents were on the aromatic ring. The reasons for the differences in the reactivity between the varying groups on the nitrogen atom of the pyrrole is not entirely clear nor is the mode of re-aromatisation given that sub-stoichiometric amounts of initiator are reported to have been used.
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Scheme 46  Intramolecular cyclisation onto pyrroles\textsuperscript{125}

2.11 Trapping of the cyclohexadienyl radical intermediate

Recent developments in radical chemistry have led to many possible routes to form spirocyclised natural products through \textit{in-situ} trapping of the cyclohexadienyl radical intermediate. Zard’s method has shown that spirolactams\textsuperscript{127} can be prepared from \textit{N-}benzyl trichloroacetamides using nickel powder/acetic acid. Furthermore, Jones’ has used this methodology towards the spirooxindole natural products-\textit{horsfiline}, (\textbf{Scheme 47}) \textit{elacomine, alstonisine} and \textit{spirotryprostatin A}.\textsuperscript{128}
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Spirodienones have been synthesised via intermolecular ipso substitution from N-methoxy-(4)-(halogeneophenyl) amides and hydroxyl (tosyloxy) iodobenzene (HTIB)/trifluoroethanol (TFEA). This methodology was developed for the synthesis of 1-azaspiro-[4,5]-decane-mediated natural products-TAN1251A-D, FR901483I, lepadiformine and cylindricine A-F. Furthermore, this methodology has been used by Curran and de Turiso in the synthesis of spirocyclohexadienone intermediates, which could be applied to synthesis of SR121463A and aza-galanthamine.

2.12 Spirocyclisation followed by rearrangement reactions

In cases where there is a good radical leaving group $\alpha$ to the intermediate cyclohexadienyl radical, it can undergo re-aromatisation with extrusion of the radical leaving group; this can result in rearrangement as shown in this example Scheme 48.

Azacoumarins have been prepared by a unique double ipso substitution from aryl benzoate. The reaction goes via an initial 1,5-ipso attack at the 2-position of the pyridine to generate the spirocyclised intermediate followed by re-aromatisation and fragmentation of the carbon-oxygen bond to furnish the carbyloxy radical intermediate. The aromatic carbyloxy radical ($k = 10^4-10^5 \text{ s}^{-1}$) is considerably slower than alkyl carbyloxy radical ($k = 10^8-10^{10} \text{ s}^{-1}$), and allows the radical intermediate time to undergo a second 1,6-ipso attack at the methoxy position. 

Scheme 47  An example of spirocyclisation

$$\text{Bu}_3\text{SnH}, \text{AIBN}$$

$$\text{N}$$

$$\text{O}$$

$$\text{CN}$$

$$\text{R}$$

$$\text{Br}$$

$$\text{N}$$

$$\text{O}$$

$$\text{CN}$$

$$\text{R}$$

$$\text{Ph}$$

$$\text{Ph}$$

$$\text{O}$$

$$\text{Ph}$$

$$\text{N}$$

$$\text{CN}$$

$$\text{R}$$

$$\text{CN}$$

$$\text{R}$$

$$\text{Ph}$$

$$\text{Ph}$$

$$\text{O}$$

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$$\text{CN}$$

$$\text{R}$$

$$\text{CN}$$

$$\text{R}$$

$$\text{Ph}$$

$$\text{Ph}$$

$$\text{O}$$

$$\text{Ph}$$

$$\text{N}$$

$$\text{CN}$$

$$\text{R}$$

$$\text{CN}$$

$$\text{R}$$

$$\text{Ph}$$

$$\text{Ph}$$

$$\text{O}$$

$$\text{Ph}$$
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leading to the aryl radical intermediate 193. This is followed by extrusion of the methoxy group to furnish the azacoumarin 194. It should be noted that the use of the methoxy group was crucial to the whole rearrangement process.

Scheme 48  Complex double ipso cyclisation to form azacoumarins\textsuperscript{131}

3.0  Aryl migration

Aryl groups can undergo migration reactions\textsuperscript{132-134} generally via the intermediacy of a spirocyclohexadienyl system followed by re-aromatisation and cleavage of the appropriate bonds. Wieland\textsuperscript{135} first reported radical aryl migration reactions in 1911. There has been an extensive investigation of 1,2-ipso aryl migrations, however, there are currently no literature reports concerning 1,3-aryl migrations, though numerous examples regarding 1,4-aryl migrations have been reported. The most frequent type of aryl migrations are 1,5-migrations. In the example illustrated in Scheme 49,\textsuperscript{136} tributyltin-mediated radical abstraction of the iodo group in 195 generated the aryl
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radical intermediate 196, which underwent an initial 5-exo-trig cyclisation resulting in the spirocyclic intermediate 197. Re-aromatisation and fragmentation gave the radical intermediate 198. There were three possible pathways observed that can occur in this system. The radical intermediate 198 can (A), undergo hydrogen atom abstraction from tributyltin hydride to give the methyl ether 199 (6%); (B) undergo the slower 6-endo/exo-trig cyclisation leading to the benzo[c]chromene radical intermediate 200 followed by re-aromatisation to the product 201 (27%); or (C) via a fragmentation process leading to the phenol 202 (46%). This last step was not rationalised by Harrowven and is currently under further investigation.

Scheme 49  Harrowven’s intramolecular cyclisation of an aryl ether$^{136}$
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Harrowven\textsuperscript{136} synthesised the natural product \textit{isoauparin} 203 through the same methodology as described above (Figure 1).

\begin{center}
\includegraphics[width=0.3\textwidth]{structure.png}
\end{center}

\textbf{Figure 1} \quad \textbf{Structure of \textit{isoaucuparin}}

Under similar conditions, tributyltin hydride-mediated radical abstraction of the \textit{ortho} halo-compound 204 furnished the aryl radical 205 which underwent a 1-5-\textit{ipso} attack to give the spirocycised radical intermediate 206 as depicted in \textbf{Scheme 50}. Re-aromatisation to give 207 followed by possible hydrogen abstraction from another molecule of tributyltin hydride resulted in the biaryl 208 \textit{via} an aryl migration.\textsuperscript{98}

Alternatively, the radical intermediate 206 underwent a neophyl rearrangement to give the $\sigma$-complex 209 which upon oxidation (re-aromatisation) led to the benzo[c]chromane 210 (Me = 36\%, OMe = 21\%). In this reaction, the cyclisation \textit{via} the neophyl rearrangement was faster than the \textit{ipso} substitution followed by fragmentation.

\begin{center}
\includegraphics[width=0.8\textwidth]{intramolecular.png}
\end{center}

\textbf{Scheme 50} \quad \textbf{Intramolecular cyclisation of benzyl ethers}
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Synthesis of biaryls can be achieved by nitrogen to carbon aryl migration. For example, $N$-methanesulfonamide 211 is converted to the $N$-(3-arylpropyl) amide 214.\(^{139}\) Formation of radical 212 by homolysis of the corresponding C-Br bond using tributyltin hydride and AIBN led to a 1,5-\textit{ipso} attack to furnish the spirocyclohexadienyl radical intermediate 213, re-aromatisation followed by homolytic cleavage of the C-N bond furnished the sulfonamide 214 in 72\% yield as depicted in Scheme 51. The reaction proceeds through a captodatively-stabilised spirocyclised radical intermediate 213. It is noted that varying the type of substituent on the nitrogen atom, affects the outcome for the rearranged product, as such, methanesulfonamide is more efficient (in furnishing the rearranged product) than the methyl ester or $p$-toluenesulfonyl group. The same authors used this approach for oxygen to carbon aryl migrations.\(^{138}\)

Scheme 51  Nitrogen to carbon aryl migration\(^{137}\)

It is rarer but also possible to get migrations occurring in a 1,4-\(^{139,140}\) and 1,6- fashion.\(^{141}\) For example, treatment of the xanthate 215 with dilauroyl peroxide gave the radical intermediate 216 which could then undergo a 1,4-\textit{ipso}\(^{139}\) cyclisation leading to a spiroazetidinone radical intermediate 217 as illustrated in Scheme 52. This was followed by re-aromatisation and cleavage of the carbon-nitrogen bond, which gives an amidyl radical intermediate 218. This can then abstract a hydrogen atom presumably from the
solvent to furnish the rearranged product 219 in 71% yield. Radical 216 was hindered from cyclisation onto the aromatic ring, due to steric effects when R = tert-butyl. However if the nitrogen substituent is changed from the tert-butyl group to a methyl group, then only the cyclised product 220 is observed in 39% yield.

Scheme 52 Smiles rearrangement

An example of 1,6-migration is illustrated in Scheme 53. Tributyltin hydride-mediated radical formation from the bromo compound 221 generated the aryl radical 222, which underwent an 1,6-ipsO attack onto one of the three phenyl rings attached to the silyl group to give the spirocyclohexadienyl radical intermediate 223. Re-aromatisation followed by homolytic cleavage of the carbon-silicon bond led to the silyl radical intermediate 224. Extrusion of the silyl group furnished the biaryl alcohol 225 in 71% yield. Phenyl migration from other groups was investigated. When the trimethyltin (Me₃Sn-) substrate was used, it did not form the expected rearranged product, but instead the aryl radical intermediate 226 underwent a S₈H type of reaction to furnish the bicyclic silylated product 227. Ring opening of the cyclic silyl ether with methyllithium
furnished the silylated benzyl alcohol $\text{228}$ in 84% yield. The use of a phenyl or methyl group gave exclusively the rearranged product.

Struder has extensively investigated aryl migrations of sulfur to carbon.\textsuperscript{132-133} The thia-neophyl type 1,2-phenyl migration from sulfur to carbon is known\textsuperscript{144} however, there is no radical 1,3-aryl migration of sulfur to carbon to date. The majority of sulfur to carbon reactions involve 1,4-, 1,5- and 1,6 aryl migration. In the following example, Studer et al.\textsuperscript{133} investigated radical 1,5-aryl migration from sulfur in sulfonates to secondary C-radicals for stereoselective bond formations (Scheme 54). Starting from the iodide $\text{229}$, tributyltin hydride and AIBN generated the secondary alkyl radical $\text{230}$ that could undergo a 1,5-\textit{ipso} attack into the phenyl ring to form the cyclohexadienyl radical intermediate $\text{231}$. Re-aromatisation from $\beta$-elimination gave the alkoxy sulfonyl radical intermediate $\text{232}$. Extrusion of SO$_2$ furnished the alkoxy radical $\text{233}$ followed by H-
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abstraction to yield the product 234 in good yield (76%) and high selectivity ($dr = 13:1$) for the unsubstituted aryl group.

![Scheme 54](image)

**Scheme 54**  1.6-**ipso** aryl migration$^{134}$

3.1. Radical cyclisation and rearrangement reactions of aryl sulfonamides

The further reactions and discussions in this thesis focus on the reactions of sulfonamides thus the following section comprises aromatic homolytic substitution and rearrangement reactions of aryl sulfonamides.

3.2. Alkyl radical cyclisation and rearrangements from aryl sulfonamides

Speckamp and Köhler$^{145}$ reported that sulfonamide 235 (Scheme 55) when suitably substituted, could undergo a radical cyclisation reaction to give 236, if treated with azobisisobutyronitrile (AIBN) and tributyltin hydride (TBTH). However in addition to the cyclised products 236a-d, f, the rearranged products$^{146}$ 237a-f and reduced products 238a-f were also detected.
a) \( X = \text{CH}_3, Y = \text{H} \); b) \( X = \text{H}, Y = \text{H} \); c) \( X = \text{OCH}_3, Y = \text{H} \); d) \( X = \text{Cl}, Y = \text{H} \); e) \( X = \text{CH}_3, Y = \text{CH}_3 \); f) \( X = \text{NO}_2, Y = \text{H} \).

**Scheme 55**  Speckamp sulfonamide reactions 1

The effect of substituents 235a-f on the rate of reaction and ratios of all three products was determined. While cyclised products 236a-d,f arise *via* cyclisation into the aromatic nucleus (see Section 2.5) the rearranged product 237a-f were obtained by the attack of the initial alkyl radical 239 (Scheme 56) into the aryl ring in an *ipso* 1,5 fashion, resulting in a spirocyclised intermediate 240. Re-aromatisation and cleavage of the C-S bond furnishes the sulfur centred radical 241 that upon elimination of SO\(_2\) furnished the observed product *via* the aminyl radical 242. The cyclised product 236 (Scheme 55) was formed from a 1,6 addition onto the aryl ring, while the reduced product 238a-f occurs *via* reduction by TBTH of 239 prior to cyclisation.
When the tosyl substrate 235a was dissolved in anisole at 22 °C for 24hrs, the cyclised product 236a predominated (68%). Conversely, with diphenylether as the solvent (190 °C/30min) the rearranged product 237a predominated (64%). This showed that increasing the temperature alters the product distribution. Of course, if the ortho aryl positions were blocked, as with the mesitylene derivative 236e, only the rearranged product 237e was isolated. Further studies investigated the effects of changing the initiating halogen on the product outcome. While the iodo-nitro derivative 235f as depicted in Scheme 57 gave the rearranged product 237f in 56% yield.
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Scheme 57  Rearranged amide from nitro compound

The corresponding bromide 243 furnished only the dimeric azo sulfonamide 244 in 51% yield (Scheme 58). This indicated that azo formation was faster than the C-Br homolysis. Therefore, only iodides were used in further investigations.

Scheme 58  Dimerisation from nitro compound

In order to broaden the scope of their reaction, Speckamp and Köhler investigated further changes to the aryl substituent. Heteroaryl sulfonamides were also tolerated, thus a pyridyl sulfonamide 245, (Scheme 49) gave the expected rearranged product 246 in 30% yield, and the reduced product 247 in 28% yield, but no cyclised product was observed.

Scheme 59  Synthesis of rearranged amine from pyridyl sulfonamide
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When a 1-naphthyl sulfonamide 248, \((\text{Scheme 60})\) was treated under the standard conditions described above, a novel dihydronaphthalene cyclised product 250 was formed in 81% yield instead of rearrangement or oxidative cyclisation. The explanation given was that the “orbital interaction between the allylic radical 249 and the extended further \(\pi\)-system is favourable”.147

![Scheme 60 Cyclisation of 1-naphthyl sulfonamide](image)

However, when the 2-naphthyl sulfonamide 251 \((\text{Scheme 61})\) was used, it led to the cyclised product 252 in 28% yield and the reduced product 253 in 14% yield, with no dihydronaphthalene derivative being isolated.

![Scheme 61 Cyclisation from 2 substituted naphthalene](image)

3.3 Aryl radical cyclisation and rearrangement of aryl sulfonamides

While Speckamp investigated the addition of alkyl radicals onto aryl sulfonamides, Motherwell has investigated aryl radical additions onto similar substrates. The two main reaction modes (cyclisation and rearrangement) were also observed. This reaction has been used as a new method of Ar-Ar coupling148 \((\text{Scheme 62})\). This has been achieved

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by reacting biaryl sulfonamides \(254a-b\) with AIBN and tributyltin hydride. When substituents are on the \textit{ortho} position of the sulfonamide \(255a\) (\(R^1 = \text{Me}, R^2 = \text{H}\)), they undergo a 1,5 addition onto the second aryl ring which leads to the rearranged product \(256a\) via the analogous pathway described earlier in Scheme 56. When the substituents are in the \textit{para} position of the sulfonamide \(254b\) they undergo a 1,6- addition leading to a 1:1 ratio of cyclised \(255b\) and rearranged product \(256b\).

\[
\begin{align*}
254a-b & \quad \text{AIBN, } Bu_3SnH \\
\text{PhH, reflux} & \quad 255a-b + 256a-b
\end{align*}
\]

(a) \(R^1 = \text{CH}_3, R^2 = \text{H}; (b) R^1 = \text{H}, R^2 = \text{CH}_3\)

\textbf{Scheme 62} Motherwell's synthesis of biaryls and cyclic sulfonamides

Similarly, to the Speckamp studies varying the type of substituents on the \textit{ortho} and \textit{meta} position of the aryl sulfonamide was investigated.\(^{149}\) Inclusion of a methylene group between the aryl ring and the sulfonyl group \(257\) led predominately to cyclised products \(258\) with no rearranged products detected by the 1,6 \textit{ipso} mode. A number of heteroaromatic sulfonamides were tested (Scheme 64)\(^{150}\) including thiophenes \(259\) and quinolines \(261\) to furnish the cyclic sulfonamides \(260\) and \(262\) respectively.

\[
\begin{align*}
257 & \quad 1,7\text{-attack} \\
258 & \quad \text{major product (55\%)}
\end{align*}
\]
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Scheme 63  Examples of 1,7-\textit{ipso} cyclisation reactions

Inserting a further carbon between the aryl groups (but incorporating an alkene, i.e. unsymmetrical stilbenes) led to loss of SO\(_2\) but \textit{via} a different mechanism to that previously discussed.\(^{151}\) Reaction of phenyl allyl sulfonamides 263 (\textbf{Scheme 64}) under standard radical conditions (AIBN, TBTH) led to an intermediate 264 \textit{via} a 5-exo radical cyclisation onto the alkene. Elimination of sulfur dioxide subsequently yielded the rearranged product 265.

\textbf{Scheme 64}  Motherwell's stilbene synthesis

3.4  Related work

Speckamp has previously shown that the use of alkyl iodides was essential for cyclisation/rearrangement with the use of bromides leading to alternative reactions i.e. azo formation in the case of \(p\)-nitroaryl substrates 243 (see \textbf{Scheme 58}). In related work,
bromoaryl-benzenesulfonamides$^{152}$ (Scheme 65) if treated with $(\text{Ph}_2\text{HSi})_2$ instead of TBTH could successfully be used to make the spirocyclised intermediate 267 which went on to yield rearranged biaryl products 268 in 61% yield, following re-aromatisation,

![Diagram of Scheme 65](image)

**Scheme 65  Togo’s synthesis of biaryls**

Similarly, when sulfonamide xanthate 269 (Scheme 66) are treated with dilauroyl peroxide (DLP), the ensuring alkyl radical 270 can undergo a 1,5-\textit{ipso} addition to give the spirocyclohexadienyl radical intermediate 271. Re-aromatisation led to the amidosulfonanyl radical 272 which upon extrusion of sulfur dioxide furnished the amidyl radical 273 which gets reduced by 2-propanol to the rearranged amide product 274 in 81% yield.$^{153}$

![Diagram of Scheme 66](image)

**Scheme 66  Zard’s rearrangement reaction of sulfonamides**
3.5 Clark’s work

While the majority of this previous work has involved the use of toxic Bu$_3$SnH, work by Clark$^{154}$ has investigated whether similar reactions can be mediated by copper (I) complexes.$^{155}$ It was found that the tosyl amide 275 when treated with Cu(I)Cl and an amine ligand led to a 1,5 addition into the aromatic ring forming an initial spiro-compound 276. After re-aromatisation and loss of sulfur dioxide a novel rearranged product 277 was formed in 30% yield as illustrated in Scheme 67. No 6-endo cyclisation of 275 was observed.

![Scheme 67 Clark’s synthesis of rearranged amides](image)

Thus, the use of Bu$_3$SnH is not essential to mediate these types of reactions. The tremendous advantage of copper reagents is that the salts are inexpensive, and have a long shelf life. They are also non-toxic and the workup at the end of the reaction is easy to accomplish since purification consists of filtration using a small silica plug, and flushing the compound with ethyl acetate. In contrast, the disadvantages of the tin reagents are well known (eg toxicity, expense, the great difficulties encountered during purification and workup) but they tend to lead to reduced products as well in these types of reactions. This lowers the yield of the desired cyclised or rearranged product. The copper salts do not suffer from this disadvantage.
CHAPTER TWO

RADICAL REACTIONS OF \( N \)-BUTYL-
(SUBSTITUTED)-ARYL SULFONAMIDES
Chapter Two

1.0 Introduction

In light of the previous work discussed in Scheme 67, where substrate 275\textsuperscript{154} was observed to undergo rearrangement to form the rearranged amide 277 under ATRC conditions (see Scheme 68). It was decided to investigate this type of reaction further. The product 277 was tentatively assigned from the crude NMR spectra, and was not isolated pure, in addition, according to Wongtap,\textsuperscript{156} the product 277 was contaminated with an uncharacterized product, tentatively assigned as the reduced product (10:90), nor was an alternative synthesis to authenticate this product proposed. The mechanism hypothesized for the rearranged amide was plausible, according to Speckamp’s work. As has been previously shown that it is possible to mediate conventional atom transfer radical cyclisation (ATRC)\textsuperscript{157-160} reaction of unactivated bromides using copper bromide/TPA\textsuperscript{161-162} 279.

![Scheme 68](image)

**Scheme 68**  Clark’s synthesis of rearranged amides

The Clark group explored the rearrangement of unactivated bromide R = H 278 to amide 281.\textsuperscript{163} In order not to complicate the analysis of these reactions due to competitive cyclisation, the nitrogen group was changed from alkenyl 275 to N-butyl 278 as depicted in Scheme 69.
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Scheme 69  Murphy’s synthesis of rearranged amides

1.1  Aims and Objectives

The initial aim of this thesis was to determine the scope and limitation of this latter reaction (Scheme 69) by investigating the effects of the aryl substituent ($R$) on the efficiency of this rearrangement. Later chapters will investigate the effects of $N$-substitution and the acyl group. During this work, the effects of temperature and solvent will be investigated to determine whether this can influence the efficiency of the rearrangement. In addition, it was anticipated that it might be possible to obtain cyclised products by 6-exo cyclisation, into the aromatic ring and this was to be investigated.

2.0  Synthesis and use of sulfonamide starting materials

In order to develop a synthesis towards compounds 278, a preparation of the $N$-butyl substituted arylsulfonylamides 283 was required. An initial synthesis of these classes of compounds is shown below (Scheme 70). A range of commercially available arylsulfonyl chlorides 281a-m as illustrated in Table 1 were carefully selected for this study, as it was necessary to have an array of electron withdrawing and electron donating substituents for kinetic studies.
Scheme 70  Synthesis of starting sulfonamides

The Clark (Fullaway) group\(^\text{163}\) had previously developed a process towards substrate 278e, thus arylsulfonyl chlorides 281a, e-f (1.0 eq.) were treated with \(n\)-butylamine 282 (1.0 eq., pKa \(\approx 11\))\(^\text{164}\) and triethylamine (TEA) in dichloromethane (DCM), followed by acidic work-up to furnish the arylsulfonamides 283a-l. A similar method developed by Miyaka’s\(^\text{165}\) involved equimolar amounts of the arylsulfonyl chloride 281, \(n\)-butylamine 282 and triethylamine Method A followed by aqueous work-up that was successful in the majority of cases. An alternative approach utilised \(n\)-butylamine 282 (3.0 eq.) alone in diethyl ether Method B. Arylsulfonamides 283a-l were purified either by recrystallization\(^\text{166}\) (using diethyl ether/hexane), or by flash chromatography.\(^\text{167}\) Method B gave higher yields for most substrates, as little purification was required. Purification of 283g using flash chromatography (petrol ether/ethyl acetate 6:1) furnished low yield (26\%). In addition, purification of the 2-cyano substrate 283m using column chromatography failed. In light of these results, either Fullaway’s method or Method B furnished excellent yields of arylsulfonamides 283.
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![Reaction Scheme](image)

| Entry | Substrate | Method | Entry | Substrate | Yield (%) |
|-------|-----------|--------|-------|-----------|-----------|
| 281a  | H         | B      | 283a  | H         | 99<sup>168</sup> |
| 281b  | 4-F       | B      | 283b  | 4-F       | 90<sup>169</sup> |
| 281c  | 4-Br      | B      | 283c  | 4-Br      | 77<sup>170</sup> |
| 281d  | 4-I       | B      | 283d  | 4-I       | 86<sup>171</sup> |
| 281e  | 4-CH<sub>3</sub> | B | 283e  | 4-CH<sub>3</sub> | 89<sup>172</sup> |
| 281f  | 2,4,6-CH<sub>3</sub> | A | 283f  | 2,4,6-CH<sub>3</sub> | a |
| 281g  | 2-Naph.   | A      | 283g  | 2-Naph.   | 26<sup>173</sup> |
| 281h  | 4-OMe     | A      | 283h  | 4-OMe     | 90<sup>174</sup> |
| 281i  | 4-CN      | B      | 283i  | 4-CN      | 80<sup>175</sup> |
| 281j  | 4-NO<sub>2</sub> | B | 283j  | 4-NO<sub>2</sub> | 87<sup>176</sup> |
| 281k  | 4-CF<sub>3</sub> | B | 283k  | 4-CF<sub>3</sub> | 92 |
| 281l  | 3,5-CF<sub>3</sub> | A | 283l  | 3,5-CF<sub>3</sub> | 62 |
| 281m  | 2-CN      | A      | 283m  | 2-CN      | 0<sup>177</sup> |

<sup>a</sup> Gift from D. Fullaway.

Table 1 Synthesis of N-butyl-arylsulfonamides 283a-m.

2.1 Synthesis and use of the radical precursor 278

With a range of sulfonamides 283a-l in hand, the next goal was to react these with the appropriate acid bromide 284, to prepare a range of radical precursors 278a-l suitable for investigation (Scheme 71).
Scheme 71  Synthesis of radical precursors 278

The primary method involved reacting sulfonamides 281b-c,j with 2 equivalents of 1.6M n-butyllithium (pKa ≈ 48) in anhydrous THF, followed by addition of the acid bromide 284. Unfortunately, upon scrutiny, this approach gave numerous unidentifiable products that could have been due to the concentration of n-butyllithium and consequently an improved procedure was required. Fullaway\textsuperscript{163} devised a good method toward the radical precursors 278 using equimolar quantities of 1.6M butyllithium, the acid bromide 284 and starting sulfonamide 283. The highest yield was for the p-tosyl compound 278e in 79% yield, followed by the phenyl compound 278a in 48% yield. However, there was negligible yield obtained for the mestylene compound 278f (7%), which could be attributed to steric effects from the two ortho methyl groups. The reaction conditions were modified (according to Fullaway’s method) so that only 1 equivalent of 1.6M n-butyllithium (1.0 eq.) Method A was used in the reactions. This significantly enhanced the reaction yields though considerable quantities of the eliminated acrylamides\textsuperscript{178} 286a-l (see Figure 2) were isolated (tentatively assigned by NMR). However, good yields for the 4-bromo derivative 278c in 70% yield, 4-trifluoromethyl derivative 278k in 70% yield and 4-CN derivative 278i in 56% yield were achieved. To confirm the identify of 286a-l, the parent 286a was prepared unambiguously as below and its NMR spectra was compared to that obtained using Method A (Scheme 72).
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Due to the formation of unwanted elimination product 286a, an alternative method was used for the majority of the rest of the precursors. This involved changing from n-butyllithium to triethylamine (2.0 eq., pKa $\approx 11$) Method B as a base. For the majority of reactions, this procedure produced poor (<32%) 278e-g,j to fair (<58%) 278a-b,d,h yields of the desired products. In the case of the 4-nitro derivative 278j even with one equivalent of triethylamine, a small amount of the eliminated acrylamide 286j was detected. In order to resolve this problem, a hindered base (N,N-diisopropylethylamine, Hünig’s base, 1.3 eq.) Method C was used to hinder competing E2 elimination. Although no elimination occurred, the reaction was significantly impeded, so that unreacted 284 was hydrolysed to the corresponding acid upon work-up. However, in the case of 3,5-trifluoromethyl derivative 278l this approach was successful. All products were purified by flash chromatography to give sufficiently pure products that could be used for further studies (see Table 2).
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![Chemical structure](image)

**Table 2** Synthesis of the N-butyl-arylsulfonamides radical precursors

| Entry | Substrate  | Method | Yield (%) |
|-------|------------|--------|-----------|
| 278a  | H          | B      | 58 (48)²⁵³ |
| 278b  | 4-F        | B      | 52        |
| 278c  | 4-Br       | A      | 70        |
| 278d  | 4-I        | B      | 43        |
| 278e  | 4-CH₃      | B      | 22 (79)²⁵³ |
| 278f  | 2,4,6-CH₃ | B      | 22 (7)²⁵³ |
| 278g  | 2-Naphthalene | B    | 18        |
| 278h  | 4-OMe      | B      | 48        |
| 278i  | 4-CN       | A      | 56        |
| 278j  | 4-NO₂      | B      | 32        |
| 278k  | 4-CF₃      | A      | 70        |
| 278l  | 3,5-CF₃    | C      | 67        |

Figure 2 Structure of eliminated product 286
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3.0 Synthesis of the amine ligand-TPA 279

One of the most important reagents involved in these radical reactions is tris(2-pyridylmethyl)amine (TPA). As will be explained shortly, the amine can interact with copper salts to form a soluble copper-amine ligand complex. The synthesis of TPA 279 was relatively straightforward using Geden’s method.\(^{162}\)

3.1 Reaction of parent compound 278a with copper (I) salt/TPA complex

As previously mentioned in Scheme 67 initial work on substituted arylsulfonamides 278 using copper (I) salts and tren\(^{154}\) showed that a rearrangement to 277 could take place. Later work using copper (I) salts and TPA 279 as ligand (instead of tren) improved yields. Consequently, a series of experiments were conducted using the phenyl substrate 278a as depicted in Scheme 73. Heating a mixture of sulfonamide 278a (1.0 eq.) with equimolar amounts of copper (I) bromide (1.2 eq.) and TPA 279 (1.2 eq.) in refluxing toluene for 48 hours, led to complete disappearance of starting material. Analysis of the crude NMR (see Appendix 1) showed two products in a ratio of 1:5. The minor component was identified as the rearranged amide 280a. The structure for 280a was determined by \(^1\)H NMR as shown in Figure 3.

\[
\text{Scheme 73 Reaction of radical precursor with CuBr and TPA 279}
\]
Figure 3  
$^1$H NMR assignment of phenyl rearranged amide

Analysis of the phenyl rearranged amide 280a was made by $^1$H NMR. Characteristic data involved a multiplex 7.4-7.25 (5H) for aromatics. A singlet at 1.55 for the dimethyl groups (6H), and peaks characteristic of the $n$-butyl group (2.92 (t), 1.46-1.39 (quintet), 1.33-1.23 (sextet), 0.80 (t). The N-H group appeared as a broad singlet at 5.41ppm. The major product Figure 4 showed four distinct aromatics peaks indicative of a cyclised product which was tentatively assigned as 287.

Figure 4  
Structure of the proposed cyclic sulfonamide 287

Mechanistically this would arise from cyclisation of the radical 288 into the aromatic ring to give 289 followed by re-aromatisation to furnish the cyclic sulfonamide 287 as depicted in scheme 74.
3.2 Purification of the radical products

The reaction of the phenyl derivative 278a was monitored by TLC, which showed two products tentatively identified as the cyclised product 287 and the rearranged amide 280a. Due to the close proximity in Rf values between the starting material 278a and the cyclic sulfonamide 287, determining the end point of the reaction was very difficult. Further difficulty involved visualisation of the products, which were present in minor quantities. Isolation of the cyclised and rearranged products was achieved using careful flash chromatograph and $^1$H NMR analysis of individual column fractions.

3.3 Characterisation of cyclised material 287

While full characterisation data for 287 and 280a was obtained, the mass spectra (EI or LSIMS-FAB) was lacking an $M^+$ for 287 (RMM = 281.1086) and instead $M^+-SO_2$ was observed (RMM = 217.1459). The extrusion of SO$_2$ in mass spectrometry of cyclic sulfonamides is well known and examples where an $M^+$ cannot be found are present in the literature. Instead $M^+-SO_2$ was observed and reported. However, while there was precedent for the extrusion of SO$_2$ in mass spectrometry, in order to be certain of the assignment of 287 a sulfur analysis was obtained. Theoretically, this should be 11.4%, instead only 0.43% was detected indicating minimal sulfur. A CHN analysis was also obtained. Theoretically this should be C, 64.2; H, 7.2; N, 17.2 for 287 instead the values obtained were C, 74.2; H, 8.6; N, 6.0. Thus it was very likely that no SO$_2$ was present in the product 287, and that the $M^+$ peak at 217 is not $M^+-SO_2$, but the correct mass for the molecular ion. Another technique to determine the presence of sulfur may be the use of $^{33}$S NMR. However this was not attempted. The major disadvantage being the small gyromagnetic ratio (1/13 that of $^1$H) and low natural abundance (0.75%), that makes determining the small quantity...
of sulfur in the product 287 very difficult. An alternative approach for determining the sulfur analysis would be either ICP-Emission, at minimum of 50μg/L of sulfur or ICP-MS, at minimum of 500μg/L.\textsuperscript{182} Other techniques not used but might be useful for analysis are \textsuperscript{15}N NMR\textsuperscript{183, 184} or the use of \textsuperscript{17}O NMR\textsuperscript{185} which might show a change in the carbonyl group. For amides, this is typically around 300ppm when using dioxane as the NMR standard. The difficulty with \textsuperscript{17}O NMR is again associated with low natural abundance (0.037\%) and sensitivity 10^5 less than a proton. A literature search suggested that the \textsuperscript{13}C NMR\textsuperscript{186} data for the current compound matched that for the known oxindole 290 (Figure 5). Based on these results, it would appear that the cyclised material was 290 and not 287 (see Appendix 2).

![Figure 5](image-url) **Figure 5** Structure of the oxindole 290

Whilst this was not the expected result, it was clear that further work would be required in order to obtain the cyclic sulfonamides if they were needed for the future. These compounds are pharmacologically important. They have well-known diuretic, antihypertensive, and anticonvulsive properties.\textsuperscript{187} Although the cyclised sulfur compound 287 is not known, the related compound 302 has been reported in the literature.\textsuperscript{187} Treatment of \textit{o}-nitrotoluene 291 (Scheme 75), with diethyl oxalate 292 in sodium ethoxide (generated \textit{in-situ} from sodium metal and ethanol), led to \textit{o}-nitrophenylpyruvic acid ethyl ester 293. Hydrolysis of the ester led to the \textit{o}-nitropyruvic acid derivative 294. Treatment of 294 with hydroxylamine hydrochloride 295 furnished the \textit{o}-nitropyruvic acid oxime 296. Hydrolysis and
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decarboxylation of the oxime 296 with acetic anhydride yield the o-nitrobenzylcyanide 297. Hydrogenation of 297 with palladium on charcoal in absolute ethanol, and hydrogen gas at 50Ib/psi atmosphere furnished the o-aminobenzylcyanide 298.\(^\text{188}\) Diazoniation of 298 from sodium nitrite and hydrochloric acid, followed by addition of sulfur dioxide and copper(II)chloride led to the o-sulfonyl chloride derivative 299. Treatment of 299 with n-butylamine 282 furnished the arylsulfonamide derivative 300. Hydrolysis of the nitrile group gave the acid derivative 301, and this was followed by acid-induced cyclisation to give the cyclic sulfonamide 302.\(^\text{189}\)

\[
\begin{align*}
\text{Scheme 75} & \quad \text{Synthesis of the cyclic sulfonamide precursor} \\
\text{Theoretically it should be possible to methylate 302 to the cyclic sulfonamide 287 as depicted in Scheme 76, which would allow Clark and Murphy to unambiguously determine if this product was presenting the crude NMR of 290. This synthetic approach however proved too lengthy (nine steps)\(^\text{187-189}\) and was not undertaken.}
\end{align*}
\]
Consequently, the structure of the oxindole 290 has been confirmed by comparison to the literature data.\textsuperscript{190}

\[
\begin{array}{c}
\text{Scheme 76 Methylation of the sulfur precursor 287}
\end{array}
\]

3.4 Potential mechanism for oxindole formation

Other groups have noted extrusion of SO\textsubscript{2}\textsuperscript{151} during cyclisation of sulfonamides. In the following example, vinylic sulfonamide 303 (Scheme 77) when treated with tributyltin hydride and AIBN furnished the aryl radical intermediate 304. This could undergo a 1,6-expo attack onto the alkene to form the cyclic radical intermediate 305. Ring opening followed by extrusion of sulfur dioxide led to the amidyl radical intermediate 306. Addition of the amidyl radical \textit{via} 1,5-expo attack onto the alkene gave the oxindole radical intermediate 307, which followed by H-abstraction of tributyltin hydride formed the oxindole derivative 308.
Scheme 77  Motherwell’s synthesis of an oxindole from sulfonamide

Motherwell has shown that radical cyclisation of vinylic sulfonate \textbf{309} (scheme 78) occurs similarly to give the 6-\textit{exo}-product \textbf{311} in 70\% yield, along with a minor amount of the ring contracted ether \textbf{310} in 5\% yield \textit{via} extrusion of SO$_2$.$^{152}$ However, no analogous pathway to these observations is available in the current reaction to give oxindole \textbf{290}.

Scheme 78  Motherwell’s cyclic ether synthesis \textit{via} SO$_2$ extrusion

Alternatively, the oxindole \textbf{290} may be formed by direct cyclisation of the amidyl radical.$^{191}$ In the following example, xanthate \textbf{312} (Scheme 79) when treated with dilauroyl peroxide generated the alkyl radical \textbf{313}, which underwent an
intermolecular attack onto the alkenyl group of the \( N \)-allylsulfonylamide 314. This was followed by formation of the \( N \)-amidosulfonyl radical intermediate 315 and extrusion of sulfur dioxide to give the amidyl radical intermediate 316 followed by rapid 5-\( \text{exo} \) cyclisation onto the terminal alkene to furnish the lactam radical intermediate 317. The radical intermediate 317 can undergo addition to another molecule of 312 to give the lactam 318 and regenerating the radical 313, which could undergo the whole radical process described above.

**Scheme 79**  Zard’s synthesis of pyrrolidines through sulfonamides

Consequently in the current reaction, the oxindole 290 (Scheme 80) may be formed by cyclisation of the amidyl radical 322 generated from the tertiary radical 319 via 1,5-\( \text{ipso} \) cyclisation and re-aromatisation to give 321 followed by loss of SO₂. Addition of the amidyl radical onto the aromatic ring followed by oxidation (presumably \( \text{via} \) Cu(II)Br₂) would yield the oxindole 290.
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Scheme 80 proposed synthetic approach to oxindole

Alternatively, it may be possible that oxindole 290 forms via extrusion of SO$_2$ directly from the cyclic sulfonamide 287 as depicted in scheme 81.

Scheme 81 Proposed synthetic approach to oxindole

It should be possible to determine which of these two mechanisms is operating if a substituent is appended to the aromatic ring. This is because both mechanisms lead to different regioisomeric oxindoles (Scheme 82).

Scheme 82 Proposed mechanisms for regioisomers
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The final solution would be to complete an unambiguous synthesis of each of the regioisomers themselves. However, before this mechanistic curiosity could be addressed, it was necessary to a) determine if this was a general reaction, b) optimise the reaction conditions to increase the yield of the reaction, and c) observe if it was possible to alter the ratio of the two products under different conditions.

An investigation towards the reaction of the phenyl derivative 278a (Scheme 83) under two experimental constraints were made. The first was to investigate the amount of copper (I) bromide and TPA 279 required to give complete conversion of the radical precursor 278a to products, and establish the effect on product outcome. Secondly, the role of using different temperatures to determine product outcome was studied as depicted in Table 3. For these experiments, both toluene and dichloromethane were used as these solvents are common solvents in ATRC. Typical experimental conditions are as follows: To a small three-necked flask was added the radical precursor 278a (1.0 eq.), copper (I) bromide (1.2 eq.) and TPA 279 (1.2 eq.). Toluene or dichloromethane was added via syringe. The reaction mixture was heated under a nitrogen atmosphere at reflux for a specified time. The reaction was quenched with ethyl acetate and the solvent evaporated in-vacuo to yield a brown or green crystalline solid. The crude product was obtained using ethyl acetate as the eluent and filtered through a silica plug to remove the inorganic copper residue.
Scheme 83  Phenyl sulfonamide radical reaction

| Entry | Reaction conditions | Conversion % | Mass balance % | Ratio 280a:290 |
|-------|---------------------|--------------|----------------|----------------|
| I     | PhMe, rt, 96h       | 0            | 100            | 0:0            |
| II    | DCM, rt, 168h       | 33           | 65             | 1:0            |
| III   | PhMe, 50 °C, 18h    | 12           | 83             | 1:1            |
| IV    | DCM, 37 °C, 18h     | 100          | 78             | 1.4:1          |
| V     | PhMe, 110 °C, 12h   | 100          | 72             | 0.3:1          |
| VI    | PhMe, 110 °C, 48h   | 100          | 66             | 0.2:1          |

Key: Mass balance is defined here as the mass of the crude product isolated, divided by the mass of radical precursor 278a used, expressed as a percentage. Conversion is defined here as the amount of [cyclised:rearranged] product obtained in the reaction minus the radical precursor, i.e. no radical precursor in NMR = 100% conversion to products.

Table 3 Table for the parent substrate 278a in solvents at varying temperature

[I]: At room temperature, the CuBr/TPA ligand complex was insoluble in toluene and that the temperature was insufficient to generate a reaction. Consequently, only starting material was re-isolated (100%).

[II]: In order to determine if a more polar solvent such as dichloromethane (DCM) would increase the solubility of the CuBr/TPA complex ligand (L) and thus facilitate the reaction at room temperature, the solvent was changed for this reaction. Notably under these conditions it was possible to mediate the reaction, however, it was relatively slow [67% starting material remained after 168h]. Moreover, only the
product assigned as the rearranged amide \(280a\) was detected, no oxindole \(290\) was isolated. The increase in solubilization of the CuBr/TPA ligand complex (L)\(^{192}\) is important in facilitating this reaction. The solvent can also change the redox potential of Cu(I)/Cu(II) salts,\(^{193}\) and by participating in bonding to the copper ligand complex geometry.\(^{194}\) Thus in DCM there may be a change in redox potential which helps to facilitate carbon-bromide bond homolysis. This eventually leads to the rearranged product \(280\) (and cyclised product). Electrochemical studies\(^{195}\) using cyclic voltammetry have provided proof that a change in redox potential occurs with different solvents.

[III]: Heating in PhMe for 18h at 50 °C did facilitate the reaction although it proceeded slowly, with only a small amount (12% conversion) of two products being produced in roughly 1:1 ratio, although the inaccuracy of this measurement is large due to small amounts of material in the crude NMR and the errors in integration of \(^1H\) NMR signals. The formation of an equal amount of the cyclised product \(280\) and the rearranged amide \(290\) would indicate that the CuBr/TPA ligand complex was more active than in experiment I. This is presumably due to the increased temperature at which the reaction was conducted leading to better solubility of the Cu complex.

[IV] Having observed that the reaction proceeded, and a possible selectivity for the rearranged product \(280a\) in DCM at RT, the next task was to increase the temperature, in order to force the reaction to completion. Thus heating at 37 °C for 18h allowed the reaction to go to completion, although now the major product was the rearranged \(280a\) instead of the cyclised \(290\) product. In this reaction, the increase in temperature has improved the solubilisation of the ligand complex and also the rate of reaction. The selectivity towards the rearranged amide, might be due to more
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efficient H-abstraction of the amidyl radical intermediate 322 from dichloromethane of higher temperatures. This hypothesis could be tested by using a poor hydrogen donor as the solvent under the same conditions (i.e. tert-BuOH) or increasing the temperature further.

[V]: The previous reactions with toluene [I] and [III] showed very poor turnover and solubility of the ligand complex. When the reaction was repeated in refluxing toluene for 12 hours the reaction proceeded to completion, but now the cyclised product 290 predominated. The reaction was shown to be complete (100% conversion) producing the two compounds 280a/290 in a 0.3/1 ratio. The increase in temperature has improved the rate of reaction as expected. However contrary to the reaction in toluene the oxindole now predominates indicating that the rate of cyclisation is greater than H-abstraction in toluene at higher temperature

[VI]: In order to determine whether an increase in time would alter the product distribution (i.e. to determine if the reaction was under kinetic or thermodynamic control), the reaction was repeated in refluxing toluene for 48 hrs instead of 12 hrs. However, heating for 48 hours (four times the length as in entry V) furnished only a similar yield and ratio of products, 0.2/1 (within the level of accuracy of measurement by NMR). This would indicate that increasing the time does not change the outcome in terms of either selectivity or overall yield. This suggests either the reaction is under kinetic control or the reaction has reached its thermodynamic equilibrium after 12 hrs. Experimental work should be conducted to determine the precise time taken for complete conversion to products.

Summary:
The results indicate that CH₂Cl₂ is a superior solvent with respect to the rate/conversion of the reaction than toluene is at the same temperature. This is
presumably due to the improved solubility of the CuBr/TPA complex in this solvent. Conducting the reaction at higher temperatures appears to increase the proportion of cyclic material with DCM at 37 °C, preferentially giving rearranged amide 280a while toluene at 110 °C preferentially furnished oxindole 290. This was interesting since similar work by Speckamp\textsuperscript{145} on related systems has shown that lower temperatures generally led to cyclised products (anisole, RT, 24h), while rearranged amides were furnished with elevated temperatures (diphenylether, 190 °C, 0.5h). Having shown that the product ratio was sensitive to temperature the following experimental work involved investigating the effect of five further solvents, notably methanol, THF, MeCN, H$_2$O, BMIM BF$_4$ (a common ionic liquid), all at the same temperature (Table 4).

![Chemical structures](image)

| Entry | Reaction Conditions | Conversion % | Mass balance | Ratio 280a:290:X$^a$ |
|-------|---------------------|--------------|--------------|----------------------|
| VII   | MeOH, 50 °C, 18h    | 69           | 66           | 2:1:3                |
| VIII  | THF, 50 °C, 18h     | 88           | 54           | 2:1:0                |
| IX    | H$_2$O, 50 °C, 18h  | 100          | 51           | 2:1:0.2              |
| X     | MeCN, 50 °C, 18h    | 100          | 74           | 1:0:6                |
| XI    | BMIM BF$_4$, 50 °C, 18h | 100          | 13           | 0.1:1:0.2            |

$^a$ Significant amounts of uncharacterised by-product.

**Table 4**: Effects of solvent on product distribution.
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Brief observations:

[VII]: The solubility of the copper ligand complex (L) was improved relative to both toluene and DCM using methanol but NMR analysis showed that the reaction had only gone to 66% completion after 18 hours and that it showed significant amounts of uncharacterised by-products.

[VIII]: In the copper ligand complex (L) was readily solubilised. The reaction was faster than in MeOH, with analysis showing the reaction had gone to 88% completion after 18 hours. It was also cleaner than in MeOH with no by-products detected.

[X]: In this experiment deionised water was degassed with nitrogen for fifteen minutes. Excellent solubility was observed with the copper ligand complex (L). There was complete conversion to products. However minor amounts of similar by-products to those detected in MeOH were produced.

[IX]: Acetonitrile readily solubilised the copper ligand complex (L). Acetonitrile is often the choice solvent for ATRC reactions, however the reaction was not clean giving significant amounts of unidentifiable products which precluded all efforts to separate them in order to glean spectroscopic information.

[XI]: N-butyl-N-methyl imidazolium tetrafluoroborate was used as an ionic liquid in order to investigate the effects of a polar environment. There was complete conversion to products under these conditions and this was selective towards the cyclised material 290 although the low mass balance was disappointing and was due to difficulty in extracting the products from the ionic liquid.

While all these solvents were able to facilitate the reaction to a certain extent, the reactions were messy with numerous compounds being produced in addition to the compounds of interest (Appendix 3). Ligand complex solubility was markedly
improved in all the solvents compared relative to toluene; however, they did not enhance the selectivity for either of the products $280a/290$ to a synthetically useful level. The exception was THF, which was cleaner and gave the ratio of $280a/290$ as 2/1 although only to 88% conversion. There were some difficulties with extraction of the crude products from some of the solvents. With highly solubilised ligand complex, the light green copper (II) bromide is sometimes present along with the crude products. This is evident from the $^1$H NMR which shows peak broadening due to paramagnetic Cu$^{2+}$ ions ([Ar]$3d^9$).$^{196}$ Although not fully characterised, it seems that the minor components (uncharacterised by-product) consist of $286a$, the corresponding sulfonamide $283a$ and the reduced$^{178}$ product $323$ (Figure 6). It became clear that the cleanest reactions with the best mass balance involved using either DCM or toluene.

![323]

**Figure 6** Pheny reduced product 323

The most probable explanation for the formation of the reduced product $323$ from some of the reactions would be H-abstraction from the solvent by radical $319$ (Scheme 84). An alterative mechanism would be via an initial intramolecular 1,5-H abstraction $319$ to $324$ followed by reduction of $324$ by the solvent.


Scheme 84  Potential mechanism for the reduced product 323

Other reactions that could come from the secondary alkyl radical intermediate 324 could give further products that may be contained in the uncharacterised mixture of products. Thus a 1,5-\textit{ipso} attack of 324 to furnish the cyclohexadienyl radical intermediate 325, followed by re-aromatisation and extrusion of sulfur dioxide to give the amidyl radical intermediate 326 could occur (Scheme 85). At this juncture, the amidyl radical intermediate 326 can be quenched via the solvent to give the rearranged amide 327 or undergoes cyclisation into the aromatic ring, followed by oxidation to the oxindole 328. Alternatively, the alkyl radical intermediate can undergo direct addition into the aromatic ring to furnish the cyclic sulfonamide 329, followed by loss of sulfur dioxide and subsequent amidyl radical addition into the aromatic ring to furnish 328.
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Scheme 85  Proposed mechanism based on 1-5 ipso and direct cyclisation

4.0 Use of tosyl sulfonamide 278e and mechanistic insights into oxindole formation

Having investigated the effects of the copper (I) bromide-TPA ligand on the neutral phenyl derivative 278a, and determining that under certain solvent conditions, that it was possible to obtain either the rearranged amide 280a or the cyclised product 290, attention was turned to substrates with varying groups on the sulfonamide aromatic ring. The purpose was to determine the effect of the copper (I) bromide-TPA and solvent effects on product outcome. The first substrate investigated was the tosyl derivative 278e (Figure 7).

Figure 7  Structure of the tosyl radical precursor 278e
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4.1 Introduction

Early work by Clark and Fullaway\textsuperscript{163} showed reacting \textbf{278e} CuBr and various amine ligands could furnish the rearranged amide \textbf{280e} and a cyclised product initially proposed as the cyclic sulfonamide \textbf{332}. A series of amine ligands were used in conjunction with Cu(II)Br to form the ligand complex (L). The first experiment involved reaction of \textbf{278e}, bipyridine (2.0 eq.) and CuBr (2.0 eq.) in dichloromethane to furnish exclusively the rearranged amide \textbf{280e} but only in 26% yield. The following reaction involved using pentyl-pyridin-2-ylmethylenamine \textbf{330} (3.0 eq.) and CuBr (2.0 eq.) in dichloromethane. Again only the rearranged amide was isolated in poor yield (21%). Further work involved using [1,10]-phenanthroline \textbf{331} (2.4 eq.) and CuBr (1.2 eq.) in dichloromethane gave no reaction. The reaction conditions were improved when equimolar amounts of tris(2-pyridinylmethyl) amine (TPA) and CuBr in dichloromethane (30 mL) were used. In this case, the rearranged amide was produced in good yield (56%). Remarkably, when the reaction was repeated with equimolar amounts of TPA and CuBr in dichloromethane (5 mL) this led to a cyclic product that was believed to be the cyclic sulfonamide \textbf{332} and the rearranged amide \textbf{280e} in 54% yield. The only difference in reaction conditions being one of concentration.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme86.png}
\caption{Fullaway’s synthesis of rearranged amide and cyclic product}
\end{figure}
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Mass Spectrometry of the cyclic compound 332 showed an M⁺ (RMM = 231), which was contrary to the expected M⁺ (RMM = 295). This could only occur from M-SO₂, indicating that it was most likely the oxindole 333 (Figure 8) and that the Clark group¹⁶⁵ had wrongly assigned the cyclic compound as 332 and not as oxindole 333. No elemental analysis was done, nor an unambiguous synthesis of the sulfur compound 332 or oxindole 333 to adequately prove the structure of the cyclic compound. Consequently, the next step was to re-investigate this reaction.

![Figure 8](image)

**Figure 8**  Structure of oxindole 333

In the previous section, it was postulated that there were two possible mechanisms (Scheme 82) for the formation of the oxindole product 290 and that carrying out the reaction would allow determining which of these two mechanisms is operational. Thus the reaction of the tosyl analogue 278e CuBr/TPA was further investigated. The presence of the para-methyl substituent would give a structural handle to determine how the reaction proceeds. If the mechanism goes via extrusion of SO₂ from the cyclised compound, 334 then oxindole¹⁹⁰ isomer 333 would be produced, if the oxindole occurs from cyclisation of the amidyl radical 335, the alternative oxindole isomer 336 should be detected.
Reacting bromide 278e with copper bromide/TPA in PhMe at reflux for 24h [I] furnished three products in a combined 94% overall yield. Chromatography of the mixture separated the rearranged amide 280e but the other two compounds eluted together. These two inseparable compounds were tentatively identified as the two possible oxindole regioisomers 333:336 in a 0.03:1 ratio.

4.2 Proposed methods for separation of regioisomers

In order to unambiguously assign the structures of the cyclised products it was necessary to separate them. However, several problems were encountered with separating these products, due to the close proximity of the Rf valves of the radical precursor 278e and both the desired cyclic compound(s) 333 or 336. The use of flash chromatography to isolate the products pure through individual column fractions was not sufficient to separate the regioisomers. Several methods have been used to prove regioisomeric oxindole structure and there has been some success in separating oxindole mixtures (by other researchers).
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Structure determination.

- NMR spectroscopic techniques\textsuperscript{197} for determining regioisomeric oxindoles:
  1. NOE\textsuperscript{198} 
  2. HMBC\textsuperscript{198} 
  3. HETCOR\textsuperscript{199} 
  4. INEPT\textsuperscript{199} 
  5. COSY\textsuperscript{199} 
  INADEQUATE.\textsuperscript{200}

- (1) X-Ray Diffraction,\textsuperscript{201} X-Ray Crystallography\textsuperscript{202}

Separation

- Separation techniques for isolating regioisomeric oxindoles: 
  1. Reverse-Phase Column Chromatography,\textsuperscript{203} 
  2. HPLC-UV detector\textsuperscript{203} 
  3. Reverse-Phase HPLC,\textsuperscript{204} 
  4. GLC\textsuperscript{204} 
  5. MPLC\textsuperscript{205}

- Capillary Electrophoresis\textsuperscript{206}

However while the methods could have been used to separate the products, ultimately an unambiguous synthesis of both of them was required.

a) Preparative TLC was used for small quantity of products (<100mg), unfortunately, the products could not be separated because the Rf values were too close.

b) Preparative HPLC was available at Warwick, although due to high demand, it was not possible to use this method continuously.

c) GLC was available at Warwick, but again due to high demand, it was not possible to use this method continuously.

One main problem with the separation and identification of the regioisomeric oxindoles was the low yield that they were isolated in. The maximum obtained was 50mg. An INADEQUATE experiment was attempted, but failed to provide good spectra, due to insufficient products.
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4.3 Radical reaction of tosyl precursor 278e

The identification of the major cyclised compound was accomplished by synthesising the oxindole 333 unambiguously. This was achieved using a modification of the Stollé synthesis (Scheme 88). In the original method, Stolle\textsuperscript{207, 208} had reacted $\alpha$-chlorocarboxylic acid chlorides with alkylated anilides to furnish precursors 337 for intramolecular Friedel-Craft alkylation reactions. The intramolecular Friedel-Craft alkylation was mediated using aluminium chloride to furnish the oxindoles 338.

Scheme 88 Stollé synthesis

For 333 a variation to this approach was used,\textsuperscript{209-212} namely preparing the related bromo-analogue 341 as outlined in Scheme 89.

Scheme 89 Synthetic route toward the oxindole 333

Key: (a) (i) NaH, DMF, (ii) n-BuI, RT, 24h; (b) TEA, 284, RT, 3h; (c) AlCl$_3$ Anh. 50ºC at 10 min. then 160ºC at 60 min.
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This approach was used to prepare a sample of the oxindole 333 although some hydrolysis of the amide bond in 341 occurred under the reaction conditions. With 333 in hand, it was possible to determine that this oxindole was the minor component of the two cyclised products (1:0.03) obtained in the copper-mediated reaction of 278e.

4.4 Attempted synthesis of the major oxindole 336

In order to be certain that the major cyclised product resulting from the copper-mediated reaction was the regiomeric oxindole 336 it was necessary to make an authentic sample of this compound as well. The outline of the synthesis is shown in Scheme 90. The oxindole 336 was prepared using the same procedure as used for the minor product 333. Although two regioisomers 346 and 336 were obtained (again inseparable), the proton NMR spectra obtained from this crude mixture, tentatively shows the product from the copper reaction to be the oxindole 336, (see Appendix 4). Whilst it cannot be said with 100% certainty, it is likely that the major cyclised product is the oxindole 336 due to these spectral similarities. This would have been formed via the amidyl radical intermediate 335 cyclising onto the aryl ring (335 to 336 as depicted in Scheme 87. Due to time constraints, it was not possible to repeat this experiment. The methyl analogue of oxindole 336 has been synthesised by Nishio’s178 group (Figure 9) and NMR was consistent with assignment of 336.

![Figure 9](image_url)

**Figure 9** Structure of Nishio oxindole 342
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Key: (a) (i) NaH, DMF, (ii) n-BuI, RT, 24h; (b) TEA, 284, RT, 3h; (c) AlCl₃, Anh. 50ºC at 10 min. then 160ºC at 60 min.

Scheme 90  Synthesis of oxindole 336

4.5 Authentic synthesis of the rearranged amide 280e

Having proven the identity of the two oxindoles 333 and 336 the next step was to prepare an authentic sample of the rearranged amide 280e for comparison with that obtained from the reaction of 278e. This approach involved the dialkylation of the known ester 347.²¹³-²¹⁶

Scheme 91  Synthesis of the di-methylated product 348

The first method for dialkylation investigated involved treating the ester 347 with sodium hydride (2.2 eq.) in anhydrous THF followed by iodomethane (2.2 eq.) at
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room temperature for 48 hours (Method A). Analysis of the crude reaction mixture by NMR showed that the reaction had failed to provide 348, and that only a monomethylated product 349 had been formed. In order to push the reaction to completion, the monomethylated product 349 was re-exposed to the reaction conditions (i.e. treated with sodium hydride (1.2 eq.) and iodomethane (2.0 eq.) at RT for 24 hours). The crude NMR analysis again showed only the monomethylated product 349. This indicated that the second alkylation was slow presumably due to alkylation of a tertiary carbon. The next step involved modifying the reaction so the ester 347 was treated with sodium metal chips (3.0 eq) in anhydrous ethanol (95%), and iodomethane (3.0 eq.) at RT for 48 hours (Method B). The crude NMR again showed only the monomethylated product 349. Thus, it seems that the second alkylation was particularly slow under these conditions as well. In light of these problems, a stronger base was used. The ester 347 was treated with n-butyllithium (1.6M) (2.2 eq.) in anhydrous THF, followed by iodomethane (2.2 eq.) (Method C). While successful in part (both 348 and 349 were produced as indicated by NMR data of the crude reaction mixture) the reaction did not provide enough 349 to continue.

An alternative procedure to Method A was next used. The ester 347 was treated sodium hydride (3.6 eq.) in anhydrous DMF and iodomethane (3.6 eq.) (Method D). Distillation of the crude product gave a mixture of 348 and 349. Further purification using flash chromatography separated the desired dialkylated ester, albeit in low yields (6%). The reaction was repeated using sodium hydride (3.0 eq.) in the more polar DMF and iodomethane (3.0 eq.). The ester 347 was added dropwise to the suspension over one hour (Method E). Again chromatography was required after initial distillation and gave the dialkylated product 347 in slightly better yield (20%).
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The *gem* methylated ester 348 was next subjected to hydrolysis with ethanolic potassium hydroxide solution to give the acid 350 in 74%. This was followed by conversion to the acid chloride 351 in 31% yield using excess oxalyl chloride. The amide 280e in 84% was then prepared from the acid chloride 351 with excess butylamine 282. The spectroscopic details matched those of the product isolated from the copper mediated reaction (Scheme 87).

\[
\begin{align*}
&\text{348} \quad \xrightarrow{[a]} \quad \text{74\%} \quad \text{350} \quad \xrightarrow{[b]} \quad \text{351} \\
&\text{84\%} \quad \xrightarrow{[c]} \quad \text{280e}
\end{align*}
\]

Key: (a) (i) KOH, Anh. EtOH refluxed 6d (ii) acidified with 2M HCl; (b) (COCl)\textsubscript{2} DCM 40 °C 24h; (c) nBuNH\textsubscript{2} (3.0 eq.), RT, 2d.

**Scheme 92**  Synthesis of the rearranged amide 280e

4.6 Reaction of tosyl substrate 278e in various solvents

As is the case from the previous reaction of the phenyl radical precursor 278a, evidence of both cyclised products and rearranged amide was presented. The next step was to determine the effects of solvent on the substrate 278e and see if it was similar to that observed with 278a. In this reaction, the methyl group would be weakly electron donating, and this effect would indicate the effect on cyclisation and rearrangement with respect to the parent precursor 278a.
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Scheme 93  Radical reaction of tosyl derivative 278e

| Entry | Reaction Conditions | Conversion | Mass Balance | Ratio |
|-------|---------------------|------------|--------------|-------|
| 278e  |                     |            |              |       |
| I     | Toluene, 50 ºC, 18h | 46         | 64           | 0.4:1 (1:1) |
| II    | Toluene, 110 ºC, 24h| 100        | 94           | 0.6:1 (0.3:1) |
| III   | DCM, 37 ºC, 18h    | 85         | 65           | 1.2:1 (1.4:1) |
| IV    | THF, 50 ºC, 18h    | 76         | 69           | 1:1 (2:1) |
| V     | H2O, 50 ºC, 18h    | 24         | 74           | 1:1 (2:1) |

*Ratios for cyclisation of parent 278a in parenthesis for comparison*

**Table 5  Effects of varying conditions on product distribution for 278e.**

As with the substituted phenyl precursor 278a a selection of solvents were used to determine the effects on product distribution and conversion. As before the reaction in toluene and DCM were the cleanest with those in THF and H2O producing other uncharacterised by-products. In addition, the reversal of selectivity moving from toluene to DCM (Entry II and III, Table 5) reflects the same trend as for the parent structure 278a (Entry IV and V, Table 3, page 100). The reason for the selectivity would most likely be due to a competition between cyclisation and rearrangement from the amidyl radical intermediate 335. In the case of a poor hydrogen donor, the reaction is pushed towards cyclisation. However, in the case of polar solvents such as DCM, the reaction is pushed towards rearrangement; this is because the amidyl radical intermediate can be quenched more readily from a better hydrogen donor.
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5.0  \(N\)-Butyl-2, 4, 6-trimethyl-benzenesulfonamide 278f

Having established that reaction of both 278a and 278e led to both rearranged and oxindole formation, the following experiment involved investigating the reaction of the mesitylene sulfonamide 278f. The presence of the \textit{ortho} methyl groups ensures that no oxindole can be formed but theoretically allowing only the rearranged compound to be produced 280f. However, the presence of the \textit{ortho} methyl groups is also likely to retard the rate of formation of the rearranged amide 280f due to increased steric hindrance for the \textit{ipso} attack at the aromatic sulfonamide carbon.

No reaction was obtained upon heating in toluene at 50 ºC for 18h (this should be compared to 46% conversion of the tosyl analogue 278e under these conditions). Interestingly it was possible to convert 278f to the desired 280f if the reaction was run in the ionic liquid BMIM BF\(_4\). Although the reaction indicated no starting material, only a 25% isolated yield of 280f was obtained (Table 6). Poor yields were attributed to difficulty in isolating the product from the ionic liquid.

\[\text{Scheme 94} \quad \text{Radical reaction of mesitylene sulphonamide 278f}\]

| Entry | Reaction Conditions | Conversion | Mass balance | Ratio 280f |
|-------|----------------------|------------|--------------|------------|
| 279f  | Toluene, 50 ºC, 18h  | 0          | 100          | 0          |
| I     | BMIM BF\(_4\), 50 ºC, 18h | 100       | 25           | 1          |

Table 6  Effects of reaction conditions on product distribution for 278f
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The exact reason why the ionic liquid is successful in this reaction is not fully understood, and further research will need to be undertaken. However, the use of the same ionic liquid in conventional 1,5-exo ATRC reactions leads to significant rate enhancement.\textsuperscript{223}

6.0 \textit{N}-Butyl-2-naphthylsulfonamide 278g

Previous work by Speckamp\textsuperscript{147} has shown that when the 2-naphthyl substrate 248 was treated with tributyltin hydride and AIBN, the cyclised product 249 was obtained together with the reduced product 250. In light of these observations, an investigation toward the reaction of the analogous sulfonamide 278g involved using the sulfonamide 278g. NMR analysis (see Appendix 5) showed the rearranged amide 280g was produced in 44\% yield. The reaction was messy and several unidentified products were produced as has been previously described with other substrates.

![Scheme 95](image1.png)

**Scheme 95** Speckamp’s naphthalene sulfonamide radical reaction

![Scheme 96](image2.png)

**Scheme 96** Radical reaction of naphthalene sulfonamide 278g
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7.0  
*N-Butyl-4-methoxy-benzenesulfonamide* 278h

Having investigated the scope of the reaction with simple substrates, it was now decided to determine the effects of various electron donating and withdrawing aryl groups on the efficiency and selectivity of the mechanism. The first substrate to be examined involved the electron donating *para* methoxy derivative *278h*.

![Scheme 97 Radical reaction of 4-methoxy sulfonamide 278h](image)

Reacting the bromo radical precursor *278h* with copper bromide/TPA in dichloromethane at 37 °C for 18h furnished 3 products in 73% overall yields. Chromatography separated two cyclised regioisomeric products 352 and 353 from the rearranged amide *280h* obtained from individual column fractions. Upon $^1$H NMR analysis of the cyclised products (*Appendix 6*), it was determined that the major cyclised product had similar $^1$H NMR characteristics to the 6-substituted oxindole 336. This would indicate that the major cyclised product was oxindole 352 (Figure 10) and might be produced *via* the same mechanistic pathway described in Scheme 87 (*via* the amidyl radical intermediate 335).

![Figure 10 Structure of regioisomeric oxindoles 352 and 353](image)
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The minor cyclised product was tentatively assigned as the 5-substituted oxindole \( \text{353}^{224} \) that was analogous to the previously synthesised oxindole \( \text{333} \). This could occur \textit{via} the extrusion of sulfur dioxide mechanism as shown in Scheme 87. A minor compound tentatively assigned as the reduced product \( \text{323h} \) was also isolated (Figure 11).

\[
\text{Figure 11 Structure of possible reduced product 323h}
\]

Analysis of mass spectrometry using LSIMS-FAB showed an M\(^+\) (100\%) at 248, which was consistent with the M\(^+\) of the oxindole \( \text{352} \). An analogous compound to \( \text{353} \) was synthesised by Hartwig.\(^{224} \) (Figure 12) Spectroscopic data was similar to the minor oxindole \( \text{353}^{225} \)

\[
\text{Figure 12 Hartwig’s N-Me oxindole 354}
\]

An important observation was that the reaction appeared to be faster than for the tosyl derivative \( \text{278e} \) (85\% conversion under the same conditions). This trend was explored more thoroughly (Table 7). Initial studies using dichloromethane at 37 °C for 3h [I] showed complete conversion to products. The reaction was repeated using toluene at 50°C [III] and 80°C [IV] for 18h. Again, there was complete conversion to products (as a comparison \( \text{278e} \) proceeded to 56\% conversion under identical conditions to entry III). The ratio of products \( \text{280h} \) to \( \text{352} \) from these reactions was
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1:1. This agrees with the observed trend for the other substrates where DCM gives a better selectivity in favour of the rearranged products 280. As before an investigation of different solvents to determine the effect on product distribution was carried out. When the reaction was conducted in methanol at 50 °C for 18h [entry V] only a slight increase in selectivity towards the rearranged amide 280h was observed (1.2:1) compared to toluene. However, when THF [entry VI] 280h was used at same temperature and time, complete selectivity for the rearranged amide was observed. The reason for this solvent effect is unclear but it was not observed when the phenyl (278a, Table 4) or tosyl (278e, Table 5) precursors were employed.

![Scheme 98 Radical reaction of 4-methoxy sulphonamide 278h](image)

| Entry | Reaction Conditions | Conversion % | Mass Balance | Ratio 280h:352 |
|-------|---------------------|--------------|--------------|----------------|
| I     | DCM, 37 ºC, 3h      | 100          | 10           | 5:1            |
| II    | DCM, 37 ºC, 18h     | 100          | 73           | 4:1            |
| III   | Toluene, 50 ºC, 18h | 100          | 45           | 1:1            |
| IV    | Toluene, 80 ºC, 18h | 100          | 45           | 1:1            |
| V     | THF, 50 ºC, 18h     | 100          | 78           | 1:0            |
| VI    | MeOH, 50 ºC, 18h    | 100          | 73           | 1.2:1          |

Table 7: The effects of reaction conditions on product distribution for the methoxy substrate 278h.
8.0 Effects of different halogens in the \textit{para} position.

Speckamp\textsuperscript{226} has investigated the effect of halogen substitution in the \textit{para} position on the related rearrangement of 235. Scheme 99. It was found that the ratio of products 236 and 237 was similar for the bromine and chlorine derivatives (1:1.2) whereas the fluoro derivative was similar to the parent (235, \(X = Y = H\)) (1:0.6). A comparison of the fluoro derivative 278h was made with the parent compound 278a and a comparison of the results for bromo 278c and iodo 278d derivatives (the chloro derivative was unavailable for this study).

![Scheme 99](image)

Key: (a) \(X = F, Y = H\); (b) \(X = Br, Y = H\); (c) \(X = Cl, Y = H\)

**Scheme 99** General reaction for Speckamp radical reaction

8.1 The fluoro radical precursor 278b

![Scheme 100](image)

**Scheme 100** Radical reaction of 4-fluoro sulphonamide 278b

Heating the fluoro substrate in refluxing toluene for 18h [II] Table 8 showed after column chromatography two products, which upon NMR analysis were shown to be the cyclised product and the rearranged amide 280b. The NMR for the cyclised product showed only one product tentatively assigned as 355. Mass spectrometry showed an \(M^+\) at 235 (85\%) indicative of an oxindole instead of the \(M^+ = 299\) for the
cyclic sulfonamide and elemental analysis of sulfur indicated 0.35% sulfur, where 10.7% was required for the cyclic sulfonamide 356 (Figure 13).

![Scheme 101 Radical reaction of 4-fluoro sulfonamide 278b]

| Entry | Solvent/Temp./Conversion | Ratio 280b:355 |
|-------|--------------------------|----------------|
| I     | 280a<sup>a</sup> DCM, 37 ºC, 100% | 1.4:1 |
| II    | 280b DCM, 37 ºC, 100% | 1.4:1 |
| III   | 280a PhMe, 110 ºC, 100% | 0.3:1 |
| IV    | 280b PhMe, 110 ºC, 100% | 0.5:1 |

Key: a = The phenyl substrate.

Table 8: The effects of solvent on product distribution of the phenyl substrate 278a and fluoro substrate 278b.

Figure 13  Structure of proposed fluoro compound 356

Due to the complex <sup>1</sup>H NMR spectra (Appendix 7), it was not possible to determine which regioisomers of the oxindole was the major material, and it was not possible to purify them further. A possible method would be to synthesis the two regioisomers as outlined in Schemes 89/90, page 112-114. It was observed that the ratio of
products for the fluoro substrate \(278b\) and the phenyl derivative \(278a\) were similar in refluxing toluene and dichloromethane (Entry I-IV).

### 8.2 The bromo and iodo radical precursors \(278c-d\)

Heating the bromo substrate \(278c\), \(X = \text{Br}\) in dichloromethane at 37 °C for 7h furnished two products which were identified from NMR analysis as the rearranged amide \(280c\) and a cyclised product \(357\) (Table 9). Careful chromatography separated the rearranged amide from the cyclised product; however, isolation of pure cyclised product was not achievable. The \(^1\text{H}\) NMR spectra of the cyclised product indicated one cyclised product only, which was similar to the NMR of the 6-substituted oxindole\(^{227}\) \(336\).

![Scheme 102 Radical reaction for 4-bromo and 4-iodo sulfonamides](image)

**Table 9: Effects of solvents/time on product distribution for the halogen substrates \(278c-d\).**

| Entry | Reaction | Conversion | Mass | Ratio \(280:357/359\) |
|-------|----------|------------|------|----------------------|
| I     | \(278c\), DCM, 37 °C, 7h | 100 | 66 | 2.4:1 |
| II    | \(278c\), THF, 50 °C, 12h | 100 | 74 | 13:1 |
| III   | \(278d\), DCM, 37 °C, 8h | 100 | 80 | 2.7:1 |

Key: \(278c\) \(X = \text{Br}\); \(278d\) \(X = \text{I}\); \(357 = X = \text{Br}\); \(359 = X = \text{I}\)

An analogous compound to \(357\), namely \(358\) has been synthesised by Atwal \textit{et al.}\(^{227}\) as shown in \textbf{Figure 14}.
Heating the iodo substrate 278d in dichloromethane at 37 ºC for 7h facilitated a similar outcome (although the reaction was messier with a range of by-products being formed) (Table 9). Once again, isolation of pure cyclised oxindole 359 was unachievable thus, it was not possible to ascertain with certainty which cyclised regioisomer product was present. However, the ratio of rearranged amide 280/cyclised 359 was similar to that obtained for the analogous bromo derivative (see Table 9). Following the interesting observation that heating the methoxy derivative 278h in THF led to the rearranged product selectively, this was repeated for one of the halogen derivatives 278c, Entry II. Although not completely selective this time when run in THF a larger selectivity for the rearranged product (2.4/1 to 13/1) was obtained. This may suggest that THF is a far better H-donar towards amidyl radicals than DCM or toluene. In fact as amidyl radicals are thought to be electrophilic radicals the polarity of abstraction (C, NCH, H-atom) from the α-position of THF is electronically matched.

The rates of reaction between the parent sulfonamide 278a and the halogens 278b-d in DCM under copper(I)bromide/TPA conditions showed that the halogens reacted faster than the parent compound 278a.

9.0 Effects of para and meta electron-withdrawing groups

Having investigated the effects of electron donating groups and halogens, the next step was to investigate the electron withdrawing groups to determine (a) whether there was a similar trend in selectivity towards the rearranged amide 280 and
cyclised 360-363 products compared to the electron donating groups, and (b) and the effects of solvents on product distribution. Consequently, the following step was to investigate the electron withdrawing groups: the cyano compound 278i and nitro compound as 278j were the chosen substrates, both containing strong electron-withdrawing groups.

9.1 The cyano and nitro radical precursor 278i-j

![Scheme 103 Radical reactions of 4-cyano and 4-nitro sulfonamides](image)

Heating the bromide 279i (R = CN) in dichloromethane at 37 ºC for 4 hours led to complete conversion to products. This was a significantly more rapid reaction than either the parent (R = H) or p-methoxy (R = OMe) substrate. The crude 1H NMR showed two products the rearranged amide 280i and the cyclised product. Chromatography separated the rearranged amide 280i being obtained pure in good yield (60%) (see Appendix 8). Only one cyclised product was present, and no minor cyclised product was observed as in the previous reactions. However, it was not possible to obtain the pure cyclised product due to co-elution with other minor by-products. In order to improve conditions, the bromide 278i was heated in refluxing toluene for 18 hours this time. The crude NMR showed three products identified as the rearranged amide 280i and the cyclised products 360 and 362 (see Appendix 9). Chromatography separated the
rearranged product 280i from the two inseparable cyclised products 360 and 362 (0.2/1). Mass spectrometry showed an M\(^+\) at 242, which had the same mass as the oxindole 360/362 (Table 10). To be certain, a sulfur analysis was obtained. Sulfur analysis showed 0.35\% sulfur instead of the theoretical 10.47\% for the cyclic sulfonamide 364 (Figure 15).

![Proposed minor cyclised sulfonamide 364](image)

**Figure 15 Proposed minor cyclised sulfonamide 364**

The CHN gave C, 74.3; H, 7.8; N, 11.6, and the calculated oxindole was C, 74.1; H, 7.8; N, 11.0. It was most likely that the cyclised products were the regioisomers of the oxindoles 360 and 362.

An analogous compound by Hartwig\(^\text{224}\) whereby a methyl group was used in place of the butyl group had similar NMR assignment and coupling constants, which showed that Hartwig’s oxindole 365 (Figure 16) was similar to the minor oxindole 360. The major cyclised product was tentatively assigned as the meta oxindole 362.

![Hartwig’s structure 365](image)

**Figure 16 Hartwig’s structure 365**
Scheme 104  Radical reaction of 4-cyano sulfonamide 278e

| Entry | Reaction Conditions | Conversion % | Mass Balance | Mass Ratio 280 :360:362 |
|-------|---------------------|--------------|--------------|--------------------------|
| I     | 278i, DCM, 37 °C, 4h | 100          | 53           | 4:0:1                    |
| II    | 278i, PhMe, 110 °C, 18h | 100         | 66           | 1.3:0.2:1                |

Table 10: Table for the cyano substrate 278i under various conditions using toluene and DCM.

Heating the nitro derivative 278j in dichloromethane at 37 °C for 2.5h led to complete conversion to products (see Table 11). This reaction was even faster than for the p-CN derivative 278i The crude NMR showed two products identified as the rearranged amide 280j and a cyclised product 366. The rearranged amide was obtained pure in fair yield (43%). The cyclised product was obtained as only one regioisomer but it was impossible to obtain pure. The reaction was repeated under identical condition but for 4h. This time the cyclised product 366 was isolated pure as one product, though in only trace amounts. In order to improve the cyclisation, the reaction was repeated for 24h; however now the crude NMR showed several products, which after chromatography led to two inseparable cyclised products (see Appendix 10) in a ratio of (0.5/1) and the rearranged amide 280j.
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Scheme 105 Radical reaction of 4-nitro sulfonamide 278j

| Entry | Reaction | Conversion | Mass Balance | Ratio 280:361:363 |
|-------|----------|------------|--------------|-------------------|
| 278i-j | Conditions | % | | |
| I 162j, DCM, 37 °C, 2.5h | 100 | 69 | 6.5:1:0 |
| II 162j, DCM, 37 °C, 4h | 100 | 74 | 4:1:0 |
| III 162j, PhMe, 110 °C, 24h | 100 | 54 | 1.3:0.5:1 |

Table 11 The effects of solvent, time and temperature on product distribution for nitro substrate 278j

Mass spectrometry using LSIMS-FAB showed an M+ at 262 (100%) for 361/363 which the mass of the oxindoles 361/363. To be certain, a sulfur analysis was obtained. Sulfur analysis showed 6.13% compared to theoretical sulfur 9.81% for the cyclic sulfonamide. CHN analysis was also obtained to determine whether this mixture contained the cyclic sulfonamide 366 (Figure 17). The theoretical content for the cyclic sulfonamide was C, 51.5; H, 5.5; N, 8.6., compared to the isolated product, which was found to be C, 55.7; H, 7.7; N, 6.6. It is unclear at present, if these inseparable mixtures of two cyclised compounds can be unambiguously assigned as the sulfonamide 366 and one corresponding oxindole. It is most likely that the high sulfur content could be attributed to the cyclic sulfonamide, since there is no evidence for any other known sulfur compound. The minor product would be
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attributed to one of the oxindoles, but it is not possible to determine which oxindole as this would be from the crude NMR.

\[ \text{Figure 17 Proposed cyclic sulfonamide 366} \]

The observation of a sulfur-containing compound was unexpected, since all compounds have shown minimum sulfur. The reason for this case is unclear and further study would be required. It is interesting to note that the reaction was rapid compared to the other compounds studied (2.5h). As in previous reactions, the cyclised compound predominated when refluxing toluene was used.

9.2 The trifluoromethyl and meta-3,5-trifluoromethyl radical precursors 278k-l

The previous compounds 278i-j predominately led to the rearranged amides 280i-j in dichloromethane at 37 °C. Although only seen as a minor by-product, a significant amount of the hydrolysed sulfonamide 283i-j (see page 86), was also isolated from these reactions. This maybe due to the electron withdrawing aryl group that would make hydrolysis of the sulfonamide more facile. Consequently, the next step was to study other compounds containing electron-withdrawing groups namely 278k-l (Scheme 106).

\[ \text{Scheme 106 Radical reaction of 4-trifluoromethylbenzenesulfonamide 278k} \]
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Heating the bromide 278k in dichloromethane at 37 °C for 4.5h led to complete disappearance of the starting material. Again the reaction was more rapid than the parent (R = H) and p-methoxy (R = OMe) with a similar rate to R = CN. The crude 1H NMR showed two compounds which were identified as the hydrolysed sulfonamide 283k (Figure 18) and the rearranged amide 280j (see Appendix 11). As before the electron-withdrawing nature of the sulfonamide led to significant decomposition. It was not possible to isolate a pure sample of the rearranged amide 280k as it co-ran with the hydrolysed sulfonamide 283k.

![Figure 18 Structure of trifluoromethylbenzenesulfonamide](image)

The reaction was repeated under identical condition using THF instead of dichloromethane, since previous studies have shown that THF can enhance selectivity towards the rearranged amide 280. The crude NMR showed that the reaction had only gone to 50% conversion. Only the rearranged amide 280k was present, but isolation of pure 280k was now unsuccessful as it was impossible to separate from unreacted starting material 278k. The next step was to investigate the 3,5-meta substrate 278l to determine the effect on product distribution. The bromide 278l was heated in dichloromethane at 37 °C for 1.5h. Although recovered in only 67% after chromatography, there was only one product. This was identified spectroscopically as the rearranged amide 280l. No oxindole 367/368 were isolated (Table 12).
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**Scheme 107  Radical reaction of 3,5-trifluoromethylbenzenesulfonamide 278l**

| Entry 278k-l | Reaction Conditions | Conversion % | Mass balance | Ratio 280:367/368:283 |
|-------------|---------------------|--------------|--------------|-----------------------|
| I 278k, DCM, 37 °C, 4h | 100 | 72 | 1:0/0:3 |
| II 278k, THF, 50 °C, 4h | 50 | 97 | 1:0/0:0 |
| III 278l, DCM, 37 °C, 1.5h | 67 | 67 | 1:0/0:0 |
| IV 278l, PhMe, 110 °C, 24h | 100 | 22 | 1:1:0 |

### Table 12:

The effects of solvents, time and temperature on product distribution for the substrates 278k-l.

The use of the electron withdrawing substituents 278l has led predominately to the rearranged amide 280l (see Appendix 12) when carried out in dichloromethane at 37 °C. This also fits the trend found with the electron donating substituents 278a-h. However, in general, changing the solvent to toluene (in all the previous examples studied) leads to a reversal in selectivity. When 278l was heated in refluxing toluene, this switch of selectivity away from the rearranged products, was also observed, (although now in equal ratios). Most intriguingly is the formation of one cyclised product 367/368. The use of strongly activated substrates such as the *para* trifluoromethyl substrate 278k, *p*-cyano 278i and *p*-nitro 278j produced unexpected results as the formation of the large amount of hydrolysed sulfonamide 283i-k was.
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detected. This may arise due to the increased ease of hydrolysis of amides and sulfonamides with strongly electron withdrawing groups

10.0 Conclusion for chapter two

As can be seen the rate and ratio of products (rearranged amides and oxindoles) is dependent upon the electronic nature of the aryl substituent. The main product arises from rearrangement via 1,5-ipso cyclisation in all cases with the relative amount increasing for the strongly electron withdrawing and donating substituents (e.g. ratio H, F < 4-Br, 4-I, 2-naphthyl < 4-NO₂, 4-CN < 4-OMe, 3, 5-CF₃). The rates of reaction also seem to be influenced by the substituent with the rate following (2-naphthyl < H, 4-CH₃ < 4-I, F, 4-Br, < 4-CN, CF₃ < 4-OMe < 4-NO₂, <3,5-CF₃). The intermediate cyclohexadienyl radical 355 will be stabilised by both electron withdrawing and donating substituents which should favour cyclisation and is reflected in this order. Furthermore, in these studies the effect of temperature and solvent on the reaction (278a for example), showed that at high temperature (toluene/110 °C), the cyclised oxindole products 293 predominated (e.g. ratio rearranged/oxindole = 0.3/1.0), whilst at lower temperature and in better H-donor solvents (dichloromethane 37 °C) the rearranged product 293 predominated (e.g. ratio rearranged/oxindole = 1.4/1.0). For all substrates 278 when ran in DCM or THF, there is a greater selectivity towards the rearranged amide over the cyclised oxindoles (compared to toluene). Reduction of the intermediate amidyl radical intermediate 355 possibly occurs via hydrogen abstraction from the solvent and is likely to be faster than DCM/THF than from toluene. This is reflected in the increased ratio of rearranged products to cyclised products in these reactions. Identification of the cyclised products as oxindoles was achieved by preparing them authentically via alternative routes and by comparing their spectroscopic details to
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those previously published. The major cyclised oxindole product appears to arise from the cyclisation of the intermediate amidyl radical and not SO$_2$ extrusion from a cyclic sulfonamide intermediate.

Further work

Further work could investigate the effect of the catalyst, concentration, on the reaction and try to develop conditions to optimise the oxindole products by retarding the rate of H-abstraction from the solvent by the amidyl radical intermediate.

An array of amine ligands should be tested. This would involve all amines used by the Clark group, in particular, the use of TMEDA proved successful for Wongtap’s work$^{156}$ (see Chapter three). Fullaway has had success with the pentyl-pyridin-2-ylmethyleneamine ligand.

A series of experiments on ligand concentration should be investigated. In the case of the nitro derivative, using excess ligand may have generated the cyclic sulfonamide based on the high sulfur content from the S analysis.

In order to push the reaction towards cyclisation. A series of poor hydrogen donor solvents should be used. In theory, this should give exclusively cyclised products.

Each substrate must be treated differently, and several methods might be required to optimise the radical conditions.
CHAPTER THREE

RADICAL REACTIONS OF N-ALKYL/(ARYL)-4-METHYL-
BENZENESULFONAMIDES
Chapter Three

1.0 Aims and Objectives

Having investigated the effect of the aryl group on the reaction outcome, a range of nitrogen substituents \( (R^1) \) 369 ranging from 1º substituents of increasing length \( (C_2H_5, C_3H_7, C_4H_9, C_5H_{11}, C_6H_{13}, C_{12}H_{25}) \) to branched alkyl groups (e.g. \( i-Bu, (\pm)-s-Bu, t-Bu \)) to chiral groups (R)-1-cyclohexyl, to extremely hindered (1-adamantyl) were chosen for investigation. In order to ascertain the effects of these substituents, the aryl group (tosyl) and initiation group (CMe\(_2\)Br) were kept constant.

![Scheme 108 General reaction scheme for N-alkyl substrates 369 with CuBr/TPA](image)

1.1 Synthesis of radical precursors

The initial approach to furnish these compounds was identical to that described in Chapter 2. Thus, \( p \)-tosyl chloride 281e (1.0 eq.) was treated with the amine of choice 373a-k, (1.0 eq.) and triethylamine (1.0 eq.) in dichloromethane Method A or with just 3 equivalents of amine 373a-k in diethyl ether Method B yields the \( N \)-alkyl-4-methylbenzenesulfonamides 374a-k in moderate to excellent yields (41-97%).
## Scheme 109  Synthesis of N-alkyl-methylbenzenesulfonamides 374a-k

| Entry | R-NH₂         | Method | Entry | Yield % |
|-------|---------------|--------|-------|---------|
| 373a  | Ethyl         | B      | 374a  | 84      |
| 373b  | Propyl        | B      | 374b  | 81      |
| 281e  | n-Butyl       | B      | 283e  | 89      |
| 373c  | Pentyl        | B      | 374c  | 92      |
| 373d  | Hexyl         | A      | 374d  | 62      |
| 373e  | Docecyli      | B      | 374e  | 92      |
| 373f  | Isopropyl     | B      | 374f  | 65      |
| 373g  | iso-Butyl     | B      | 374g  | 85      |
| 373h  | (±)-sec-Butyl | B      | 374h  | 41      |
| 373i  | tert-Butyl    | B      | 374i  | 76      |
| 373j  | (R)-(−)-1-Cyclohexylethyl | A | 374j  | 97      |
| 373k  | Adamantan-1-yl | A | 374k  | 76      |

Key: a = Synthesised by D. Fullaway. |283e = 88%, 374g = 95%, 374h = 85%  

| Table 13  | N-alkyl-4-methylbenzenesulfonamide |
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1.2 Current synthesis of radical precursors

With a range of sulfonamides 374a-k in hand, the next goal was to react these with 2-methyl-2-isobutyryl bromide 284, to prepare the range of substrates 369a-k suitable for investigation (Table 14). Initially triethylamine (1.0 eq.) was used followed by addition of the acid bromide 284, (see Method C). For the majority of reactions this method worked 369a-e,g-h, albeit with low yields for hindered and longer chain amines. However, for the hindered amines 369f,i-k only starting material 374 was recovered. By changing the conditions to use equimolar amounts of n-BuLi (1.6M) Method D, it was hoped to be able to force the formation of the hindered substrates 369f,i-k. However, even under these conditions no products were detected. Therefore this synthesis was abandoned, and the rest of the work concentrated on the substrates 369a-e, g-h. For sulfonamides 278e, 374c-d, g-h traces of an olefinic product (tentatively assigned as 375 (Figure 19) based upon $^1$H NMR and previous precedent), was also isolated (See Chapter Two).
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Scheme 110  Synthesis of the radical precursors 369

| Entry | Substrate            | Method | Yield |
|-------|----------------------|--------|-------|
| 369a  | Ethyl                | C      | 58    |
| 369b  | Propyl               | C      | 52    |
| 278e  | n-Butyl              | C      | 70\(^a\) |
| 369c  | Pentyl               | C      | 43    |
| 369d  | Hexyl                | C      | 22    |
| 369e  | Dodecyl              | C      | 22    |
| 369f  | iso-Propyl           | C      | 0     |
| 369g  | iso-Butyl            | C      | 48\(^a\) |
| 369h  | (±) sec-Butyl        | C      | 56\(^a\) |
| 369i  | tert-Butyl           | C      | 0     |
| 369j  | (R)-(-)-Cyclohexylethyl | C/D | 0     |
| 369k  | Adamantyl            | C/D    | 0     |

Key: \(^a\) = previously synthesised by D. Fullaway\(^{153}\). Yield: 278e = 79\%, 379g = 62\%, 369h = 50\%

Table 14 Synthesis of radical precursors 278e, 369a-k

Figure 19 The structure of the acrylamide 375
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2.0 Reaction of \(N\)-alkyl-4-methylbenzenesulfonamide with copper (I) bromide and TPA

As previously mentioned in Chapter 2, the reaction of substituted aryl sulfonamides when heated in refluxing toluene in the presence of copper (I) bromide and TPA led predominately to the cyclised oxindole products. On the other hand changing the solvent to either DCM or (in some cases) THF led predominately to the rearranged amide. In light of these results an investigation was conducted on the effects of the alkyl \(N\)-substituent on the outcome of the reaction in DCM. Previous work by Fullaway\(^{163}\) had shown that for the \(iso\)-butyl sulfonamide 369g, using a slight excess of the copper (I) bromide/TPA complex in dichloromethane furnished the rearranged amide 370g in 26% yield and the cyclised product 371g/372g in 20%. On repeating the reaction for the \(N\)-iso-butyl substrate 369g under similar conditions, there was greater selectivity towards the rearranged amide 370g in 76% yield and the cyclised product 371g/372g in 24% yield. The drawback with Fullaway’s method, was that the conditions used in these experiments were not recorded, so it is uncertain as to what temperature was used and the length of time taken for complete conversion to products. Further work by Fullaway was done using the \(N\)-sec-butyl sulfonamide 369h, using a slight excess of the copper (I) bromide/TPA complex in dichloromethane. Again, there was greater selectivity over the rearranged amide versus the cyclised product 2:1 ratio. There was no indication concerning neither the temperature used nor the length of time taken for complete conversion to products.

2.1 Current work

Consequently, this work involved a re-investigation of these reactions. Heating the bromides 369a-h in dichloromethane at 37 °C for 18 hours furnished the expected products arising from rearrangement 370a-h and the two cyclised oxindoles
regioisomers 371a-h and 372a-h, as illustrated in Table 15. Entry I, Table 15 is for the parent compound aromatic = phenyl obtained in Chapter 2 and is listed as a comparison.

![Scheme 111 General scheme for N-alkyl substrates 369 with CuBr/TPA](image)

| Entry 369 | Reaction Conditions | Conversion % | Mass balance | 370:371/372 Ratio |
|-----------|---------------------|--------------|--------------|------------------|
| I (278a)  | DCM, 37 ºC, 18h     | 100          | 78           | 1.4:1            |
| II (369a) | DCM, 37 ºC, 18h     | 96           | 67           | 10:1             |
| III (278e)| DCM, 37 ºC, 18h     | 85           | 65           | 1.3:1\(^a\)      |
| IV (369c) | DCM, 37 ºC, 18h     | 100          | 81           | 2.5:1            |
| V (369d)  | DCM, 37 ºC, 18h     | 100          | 75           | 3.3:1            |
| VI (369e) | DCM, 37 ºC, 18h     | 100          | 74           | 1:0              |
| VII (369g)| DCM, 37 ºC, 18h     | 100          | 73           | 1.4:1\(^a\)      |
| VIII (369h)| DCM, 37 ºC, 18h   | 100          | 72           | 1.4:1\(^a\)      |

Key: 369a = ethyl, 278e = n-butyl, 369c = pentyl, 369d = hexyl, 369e = dodecyl, 369g = iso-butyl, 369h = sec-butyl. \(^a\) = previously synthesised by Fullaway.\(^{163}\)

Table 15 The effects of dichloromethane on product distribution

The table for the C\(_4\) series 278a (parent, Ar = Ph, N-n-Bu), 278e (N-n-Bu), 369g (N-i-Bu), 369h (N-s-Bu) shows the ratio of rearranged 370 to cyclised products 371:372 remains fairly constant (1.4:1 to 1.3:1). However when the chain length was
increased from C_4, C_5, C_6, C_{12} (i.e. 369c-e) the reaction becomes more selective for the rearranged product 370 (1.4:1, 2.5:1, 3.3:1 to 1:0). Full characterisation of the N-pentyl cyclised 371d/372d products was not possible due to the small amounts of isolated product (see Appendix 13). No cyclised material was isolated with the longest dodecyl substituted precursor 369e.

On the other hand, the smaller N-Et substituent 369a did not fit this trend as the reaction was also selective for the rearranged product 370a. An authentic sample of 370a was prepared from the acid chloride 351, (see Chapter 2, Scheme 92) in order to unambiguously assign the structure of this compound.

The reasons for the trends are not clear. Presumably, the product distribution is determined from the relative rates of cyclisation versus reduction of the intermediate amidyl radical 335, (see Chapter 2, Scheme 87). The factors, which govern these rates, must be relatively complicated as in n-Bu, i-Bu, s-Bu series where there are slowly increasing steric hinderance at the nitrogen atom (but keeping the number of carbons constant) the ratios are very similar. Hence, steric effects alone cannot explain the trends. Reduction of the intermediate amidyl radicals can theoretically occur via two pathways; a) reduction by abstraction of an H-atom from the solvent, or b) reduction by intramolecular H-translocation followed by solvent (see 376 → 377) as depicted in Scheme 112.

![Scheme 112](image-url)  
**Scheme 112  Proposed mechanism for radical hydrogen translocation**
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There are two characteristic experiments, which might determine whether this intramolecular approach to reducing the amidyl radical intermediate is taking place. The first method would involve using a series of poor hydrogen donor solvents (t-BuOH, etc), and determining their effect on product outcome. The poor hydrogen donor solvents should retard the rate of intermolecular reduction but not that of intramolecular reduction and larger ratios of cyclisation should occur, since there would be poorly abstractable hydrogen atoms on the solvent. Another approach would be to use alternative groups at the C-5 position, to ensure that 1,5-H abstraction could not take place. As a suggestion, the following compound 378 (Figure 20) could be used. In this case, the C-F bond is much stronger than the C-H and thus would be more difficult to break. The result being that a 1,5-abstraction could not take place.

![Figure 20](image)

**Figure 20  Structure of compound to block 1-5-H abstraction 378**

Alternatively, the nature of the R group might affect the relative rates of oxindole formation. Presumably, with the small N-ethyl group, reduction via pathway (a) is relatively fast and/or cyclisation must be slow. Reduction via intramolecular 1,3-H abstraction is unlikely to occur. The smallest N-alkyl group capable of a 1,5-H translocation is the N-Bu precursor 278e. As the N-alkyl group increases in size potentially more H-translocation pathways may be possible (1.6, -1.7 etc). This may explain why more selectivity towards reduction of the intermediate amidyl radical
(leading to rearrangement) is observed; alternatively the larger chain alkyl groups may retard the cyclisations.

2.2 Reactions in other solvents

In Chapter 2 it was shown that changing the solvent for the reaction from DCM to toluene led to a reversal of selectivity (i.e., in DCM the rearranged products normally predominated, but in toluene the cyclised compounds predominated). This was explained as DCM being a better H-donor towards the amidyl radicals. An investigation of the reaction of three precursors 369a, 278e and 369g in toluene and in the ionic liquid BMIM BF₄, were conducted and compared with the results from DCM. A brief investigation of the effect of temperature on product outcome was also conducted (Table 16).
Scheme 113 General reaction scheme for N-alkyl substrates 369 with CuBr/TPA

| Entry | Solvent | Temp. | Conv. | Ratio 370:371/372 |
|-------|---------|-------|-------|-------------------|
| I     | 369a    | Toluene | 50   | 47                | 0.8:1 |
| II    | 369a    | Toluene | 110  | 100               | 0.7:1 |
| III   | 369a    | IL     | 50   | 91                | 1:1   |
| IV    | 278e    | Toluene | 50   | 46                | 0.4:1 |
| V     | 278e    | Toluene | 110  | 94                | 0.6:1 |
| VI    | 278e    | IL     | 50   | 91                | 0.2:1 |
| VII   | 369g    | Toluene | 50   | 14                | 0:1   |
| VIII  | 369g    | Toluene | 110  | 73                | 0.6:1 |
| IX    | 369g    | IL     | 50   | 94                | 0.5:1 |

Key: 369a = Ethyl, 278e = n-butyl, 369g = iso-butyl

Table 16 The effects of toluene and ionic liquid BMIM BF₄ on product distribution.

As can be seen from Table 16 the expected reversal of selectivity is observed upon switching from DCM to toluene (e.g. 369a DCM 10:1 to toluene 0.8:1, 278e DCM 1.3:1 to toluene 0.4:1, 369g DCM 1.4:1 to toluene 0:1). The conversion however is less in toluene when compared to DCM presumably due to the relatively insoluble nature of the CuBr/TPA in toluene compared to DCM.
Comparing the reactions in toluene at 50 °C and 110 °C the N-Et 369a undergoes the fastest reaction, followed by N-n-Bu 278e and N-i-Bu 369g. This would be expected on steric grounds. The low conversion of N-i-Bu (369g Entry VII) made determining the product ratio difficult from the crude NMR and so the result of this experiment should be treated with caution.

In toluene at 110 °C the ratio for all three reactions II, IV and VI remain similar (0.7:1 to 0.6:1). This maybe due to the fact that the CuBr/TPA complex is more soluble than in toluene but that the H-abstraction properties of both solvents might be similar.

This would indicate that the ionic liquid whilst only attaining similar selectivities for the rearranged amide/cyclised products shows that the ionic liquid has a higher rate of conversion. Further work would be required to determine with certainty this rate difference. Presumably, the ionic liquid can coordinate with the ligand complex and structure more favourably than that for toluene at the same temperature.

2.3 Other reactions

The following investigation concerning the reaction of the N-Et 369a, N-Pr derivative 369b and N-nBu 281e in the ionic liquid BMIM BF₄ at 50 °C for 18hs as depicted in Table 17.
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Scheme 114 General reaction scheme for N-alkyl substrates 369 with CuBr/TPA

| Entry       | Ratio 370:371/372 |
|-------------|-------------------|
| N-Et (369a) | 1:1               |
| N-Pr (369b) | 0.5:1             |
| N-nBu (281e)| 0.2:1             |

Table 17 The effects of the ionic liquid BMIM BF₄ on product distribution.

In this case as the chain length increases the relative amounts of cyclised materials increases (in the case of the N-propyl, the cyclised products were isolated although full characterisation was not possible due to other by-products—see Appendix 14). This is opposite to the trend observed in DCM with increasing chain length. In order to investigate this further, similar experiments using C₅, C₆ and C₁₂ alkyl groups should be conducted and compared to toluene at both 50 ºC and 110 ºC. However, due to time constraints this was not achieved.

2.4 Effects of dichloromethane at room temperature on product distribution

Having previously investigated the effects on substrates 369 (Table 15) in dichloromethane at 37 ºC, an investigation of the following substrates N-ethyl 369a, N-hexyl 369d, N-dodecyl 369e, N-i-butyl 369g, N-s-butyl 369h at room temperature
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(3 days) was conducted (Table 18). These results show that there is excellent selectivity towards the rearranged amide 370 compared to the cyclised regioisomeric oxindoles 371/372. It is uncertain as to whether this increased selectivity is due to the lower temperature used (room temperature) or the longer reaction time (3 days), or a combination of both. Results from Table 15 (DCM 37 °C, 18hrs) are represented here as a comparison.

![Scheme 115 General reaction scheme for N-alkyl substrates 369 with CuBr/TPA](image)

Key: 369a = ethyl, 369c = hexyl, 369d = dodecyl, 369g = iso-butyl, 369h = sec-butyl.

| Entry | Reaction Conditions | Conversion % | Mass Balance | Ratio 370:371/372/a |
|-------|---------------------|--------------|--------------|---------------------|
| I (369a) | DCM, rt, 72h | 100 | 33 | 25:1 (10:1) |
| II (369d) | DCM, rt, 72h | 93 | 53 | 10:1 (3.3:1) |
| III (369e) | DCM, rt, 72h | 75 | 22 | 1:0 (1:0) |
| IV (369g) | DCM, rt, 72h | 87 | 56 | 7.7:1 (1.4:1) |
| V (369h) | DCM, rt, 72h | 58 | 68 | 6.2:1 (1.4:1) |

*a The ratios from Table 12 (DCM 37 °C 18h) in parenthesis.

Table 18 The effects of dichloromethane at room temperature on product distribution.
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3.0 Synthesis of N-(hetero)aromatic radical precursors 380a-i

Having investigated the effects of simple alkyl chains attached to the nitrogen atom and their effects on product outcome, a further study was initiated whereby replacing the alkyl groups with benzyl derivatives such as (4-methyl benzyl, 4-methoxy benzyl and 2-trifluoromethyl benzyl) as well as aryl groups (phenyl, pyridylmethyl, quinuclidine, furan and thiophene) was investigated. In order to ascertain the effects of these substituents, the aryl acceptor group (tosyl) and initiation group (CMe₂Br) were kept constant.

Figure 21 General structure for the (hetero)aryl derivatives 381

The approach to furnish these compounds was identical to that described in Section 3.1. Thus, p-tosyl chloride (1.0 eq.) 281e was treated with the amine of choice (1.0 eq.) 379a-i and triethylamine (1.0 eq.) in dichloromethane (Method A), as depicted in Table 19 to furnished the N-(hetero)aryl-(4-methyl)-benzenesulfonamides 380a-i (Scheme 116).
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Scheme 116  Synthesis of $N$-hetero(aromatic) substrates $380a$-$i$

| Entry | $R$-$NH_2$                  | Method | Entry | Yield % |
|-------|-----------------------------|--------|-------|---------|
| 379a  | $N$-$p$-Methylbenzyl         | A      | 380a  | 22      |
| 379b  | $N$-$p$-Methoxybenzyl        | A      | 380b  | 33      |
| 379c  | $N$-$o$-Trifluoromethylbenzyl| A      | 380c  | 83      |
| 379d  | $N$-Pyridin-2-ylmethyl       | A      | 380d  | 32      |
| 379e  | $N$-Furfuryl                 | A      | 380e  | 75      |
| 379f  | $N$-Thiophenemethyl          | A      | 380f  | 75      |
| 379g  | $N$-Phenyl                   | A      | 380g  | 0       |
| 379h  | $N$-Pyrid-2-yl               | A      | 380h  | 0       |
| 379i  | $N$-Quinuclidinyl            | A      | 380i  | 1       |

Table 19: Synthesis of $N$-(hetero)aromatic-4-methylbenzenesulfonamides

The $N$-benzyl derivatives, (with the exception of the trifluoromethyl group $380c$) gave poor yields (< 33%). Better yields were obtained for the heterocyclic substrates (furfuryl $380e$ in 75% yield and 2-thiophenemethyl $380f$ in 75% yield). No product could be isolated from the phenyl $380g$, pyrid-2-yl $380h$ and quinuclidine $380i$ substrates. Consequently, this work focussed only on the substrates $380a$-$f$. 
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3.1 Synthesis of radical precursors

With the sulfonamides 380a-f in hand, the next goal was to react these with 2-methyl-2-isobutyryl bromide 284, to prepare the range of substrates 381a-f suitable for investigation (Scheme 117). This method involved triethylamine (1.0 eq.) followed by addition of the acid bromide 284 (Method B) as depicted in Table 20. For the majority of reactions this method worked 381a-e. However, for the thiophene derivative 381f only starting material 380f was re-isolated. Unlike the previous substrates, there was no presence of any elimination product in the crude NMR.

![Scheme 117 Synthesis of N-(hetero)aromatic sulfonamide radical precursors](image)

| Entry | Substrate            | Method | Yield |
|-------|----------------------|--------|-------|
| 381a  | 4-Methylbenzyl       | B      | 72    |
| 381b  | 4-Methoxybenzyl      | B      | 91    |
| 381c  | 2-Trifluoromethyl-benzyl | B  | 79    |
| 381d  | 2-Pyridylmethyl      | B      | 100   |
| 381e  | 2-Furfuryl           | B      | 100   |
| 381f  | 2-Thiophenemethyl-   | B      | 0     |

Table 20: Synthesis of N-(hetero)aromatic sulfonamide radical precursors.

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3.2 Attempted radical reactions of (hetero)aromatic sulfonamides

Motherwell\(^\text{151}\) has shown that benzylic sulfonamides can selectively furnish cyclic sulfonamides as depicted in Scheme 118. In all these reactions, a 1,7 addition onto the sulfonamide aromatic ring furnished the cyclic sulfonamides. In the following example, the pyridyl sulfonamide 257 furnished the desired cyclic product 258 (55\%) and the dihydropyridine 382. Switching to sulfur heterocyclics, the thiophene sulfonamide 259 led to the desired cyclised product 383 and two dihydroheteroaromatics 260 and 384 and 23\% and 8\% yield respectively. When the reaction was repeated for the quinoline sulfonamide 261 only the cyclised product 262 in 9\% yield was furnished.

\[
\begin{align*}
\text{Scheme 118  Motherwell radical cyclisation onto heteroaromatics}
\end{align*}
\]
Based on these observations, it may be possible for the radical 385 produced from \(N\)-4-methoxybenzyl substrate 381b (Scheme 119), to undergo two competitive cyclisation pathways. (A) Radical cyclisation onto the benzylic group via a 1,6-addition to furnish analogous cyclic sulfonamide 386 as above. (B) Addition into the ipso position of the sulfonamide via a 1,5- addition (as observed in our previous studies) to lead to the rearranged amide 387. It should be noted that a previous reaction by Wongtap\textsuperscript{156} using the substrate 381a furnished the rearranged amide analogous to 387.

![Scheme 119 Proposed radical mechanism for the substrate 387](image)

The first experiment involved treating the benzyl bromide 381b with CuBr/TPA in tetrahydrofuran at 50 °C for 24h. Unfortunately, the crude NMR showed several products. None of these products could be unambiguously identified and no evidence of either cyclised products 386 or rearranged amide 387 could be detected. In light of this result, and due to time constraints additional investigations for the benzylic precursors 381a,c were cancelled, and instead analysis of the heterocyclic aromatic derivatives, (e.g. the N-furan derivative 381e) was performed.

Zard\textsuperscript{245} has recently shown that a suitably substituted furan xanthate 388 can undergo ipso-type radical cyclisation to furnish spirocyclised products (e.g. 392). (Scheme
Chapter Three

120). The xanthate 388 was treated with DLP (dilauroyl peroxide) to give the acyl radical intermediate 389, which underwent an *ipso*-type cyclisation leading to the spirocyclised radical intermediate 390 followed by oxidation to the cation 391 which is quenched by the solvent to give the spirocyclised product 392.

Scheme 120  Zard’s synthetic approach to spirocyclised products using furan xanthates

It may be possible for the present substrate 381e to undergo a similar type of cyclisation to furnish spirocyclised products as well as the radical rearrangement 395 and oxindole formation that have been observed in related studies to this work, alternatively, the substrate may undergo other cyclisations as shown in Scheme 121.

Scheme 121  Proposed radical mechanisms for the substrate 381e
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However, on heating the bromide 381e in tetrahydrofuran at 50 °C for 24 hours the crude NMR and the TLC indicated several products as before with 381b. None of these could be properly isolated and purified and therefore they were not exhaustively analysed. Consequently, due to both 381b and 381e that gave complicated mixtures, this resulted in cessation of further investigations into this class of substrates.

4.0 Conclusion for Chapter Three

The starting sulphonamides were treated with 2-bromo-2-isobutyl bromide and triethylamine to yield the radical precursors. The N-butyl group gave the best yield (70%). The yields decreased from N-butyl to N-dodecyl. With more hindered substrates the reaction failed presumably due to steric hinderance. The iso-butyl and sec-butyl substrates gave average yields of 48% and 56% respectively. Again, steric hindrance was responsible for the lower yield.

As with Chapter 2, in the copper mediated radical reactions there was a similar trend in selectivity towards the rearranged amide 370 (in dichloromethane), and regioisomeric oxindoles 371:372 (in toluene or ionic liquid BMIM BF₄). The initial study on a range of substrates 369 in dichloromethane at 37 °C, showed marked selectivity towards the rearranged amide 370 (compared to the parent compound 278a). It was shown that as the N-alkyl chain increases, the selectivity towards the rearranged amide increases also, with the exception of 369a which showed high selectivity. The reasons for this trend are reduction of the amidyl radical which leads to amide 370 whereas cyclisation leads to 371/372. The reduction of the amidyl radical could arise from two possible pathways, (a) hydrogen abstraction of the H-atom from the solvent or (b) from an intramolecular H-translocation. The efficiency of the latter would be expected to increase with increasing chain length (as
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observed). The selectivity observed with the $N$-Et group would indicate that there is a rapid reduction of the amidyl radical from the solvent (DCM), relative to cyclisation. Dichloromethane at room temperature has a greater selectivity towards the rearranged amide $370$, (but keeping the trend the same) compared to dichloromethane at $37^\circ$C. The nature of the $N$-alkyl group has two possible rules. It is known that it can affect rates of cyclisations of both carbon and nitrogen based radicals and also provides pathways for intramolecular reduction. In 5-exo cyclisation of $\alpha$-amide radicals, small nitrogen substituents cause a relatively slow rate of cyclisation due to unfavorable rotamer ratios. However, in this case (amidyl radicals) cyclisation has been shown to be retarded by bulky substituents. Thus it is unclear why the relative rate of cyclisation for the $N$-ethyl substituent is slow. This suggests that it is the rate of reduction which is fast (presumably intermolecular reduction).

In a another set of reactions, (this time using toluene at both 50 ºC and refluxing temperature (110 ºC) and ionic liquid at 50 ºC) of three substrates, $N$-Et $369a$, $N$-$n$-Bu $369d$ and $N$-$i$-Bu $369i$ the expected reversal of selectivity leading to the cyclised products $371$:$372$ was observed. As in Chapter Two, the selectivity towards the cyclised products was evident. The explanation for this is that toluene is a poor hydrogen donor compared to DCM, and that the major path must be through addition onto the aromatic ring via the amidyl radical intermediate $335$. Interesting, when the ionic liquid-BMIM BF$_4$ was compared to toluene at 50 ºC, there was a greater rate of conversion presumably due to increased solubility of CuBr/TPA, but a similar ratio of products were observed due to similar H-donor ability to toluene. With the ionic liquid reactions, there was a reversal of selectivity toward cyclisation ($C_2$-$C_5$). The reason for this remains unclear. Further investigation by replacing the alkyl group
Chapter Three

with an aryl or heteroaromatic group was conducted. It was not possible to obtain any meaningful data however.
CHAPTER FOUR

REACTIONS OF N-ETHYL-N-
TRICHLOROACETYL-4-
METHYLBENZENESULFONAMIDE
AND HALO-AMIDES WITH CuX/TPA
Chapter Four

1.0 Introduction

Having investigated the effects of \(N\)-butyl-(substituted)-benzenesulfonamides 278, \(N\)-alkyl-4-methylbenzenesulfonamides 369 and \(N\)-aryl-4-methylbenzenesulfonamides 381 upon product outcome, a series of radical initiators were investigated as depicted in Figure 22.

![Figure 22](attachment:image.png)

**Figure 22** Structure of arylsulfonamide using various radical initiators

All previous investigations have been conducted using unactivated radical initiators, as described in both Chapter 2 and 3. Due to time constraints, a thorough investigation of all initiators was not possible. Therefore, substrates were used based on the previous work by the Clark group\(^{154}\) as described in Chapter 1 section 3.5 on page 81. In this case, the radical precursor 275 when treated with copper (I) chloride and TPA complex lead to the rearranged amide 277 as depicted in Scheme 122. Although, this was only determined through the crude proton NMR, as it was not possible to obtain the pure product.

![Scheme 122](attachment:image.png)

**Scheme 122** Clark’s rearrangement reaction using arylsulfonamide 275

1.1 Investigation of the trichloroacetamide substrate 396

A brief investigation of the effects of varying the initiator portion of the molecule on one of the previously investigated derivative 369a was undertaken as depicted in
Chapter Four

Figure 22. In this case, the unactivated bromide initiator (CMe₂Br) was substituted for an activated (CCl₃) initiator 396.

![Chemical structures](image1)

Figure 23  The structures of the radical precursors 369a and 396

The precursor 396 was prepared from commercially pure 369a (1.0 eq.) with trichloroacetyl chloride 397 (1.0 eq.) and n-butyllithium (1.0 eq.) in excellent yields in 84% yield as depicted in Scheme 123.

![Synthesis scheme](image2)

Scheme 123  Synthesis of trichloroacetamide 396

It should be possible to observe a similar reaction with the substrate 396 to furnish the rearranged amide 398 as outlined below.

![Reaction scheme](image3)

Scheme 124  General reaction scheme for substrate 396 with CuBr/TPA
1.2 Radical reaction of the trichloroacetamide 396

The next step was to react this under identical conditions to that in Chapter Three-Table 15. The trichloroacetamide 396 was heated in dichloromethane at 37 °C for 18 hours. The reaction was carefully monitored by TLC, which showed several products which included unreacted starting material 396. In addition it was possible to identify the expected rearranged amide 398, and the cyclised product 399 (see Scheme 125) in a ratio of [1.0:1.6] 398:399 (based upon crude NMR spectra). Based on the analogous reaction with the bromide 369a it was observed that the use of the trichloroacetamide 396 as a substrate was less efficient in mediating the rearranged amide (compared to the bromide where there was excellent selectivity for 370a, e.g. 10:1 versus 1.6:1).

![structures](370a_371_372.png)

**Figure 24** Structures of the N-ethyl cyclised and rearranged products

![Scheme 125](396_398_399.png)

**Scheme 125** Radical reaction of trichloroacetamide with CuBr/TPA

An analogous reaction by Wongtap156 with N-butyl trichloroacetamide furnished the rearranged amide in excellent yield (100%), but surprisingly as shown in Chapter One-Section 3.5, the N-allyl derivatives 275 furnished only a low yield (10%), although only tentatively assigned by NMR.
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2.0 Synthesis of oxindoles from halo-amides

Oxindoles have been prepared via radical cyclisation onto aromatic rings. An example is Nishio’s radical cyclisation\textsuperscript{178} (Scheme 126) whereby the bromide 400 when treated with tributyltin hydride and AIBN underwent radical cyclisation into the aromatic ring to give the radical intermediate 401, followed by re-aromatisation to furnish the oxindole 402. Another related reaction is Storey’s\textsuperscript{59} (Scheme 127) tributyltin hydride radical cyclisation of ortho halo anilides derivatives (not shown) to furnish oxindoles (eg. 405). In this case 1,5-H translocation of the aryl radical 403 to 404 followed by addition into the aromatic and oxidation furnishes the observed product.

![Scheme 126 Nishio’s radical approach to oxindoles](image)

![Scheme 127 Storey’s radical approach to oxindoles](image)

The following investigation to determine if similar cyclisations of haloacetamides (eg. \textsuperscript{278}e, 406-409) could be mediated by copper-TPA complex was undertaken. Thus it was postulated that generating the radical from the precursors 406-408 using either CuBr or CuCl and TPA would lead to a radical cyclisation into the aromatic ring followed by oxidation via the copper (II) halide complex to give the cyclised oxindole products 409-411 (Scheme 128).

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Scheme 128  Proposed mechanism for oxindole synthesis using CuBr/TPA

Cyclisation precursors were prepared whereby the initiating radical would be produced from functionality which contained the tertiary bromide \( 341 \), a dichloroacetamide \( 406 \), a trichloroacetamide \( 407 \) and a primary bromide \( 408 \) (Figure 24).

**Figure 25**  The functionized initiators \( 341 \) and \( 406-408 \)

2.1  Synthesis of precursors \( 278e, 406-408 \)

The dichloroacetamide \( 406 \) was prepared by reacting the amine (1.0 eq.) \( 340 \) with dichloroacetyl chloride (1.0 eq.) \( 412 \) with butyllithium (1.0 eq.) as a base. NMR spectroscopic analysis showed the desired precursor \( 406 \) was produced (in 46% yield) but also the de-alkylated amide \( 413 \) was obtained and this was inseparable by chromatography from \( 406 \) (Scheme 129).
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Scheme 129  Synthetic approach to dichloro precursor 406

The trichloroacetamide (1.0 eq.) 407 was prepared successfully by simply reacting the amine (1.0 eq.) 340 with trichloroacetyl chloride (1.0 eq.) 397 and butyllithium (1.0 eq.) in excellent yield (82%). The primary bromide 408 was prepared by reacting the amine 340 with acetyl bromide and triethylamine (1.0 eq).

2.2  Reactions of radical precursors 281e, 409-411

The precursor 281e was heated in refluxing toluene with one equivalent of CuBr and TPA for 24 hours. The crude NMR showed one compound, which was identified as the oxindole 333 upon purification (98%) as depicted in Scheme 130. Oxindole 333 may be formed via the desired radical cyclisation mechanism outlined earlier (see Scheme 87, page 110) or it could be produced by a similar mechanism to the Friedel-Crafts alkylation (with the CuBr acting as a Lewis acid mediator). The radical process would likely be catalytic as the copper (II) bromide formed in the initiation event would oxidise the intermediate cyclohexadienyl radical 414 to the aromatic oxindole and regenerate the copper (I) bromide. On the other hand, Friedel-Crafts alkylation reactions are not generally catalytic and stoichiometric amounts of lewis acid reagent are required.
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Scheme 130  Copper-mediated radical cyclisation of precursor 341

It was impossible to distinguish between these mechanisms because one equivalent of CuBr/TPA was used. In light of this result, and in order to determine whether a stoichiometric amount of copper bromide was required, the reaction was repeated using 30% CuBr/TPA under otherwise identical conditions as before. Although NMR analysis of the crude reaction confirmed that the oxindole 333 was present, there were a number of other by-products formed. The oxindole 333 was formed in only 16% isolated yield. In this case, because of the low yield, it was still unclear whether a catalytic radical process was involved, or a stoichiometric Friedel-Craft cyclisation—although it may suggest the latter.

2.3 Additional reactions

The next step was to investigate the reaction of the trichloroacetamide 407 to determine if this too would undergo a similar reaction. Thus 407 was heated in refluxing toluene for 24 hours with CuCl and TPA and the reaction was monitored by TLC. The crude NMR showed unreacted starting material and oxindole 415 (Scheme 131) (tentatively assigned from the NCH$_2$ group and by comparison of spectroscopic details of the related oxindole 333. As with the sulfonamide analogue 396 there were a number of by-products.
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Scheme 131  Copper-mediated radical cyclisation of trichloroacetamide 396

Finally, an investigation of the primary bromide precursor 408 was performed to determine if cyclisation could occur. The primary halide is likely to be much more difficult to cleave homolytically due to a stronger C-Br bond than the tertiary bromide 341. In fact, previous work in the group had shown that generating radicals from primary bromides often did not succeed. The halide was heated in refluxing toluene for 48 hours with a stoichiometric amount of CuBr and TPA. This time, the crude NMR showed unreacted starting material.

3.0 Conclusion for Chapter Four

Firstly changing the initiating group from tertiary bromide 284 to trichloroacetyl 397 in the CuCl/TPA mediated rearrangement reactions was found to be detrimental to the rate, yield and substituents of the process. This highlights the limitation of the rearrangement reactions described.

Secondly it has been shown that it is possible to prepare oxindoles directly from dimethylbromoacetylalamides by heating with CuBr/TPA. Mechanistically this reaction might proceed by a Friedel-Crafts alkylation mediated by the copper lewis acid or a radical addition/oxidation process. The low yield produced with sub-stoichiometric amounts of reagent tentatively indicated the former process. As with the rearrangement reactions of sulfonamides, changing the group from tertiary bromide 284 to trichloroacetyl 397 was detrimental to the overall yield of the process. Attempted cyclisation of the bromoacetamide 408 failed, either because the C-Br
bond could not be broken (either homolytically or heterolytically) or due to relatively slow cyclisation of primary bromides relative to tertiary bromides \(284\) (due to absence of the \textit{gem} methyl effect).

4.0 Future work

The following recommendation may help improve the oxindole forming reaction and thus improve yields.

- The use of a series of different ligands should be tested. In these studies only the copper (I) bromide (chloride) and TPA were used. Varying the ligand may effect solubility, reactivity and mechanistic properties.
CHAPTER FIVE

EXPERIMENTAL
Experimental

1.0 General

$^1$H NMR spectra were recorded at 300, 400 and 500MHz on the Bruker DPX300, DPX400 and DPX500 spectrometer respectively, and are in CDCl$_3$ unless otherwise stated. All chemical shifts ($\delta$) are quoted in parts per million (ppm) with deuterated chloroform (CDCl$_3$, $\delta_H = 7.26$ ppm) in tetramethylsilane (Si(CH$_3$)$_4$, TMS), $\delta_H = 0.00$) as internal reference unless otherwise stated. Coupling constants ($J$) were measured in Hz.

$^{13}$C NMR (DEPT) were recorded at 75.5, 100.6 and 125.8MHz on the Bruker DPX300, DPX400, and DPX500 spectrometer respectively, with CDCl$_3$ in TMS as internal reference unless otherwise stated. Infrared spectra were recorded on a Perkin-Elmer 1720X fourier-transform infrared spectrometer (Golden-Gate method). Mass Spectra were recorded using a Micromass Autospec. Mass Spectra were recorded using EI (Electron Impact), CI (Chemical Ionisation), or LSIMS (Liquid Secondary Ion Mass Spectrometry)-FAB (Fast Atom Bombardment) at both low and high resolution. LSIMS were carried out in a PEG300 in 3-NBA matrix. Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Analytical TLC were performed using Merck aluminium sheet silica gel 60 F$_{254}$. Column chromatography was performed with Fluorochem® silica gel 40-63 60Å. Visualizations were performed using ultraviolet radiation at 254nm, acidic polymolybdenate or basic potassium permanganate, unless otherwise stated. All chemicals were commercially available from Aldrich and used without further purification. All solvents were used without further purification. All organic reactions were performed under nitrogen atmosphere unless otherwise stated. All organic products were dried over either anhydrous magnesium sulfate or anhydrous sodium sulfate. Nomenclature for the compounds was obtained from Beilstein Autonom software programmes. All elemental analysis was obtained
Experimental

from Warwick Analytical Service or Medac Elemental Analysis. The following compounds **283b-j, 374b-j.l** and **379a-b,d-f** are commercially available in milligram quantities only.

**Abbreviations:**

s = singlet, bs = broad singlet, bd = broad doublet, d = doublet, t = triplet, q = quartet, quin. = quintet, sxt. = sextet, spt. = septet, oct. = octet d.t = doublet of triplets, t.t = triplet of triplets, d.d = doublet of doublets, s = quarternary carbon (C), d methide carbon (CH), t = methylene carbon (CH₂), q = methyl carbon CH₃, app. = apparent, m. = multiplet, WAS = Warwick Analytical Service.

1.1 General synthesis of N-butyl-(substituted)-arylsulfonamides

1.1.1 Method A

To a stirred solution of the arylsulfonyl chloride **281** (1.2 eq.) in dichloromethane (DCM) (50 mL) was added n-butylamine **282** (1.0 eq.) and triethylamine (TEA) (1.36 eq.). The solution was stirred at 0 °C (ice bath) for four hours unless otherwise stated. The reaction was quenched with distilled water (50 mL) and the product extracted with DCM or ether (3 x 50 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and the solvent removed in vacuo to yield the crude arylsulfonamide **283**. Purification was by recrystallization (diethyl ether/hexane) or flash chromatography (petroleum ether/ethyl acetate).
Experimental

1.1.2 Method B

As above but arylsulfonyl chloride (1.0 eq.) 281 and amine (3.0 eq.) 282 were reacted in diethyl ether. No purification was required with this method.

\[ \text{N-Butyl-benzenesulfonamide 283a}^{168} \]

![Image of N-Butyl-benzenesulfonamide 283a]

Commercially available from Aldridge [3622-84-2]. Method B: Furnished N-butyl-benzenesulfonamide 283a as a clear oil (27.60g, 99%). IR (neat) \( \nu_{\text{max}} \): 3274, 2958, 2869, 1316, 1155, 795, 687 cm\(^{-1}\). \(^1\)H NMR (400MHz, CDCl\(_3\), \( \delta \)): 7.92-7.89 (d, \( J = 7.0 \), 2H, ArCH), 7.58-7.48 (m, 3H, ArCH), 5.41 (bs, 1H, NH), 2.92 (t, \( J = 7.0 \), 2H, CH\(_2\)), 1.46-1.39 (quin., \( J = 7.0 \), 2H, CH\(_3\)), 1.33-1.23 (sxt., \( J = 7.0 \), 2H, CH\(_2\)), 0.80 (t, \( J = 7.0 \), 3H, CH\(_3\)). \(^{13}\)C NMR (100.5MHz, CDCl\(_3\), \( \delta \)): 139.9 (s, C-SO\(_2\)), 132.5 (d, ArCH), 129.1 (2 x d, ArCH), 127.0 (2 x d, ArCH), 42.9 (t, CH\(_2\)), 31.4 (t, CH\(_2\)), 20.0 (t, CH\(_2\)), 13.5 (q, CH\(_3\)). LRMS (LSIMS-FAB\(^+\)) \( m/\varepsilon \): 214 (MH\(^+\) = 100%), 154 (57), 136 (40). HRMS (LSIMS-FAB\(^+\)) \( m/\varepsilon \): calcd for C\(_{10}\)H\(_{15}\)NO\(_2\)S, 214.0902; found, 214.0895.

\[ \text{N-Butyl-4-fluoro-benzenesulfonamide 283b}^{169} \]

![Image of N-Butyl-4-fluoro-benzenesulfonamide 283b]

Commercially available from ZereneX Molecular Limited [312-67-4]. Method B: Furnished N-butyl-4-fluoro-benzenesulfonamide 283b as a yellow crystalline solid (5.78g, 90%). Hydroscopic, mp 44-45 °C (lit.\(^{169}\) (EtOH) 37 °C). IR (neat) \( \nu_{\text{max}} \): 3280, 2958, 2929, 2868, 1325, 1155, 788 cm\(^{-1}\). \(^1\)H NMR (300MHz, CDCl\(_3\), \( \delta \)): 7.92-7.86 (m, 2H, ArCH), 7.22-7.14 (app. t, \( J = 9 \), 2H, ArCH), 4.94 (bs, 1H NH), 2.92 (t, \( J = 7.0 \), 2H,
Experimental

CH₂), 1.48-1.38 (quin. J = 7.0, 2H, CH₂), 1.34-1.21 (sxt. J = 7.0, 2H, CH₂), 0.85 (t, J = 7.0, 3H, CH₃). ¹³C NMR (75.5MHz, CDCl₃, δ): 165.0 (s, J = 254.5, C-F), 136.4 (s, C-SO₂⁻), 130.1 (2 x d, ArCH), 116.6 (2 x d, ArCH), 43.3 (t, CH₂), 31.9 (t, CH₂), 13.9 (q, CH₃). LRMS (EI⁺) m/z: 232 (100% M⁺), 188 (95), 176 (15), 159 (65). HRMS (EI) m/z: calcd for C₁₀H₁₄FNO₂S, 231.0729; found, 231.0729.

4-Bromo-N-butyl-benzenesulfonamide 283c

Commercially available from Aurora Fine Chemicals [1984-28-7]. Method B: Furnished 4-bromo-N-butyl-benzenesulfonamide 283c as a pale yellow crystalline solid (3.34g, 42%). mp (neat) 59.8 °C. IR (neat) νmax: 3262, 2955, 2867, 1321, 1153, 1088, 736 cm⁻¹. ¹H NMR (300MHz, CDCl₃, δ): 7.74-7.71 (d.t, J = 9.0 and 2.0, 2H, ArCH), 7.61-7.59 (d.t, J = 9.0 and 2.0, 2H, ArCH), 4.90 (bs, 1H, NH), 2.93, (t, J = 7.0, 2H, CH₂), 1.47-1.39 (quin., J = 7.0, 2H, CH₂), 1.31-1.22 (sxt., J = 7.0, 2H, CH₂), 0.83 (t, J = 7.0, 3H, CH₃). ¹³C NMR (75.5MHz, CDCl₃, δ): 139.1 (s, C-SO₂⁻), 132.4 (2 x d, ArCH), 128.6 (2 x d, ArCH), 127.5 (s, C-Br), 42.9 (t, CH₂), 31.5 (t, CH₂), 19.7 (t, CH₂), 13.9 (q, CH₃). LRMS (EI⁺) m/z: 294 (⁸¹Br MH⁺ 2%), 293 (⁸¹Br M⁺ 7), 292 (⁷⁹Br MH⁺ 6), 291 (⁷⁹Br M⁺ 10), 250 (⁸¹Br 98), 248 (⁷⁹Br 96), 156 (⁸¹Br 75), 154 (⁷⁹Br 76). HRMS (CI) m/z: calcd for C₁₀H₁₄BrNO₂S, 290.9929 (M⁺); found, 290.9915. Elemental Analysis (WAS): Calcd for C₁₀H₁₄BrNO₂S: C, 41.1; H, 4.8; N, 4.7. Found: C, 41.4, H, 5.0, N, 4.8%. 

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Experimental

*N-Butyl-4-iodo-benzenesulfonamide 283d*\(^{171}\)

![Chemical structure of N-Butyl-4-iodo-benzenesulfonamide 283d]

Commercially available from Aurora Screening Library [600638-58-2]. Method A: Recrystallisation furnished *N-butyl-4-iodo-benzenesulfonamide 283d* as a crystalline solid (5.04g, 89%). IR (neat) \(\nu_{\text{max}}\): 3282, 2958, 2932, 2870, 1570, 1325, 1160, 818 cm\(^{-1}\).

\(^1\)H NMR (400MHz, CDCl\(_3\), \(\delta\)): 7.91-7.86 (d,t, \(J = 9.0 \text{ and } 2.0\), 2H, ArC\(\_H\)), 7.62-7.58 (d,t, \(J = 9.0 \text{ and } 2.0\), 2H, ArCH), 4.91 (bs, 1H, NH), 2.94 (q, \(J = 7.0\), 2H, CH\(_2\)), 1.50-1.42 (quin., \(J = 7.0\), 2H, CH\(_2\)), 1.35-1.26 (sxt., \(J = 7.0\), 2H, CH\(_2\)), 0.87 (t, \(J = 7.0\), 3H, CH\(_3\)).

\(^13\)C NMR (100MHz, CDCl\(_3\), \(\delta\)): 139.7 (s, C-SO\(_2\)), 138.3 (2 x d, ArCH), 128.5 (2 x d, ArCH), 99.8 (s, C-I), 43.0 (t, CH\(_2\)), 31.5 (t, CH\(_2\)), 19.8 (t, CH\(_2\)), 14.0 (q, CH\(_3\)).

LRMS (LSIMS-FAB\(^+\)) \(m/z\): 340 (M\(^+\) = 73%). HRMS (LSIMS-FAB\(^+\)) \(m/z\): (MH\(^+\)) calcd for C\(_{10}\)H\(_{15}\)INO\(_2\)S, 339.9868; found, 339.9879.

*N-Butyl-4-methyl-benzenesulfonamide 283e*\(^{172}\)

![Chemical structure of N-Butyl-4-methyl-benzenesulfonamide 283e]

Commercially available from ABCR GmbH KG [1907-65-9]. Previously synthesised by Fullaway.\(^{163}\) Method B: Recrystallisation furnished *N-butyl-4-methyl-benzenesulfonamide 283e*, as a yellow crystalline solid (6.39g, 89%). mp 40-41 °C. IR (neat) \(\nu_{\text{max}}\): 3244, 2937, 2868, 1427, 1316, 1155, 668 cm\(^{-1}\). \(^1\)H NMR (400MHz, CDCl\(_3\), \(\delta\)): 7.68 (d, \(J = 8.0\), 2H, ArCH), 7.19 (d, \(J = 8.0\), 2H, ArCH), 5.26 (app.t, \(J = 6.0\), 1H, NH), 2.80 (q, \(J = 7.0\), 2H, CH\(_2\)), 2.31 (s, 3H, ArCH\(_3\)), 1.37-1.29 (app. quin. \(J = 7.0\), 2H, CH\(_2\)), 1.22-1.13 (app. sxt. \(J = 7.0\), 2H, CH\(_2\)), 0.72 (t, \(J = 7.0\), 3H, CH\(_3\)). \(^13\)C NMR (100.5MHz,
Experimental

CDCl$_3$, $\delta$: 143.2 (s, C-Me), 137.0 (s, C-SO$_2$-), 129.7 (2 x d, ArCH), 127.1 (2 x d, ArCH), 42.9 (t, CH$_2$), 31.5 (t, CH$_2$), 21.5 (q, ArCH$_3$), 20.0 (t, CH$_2$), 14.9 (q, CH$_3$).

LRMS (EI$^+$) m/z: 227 (M$^+$ = 10), 184 (72), 154 (100). HRMS (LSIMS-FAB$^+$) m/z: calcd for C$_{11}$H$_{17}$NO$_2$S, 227.0980; found, 227.0974. Elemental Analysis (WAS): Calcd for C$_{11}$H$_{17}$NO$_2$S: C. 58.1; H. 7.5; N. 6.2. Found: C. 58.1; H. 7.4; N. 6.2%.

Naphthalene-2-sulfonic acid-butyramide 283g

![Naphthalene-2-sulfonic acid-butyramide](image)

Commercially available from Aurora Fine Chemicals [40207-14-5]. Method A: Purified by flash chromatography (petrol ether/ethyl acetate 6:1), to furnish naphthalene-2-sulfonic acid-butyramide 283g as beigh translucent crystalline solid (4.54g, 26%). mp 56 °C (lit. 248 54-55 °C). $^1$H NMR (300MHz, CDCl$_3$, $\delta$): 8.50 (s, 1H, Ar C$_2$H), 7.92-7.85 (m, 4H, ArCH), 7.63-7.52 (m, 2H, ArCH), 5.57 (app t, $J$ = 6.0, 1H, NH), 2.96 (q, $J$ = 7.0, 2H, CH$_2$), 1.49-1.39 (quin., $J$ = 7.0, 2H, CH$_2$), 1.31-1.19 (sxt., $J$ = 7.0, 2H, CH$_2$), 0.77 (t, $J$ = 7.0, 3H, CH$_3$). $^{13}$C NMR (100.5MHz, CDCl$_3$, $\delta$): 136.8 (s, C), 134.8 (s, C), 132.2 (s, C), 129.5 (d, ArCH), 129.2 (d, ArCH), 128.7 (d, ArCH), 128.4 (d, ArCH), 127.9 (d, ArCH), 127.5 (d, ArCH), 122.4 (d, ArCH), 43.0 (t, CH$_2$), 31.6 (t, CH$_2$), 20.1 (t, CH$_2$), 14.6 (q, CH$_3$). LRMS (LRMS-FAB$^+$) m/z: 264 (MH$^+$ = 100), 220 (10), 191 (52), 154 (40), 137 (27), 127 (46), 115 (16). HRMS (LSIMS-FAB$^+$) m/z: calcd for C$_{14}$H$_{17}$NO$_2$S, 263.0980; found 263.0978. Elemental Analysis (WAS): Calcd for C$_{14}$H$_{17}$NO$_2$S: C, 63.8; H, 6.5; N, 5.3. Found: C, 63.5; H, 6.5; N, 5.2 %.
Commercially available from Ambinter [35088-85-8]. Method A: Recrystallization yielded \textit{N-butyl-4-methoxy-benzenesulfonamide} 283h as a golden yellow solid, (5.71g, 94%). mp 39-40 °C. IR (neat) $\nu_{\text{max}}$: 3272, 2957, 2868, 1596, 1301, 1148, 1023, 803 cm$^{-1}$.

$^1$H NMR (300MHz, CDCl$_3$, $\delta$): 7.80 (app. d, $J = 9.0$, 2H, ArCH$_2$), 6.97 (app. d, $J = 9.0$, 2H, ArCH$_2$), 4.43 (t, $J = 6.0$, 1H, NH), 3.87 (s, 3H, OCH$_3$), 2.93 (q, $J = 7.0$, 2H, CH$_2$), 1.49-1.39 (quin., $J = 7.0$, 2H, CH$_2$), 1.35-1.23 (sxt., $J = 7.0$, 2H, CH$_2$), 0.85 (t, $J = 7.0$, 3H, CH$_3$): $^{13}$C NMR (75.5MHz, CDCl$_3$, $\delta$): 161.7 (s, C-OMe), 130.5 (s, C-SO$_2$-), 128.2 (2 x d, ArCH), 113.2 (2 x d, ArCH), 54.6 (q, OCH$_3$), 41.9 (t, CH$_2$), 30.5 (t, CH$_2$), 18.7 (t, CH$_2$), 12.5 (q, CH$_3$). LRMS (LSIMS-FAB$^+$) $m/z$: 243 (M$^+$= 40), 200 (54), 171 (100), 155 (15). HRMS (LSIMS-FAB$^+$) $m/z$: calcd for C$_{11}$H$_{17}$NO$_3$S, 243.0929; found, 243.0924. Elemental Analysis (WAS): Calcd for C$_{11}$H$_{17}$NO$_3$S: C, 54.3; H, 7.0; N, 5.8. Found: C, 54.1; H, 7.0; N, 5.7%.

\textit{N-Butyl-4-cyano-benzenesulfonamide} 283i 176

Commercially available from Ambinter [858497-76-4]. Method A: Recrystallisation furnished \textit{N-butyl-4-cyano-benzenesulfonamide} 283i as a pale yellow crystalline solid (4.79g, 85%). mp 104.5-105.5 °C (lit. 176 99 °C). IR (neat) $\nu_{\text{max}}$: 3282, 2959, 2931, 2870, 2237, 1329, 1158, 735cm$^{-1}$. $^1$H NMR (300MHz, CDCl$_3$, $\delta$): 7.98 (app. d, $J = 8.0$, 2H, ArCH), 7.83 (app. d, $J = 8.0$, 2H, ArCH), 4.5 (bs, 1H, NH), 3.0 (q, $J = 7.0$, 2H, CH$_2$), 1.49-1.39 (quin., $J = 7.0$, 2H, CH$_2$), 1.35-1.23 (sxt., $J = 7.0$, 2H, CH$_2$), 0.85 (t, $J = 7.0$, 3H, CH$_3$): $^{13}$C NMR (75.5MHz, CDCl$_3$, $\delta$): 161.7 (s, C-OMe), 130.5 (s, C-SO$_2$-), 128.2 (2 x d, ArCH), 113.2 (2 x d, ArCH), 54.6 (q, OCH$_3$), 41.9 (t, CH$_2$), 30.5 (t, CH$_2$), 18.7 (t, CH$_2$), 12.5 (q, CH$_3$). LRMS (LSIMS-FAB$^+$) $m/z$: 243 (M$^+$= 40), 200 (54), 171 (100), 155 (15). HRMS (LSIMS-FAB$^+$) $m/z$: calcd for C$_{11}$H$_{17}$NO$_3$S, 243.0929; found, 243.0924. Elemental Analysis (WAS): Calcd for C$_{11}$H$_{17}$NO$_3$S: C, 54.3; H, 7.0; N, 5.8. Found: C, 54.1; H, 7.0; N, 5.7%.
Experimental

1.52-1.42 (quin., \( J = 7.0 \), 2H, CH\(_2\)), 1.36-1.24 (sxt., \( J = 7.0 \), 2H, CH\(_2\)), 0.87 (t, \( J = 7.0 \), 3H, CH\(_3\)). \(^{13}\)C NMR (75.5MHz, CDCl\(_3\), \( \delta \)): 144.8 (s, C-SO\(_2\)-), 133.4 (2 x d, ArCH), 128.1 (2 x d, ArCH), 117.8 (s, C-C≡N), 116.6 (s, C-C≡N), 43.4 (t, CH\(_2\)), 31.9 (t, CH\(_2\)), 20.0 (t, CH\(_2\)), 13.9 (q, CH\(_3\)). LRMS (LSIMS-FAB\(^+\) \( m/z \): 239 (MH\(^+\) = 28%), 154 (100), 137 (70). HRMS (LSIMS-FAB\(^+\) \( m/z \): calcd for C\(_{11}\)H\(_{14}\)N\(_2\)O\(_2\)S, 239.0854; found, 239.0857.

\( \text{N-Butyl-4-nitro-benzenesulfonamide 283j} \)\(^{176} \)

![Structure of N-Butyl-4-nitro-benzenesulfonamide 283j](image)

Commercially available from Aurora Fine Chemicals [66473-14-1]. Method B: Furnished \( \text{N-butyl-4-nitro-benzenesulfonamide 283j} \) as a pale yellow crystalline solid (20.19g, 86%). mp 80-81 °C. (Lit. mp.\(^{176} \) 84 °C). IR (neat) \( \nu_{\text{max}} \): 3294, 2939, 2860, 1522, 1345, 1305, 1151, 852 cm\(^{-1}\). \(^1\)H NMR (300MHz, CDCl\(_3\), \( \delta \)): 8.37 (d.t, \( J = 9.0 \) and 2.0, 2H, ArCH), 8.06 (d.t, \( J = 9.0 \) and 2.0, 2H, ArCH), 4.57 (bs, 1H, NH), 3.02 (q, \( J = 7.0 \), 2H, CH\(_2\)), 1.52-1.43 (quin., \( J = 7.0 \), 2H, CH\(_2\)), 1.37-1.25 (sxt., \( J = 7.0 \), 2H, CH\(_2\)), 0.83 (t, \( J = 7.0 \), 3H, CH\(_3\)). \(^{13}\)C NMR (75.5MHz, CDCl\(_3\), \( \delta \)): 150.4 (s, C-NO\(_2\)), 146.4 (s, C-SO\(_2\)-), 128.7 (2 x d, ArCH), 124.8 (2 x d, ArCH), 43.5 (t, CH\(_2\)), 32.0 (t, CH\(_2\)), 20.0 (t, CH\(_2\)), 13.9 (q, CH\(_3\)). LRMS (EI+) \( m/z \): 259 (M\(^+\) = 10), 216 (12), 210 (100), 185 (65), 122 (29); HRMS (LSIMS-FAB\(^+\) \( m/z \): (MH\(^+\)) calcd for C\(_{10}\)H\(_{15}\)N\(_2\)O\(_4\)S, 258.0674; found 258.0670.
Experimental

\(\text{N-Butyl-4-trifluoromethyl-benzenesulfonamide 283k}\)

Method A: Recrystallization yielded \(\text{N-butyl-4-trifluoromethyl-benzenesulfonamide 283k}\) as a beige reflective crystalline solid (3.61g, 94%). \(\text{mp 76-77 °C. IR (neat) } \nu_{\text{max}}: 3263, 2960, 2931, 2867, 1322, 1162, 713 \text{ cm}^{-1}.\) \(^1\)H NMR (300MHz, CDCl\(_3\), \(\delta\)): 8.01 (d, \(J = 8.5, 2\text{H, ArCH}\)), 7.79 (d, \(J = 8.5, 2\text{H, ArCH}\)), 4.68 (bs, 1H, NH), 2.97 (t, \(J = 7.0, 2\text{H, CH}_2\)), 1.51-1.42 (m, 2H, \(\text{CH}_2\)), 1.36-1.24 (sxt., \(J = 7.0, 2\text{H, CH}_2\)), 0.87 (t, 7.0, 3H, \(\text{CH}_3\)). \(^{13}\)C NMR (100.5MHz, CDCl\(_3\), \(\delta\)): 144.0 (s, \(\text{C-SO}_2\)), 134.5 (s, \(J = 286.6, \text{C-CF}_3\)), 127.6 (2 x d, ArCH), 126.4 (2 x d, ArCH), 124.5 (s, \(J = 34, \text{ArC-CF}_3\)), 43.0 (t, \(\text{CH}_2\)), 19.9 (t, \(\text{CH}_2\)), 13.6 (q, \(\text{CH}_3\)). LRMS (LSIMS-FAB\(^+\)) \(m/z: 282 (M^+ = 100\%), 280 (15), 226 (26), 209 (17), 154 (43).\) HRMS (LSIMS-FAB\(^+\)) \(m/z: (\text{MH}^+)\) calcd for \(\text{C}_{11}\text{H}_{15}\text{F}_3\text{NO}_2\text{S}, 282.0776; \text{found, 282.0772.}\)

\(\text{N-Butyl-(bis-3, 5-trifluoromethylbenzene)-sulfonamide 283l}\)

Method A: Purified using column chromatography (diethyl ether/hexane; 3:1) to furnish \(\text{N-butyl-(bis-3,5-trifluoromethylbenzene)-sulfonamide 283l}\) as an off-white (beige) crystalline solid (2.86, 76%). \(\text{mp 83.8-84.8 °C. IR (neat) } \nu_{\text{max}}: 3287, 2967, 2934, 2872, 1340, 1136, 904, 689 \text{ cm}^{-1}.\) \(^1\)H NMR (300MHz, CDCl\(_3\), \(\delta\)): 8.31 (s, 2H, ArCH), 8.07 (s, 1H, ArCH), 4.67 (t, \(J = 6.0, 1\text{H, NH}\)), 3.04 (q, \(J = 7.0, 2\text{H, CH}_2\)), 1.54-1.44 (quin., \(J = 7.0, 2\text{H, CH}_2\)), 1.37-1.25 (sxt., \(J = 7.0, 2\text{H, CH}_2\)), 0.87 (t, \(J = 7.0, 3\text{H, CH}_3\)). \(^{13}\)C NMR
**Experimental**

(75.5MHz, CDCl$_3$, $\delta$): 142.1 (s, ArC-SO-), 132.1 (2 x s, $J = 273.4$, C-CF$_3$), 126.29 (2 x d, ArCH), 125.1 (d, ArCH), 121.0 (2 x s, $J = 34.4$, ArC-CF$_3$), 42.1 (t, CH$_2$), 30.56 (t, CH$_2$), 18.6 (t, CH$_2$), 12.3 (q, CH$_3$). LRMS (EI$^+$) m/z: 350 (MH$^+ = 83$), 213 (100), 195 (28), 145 (21) and 121 (50). HRMS (Cl): calcd for C$_{12}$H$_{13}$F$_6$NO$_2$S, 349.0571; found, 349.0571; Elemental Analysis (WAS): Calcd for C$_{12}$H$_{13}$F$_6$NO$_2$S: C, 41.3; H, 4.0; N, 3.8. Found: C, 41.5; H, 3.8; N, 4.0%.

2.0 General synthesis of N-alkyl-4-methyl-benzenesulfonamides

2.1 Method A

To a stirred solution of 4-methyl-benzenesulfonyl chloride 281 (1.2 eq.) in dichloromethane (DCM) (50 mL) was added the alkylamine 373 (1.0 eq.) and triethylamine (TEA) (1.36 eq.). The solution was stirred at 0 °C (ice bath) for four hours unless otherwise stated. The reaction was quenched with distilled water (50 mL) and the product extracted with DCM or ether (3 x 50 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and the solvent removed in vacuo to yield the crude arylsulfonamide 374. Purification was by recrystallization (diethyl ether/hexane) or flash chromatography (petroleum ether/ethyl acetate).

2.2 Method B

As above but 4-methylbenzenesulfonyl chloride 281 and alkylamine 373 (3.0 eq.) were reacted in diethylether. No purification was required with this method.
Experimental

*N*-Ethyl-4-methyl-benzenesulfonamide 374a

Commercially available from Aldrich [80-39-7]. Method B: Furnished *N*-ethyl-4-methyl-benzenesulfonamide 374a as an hydroscopic white crystallized solid (4.78g, 84%). mp 67.9-68.9 °C. IR (neat) ν_max: 3268, 2978, 2876, 2361, 1322, 1157, 814 cm\(^{-1}\). \(^1\)H NMR (300MHz, CDCl\(_3\), δ): 7.79 (d, J = 8.0, 2H, ArCH), 7.32 (d, J = 8.0, 2H, ArCH), 5.11 (app. t, J = 5.0, 1H, NH), 2.97 (quin., J = 7.0, 2H, CH\(_2\)), 2.42 (s, 3H, ArCH\(_3\)), 1.08 (t, J = 7.0, 3H, CH\(_3\)). \(^{13}\)C NMR (75.5MHz, CDCl\(_3\), δ): 143.1 (s, C-Me), 136.7 (s, C-SO\(_2\)-), 129.4 (2 x d, ArCH), 126.9 (2 x d, ArCH), 37.3 (t, CH\(_2\)), 21.3 (q, ArCH\(_3\)), 14.7 (q, CH\(_3\)). LRMS (EI\(^+\)) m/z: 199 (M\(^+\) = 20%), 184 (90), 155 (100). HRMS (LSIMS-FAB\(^+\)) m/z: calcd for C\(_9\)H\(_{14}\)NO\(_2\)S (MH\(^+\)), 200.0745; found, 200.0742. Elemental Analysis (WAS): Calcd. for C\(_9\)H\(_{13}\)NO\(_2\)S: C, 54.2; H, 6.6; N, 7.0. Found: C, 54.3; H, 6.5; N, 7.0%.

*N*-Propyl-4-methyl-benzenesulfonamide 374b

Commercially available from Interchim [1133-12-6]. Method B: Furnished *N*-propyl-4-methyl-benzenesulfonamide 374b as a yellow viscous solid (5.43g, 81%). mp 27-28 °C. IR (neat) ν_max: 3275, 2968, 2875, 1315, 1156 and 814 cm\(^{-1}\). \(^1\)H NMR (300MHz, CDCl\(_3\), δ): 7.66 (d, J = 8.0, 2H, ArCH), 7.17 (d, J = 8.0, 2H, ArCH), 5.52 (app.t, J = 5.0, 1H, NH), 2.75 (t, J = 7.0, 2H, CH\(_2\)), 2.28 (s, 3H, ArCH), 1.40-1.31 (sxt., J = 7.0, 2H, CH\(_2\)), 0.72 (t, J = 7.0, 3H, CH\(_3\)). \(^{13}\)C NMR (100MHz, CDCl\(_3\), δ): 143.0 (s, C-Me), 136.8 (s, C-SO\(_2\)-), 129.4 (2 x d, ArCH), 126.9 (2 x d, ArCH), 44.7 (t, CH\(_2\)), 22.6 (t, CH\(_2\)), 21.1 (q,
Experimental

ArCH$_3$), 10.9 (q, CH$_3$). LRMS (CI) $m/z$: 214 MH$^+$ = 22%, 196 (35), 184 (67), 155 (90), 139 (15). HRMS (CI) calcd for C$_{10}$H$_{15}$NO$_2$S; 213.0823, found 213.0817. Elemental Analysis (WAS): Calcd. for C$_{10}$H$_{15}$NO$_2$S; C, 56.1; H, 7.1; N, 6.6. Found: C, 55.9; H, 7.1; N, 6.4%.

4-Methyl-N-pentyl-benzenesulfonamide 374d

![Chemical Structure](image)

Commercially available from Aurora Fine Chemicals [106011-68-1]. Method B: Furnished 4-methyl-N-pentyl-benzenesulfonamide 374d as a colourless oil (5.80g, 92%). IR (neat) $\nu_{\text{max}}$: 3276, 2929, 1322, 1155, 813, 659 cm$^{-1}$. $^1$H NMR (300MHz, CDCl$_3$, $\delta$): 7.74 (d.t, $J = 8.0$ and 2.0, 2H, ArCH), 7.30 (d, $J = 8.0$, 2H, ArCH), 4.35 (t, $J = 6.0$, 1H, NH), 2.92 (q, $J = 7.0$, 2H, CH$_2$), 2.43 (s, 3H, ArCH$_3$), 1.49-1.41 (app. quin., $J = 7.0$, 2H, CH$_2$), 1.27-1.21 (m, 4H, CH$_2$), 0.84 (t, $J = 7.0$, 3H, CH$_3$). $^{13}$C NMR (100MHz, CDCl$_3$, $\delta$): 143.3 (s, C-Me), 137.0 (s, C-SO$_2$), 129.7 (2 x d, ArCH), 127.1 (2 x d, ArCH), 43.2 (t, CH$_2$), 29.2 (t, CH$_2$), 28.7 (t, CH$_2$), 22.1 (t, CH$_2$), 21.5 (q, ArCH$_3$), 14.3 (q, CH$_3$). LRMS (LSIMS-FAB$^+$) $m/z$: 242 (MH$^+$ 100%), 154 (22%), 137 (16%). HRMS (LSIMS-FAB$^+$) $m/z$: (MH$^+$) calcd for C$_{12}$H$_{20}$NO$_2$S, 242.1215; found, 242.1210. Elemental Analysis (WAS): Calcd for C$_{12}$H$_{19}$NO$_2$S: C, 59.7; H, 7.9; N, 5.8. Found: C, 59.5; H, 7.8; N, 5.7%.
Commercially available from Interchim [1143-01-7]. Method A: Recrystallisation furnished *N*-hexyl-4-methylbenzenesulfonamide 374e as a white crystallised solid (4.34g, 62%). mp 83.0-84.0 °C (lit. 231 DCM/Pentane 59.5 °C). IR (neat) ν max: 3280, 2922, 2854, 1319, 1153, 664 cm\(^{-1}\). \(^1\)H NMR (300MHz, CDCl\(_3\), δ): 7.74 (d.t, J = 8.0 + 2.0, 2H, ArCH), 7.29 (d, J = 8.0, 2H, ArCH), 4.39 (app. t, J = 6.0, 1H, NH), 2.89 (t, J = 7.0, 2H, CH\(_2\)), 2.42 (s, 3H, ArC\(_3\)H), 1.48-1.36 (sxt., J = 7.0, 2H, CH\(_2\)), 1.29-1.13 (m, 6H, 3 x CH\(_2\)), 0.83 (t, J = 7.0, 3H, CH\(_3\)). \(^{13}\)C NMR (100MHz, CDCl\(_3\), δ): 143.2 (s, C-Me), 137.0 (s, C-SO\(_2\)), 129.6 (2 x d, ArCH), 127.1 (2 x d, ArCH), 43.2 (t, CH\(_2\)), 31.2 (t, CH\(_2\)), 29.5 (t, CH\(_2\)), 26.2 (t, CH\(_2\)), 22.4 (t, CH\(_2\)), 21.5 (q, ArCH\(_3\)), 15.0 (q, CH\(_3\)). LRMS (Cl) m/z: 256 (MH\(^+\) 23%), 184 (80), 155 (100), 100 (28), 91 (80). HRMS (EI\(^+\)) calcd for C\(_{13}\)H\(_{21}\)NO\(_2\)S, 255.1293; found, 255.1293. Elemental Analysis (WAS): Calcd for C\(_{13}\)H\(_{21}\)NO\(_2\)S: C, 61.1; H, 8.3; N, 5.5. Found: C, 61.0; H, 8.1; N, 5.5%.

*N*-Docecyl-4-methyl-benzenesulfonamide 374f

Commercially available from Aurora Fine Chemicals [1635-09-2]. Method B: Furnished *N*-dodecyl-4-methylbenzenesulfonamide 374f as a white crystallised solid (4.19g, 45%). mp 86.0-87.0 °C. IR (neat) ν max: 3284, 2914, 2845, 1324, 1157, 814, 670 cm\(^{-1}\). \(^1\)H NMR (300MHz, CDCl\(_3\), δ): 7.74 (d.t, J = 8.0 + 2.0, 2H, ArCH), 7.30 (d, J = 8.0, 2H, ArCH), 5.0 (bs, 1H, NH), 2.90 (t, J = 7.0, 2H, CH\(_2\)), 2.42 (s, 3H, ArCH\(_3\)), 1.19-1.46 (m, 20H
Experimental

CH$_2$), 0.87 (t, $J = 7.0$, 3H, CH$_3$). $^{13}$C NMR (75.5MHz, CDCl$_3$, $\delta$): 143.6 (s, C-Me), 137.4 (s, C-SO$_2$), 130.0 (2 x d, ArCH), 127.5 (2 x d, ArCH), 43.6 (t, CH$_2$), 32.3 (t, CH), 30.0 (t, CH$_2$), 29.9 (t, CH$_2$), 29.9 (t, CH$_2$), 29.8 (t, CH$_2$), 29.7 (t, CH$_2$), 29.5 (t, CH$_2$), 26.9 (t, CH$_2$), 23.1 (t, CH$_2$), 21.9 (q, ArCH$_3$), 14.5 (q, CH$_3$).

 LRMS (EI$^+$) m/z: 340 (MH$^+$ 35%), 184 (100), 172 (40), 155 (98), 91 (85%). HRMS (EI$^+$) m/z: calcd for C$_{19}$H$_{33}$NO$_2$S, 339.2232; found, 339.2246. Elemental Analysis (WAS): Calcd for C$_{19}$H$_{33}$NO$_2$S: C, 67.2; H, 9.8; N, 4.1. Found: C, 66.8; H, 9.6; N, 3.8%.

$N$-Isopropyl-4-methyl-benzenesulfonamide 374g$^{234}$

![Structure of N-Isopropyl-4-methyl-benzenesulfonamide](image)

Commercially available from Aurora Fine Chemicals [21230-07-9]. Method B: Furnished $N$-isopropyl-4-methylbenzenesulfonamide 374g, as a pale yellow crystalline solid (3.66g, 65%). mp 55.2-56.2 °C. IR (neat) $\nu_{\text{max}}$: 3275, 2974, 1320, 1141, 1092, 729.

$^1$H NMR (400MHz, CDCl$_3$, $\delta$): 7.76 (d.t, $J = 8.0$ and 2.0, 2H, ArCH), 7.29 (d, $J = 8.0$, 2H, ArCH), 4.26 (d, $J = 7.0$, 1H, NH), 3.45 (oct, $J = 7.0$, 1H, CH), 2.43 (s, 3H, ArCH$_3$), 1.07 (d, $J = 7.0$, 6H, 2 x CH$_3$). $^{13}$C NMR (100MHz, CDCl$_3$, $\delta$): 143.6 (s, C-Me), 138.5 (s, C-SO$_2$), 130.5 (2 x d, ArCH), 127.4 (2 x d, ArCH), 46.4 (d, CH), 24.1 (2 x q, CH$_3$), 21.9 (q, ArCH$_3$). LRMS (LSIMS-FAB$^+$) m/z: 214 (MH$^+$ 100%), 172 (30), 155 (15), 137 (13). HRMS (LSIMS-FAB$^+$) m/z: calcd for C$_{10}$H$_{16}$NO$_2$S, 214.0902; found, 214.0912; Elemental Analysis (WAS): Calcd for C$_{10}$H$_{15}$NO$_2$S: C, 56.3; H, 7.1; N, 6.5. Found: C, 56.1; H, 7.1; N, 6.4%.
Experimental

*N-Isobutyl-4-methyl-benzenesulfonamide 374h*\(^{235}\)

![Structure of N-Isobutyl-4-methyl-benzenesulfonamide](image)

Commercially available from Ambinter [23705-38-6]. Previously synthesised by Fullaway.\(^{164}\) Method B: Furnished *N-isobutyl-4-methylbenzenesulfonamide 374h* as a pale yellow crystallised solid (5.14g, 85%). mp (neat) 80.0-81.0 °C (lit. 77-78 °C). IR (neat) \(\nu_{\text{max}}\): 3273, 2960, 2872, 1320, 1155, 729 cm\(^{-1}\). \(^1\)H NMR (300MHz, CDCl\(_3\), \(\delta\)): 7.74 (d, \(J = 8.0, 2\)H, ArCH\(_2\)), 7.30 (d, \(J = 8.0, 2\)H, ArCH\(_2\)), 4.55 (bs, 1H, NH), 2.74 (t, \(J = 7.0, 2\)H, CH\(_2\)), 2.43 (s, 3H, ArCH\(_3\)), 1.71 (spt., \(J = 7.0, 1\)H, CH), 0.86 (d, \(J = 7.0, 6\)H, 2 x CH\(_3\)). \(^13\)C NMR (75.5MHz, CDCl\(_3\), \(\delta\)): 143.1 (s, C-Me), 136.8 (s, C-SO\(_2\)), 129.5 (2 x d, ArCH), 126.8 (2 x d, ArCH), 50.3 (t, CH\(_2\)), 21.9 (q, ArCH\(_3\)), 19.7 (2 x q, CH\(_3\)). LRMS (LSIMS-FAB\(^+\)) \(m/z\): 228 (MH\(^+\) 100%), 154 (100), 137 (70). HRMS (LSIMS-FAB\(^+\)) \(m/z\): (MH\(^+\)) calcd. 228.1058 for C\(_{11}\)H\(_{18}\)NO\(_2\)S; found, 228.1065.

Elemental Analysis (WAS): Calcd for C\(_{11}\)H\(_{17}\)NO\(_2\)S: C, 58.1; H, 7.5; N, 6.1. Found: C, 57.8; H, 7.4; N, 6.1%.

*N-sec-Butyl-4-methyl-benzenesulfonamide 374i* \(^{235}\)

![Structure of N-sec-Butyl-4-methyl-benzenesulfonamide](image)

Commercially available from Interchim [23705-40-0]. Previously synthesised by Fullaway.\(^{164}\) Method A: Recrystallisation furnished *N-sec-butyl-4-methyl-benzenesulfonamide 374i* as a yellow crystalline solid (2.89g, 41%). mp (neat) 61.5-62.5 °C (lit. 56-57 °C). IR \(\nu_{\text{max}}\) (neat) 3274, 2969, 2875, 1313, 1157, 814, 661 cm\(^{-1}\). \(^1\)H NMR (300MHz, CDCl\(_3\), \(\delta\)): 7.79 (d.t, \(J = 8.0 + 2.0, 2\)H ArCH), 7.29 (d, \(J = 8.0, 2\)H, ArCH),
Experimental

4.99 (bs, 1H, NH), 3.28-3.17 (app. sxt., J = 7.0, 1H, CH), 2.42 (s, 3H, ArCH₃), 1.45-1.35 (app. quin., J = 7.0, 2H, CH₂), 1.00 (d, J = 7.0, 3H, CH₃), 0.79 (t, J = 7.0 , 3H, CH₃). ¹³C NMR (75.5 (MHz, CDCl₃, δ) 142.8 (s, C-Me), 138.1 (s, C-SO₂), 129.4 (2 x d, ArCH), 126.8 (2 x d, ArCH), 51.1 (d, CH), 30.0 (t, CH₂), 21.6 (q, ArCH₃), 21.1 (q, CH₃), 9.7 (q, CH₃). LRMS (LSIMS-FAB⁺) m/z: 228 (MH⁺ 100%), 226 (15), 198 (25), 172 (67), 155 (45), 139 (26), 136 (24). HRMS (LSIMS-FAB⁺) m/z: (MH⁺) calcd. for C₁₁H₁₈NO₂S, 228.1058; found, 228.1051. Elemental Analysis (WAS): Calcd for C₁₁H₁₇NO₂S: C, 58.1; H, 7.5; N, 6.1. Found: C, 58.0; H, 7.4; N, 6.1%.

*N*-tert-Butyl-4-methyl-benzenesulfonamide 374j

![Structure of N-tert-Butyl-4-methyl-benzenesulfonamide 374j](image)

Commercially available from Maybridge [2849-81-2]. Method B: Furnished *N*-tert-butyl-4-methylbenzenesulfonamide 374j as a lemon-yellow crystallised solid (4.37g, 72%). mp 121.5-122.5 ºC. IR ν max (neat): 3262, 2921, 2852, 1300, 1134, 656 cm⁻¹. ¹H NMR (400MHz, CDCl₃, δ): 7.78 (d, J = 8.0, 2H, ArCH), 7.27 (d, J = 8.0, 2H, ArCH), 4.88 (bs, 1H, NH), 2.42 (s, 3H, ArCH₃), 1.21 (s, 9H, 3 x CH₃). ¹³C NMR (75.5MHz, CDCl₃, δ): 142.5 (s, C-Me), 140.3 (s, C-SO₂), 129.2 (2 x d, ArCH), 126.7 (2 x d, ArCH), 54.3 (s, C-(CH₃)₃), 29.9 (3 x q, CH₃), 21.26 (q, ArCH₃). LRMS (LSIMS-FAB⁺) m/z: 228 (MH⁺ 100), 212 (35), 172 (100), 137 (58). HRMS (LSIMS-FAB⁺) m/z: calcd. for C₁₁H₁₈NO₂S, 228.1058; found, 228.1051. Elemental Analysis (WAS): Calcd for C₁₁H₁₇NO₂S: C, 58.4; H, 7.6; N, 6.0. Found: C, 58.1; H, 7.5; N, 6.1%.
Experimental

\(N\)-(R)-(-)-(1-Cyclohexylethyl)-4-methylbenzenesulfonamide 374k\) \(^{237}\)

\[
\text{HN-SO}_2
\]

\[
\text{O}
\]

Method A: Recrystallisation furnished \(N\)-(R)-(-)-(1-cyclohexyl-ethyl)-4-methylbenzene sulfonamide 374k\) as a white powdery crystalline solid (7.18g, 97%). mp 131.5-132.5 °C. IR (neat) \(\nu_{\text{max}}\): 3288, 2916, 2860, 1321, 1159 and 671 cm\(^{-1}\). \(^1\)H NMR (300MHz; CDCl\(_3\), \(\delta\)): 7.77-7.74 (d.t, \(J = 8.0\) and 2.0, 2H, ArCH), 7.29 (d, \(J = 8.0\), 2H, ArCH), 4.30 (bd, \(J = 8.0\), 1H, NH), 3.19-3.10 (m, 1H, NH), 2.42 (s, 3H, ArCH\(_3\)), 1.72-1.52 (m, 6H, CH\(_2\)), 1.29-0.76 (m, 8H, CH\(_2\) + CH\(_3\) overlap). \(^{13}\)C NMR (100MHz, CDCl\(_3\), \(\delta\)): 143.1 (s, C-Me), 138.4 (s, C-SO\(_2\)), 129.6 (2 x d, ArCH), 127.1 (2 x d, ArCH), 54.4 (d, CH), 43.5 (d, CH), 28.5 (2 x t, CH\(_2\)), 26.1 (3 x t, CH\(_2\)), 21.5 (q, ArCH\(_3\)), 19.5 (q, CH\(_3\)). LRMS (LSIMS-FAB\(^{+}\)) \(m/z\): 282 (MH\(^+\) = 70%), 198 (30), 172 (24), 154 (100), 136 (95), 120 (20). HRMS (LSIMS-FAB\(^{+}\)) \(m/z\): (MH\(^+\)) calcd for C\(_{15}\)H\(_{24}\)NO\(_2\)S, 282.1528; found, 282.1541.

\(N\)-Adamantan-1-yl-4-methylbenzenesulfonamide 374l\) \(^{238}\)

\[
\text{HN-SO}_2
\]

\[
\text{O}
\]

Commercially available from Ambinter [56432-99-6]. Method A: Recrystallisation furnished \(N\)-adamantan-1-yl-4-methylbenzene sulfonamide 374l\) as a white floury solid (6.10g, 76%); IR (neat) \(\nu_{\text{max}}\): 3228, 2971, 2844, 1328, 1114 `and 665 cm\(^{-1}\); \(^1\)H NMR (400MHz, CDCl\(_3\), \(\delta\)) 7.77 (d.t, \(J = 8.0\) and 2.0, 2H, ArCH), 7.27 (d, \(J = 8.0\), 2H, ArCH),
Experimental

4.45 (s, 1H, NH), 2.42 (s, 3H, ArCH3), 2.00 (bs, 3H, CH), 1.78 (app. s, 6H, CH2), 1.57 (m, 6H, CH2). 13C NMR (100MHz, CDCl3, δ) 142.7 (s, C-Me), 141.1 (s, C-SO2-), 129.4 (2 x d, ArCH), 126.9 (2 x d, ArCH), 55.1 (s, C-NH-), 43.1 (3 x t, CH2), 35.9 (3 x t, CH2), 29.5 (3 x d, CH), 21.5 (q, ArCH). LRMS (LSIMS-FAB+) m/z: 306 (MH+ = 46%), 154 (32), 135 (100). HRMS (LSIMS-FAB+) m/z: calcd for C17H23NO2S; 304.1371, found 304.1370. Elemental Analysis (WAS): Calcd for C, 66.8, H, 7.6, N, 4.6; C17H23NO2S, Found: C, 66.7, H, 7.5, N, 4.6%.

3.0 General synthesis of N-alkyl-(4-methyl)-benzenesulfonamides

3.1 Method A

To a stirred solution of 4-methylbenzenesulfonyl chloride 281e (1.2 eq.) in dichloromethane (DCM) (50 mL) was added the amine 379 (1.0 eq.) and triethylamine (TEA) (1.36 eq.). The solution was stirred at 0 °C (ice bath) for four hours unless otherwise stated. The reaction was quenched with distilled water (50 mL) and the product extracted with DCM or ether (3 x 50 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and the solvent removed in vacuo to yield the crude arylsulfonamide 380. Purification was by recrystallization (diethyl ether/hexane) or flash chromatography (petroleum ether/ethyl acetate).

5.3.2 Method B

As above but 4-methyl-benzenesulfonyl chloride (1.0 eq.) 281e and arylamine (3.0 eq.) 379 were reacted in diethylether. No purification was required with this method.
Experimental

**4-Methyl-N-(4-methylbenzyl)-benzenesulfonamide 380a**

Commercially available from Ambinter [10504-92-4]. Method A: Recrystallization furnished 4-methyl-N-(4-methylbenzyl)-benzenesulfonamide 380a as a yellow crystallised solid (1.59g, 22%). mp 80.5-81.5 °C. IR (neat) $\nu_{\text{max}}$: 3270, 2916, 1324, 1152, 843, 798, 741, 657 cm$^{-1}$. $^1$H NMR (400MHz; CDCl$_3$, $\delta$): 7.76 (d, $J = 8.0$, 2H, ArCH), 7.27 (d, $J = 8.0$, 2H, ArCH), 7.10 (d, $J = 8.0$, 2H, ArCH), 7.08 (m, 2H, ArCH), 5.50 (t, $J = 6.0$, 1H, NH), 4.06 (d, $J = 6.0$, 2H, CH$_2$), 2.43 (s, 3H, ArCH$_3$), 2.31 (s, 3H, CH$_3$). $^{13}$C NMR (100MHz, CDCl$_3$, $\delta$): 143.3 (s, C-Me), 137.3 (s, C-CH$_2$), 137.0 (s, C-SO$_2$-), 133.6 (s, C-Me), 129.7 (2 x d, ArCH), 129.3 (2 x d, ArCH), 127.9 (2 x d, ArCH), 127.2 (2 x d, ArCH), 46.9 (t, CH$_2$), 21.5 (q, ArCH$_2$), 21.0 (q, ArCH$_3$). LRMS (LSIMS-FAB$^+$) $m/z$: 276 (MH$^+$ = 68%), 184 (26), 154 (100), 137 (70). HRMS (LSIMS-FAB$^+$) $m/z$: calcd for C$_{15}$H$_{17}$NO$_2$S, 276.1058; found, 276.1050.

**N-(4-Methoxybenzyl)-4-methylbenzenesulfonamide 380b**

Commercially available from Ambinter [54979-64-0]. Method A: Recrystallisation furnished N-(4-methoxybenzyl)-4-methylbenzene sulfonamide 380b as hydroscopic lemon-yellow (2.56g, 33%). mp 127.5-128.5 °C. IR (neat) $\nu_{\text{max}}$: 3245, 2974, 2837, 1251, 1319, 1154 and 815 cm$^{-1}$. $^1$H NMR (400MHz; CDCl$_3$, $\delta$): 7.75 (app. d, $J = 8.0$, 2H, ArCH), 7.31 (d, $J = 8.0$, 2H, ArCH), 7.10 (d.t, $J = 8.0$ and 3.0, 2H, ArCH), 6.79 (d.t, $J$
Experimental

= 8.0 and 3.0, 2H, ArCH), 4.55 (app. t., \(J = 5.0, 1H, NH\)), 4.05 (d, \(J = 6.0, 2H, CH_2\), 3.77 (s, 3H, OCH_3), 2.44 (s, 3H, ArCH_3). \(^{13}\)C NMR (100MHz, CDCl_3, \(\delta\)): 159.4 (s, C-\(\text{OMe}\)), 143.5 (s, C-Me), 136.9 (s, C-SO_2\(-\)), 129.7 (2 x \(d, \text{ArCH}\)), 129.1 (2 x \(d, \text{ArCH}\)), 128.3 (s, C-\(\text{CH}_2\)-), 127.2 (2 x \(d, \text{ArCH}\)), 114.1 (2 x \(d, \text{ArCH}\)), 55.3 (q, OCH_3), 46.8 (t, CH_2), 21.5 (q, ArCH_3). LRMS (LSIMS) \(m/z\): 291 (M\(^+\) = 100%), 219 (20), 154 (100), 136 (100), 121 (65). HRMS (LSIMS-FAB\(^+\)) \(m/z\): (MH\(^+\)) calcd for \(\text{C}_{15}\text{H}_{18}\text{NO}_3\text{S}\), 292.1007; found, 292.1015.

4-Methyl-N-(2-trifluoromethylbenzyl)-benzenesulfonamide \(380c\)

Method A: Recrystallisation furnished 4-methyl-N-(2-trifluoromethylbenzyl)-benzenesulfonamide \(380c\) as a very pale yellow crystallised solid (7.13g, 83%). IR (neat) \(\nu_{\text{max}}\): 3236, 2361, 1308, 1152, 714. mp. 98.5-99.5 °C. \(^1\)H NMR (400MHz, CDCl_3, \(\delta\)): 7.74 (d, \(J = 8.0, 2H, \text{ArCH}\)), 7.59 (t, \(J = 8.0, 2H, \text{ArCH}\)), 7.49 (t, \(J = 8.0, 1H, \text{ArCH}\)), 7.37 (t, \(J = 8.0, 1H, \text{ArCH}\)), 7.30 (d, \(J = 8.0, 2H, \text{ArCH}\)), 4.85 (app. t, \(J = 7.0, 1H, NH\)), 4.29 (d, \(J = 7.0, 2H, \text{CH}_2\)), 2.43 (s, 3H, ArCH_3). \(^{13}\)C NMR (100MHz, CDCl_3, \(\delta\)): 143.7 (s, C-Me), 136.8 (s, C-\(\text{CH}_2\)-), 134.9 (s, C-SO_2\(-\)), 132.3 (d, ArCH), 130.8 (d, ArCH), 129.8 (2 x \(d, \text{ArCH}\)), 128.0 (2 x \(d, \text{ArCH}\)), 127.1 (2 x \(d, \text{CH}\)), 125.5-123.5 (s, \(J = 200.0, \text{C-C-F}\)), not observed (CF_3), 43.7 (t, CH_2), 21.5 (q, ArCH_3). (LSIMS-FAB\(^+\)) \(m/z\): 330 (MH\(^+\) = 100%), 159 (23), 137 (12). HRMS (LSIMS-FAB\(^+\)) \(m/z\): (MH\(^+\)) calcd. for \(\text{C}_{15}\text{H}_{18}\text{F}_3\text{NO}_3\text{S}\); 330.0775, found 330.0778. Elemental Analysis (WAS): Calcd for \(\text{C}_{15}\text{H}_{14}\text{F}_3\text{NO}_3\text{S}: C, 54.6; H, 4.2; N, 4.1. Found: C, 54.7; H, 4.2; N, 4.2.
Experimental

4-Methyl-N-pyridin-2-ylmethylbenzenesulfonamide 380d

Commercially available from Ambinter [75391-97-8]. Method A: recrystallisation furnished 4-methyl-N-pyridin-2-ylmethylbenzenesulfonamide 380d as hydrosopic lemon-yellow crystallised solid (2.21g, 32%). IR (neat) $\nu_{\text{max}}$: 3059, 2920, 2852, 1326, 1155 and 811 cm$^{-1}$. $^1$H NMR (300MHz; CDCl$_3$, $\delta$): 8.5 (app. s, 1H, ArCH$_2$), 7.75 (d.t, $J = 8.0$ and 2.0, 2H, ArCH$_2$), 7.64 (app. d.t, $J = 8.0$ and 2.0, 1H, ArCH), 7.26-7.18 (m, 4H, ArCH$_3$), 5.98 (app. t, $J = 5.0$, 1H, NH), 4.25 (d, $J = 5.0$, 2H, CH$_2$), 2.39 (s, 3H, ArCH$_3$). $^{13}$C NMR (100MHz, CDCl$_3$, $\delta$): 155.2 (s, C- pyridine), 148.9 (d, ArCH), 143.8 (2 x s, C), 137.7 (d, ArCH), 130.0 (2 x d, ArCH), 127.6 (2 x d, ArCH), 123.2 (d, ArCH), 122.6 (d, ArCH), 47.6 (t, CH$_2$), 21.9 (q, ArCH$_3$). LRMS (LSIMS-FAB$^+$) $m/z$: 263 (MH$^+$ = 35%), 154 (100), 137 (67), 136 (60). HRMS (LSIMS-FAB$^+$) $m/z$: (MH$^+$) calcd for C$_{13}$H$_{14}$N$_2$O$_3$S, 263.0854; found, 263.0858.

N-Furan-2-ylmethyl-4-methylbenzenesulfonamide 380e

Commercially available from Ambinter [121564-33-8]. Method A: Recrystallisation furnished N-furan-2-ylmethylbenzenesulfonamide 380e as an hydrosopic golden yellow crystallised solid (4.95g, 75%). IR (neat) $\nu_{\text{max}}$: 3275, 2918, 2839, 1321, 1185, 686 cm$^{-1}$. $^1$H NMR (400MHz; CDCl$_3$, $\delta$): 7.72 (d.t, $J = 8.0$ and 2.0, 2H, ArCH), 7.27 (d, $J = 8.0$, 2H, ArCH), 7.24 (app. d, $J = 2.0$, 1H, ArCH), 6.21 (app. q., $J = 2.0$, 1H, ArCH), 6.09
Experimental

(app. d, $J = 3.0$, 1H, ArCH), 4.78 (app. t, $J = 6.0$, 1H, NH), 4.16 (d, $J = 6.0$, 2H, CH$_2$), 2.42 (s, 3H, ArCH$_3$). $^{13}$C NMR (100MHz, CDCl$_3$, δ): 149.9 (s, C-furan), 143.9 (s, C-Me), 142.9 (d, CH), 137.21 (s, C-SO$_2$-), 130.6 (2 x d, ArCH), 127.5 (2 x d, ArCH), 110.8 (d, CH), 108.6 (d, CH), 40.5 (t, CH$_2$), 21.9 (q, ArCH$_3$). LRMS (LSIMS-FAB$^+$) $m/z$: 252 (MH$^+$ = 20%), 250 (33), 184 (64), 154 (100), 133 (54), 128 (25), 120 (15). HRMS (LSIMS-FAB$^+$) $m/z$: (MH$^+$) calcld for C$_{12}$H$_{14}$NO$_3$S, 252.0694; found, 252.0696. Elemental Analysis (WAS): Calcd. for C$_{12}$H$_{13}$NO$_3$S: C, 57.3; H, 5.2; N, 5.6.

Found: C, 57.1; H, 5.2; N, 5.5%.

4-Methyl-N-(2-thienylmethyl)-benzenesulfonamide 380f

Commercially available from Ambinter [545358-50-7]. Method A: Recrystallisation furnished 4-Methyl-N-(2-thienylmethyl)-benzenesulfonamide 380f as golden yellow crystallised solid (4.95g, 75%). IR (neat) $\nu_{\text{max}}$: 3286, 2977, 2862, 1320, 1117, 613 cm$^{-1}$. $^1$H NMR (400MHz; CDCl$_3$, δ ): 7.73 (d, $J = 8.0$, 2H, ArCH), 7.28 (d, $J = 8.0$, 2H, ArCH), 7.16 (app. d., $J = 1.0$, 1H, ArCH), 6.85 (app. quin., $J = 3.0$, 2H, ArCH), 5.00 (bs, 1H, NH), 4.31 (s, 2H, CH$_2$), 2.42 (s, 3H, ArCH$_3$). $^{13}$C NMR (100MHz, CDCl$_3$, δ): 143.6 (s, C-Me), 139.0 (s, C-thiophene), 136.8 (s, C-SO$_2$-), 129.8 (2 x d, ArCH), 127.8 (d, CH), 126.9 (d, CH), 126.5 (d, CH), 125.8 (2 x d, ArCH), 42.1 (t, CH$_2$), 21.6 (q, ArCH$_3$). LRMS (LSIMS-FAB$^+$) $m/z$: 268 (MH$^+$ = 28%), 219 (20), 184 (40), 154 (100), 136 (70). Elemental analysis (WAS): Calcd for C$_{12}$H$_{13}$NO$_3$S$_2$: C, 53.9; H, 4.9; N, 5.2.

Found: C, 53.7; H, 4.8; N, 5.1%.
Experimental

4.0 General procedure for radical precursors 278a-l

![Chemical structure]

4.1 N-BUTYLLITHIUM METHOD:

To a stirred solution of N-butyl-4-(substituted)-benzenesulfonamide 283 (1.0 eq.) in anhydrous tetrahydrofuran was added n-butyllithium (1.6 M in hexanes) (1.0 eq.) and 2-bromo-isobutyryl bromide 284 (1.0 eq.) at -78°C (dry ice/acetone) overnight. The reaction was quenched with saturated ammonium chloride (10 mL), and the product extracted with dichloromethane (200 mL), followed by saturated sodium bicarbonate (200 mL). The aqueous phase was washed with dichloromethane (2 x 200 mL) and the combined organic fractions were washed with saturated sodium chloride. The organic phase was dried with magnesium sulfate, and the solvent evaporated in vacuo to yield a crude product. Purification of the crude product (petrol ether: ethyl acetate) furnished the radical precursor 278.

4.2 TRIETHYLAMINE METHOD

To a stirred solution of N-butyl-(substituted) benzenesulfonamide 283 (1.0 eq.) in dry dichloromethane was added triethylamine (1.0 eq.) and 2-bromo-isobutyryl bromide 284 (1.0 eq.), under nitrogen at room temperature overnight. The reaction was quenched with distilled water (50 mL), and the product extracted with diethyl ether (3 x 50 mL). The combined organic extracts were dried over magnesium sulfate and the solvent evaporated in vacuo to furnish the crude product. Purification with petrol ether: ethyl acetate, yield the radical precursor 278.
4.3 HÜNIG’S BASE METHOD

To a solution of \(N\)-butyl-(substituted)-benzenesulfonamide (1.0 eq.) \(\text{283}\) in dichloromethane, was added \(N\)-ethyldiisopropylamine (Hünig’s base, 1.3 eq.) and 2-bromo-isobutyryl bromide (1.1 eq.) \(\text{284}\) at room temperature overnight. The reaction was quenched with distilled water (50 mL), and the product was extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried with magnesium sulfate and the solvent evaporated \textit{in-vacuo} to yield the crude product.

Purification with petrol ether: ethyl acetate furnished the radical precursor \(\text{278}\).

4.4 IMPROVED METHOD

When the radical precursor \(\text{283}\) (1.0 eq.), triethylamine (1.0 eq.) and the acid bromide \(\text{284}\) (3.0 eq.) are used, no eliminated product \(\text{286}\) is observed. Work up is same as for method 2.

\[N\text{-}(2\text{-Bromo}-2\text{-methyl-propyionyl})\text{-N\text{-}butyl-benzenesulfonamide} \text{278a}\]

Flash chromatography (petrol ether/ethyl acetate, 6:1) furnished \(N\text{-}(2\text{-bromo}-2\text{-methyl-propyionyl})\text{-N\text{-}butyl-benzenesulfonamide} \text{278a}\) as a light yellow viscous solid (13.17g, 31%). IR (neat) \(\nu_{\text{max}}\): 2955, 1675, 1346, 1166, 1069, 723 cm\(^{-1}\). \(^1\)H NMR (400MHz/CDCl\(_3\), \(\delta\)): 7.99-7.96 (app. d.t, \(J = 8.0\) and 2.0, 2H, ArCH), 7.61-7.59 (m, 1H, ArCH), 7.54-7.50 (m, 2H, ArCH) 4.19 (app. t, \(J = 8.0\), 2H, CH\(_2\)), 1.96-1.88 (m, 8H, CH\(_2\) and C (CH\(_3\))\(_2\)) 1.46-1.37 (app. sxt., \(J = 7.0\), 2H, CH\(_2\)), 0.99 (t, \(J = 7.0\), 3H, CH\(_3\)).

\(^{13}\)C NMR (75.5MHz, CDCl\(_3\), \(\delta\)): 170.8 (s, C=O), 139.7 (s, C-SO\(_2\)), 133.9 (d, ArCH),

184
Experimental

133.0 (d, ArCH), 128.8-128.1 (3 x d, ArCH), 57.0 (s, C-(CH₃)₂), 48.8 (t, CH₂), 33.3 (2 x q, C(CH₃)₂), 31.7 (t, CH₂), 19.9 (t, CH₂), 13.7 (q, CH₃). LRMS (EI⁺) m/z: 364 (¹³Br MH⁺ = 54%), 362 (⁷⁹Br MH⁺ = 56), 284 (¹³Br = 15), 282 (⁷⁹Br = 98), 206 (¹³Br = 65), 204 (⁷⁹Br = 66), 170 (55), 141 (100). HRMS (EI⁺) m/z: (MH⁺) calcd for C₁₄H₂₀BrNO₃S, 362.0425; found, 362.0425.

\[ N-(2-Bromo-2-methyl-propionyl)-N-butyl-4-fluoro-benzenesulfonamide \text{ 278b} \]

\[ \text{F} \begin{array}{c} \text{S} \\ \text{O} \\ \text{N} \end{array} \begin{array}{c} \text{O} \\ \text{Br} \end{array} \]

Flash chromatography (petrol ether/ethyl acetate, 6:1) furnished \( N-(2\text{-bromo-2-methyl-propionyl})-N\text{-butyl-4-fluoro-benzenesulfonamide} \text{ 278b} \) as a yellow viscous solid (2.52g, 52%). IR (neat) \( \nu_{\text{max}} \): 2955, 1669, 1350, 1156, 1068, 838 and 696 cm⁻¹. \(^1\)H NMR (400MHz, CDCl₃, \( \delta \)): 8.03-7.99 (m, 2H, ArCH), 7.18 (app. t, \( J = 8.0 \), 2H, ArCH), 4.19 (app. t, \( J = 8.0 \), 2H, CH₂), 1.93-1.85 (m, 8H, CH₂ and C(CH₃)₂), 1.46-1.36 (sxt., \( J = 7.0 \), 2H, CH₂), 0.99 (t, \( J = 7.0 \), 3H, CH₃). \(^{13}\)C NMR (100MHz, CDCl₃, \( \delta \)): 170.5 (s, C═O), 165.0 (s, \( J = 256 \), C-F), 136.0 (s, C-SO₂⁻), 131.6 (2 x d, \( J^{\text{CF}} = 9.6 \), CH), 115.9 (2 x d, \( J^{\text{CF}} = 22.8 \), CH), 56.5 (s, C-(CH₃)₂), 48.9 (t, CH₃), 32.9 (t, CH₂), 31.8 (2 x q, C(CH₃)₂) 20.0 (t, CH₂) 14.0 (q, CH₃). LRMS (EI/Cl⁻) m/z: 382 (¹³Br-M⁺ = 100), 380 (⁷⁹Br-M⁺ = 100), 159 (20), 135 (¹³Br 68), 133 (⁷⁹Br 70). HRMS (EI⁺) m/z: (MH⁺) calcd for C₁₄H₂₀BrFNO₃S, 380.0331; found, 380.0314; Elemental Analysis (WAS): Calcd. for C₁₄H₁₉BrFNO₃S: C, 44.2; H, 5.0; N, 3.7. Found: C, 44.4; H, 5.0; N, 3.6.
**Experimental**

4-bromo-\(N\)-(2-Bromo-2-methyl-propionyl)-\(N\)-butyl-benzenesulfonamide 278c

![Chemical Structure](image)

Flash chromatography (petrol ether/ethyl acetate, 8:1) afforded 4-bromo-\(N\)-(2-bromo-2-methyl-propionyl)-\(N\)-butyl-benzenesulfonamide 278c as a yellow viscous solid. (1.43 g, 70%). IR (neat) \(\nu_{\text{max}}\): 2960, 2933, 2361, 1681, 1355, 1170 1068, 739 cm\(^{-1}\). \(^1\)H NMR (300MHz, CDCl\(_3\), \(\delta\)): 7.85-7.81 (d.t, \(J = 8.0\) and 2.0, 2H, ArCH), 7.66-7.61 (d.t, \(J = 8.0\) and 2.0, 2H, ArCH), 4.17 (app. t, \(J = 7.0\), 2H, CH\(_2\)), 1.94-1.85 (m, 8H, (CH\(_3\))\(_2\) + CH\(_2\)), 1.39 (sxt., \(J = 7.0\), 2H, CH\(_2\)), 1.00 (t, \(J = 7.0\), 3H, CH\(_3\)). \(^{13}\)C NMR (100MHz, CDCl\(_3\), \(\delta\)): 170.0 (s, C=O), 137.7 (s, C-SO\(_2\)), 131.3 (2 x d, ArCH), 129.5 (2 x d, ArCH), 128.1 (s, C-Br), 56.0 (s, C(CH\(_3\))\(_2\)), 48.3 (t, CH\(_2\)), 32.3 (t, CH\(_2\)), 31.1 (2 x q, C(CH\(_3\))\(_2\)), 20.0 (t, CH\(_2\)), 14.5 (q, CH\(_3\)). LRMS (EI\(^{+}\)) \(m/z\) 443 (\(^{81}\)Br M\(^{+}\) = 10%), 441 (\(^{79}\)Br M\(^{+}\) = 20), 361 (\(^{81}\)Br = 25), 359 (\(^{79}\)Br = 24), 249 (\(^{81}\)Br = 31), 247 (\(^{79}\)Br = 30), 219 (\(^{81}\)Br = 99), 217 (\(^{79}\)Br = 98), 204 (\(^{81}\)Br = 100), 202 (\(^{79}\)Br = 99), 157 (\(^{81}\)Br = 82), 155 (\(^{79}\)Br = 81), 123 (\(^{81}\)Br = 88), 121 (\(^{79}\)Br = 87). HRMS (LSIMS) calcd for C\(_{14}\)H\(_{19}\)Br\(_2\)NO\(_3\)S, 441.9510, found 441.9507.
Experimental

\[ \text{N-(2-Bromo-2-methyl-propionyl)-N-butyl-4-iodo-benzenesulfonamide 278d} \]

Flash chromatography (petrol ether: ethyl acetate, 4.1) furnished \( \text{N-(2-bromo-2-methyl-propionyl)-N-butyl-4-iodo-benzenesulfonamide 278d} \) as a greyish-white viscous solid (1.82g, 43%). IR (neat) \( \nu_{\text{max}}: \) 2961, 2361, 1681, 1354, 1170, 1073, 738 cm\(^{-1}\). \(^1\)H NMR (300MHz, CDCl\(_3\), \( \delta \)): 7.89-7.85 (d.t, \( J = 9.0 \) and 2.0, 2H, ArCH), 7.68-7.66 (d.t, \( J = 9.0 \) and 2.0, 2H, ArCH), 4.18-4.14 (app.t, \( J = 8.0 \), 2H, CH\(_2\)), 1.95-1.88 (m, 8H, CH\(_2\)) and C(CH\(_3\))\(_2\)), 1.37-1.47 (sxt., \( J = 7.0 \), 2H, CH\(_2\)), 0.98 (t, \( J = 7.0 \), 3H, CH\(_3\)). \(^{13}\)C NMR (100MHz, CDCl\(_3\), \( \delta \)) 170.2 (s, C═O), 139.0 (s, C-SO\(_2\)-), 137.7 (2 x d, ArCH), 129.7 (2 x d, ArCH), 101.3 (s, C-I), 56.2 (s, C-(CH\(_3\))\(_2\)), 48.7 (t, CH\(_2\)), 32.0 (t, CH\(_2\)), 31.3 (2 x q, C(CH\(_3\))\(_2\)), 19.5 (t, CH\(_3\)), 13.4 (q, CH\(_3\)). LRMS (EI\(^+\)) \( m/z \) 489 (\(^{81}\)Br M\(^+\) = 12%), 487 (\(^{79}\)Br M\(^+\) = 12), 343 (25), 296 (49), 267 (100), 206 (\(^{81}\)Br 81), 204 (\(^{79}\)Br 100). HRMS (Cl) \( m/z \): (MH\(^+\)) calcd for C\(_{14}\)H\(_{20}\)\(^{79}\)BrINO\(_3\)S 487.9392, found: 487.9390.

\[ \text{N-(2-Bromo-2-methyl-propionyl)-N-butyl-4-methyl-benzenesulfonamide 278e} \]

Previously synthesised by Fullaway.\(^{165}\) Flash chromatography (petrol ether/ethyl acetate, 6:1) furnished \( \text{N-(2-bromo-2-methyl-propionyl)-N-butyl-4-methyl-benzenesulfonamide 278e} \) as a viscous yellow crystallised solid (2.20g, 25%). IR (neat) \( \nu_{\text{max}}: \) 2979, 2361, 1710, 1173, 1071 cm\(^{-1}\). \(^1\)H NMR (400MHz, CDCl\(_3\), \( \delta \)): 7.85 (d, \( J = 8.0 \), 2H, ArCH),
Experimental

7.30 (d, \( J = 8.0 \), 2H, ArCH), 4.16 (bt, \( J = 7.0 \), 1H, NH), 2.43 (s, 3H, ArCH\(_3\)), 1.96-1.87 (m, 8H, CH\(_2\) + (CH\(_3\))\(_2\)), 1.45-1.36 (sxt, \( J = 7.0 \), 2H, CH\(_2\)), 0.98 (t, \( J = 7.0 \), 3H, CH\(_3\)). \(^{13}\)C NMR (100MHz, CDCl\(_3\), \( \delta \)) 165.7 (s, C═O), 144.4 (s, C-Me), 136.41 (s, C-SO\(_2\)-), 129.3 (2 x d, ArCH), 128.6 (2 x d, ArCH), 56.7 (s, C-(CH\(_3\))\(_2\)), 48.8 (t, CH\(_2\)), 32.9 (2 x q, C(CH\(_3\))\(_2\)), 21.6 (q, ArCH\(_3\)), 20.0 (t, CH\(_2\)), 14.5 (q, CH\(_3\)). LRMS (EI\(^+\)) \( m/\zeta \): 378 (\(^{81}\)Br MH\(^+\) = 20%), 377 (\(^{81}\)Br M\(^+\) = 98), 375 (\(^{79}\)Br MH\(^+\) = 100), 296 (42), 234 (32), 206 (\(^{81}\)Br 62), 204 (\(^{79}\)Br 60), 155 (46). HRMS (EI\(^+\)) \( m/\zeta \): (MH\(^+\)) calcd for C\(_{15}\)H\(_{22}\)BrNO\(_3\)S, 376.0582; found, 376.0568.

\( N-(2\text{-Bromo-2-methyl-propionyl})\)-N\(_4\)-butyl-2,4,6-trimethyl-benzenesulfonamide 278f

Previously synthesised by Fullaway.\(^{165}\) Flash chromatography furnished (petrol ether/ethyl acetate, 6:1) \( N-(2\text{-bromo-2-methyl-propionyl})\)-n\(_4\)-butyl-2,4,6trimethyl-benzenesulfonamide 278f as a yellow crystallised solid (2.74g, 34%). IR (Neat) \( \nu_{\text{max}} \): 2972, 2361, 1709, 1345, 1164, 1066, 811 cm\(^{-1}\). \(^1\)H NMR (400MHz, CDCl\(_3\), \( \delta \)) 6.95 (app.s 2H, ArCH), 4.20 (app. t, \( J = 8.0 \), 2H, CH\(_2\)), 2.65 (s, 3H, ArCH\(_3\)), 2.28 (s, 3H, ArCH\(_3\)), 2.08-1.93 (m, 8H, CH\(_2\) and C(CH\(_3\))\(_2\)), 1.87 (s, 3H, ArCH\(_3\)), 1.49-1.37 (sxt, \( J = 7.0 \), 2H, CH\(_2\)), 1.00 (t, \( J = 7.0 \), 3H, CH\(_3\)). \(^{13}\)C NMR (100MHz, CDCl\(_3\), \( \delta \)) 170.4 (s, C═O), 143.0 (s, C-Me), 140.4 (s, C-SO\(_2\)-), 138.0 (s, C-Me), 133.8 (s, C-Me), 132.3 (d, ArCH), 131.9 (d, ArCH), 56.9 (s, C-(CH\(_3\))\(_2\)), 47.8 (t, CH\(_2\)), 33.0 (t, CH\(_3\)), 31.6 (2 x q, C(CH\(_3\))\(_2\)) 22.4 (q, ArCH\(_3\)), 21.0 (q, ArCH\(_3\)), 20.0 (t, CH\(_2\)), 18.00 (q, ArCH\(_3\)), 13.5 (q, CH\(_3\)).
Experimental

2-Naphthalene-sulfonic-acid-(2-bromo-2-methyl-propionyl)-butylamide 278g

Flash chromatography (petrol ether/ethyl acetate 4:1) furnished 2-naphthalene-sulfonic-acid-(2-bromo-2-methyl-propionyl-butylamide 278g as a light yellow viscous solid (0.90g, 20%). IR (neat) ν max: 2927, 1681, 1347, 1167, 1134, 1070, 750 cm⁻¹. ¹H NMR (300MHz, CDCl₃, δ): 8.58 (s, 1H, ArCH), 8.02-7.93 (m, 1H, ArCH), 7.93-7.88 (m, 3H, ArCH), 7.69-7.59 (m, 2H, ArCH), 4.25 (app.t, J = 8.0, 2H, CH₂), 2.02-1.92 (m, 2H, CH₂), 1.87 (s, 6H, 2 x CH₃), 1.43 (sxt., J = 7.0, 2H, CH₂), 1.01 ( t, J = 7.0, 3H, CH₃).

¹³C NMR (100MHz, CDCl₃, δ): 170.5 (s, C=O), 136.2 (s, C-SO₂-), 135.2 (s, C-C), 131.8 (s, C-C), 130.7 (d, ArCH), 129.6 (d, ArCH), 129.2 (d, ArCH), 128.8 (d, ArCH), 127.9 (d, ArCH), 127.5 (d, ArCH), 122.9 (d, ArCH), 56.6 (s, C-(CH₃)₂), 49.0 (t, CH₂), 33.0 (t, CH₂), 31.8 (2 x q, C(CH₃)₂), 20.0 (t, CH₂), 15.0 (q, CH₃). LRMS (El⁺) m/z: 414 (⁸¹Br MH⁺ = 90%), 412 (⁷⁹Br MH⁺ 90), 334 (⁸¹Br 15), 332 (⁷⁹Br 33), 270 (⁸¹Br 71), 268 (⁷⁹Br 90), 206 (⁸¹Br 60), 204 (⁷⁹Br 54), 144 (⁸¹Br 100). Elemental Analysis (WAS): Calcd C₁₈H₂₂BrNO₃S: C, 52.4; H, 5.3; N, 3.4. Found: C; 52.4; H, 5.4; N, 3.3.
Experimental

*N-(2-Bromo-2-methyl-propionyl)-N-butyl-4-methoxy-benzenesulfonamide* 278h

Flash chromatography (petrol ether/ethyl acetate, 4:1) furnished *N-(2-bromo-2-methyl propionyl)-N-butyl-4-methoxy-benzenesulfonamide* 278h as a white viscous solid (3.48g, 46%). IR (neat) $\nu_{\text{max}}$: 2956, 2927, 1711, 1664, 1351, 1156, 840 cm$^{-1}$. $^1$H NMR (400MHz, CDCl$_3$, $\delta$): 7.91 (d.t, $J = 9.0$ and 3.0, 2H, ArCH); 6.96 (d.t, $J = 9.0$ and 3.0, 2H, Ar-CH), 4.15 (app. t, $J = 7.0$, 2H, CH$_2$), 3.85 (s, 3H, OCH$_3$), 1.92-1.85 (m, 8H, CH$_2$ and C(CH$_3$)$_2$), 1.44-1.35 (sxt., $J = 7.0$, 2H, CH$_2$), 0.98 (t, $J = 7.0$, 3H, CH$_3$). $^{13}$C NMR (100MHz, CDCl$_3$, $\delta$): 170.4 (s, C=O), 163.5 (s, C-OMe), 131.0 (2 x d, ArCH), 130.5 (s, C-SO$_2$), 113.7 (2 x d, ArCH), 56.7 (s, C-(CH$_3$)$_2$), 55.7 (q, OCH$_3$), 48.7 (d, CH$_2$), 32.9 (t, CH$_2$), 31.8 (2 x q, C(CH$_3$)$_2$), 19.9 (t, CH$_2$), 13.0 (q, CH$_3$). LRMS (LSIMS) m/z: 394 ($^{81}$Br-M$^+$ = 99%) 392 ($^{79}$Br-M$^+$ = 100), 314 ($^{81}$Br 30), 312 ($^{79}$Br 10), 250 ($^{81}$Br 100), 248 ($^{79}$Br 55), 205 ($^{81}$Br 59), 203 ($^{79}$Br 62) 149 ($^{81}$Br 91), 148 ($^{79}$Br$^+$ 30). HRMS (CI): calcd for C$_{15}$H$_{22}$BrNO$_4$S, 392.0531; found, 392.0523.

*N-(2-Bromo-2-methyl-propionyl)-N-butyl-4-cyano-benzenesulfonamide* 278i

Flash chromatography (petrol ether/ethyl acetate, 4:1) furnished *N-(2-bromo-2-methyl-propionyl)-N-butyl-4-cyano-benzenesulfonamide* 278i as transparent crystalline flakes, (1.16g, 57%). IR (neat) $\nu_{\text{max}}$: 2961, 1681, 1463, 1356, 1168, 1072, 911 and 729 cm$^{-1}$. $^1$H
Experimental

NMR (300MHz, CDCl₃, δ): 8.11 (d.t, J = 8.5 and 2.0, 2H, ArCH), 7.84 (d.t, J = 8.5 and 2.0, 2H, ArCH), 4.22 (app. t, J = 7.0, 2H, CH₂), 1.92 (m, 8H, CH₂ and C(CH₃)₂), 1.49-1.38 (app. quin., J = 7.0, 2H, CH₂), 1.10 -0.98 (m, 3H, C(CH₃)₃).

¹³C NMR (75.5MHz, CDCl₃, δ): 171.0 (s, C═O), 143.9 (s, C-SO₂-), 132.9 (2 x d, ArCH), 129.4 (2 x d, ArCH), 117.6 (s, C≡N), 117.4 (s, ArC-C≡N), 56.7 (s, C-(CH₃)₂), 49.4 (t, CH₂), 32.7 (t, CH₂), 32.0 (2 x q, C(CH₃)₂), 20.5 (t, CH₂), 14.0 (q, CH₃).

LRMS (LSIMS-FAB⁺) m/z: 389 (⁺¹⁸Br M⁺ = 1%), 387 (⁺¹⁷Br M⁺ = 15), 154 (100), 137 (76). HRMS (LSIMS-FAB⁺) m/z: (M⁺) calcd for C₁₅H₁₉BrN₂O₃S, 387.0378; found, 387.0376.

N-(2-Bromo-2-methyl-propionyl)-N-butyl-4-nitro-benzenesulfonamide 278j

Flash chromatography (petrol ether/ethyl acetate, 4:1), furnished N-(2-bromo-2-methyl-propionyl)-N-butyl-4-nitro-benzenesulfonamide 278j as a light yellow viscous solid (2.89g, 90%). IR (neat) νmax: 2936, 1671, 1350, 1170 and 742, cm⁻¹. ¹H NMR (400MHz, CDCl₃, δ): 8.65 (d, J = 7.0, 2H, ArCH), 8.16 (d.t, J = 7.0, 2H, ArCH), 4.22 (app. t, J = 8.0, 2H, CH₂), 2.06-1.87 (m, 8H, CH₂ + C(CH₃)₂), 1.48-1.39 (sxt., J = 7.0, 2H, CH₂), 1.00 (t, J = 7.0, 3H, CH₃). ¹³C NMR (100MHz, CDCl₃, δ): 171.0 (s, C═O), 150.4 (s, C-NO₂), 145.0 (s, C-SO₂-), 129.8 (2 x d, ArCH), 123.9 (2 x d, ArCH), 56.2 (s, C-(CH₃)₂), 49.1 (t, CH₂), 33.0 (t, CH₂), 30.5 (2 x q, C(CH₃)₂), 19.9 (t, CH₂), 14.0 (q, CH₃). LRMS (EI⁺) m/z: 409 (⁺¹⁸Br-M, 8%), 407 (⁺¹⁷Br-M, 8%), 327 (19), 206 (40), 186 (100), 165 (50), 122 (⁺¹⁸Br, 72), 120 (⁺¹⁷Br, 75). HRMS (EI⁺) m/z: (MH⁺) calcd for C₁₄H₂₀BrN₂O₃S, 407.0276; found: 407.0267.
Experimental

N-(2-Bromo-2-methyl-propionyl)-N-butyl-4-trifluoromethyl-benzenesulfonamide

278k

Flash chromatography (petrol ether/ethyl acetate, 4:1) furnished N-(2-bromo-2-methyl propionyl)-N-butyl-4-trifluoromethyl-benzenesulfonamide 278k as a pale yellow viscous solid (1.12g, 2.62mmol, 36.9%). IR (neat) \( \nu_{\text{max}} \): 2965, 1326, 1161, 1129, 839, cm\(^{-1}\). \(^1\)H NMR (300MHz, CDCl\(_3\), \( \delta \)): 8.03 (d, \( J = 8.0 \), 2H, ArCH), 7.70 (d, \( J = 8.0 \), 2H, ArCH), 4.15-4.05 (app. t, \( J = 8.0 \), 2H, CH\(_2\)), 1.87-1.80 (m, 8H, CH\(_2\) and C (CH\(_3\))\(_2\)), 1.38-1.27 (app. sxt, \( J = 7.0 \), 2H, CH\(_2\)), 0.91 (m, 3H, CH\(_3\)). \(^{13}\)C NMR (75.5MHz, CDCl\(_3\), \( \delta \)): 170.9 (s, C═O), 143.4 (s, C-SO\(_2^\text{−}\)), 135.0 (s, \( J = 33 \), C-CF\(_3\)), 127.6 (2 x d, ArCH), 126.3 (2 x d, ArCH), 121.7 (s, \( J = 273\text{Hz}, \) CF\(_3\)), 55.3 (s, C-(CH\(_3\))\(_2\)) 49.3 (t, CH\(_3\)), 33.5 (t, CH\(_2\)), 31.3 (2 x q, C(CH\(_3\))\(_2\)), 21.2 (t, CH\(_2\)), 12.1 (q, CH\(_3\)). LRMS (LSIMS) \( m/z \): 431 (\(^{81}\)Br M\(^+\) = 45%), 429 (\(^{79}\)Br M\(^+\) = 44), 349 (10), 153 (100), 137 (90); HRMS (LSIMS) \( m/z \): calcd for C\(_{13}\)H\(_{19}\)BrF\(_3\)NO\(_3\)S, 430.0299; found 430.0309.
Experimental

\textit{N-(2-Bromo-2-methyl-propionyl)-N-butyl-3,5-trifluoromethyl-benzenesulfonamide} 278l

Flash chromatography (petrol ether/ethyl acetate, 4:1) furnished \textit{N-(2-bromo-2-methyl-propionyl)-N-butyl-3,5-trifluoromethyl-benzenesulfonamide} 278l as a yellow oil (2.70g, 97\%). IR (neat) \(\nu_{\text{max}}\): 2964, 1685, 1360, 1279, 1142, 839 cm\(^{-1}\). \(^1\)H NMR (300MHz, CDCl\(_3\), \(\delta\)): 8.40 (s, 2H, ArC\(\text{-H}\)), 8.08 (s, 1H, ArCH), 4.20 (app.t, \(J = 8.0\), 2H, CH\(_2\)), 1.93-1.84 (m, 8H, CH\(_2\) and C (CH\(_3\))\(_2\)), 1.37 (sxt., \(J = 7.0\), 2H, CH\(_2\)), 0.92 (t, \(J = 7.0\), 3H, ArCH\(_3\)). \(^{13}\)C NMR (75.5MHz, CDCl\(_3\), \(\delta\)): 171.2 (s, C═O), 142.5 (s, C-SO\(_2\)-), 133.0 (2 x s, \(J = 34.6\)Hz, (C(CF\(_3\))\(_2\)), 129.3 (d, CH), 128.2 (2 x d, CH), 121.0 (2 x q, \(J = 273.6\), (CF\(_3\))\(_2\)), 56.5 (s, C-(CH\(_3\))\(_2\)), 49.7 (t, CH\(_2\)), 32.8 (t, CH\(_2\)) 30.0 (2 x q, C(CH\(_3\))\(_2\)), 20.8 (t, CH\(_2\)), 14.00 (q, CH\(_3\)). LRMS (El\(^+\)) \(m/\text{z}\): 500 (\(^{81}\)Br MH\(^+\) = 30\%), 498 (\(^{79}\)Br M\(^+\) = 78), 420 (\(^{81}\)Br M\(^+\) = 22), 418 (\(^{79}\)Br = 100), 277 (78), 213 (82), 206 (\(^{81}\)Br 30), 204 (\(^{79}\)Br 32). HRMS (El\(^+\)) \(m/\text{z}\): (MH\(^+\)) calcd for C\(_{16}\)H\(_{19}\)BrF\(_6\)NO\(_3\)S, 498.0173; found 498.0169.
Experimental

5.0 General procedure for synthesis of radical procedures 369

\[
\begin{array}{c}
\text{R} = \text{alkyl} \\
\end{array}
\]

5.1 N-BUTYLLITHIUM METHOD:
To a stirred solution of \( N \)-alkyl-4-methylbenzenesulfonamide 374 (1.0 eq.) in anhydrous tetrahydrofuran was added \( n \)-butyllithium (1.6 M in hexanes) (1.0 eq.) and 2-bromo-isobutyryl bromide 287 (1.0 eq.) at -78°C (dry ice/acetone) overnight. The reaction was quenched with saturated ammonium chloride (10 mL), and the product extracted with dichloromethane (200 mL), followed by saturated sodium bicarbonate (200 mL). The aqueous phase was washed with dichloromethane (2 x 200 mL) and the combined organic fractions were washed with saturated sodium chloride. The organic phase was dried with magnesium sulfate, and the solvent evaporated \( \text{in-vacuo} \) to yield a crude product. Purification of the crude product (petrol ether: ethyl acetate) furnished the radical precursor 369.

5.2 TRIETHYLAMINE METHOD
To a stirred solution of \( N \)-alkyl-4-methylbenzenesulfonamide 374 (1.0 eq.) in dry dichloromethane was added triethylamine (1 eq.) and 2-bromo-isobutyryl bromide 284 (1 eq.), under nitrogen at room temperature overnight. The reaction was quenched with distilled water (50 mL), and the product extracted with diethyl ether (3 x 50 mL). The combined organic extracts were dried over magnesium sulfate and the solvent evaporated \( \text{in vacuo} \) to furnish the crude product. Purification with petrolether: ethyl acetate, yield the radical precursor 369.
Experimental

N-(2-Bromo-2-methyl-propionyl)-N-ethyl-4-methyl-benzenesulfonamide 369a

Flash chromatography (petrol ether/ethyl acetate, 6:1) furnished N-(2-bromo-2-methyl-propionyl)-N-ethyl-4-methyl-benzenesulfonamide 369a as a light yellow crystallised solid (4.48g, 25%). mp 98.5-98.6 °C. IR (neat) v_max: 2978, 1709, 1391, 1163, 811 cm⁻¹.

1H NMR (400MHz, CDCl₃, δ): 7.86 (d, J = 8.0, 2H, ArCH), 7.30 (d, J = 8.0, 2H, ArCH), 4.33 (q, J = 7.0, 2H, CH₂), 2.42 (s, 3H, ArCH₃), 1.96 (s, 6H, C(CH₃)₂), 1.51 (t, J = 7.0, 3H, CH₃). 13C NMR (100MHz, CDCl₃, δ): 171.5 (s, C═O), 144.5 (s, C-Me), 136.5 (s, C-SO₂⁻), 129.3 (2 x d, ArCH), 128.6 (2 x d, ArCH), 56.6 (s, C-(CH₃)₂), 44.0 (t, CH₂), 31.8 (2 x q, C(CH₃)₂), 21.7 (q, ArCH₃), 17.0 (q, CH₃). LRMS (LSIMS-FAB⁺) m/z: 350 (81Br-MH⁺ = 12%), 348 (79Br-MH⁺ = 10), 154 (100), 137 (68). HRMS (LSIMS-FAB⁺) calcd for C₁₃H₁₈BrNO₃S, 348.0269; found, 348.0262.

N-(2-Bromo-2-methyl-propionyl)-N-propyl-4-methyl-benzenesulfonamide 369b

Flash chromatography (6:1 petrol ether:ethyl acetate) furnished N-(2-bromo-2-methyl-propionyl)-N-propyl-4-methyl-benzenesulfonamide 369b as a viscous lemon-yellow crystallised solid (1.19g, 34%). IR (neat) v_max: 2968, 1710, 1349, 1161, 814 cm⁻¹. 1H NMR (400MHz, CDCl₃, δ): 7.75 (d, J = 8.5, 2H, ArCH), 7.19 (d, J = 8.5, 2H, ArCH), 4.03 (app.t, J = 8.5, 2H, CH₂), 2.31 (s, 3H, ArCH₃), 1.88-1.82 (app. quin., J = 7.0, 2H,
Experimental

CH₂), 1.78 (s, 6H, 2 x CH₃), 0.88 (t, J = 7.0, 3H, CH₃). ¹³C NMR (100MHz, CDCl₃, δ)
169.2 (s, C=O), 143.5 (s, C-Me), 135.2 (s, C-SO₂⁻), 128.2 (2 x d, ArCH), 127.5 (2 x d, ArCH), 55.6 (s, C-(CH₃)₂), 49.2 (t, CH₂), 30.7 (2 x q, C(CH₃)₂), 23.2 (t, CH₂), 20.6 (q, ArCH₃), 15.0 (q, CH₃). LRMS (LSIMS-FAB⁺) m/z: 364 (⁸¹Br MH⁺ = 30%), 362 (⁷⁹Br MH⁺ = 28), 155 (35), 154 (100), 137 (70), 136 (60). HRMS (LSIMS-FAB⁺) m/z: calcd
for C₁₄H₂₀BrNO₃S, 362.0425; found, 362.0434.

N-(2-Bromo-2-methyl-propionyl)-N-pentyl-4-methyl-benzenesulfonamide 369d

Discernible data:

\[
\begin{align*}
\text{Flash chromatography (6:1 petrol ether:ethyl acetate) furnished } & \\
\text{N-(2-bromo-2-methyl-propionyl)-N-pentyl-4-methyl-benzenesulfonamide 369d as a yellow oil (0.54g, 22%). IR} & \\
\text{(neat) } & \\
\nu_{\text{max}}: 2929, 1598, 1494, 1321, 1155, 1092, 1019, 813 \text{ cm}^{-1}. & \\
\text{¹H NMR (400MHz, } & \\
\text{CDCl₃, δ): 7.85 (d, J = 8.0, 2H, ArCH), 7.30 (d, J = 8.0, 2H, ArCH), 4.16 (app. t. J =} & \\
8.0, 2H, CH₂), 2.41 (s, 3H, ArCH₃), 1.96-1.88 (m, 8H, CH₂ + C(CH₃)₂), 1.44-1.30 (m, 4H, 2 x CH₂), 0.92 (t, J = 7.0, 3H, CH₃). & \\
\text{LRMS (LSIMS-FAB⁺) m/z: 392 (⁸¹Br-MH⁺ =} & \\
100), 390 (⁷⁹Br-MH = 98), 310 (43), 154 (32), 136 (32). & \\
\text{HRMS (LSIMS-FAB⁺) calcd} & \\
\text{for C₁₆H₂₄BrNO₃S, 390.0738; found, 390.0735.} & \\
\end{align*}
\]
Experimental

*N-(2-Bromo-2-methyl-propionyl)-N-hexyl-4-methyl-benzenesulfonamide 369e*

Flash chromatography (4:1 petrol ether:ethyl acetate) furnished *N-(2-bromo-2-methyl-propionyl)-N-hexyl-4-methyl-benzenesulfonamide 369e* as lemon-yellow crystallised solid (2.92g, 91%). mp. 55.4-55.5 ºC. IR (neat) νmax: 2927, 1679, 1348, 1163, 1072, 811 cm⁻¹. ¹H NMR (400MHz, CDCl₃, δ): 7.85 (d.t, J = 8.0 and 2.0, 2H, ArCH), 7.30 (d, J = 8.0, 2H, ArCH), 4.15 (app. t. J = 8.0, 2H, CH₂), 2.43 (s, 3H, ArCH₃), 1.93-1.89 (m, 8H, CH₂ + (CH₃)₂), 1.38-1.26 (m, 6H, 3 x CH₂), 0.90 (t, J = 7.0, 3H, CH₃). ¹³C NMR (100MHz, CDCl₃, δ): “not observed” (C=O), 145.0 (s, C-Me), 135.0 (s, C-SO₂⁻), 129.0 (2 x d, ArCH), 128.3 (2 x d, ArCH), 56.4 (s, C(CH₃)₂), 48.8 (t, CH₃), 31.6 (2 x q, CH₃), 31.0 (t, CH₂), 30.7 (t, CH₂), 26.1 (t, CH₂), 22.4 (t, CH₂), 21.4 (q, ArCH₃), 13.8 (q, CH₂). LRMS (LSIMS-FAB⁺) m/z: 406 (⁸¹Br MH⁺ = 60%), 404 (⁷⁹Br MH⁺ 60), 324 (30), 256 (31), 170 (20), 154 (100), 137 (81). HRMS (LSIMS-FAB⁺) m/z: (MH⁺) calcd for C₁₇H₂₇⁷⁹BrNO₃S, 404.0895; found, 404.0909.
Experimental

\[ N-(2\text{-Bromo-2-methyl-propionyl})-N\text{-dodecyl-4-methyl-benzenesulfonamide} \]

Flash Chromatography (6:1 petrol ether:ethyl acetate) furnished \( N-(2\text{-bromo-2-methyl-propionyl})-N\text{-dodecyl-4-methyl-benzenesulfonamide} \) as a white crystallised solid (1.79g, 41%). IR (neat) \( \nu_{\text{max}} \): 2915, 1679, 1345, 1159, 1066, 886 cm\(^{-1}\). \(^1\)H NMR (400MHz, CDCl\(_3\), \( \delta \)): 7.78 (d, \( J = 8.0 \), 2H, ArCH), 7.19 (d, \( J = 8.0 \), 2H, ArCH), 4.09 (t, \( J = 8.0 \), 2H, \( CH_2 \)), 2.30 (s, 3H, ArCH\(_3\)), 1.86-1.79 (m, 8H, \( CH_2 \)+ (CH\(_3\))\(_2\)), 1.29-1.22 (m, 18H, 9 x \( CH_2 \)), 0.83 (t, \( J = 7.0 \), 3H, \( CH_3 \)). \(^{13}\)C NMR (100MHz, CDCl\(_3\), \( \delta \)): 170.2 (s, C=O), 144.2 (s, C-Me), 136.5 (s, C-SO\(_2\)), 129.1 (2 x d, ArCH), 128.6 (2 x d, ArCH), 56.7 (s, C-(CH\(_3\))\(_2\)), 49.9 (t, \( CH_2 \)), 32.5 (t, \( CH_2 \)), 31.7 (t, \( CH_2 \)), 31.7 (2 x q, C(CH\(_3\))\(_2\)), 29.3-29.1 (6 x t, \( CH_2 \)), 26.6 (t, \( CH_2 \)), 22.7 (t, \( CH_2 \)), 21.5 (q, ArCH\(_3\)), 14.7 (q, \( CH_3 \)).

LRMS (LSIMS-FAB\(^+\)) \( m/z \): 490 \((^{81}\text{Br} \text{MH}^+ = 95\%)\), 489 \((^{81}\text{Br} \text{M}^+ = 94)\), 408 (41), 340 (48), 155 (45), 154 (100), 138 (48), 137 (100). HRMS (LSIMS-FAB\(^+\)) \( m/z \): (MH\(^+\)) calcd for \( C_{23}H_{39}^{^{81}}\text{BrNO}_3S \), 488.1834; found 488.1814.
Experimental

\(N-(2\text{-Bromo-2-methyl-propionyl})\text{-}N\text{-iso}-butyl\text{-}4\text{-methyl-benzenesulfonamide} \ 369h\)

Previously synthesised by Fullaway.\(^{163}\) Flash Chromatography (6:1 petrol ether:ethyl acetate) furnished \(N-(2\text{-bromo-2-methyl-propionyl})\text{-}N\text{-iso}-butyl\text{-}4\text{-methyl-benzenesulfonamide} \ 369h\) as pale yellow crystallised solid (3.06g, 90%). mp 91.3-91.5 ºC. IR (neat) \(\nu_{\text{max}}\): 2964, 1813, 1323, 1159, 1040 and 812 cm\(^{-1}\). \(^1\)H NMR (400MHz, CDCl\(_3\), \(\delta\)):

- 7.74 (d, \(J = 8.0, 2\text{H, ArCH})
- 7.30 (d, \(J = 8.0, 2\text{H, ArCH})
- 3.90 (d, \(J = 8.0, 2\text{H CH}_2)
- 2.42 (s, 3H, ArCH\(_3\))
- 1.96 (s, 6H, (CH\(_3\))\(_2\))
- 1.74-1.68 (spt., \(J = 7.0, 1\text{H, CH})
- 1.07 (d, \(J = 7.0, 6\text{H, (CH\(_3\))}\(_2\))

\(^{13}\)C NMR (100MHz, CDCl\(_3\), \(\delta\)):

- 176.00 (s, C\(\equiv\)O)
- 165.76 (s, C-Me)
- 143.32 (s, C-SO\(_2\)\(-\))
- 129.70 (2 x d, ArCH)
- 127.07 (2 x d, ArCH)
- 55.01 (s, C-(CH\(_3\))\(_2\))
- 50.55 (t, CH\(_2\))
- 30.01 (2 x q, C(CH\(_3\))\(_2\))
- 19.88 (2 x q, C(CH\(_3\))\(_2\))

LRMS (LSIMS) \(m/z\):

- \(61\) Br M\(^+\) = 19%, 376 \(^{79}\) Br M\(^+\) = 20%, 296 (25), 228 \(^{79}\) Br 100), 154 (30), 137 (35).

\(N-(2\text{-Bromo-2-methyl-propionyl})\text{-}N\text{-sec-butyl-4-methyl-benzenesulfonamide} \ 369i\)

Previously synthesised by Fullaway.\(^{163}\) Flash chromatography (6:1 petrol ether:ethyl acetate) furnished \(N-(2\text{-bromo-2-methyl-propionyl})\text{-}N\text{-sec-butyl-4-methyl-benzenesulfonamide} \ 369i\) as a pale yellow crystallised solid (2.88g, 85%). mp 105.4-105.5 ºC.
Experimental

IR (neat) ν<sub>max</sub>: 2971, 1712, 1297, 1157, 1090, 663 cm<sup>-1</sup>. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>, δ): 7.86 (d,t, J = 8.0 and 2.0, 2H, ArCH), 7.29 (d, J = 8.0, 2H, ArCH), 4.61 (app. spt. J = 7.0, 1H, CH), 2.42 (s, 3H, ArCH<sub>3</sub>), 2.40-2.30 (m, 1H, CH), 2.13-2.03 (m, 1H, CH), 1.90 (s, 6H, (CH<sub>3</sub>)<sub>2</sub>), 1.69 (d, J = 7.0, CH<sub>3</sub>), 1.03 (t, J = 7.0Hz, CH<sub>3</sub>). <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>, δ): 176.6 (s, C═O), 143.2 (s, C-Me), 138.2 (s, C-SO₂⁻), 129.5 (2 x d, CH), 127.0 (2 x d, CH), 55.3 (s, C-(CH<sub>3</sub>)<sub>2</sub>), 51.4 (d, CH), 30.6 (2 x q, CH<sub>3</sub>)<sub>2</sub>, 30.2 (t, CH<sub>2</sub>) 21.6 (2 x q, CH<sub>3</sub>), 15.0 (q, CH<sub>3</sub>).

6.0  N-(Hetero)aryl-4-methylbenzene sulfonamides 381

6.1  TRIETHYLAMINE METHOD

To a stirred solution of N-(hetero)aryl-4-methylbenzenesulfonamide 380 (1.0 eq.) in dry dichloromethane was added triethylamine (1 eq.) and 2-bromo-isobutyryl bromide 284 (1 eq.), under nitrogen at room temperature overnight. The reaction was quenched with distilled water (50 mL), and the product extracted with diethyl ether (3 x 50 mL). The combined organic extracts were dried over magnesium sulfate and the solvent evaporated in vacuo to furnish the crude product. Purification with petrolether: ethyl acetate, yield the radical precursor 381.
Experimental

\[N-(2\text{-bromo-2-methyl-propionyl})-4\text{-methyl-N-(4-methyl-benzyl)benzenesulfonamide \ 381a}\]

\[\text{\begin{tikzpicture}
\node (image) at (0,0) {\includegraphics[width=0.4\textwidth]{image}};
\end{tikzpicture}}\]

\[N-(2\text{-bromo-2-methyl-propionyl})-4\text{-methyl-N-(4-methyl-benzyl)benzenesulfonamide \ 381a}\] obtained as a light brown crystallised solid (3.14g, 100%). IR (neat) \(\nu_{\max}\): 2919, 1690, 1320, 1165, 725 cm\(^{-1}\). \(^1\)H NMR (400MHz, CDCl\(_3\), \(\delta\)): 7.64 (d.t, \(J = 7.0\) and 2.0, 2H, ArCH), 7.18 (app. t. \(J = 8.0\), 4H, ArCH), 7.12 (app. d., \(J = 8.0\), 2H, ArCH), 5.51 (bs, 2H, CH\(_2\)), 2.39 (s, 3H, ArCH\(_3\)), 2.34 (s, 3H, ArCH\(_3\)), 1.86 (s, 6H, CH\(_3\)_2). \(^{13}\)C NMR (100MHz, CDCl\(_3\), \(\delta\)): 170.94 (s, C═O), 144.39 (s, C-Me), 137.38 (s, C-Me), 133.32 (s, C-SO\(_2\)), 128.80 (d, ArCH), 128.78 (d, ArCH), 128.31 (d, ArCH), 128.21 (d, ArCH), 127.93 (d, ArCH), 127.66 (d, ArCH), 127.38 (d, ArCH), 126.99 (d, ArCH), 60.00 (s, C-(CH\(_3\)_2), 51.72 (t, CH\(_3\)), 31.84 (2 x q, C(CH\(_3\)_2), 21.47 (q, ArCH\(_3\)), 21.34 (q, ArCH\(_3\)). LRMS (LSIMS-FAB\(^+\)) \(m/z\): 426 (MH\(^+\) = 100%), 154 (100), 137 (50).
Experimental

*N-(2-Bromo-2-methyl-propionyl)-4-methyl-N-(4-methoxy-benzyl)-benzene-sulfonamide 381b*

![Chemical Structure](image)

*381b* obtained pure as a light brown solid (2.72g, 91%). IR (neat) $\nu_{\text{max}}$: 2928, 1676, 1336, 1168, 1088 and 811 cm$^{-1}$. $^1$H NMR (400MHz, CDCl$_3$, $\delta$): 7.61 (d., $J = 8.0$, 2H, ArCH), 7.21 (app. t., $J = 8.0$, 4H, ArCH), 6.85 (d.t, $J = 8.0$ and 3.0, 2H, ArCH), 5.47 (s, 2H, CH$_2$), 3.80 (s, 3H, OCH$_3$), 2.40 (s, 3H, ArCH$_3$), 2.95 (s, 6H, C(CH$_3$)$_2$). $^{13}$C NMR (100MHz, CDCl$_3$, $\delta$): 171.34 (s, C=$\equiv$O), 159.11 (s, C-OMe), 144.59 (s, C-Me), 128.45 (s, C-SO$_2$-), 129.04 (2 x d, ArCH), 129.01 (2 x d, ArCH), 128.45 (d, ArCH), 128.40 (d, ArCH), 114.37 (d, ArCH), 114.04 (d, ArCH), 57.20 (s, C-(CH$_3$)$_2$), 55.38 (q, OCH$_3$), 51.70 (t, CH$_2$), 32.08 (2 x q, C(CH$_3$)$_2$), 21.70 (q, ArCH$_3$). LRMS (LSIMS-FAB$^+$) $m/z$: 442 (MH$^+$ = 5%), 154 (100), 137 (65), 121 (38).
Experimental

\[ N-(2\text{-bromo-2-methyl-propionyl})-4\text{-methyl-}N-(2\text{- trifluoromethyl-benzyl})\text{-benzene-sulfonamide} \text{ 381c} \]

Discernible data

\[ N-(2\text{-bromo-2-methyl-propionyl})-4\text{-methyl-}N-(2\text{- trifluoromethyl-benzyl})\text{-benzene-sulfonamide} \text{ 381c} \] as a light brownish-yellow crystallised solid (2.31g, 79%). IR (neat) \( \nu_{\text{max}}: \) 2361, 1681, 1311, 1036, 775 cm\(^{-1}\). \(^1\)H NMR (300MHz, CDCl\(_3\), \( \delta \)): 7.87 (d.t, \( J = 8.0 \) and 2.0, 2H, ArCH), 7.71 (d, \( J = 8.0 \), 1H, ArCH), 7.65 (d, \( J = 8.0 \), 1H, ArCH), 7.58 (t, \( J = 8.0 \), 1H, ArCH), 7.41 (t, \( J = 8.0 \), 1H, ArCH), 7.32 (d, \( J = 8.0 \), 2H, ArCH), 5.83 (s, 2H, CH\(_2\)), 2.46 (s, 2H, ArCH\(_3\)), 1.73 (s, 6H, 2 x CH\(_3\)). LRMS (LSIMS-FAB\(^+\)) \( m/\varepsilon \): 480 (\(^{81}\)Br MH\(^+\) = 20\%), 477 (\(^{79}\)Br MH\(^+\) = 18), 154 (100), 136 (74), 120 (12). HRMS (LSIMS-FAB\(^+\)) \( m/\varepsilon \) (MH\(^+\)) calcd for C\(_{19}\)H\(_{20}\)BrF\(_3\)NO\(_3\)S, 478.0299; found, 478.0305.

\[ N-(2\text{-bromo-2-methyl-propionyl})-4\text{-methyl-}N\text{-pyridin-2-yl-methyl-benzenesulfonamide} \text{ 381d} \]

\[ N-(2\text{-bromo-2-methyl-propionyl})-4\text{-methyl-}N\text{-pyridin-2-yl-methyl-benzenesulfonamide} \text{ 381d} \] as a light brown crystallised solid (3.14g, 100%). IR (neat) \( \nu_{\text{max}}: \) 2923, 1682, 1346, 1168, 1112, 1086 and 782 cm\(^{-1}\). \(^1\)H NMR (400MHz, CDCl\(_3\), \( \delta \)): 8.59 (app. d, \( J = 5.0 \),
Experimental

1H, ArCH), 7.81-7.76 (app. d., J = 8.0, 3H, ArCH), 7.55 (d, J = 8.0, 1H, ArCH), 7.27 (app.d, J = 8.0, 3H, ArCH), 5.71 (s, 2H, CH2), 2.43 (s, 3H, ArCH), 1.97 (s, 6H, (CH3)2).

13C NMR (100MHz, CDCl3, δ): 170.29 (s, C═O), 156.13 (s, C-pyridine), 148.23 (d, ArCH), 144.73 (s, C-Me), 137.77 (d, ArCH), 135.31 (s, C-SO2-), 129.10 (2 x d, ArCH), 128.75 (2 x d, ArCH), 122.60 (d, ArCH), 121.33 (d, ArCH), 56.73 (s, C-(CH3)2), 52.50 (t, CH2), 30.64 (2 x q, C(CH3)2), 21.50 (q, ArCH3). LRMS (LSIMS-FAB⁺) m/z: 412 (81Br M⁺ = 18%), 410 (79Br M⁺ = 18), 331 (16), 219 (20), 165 (20), 154 (100), 136 (36).

HRMS (LSIMS-FAB⁺) calcd for C17H19BrN2O3S, 411.0378; found, 411.0371.

N-(2-Bromo-2-methyl-propionyl)-N-(furan-2-ylmethyl)-4-methyl-benzene-sulfonamide 381e

N-(2-bromo-2-methyl-propionyl)-N-(furan-2-ylmethyl)-4-methyl-benzenesulfonamide 381e obtained pure as a golden crystallised solid (3.56g, 100%). IR (neat) νmax: 2977, 1709, 1348, 1161, 1087, 811 cm⁻¹. 1H NMR (400MHz, CDCl3, δ): 7.58 (d, J = 8.0, 2H, ArCH), 7.30 (app s., 1H, furan-H), 7.21 (d, J = 8.0, 2H, ArCH), 6.45 (app. d, J = 3.0, 1H, furan-H), 6.38 (app.q. J = 3.0, 1H, furan-H), 5.47 (s, 2H, CH2), 2.40 (s, 3H, ArCH3), 1.95 (app d. J = 4.0, 6H, (CH3)2). 13C NMR (100MHz, CDCl3, δ): 176.8 (s, C═O), 149.6 (s, C-furan), 144.5 (s, C-Me), 142.3 (2 x d, ArCH), 135.9 (s, C-SO2-), 129.1 (d, ArCH), 128.9 (d, ArCH), 110.7 (d, CH), 109.7 (d, CH) 57.4 (s, C-(CH3)2), 45.2 (t, CH2), 32.3 (2 x q, CH3), 30.5 (q, C(CH3)2), 21.7 (q, ArCH3). LRMS (LSIMS) m/z: 402 (81Br-M⁺ = 13%), 400 (79Br-M⁺ = 15), 244 (20), 219 (15), 154 (100), 136 (76).
7.0 Synthesis of cyclised and rearranged amides from radical precursors 278

7.1 General method for copper-mediated radical reactions

To a stirred solution of the radical precursor 278 (1.0 eq.) in dichloromethane (DCM) was added of tris-[(2-pyridyl)methyl]-amine (1.1 eq.) 279 and copper bromide (1.1 eq.). The reaction was stirred under nitrogen at 37°C, and monitored by TLC until the disappearance of starting material. Filtering the crude product through a silica plug with ethyl acetate quenched the reaction mixture. The solvent was evaporated in vacuo to yield an emerald green crude product. Purification by flash chromatography led to an isolation of both the cyclised and rearranged products. Reactions done in toluene were performed under inert atmosphere at reflux temperature unless otherwise stated.

2-(Phenyl)-N-butyl-isobutyramide 280a

Purification by column (petrol ether/ethyl acetate 8:1), furnished 2-(phenyl)-n-butyl-isobutyramide 280a as apple-white translucent spherical solid (0.13g, 40%). IR (CH\(_2\)Cl\(_2\)) \(\nu_{\text{max}}\): 3359, 2928, 1643, 1525, 1365, 1164, 762 cm\(^{-1}\). \(^1\)H NMR (300MHz, CDCl\(_3\), \(\delta\)): 7.36 (s, 4H, ArC\(_\text{H}\)), 7.29-7.24 (m, 1H, ArCH), 5.18 (s, 1H, NH), 3.15 (q, \(J = 7.0, 2H, \text{CH}_2\)), 1.56 (s, 6H, C(CH\(_3\))\(_2\)), 1.40-1.30 (quin., \(J = 7.0, 2H, \text{CH}_2\)), 1.26-1.14 (sxt., \(J = 7.0, 2H, \text{CH}_2\),
Experimental

**N-Butyl-3,3-dimethyl-1,3-dihydro-indol-2-one 290**

Previously synthesised. Purification by flash chromatography furnished 1-buty]-3,3-dimethyl-1,3-dihydro-indol-2-one 290 as a transparent spherical film (0.14g, 59%). IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$: 2962, 2928, 2868, 1357, 1133, 749 cm$^{-1}$. $^1$H NMR (400MHz, CDCl$_3$, $\delta$): 7.21 (app. q., $J$ = 7.5, 2H, ArCH), 7.04 (m, 1H, ArCH), 6.87 (d, $J$ = 7.0, 1H, ArCH), 3.71 (t, $J$ = 7.0, 2H, CH$_2$), 1.71-1.61 (app. quin., $J$ = 7.0, 2H, CH$_2$), 1.44-1.31 (m, 8H, CH$_2$ + (CH$_3$)$_2$), 0.95 (t, $J$ = 7.0, 3H, CH$_3$). $^{13}$C NMR (75.5MHz, CDCl$_3$, $\delta$) 181.3 (s, C=O), 142.1 (s, C-N), 136.0 (s, C-C(CH$_3$)$_2$), 127.6 (2 x d, ArCH), 122.2 (d, ArCH), 108.3 (d, ArCH), 44.1 (s, C-(CH$_3$)$_2$), 39.6 (t, CH$_2$), 29.5 (t, CH$_2$), 24.5 (2 x q, C(CH$_3$)$_2$), 20.1 (t, CH$_2$), 14.1 (q, CH$_3$). LRMS (EI$^+$) $m/z$: 218 (M-SO$_2$ = 13%), 217 (M-SO$_2$ = 82%), 174 (82), 146 (100), 130 (23). HRMS (LSIMS-FAB$^+$) $m/z$: (M$^+$) calcd for C$_{14}$H$_{19}$NO, 217.1467; found, 217.1459.
Experimental

Authentic synthesis of the rearranged amide

2-Methyl-2-p-tolyl-propionic acid ethyl ester 348

Synthesised according to Künzkel _et al._ procedure. To a solution of anhydrous dimethylformamide (DMF) (25 mL), was added ethyl-p-tolylacetate (10g, 9.9 mL, 56 mmol) (Flask A). In a separate flask (B) was added sodium hydride in mineral oil (60%) (7.85g, 196 mmol) which was thrice washed in pentane under a nitrogen atmosphere and the mineral oil decanted. To flask B between 5-10 °C was added anhydrous dimethylformamide (DMF) (300 mL), and methyl iodide (CAUTION: Carcinogenic) (12.16g, 196 mmol) to give a dark grey turbid solution. Ethyl-p-tolylacetate (Flask A) was added dropwise over one hour. The mixture was stirred under nitrogen at room temperature for 46 hours. The mixture was quenched with ethanol (100mL) and saturated ammonium chloride (100mL). Extraction with ether (5 x 100mL) and washing the organic layer with water (5 x 100mL), to neutrality, and drying over anhydrous magnesium sulfate. The solvent was removed in-vacuo to an light reddish-orange mobile oil (6.78g). The desired product 2-methyl-2-p-tolyl-propionic acid ethyl ester 348 was furnished as a light greenish-yellow oil (2.36, 20%) following flash chromatography (petrol ether:diethyl ether 20:1).

1H NMR (300MHz, CDCl3, δ): 7.24-7.15 (app. d.t. J = 8.0 and 2.0, 2H, ArCH3), 7.09 (app. d, J = 8.0, 2H, ArCH2), 4.14-4.05 (app. q, J = 7.0, 2H, CH2), 2.15 (s, 3H, ArCH3), 1.54 (s, 6H, (C(CH3)2), 1.21-1.12 (t J = 7.0, 3H, CH3). 13C NMR (100MHz, CDCl3, δ): 176.9 (s, C═O), 141.2 (s, C-Me), 136.2 (s, C-C(CH3)2), 129.0 (2 x d, ArCH), 125.5 (2 x d, ArCH), 60.7 (t, CH2), 29.7 (2 x q, C-(CH3)2), 20.9 (q, ArCH3), 15.0 (q, CH3).
Experimental

α,α, 4-Trimethylbenzeneacetic acid 350

![Structure of α,α, 4-Trimethylbenzeneacetic acid](image)

Commercially available from Interchim [20430-18-6]. Previously synthesised by Smith III *et al.* To a flask containing the gem ester (1.5g) with potassium hydroxide pellets (0.61g) was added absolute ethanol (50 mL), and the solution was stirred at reflux for six days. The solvent was removed in-vacuo to yield an orange-yellow solid (2.30g). The crude solid was treated with diethyl ether (2 x 125 mL) and then acidified down to pH 2 with hydrochloric acid (2M HCl). The organic phase was dried over anhydrous magnesium sulfate. The solvent was removed in-vacuo to furnish a yellow solid (1.20g) as α,α, 4-trimethylbenzeneacetic acid 350. $^1$H NMR (400MHz, CDCl$_3$, δ): 9.4 (bs, 1H, COOH), 7.10 (d.t, $J = 8.0$ and 2.0, 2H, ArCH), 6.99 (t, $J = 8.0$, 2H, ArCH), 2.19 (s, 3H, ArCH$_3$), 1.44 (s, 6H, (C(CH$_3$)$_2$)$_2$). $^{13}$C NMR (100MHz, CDCl$_3$, δ): 177.0 (s, C=O), 141.9 (s, C-Me), 137.0 (s, C-C(CH$_3$)$_2$), 129.2 (2 x d, ArCH), 125.7 (2 x d, ArCH), 46.2 (s, C- (CH$_3$)$_2$), 26.6 (2 x q, C(CH$_3$)$_2$), 21.0 (q, ArCH$_3$).

2-Methyl-2-p-tolyl-propionyl chloride 351

![Structure of 2-Methyl-2-p-tolyl-propionyl chloride](image)

Previously synthesised by Buckle *et al.* To a flask containing the gem acid (0.40g) was added oxalyl chloride (0.88g, 0.60 mL) and the mixture refluxed vigourously for 24h. The excess oxalyl chloride was removed in-vacuo to furnish 2-methyl-2-p-tolyl-propionyl chloride 351 as a yellow oil (0.14g) $^1$H NMR (300MHz, CDCl$_3$, δ): 7.16-7.08 (m, 4H, ArCH), 2.32 (s, 3H, ArCH$_3$), 1.58 (s, 6H, (C(CH$_3$)$_2$)).
Experimental

**Authentic Synthesis of N-Butyl-2-p-tolyl-isobutyramide 280e**

![Chemical Structure](image)

To a stirred solution of 2-methyl-2-phenyl-propionyl chloride (0.02g, 0.1mmol) in diethyl ether (2 mL), was added n-butyamine (0.01 mL, 0.3 mmol) at room temperature for 2 days. The reaction was quenched with water (5 mL) and the organic phase extracted with diethyl ether (5 x 5 mL), and dried with anhydrous magnesium sulfate. The solvent was removed *in-vacuo* to furnish N-butyl-2-p-tosyl-isobutyramide 280e a yellow viscous solid (0.012g, 26%). $^1$H NMR (400MHz, CDCl$_3$, $\delta$): 7.18 (d.t, $J = 8.0$ and 2.0, 2H, ArCH), 7.08 (d, $J = 8.0$, 2H, ArCH), 5.05 (bs, 1H, NH), 3.07 (q, $J = 7.0$, 2H, CH$_2$), 2.27 (s, 3H, ArCH$_3$), 1.47 (s, 6H, 2 x CH$_3$), 1.31-1.24 (quin. $J = 7.0$, 2H, CH$_2$), 1.19-1.09 (app. sxt., $J = 7.0$, 2H, CH$_2$), 0.78 (t, $J = 7.0$, 3H, CH$_3$). $^{13}$C NMR (100MHz, CDCl$_3$, $\delta$): 177.6 (s, C═O), 142.3 (s, C-Me), 136.6 (s, C-C(CH$_3$)$_2$), 129.3 (2 x d, ArCH), 126.4 (2 x d, ArCH), 46.7 (s, C-(CH$_3$)$_2$), 39.4 (t, CH$_2$), 31.6 (t, CH$_2$), 27.2 (2 x q, C(CH$_3$)$_2$), 20.9 (q, ArCH$_3$), 20.0 (t, CH$_2$), 14.8 (q, CH$_3$). LRMS (LSIMS-FAB$^+$) $m/z$: 234 (MH$^+$ = 100%), 154 (100), 137 (66), 133 (22), 120 (12). HRMS (LSIMS-FAB) $m/z$: (MH$^+$) calcd for C$_{15}$H$_{24}$NO, 234.1858; found, 234.1868.

**Authentic Synthesis of 1-butyl-3,3,5-trimethyl-1,3-dihydroindol-2-one**

![Chemical Structure](image)

Commercially available from Wako Pure Chemicals [10387-24-3]. A flask (A) containing sodium hydride in 60% mineral oil was thrice washed with pentane, and the
Experimental

oil decanted. In a separate flask (B) was added \( p \)-toluidine (10g) in dimethylformamide (DMF) (50 mL) which was transferred via syringe to flask (A) which formed a light grey turbid solution. The solution turned dark brown over one hour. Addition of \( n \)-butyl iodide (CAUTION: CARCINOGENIC), to flask (A) gave a brownish-yellow solution. The solution was stirred overnight at room temperature where upon the solution had become olive green. The reaction mixture was quenched with 95% ethanol and strong effervescing was observed. The solution had changed to dark brown. With addition of saturated ammonium chloride a bright orange solution was obtained. Work up consisted of ether (5 x 50 mL) followed by water (10 x 50 mL), drying the organic phase over anhydrous magnesium sulfate and removal of the solvent in-vacuo to give an orange oil. Purification via distillation (bp 143 °C/10Torr) gave dark brown oil identified as \( N-n \)-butyl-\( p \)-toluidine. \(^{1}\)H NMR (400MHz, CDCl\(_3\), \( \delta \)): 6.90 (d, \( J = 8.0, 2H, \text{ArCH} \)), 6.45 (d,t, \( J = 8.0 \) and 2.5, 2H, ArCH), 3.01 (t, \( J = 7.0, 2H, \text{CH}_2 \)), 2.16 (s, 3H, ArCH\(_3\)), 1.55-1.48 (q, \( J = 7.0, 2H, \text{CH}_2 \)), 1.40-1.30 (sxt, \( J = 7.0, 2H, \text{CH}_2 \)), 0.88 (t, \( J = 7.0, 3H, \text{CH}_3 \)). \(^{13}\)C NMR (100MHz, CDCl\(_3\), \( \delta \)): 146.3 (s, C=N-), 129.7 (2 x d, ArCH), 126.3 (s, C-Me), 122.9 (2 x d, ArCH), 44.1 (t, CH\(_2\)), 31.8 (t, CH\(_2\)), 20.4 (t, CH\(_2\)), 20.4 (q, ArCH\(_3\)), 15.0 (q, CH\(_3\)).

\[ \text{2-Bromo-}N\text{-butyl-2-methyl-}N\text{-p-tolyl-propionamide 341} \]

\[ \text{N} \quad \text{O} \quad \text{Br} \]

To a flask containing \( N \)-butyl-\( p \)-toluidine (50 mL) was added triethylamine (1.41g) and 2-bromo-2-isobutyryl bromide (5.5 mL). The reaction mixture
Experimental

was stirred for 3 hours. The reaction mixture was quenched with ether (2 x 100 mL) followed by water (100 mL) and dilute hydrochloric acid (1M, 100 mL). The organic phase was washed with sodium bicarbonate and the organic phase dried over anhydrous magnesium sulfate. The solvent was removed in-vacuo to give brown viscous oil (1.65 g).

Flash chromatography (petrol ether:ethyl acetate 6:1) furnished 2-bromo-N-butyl-2-methyl-N-p-tolyl-propionamide 341 as a yellow oil (0.39 g, 31%). $^1$H NMR (300MHz, CDCl$_3$, δ): 7.29-7.12 (m, 4H, ArC$_H$), 3.65 (t, $J = 7.0$, 2H, CH$_2$), 2.39 (s, 3H, ArCH), 1.70 (s, 6H, (CH$_3$)$_2$), 1.57-1.51 (app. quin., $J = 7.0$, 2H, CH$_2$), 1.37-1.25 (app. sxt., $J = 7.0$, 2H, CH$_2$), 0.89 (t, $J = 7.0$, 3H, CH$_3$). $^{13}$C NMR (100MHz, CDCl$_3$, δ): 169.5 (s, C=O), 139.9 (s, C-N-), 137.5 (s, C-Me), 129.4 (4 x d, ArCH), 59.0 (s, C-(CH$_3$)$_2$), 53.2 (t, CH$_2$), 29.8 (2 x q, C(CH$_3$)$_2$), 28.9 (t, CH$_2$), 20.9 (q, ArCH$_3$), 19.8 (t, CH$_2$), 13.7 (q, CH$_3$). LRMS (LSIMS-FAB$^+$) m/z: 314 ($^{81}$Br MH$^+$ = 98%), 313 ($^{81}$Br M$^+$ = 60), 312 ($^{79}$Br MH$^+$ = 100), 311 ($^{79}$Br M$^+$ = 40), 232 (43), 154 (70), 138 (30), 136 (50). HRMS (LSIMS-FAB$^+$) m/z: calcd for C$_{15}$H$_{22}$BrNO, 311.0885; found, 311.0882.

1-Butyl-3,3,5-trimethyl-1,3-dihydroindol-2-one 333 $^{210}$

Anhydrous aluminium chloride was kept under a stream of nitrogen and to a single necked flask was added (0.54 g) and the precursor 341 (0.50 g). An air condenser was attached and the mixture was heated to 50 °C for 10 min, then maintained at 160 °C for 1 h. A black viscous solid was obtained upon cooling. The reaction mixture was washed with water (5 x 50 mL) furnished a yellow solution, and the organic phase extracted with
Experimental

diethyl ether. The ethereal phase was dried with anhydrous magnesium sulfate, and the solvent removed in-vacuo to furnish a yellow oil (0.41g). Purification from flash chromatography (petrol ether:ethyl acetate 9:1) furnished \textit{1-butyl-3,3,5-trimethyl-1,3-dihydroindol-2-one 333} as a light yellow oil (0.17g, 46%). IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$: 2927, 1641, 1510, 1108 and 822 cm$^{-1}$. $^1$H NMR (400MHz, CDCl$_3$, $\delta$) 6.94 (d, $J = 7.0$, 2H, ArCH), 6.64 (app. d, $J = 7.0$, 1H, ArCH), 3.60 (t, $J = 7.0$, 2H, C$_2$H), 2.24 (s, 3H, ArCH$_3$), 1.59-1.52 (quin., $J = 7.0$, 2H, CH$_2$), 1.32-1.22 (m, 8H, CH$_2$ + (CH$_3$)$_2$), 0.85 (t, $J = 7.0$, 3H, CH$_3$). $^{13}$C NMR (100MHz, CDCl$_3$, $\delta$) 180.1 (s, C═O), 138.6 (s, C-N-), 135.0 (s, C-Me), 130.6 (s, C-C(CH$_3$)$_2$) 126.7 (d, ArCH), 122.2 (d, ArCH), 107.0 (d, ArCH), 43.0 (s, C-(CH$_3$)$_2$), 38.5 (t, CH$_2$), 28.5 (t, CH$_2$), 23.4 (2 x q, C(CH$_3$)$_2$), 20.0 (q, ArCH$_3$), 19.7 (t, CH$_2$), 13.5 (q, CH$_3$); m/z (LSIMS) 232 (MH$^+$ = 32%), 207 (27), 165 (11), 154 (100), 136 (80), 120 (27).

\textbf{1-Butyl-3,3,5-trimethyl-1,3-dihydroindol-2-one 333}

Copper-mediated radical reaction

\begin{center}
\includegraphics[width=0.2\textwidth]{dihydroindol-2-one.png}
\end{center}

To a three necked RB flask was added 341 (0.58g, 1.0 eq.), tris-(2-pyridylmethyl)-amine 279 (0.67g, 1.1 eq) and copper bromide (0.39g, 1.1 eq.) in toluene (16 mL) and the reaction mixture stirred under nitrogen at 120 °C for 24 h. The crude product was filtered through a silica plug with ethyl acetate to yield a pale yellow oil (0.42g, 98%) as \textit{1-butyl-3,3,5-trimethyl-1,3-dihydroindol-2-one 333}. IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ 2927, 1706, 1494, 1192, 803cm$^{-1}$; $^1$H NMR (400MHz, CDCl$_3$) 6.93 (d, $J = 7.0$, 2H, ArCH), 6.65 (d, $J = 212$
Experimental

7.0, 1H, ArCH), 3.59 (t, J = 7.0, 2H, CH₃), 2.24 (s, 3H, ArCH₃), 1.59-1.51 (quin. J = 7.0, 2H, CH₂), 1.29-1.21 (m, 8H, CH₂ + (CH₃)₂), 0.84 (t, J = 7.0, 3H, CH₃). ¹³C NMR (100MHz, CDCl₃, δ) “not observed” (s, C=O), 139.90 (s, C-N), 136.1 (s, C-Me), 131.7 (s, C-C(CH₃)₂), 127.7 (d, ArCH), 123.3 (d, ArCH), 108.0 (d, ArCH), 68.2 (s, C-(CH₃)₂), 39.6 (t, CH₂), 29.5 (t, CH₂), 24.5 (2 x q, C(CH₃)₂), 22.5 (q, ArCH₃), 20.09 (t, CH₂), 14.75 (q, CH₃).

Discernible data for butyl-3,3,6-trimethyl-1,3-dihydroindol-2-one 336

Butyl-m-tolylamine 343

Procedure same as above for 340. Distilled at 114 ºC/10Torr to furnish green mobile oil (3.0g, 20%). ¹H NMR (300MHz, CDCl₃, δ): 7.14-7.06 (m, 1H, ArCH), 6.55 (app. d. J = 7.0, 1H, ArCH), 6.46 (app. d. J = 7.0, 2H, ArCH), 3.56 (bs, 1H, NH), 3.14 (t, J = 7.0, 2H, CH₂), 2.31 (s, 3H, ArCH₃), 1.68-1.59 (m, 2H, CH₃), 1.50-1.40 (m, 2H, CH₂), 1.00 (app. t, J = 7.0, 3H, CH₃).

2-Bromo-N-butyl-2-methyl-N-m-tolyl-propionamide 345

Same procedure as for 341. Flash chromatography (petrol ether: ethyl acetate 6:1) furnished 2-bromo-N-butyl-2-methyl-N-m-tolyl-propionamide 345 as yellow oil (1.65g). ¹H NMR (300MHz, CDCl₃, δ) 7.35-7.13 (m, 4H, ArCH), 3.67 (t, J = 7.5, 2H, CH₃), 2.77 (d, J = 7.0, 3H, ArCH₃), 2.46 (t, J = 7.5, 2H, CH₂), 1.00 (app. t, J = 7.0, 3H, CH₃).
Experimental

2.35 (s, 3H, ArCH₃), 2.00 (s, 6H, C(CH₃)₂), 1.61-1.50 (m, 2H, CH₂), 1.38-1.32 (m, 2H, CH₂), 0.90 (t, J = 7.5, 3H, CH₃).

Butyl-3,3,6-trimethyl-1,3-dihydroindol-2-one 336

AlCl₃ anhydrous reaction

![Butyl-3,3,6-trimethyl-1,3-dihydroindol-2-one](image)

Same procedure as used for 333. Flash chromatography (petrol ether:ethyl acetate 9:1) furnished butyl-3,3,5-trimethyl-1,3-dihydroindol-2-one 336 inseparable mixture as colourless oil (0.02g). ¹H NMR (400MHz, CDCl₃, δ) 7.08 (d, J = 7.5, 1H, ArCH), 6.85 (d, J = 7.5, 1H, ArCH), 6.68 (s, 1H, ArCH), 3.69 (t, J = 7.5, 2H, CH₂), 2.38 (s, 3H, ArCH₃), 1.69-1.60 (m, 2H, CH₂), 1.40-1.30 (m, 8H, CH₂ + (CH₃)₂), 0.94 (t, J = 7.5, 3H, CH₃).

Butyl-3,3,6-trimethyl-1,3-dihydroindol-2-one 336

Copper (I) bromide/TPA reaction

![Butyl-3,3,6-trimethyl-1,3-dihydroindol-2-one](image)

Same procedure as used for 333. Purification from flash chromatography (petrol ether:ethyl acetate 1:6) furnished 336 as a clear liq (0.04g, 10%); IR (neat) ν max 2963, 1713, 1609, 1384, 1117 and 810 cm⁻¹. ¹H NMR (300MHz, CDCl₃, δ) 7.08 (d, J = 7.5, 1H, ArCH), 6.85 (d, J = 7.5, 1H, ArCH), 6.68 (s, 1H, ArCH), 3.69 (t, J = 7.5, 2H, CH₂), 2.38 (s, 3H, ArCH₃), 1.69-1.61 (m, 2H, CH₂), 1.42-1.31 (m, 8H, CH₂ + (CH₃)₂), 0.95 (t, J = 7.5, 3H, CH₃); ¹³C NMR (100MHz, CDCl₃, δ) 182.5 (s, C=O), 142.1 (s, C-N), 214
Experimental

137.6 (s, C-Me), 133.2 (s, C-C(CH₃)₂), 122.7 (d, ArCH), 122.1 (d, ArCH), 109.3 (d, ArCH), 43.9 (s, C-(CH₃)₂), 39.5 (t, CH₂), 31.8 (t, CH₂), 29.6 (t, CH₂), 21.8 (2 x q, C(CH₃)₂), 20.0 (q, ArCH₃), 14.9 (q, CH₃).

*N-Butyl-2,4,6-trimethyl-phenyl-isobutryramide 280f*

![Chemical structure](image)

Purification by column chromatography (petrol ether: ethyl acetate 6:1) furnish *N-butyl-2,4,6-trimethyl-phenyl-isobutryramide 280f* and trace of *N-butyl-2,4,6-trimethyl-benzenesulphonamide 278f* (1.0:0.1) as a colourless oil (0.05g, 10%). IR (CH₂Cl₂) νₘₚₚ: 3316, 2958, 1736, 1521, 1161, 850 cm⁻¹. ¹H NMR (400MHz; CDCl₃, δ) 6.80 (s, 2H, ArCH), 5.28 (s, 1H, NH), 3.18 (q, J = 7.0Hz, 2H, CH₂), 2.35 (s, 6H, 2 x ArCH₃), 2.23 (s, 3H, ArCH₃), 1.62 (s, 6H, (CH₃)₂), 1.46-1.37 (quin., J = 7.0, 2H, CH₂), 1.30-1.21 (sxt, J = 7.0, 2H, CH₂), 0.88 (t, J = 7.0, 3H, CH₃). ¹³C NMR (100MHz, CDCl₃, δ) 180.3 (s, C=O), 138.2 (s, C-C(CH₃)₂), 137.8 (2 x s, C-Me), 135.8 (s, C-Me), 131.9 (d, ArCH), 131.9 (d, ArCH), 49.7 (s, C-(CH₃)₂), 39.8 (t, CH₂), 31.4 (t, CH₂), 30.9 (q, ArCH₃), 28.7 (q, ArCH₃), 23.4 (2 x q, C(CH₃)₂), 20.3 (q, ArCH₃), 20.0 (t, CH₂), 14.7 (q, CH₃).

LRMS (LSIMS-FAB⁺) m/z: 262 (MH⁺ = 100%), 161 (33), 154 (51), 136 (43 ). HRMS (LSIMS-FAB⁺) m/z: calcd for C₁₇H₂₈NO, 262.2171; found, 262.2170.
Experimental

*N-Butyl-2-naphthalen-2-yl-isobutyramide 280g*

Purification by column (petrol ether/ethyl acetate 4:1) furnished *N*-butyl-2-naphthalen-2-yl-isobutyramide 280g as a yellow oil (0.12g, 44%). IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$: 3347, 2960, 2930, 1649, 1527, 748 cm$^{-1}$. $^1$H NMR (300MHz, CDCl$_3$, $\delta$): 7.82 (m, 3H, ArC$_6$H$_3$), 7.41-7.51 (m, 4H, ArC$_6$H$_4$), 5.19 (bs, 1H, NH), 3.15 (q, $J$ = 7.0, 2H, CH$_2$), 1.64 (s, 6H, C(CH$_3$)$_2$), 1.12-1.34 (m, 4H, CH$_2$), 0.83 (t, $J$ = 7.0, 3H, CH$_3$). $^{13}$C NMR (125.8MHz, CDCl$_3$, $\delta$) 177.2 (s, C═O), 142.8 (s, C-C(CH$_3$)$_2$), 133.3 (s, C-C), 132.3 (s, C-C), 129.5 (d, ArCH), 128.5 (d, ArCH), 127.7 (d, ArCH), 126.4 (d, ArCH), 126.1 (d, ArCH), 125.5 (d, ArCH), 124.4 (d, ArCH), 47.2 (s, C-(CH$_3$)$_2$), 39.5 (t, CH$_2$), 31.6 (t, CH$_2$), 27.0 (2 x q, C(CH$_3$)$_2$), 19.9 (t, CH$_3$), 13.6 (q, CH$_3$). LRMS (LSIMS-FAB$^+$) $m/z$: 270 (MH$^+$ = 87%), 219 (65), 169 (73), 154 (93), 133 (100), 129 (52). HRMS (LSIMS-FAB$^+$) $m/z$: (MH$^+$) calcd for C$_{18}$H$_{24}$NO, 270.1858; found, 270.1858.

*N-Butyl-2- (4-methoxy-phenyl)-isobutyramide 280h*

Purification by column (petrol ether/ethyl acetate 4:1), furnished *N*-butyl-2-(4-methoxy-phenyl)-isobutyramide 280h as a transparent crystalline solid (0.02g 9%); IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$: 3349, 2960, 1645, 1511, 1249, 1182, 1017, 839 cm$^{-1}$. $^1$H NMR (300MHz, CDCl$_3$, $\delta$): 7.27 (d.t, $J$ = 9.0 and 3.0, 2H, ArCH), 6.88 (d.t, $J$ = 9.0 and 3.0, 2H, ArCH) 5.13 (bs, 1H, NH), 3.82 (s, 3H, OCH$_3$), 3.15 (q, $J$ = 7.0, 2H, CH$_2$), 1.54 (s, 6H, C(CH$_3$)$_2$), 1.40-
Experimental

1.30 (quin., J = 7.0, 2H, CH₂), 1.27-1.15 (sxt, J = 7.0, 2H, CH₂), 0.87 (t, J = 7.0, 3H, CH₃). ¹³C NMR (75.5MHz, CDCl₃, δ) 177.5 (s, C=O), 158.2 (s, C-OMe), 137.1 (s, C-Me), 127.4 (2 x d, ArCH), 113.7 (2 x d, ArCH), 55.1 (q, OCH₃), 46.1 (s, C-(CH₃)₂), 39.2 (t, CH₂), 31.3 (t, CH₂), 27.0 (2 x q, C(CH₃)₂), 19.7 (t, CH₂), 13.5 (q, CH₃). LRMS (LSIMS-FAB⁺) m/z 250 (MH⁺ = 100), 154 (22), 149 (42), 136 (15). HRMS (LRMS-FAB⁺) m/z: (MH⁺) calcd for C₁₅H₂₄NO₂, 250.1807; found, 250.1811.

Butyl-5-methoxy-3,3-dimethyl-1,3-dihydro-indol-2-one 352

Purification by flash chromatography furnished an inseparable mixture of 1-butyl-5-methoxy-3,3-dimethyl-1,3-dihydro-indol-2-one 352 as the major product (0.006g, 0.7%); IR (CH₂Cl₂) νmax: 2966, 2203, 1712, 1624, 1504, 1384, 750 cm⁻¹. ¹H NMR (400MHz, CDCl₃, δ): 7.00 (app. d, J = 8.0, 1H, ArCH), 6.55 (m, 1H, ArCH), 6.45 (app. d, J = 2.0, 1H, ArCH), 3.81 (s, 3H, OCH₃), 3.68 (t, J = 7.0, 2H, CH₂), 1.70-1.61 (quin., J = 7.0, 2H, CH₂), 1.42-1.31 (m, 8H, CH₂ + (CH₃)₂), 0.94 (t, J = 7.0, 3H, CH₃). ¹³C NMR (100MHz, CDCl₃, δ): 182.1 (s, C=O), 159.8 (s, C-OCH₃), 143.1 (s, C-N-), 128.2 (s, C-C(CH₃)₂), 122.8 (d, ArCH), 105.8 (d, ArCH), 96.7 (d, ArCH), 55.5 (q, OCH₃), 43.7 (s, C(CH₃)₂), 39.6 (t, CH₂), 30.8 (t, CH₂), 24.4 (2 x q, C(CH₃)₂), 20.0 (t, CH₂), 13.50 (q, CH₃). LSRM (LSIMS-FAB⁺) m/z: 248 (MH⁺ = 100%), 232 (25), 176 (25), 154 (78), 136 (67). HRMS (LSIMS-FAB⁺) m/z: calcd for C₁₅H₂₄NO₂, 247.1572; found, 247.1577.
Experimental

\textit{N-Butyl-2-(4-fluorophenyl)-isobutyramide 280b}

Purification by flash chromatography (petrol ether/ethyl acetate 6:1) furnished \textit{N-butyl-2-(4-fluorophenyl)-isobutyramide 280b} as an apple white oil (0.12g, 41%). IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$: 3345, 2960, 1641, 1164, 833 cm$^{-1}$. $^1$H NMR (400MHz, CDCl$_3$, $\delta$): 7.36-7.30 (m, 2H, ArCH), 7.06-7.00 (m, 2H, ArCH), 5.10 (s, 1H, NH), 3.16 (q, $J = 7.0$, 2H, C$_2$H$_2$), 1.55 (s, 6H, C(C$_3$H$_3$)$_2$), 1.40-1.33 (quin., $J = 7.0$, 2H, CH$_2$), 1.27-1.17 (sxt., $J = 7.0$, 2H, CH$_2$), 0.86 (t, $J = 7.0$, 3H, CH$_3$). $^{13}$C NMR (100MHz, CDCl$_3$, $\delta$): 177.0 (s, C=O), 162.8-160.0 (d, $J = 281$, C-F), 141.1 (s, C-C(CH$_3$)$_2$), 128.1 (2 x d, ArCH), 115.5 (2 x d, ArCH), 46.5 (s, C-(CH$_3$)$_2$), 39.5 (t, CH$_2$), 31.5 (t, CH$_2$), 27.2 (2 x q, C(CH$_3$)$_2$), 19.9 (t, CH$_2$), 14.5 (q, CH$_3$). LRMS (LSIMS-FAB$^+$) $m/z$: 238 (MH$^+$ = 100%), 154 (42), 137 (44). HRMS (LSIMS-FAB$^+$) $m/z$: (MH$^+$) calcd for C$_{14}$H$_{21}$FNO, 238.1607; found, 238.1598.

\textit{1-Butyl-(6)-fluoro-3,3-dimethyl-1,3-dihydroindol-2-one 355b}

Purification by flash chromatography (petrol ether/ethyl acetate 10:1) furnished \textit{1-butyl-(6)-fluoro-3,3-dimethyl-1,3-dihydroindol-2-one 355b} as a clear oil (0.16g, 53%). IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$: 3292, 2960, 1667, 1514, 1284, 1127, 812 cm$^{-1}$. $^1$H NMR (400MHz, CDCl$_3$, $\delta$): 7.03 (app q, $J = 8.0$, 1H, ArCH), 6.62 (app. d.t $J = 8.0$ and 2.0, 1H, ArCH),
Experimental

6.50 (app. d.d J = 9.0 and 2.0, 1H, ArCH), 3.60 (t, J = 7.0, 2H, CH₂), 1.61-1.53 (quin. J = 7.0, 2H, CH₂), 1.34-1.24 (m, 8H, C(CH₃)₂), 0.87 (t, J = 7.0, 3H, CH₃). ¹³C NMR (100MHz, CDCl₃, δ): 182.0 (s, C═O), 163.9-161.5 (d, J = 242, C-F), 145.0 (s, C-N-), 131.2 (s, C-C(CH₃)₂), 123.2 (d, ArCH), 108.1 (d, ArCH), 97.1 (d, ArCH), 43.7 (s, C-(CH₃)₂), 39.7 (t, CH₂), 29.4 (t, CH₂), 24.5 (2 x q, C(CH₃)₂), 20.0 (t, CH₂), 13.0 (q, CH₃). LRMS (EI⁺) m/z: 235 (M⁺ = 80%), 192 (55), 164 (100), 148 (20). HRMS (EI⁺) m/z: calcd for C₁₄H₁₈FNO, 235.1372; found, 235.1370.

2-(4-bromo-phenyl)-N-butyli-sobutyramide 280c

Purification by column petrol ether/ethyl acetate (4:1) furnished 2-(4-bromo-phenyl)-N-butyli-sobutyramide 280c (0.41g, 58%) as a clear oil. IR (CH₂Cl₂) νmax: 3357, 2933, 1651, 1519, 1169, 853 cm⁻¹. ¹H NMR (400MHz, CDCl₃, δ): 7.45 (app. d.t, J = 8.5 and 2.0, 2H, ArCH), 7.23 (app. d.t, J = 8.5 and 2.0, 2H, ArCH), 5.16 (bs, 1H, NH), 3.15 (t, J = 7.0, 2H, CH₂), 1.53 (s, 6H, C(C(H₃)₂), 1.40-1.32 (quin., J = 7.0, 2H, CH₂), 1.26-1.19 (app. sxt., J = 7.0, 2H, CH₂), 0.86 (t, J = 7.0, 3H, CH₃). ¹³C NMR (75.5MHz, CDCl₃, δ): 175.7 (s, C═O), 151.1 (s, C-C(CH₃)₂), 132.3 (2 x d, ArCH), 127.1 (2 x d, ArCH), 110.5 (s, C-Br), 47.2 (s, C-(CH₃)₂), 39.5 (t, CH₂), 31.4 (t, CH₂), 26.8 (2 x q, C(CH₃)₂), 20.0 (t, CH₂), 13.5 (q, CH₃). LRMS (EI⁺) m/z: 299 (¹¹²Br-M⁺ = 7%), 297 (¹²⁹Br-M⁺ 8), 218 (69), 199 (¹¹²Br 98), 197 (¹²⁹Br 97), 183 (20), 170 (24), 169 (25), 119 (72). HRMS (EI⁺) m/z: calcd for C₁₄H₂₀¹¹²BrNO₂, 299.0708; found, 299.0710.
Experimental

6-Bromo-1-butyl-3,3-dimethyl-dihydro-indol-2-one 357b

Discernible data for major oxindole:

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{Br} & \quad \\
\end{align*}
\]

Purification by flash chromatography (petrol ether/ethyl acetate (6:1) furnished 6-bromo-1-butyl-3,3-dimethyl-dihydro-indol-2-one 357b as an inseparable clear globular oil (0.035g, 13%); IR (CH\textsubscript{2}Cl\textsubscript{2}) \(\nu\text{max}: 2961, 1712, 1603, 1485, 1360, 1123\) and 808 cm\(^{-1}\).

\(^1\)H NMR (400MHz, CDCl\textsubscript{3}, \(\delta\)):
- 7.19 (d, \(J = 8.0, 1\text{H, ArCH}\)), 7.07 (d, \(J = 8.0, 1\text{H, ArCH}\)), 7.03 (s, 1\text{H, ArCH})), 3.70 (t, \(J = 7.0, 2\text{H, CH}_2\)), 1.70-1.62 (app. quin., \(J = 7.0, 2\text{H, CH}_2\)), 1.43-1.36 (m, 8\text{H (CH}_3\text{)}\textsubscript{2}\) + CH\textsubscript{2}\)), 0.98 (t, \(J = 7.0, 3\text{H CH}_3\)).

\(N\)-Butyl-2- (4-iodo-phenyl)-isobutyramid 280d

Purification by column (petrol ether/ethyl acetate 4:1), furnished 2-(4-iodo-phenyl)-n-butyl-isobutyramid 280d as clear oil (0.16g, 28%). IR (CH\textsubscript{2}Cl\textsubscript{2}) \(\nu\text{max: 3332, 2932, 1718, 1276, 1130, 895 \text{ cm}^{-1}\). \(^1\)H NMR (400MHz, CDCl\textsubscript{3}, \(\delta\)):
- 7.67 (d.t, \(J = 9.0 \text{ and } 3.0, 2\text{H, ArCH}\)), 7.11 (d.t, \(J = 9.0 \text{ and } 3.0, 2\text{H, ArCH}\)), 5.12 (bs, 1\text{H, NH})), 3.16 (q, \(J = 7.0, 2\text{H, CH}_2\)), 1.53 (s, 6\text{H, C(CH}_3\text{)}\textsubscript{2}\)), 1.41-1.38 (quin., \(J = 7.0, 2\text{H, CH}_2\)), 1.27-1.18 (sxt., \(J = 7.0, 2\text{H, CH}_2\)), 0.87 (t, \(J = 7.0, 3\text{H, CH}_3\)). \(^{13}\)C NMR (100MHz, CDCl\textsubscript{3}, \(\delta\)):
- 175.7 (s, C=O), 144.1 (s, C-C(CH\textsubscript{3}\textsubscript{2}\)), 136.7 (2 x d, ArCH), 127.5 (2 x d, ArCH), 91.5 (s, C-I), 45.8 (s, C-(CH\textsubscript{3}\textsubscript{2}\)), 38.6 (t, CH\textsubscript{2}), 30.5 (t, CH\textsubscript{2}), 25.9 (2 x q, C(CH\textsubscript{3}\textsubscript{2}\)), 19.8 (t, CH\textsubscript{2}), 13.5 (q, CH\textsubscript{3}\)). LRMS (LSIMS-FAB\textsuperscript{+}) \(m/z\): 346 (MH\textsuperscript{+} = 100%), 244.96 (20), 136 (15),
Experimental

133 (10). HRMS (LSIMS-FAB⁺) m/z: (MH⁺) Calc for C₁₄H₂₁INO 346.0668, found 346.0738.

**N-Butyl-2- (4-cyano-phenyl)-isobutyramide 280i**

Purification by column (petrol ether/ethyl acetate 4:1) furnished 2-(4-cyano-phenyl)-n-butyl-isobutyramide 280i as translucent spherical film (0.10g, 60%); IR (CH₂Cl₂) νₘₐₓ: 2928, 2867, 1685, 1509, 1205, 804 cm⁻¹. ¹H NMR (400MHz, CDCl₃, δ): 7.56 (d.t, J = 8.5 and 2.0, 2H, ArCH); 7.41 (d.t, J = 8.5 and 2.0, 2H, ArCH), 5.28 (bs, 1H, NH), 3.11 (q, J = 7.0, 2H, CH₂), 1.50 (s, 6H, C(CH₃)₂), 1.37-1.27 (app. quin., J = 7.0, 2H, CH₂), 1.20-1.11 (app. sxt, J = 7.0, 2H, CH₂), 0.80 (t, J = 7.0, 3H, CH₃). ¹³C NMR (100MHz, CDCl₃, δ): 176.6 (s, C=O), 144.5 (s, C-C(CH₃)₂), 131.7 (2 x d, ArCH), 128.2 (2 x d, ArCH), 120.9 (s, C-C≡N), 111.1 (s, C-C≡N) 46.7 (s, C(CH₃)₂), 39.7 (t, CH₂), 31.5 (t, CH₂), 27.0 (2 x q, C(CH₃)₂), 20.0 (t, CH₂), 14.1 (q, CH₃). LRMS (LSIMS-FAB⁺) m/z: 245 (30), 154 (100), 136 (70). HRMS (LSIMS-FAB⁺) m/z: (MH⁺) calcd for C₁₅H₂₁N₂O, 245.1654; found 245.1647.
Experimental

1-Butyl-3,3-dimethyl-2-oxo-2,3-dihydro-1H-indol-6-carbonitrile 360 and 1-butyl-3,3-dimethyl-2-oxo-2,3-dihydro-1H-indole-5-carbonitrile 362

Purification by column (petrol ether/ethyl acetate 4:1), furnished 1-butyl-3,3-dimethyl-2-oxo-2,3-dihydro-1H-indol-6-carbonitrile 360 and 1-butyl-3,3-dimethyl-2-oxo-2,3-dihydro-1H-indole-5-carbonitrile 362 as a yellow translucent oil (0.05g, 30%).

Discernible data for 360: $^1$H NMR (400MHz, CDCl$_3$, $\delta$): 7.59 (app. d, $J = 8.0$, 1H, ArCH), 7.45 (app. s, 1H, ArCH), 6.92 (d, $J = 8.0$, 1H, ArCH), 3.73 (t, $J = 7.5$, 2H, C$_2$H), 1.69-1.61 (app. quin., $J = 7.5$, 2H, CH$_2$), 1.41-1.35 (m, 8H, C$_2$H$_2$ and ((C$_3$H$_3$)$_2$), 0.96 (t, $J = 7.5$, 3H, CH$_3$). $^{13}$C NMR (100MHz, CDCl$_3$, $\delta$): 180.9 ($s$, C═O), 142.9 ($s$, C−N), 133.1 ($d$, ArCH), 136.0 ($s$, C-C(CH$_3$)$_2$), 125.9 ($d$, ArCH), 119.5 ($s$, C≡N), 111.4 ($s$, C−C≡N), 108.7 ($d$, ArCH), 44.0 ($s$, C(CH$_3$)$_2$), 39.8 ($t$, CH$_2$), 29.4 ($t$, CH$_2$), 24.2 (2 x q, C(CH$_3$)$_2$), 20.0 ($t$, CH$_2$), 14.7 ($q$, CH$_3$).

Discernible data for 362: $^1$H NMR (400MHz, CDCl$_3$, $\delta$): 7.39 (app. d, $J = 7.0$, 1H, ArCH), 7.29 (d, $J = 7.0$, 1H, ArCH), 7.08 (s, 1H, ArCH), 3.73 (t, $J = 7.5$, 2H, CH$_2$), 1.69-1.61 (app. quin., $J = 7.5$, 2H, CH$_2$), 1.41-1.35 (m, 8H, CH$_2$ + ((CH$_3$)$_2$), 0.97 (t, $J = 7.5$, 3H, CH$_3$). $^{13}$C NMR (100MHz, CDCl$_3$, $\delta$): 180.4 ($s$, C≡O), 141.2 ($s$, C-N), 136.0 ($s$, C-C(CH$_3$)$_2$), 119.0 ($s$, C≡N), 111.4 ($s$, C-C≡N), 126. 9 ($d$, ArCH), 123.1 ($d$, ArCH), 110.8 ($d$, ArCH), 44.3 ($s$, C(CH$_3$)$_2$), 39.8 ($t$, CH$_2$), 29.3 ($t$, CH$_2$), 24.1 (2 x q, C(CH$_3$)$_2$), 20.0 ($t$, CH$_2$), 14.7 ($q$, CH$_3$). LRMS (El$^+$) 360 and 362 242 (M = 81%), 204 (27), 199 (71), 186 (34), 171 (100), 155 (26), 141 (96), 121 (18). HRMS (LSIMS-FAB$^+$) 362
Experimental

calcld for C_{15}H_{18}N_{2}O, 242.1419; found, 242.1423. Data for \textbf{360/362}. Elemental Analysis (WAS) Calcld for C_{15}H_{18}N_{2}O: C, 74.3; H, 7.5; N, 11.5; S, 10.5. Found C, 74.1; H, 7.8; N, 11.0; S, 0.35%.

\textit{N-Butyl-2-(4-nitro-phenyl)-isobutyramide 280j}

Purification by column (petrol ether/ethyl acetate 4:1), furnished \textit{2-(4-nitro-phenyl)-n-butyl-isobutyramide 280j} as a yellow oil (0.14g, 43%). IR (CH_{2}Cl_{2}) \nu_{\text{max}}: 3346, 2961, 1648, 1600, 1518, 1466, 1344, 1279, 855 cm^{-1}. \textsuperscript{1}H NMR (300MHz, CDCl_{3}, \delta): 8.17 (d.t, J = 7.0 and 2.0, 2H, ArCH), 7.54 (d.t, J = 7.0 and 2.0, 2H, ArCH), 5.40 (bs, 1H, NH), 3.20 (q, J = 7.0, 2H, CH_{2}), 1.61 (s, 6H, C(CH_{3})_{2}), 1.47-1.37 (quin., J = 7.0, 2H, CH_{2}), 1.16-1.31 (sxt, J = 7.0, 2H, CH_{2}), 0.88 (t, J = 7.0, 3H, CH_{3}). \textsuperscript{13}C NMR (75.5MHz, CDCl_{3}, \delta): 175.2 (s, C═O), 152.8 (s, C-NO_{2}), 146.5 (s, C-C(CH_{3})_{2}), 127.0 (2 x d, ArCH), 123.5 (2 x d, ArCH), 47.1 (s, C(CH_{3})_{2}), 39.4 (t, CH_{2}), 31.3 (t, CH_{2}), 26.7 (2 x q, C(CH_{3})_{2}), 19.7 (t, CH_{2}), 13.5 (q, CH_{3}). LRMS (El\textsuperscript{+}) m/z: 266 (MH\textsuperscript{2+} = 31%), 265 (MH\textsuperscript{+} = 37), 206 (31), 204 (36), 165 (100), 149 (52), 135 (36). HRMS (LSIMS-FAB\textsuperscript{+}) m/z: (MH\textsuperscript{+}) calcld for C_{14}H_{21}N_{2}O, 265.1552, found 265.1561.
Experimental

1-Butyl-3,3-dimethyl-6-nitro-1,3-dihydroindol-2-one 361, 2-butyl-4,4-dimethyl-6-nitro-1,1-dioxo-1,4-dihydro-2H-1λ6-benzo[e][1,2]-thiazin-3-one 366

Purification by flash chromatography (petrol ether/ethyl acetate 6:1) furnished as an inseparable mixture tentatively assigned as for butyl-4,4-dimethyl-(6)-nitro-1,1-dioxo-1,4-dihydro-2H-1λ6-benzo[e][1,2]-thiazin-3-one 366 and 1-butyl-3,3-dimethyl-6-nitro-1,3-dihydroindol-2-one 361 as a golden yellow viscous oil (0.31g, 26%). Found by elemental analysis to be C_{14}H_{18}N_{2}O_{5} and C_{14}H_{19}N_{2}O_{3} [3:1].

**Data** for 2-butyl-4,4-dimethyl-6-nitro-1,1-dioxo-1,4-dihydro-2H-1λ6-benzo[e][1,2]-thiazin-3-one 366. IR (CH_{2}Cl_{2}) mixture ν_{max}: 2960, 2361, 1722, 1527, 1385, 1269, 1124, 1070, 885 cm^{-1}. 1H NMR (300MHz, CDCl_{3}, δ): 7.95 (app. d, J = 8.0, 1H, ArCH), 7.64 (app. s, 1H, ArCH), 7.31 (d, J = 8.0, 1H, ArCH), 7.35 (t, J = 7.0, 2H, CH_{2}), 1.71-1.61 (m, 2H, CH_{2}), 1.43-1.30 (m, 8H, CH_{2} + (CH_{3})_{2}), 0.95 (t, J = 7.0, 3H, CH_{3}). 13C NMR (75.5MHz, CDCl_{3}, δ) 179.5 (s, C=O), 166.0 (s, C-NO_{2}), 142.0 (s, C-SO_{2}-), 130.5 (s, C-\text{C(CH}_{3})_{2}), 124.1 (d, ArCH), 117.4 (d, ArCH), 102.16 (d, ArCH), 43.3 (s, C(CH_{3})_{2}), 38.9 (t, CH_{2}), 28.4 (t, CH_{2}), 23.1 (2 x q, C(CH_{3})_{2}), 19.5 (t, CH_{2}), 13.7 (q, CH_{3}). LRMS (El^+) m/z: data for 409 (M^+ + ^{81}BrH = 64%), 327 (MH^+ = 80), 285 (35), 241 (17), 215 (33), 206 (83), 186 (100), 121 (75).

**Data** for 1-butyl-3,3-dimethyl-6-nitro-1,3-dihydro-indol-2-one 361

1H NMR (300MHz, CDCl_{3}, δ): 8.23 (app. d, J = 8.5, 1H, ArCH), 8.08 (app. s, 1H, ArCH), 6.90 (d, J = 8.5, 1H, ArCH), 3.76 (t, J = 7.0, 2H, CH_{2}), 1.73-1.63 (m, 2H, CH_{2}),
Experimental

1.45-1.35 (m, 8H, CH$_2$ + ((CH$_3$)$_2$), 0.81 (t, $J = 7.0$, 3H, CH$_3$). $^{13}$C NMR (75.5MHz, CDCl$_3$, $\delta$): 181.0 (s, C=O), 166.0 (s, C-NO$_2$), 142.0 (s, C-N-), 130.5 (s, C-(C(CH$_3$)$_2$), 124.1 (d, ArCH), 117.4 (d, ArCH), 106.8 (d, ArCH), 43.3 (s, C(CH$_3$)$_2$), 39.0 (t, CH$_2$), 28.7 (t, CH$_2$), 23.1 (2 x q, C(CH$_3$)$_2$), 19.5 (t, CH$_2$), 13.7 (q, CH$_3$). $m/z$ 264 (M$^+$ = 40% ), 154 (100), 137 (65). HRMS (LSIMS-FAB$^+$) $m/z$: (MH$^+$) Calcd for 263.1396, C$_{14}$H$_{19}$N$_2$O$_3$; Found, 263.1399. Elemental Analysis (WAS): C, 55.7; H, 7.7; N, 6.6; S, 6.3 requires C, 51.5; H, 5.6; N 8.5; S, 9.82. S analysis for 366 (67%) S = 6.6. HRMS (LSIMS) $m/z$: (M$^+$-SO$_2$) calcd for C$_{14}$H$_{18}$N$_2$O$_5$S, 263.1396; found, 263.1399.

$N$-Butyl-(4-nitrobenzene)-sulphonamide 283j$^{280}$

\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{S} \\
\text{O} & \quad \text{N} \\
\text{H} & \quad \text{CH}_3 \quad \text{CH}_2 \\
\end{align*}
\]

Purification by flash chromatography (petrol ether/ethyl acetate 6:1) from radical reaction furnished $N$-butyl-(4-nitrobenzene)-sulphonamide as a pale yellow crystalline solid 283j. $^1$H NMR (300MHz, CDCl$_3$, $\delta$): 8.34 (app. d, $J = 9.0$, 2H, ArCH), 8.06 (app d, $J = 9.0$, 2H, ArCH), 4.96 (bs, 1H, NH), 3.03 (app. q, $J = 7.0$, 2H, CH$_2$), 1.52-1.43 (app. quin., $J = 7.0$, 2H, CH$_2$), 1.37-1.25 (app. sxt, $J = 7.0$, 2H, CH$_2$), 0.83 (t, $J = 7.0$, 3H, CH$_3$).
Experimental

_N-Butyl-2-(4-trifluoromethylphenyl)isobutyramide 280k_

Discernible data:

![Chemical Structure](image)

Purification by column (petrol ether/ethyl acetate 4:1) furnished _2-(4-trifluoromethyl-phenyl)-n-butyl-isobutyramide 280k_ as transparent spherical crystals (0.02g 9%). IR (CDCl₃) νₘₐₓ: 3332, 2962, 1643, 1328, 1125 and 840 cm⁻¹. ¹H NMR (400MHz, CDCl₃, δ): 7.60 (d, J = 8.0, 2H, ArCH), 7.48 (d, J = 8.0, 2H, ArCH), 5.16 (bs, 1H, NH), 3.18 (q, J = 7.0, 2H, CH₂), 1.58 (s, 6H, C(C₃H₇)₂), 1.43-1.35 (app. quin., J = 7.0, 2H, CH₂), 1.28-1.18 (app. sxt, J = 7.0, 2H, CH₂), 0.87 (t, J = 7.0, 3H, CH₃); ¹³C NMR (100MHz, CDCl₃, δ) 176.6 (s, C=O), 149.9 (s, C-C(CH₃)₂), 129.9-129.4 (s, J = 44, C(CF₃), 126.7 (2 x d, ArCH), 125.6 (2 x d, ArCH), 125.3-122.5 (s, J = 277, C(CF₃), 47.1 (s, C(CH₃)₂), 39.6 (t, CH₂), 31.5 (t, CH₂), 27.0 (2 x q, C(CH₃)₂), 20.0 (t, CH₂), 14.7 (q, CH₃). (LSIMS) m/z: 273 (M⁺ = 6%), 154 (100), 136 (70), 120 (14).

_N-Butyl-2-(3,5-bis-trifluoromethyl-phenyl)-isobutyramide 280l_

Purification by column chromatography furnished _N-butyl-2-(3,5-bis-trifluoromethyl-phenyl)-isobutyramide 280l_. As a clear crystalline solid (0.01g, 26%). IR (CH₂Cl₂) νₘₐₓ: 3301, 2933, 1644, 1281, 1130, 896 cm⁻¹. ¹H NMR (400MHz, CDCl₃, δ): 7.81 (s, 2H, ArCH), 7.79 (s, 1H, ArCH), 5.42 (bs, 1H, NH), 3.23 (q, J = 7.0, 2H, CH₂), 1.62 (s, 6H,
Experimental

(CH₃)₂, 1.46-1.39 (app. quin., J = 7.0, 2H, CH₂), 1.29-1.20 (app. sxt, J = 7.0, 2H, CH₂), 0.88 (t, J = 7.0, 3H, CH₃). ¹³C NMR (125MHz, CDCl₃, δ): 175.1 (s, C=O), 148.3 (s, C-C(CH₃)₂), 132.0-131.8 (2 x s, J = 33.1, C(CF₃), 126.5 (2 x d, ArCH), 124.3-122.2 (2 x d, J = 271.5, C(CF₃), 121.0 (d, ArCH), 47.1 (s, C(CH₃)₂), 39.7 (t, CH₂), 31.5 (t, CH₂), 27.0 (2 x q, (CH₃)₂), 20.0 (t, CH₂), 13.6 (q, CH₃). LRMS (LSIMS-FAB⁺) m/z: 355 (M⁺ = 10%), 220 (15), 154 (15), 147 (100), 136 (30) HRMS (LSIMS-FAB⁺) m/z: (MH⁺) calcd for C₁₆H₂₀F₆NO, 356.1449; found 356.1463.

8.0 Synthesis of cyclised and rearranged amides from radical precursors 369

8.1 General method for copper-mediated radical reactions

To a stirred solution of the radical precursor 369 (1.0 eq.) in dichloromethane (DCM) was added of tris-[(2-pyridyl)methyl]-amine (1.1 eq.) 279 and copper bromide (1.1 eq.). The reaction was stirred under nitrogen at 37 °C, and monitored by TLC until the disappearance of starting material. Filtering the crude product through a silica plug with ethyl acetate quenched the reaction mixture. The solvent was evaporated in vacuo to yield an emerald green crude product. Purification by flash chromatography led to an isolation of both the cyclised and rearranged products. Reactions done in toluene were performed under inert atmosphere at reflux temperature unless otherwise stated.
Experimental

Authentic synthesis of N-ethyl-2-tolyl-isobutyramide 370a

General method: To a single-necked RB flask was added the gem-acid chloride 351 (0.02g) in diethyl ether (2 mL). Ethylamine 373a (0.01g, 3.0 eq.) was added dropwise, and a turbid solution was observed. The reaction mixture was stirred for 48h. The reaction was quenched with water (3 x 5 mL) followed by diethyl ether (5 x 5 mL). The organic layer was dried over anhydrous magnesium sulfate, and the solvent removed in-vacuo to furnish a yellow viscous solid (0.012g) as N-ethyl-2-p-tolyl-isobutyramide 370a. IR (CH₂Cl₂) νₑₓₘₐₓ: 3370, 2971, 1706, 1513, 1130, 820 cm⁻¹. ¹H NMR (400MHz, CDCl₃, δ): 7.24 (d, J = 8.0, 2H, ArCH), 7.16 (d, J = 8.0, 2H, ArCH), 5.14 (bs, 1H, NH), 3.20 (quin., J = 7.0, 2H, CH), 2.34 (s, 3H, ArCH₃), 1.54 (s, 6H, (CH₃)₂), 1.02 (t, J = 7.0, 3H, CH₃). ¹³C NMR (100MHz, CDCl₃, δ) 177.6 (s, C═O), 142.3 (s, C-Me), 136.6 (s, C-C(CH₃)₂), 129.4 (2 x d, ArCH), 126.4 (2 x d, ArCH), 46.6 (s, C-C(CH₃)₂), 34.6 (t, CH₂), 27.2 (2 x q, C(CH₃)₂), 21.0 (q, ArCH₃), 13.0 (q, CH₃). LRMS (LSIMS-FAB⁺) m/z: 206 (M⁺ = 57%), 204 (100), 154 (87), 136 (62), 124 (10). HRMS (LSIMS-FAB⁺) m/z: (MH⁺) calcd for C₁₃H₂₀NO, 206.1545; found, 206.1552.
Experimental

1-Ethyl-3,3,5-trimethyl-1,3-dihydro-indol-2-one 372a, N-ethyl-2-p-tolyl-isobutyramide 370a

Purification by flash chromatography (petrol ether/ethyl acetate 6:1) furnished an inseparable mixture (3:1) of 1-ethyl-3,3,5-trimethyl-1,3-dihydro-indol-2-one 372a and N-ethyl-2-p-tolyl-isobutyramide 370a as a yellow oil (0.57g). Data for 372a. IR (CH₂Cl₂) ν_max: 2968, 1646, 1515, 1462, 1352, 1169, 819 cm⁻¹.¹H NMR (400MHz, CDCl₃, δ): 6.97 (d, J = 7.0, 1H, ArC_H), 6.74 (d, J = 7.0, 1H, ArC_H), 6.60 (s, 1H, ArC_H), 3.63 (q, J = 7.0, 2H, C_H₂), 2.28 (s, 3H, ArC_H₃), 1.21 (s, 6H, (C_H₃)₂), 1.15 (t, J = 7.0, 3H, C_H₃).¹³C NMR (100MHz, CDCl₃, δ): 181.2 (s, C═O), 141.7 (s, C-N-), 136.4 (s, C-Me), 133.0 (s, C-(CH₃)₂), 122.7 (d, ArCH), 122.2 (d, ArCH), 109.1 (d, ArCH), 43.8 (s, C-(CH₃)₂), 41.9 (t, CH), 24.4 (2 x q, CH₃), 21.0 (q, ArCH₃), 13.5 (q, CH₃). LRMS (LSIMS-FAB⁺) m/z: 270 (M⁺ + SO₂) 206 (M⁺ - SO₂ = 57%), 188 (15), 154 (86), 139 (55), 133 (35).

Data for N-ethyl-2-p-tolyl-isobutyramide 370a. IR (CH₂Cl₂) ν_max: 3370, 2971, 1706, 1513, 1130, 820 cm⁻¹.¹H NMR (400MHz, CDCl₃, δ): 7.14 (d, J = 8.0, 2H, ArCH), 7.04 (d, J = 8.0, 2H, ArCH), 5.23 (bs, 1H, NH), 3.09 (quin., J = 7.0, 2H, CH), 2.23 (s, 3H, ArCH₃), 1.44 (s, 6H, (CH₃)₂), 1.13 (t, J = 7.0, 3H, CH₃).¹³C NMR (100MHz, CDCl₃, δ): 177.8 (s, C═O), 143.3 (s, C-Me), 136.1 (s, C-(CH₃)₂), 129.3 (2 x d, ArCH), 126.3 (2 x d, ArCH), 47.2 (s, C-(CH₃)₂), 34.6 (t, CH), 27.1 (2 x q, C(CH₃)₂), 21.8 (q, ArCH₃), 13.3 (q, CH₃). LRMS (LSIMS-FAB⁺) m/z: 203 (M⁺ = 30%), 154 (100), 136 (70), 120
Experimental

(10). HRMS (LSIMS) m/z: for 370a (MH⁺) calcd for C₁₃H₂₀NO 206.1545; found, 206.1552.

**N-Propyl-2-p-tolyl-isobutyramide 370b**

\[ \text{\( \text{H}_3\text{C} - \text{CH_2} - \text{CH}_2 - \text{C}_6\text{H}_4\text{CH}_3\)} \]

Data for \text{N-propyl-2-p-tolyl-isobutyramide 370b} furnished as a partially separated mixture with \text{3,3,5-trimethyl-1-propyl-1,3-dihydroindol-2-one 372b} (4:1) as a colourless oil, 0.13 g. Data for 370b. IR (CH₂Cl₂) νmax: 3351, 2924, 2360, 1644, 1512 and 816 cm⁻¹.

$^1$H NMR (300MHz, CDCl₃, δ) 7.25 (d, J = 8.0, 2H, ArCH), 7.15 (d, J = 8.0, 2H, ArCH), 5.20 (bs, 1H, NH), 3.11 (q, J = 7.0, 2H, CH₂), 2.38 (s, 3H, ArCH₃), 1.55 (s, 6H, (CH₃)₂), 1.44-1.36 (quin., J = 7.0, 2H, CH₂), 0.81 (t, J = 7.0, 3H, CH₃). $^{13}$C NMR (125MHz, CDCl₃, δ) 178.0 (s, C═O), 142.7 (s, C-Me), 137.0 (s, C-C(CH₃)₂), 129.7 (2 x d, ArCH), 126.8 (2 x d, ArCH), 47.1 (s, C-(CH₃)₂), 41.7 (t, CH₃), 28.4 (2 x q, C(CH₃)₂), 23.1 (t, CH₂), 21.3 (q, ArCH₃), 11.6 (q, CH₃); LRMS (LSIMS) m/z 220 (MH⁺ = 15%), 154 (100), 138 (38), 137 (64), 136 (70), 120 (15); HRMS (LSIMS) m/z: (MH⁺) calcd for C₁₄H₂₂NO; 220.1701, found, 220.1708.

**3,3,5-Trimethyl-1-propyl-1,3-dihydroindol-2-one 372b**

\[ \text{\( \text{H}_3\text{C} - \text{N} - \text{C}_6\text{H}_4\text{CH}_3\)} \]

Purification by flash chromatography furnished \text{3,3,5-trimethyl-1-propyl-1,3-dihydroindol-2-one 372b} and a minor tentatively assigned reduced product 375b (7:1) as a mixture (yellow oil, 0.19 g); Data for 372b IR (CH₂Cl₂) νmax: 2966, 1720, 1618, 1457,
Experimental

1384, 1360, 1131, 810 cm\(^{-1}\); \(^1\)H NMR (400MHz, CDCl\(_3\), \(\delta\)) 7.08 (d, \(J = 7.5\), 1H, ArCH), 6.85 (d, \(J = 7.5\), 1H, ArCH), 6.68 (s, 1H, ArCH), 3.66 (t, \(J = 7.0\), 2H, CH\(_2\)), 2.38 (s, 3H, ArCH\(_3\)), 1.76-1.66 (sxt, \(J = 7.0\), 2H, CH\(_2\)), 1.34 (s, 6H, CH\(_3\)\(_2\)), 0.95 (t, \(J = 7.0\), 3H, CH\(_3\)); \(^{13}\)C NMR (100MHz, CDCl\(_3\), \(\delta\)) 182.0 (s, C═O), 142.2 (s, C-N-), 137.6 (s, C-Me), 133.1 (s, C-C(CH\(_3\))\(_2\)), 122.6 (d, ArCH), 122.1 (d, ArCH), 109.2 (d, ArCH), 48.2 (s, C(CH\(_3\))\(_2\)), 41.3 (t, CH\(_2\)), 24.6 (2 x q, C(CH\(_3\))\(_2\)), 21.8 (q, ArCH\(_3\)), 20.5 (t, CH\(_2\)), 11.0 (q, CH\(_3\)). LRMS (LSIMS-FAB\(^+\)) \(m/z\) 218 (MH\(^+\) = 100%), 217 (M\(^+\) = 75), 154 (55), 149 (78), 136 (45). HRMS (LSIMS-FAB\(^+\)) \(m/z\): (MH\(^+\)) calcd. for C\(_{14}\)H\(_{19}\)NO\(_2\), 218.1467, found 217.1472.

\(N\)-Pentyl-2-p-tolyl-isobutramide 370c

Discernible data:

\[
\begin{align*}
&\text{Discernible data:} \\
&\text{Purification from flash chromatography (petrol ether/ethyl acetate 6:1) furnished } N- \text{penta}y-2-p-tolyl-isobutramide 370c \text{ as a colourless globular film (0.14g, 57%). IR (neat)} \\
&\nu_{\text{max}}: 3354, 2928, 1620, 1513, 1161 \text{ and } 816 \text{ cm}^{-1}. \quad \text{\(^1\)H NMR (400MHz, CDCl\(_3\), \(\delta\)) 7.25} \\
&(d, \(J = 8.0\), 2H, ArCH), 7.15 (d, \(J = 8.0\), 2H, ArCH), 5.20 (bs, 1H, NH), 3.13 (q, \(J = 7.0\), 2H, CH\(_2\)), 2.34 (s, 3H, ArCH\(_3\)), 1.54 (s, 6H, (CH\(_3\))\(_2\)), 1.40-1.33 (app. quin., \(J = 7.0\), 2H, CH\(_2\)), 1.28-1.22 (app. sxt, \(J = 7.0\), 2H, CH\(_2\)), 1.19-1.13 (app. quin., \(J = 7.0\), 2H, CH\(_2\)), 0.84 (t, \(J = 7.0\), 3H, CH\(_3\)). \quad \text{\(^{13}\)C NMR (100MHz, CDCl\(_3\), \(\delta\)) 177.6 (s, C=O), 142.3 (s, C-Me), 136.5 (s, C-C(CH\(_3\))\(_2\)), 129.4 (2 x d, ArCH), 126.4 (2 x d, ArCH), 46.6 (s, C(CH\(_3\))\(_2\)), 39.6 (t, CH\(_2\)), 29.1 (t, CH\(_2\)), 28.9 (t, CH\(_2\)), 27.1 (2 x q, C(CH\(_3\))\(_2\)), 22.3 (t, CH\(_2\)), 20.9 (q, ArCH\(_3\)), 14.7 (q, CH\(_3\)).
\end{align*}
\]
**Experimental**

*N*-Hexyl-2-<i>p</i>-tolyl-isobutyramide 370d

![Chemical Structure](image)

Data for *N*-hexyl-2-<i>p</i>-tolyl-isobutyramide 370d as a colourless oil (0.14g, 57%). IR (neat) *ν*\(_{\text{max}}\): 3344, 2926, 1620, 1513 and 815 cm\(^{-1}\). \(^{1}\)H NMR (400MHz, CDCl\(_3\), \(\delta\)) 7.25 (d, \(J = 8.0\), 2H, ArCH), 7.15 (d, \(J = 8.0\), 2H, ArCH), 5.19 (bs, 1H, NH), 3.13 (q, \(J = 7.0\), 2H, CH\(_2\)), 2.34 (s, 3H, ArCH\(_3\)), 1.54 (s, 6H, (CH\(_3\))\(_2\)), 1.39-1.32 (app. quin., \(J = 7.0\), 2H, CH\(_2\)), 1.28-1.14 (m, 6H, 3 x CH\(_2\)), 0.85 (t, \(J = 7.0\), 3H, ArCH\(_3\)). \(^{13}\)C NMR (100MHz, CDCl\(_3\), \(\delta\)) 177.5 (s, C═O), 142.3 (s, C-Me), 136.5 (s, C-C(CH\(_3\))\(_2\)), 129.3 (2 x d, ArCH), 126.3 (2 x d, ArCH), 46.6 (s, C(CH\(_3\))\(_2\)), 39.7 (t, CH\(_2\)), 31.4 (t, CH\(_2\)), 29.4 (t, CH\(_2\)), 27.1 (2 x q, C(CH\(_3\))\(_2\)), 26.4 (t, CH\(_2\)), 22.5 (t, CH\(_2\)), 20.9 (q, CH\(_3\)), 14.0 (q, CH\(_3\)). LRMS (LSIMS-FAB\(^{+}\)) \(m/z\) 262 (MH\(^{+}\) = 100%), 154 (18), 136 (10), 134 (18), 133 (60). HRMS (LSIMS-FAB\(^{+}\)) \(m/z\) (MH\(^{+}\)) calcd for C\(_{17}\)H\(_{28}\)NO; 262.2171, found 262.2161.

**Authentic synthesis of *N*-hexyl-2-<i>p</i>-tolyl-isobutyramide 370d**

![Chemical Structure](image)

General method: To a single-necked RB flask was added the acid chloride 351 (0.02g) in diethyl ether (2 mL). Hexylamine (0.01g, 3.0 eq.) 374d was added dropwise, and a turbid solution was observed. The reaction mixture was stirred for 48h. The reaction was quenched with water (3 x 5 mL) followed by diethyl ether (5 x 5 mL). The organic layer was dried over anhydrous magnesium sulfate, and the solvent removed in-vacuo to
Experimental

furnish a yellow viscous solid (0.015g) as \( N\)-hexyl-2-p-tolyl-isobutyramide 370d; \(^1\)H NMR (400MHz, CDCl\(_3\), \( \delta \)) 7.25 (d, \( J = 8.0\), 2H, ArCH), 7.15 (d, \( J = 8.0\), 2H, ArCH), 5.12 (bs, 1H, NH), 3.13 (q, \( J = 7.0\)Hz, 2H, CH\(_2\)), 2.34 (s, 3H, ArCH\(_3\)), 1.55 (s, 6H, 2 x CH\(_3\)), 1.39-1.30 (quin., \( J = 7.0\)Hz, 2H, CH\(_2\)), 1.26-1.15 (m, 6H, 3 x CH\(_2\)), 0.85 (t, \( J = 7.0\)Hz, 3H, CH\(_3\)); \(^{13}\)C NMR (100MHz, CDCl\(_3\), \( \delta \)) 177.5 (s, C═O), 142.3 (s, C-Me), 136.6 (s, C-C(CH\(_3\))\(_2\)), 129.6 (2 x d, ArCH), 126.4 (2 x d, ArCH), 46.7 (s, C(CH\(_3\))\(_2\)), 39.4 (t, CH\(_2\)), 31.4 (t, CH\(_2\)), 29.4 (t, CH\(_2\)), 27.1 (2 x q, C(CH\(_3\))\(_2\)), 26.4 (t, CH\(_2\)), 22.5 (t, CH\(_2\)), 21.0 (q, CH\(_3\)), 14.8 (q, CH\(_3\)); LRMS (LSIMS-FAB\(^+\)) \( m/z \): 262 (MH\(^+\)= 20%), 155 (100), 137 (72). HRMS (LSIMS) \( m/z \): (MH\(^+\)) calcd for C\(_{17}\)H\(_{28}\)NO; 262.2171, found, 262.2161.

\[ \text{1-Hexyl-3,3,5-trimethyl-1,3-dihydroindole-2-one 372d} \]

Purification by flash chromatography furnished \( 1\)-hexyl-3,3,5-trimethyl-1,3-dihydroindole-2-one 372d as a colourless oil (8%); IR (CH\(_2\)Cl\(_2\)) \( \nu_{\text{max}} \): 2928, 1720, 1620, 1458, 1384, 1132 and 809 cm\(^{-1}\). \(^1\)H-NMR (400MHz, CDCl\(_3\), \( \delta \)) 7.08 (d, \( J = 7.0\), 1H, ArCH), 6.85 (d, \( J = 7.0\), 1H, ArCH), 6.67 (s, 1H, ArCH), 3.68 (t, \( J = 7.0\), 2H, CH\(_2\)), 2.38 (s, 3H, ArCH\(_3\)), 1.68-1.64 (m, 2H, CH\(_2\)), 1.37-1.21 (m, 12H, 3 x CH\(_2\)) and 2 x CH\(_3\)), 0.87 (t, \( J = 7.0\), 3H, CH\(_3\)). \(^{13}\)C NMR (100MHz, CDCl\(_3\), \( \delta \)) 182.0 (s, C═O), 142.2 (s, C-N-), 137.6 (s, C-Me), 133.2 (s, C-C(CH\(_3\))\(_2\)), 122.6 (d, ArCH), 122.1 (d, ArCH), 109.2 (d, ArCH), 43.8 (s, C(CH\(_3\))\(_2\)), 39.8 (t, CH\(_2\)), 31.5 (t, CH\(_2\)), 27.4 (t, CH\(_2\)), 24.5 (2 x q, C(CH\(_3\))\(_2\)), 22.6 (t, CH), 21.8 (q, CH\(_3\)), 22.5 (t, CH\(_2\)), 14.7 (q, CH\(_3\)). LRMS (LSIMS-
Experimental

FAB\(^{+}\) m/z 260 (MH\(^{+}\) = 100%), 259 (M = 75), 160 (20), 154 (35), 136 (25). HRMS (LSIMS-FAB\(^{+}\)) m/z: calcd 259.1936 for C\(_{17}\)H\(_{25}\)NO, found 259.1933.

\(N\)-Dodecyl-2-p-tolyl-isobutyramide 370e

\[
\text{HN} \quad \text{O}
\]

Data for \(N\)-dodecyl-2-p-tolyl-isobutyramide 370 as colourless globular oil (0.55g, 79%).

IR (neat) \(\nu_{\max}\): 3351, 2900, 1644, 1514, 1465 and 816 cm\(^{-1}\). \(^1\)H NMR (400MHz, CDCl\(_3\), \(\delta\)) 7.24 (d.t, \(J = 8.0\) and \(2.0\), 2H, ArCH), 7.14 (d, \(J = 8.0\), 2H, ArCH), 5.20 (s, 1H, NH), 3.13 (t, \(J = 7.0\), 2H, CH\(_2\)), 2.03 (s, 3H, ArCH\(_3\)), 1.54 (s, 6H, (CH\(_3\))\(_2\)), 1.39-1.12 (m, 20H, 10 x CH\(_2\)), 0.90-0.82 (m, 3H, CH\(_3\)). \(^13\)C NMR (100MHz, CDCl\(_3\), \(\delta\)) 172.3 (s, C═O), 144.6 (s, C-Me), 140.9 (s, C-C(CH\(_3\))\(_2\)), 129.5 (2 x d, ArCH), 122.6 (2 x d, ArCH), 43.8 (s, C-(CH\(_3\))\(_2\)), 39.7 (t, CH\(_2\)), 31.9 (t, CH\(_2\)), 29.6 (t, CH\(_2\)), 29.5 (t, CH\(_2\)), 29.3 (t, CH\(_2\)), 27.3 (2 x t, CH\(_2\)), 27.0 (t, CH\(_2\)), 24.9 (2 x q, C(CH\(_3\))\(_2\)), 23.0 (t, CH\(_2\)), 22.5 (q, ArCH\(_3\)), 14.7 (q, CH\(_3\)). LRMS (LSIMS-FAB\(^{+}\)) m/z 346 (MH\(^{+}\) = 100%), 344 (10), 226 (10), 136 (10), 133 (92), 119 (12). HRMS (LSIMS-FAB\(^{+}\)) m/z: (MH\(^{+}\)) calcd. for C\(_{23}\)H\(_{40}\)NO; 346.3110, found 346.3104.
**Experimental**

**Authentic synthesis of N-isobutyl-2-p-tolyl-isobutyramide**

![Chemical structure](image)

General method: To a single-necked RB flask was added the acid chloride 351 (0.02g) in diethyl ether (2 mL). Iso-butylamine 374g (0.01g, 3.0 eq.) was added dropwise, and a turbid solution was observed. The reaction mixture was stirred for 48h. The reaction was quenched with water (3 x 5 mL) followed by diethyl ether (5 x 5 mL). The organic layer was dried over anhydrous magnesium sulfate, and the solvent removed in vacuo to furnish a yellow viscous solid (0.016g) as N-isobutyl-2-p-tolyl-isobutyramide 370g.  

$^1$H NMR (400MHz, CDCl$_3$, $\delta$) 7.19 (d,t, $J = 8.0$ and $3.0$, 2H, ArCH), 7.09 (d, $J = 8.0$, 2H, ArCH), 5.10 (bs, 1H, NH), 2.90 (t, $J = 7.0$, 2H, CH$_2$), 2.27 (s, 3H, ArCH$_3$), 1.61-1.52 (spt., $J = 7.0$, 1H, CH), 1.48 (s, 6H, (CH$_3$)$_2$), 0.70 (d, $J = 7.0$, 6H, (CH$_3$)$_2$); $^{13}$C NMR (100MHz, CDCl$_3$, $\delta$) 177.9 (s, C═O), 142.5 (s, C-Me), 136.9 (s, C-C(CH$_3$)$_2$), 129.9 (2 x d, ArCH), 126.7 (2 x d, ArCH), “not observed” (C(CH$_3$)$_2$), 47.2 (t, CH$_2$), 28.7 (s, CH), 27.4 (2 x q, C(CH$_3$)$_2$), 20.2 (q, ArCH$_3$), 19.5 (2 x q, CH$_3$); LRMS (LSIMS-FAB$^+$) m/z 233 (M$^+$ = 100%), 154 (100), 137 (74), 120 (12); HRMS (LSIMS-FAB$^+$) Calc for 234.1858 (MH$^+$) calc for C$_{15}$H$_{23}$NO Found 234.1858.

**9.0 Synthesis of radical precursors 396, 407, 408, 406 and 413**

**9.1 N-butyllithium method:**

To a stirred solution of N-alkyl-4-methylbenzenesulfonamide 284e (1.0 eq.) in dry dichloromethane was added n-butyllithium (1.1M) (1.0 eq.) and acid halide (1.0 eq/ at -78 °C (dry ice/acetone) overnight. The reaction was quenched with saturated ammonium
Experimental

chloride (10 mL), and the product extracted with dichloromethane (200 mL), followed by saturated sodium bicarbonate (200 mL). The aqueous phase was washed with dichloromethane (2 x 200 mL) and the combined organic fractions were washed with saturated sodium chloride. The organic phase was dried with magnesium sulfate, and the solvent evaporated in-vacuo to yield a crude product. Purification of the crude product (petrol ether/ EtOAc) gave the radical precursor.

\[
N\text{-Ethyl-4-methyl-N-trichloromethylbenzenesulfonamide 396}
\]

Flash chromatography (6:1 petrol ether/ethyl acetate) furnished \(N\text{-ethyl-4-methyl-N-trichloromethylbenzenesulfonamide 396}\) as a white crystallised solid (2.5g, 84%).

\(^1\)H NMR (400MHz, CDCl\(_3\), \(\delta\)) 7.91 (d.t, \(J = 8.0\) and 2.0, 2H, ArCH), 7.33 (d, \(J = 8.0\), 2H, ArCH), 4.33 (q, \(J = 7.0\), 2H, CH\(_2\)), 2.45 (s, 3H, ArCH\(_3\)), 1.55 (t, \(J = 7.0\), 3H, CH\(_3\)).

\(^{13}\)C NMR (100MHz, CDCl\(_3\), \(\delta\)) 158.8 (s, C═O), 145.6 (s, C-Me), 134.9 (s, C-SO\(_2\)-), 129.5 (2 x d, ArCH), 129.1 (2 x d, ArCH), 92.5 (s, CCl\(_3\)) 44.8 (t, CH\(_2\)), 21.7 (q, ArCH\(_3\)), 15.5 (q, CH\(_3\)); LRMS (LSIMS-FAB\(^+\)) \(m/\ell\) 343 (M\(^+\) = 10%), 155 (100), 137 (72), 136 (66), 120 (13). HRMS (LSIMS-FAB\(^+\)) \(m/\ell\): (M\(^+\)) calcd for C\(_{11}\)H\(_{12}\)Cl\(_3\)NO\(_3\)S; 343.9681, found 343.9671.
Experimental

\(N\)-Butyl-2,2,2-trichloro-\(N\)-tolyl-acetamide 407

Discernible data:

\[
\begin{align*}
N & \quad O \\
\text{Cl} & \quad \text{Cl} \\
\text{Cl} & \quad \text{O} \\
\end{align*}
\]

Flash chromatography (6:1 petrol ether/ethyl acetate) furnished \(N\)-butyl-2,2,2-trichloro-\(N\)-tolyl-acetamide 407 as a dark yellow oil (1.56g, 82%). \(^1\)H NMR (300MHz, CDCl\(_3\), \(\delta\)) 7.12 (s, 4H, ArCH), 3.67 (bs, 2H, CH\(_2\)), 2.31 (s, 3H, ArCH\(_3\)), 1.57-1.46 (quin. \(J = 7.0\), 2H, CH\(_2\)), 1.31-1.17 (sxt, \(J = 7.0\), 2H, CH\(_2\)), 0.83 (t, \(J = 7.0\), 3H, CH\(_3\)). LRMS (LSIMS-FAB\(^+\)) \(m/z\) 310 (\(^{81}\)Br MH\(^+\) = 39%), 308 (\(^{79}\)Br MH\(^+\) = 49%), 155 (26), 155 (100), 139 (13), 138 (30), 137 (63), 136 (70), 120 (10). HRMS (LSIMS-FAB\(^+\)) \(m/z\): (MH\(^+\)) calcd for \(C_{13}H_{17}Cl_3NO\) 308.0376, found 308.0363.

\(2\)-Bromo-\(N\)-butyl-\(N\)-\(p\)-tolyl-acetamide 408

\[
\begin{align*}
H & \quad \text{Br} \\
\text{H} & \quad \text{N} \\
\text{O} & \quad \text{C} \\
\end{align*}
\]

Flash chromatography (6:1 petrol ether:EtOAc) furnished 2-bromo-\(N\)-butyl-\(N\)-\(p\)-tolyl-acetamide 408 as a yellow oil (3.08g, 31%). \(^1\)H NMR (300MHz, CDCl\(_3\), \(\delta\)) 7.15 (d, \(J = 8.0\), 2H, ArCH), 7.05 (d.t, \(J = 8.0\) and 2.0, 2H, ArCH), 3.59 (t, \(J = 7.0\), 2H, CH\(_2\)), 3.53 (s, 2H, CH\(_2\)), 2.30 (s, 3H, ArCH\(_3\)), 1.45-1.35 (quin., \(J = 7.0\), 2H, CH\(_2\)), 1.28-1.15 (sxt., \(J = 7.0\), 2H, CH\(_2\)), 0.79 (t, \(J = 7.0\), 3H, CH\(_3\)). \(^{13}\)C NMR (100MHz, CDCl\(_3\), \(\delta\)) 165.9 (s, C=O), 138.6 (s, C-N-), 138.3 (s, C-Me, 130.2 (2 x d, ArCH), 127.5 (2 x d, ArCH), 51.5
Experimental

(t, CH₂), 29.2 (t, CH₂), 27.3 (t, CH₂), 20.8 (q, ArCH₃), 19.6 (t, CH₂), 13.5 (q, CH₃). m/z (LSIMS) 286 (²¹Br MH⁺ = 98%), 284 (²⁹Br MH⁺ = 100), 204 (24), 154 (54), 136 (41), 120 (26). HRMS (LSIMS) m/z: (MH⁺) calcd for C₁₃H₁₀BrNO, 284.0650; found 284.0652.

N-Butyl-2,2-dichloro-N-p-tolyl acetamide 406 and 2,2-dichloro-N-p-tolyl-acetamide 413

Purification by flash chromatography (6:1 petrol ether:ethyl acetate) furnished N-butyl-2,2-dichloro-N-p-tolyl acetamide 409 as a yellow oil (0.78g, 46%); IR ν max (neat) 2960, 1728, 1385, 1269, 1124, 1070 and 744 cm⁻¹. ¹H NMR (400MHz, CDCl₃, δ) 7.28 (d, J = 8.0, 2H, ArCH), 7.12 (app. d, J = 8.0, 2H, ArCH), 5.83 (s, 1H, CH), 3.70 (app. t, J = 7.0, 2H, CH₂), 2.42 (s, 3H, ArCH₃), 1.56-1.49 (app. quin., J = 7.0, 2H, CH₂), 1.38-1.26 (app. sxt., J = 7.0, 2H, CH₂), 0.90 (t, J = 7.0, 3H, ArCH₃). ¹³C NMR (100MHz, CDCl₃, δ) 164.0 (s, C=O), 139.4 (s, C-N-), 137.5 (s, C-Me), 130.8 (2 x d, ArCH), 127.7 (2 x d, ArCH), 64.0 (d, CH), 50.3 (t, CH₂), 29.3 (t, CH₂), 21.1 (q, ArCH₃), 20.0 (t, CH₂), 19.5 (q, CH₃). LRMS (EI) m/z: 274 (M⁺ = 15%), 134 (100), 106 (80).

Purification by flash chromatography (6:1 petrol ether:ethyl acetate) furnished 2,2-dichloro-N-p-tolyl-acetamide 413 as a yellow-orange viscous solid (0.04g, 3%); IR ν max (neat) 2961, 1707, 1645, 1508, 1229, 1164 and 833 cm⁻¹. ¹H NMR (400MHz, CDCl₃, δ) 8.24 (s, 1H, NH), 7.45 (app. d, J = 8.0, 2H, ArCH), 7.17 (d, J = 8.0, 2H, ArCH), 6.08 (s, 1H, CH), 2.34 (s, 3H, ArCH₃). ¹³C NMR (100MHz, CDCl₃, δ) 161.1 (s, C=O), 135.0 (s,
Experimental

C-N), 133.9 (s, C-Me), 129.7 (2 x d, ArCH), 120.3 (2 x d, ArCH), 67.0 (d, CH), 21.0 (q, ArCH). LRMS (EI) m/z: 217 (M+ = 70), 202 (12), 146 (15), 134 (100), 106 (78).

5.10 General reactions

*N-Butyl-N-(2-methylacryloyl)-benzenesulfonamide 286a*

![Chemical Structure](image)

To a stirred solution of N-butyl benzenesulfonamide 283a (0.21g, 0.97 mmol) in anhydrous dichloromethane (DCM) (10 mL) was added via syringe methacryloyl chloride 285 0.09 mL, 0.94 mmol) followed by triethylamine (TEA) (0.13 mL, 0.94%). The solution became turbid and was stirred at room temperature under nitrogen for 3h. The crude mixture was quenched with water (50 mL) followed by extraction of the product with diethyl ether (3 x 50 mL). The organic layer was dried over anhydrous magnesium sulfate and the solvent removed in-vacuo, to furnish a yellow oil. Purification via flash chromatography (petrol ether:ethyl acetate 6:1) furnished *N-butyl-N-(2-methylacryloyl)-benzenesulfonamide 286a* as a colourless oil (0.08g, 79%).

IR (neat) νmax 2959, 1686, 1353, 1168, 1026 and 686 cm⁻¹. ¹H NMR (300MHz, CDCl₃, δ) 7.89 (d, J = 7.0, 2H, ArCH), 7.61 (app. t, J = 7.0, 1H, ArCH), 7.52 (t, J = 7.0, 2H, ArCH), 5.26 (brs, 1H, C=CH₂), 5.09 (s, 1H, C=CHH), 3.74 (t, J = 7.0, 2H, CH₂), 1.92 (s, 3H, CH₃), 1.69-1.59 (quin. J = 7.0, 2H, CH₂), 1.36-1.24 (sxt., J = 7.0, 2H, CH₂), 0.90 (t, J = 7.0, 3H, CH₃). ¹³C NMR (100MHz, CDCl₃, δ) 172.7 (s, C=O), 141.2 (s, C-SO₂⁻), 139.8 (s, C=CH₂), 134.0 (d, ArCH), 129.3 (2 x d, ArCH), 128.5 (2 x d, ArCH), 119.5 (t, C=CH₂), 47.7 (t, CH₂), 32.2 (t, CH₂), 20.3 (t, CH₂), 20.0 (q, ArCH₃), 14.0 (q,
Experimental

CH$_3$). LRMS (LSIMS) $m/z$: 282 (MH$^+$ = 100%), 165 (12), 154 (91), 136 (100), 115 (20).

HRMS (LSIMS-FAB$^-$) $m/z$: (MH$^-$) calcd for C$_{14}$H$_{20}$NO$_3$S; 282.1164, found 282.1166.

**Tris-(2-pyridylmethyl)-amine$^{162}$ 279**

![Tris-(2-pyridylmethyl)-amine](image)

To a three necked RB flask was added 2-picolyol chloride HCl (38.97g, 234 mmol, 2.0 eq.) and 2-picolylamine (12.98g, 12.37 mL, 117 mmol, 1.0 eq.), the reaction mixture became a turbid dark red solution and slightly exothermic. To the mixture was added sodium hydroxide (10 M, 24g, 60 mL water) at a rate of one drop per minute. The reaction was stirred magnetically for 2 hr at room temperature. The crude product was extracted with chloroform (3 x 150 mL), and the organic phase was dried over anhydrous sodium sulfate. The solvent was removed in-vacuo to furnish dark red oil (35.71g). To the crude product was added hot diethyl ether, the resulting blood red solution was decanted leaving a black viscous oil residue. The solvent was removed in-vacuo to furnish a bright orange red crystalline solid (32.02g). Recrystallisation with hot diethyl ether and rapid cooling lead to beautiful golden crystals tris-(2-pyridylmethyl)-amine 279 (12.68g, 71%). IR (neat) $\nu_{max}$: 2823, 1589, 1433, 1366, 1147 and 766 cm$^{-1}$.

$^1$H NMR (300MHz, CDCl$_3$, $\delta$) 8.54 (s, 3H, ArH), 7.68-7.57 (m, 6H, ArH), 7.15 (m, 3H, ArH), 3.89 (s, 6H, (CH$_3$)$_2$). $^{13}$C NMR (100MHz, CDCl$_3$, $\delta$) 159.4 (3 x s, C-py), 149.1 (3 x d, ArCH), 136.4 (3 x d, ArCH), 123.0 (3 x d, ArCH), 122.0 (3 x d, ArCH), 60.1 (3 x d, ArCH).
Experimental

t, CH₂); LRMS (EI⁺) m/z: 291 (MH⁺ = 100%), 198 (100%), HRMS (EI⁺) Calc. 290.1531
for C₁₈H₁₈N Found 290.1525.
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APPENDICES

PROTON NMR SPECTRA
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