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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

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0.2	**List of Abbreviations**
[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 = **C**H)
dd	Doublet of doublets
dt	Doublet of triplets
DCE	Dichloroethane
DCM	Dichloromethane
DEPT	Distortionless Enhancement through Polarization Transfer
DLP	Dilauroyl peroxide

DPDC	Di-isopropyl peroxydicarbonate
dr	Diasteroisomeric 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

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 = **C**H_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
Sxt.	Sextet
t	Triplet
t	Triplet (in ^{13}C NMR- a methylene carbon = **C**H_2)
t.t	triplet of triplets

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

I would like to express my thanks to my Supervisor Dr Andrew Clark, for giving me this excellent opportunity to pursue this major part of my career, in addition all advice and help is appreciated. In particular, I would like to express my sincere gratitude to the EPSRC for their financial support, without whose help; this PhD would not have been possible. I would also like to express my thanks to Dr Paul Taylor and Professor Martin Wills for their advice during the first and second year viva-voca examinations. I also acknowledge the technical team at Warwick University, MEDEC from Exeter for the CHN/ sulfur analysis, and especially to Peter from the glassblowers for all his help.

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For recreation, there was the Art Centre and Xananas- Most of my mates went to Xananas, and I found it a good place to chill out. To the Language Society and especially the truly wonderful people I met at Mass in the Chaplaincy on Sundays. My favorite place was Leamington, and I enjoyed living there from 2004-2006. I am very happy to have met some genuinely nice people-all the Greeks for your hospitality.

I am very grateful to Professor Martin Wills and Professor Keith Jones for their advice during the PhD Viva. Since resubmitting the Thesis, I would like to express my thanks to the many organizations that have made pursuing my research possible. The Royal Society of Chemistry Library, the Imperial College Library and the British Library, and

librarians who have been helpful. I would like to express my sincere gratitude to Dr John Storey and Dr Andrew Clark for proofreading the revised Thesis.

This PhD would not be complete without mentioning all those who have helped me in the past. I would like to express my thanks especially to Lloyd Vidale who first taught me Chemistry and encouraged me to go to University. At Kingston, I would like to express my thanks to Dr Cooper who was my Industrial Supervisor in 1998. To Dr Buckley-Dhoot for all her help and especially to Dr John Storey who was my third year supervisor. In addition, special thanks to Dr Klaus Jürgen Pees and Pieter Liers at Schwabenheim. I dedicate this work to my parents, brother and sister and my nieces. Also to all who have given me, support to be here.

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

LITERATURE REVIEW

Chapter One

1.0 Introduction to radical chemistry

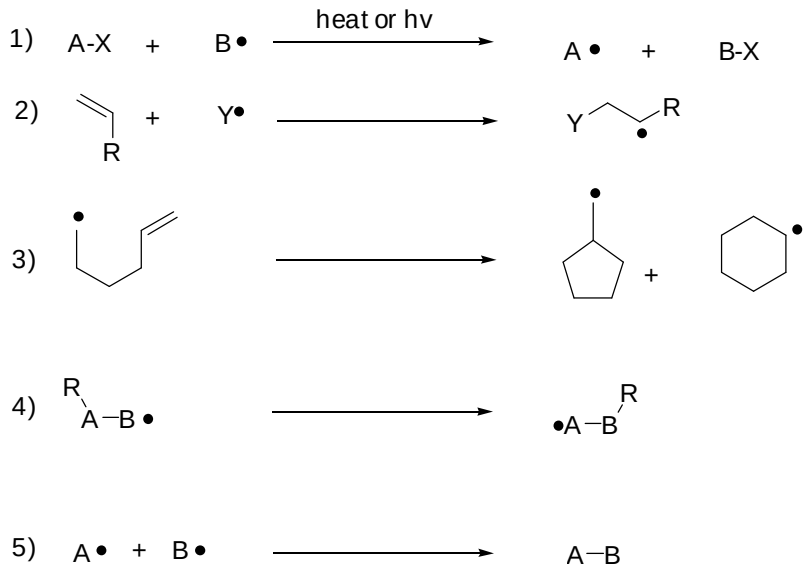
Radicals are defined as chemical species that contain one or more unpaired electrons. Amongst the several types of radicals known to the chemist, it is the carbon-centred radical, which has received the most attention. This has been particularly the case in reactions involving the formation of new C—C 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. $\bullet CH_3$) are trigonal planar in structure (similar to carbocations), although some exceptions are possible. When hydrogen atoms on a methyl radical are replaced by an σ-attractor, π-donor component or group (halogen, OH, NH_2) this leads to pyramidalization of the radical. In the case of $\bullet CF_3$, 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. *1*)[10] intermolecular addition (eq. *2*)[11] intramolecular addition (eq. *3*)[12] rearrangement (eq. *4*)[13] and radical-radical reaction (eq. 5)[14] as outlined in **Scheme 1**.

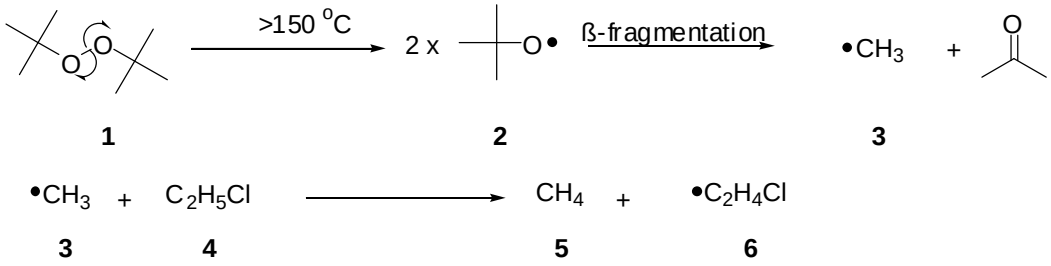
Chapter One



Scheme 1 Possible radical reactions

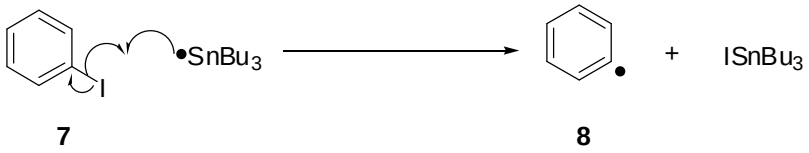
1.2 Radical abstraction reactions

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[15] investigated the abstraction of halogen atoms by methyl radicals. Thermal homolytic dissociation of di-*tert*-butylperoxide **1** gives two molecules of *tert*-butyl peroxide radical **2**.[16] The *tert*-butyl peroxide radical **2** formed can then undergo a β-fragmentation to give a methyl radical **3** and acetone. A high temperature (>150ºC) is required to produce the methyl radical **3**, since the activation energy is between 6-8 kcal/mol higher for β-fragmentation than that of hydrogen abstraction by *tert*-butyl peroxide radical **2**. Reaction of a methyl radical **3** and ethyl chloride **4** yield both methane **5** and the 1-chloroethyl radical **6** as shown in **Scheme 2**.



Scheme 2 Hydrogen atom abstraction by methyl radical[15]

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,[9] PhSe,[17] Barton esters[18] and xanthates[19] (which are popular ways to achieve de-oxygenation of alcohols).[20] Abstraction of atoms other than hydrogen (e.g. halogens) have also been reported.[21] In this case tributyltin radical abstracts an iodine atom from iodobenzene **7** to give an aryl radical **8** and tributyltin iodide as depicted in **Scheme 3**.



Scheme 3 Halogen abstraction from an aromatic ring

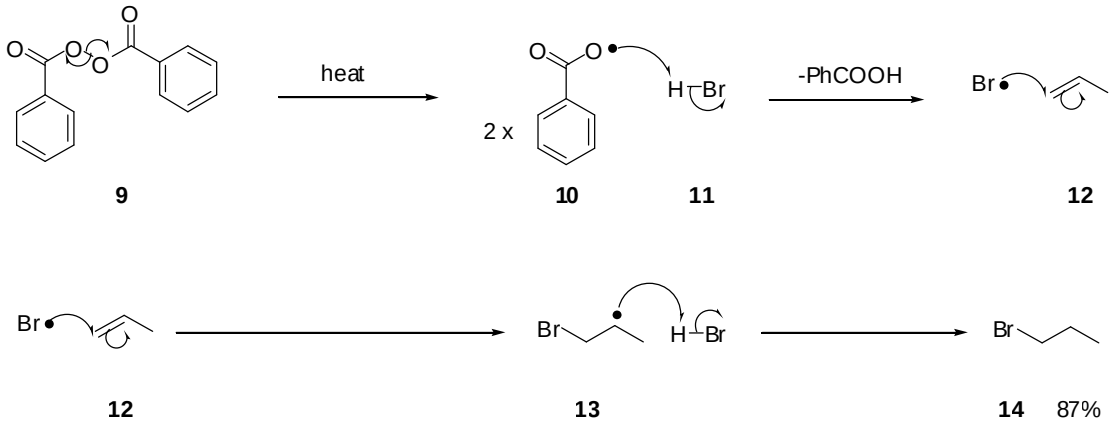
1.3 Radical addition reactions

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[22] on the addition of hydrogen bromide **11** to propylene **12** were studied. Homolytic dissociation of di-benzoyl peroxide **9** at room temperature gave two molecules of benzoyl peroxide radical **10**. In the presence of a benzoyl peroxide radical **10**, rapid abstraction of the hydrogen

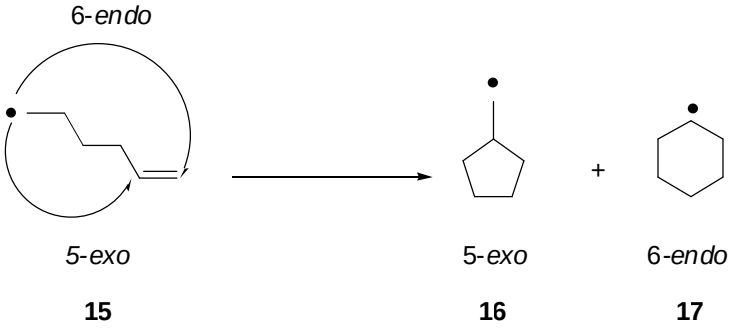
atom from hydrogen bromide **11** led to the bromine radical, which could then add to propylene **12**. This was followed by formation of a secondary alkyl radical intermediate **13**, which underwent hydrogen atom transfer to furnish the anti-Markovikov product 1-bromopropane **14** in 87% at room temperature, 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[22]

1.4 Intramolecular addition reactions (cyclisations)[23-26]

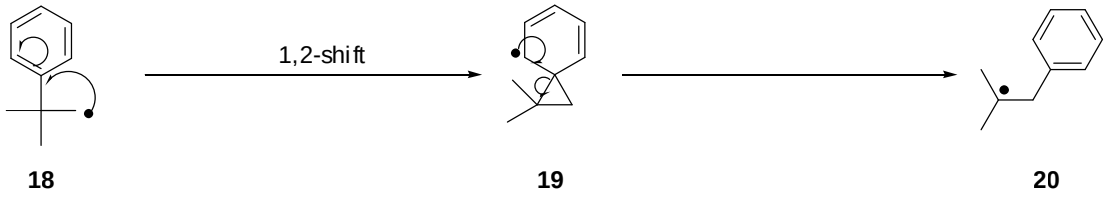
With the exception of radical polymerisation reactions, intramolecular radical reactions have probably received the most attention. Baldwin's rules[27] generally govern the regiochemical outcomes of these cyclisations, hence, the 5-hexenyl radical **15** preferentially cyclises to give the 5-*exo* product **16** *via* a chair-like transition state.[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[29] and aromatics are also possible (see **Section 2.0**).



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 [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** .

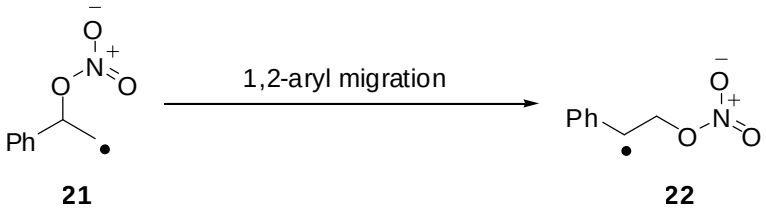


Scheme 6 Possible radical rearrangement reaction

1.5.1 Group transfer reactions

Urry and Kharasch explored neophyl rearrangements in 1944.[31] These are 1,2-migrations[32] typified by the reaction shown in **Scheme 7**. Groups that undergo this type of migration include nitrates[33] **22**, phosphate,[34] ester[35] and sulfonate derivatives.[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

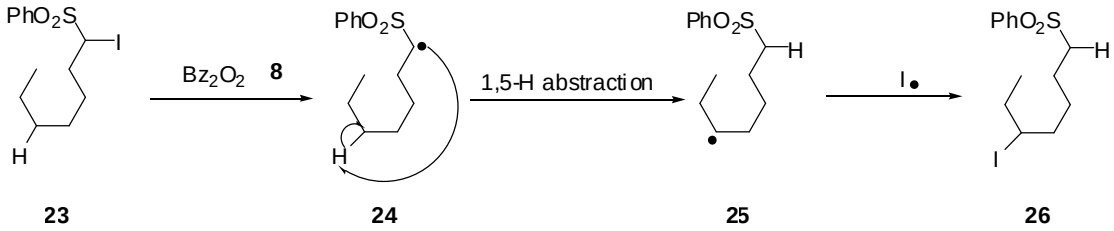
Scheme 7. O-Neophyl rearrangement of 1,1-diarylalkoxyl radicals have also been reported.[36] These sorts of migration can also occur *in vivo*, normally mediated by vitamin B_{12} and cobalt dependent enzymes.[37]



Scheme 7 An 1,2-aryl migration

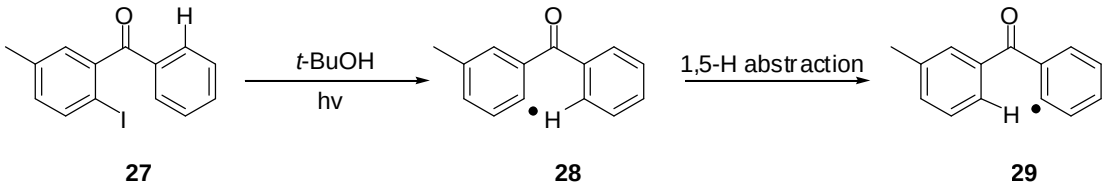
1.5.2 Hydrogen abstraction reaction

Other rearrangement can occur *via* hydrogen abstractions. A range of H-abstraction reactions have been reported (eg. 1,2-;[38] 1,4-;[38] 1,5-;[39] 1,6-,[40] 1,7-;)[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.[39]



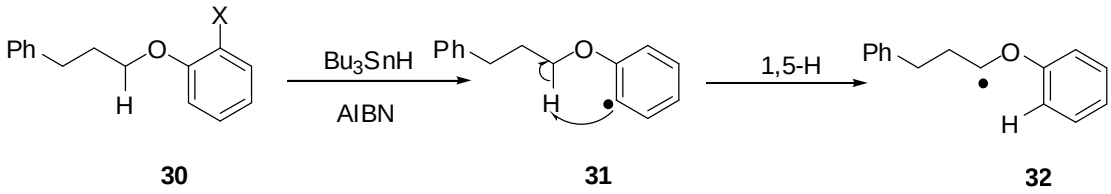
Scheme 8 An 1,5-H abstraction from alkyl iodide

Hydrogen abstractions can also occur from aromatics.[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**.



Scheme 9 An 1,5-H abstraction from an iodo aromatic compound[42]

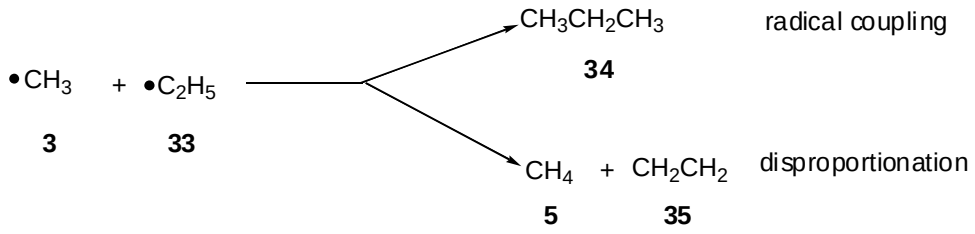
In another example, Curran[43] has treated an *ortho*-halo-aromatic **30** (**Scheme 10**) with tributyltin hydride/AIBN to form the aryl radical intermediate **31**, which underwent an 1,5-H atom abstraction to furnish the alkyl radical intermediate **32**.



Scheme 10 An 1,5-H abstraction from an aryl radical to form an alkyl radical

1.6 Radical-radical reactions[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 **3** and ethyl radical **33** re-combine to give the radical coupled product propane **34** or through disproportionation to furnish methane **5** and ethylene **35** as depicted in **Scheme 11** When two of the same radical fragments re-combine, this is called dimerisation. A classic example is the Kolbe[44] aniodic oxidation of carboxylic acid salts.

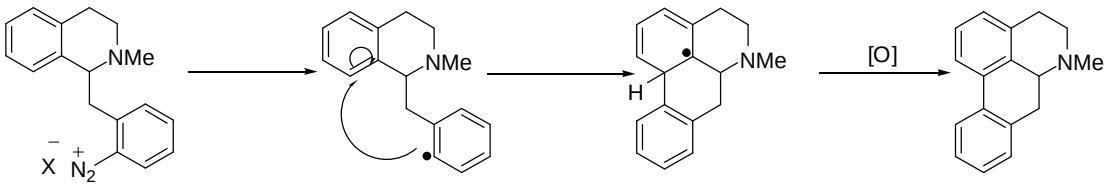


Scheme 11 Possible radical coupling and disproportionation reaction

Chapter One

2.0 Aromatic radical reactions-Addition to aromatic ring.

Intermolecular addition onto an aromatic ring[45-47] can go through three possible mechanistic pathways. These include; (1) aromatic nucleophilic substitution[45]-an attack by a nucleophile (Nu^-), giving an anionic σ-complex, and loss of an anion; (2) aromatic electrophilic substitution[46]-an attack by an electrophile (E^+), giving a cationic σ-complex, and loss of a cation; and (3) aromatic homolytic substitution[47]-an attack by a radical ($R^\bullet$), giving a radical σ-complex and loss of a leaving group (which is normally hydrogen, $H^\bullet$). An early example of an intramolecular homolytic aromatic substitution involves the Pschorr reaction[48-50] as illustrated in **Scheme 12**. In this example, the radical precursor **36** when treated with copper (I) chloride furnished the aryl radical **37** through loss of nitrogen gas. This aryl radical can then add into the aromatic ring to give the cyclohexadienyl radical intermediate **38** followed by re-aromatisation to the tetracyclic product **39**.



36 **37** **38** **39**

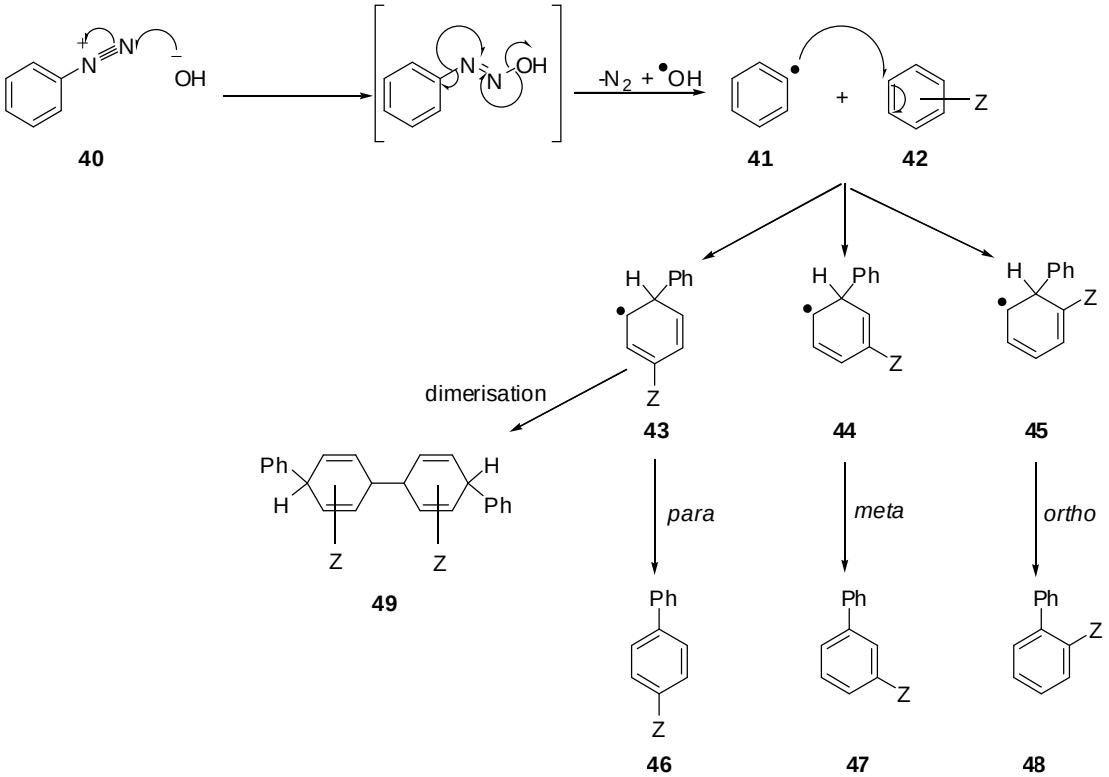
Scheme 12 The Pschorr reaction (1900)[50]

2.1 Introduction[51-55]

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.

2.2 Mechanistic aspects of aromatic homolytic substitution reactions

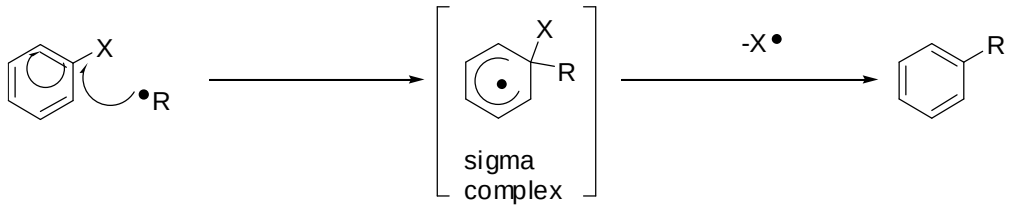
Historically, homolytic aromatic substitutions have resulted in poor yields and product mixtures. A prime example of this is the Gomberg reaction,[56] that not only gives every possible regioisomer, but also radical-radical coupling by-products as shown in **Scheme 13**. In this example, the aryl diazonium salt **40** when treated with a base ($^{-}$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**.



Scheme 13 The Gomberg reaction

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• 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_3SnH 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.[47] The intermolecular reaction proceeds *via* a sigma (σ) complex intermediate **50** as illustrated in **Scheme 14**, followed by extraction of the leaving group and re-aromatisation.[57] The mechanism for the re-aromatisation will depend upon the reaction conditions employed, and the leaving group X.



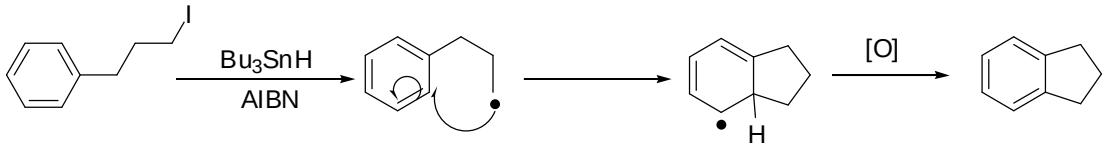
50

Scheme 14 Homolytic aromatic substitution-mechanistic outline

Intermolecular addition reactions of the type outline in **Scheme 14** have been previously investigated. Traynham[58] has conducted mechanistic studies on the effects of substituents on the aromatic ring (*ipso* substitution).

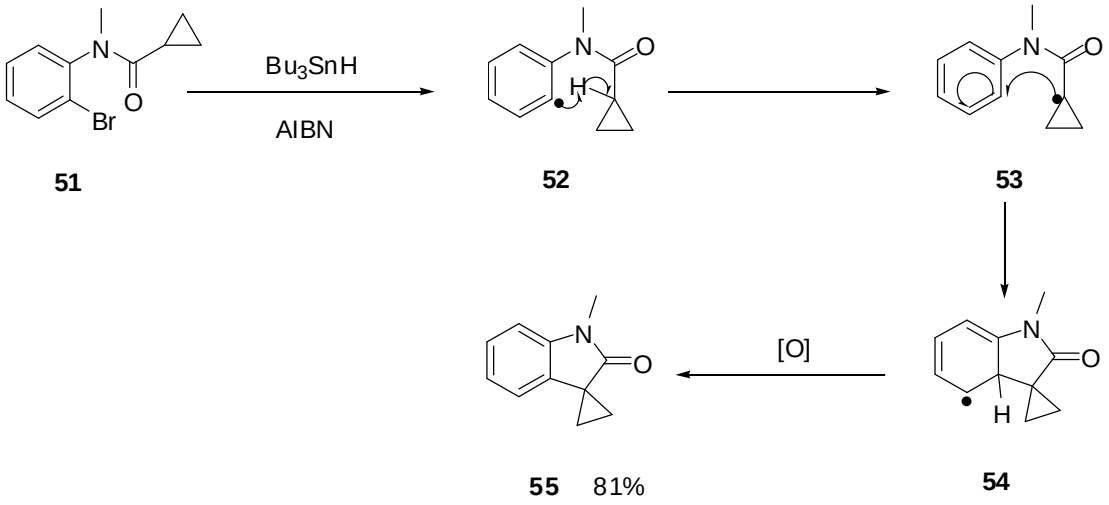
2.3 Alkyl radical cyclisation onto aromatics

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.



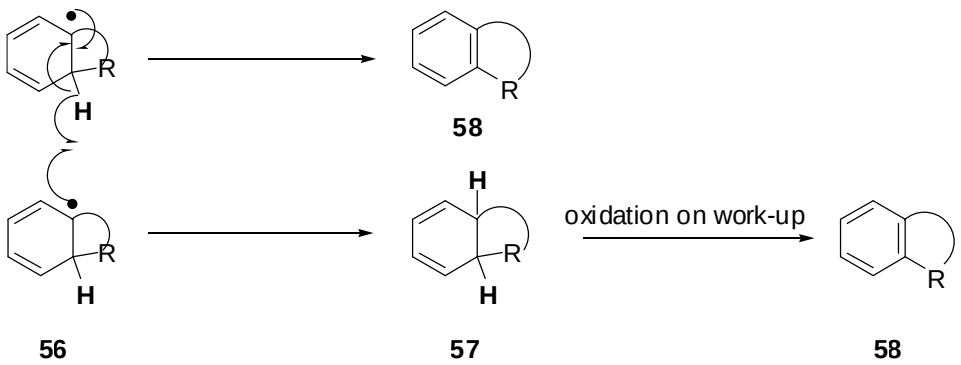
Scheme 15 General mechanism for intramolecular cyclisation

The uses of aryl halides[59-60] as substrates to initiate cyclisations onto monoaromatics have also been investigated. Beckwith and Storey[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**.



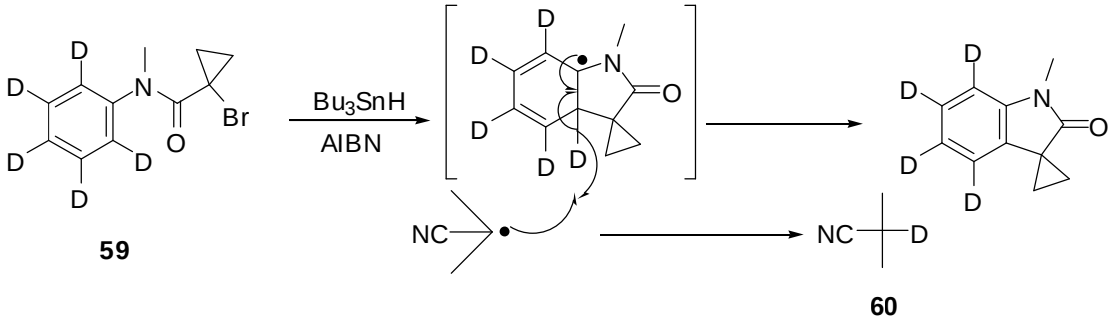
Scheme 16 Synthesis of a spirocyclic oxindole[60]

Three possible mechanisms for re-aromatisation have been postulated; (1) oxidation of **54** by AIBN as mentioned by Curran.[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

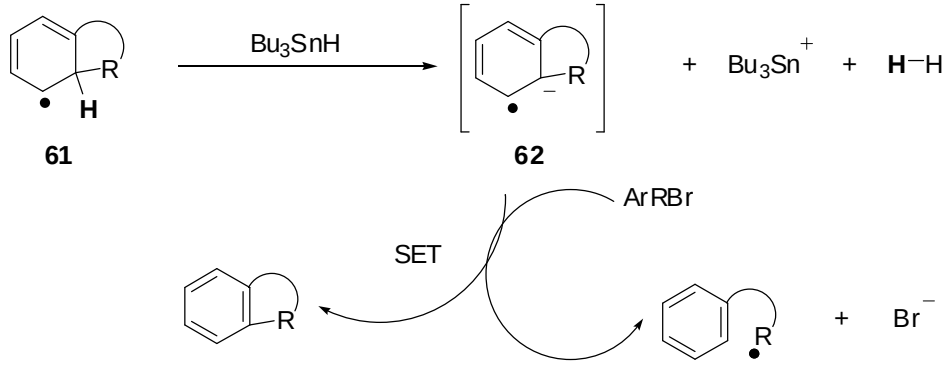
The third possibility invokes a mechanism involving the intervention of the initiator fragments, and later proven by Beckwith, Storey and Bowman as illustrated in **Scheme 18**. By using the fully deuterated aromatic substrate **59** the production of the deuterated initiator fragment **60** was proven.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



59 **60**

Scheme 18 Investigation of re-aromatisation using deuterated arenes.

Until recently the mechanism proposed by Bowman[62] was generally accepted as an adequate explanation for oxidation in Bu_3SnH mediated reactions. This involved Bu_3SnH 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**.

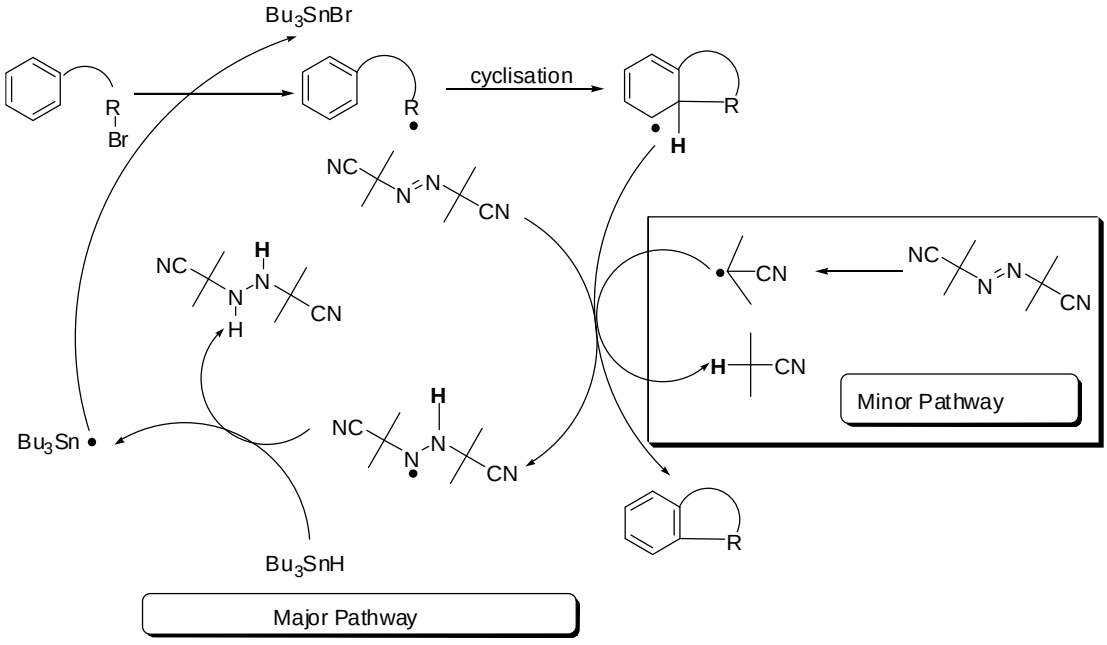


61 **62**

Scheme 19 Bowman's hypothetic mechanism for re-aromatisation

More recently a thorough investigation of the mechanism of general re-aromatisation under different conditions has been published.[57] 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.

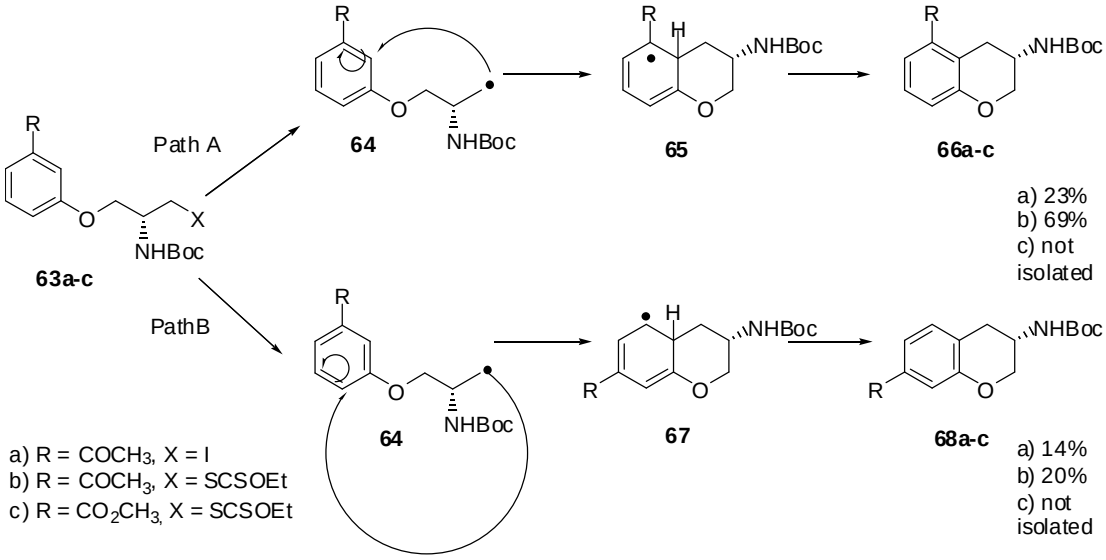


Scheme 20 Bowman and Storey proposed mechanism for re-aromatisation

Storey has applied this methodology to the synthesis of aza-oxindoles[63] 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.[64]

2.3.1 Cyclisation of xanthates

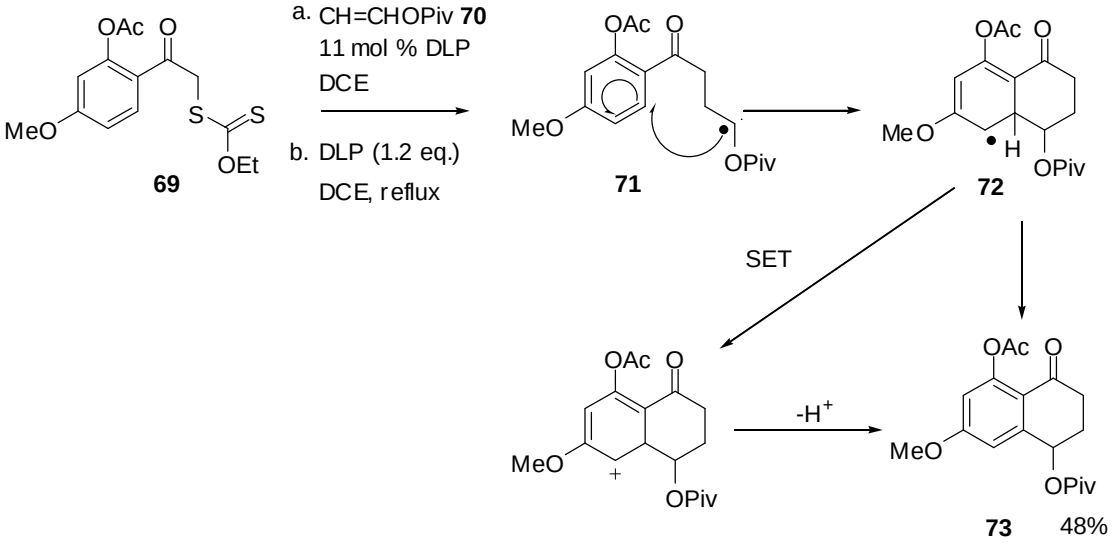
(S)-Aryl ether xanthates **63** was treated with dilauroyl peroxide, and the alkyl radical **64** was produced (**Scheme 21**).[65] This then cyclised to give a mixture of products. Interestingly, radical cyclisation *via* path A predominates leading to the (S) 3-aminochromane with the substituent in the 5-position **66**. Radical cyclisation *via* the cyclohexadienyl radical intermediate **67** (path B) led to the (S) 3-aminochromane with the ketone substituent in the 7-position **68**. Re-aromatisation under these xanthate-mediated conditions was postulated to go through a single electron transfer-SET process as described by Zard,[66] however, it would seem feasible, that the lauroyl radical could abstract the hydrogen atom from intermediate **65** or **66** to produce re-aromatisation.



Scheme 21 Guillaumet synthesis of aminochromane[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**.

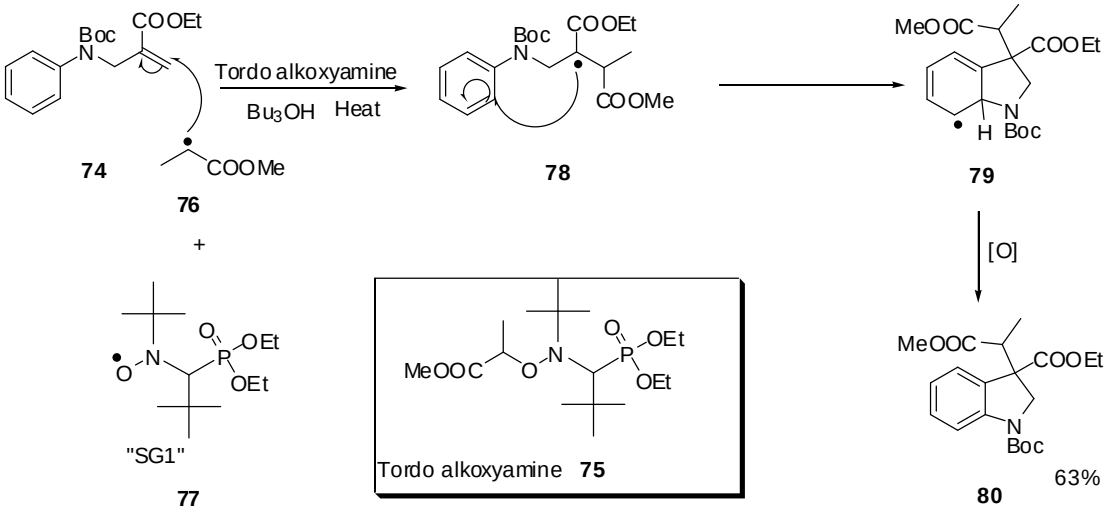
Similarly, α-tetralone derivative **73** have also been synthesised using an alkyl radical cyclisation (48%). Zard[67] investigated the radical addition of acetophenone xanthate **69** onto vinyl pivalate **70** in the presence of dilauroyl peroxide (DLP) to give the radical adduct **71** (**scheme 22**). This alkyl radical **71** then underwent cyclisation onto the aromatic ring leading to **73** (48%), after re-aromatisation of **72**.[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.



Scheme 22 Zard's synthesis of α-tetralone[67]

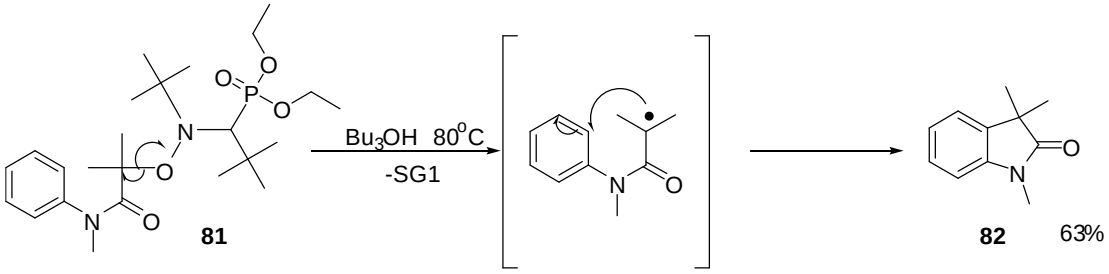
2.4 Sequential intermolecular/intramolecular radical cyclisation onto aromatics

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 nitroxide 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.



Scheme 23 Tordo's synthesis of indole[71]

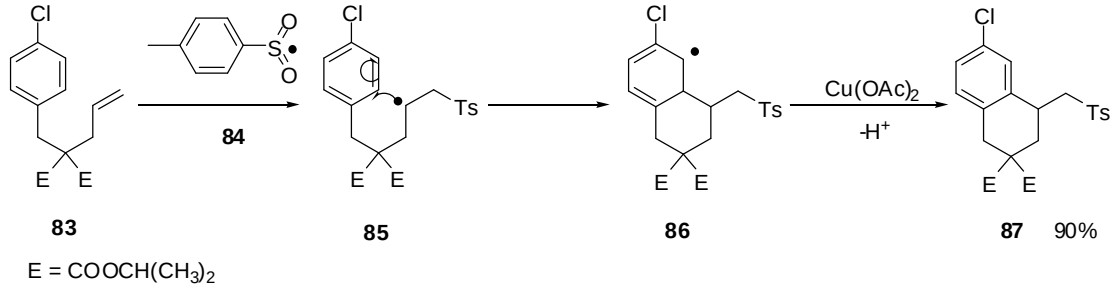
The same method was used in synthesising oxindole **82**. The nitroxide radical[74] ("SG1")-tethered substrate **81** underwent aromatic homolytic substitution and re-aromatisation to furnish **82** in 63% yield as depicted in **Scheme 24**.



Scheme 24 Synthesis of *N*-methyl-3,3-dimethyloxindole

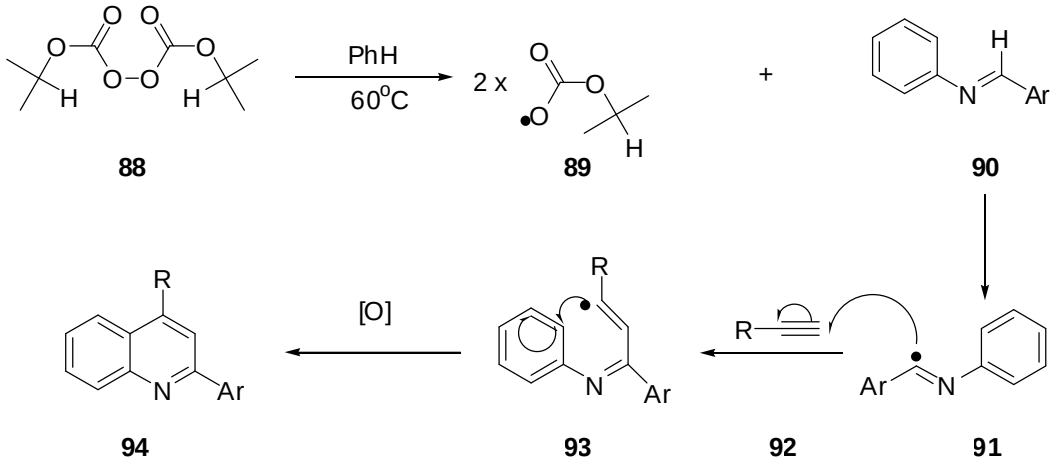
Carbocycles can also be produced *via* intramolecular addition (**Scheme 25**). Addition of a tosyl radical **84** onto the terminal alkene **83** furnished the more stable secondary alkyl radical intermediate **85**, which could undergo cyclisation onto the aromatic ring leading to the cyclohexadienyl 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 Cu^{2+} gives the cyclohexadienyl cation (not shown), which loses a proton generating acetic acid and Cu^{I}. When the reactions were carried out under acidic

conditions (acetic acid), high yields were obtained (90%, 48h), when formic acid was used, the reaction was accelerated 82%, (9h).



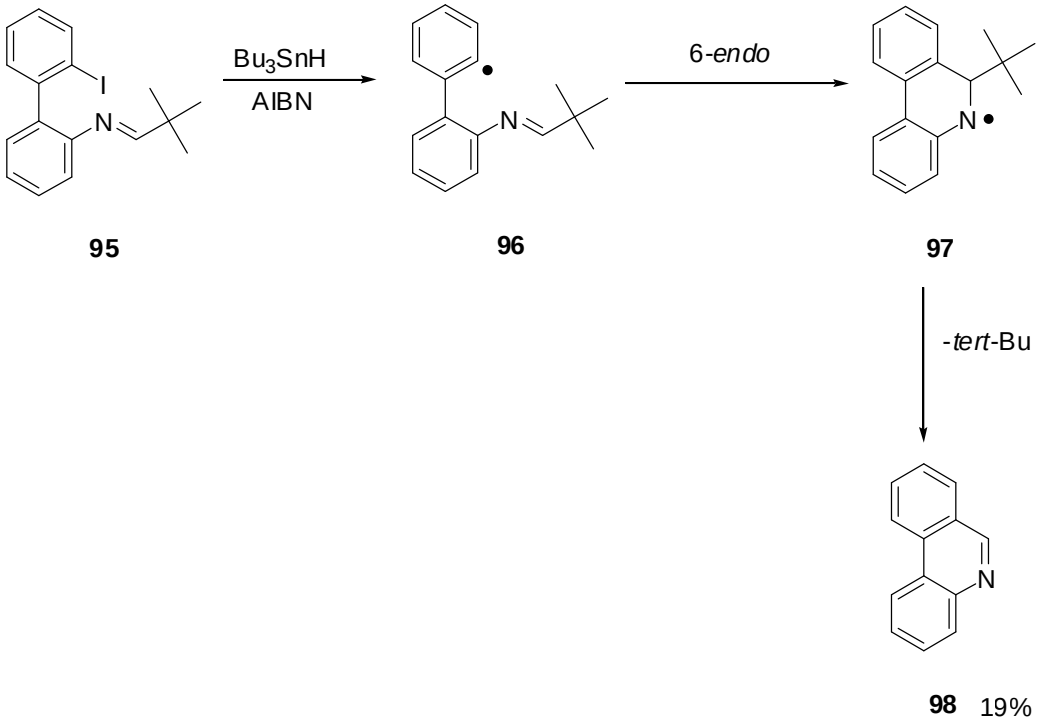
Scheme 25 Synthesis of carbocyclics[75]

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 ºC gave the isopropyloxycarbonyl radical **89** which could then abstract a hydrogen atom from *N*-benzylidineamine **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 Me_3Sn• radicals or *tert*-butoxyl radicals. In this example, a high concentration of hexamethylditin 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.



Scheme 26 Synthesis of quinoline derivative[24]

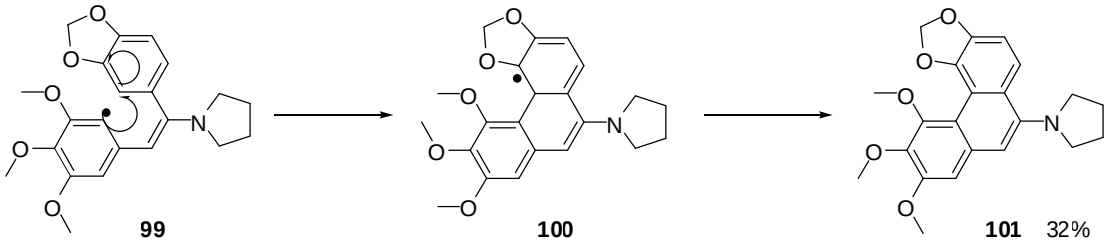
A similar class of reactions were used by Bowman in the synthesis of C*amptothecin,*[76-80] *mappicine*, *luotonin*[76] and Zanardi's synthesis of phenanthridine **98** (**Scheme 27**).[77] The key step in these reactions was a 6-*endo* attack of an aryl radical **96** onto the imine, to give the aminyl radical intermediate **97**. This was followed by re-aromatisation to furnish phenanthridine **98** in 19% yield. The mechanism of re-aromatisation for this reaction involves extrusion of the *tert*-Bu group.[77] Reactions involving re-aromatisation from extrusion of an alkyl group have been reviewed by Bowman *et al*.[78-79]



Scheme 27 Zanardi's synthesis of phenanthridine[77]

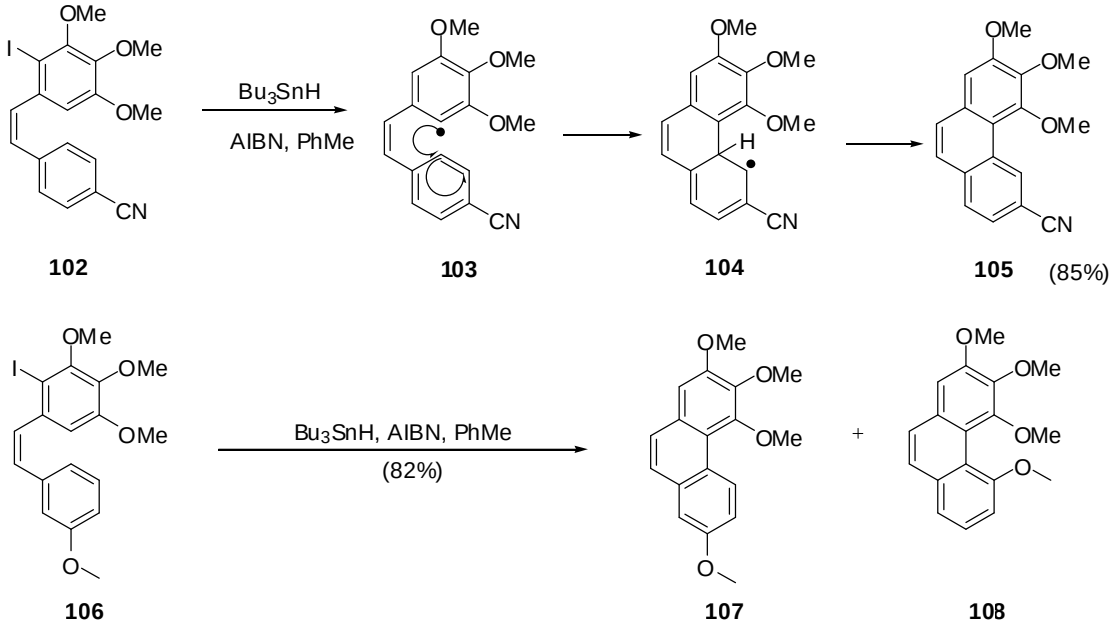
2.5 Aromatic radical cyclisation onto aromatics

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_3SnH (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]



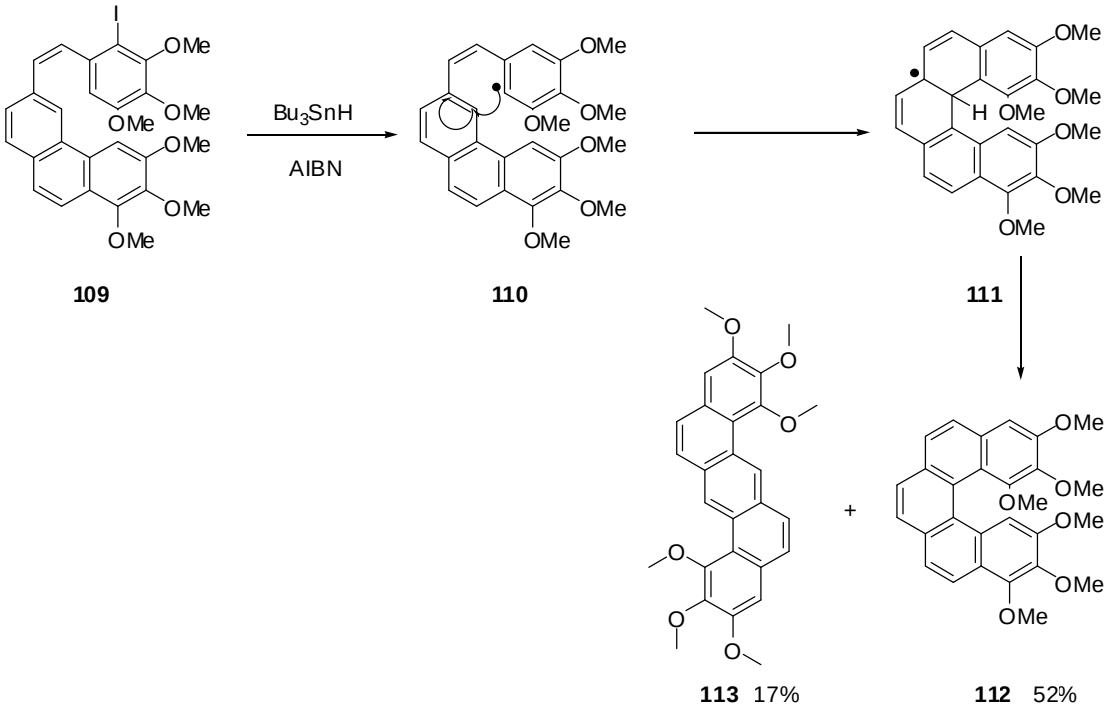
Scheme 28 Narasimhan synthesis of phenanthrene[81]

In addition to the above example, this methodology has been used to synthesise a range of polyaromatic natural products e.g. *β-copaena*, *β-ylangene*, *lemnalol*,[83-84] *seychellene*,[85] and towards the synthesis of *vitamin D3*.[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. C*is*-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).



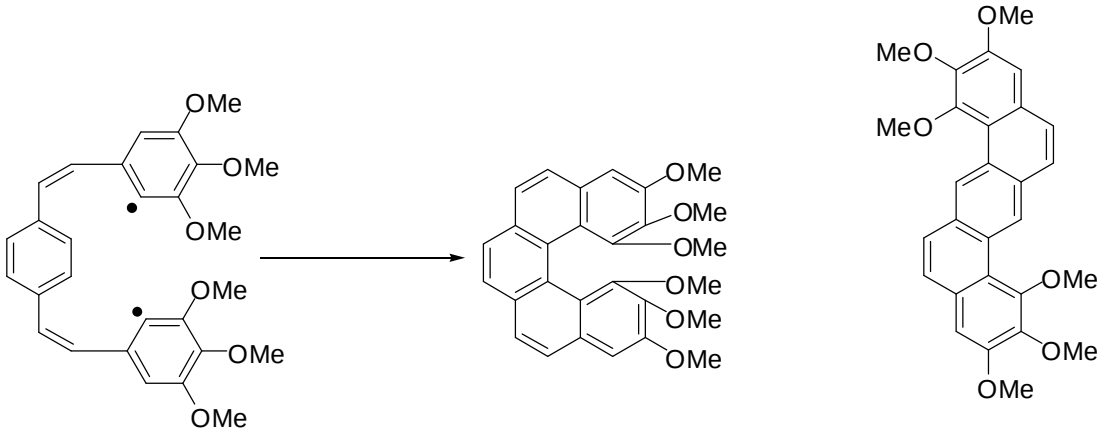
Scheme 29 Harrowven's synthesis of phenanthridines[82]

Harrowven[87] has also shown that the *cis* stilbene **109** (**Scheme 30**) when treated with tributyltin hydride furnished the aryl radical intermediate **110**. This radical then added onto to the aromatic ring to give the cyclohexadienyl radical intermediate **111**. Re-aromatisation furnished the helicene **112** in 52% yield. Alternatively, the radical intermediate **110** can undergo addition onto C-7, leading through re-aromatisation to furnish dibenzo[*a*,*h*]anthracene **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.



Scheme 30 Harrowven's synthesis of helicene-1[87]

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.

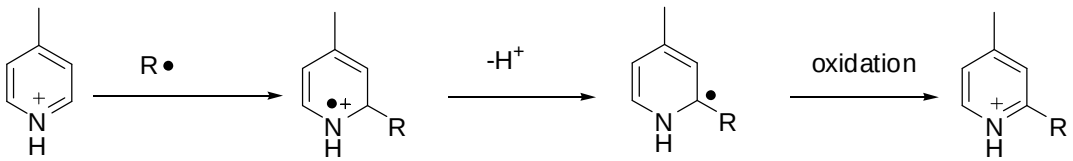


114 **112** 35% **113** 27%

Scheme 31 Harrowven's synthesis of helicene and phenanthrene[88]

2.6 Alkyl radical cyclisation onto heteroaromatics

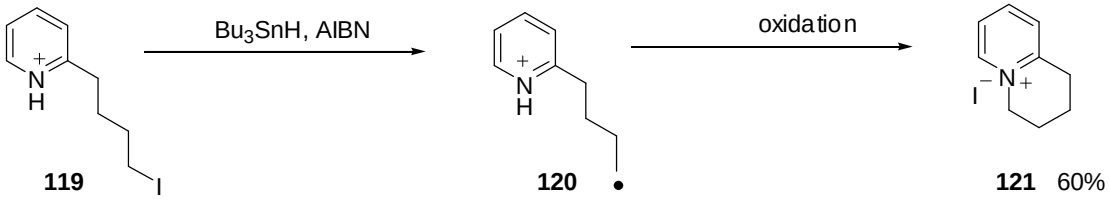
Cyclisation of radicals into heteroaromatics is a relatively new process. The first example of this involves cyclisation of an alkyl radical into a protonated pyridinium salt.[89] Intermolecular and intramolecular aromatic homolytic substitutions into heterocycles are relatively well researched. An example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



115 **116** **117** **118**

Scheme 32 Murphy's reaction of protonated pyridinium salts

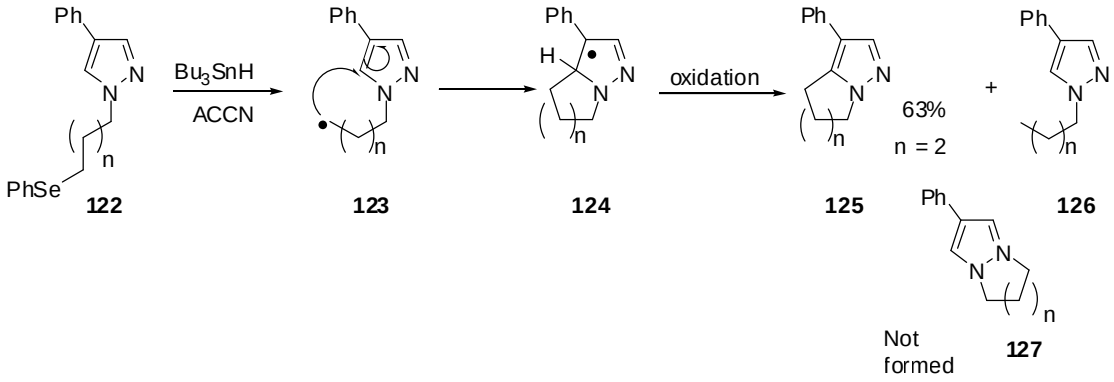
An intramolecular version of this reaction was accomplished by Murphy.[91-92] In this example (**Scheme 33**), treatment of the 2-iodoalkyl pyridinium salt **119** with tributyltin hydride (1.3 eq.) and AIBN (1.2 eq.) gave the nucleophilic alkyl radical **120** which could add into the pyridinium ring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



Scheme 33 Murphy's intramolecular addition into pyridinium salt

2.6.1 Radical cyclisation onto pyrazoles

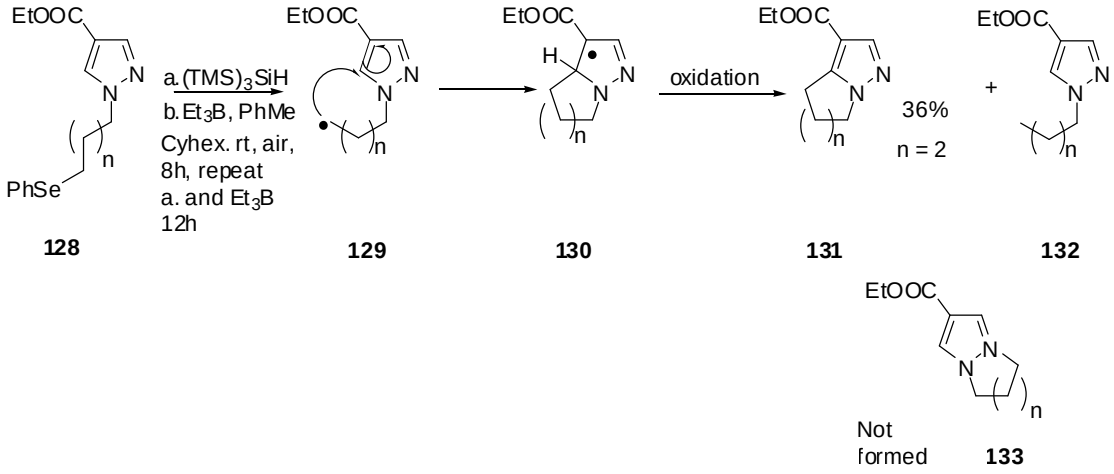
Intramolecular cyclisation onto pyrazoles have been accomplished to give 4-phenyl pyrazole derivatives **125**.[93] Reaction of a 4-phenylpyrazole phenylselenyl precursor **122** with tributyltin hydride (1.3 eq.) and ACCN (1.5 eq.) gave the alkyl radical intermediate **123** (**Scheme 34**), which underwent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



Z = Ph, n = 1 **125a** = 38%; **126** = 17%; n = 2 **125b** = 63%; **126** = 0%; n = 3 **125c** = 37%; **126** = 48%

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_3B) (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).



128 **129** **130** **131** **132** **133**

Z = COOEt, n = 1 **131a** = 0%; **132** = 73%; n = 2 **131b** = 36%; **132** = 0%; n = 3 **131c** = 0%; **132** = 62%

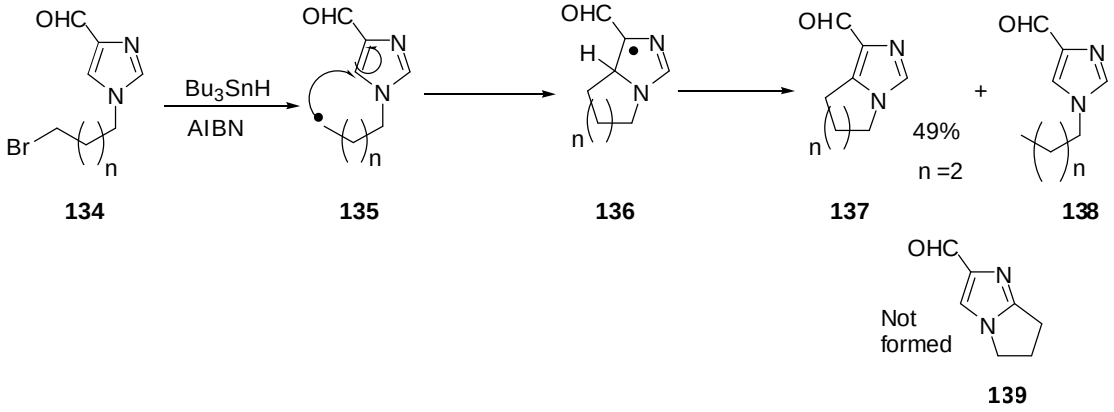
Scheme 35 Reaction of pyrazole (ester) on radical cyclisation[93]

The mechanism for the oxidative step **130** to **131** is not clear, but it is reported that the stability of the π-radical intermediate **131** is crucial (to aromatisation).[94-98] The re-aromatisation could occur from H-abstraction by the ethyl radical formed during the oxygen-generated breakdown of Et_3B 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.[57, 94-103]

2.6.2 Radical cyclisation onto imidazoles

Further studies were conducted involving cyclisation onto imidazoles[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 π-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

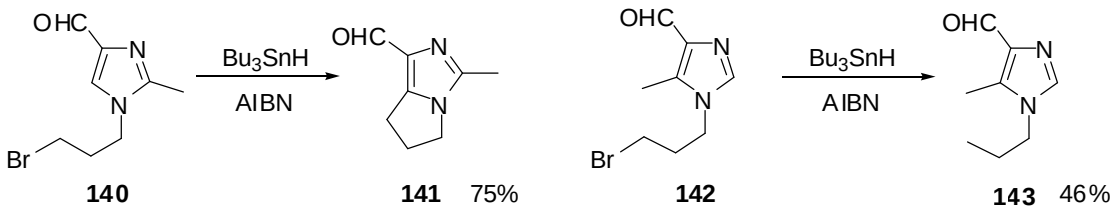
reduced product **138**). There was no regioisomer **139** resulting from cyclisation onto the C-5 position.



Key: a) n = 1, **137 =** 42%; **138 =** 10% b) n = 2, **137** = 49%; **138** = 0% c) n = 3, **137** = 14%; **138** = 8%.

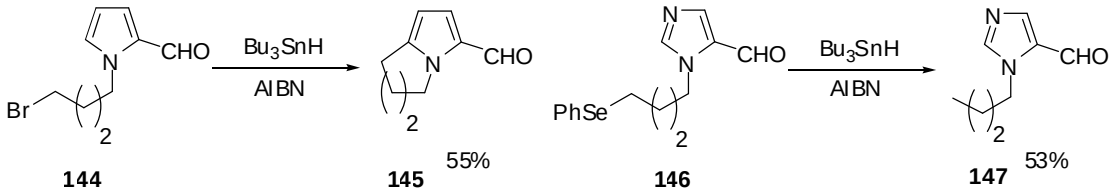
Scheme 36 Intramolecular cyclisation of imidazole[94]

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 β-position of the imidazole. This reaction was also investigated with tributylgeranium hydride.[104]



Scheme 37 Blocking of the C-2 and C-5 with methyl group[94]

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**.



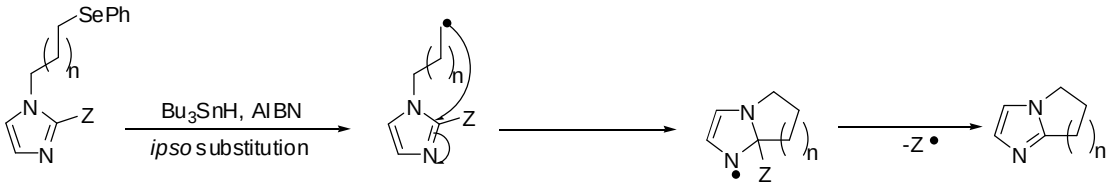
Scheme 38 Intramolecular cyclisation of pyrrole and imidazole[99]

In this paper, there is no specific proposed mechanism to explain the oxidative radical cyclisation of these substrates with Bu_3SnH. 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-$S_{RN}1$ 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

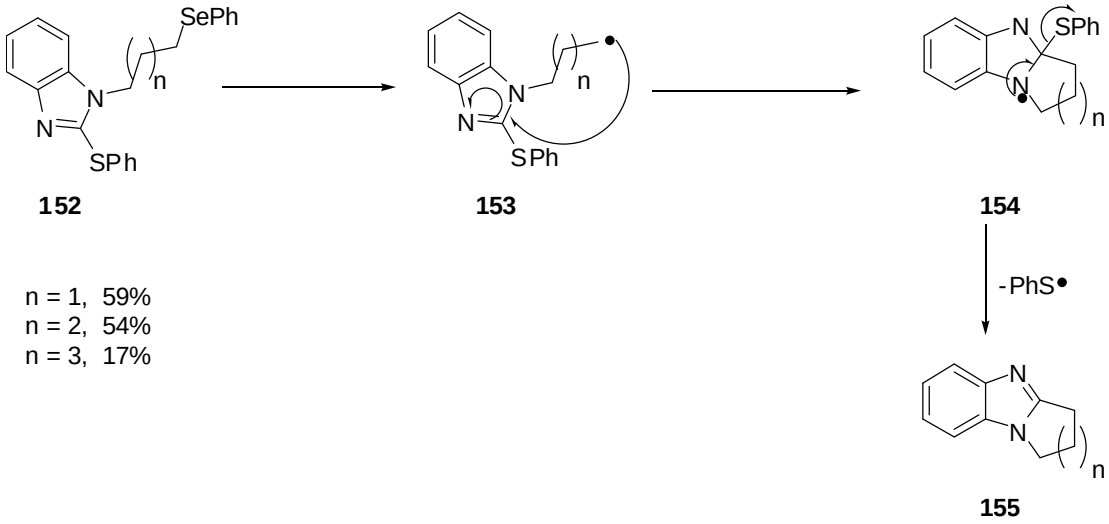
radical leaving group, *ipso* substitution with loss of this group can occur. Caddick has used this methodology to furnish [1,2-*a*] indoles using sulfone, sulfide and sulfoxide groups as leaving groups in substituted indoles.[108] Highest yields were obtained from 6-*exo* attack onto sulfoxides (tosyl group).



Z = Ts, n = 1; **151a** = 52%, n = 2; **151b** = 48%, n = 3; **151c** = 63%, Z = $PhSO_2$, n = 1; **151a** = 51%, Z = PhS, n = 1; **151a** = 16%.

Scheme 39 Intramolecular *ipso* cyclisation of imidazoles[107]

There was no noticeable change in yield for n = 1 on varying the tosyl leaving group **151a** in 52% yield and the phenylsulfonyl leaving group **151a** in 51% yield. The low yield for the phenylsulfanyl group **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 **152** as depicted in **Scheme 40**.[108-110] The radical precursor **152** was treated with tributyltin hydride and AIBN to give the alkyl radical intermediate **153**. This underwent an attack on the electrophilic C-2 carbon of the benzimidazole to give the π-radical intermediate **154**, and elimination of the phenylsulfanyl group to give the product **155**.

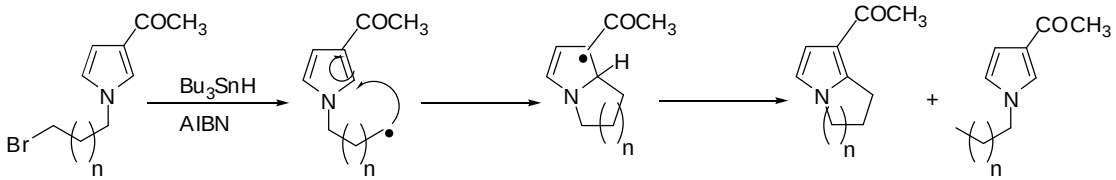


Scheme 40 Intramolecular *ipso* cyclisation of benzimidazole[110]

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[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 π-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**.



156 **157** **158** **159** **160**

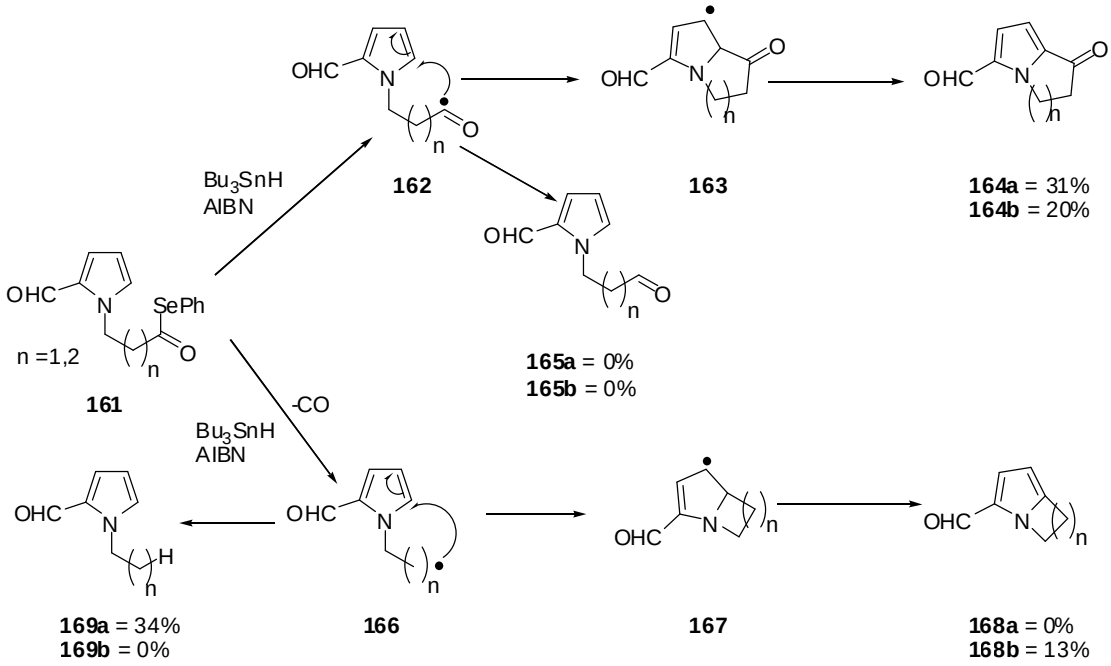
Key: a) n = 1, **159** = 46%; **160** = 11%; b) n = 2, **159** = 45%; **160** = 0%; c) n = 3, **159** = 54%; **160** = 18%.

Scheme 41 Intramolecular cyclisation of pyrrole-2[94]

Several cyclisations onto the C-2 position of imidazoles proceed by reductive cyclisation and not aromatic homolytic substitution[48] that indicates that reduction of the intermediate radical by Bu_3SnH 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.[111-116]

2.9 Acyl radical cyclisation on pyrroles

Acyl radicals also undergo addition reactions.[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 π-radical intermediate **163**, followed by oxidation to the product **164a** (n = 1) in 31% yield and **164b** (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 π-radical intermediate **167**, followed by oxidation to the product **168a** (n = 1) in 0% yield and **168b** (n = 2) in 13%. Only the reduced product **169a** (n = 1) was isolated in 34% yield.

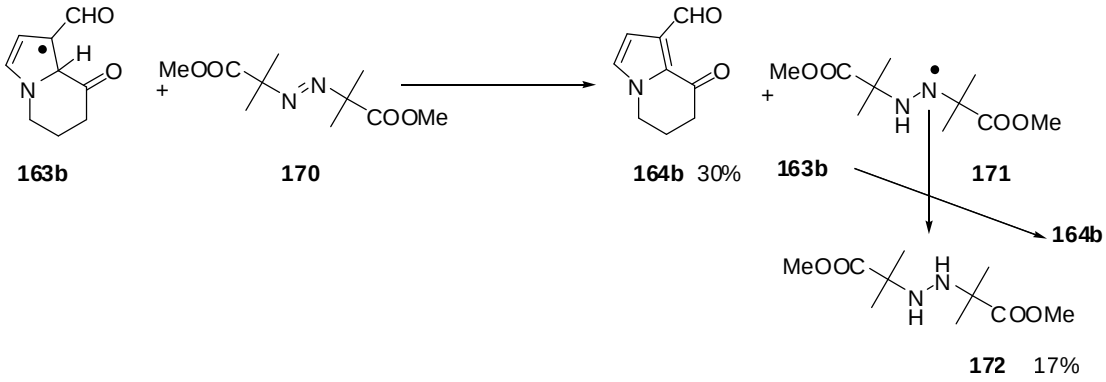


Scheme 42 Intramolecular cyclisation of pyrroles using acyl radicals[97]

It should be noted that decarbonylation is an exothermic process. The rate of CO loss (approximately 2 x 10^2 M^{-1} s^{-1}) at 80 ºC to generate a primary alkyl radical, is much slower than CO addition (6.3 x 10^5 M^{-1} s^{-1}) at 80 ºC for primary alkyl radicals.[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[119] from 2-indolylacyl radicals. The mechanism for re-aromatisation[98] in this reaction is still unclear. In the Bu_3SnH 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

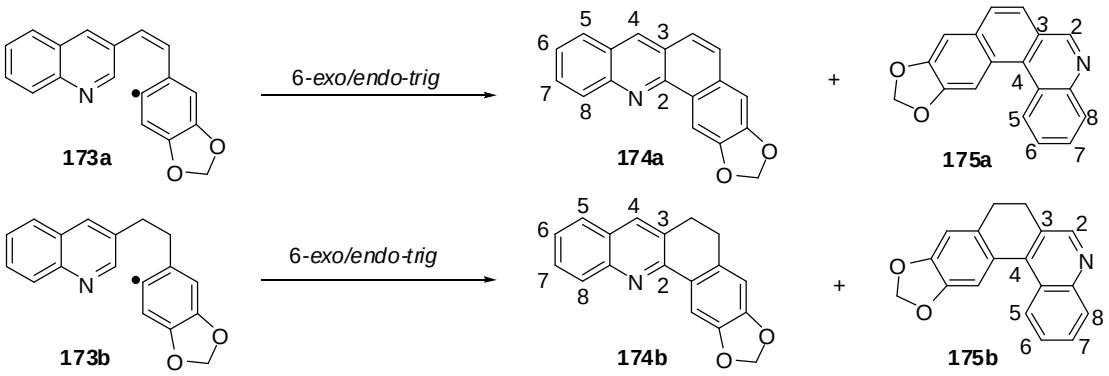
164b and dihydro-AIBN **171** indicating that AIBMe **170** was responsible for the oxidative step.



Scheme 43 Mechanism indicating AIBN involvement in re-aromatisation

2.10 Aryl radical cyclisation onto heteroaromatics

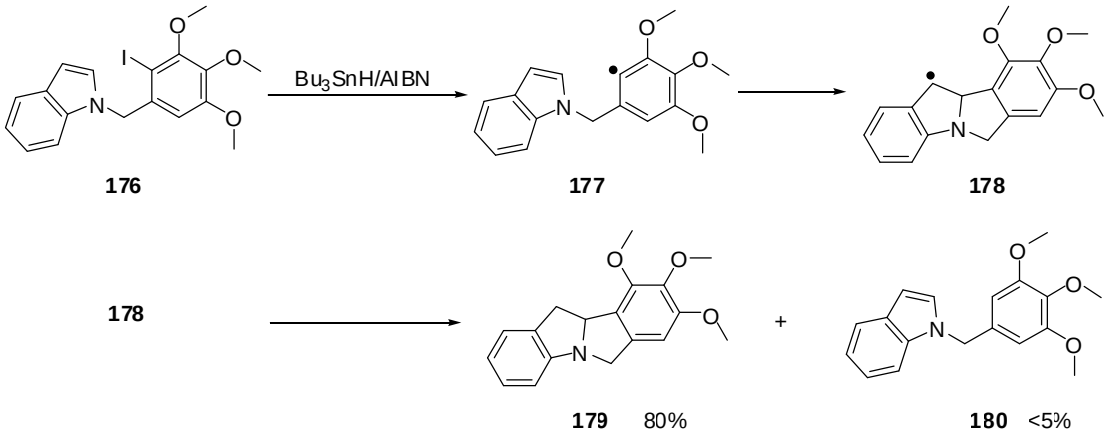
A popular approach to polyheteroaromatics[119-120] is the addition of an aryl radical onto another heteroaromatic such as quinoline (**Scheme 44**). Radical intermediates **173a** and **173b** are produced from homolysis of the corresponding C-X bonds with Bu_3SnH (not shown). The use of iodo aromatics 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.[119] 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.*[119] Similar methodology using cobalt (II)-salophen was used in the synthesis of *Toddaquinoline*.[121]



Key: Bromo precursor Bu_3SnH, 0.9 eq. AIBN, PhMe, 80ºC; **1747a** = 24%, **175a** = 46%; **174b** = 18%, **175b** = 15%; Iodo precursor Bu_3SnH, 0.1 eq. AIBN, PhMe, 80ºC; **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**.

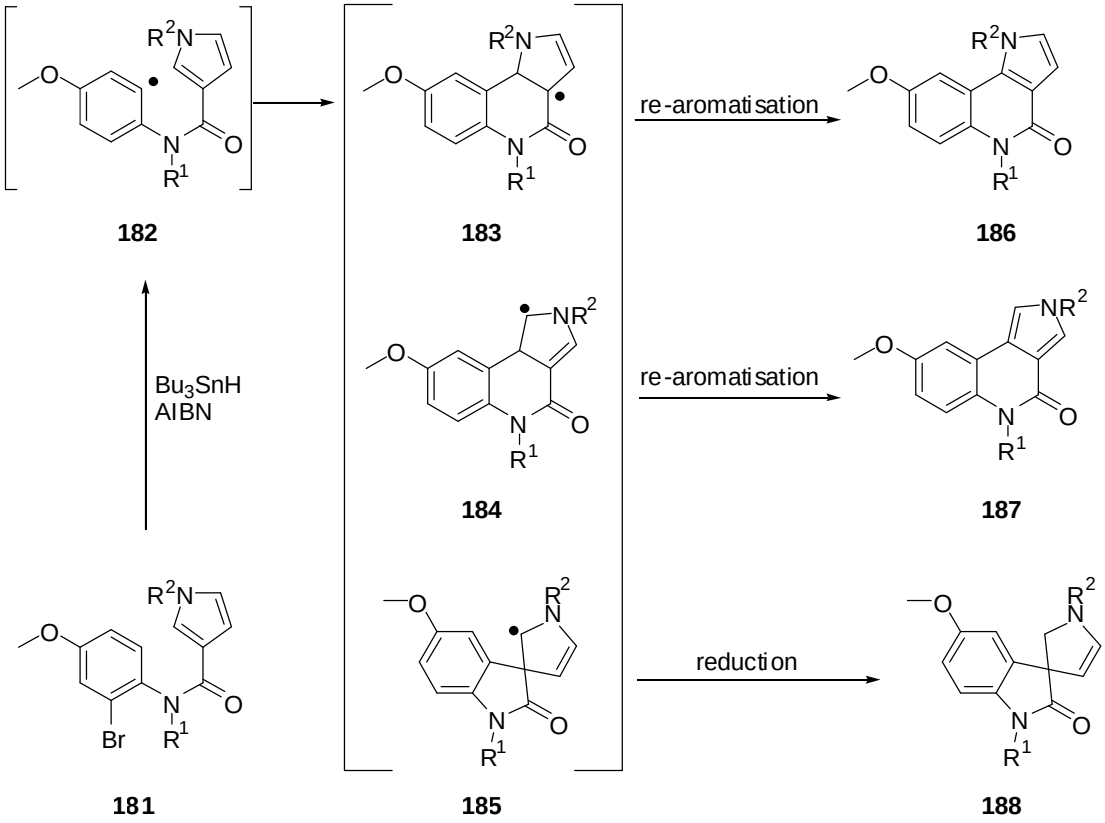


Scheme 45 Intramolecular cyclisation of indoles

Further developments of this reaction were employed in the synthesis of several heterocycles namely-*deoxyvascinone, mackinazoline, luotinin A, tryptanthrin*.[123]

The Jones' group has developed cyclisation onto pyrroles further.[124-126] An *ortho* bromo anilide derivative **181** when treated with tributyltin hydride (0.02M) and sub-stoichiometric amount of AIBN furnished the aryl radical intermediate **182** as illustrated in **Scheme 46**. This could undergo three reactive pathways. The radical intermediate **182** could undergo 6-*endo* cyclisation *via* the radical intermediate **183** onto the pyrrole to furnish the product **186**. It could undergo 6-*exo* cyclisation *via* the radical intermediate **184** onto the pyrrole to give the regioisomeric product **187**. Finally, it could undergo 5-*exo* cyclisation *via* the radical intermediate **185** to furnish the spirocyclised product **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^2 = H), then regioisomeric products **186a** (R^1 = Me, R^2 = H, 37%) and **187a** (R^1 = Me, R^2 = H, 15%) dominated. Conversely, cyclisation using *N-t*-Boc group led predominately to the spirocyclised product **188b** (R^1 = Me, R^2 = Boc) in 31% yield, with the regioisomers as minor products (**186b**/**187b** = 18%/1%). If an electron-withdrawing group was attached to the nitrogen atom of the pyrrole, only **186c** (R^1 = SEM, R^2 = Me) was furnished in 43% yield. The regioselectivity was unaffected when substitutents 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.

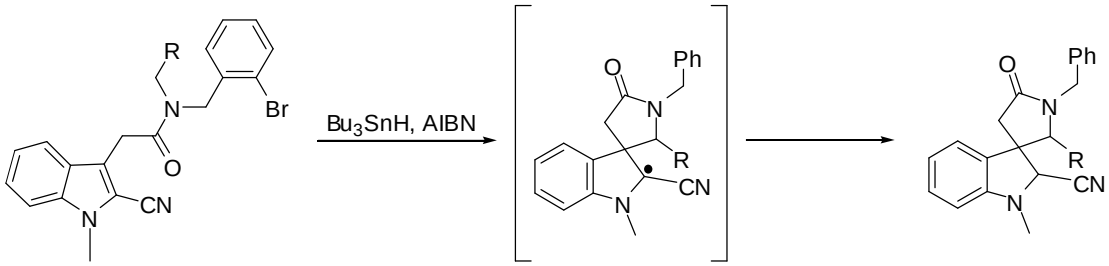


Key: R^1 = Me, R^2 = H; **186a** = 37%, **187a** = 15%; R^1 = Me, R^2 = Boc; **186b** = 18%, **187b** = 1%, **188b** = 31%; R^1 = SEM, R^2 = Me; **186c** = 43%

Scheme 46 Intramolecular cyclisation onto pyrroles[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 *in-situ* trapping of the cyclohexadienyl radical intermediate. Zard's method has shown that spirolactams[127] can be prepared from *N*-benzyl trichloroacetamides using nickel powder/acetic acid. Furthermore, Jones' has used this methodology towards the spirooxindole natural products-*horsfiline*, (**Scheme 47**) *elacomine, alstonisine* and *spirotryprostatin A.*[128]



Scheme 47 An example of spirocyclisation[128]

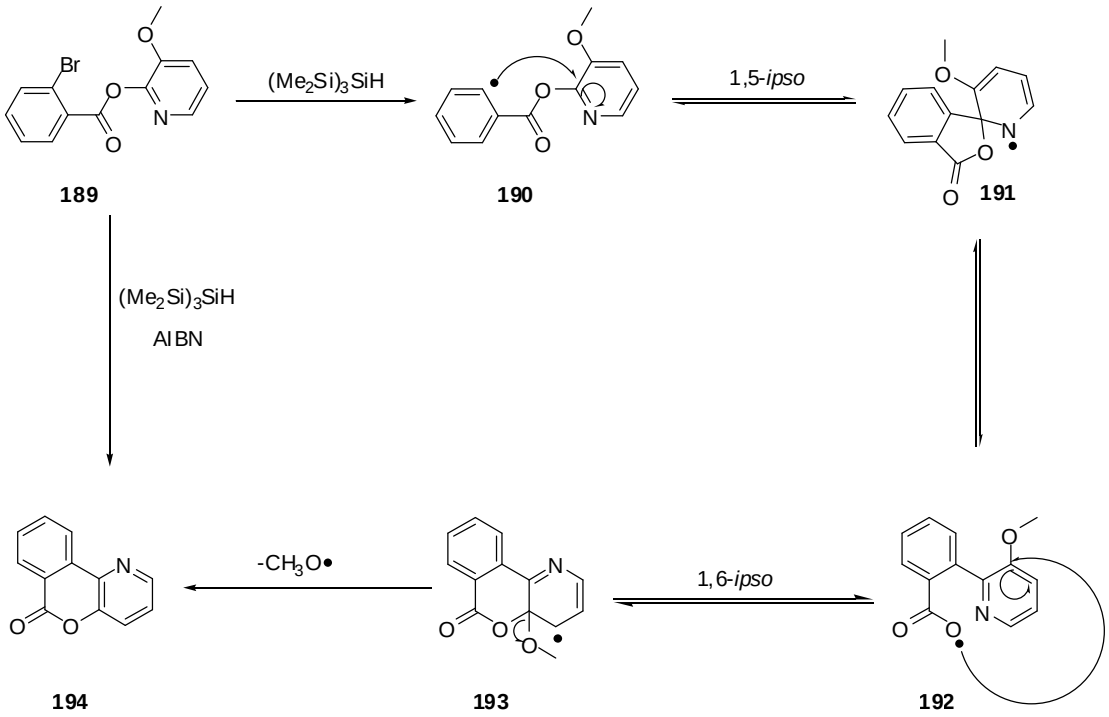
Spirodienones have been synthesised *via* intermolecular *ipso* substitution from *N*-methoxy-(4)-(halogeneophenyl) amides and hydroxyl (tosyloxy) iodobenzene (HTIB)/trifluoroethanol (TFEA). This methodology was developed for the synthesis of 1-azaspiro-[4,5]-decane-mediated natural products-*TAN1251A-D, FR901483I, lepadiformine* and *cylindricine A-F*.[129] 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*.[130]

2.12 Spirocyclisation followed by rearrangement reactions

In cases where there is a good radical leaving group α 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 **194**[131] have been prepared by a unique double *ipso* substitution from aryl benzoate **189**. The reaction goes *via* an initial 1,5-*ipso* attack at the 2-position of the pyridine **190** to generate the spirocyclised intermediate **191** followed by re-aromatisation and fragmentation of the carbon-oxygen bond to furnish the carbonyloxy radical intermediate **192**. The aromatic carbonyloxy radical ($k = 10^4$-10^5 s^{-1}) is considerably slower than alkyl carbonyloxy radical ($k = 10^8$-10^{10} s^{-1}), and allows the radical intermediate **192** time to undergo a second 1,6-*ipso* attack at the methoxy position

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.

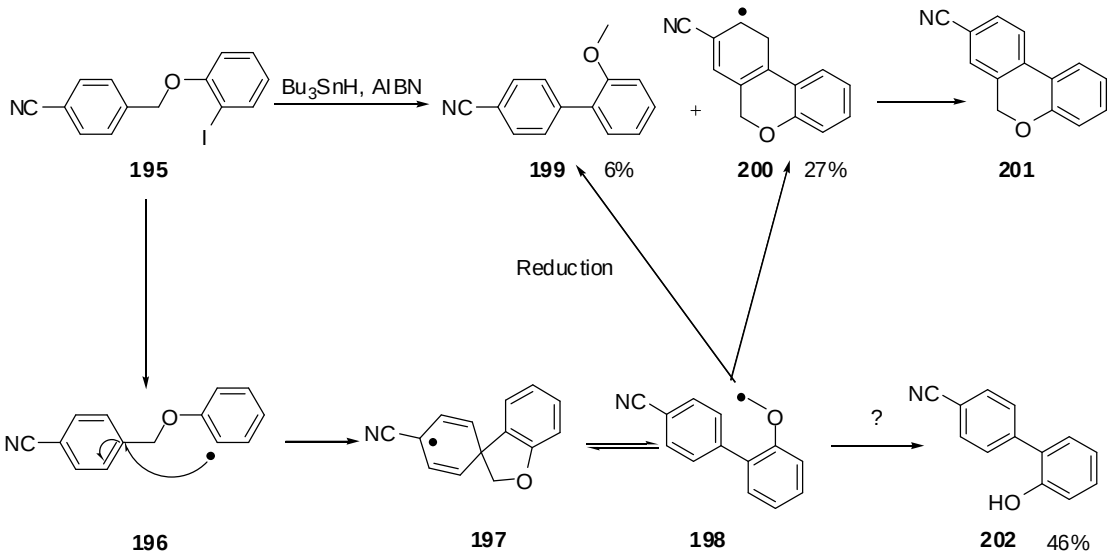


Scheme 48 Complex double *ipso* cyclisation to form azacoumarins[131]

3.0 Aryl migration

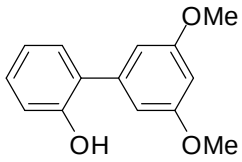
Aryl groups can undergo migration reactions[132-134] generally *via* the intermediacy of a spirocyclohexadienyl system followed by re-aromatisation and cleavage of the appropriate bonds. Wieland[135] first reported radical aryl migration reactions in 1911. There has been an extensive investigation of 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**,[136] tributyltin-mediated radical abstraction of the iodo group in **195** generated the aryl

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]

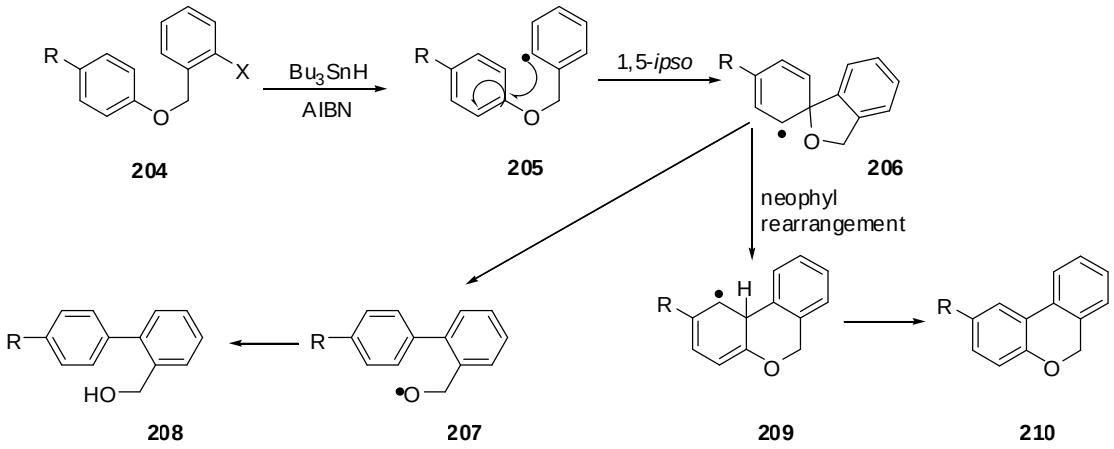
Harrowven[136] synthesised the natural product *isoauparin* **203** through the same methodology as described above (**Figure 1**).



203

Figure 1 Structure of *isoaucuparin*

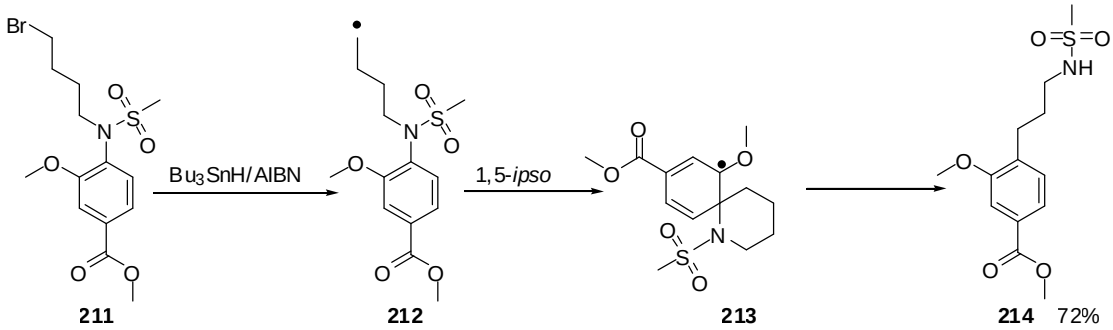
Under similar conditions, tributyltin hydride-mediated radical abstraction of the *ortho* halo-compound **204** furnished the aryl radical **205** which underwent a 1-5-*ipso* attack to give the spirocyclised radical intermediate **206** as depicted in **Scheme 50**. Re-aromatisation to give **207** followed by possible hydrogen abstraction from another molecule of tributyltin hydride resulted in the biaryl **208** *via* an aryl migration.[98] Alternatively, the radical intermediate **206** underwent a neophyl rearrangement to give the σ-complex **209** which upon oxidation (re-aromatisation) led to the benzo[*c*]chromane **210** (Me = 36%, OMe = 21%). In this reaction, the cyclisation *via* the neophyl rearrangement was faster than the *ipso* substitution followed by fragmentation.



204 **205** **206** **208** **207** **209** **210**

Scheme 50 Intramolecular cyclisation of benzyl ethers

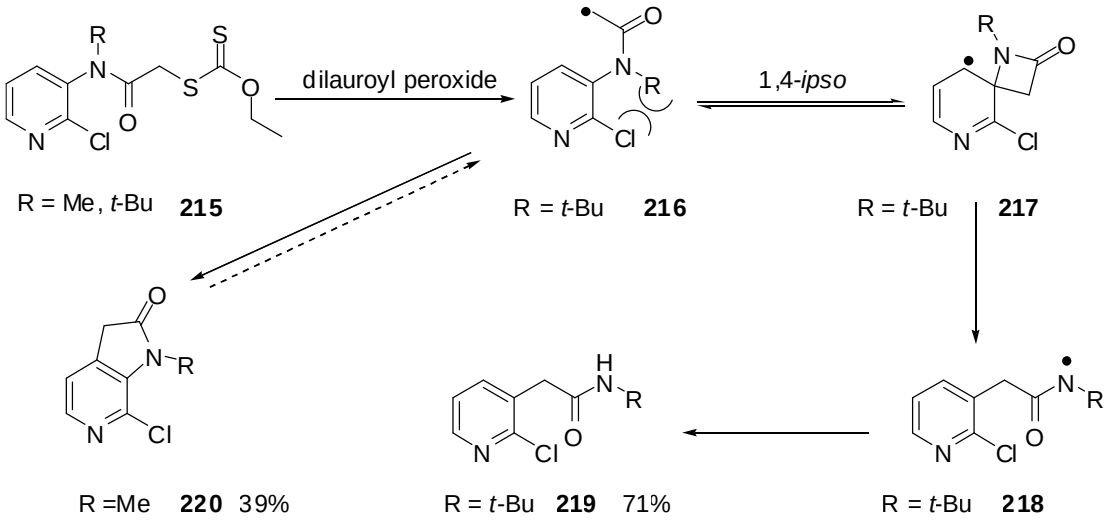
Synthesis of biaryls can be achieved by nitrogen to carbon aryl migration. For example, *N*-methanesulfonamide **211** is converted to the *N*-(3-arylpropyl) amide **214**.[139] Formation of radical **212** by homolysis of the corresponding C-Br bond using tributyltin hydride and AIBN led to a 1,5-*ipso* 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-*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

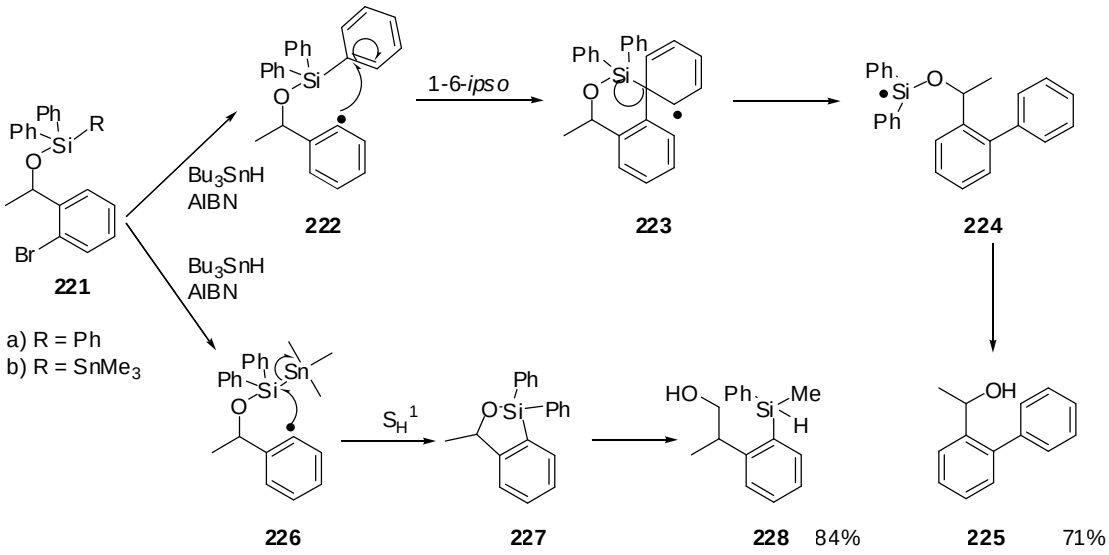
solvent to furnish the rearranged product **219** in 71% yield. Radical **216** was hindered from cyclisation onto the aromatic ring, due to steric effects when R = *tert*-butyl. However if the nitrogen substituent is changed from the *tert*-butyl group to a methyl group, then only the cyclised product **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**.[142-143] 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 (Me_3Sn-) substrate was used, it did not form the expected rearranged product, but instead the aryl radical intermediate **226** underwent a S_H1 type of reaction to furnish the bicyclic silylated product **227**. Ring opening of the cyclic silyl ether with methyllithium

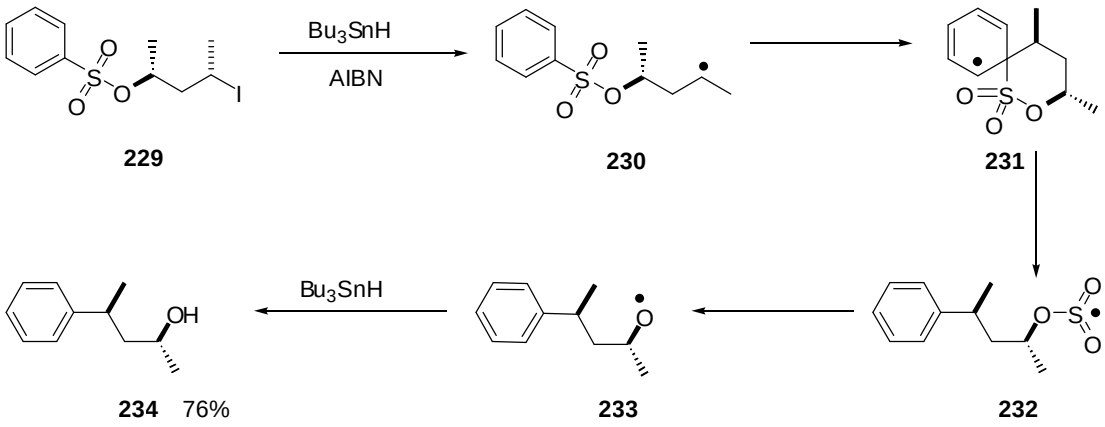
furnished the silylated benzyl alcohol **228** in 84% yield. The use of a phenyl or methyl group gave exclusively the rearranged product.



Scheme 53 Silicon to carbon aryl migration[142]

Struder has extensively investigated aryl migrations of sulfur to carbon.[132-133] The thia-neophyl type 1,2-phenyl migration from sulfur to carbon is known[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.*[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 **229**, tributyltin hydride and AIBN generated the secondary alkyl radical **230** that could undergo a 1,5-*ipso* attack into the phenyl ring to form the cyclohexadienyl radical intermediate **231**. Re-aromatisation from β-elimination gave the alkoxysulfonyl radical intermediate **232**. Extrusion of SO_2 furnished the alkoxy radical **233** followed by H-

abstraction to yield the product **234** in good yield (76%) and high selectivity (*dr* = 13:1) for the unsubstituted aryl group.



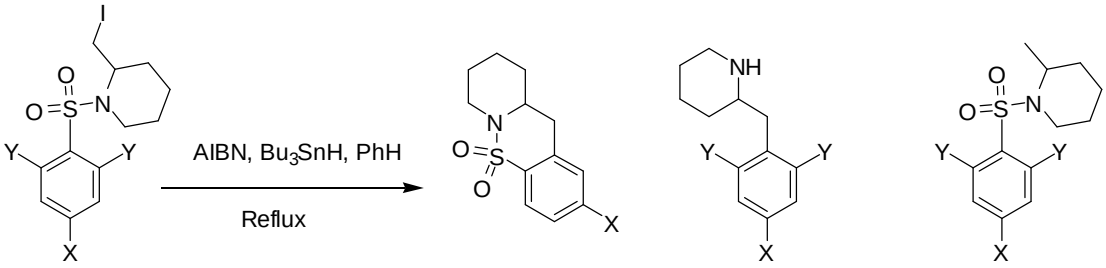
Scheme 54 1.6-*ipso* aryl migration[134]

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.

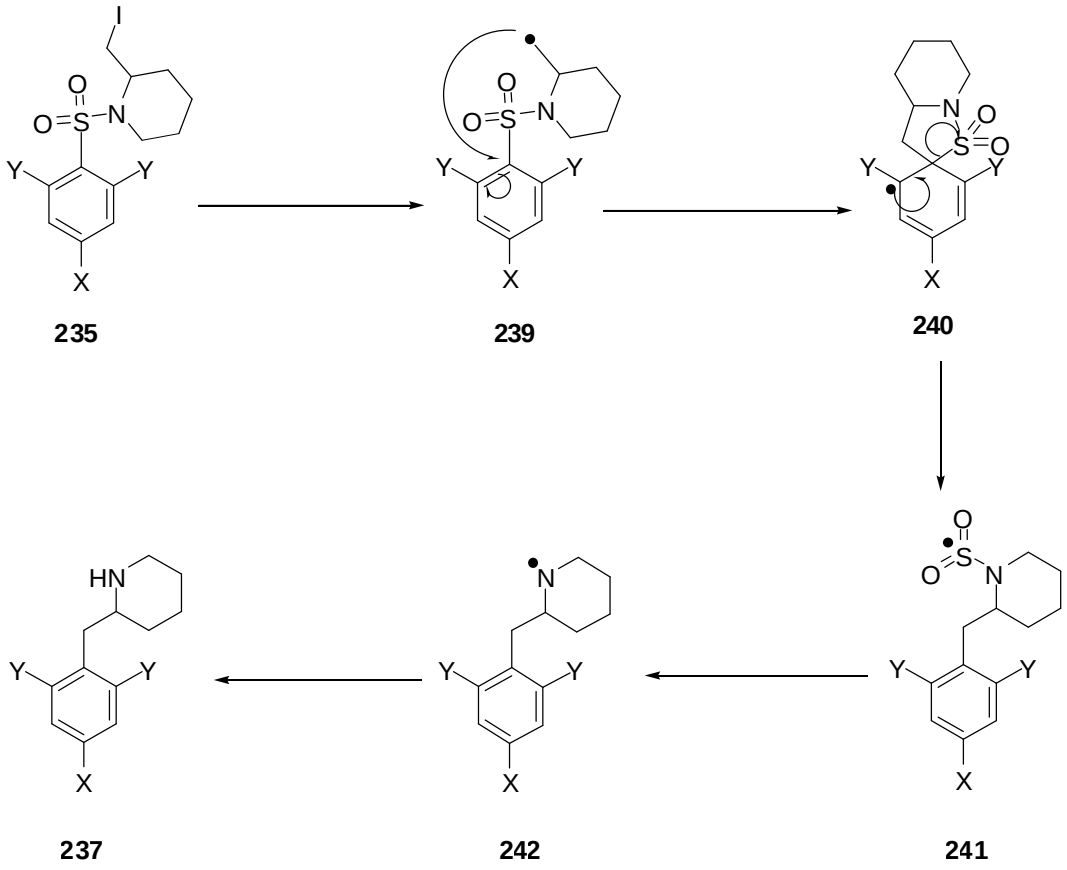


235 **236** **237** **238**

a) X = CH_3, Y = H; b) X = H, Y = H; c) X = OCH_3, Y = H; d) X = Cl, Y = H; e) X = CH_3, Y = CH_3; f) X = NO_2, Y = H.

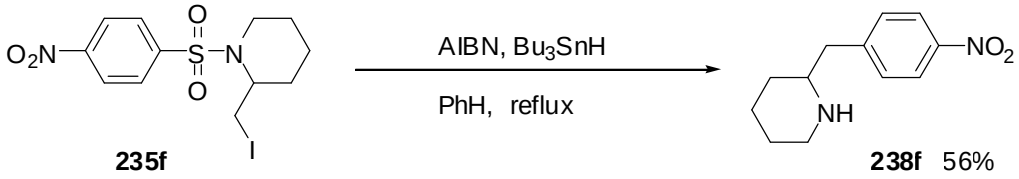
Scheme 55 Speckamp sulfonamide reactions 1[145]

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.



Scheme 56 Mechanism for rearranged amine 237

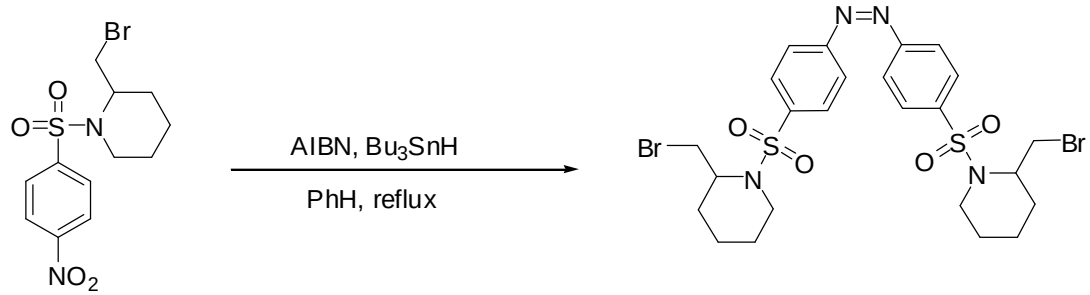
When the tosyl substrate **235a** was dissolved in anisole at 22 °C for 24hrs, the cyclised product **236a** predominated (68%). Conversely, with diphenylether as the solvent (190 °C/30min) the rearranged product **237a** predominated (64%). This showed that increasing the temperature alters the product 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.[147] While the iodo-nitro derivative **235f** as depicted in **Scheme 57** gave the rearranged product **237f** in 56% yield.



235f **238f** 56%

Scheme 57 Rearranged amide from nitro compound[147]

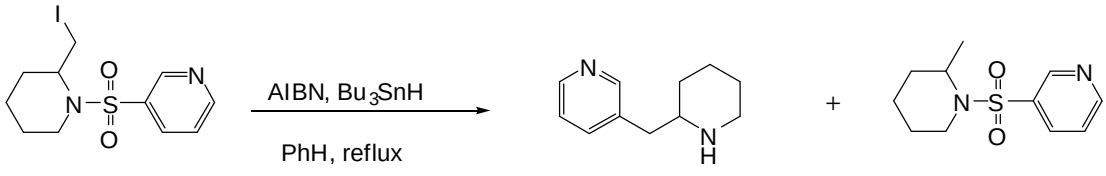
The corresponding bromide **243** furnished only the dimeric azo sulfonamide **244** in 51% yield (**Scheme 58**). This indicated that azo formation was faster than the C-Br homolysis. Therefore, only iodides were used in further investigations.



243 **244**

Scheme 58 Dimerisation from nitro compound

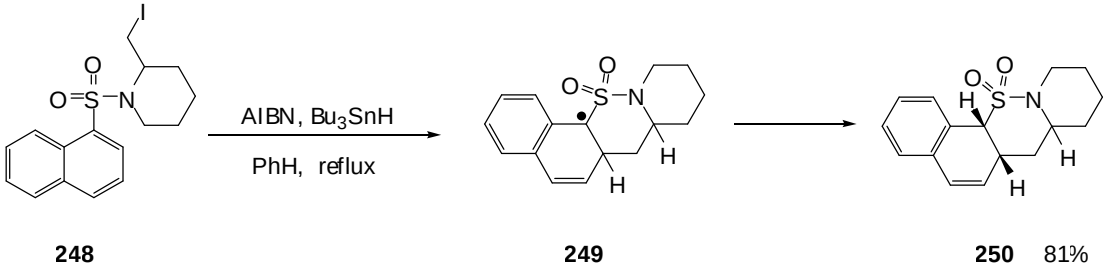
In order to broaden the scope of their reaction, Speckamp and Köhler investigated further changes to the aryl substituent. Heteroaryl sulfonamides were also tolerated, thus a pyridyl sulfonamide **245**, (**Scheme 49**) gave the expected rearranged product **246** in 30% yield, and the reduced product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



245 **246** **247**

Scheme 59 Synthesis of rearranged amine from pyridyl sulfonamide

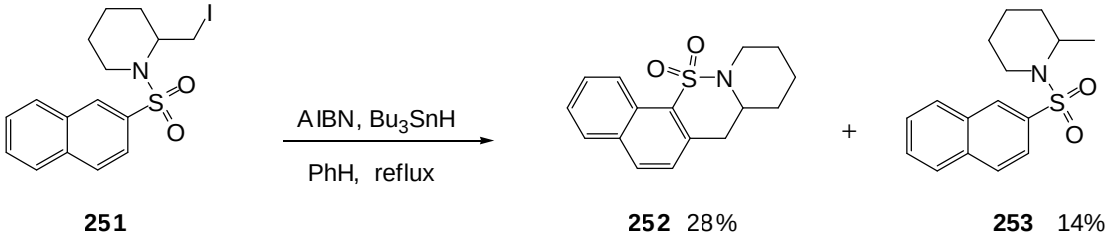
When a 1-naphthyl sulfonamide **248**, (**Scheme 60**) was treated under the standard conditions described above, a novel dihydronaphthalene cyclised product **250** was formed in 81% yield instead of rearrangement or oxidative cyclisation. The explanation given was that the "orbital interaction between the allylic radical **249** and the extended further π-system is favourable".[147]



248 **249** **250** 81%

Scheme 60 Cyclisation of 1-naphthyl sulfonamide

However, when the 2-naphthyl sulfonamide **251** (**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.



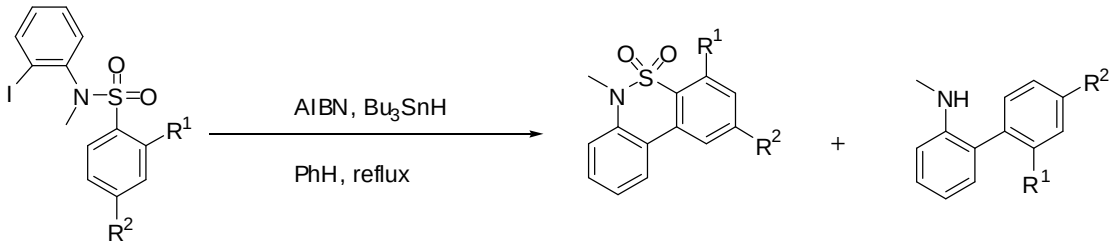
251 **252** 28% **253** 14%

Scheme 61 Cyclisation from 2 substituted naphthalene

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 coupling[148] (**Scheme 62**). This has been achieved

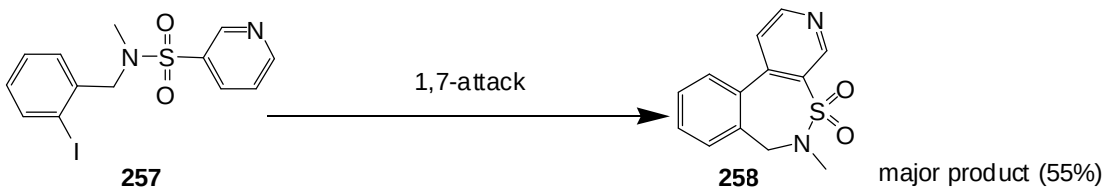
by reacting biaryl sulfonamides **254a-b** with AIBN and tributyltin hydride. When substituents are on the *ortho* position of the sulfonamide **255a** (R^1 = Me, R^2 = H), they undergo a 1,5 addition onto the second aryl ring which leads to the rearranged product **256a** *via* the analogous pathway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

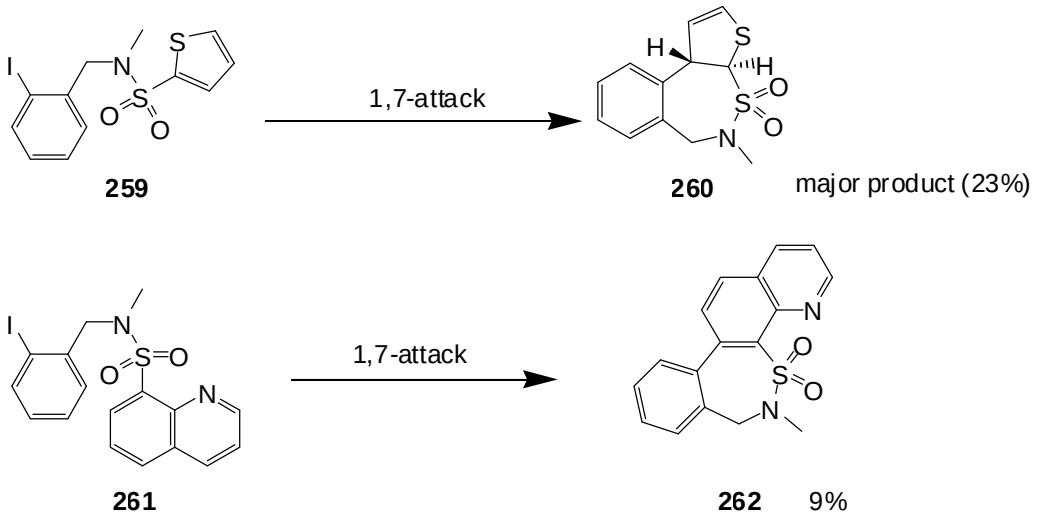


a) $R^1 = CH_3$, R^2 = H; b) R^1 = H, $R^2 = CH_3$

Scheme 62 Motherwell's synthesis of biaryls and cyclic sulfonamides

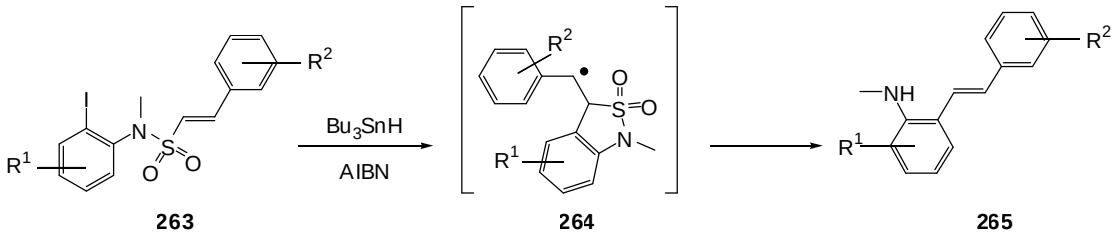
Similarly, to the Speckamp studies varying the type of substitutents on the *ortho* and *meta* position of the aryl sulfonamide was investigated.[149] Inclusion of a methylene group between the aryl ring and the sulfonyl group **257** led predominately to cyclised products **258** with no rearranged products detected by the 1,6 *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.





Scheme 63 Examples of 1,7-*ipso* cyclisation reactions[150]

Inserting a further carbon between the aryl groups (but incorporating an alkene, i.e. unsymmetrical stilbenes) led to loss of SO_2 but *via* a different mechanism to that previously discussed.[151] Reaction of phenyl allyl sulfonamides **263** (**Scheme 64**) under standard radical conditions (AIBN, TBTH) led to an intermediate **264** *via* a 5-*exo* radical cyclisation onto the alkene. Elimination of sulfur dioxide subsequently yielded the rearranged product **265**.

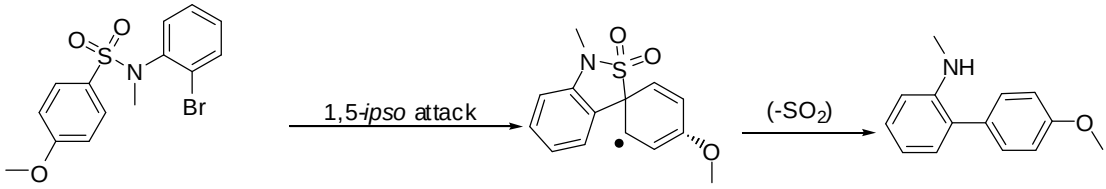


Scheme 64 Motherwell's stilbene synthesis

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 **Scheme 58**). In related work,

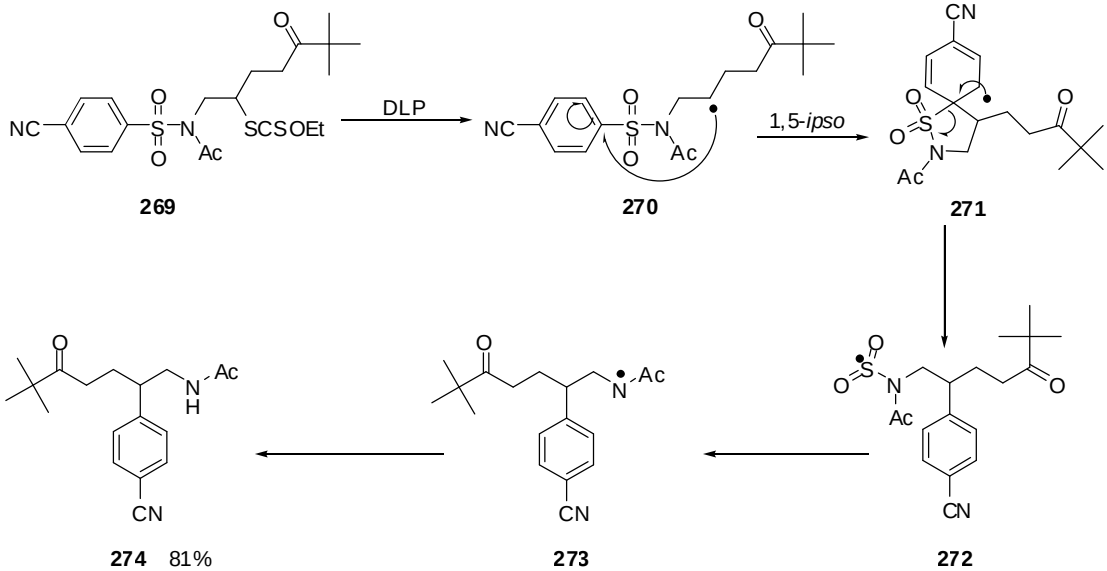
bromoaryl)-benzenesulfonamides[152] **266** (**Scheme 65**) if treated with $(Ph_2HSi)_2$ instead of TBTH could successfully be used to make the spirocyclised intermediate **267** which went on to yield rearranged biaryl products **268** in 61% yield, following re-aromatisation,



266 **267** **268** 61%

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-*ipso* addition to give the spirocyclohexadienyl radical intermediate **271**. Re-aromatisation led to the amidosulfonyl 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]



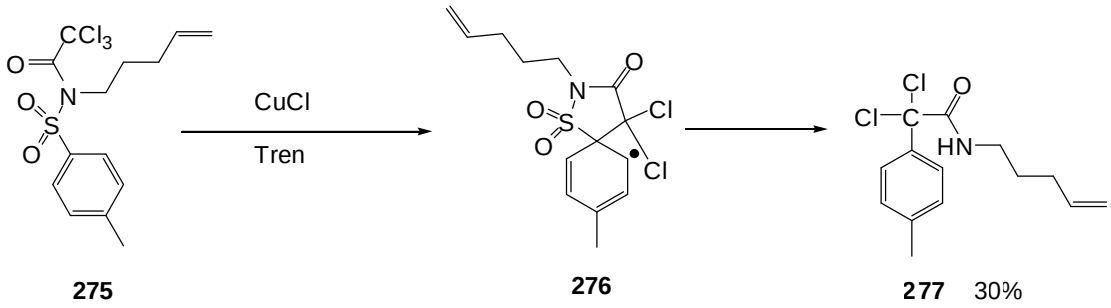
269 **270** **271**

274 81% **273** **272**

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_3SnH, 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.



275 **276** **277** 30%

Scheme 67 Clark's synthesis of rearranged amides

Thus, the use of Bu_3SnH 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.

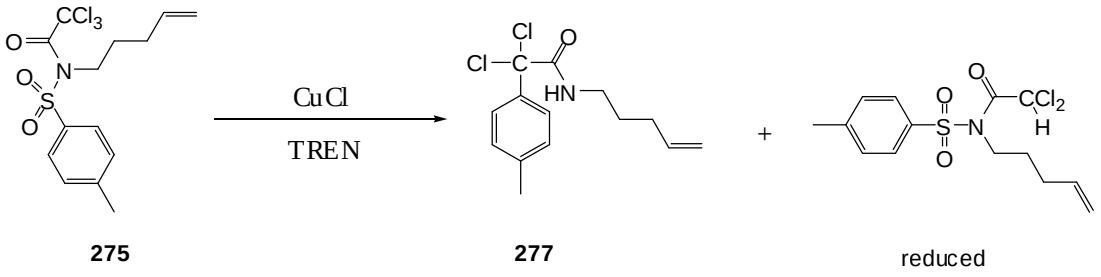
CHAPTER TWO

RADICAL REACTIONS OF *N*-BUTYL-(SUBSTITUTED)-ARYL SULFONAMIDES

Chapter Two

1.0 Introduction

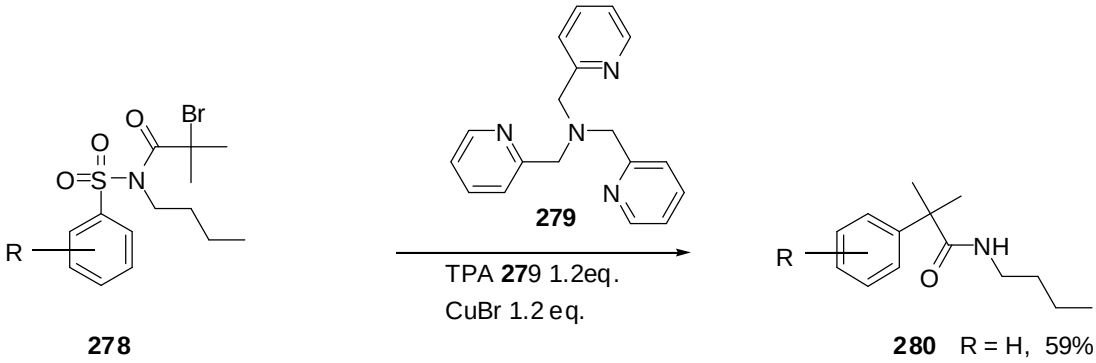
In light of the previous work discussed in **Scheme 67**, where substrate **275**[154] was observed to undergo rearrangement to form the rearranged amide **277** under ATRC conditions (see **Scheme 68**). It was decided to investigate this type of reaction further. The product **277** was tentatively assigned from the crude NMR spectra, and was not isolated pure, in addition, according to Wongtap,[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)[157-160] reaction of unactivated bromides using copper bromide/TPA[161-162] **279**.



275 **277** reduced

Scheme 68 Clark's synthesis of rearranged amides

The Clark group explored the rearrangement of unactivated bromide R = H **278** to amide **281**.[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**.



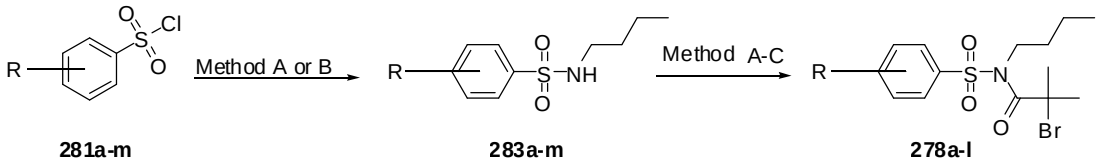
Scheme 69 Murphy's synthesis of rearranged amides

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.

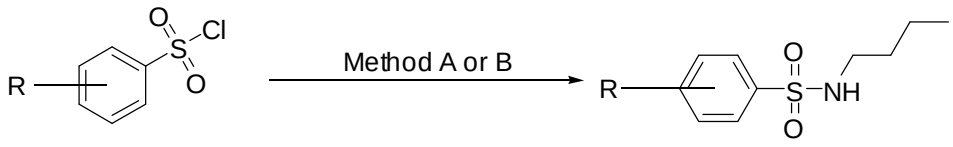
2.0 Synthesis and use of sulfonamide starting materials

In order to develop a synthesis towards compounds **278**, a preparation of the *N*-butyl substituted arylsulfonamides **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[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 ≈ 11)[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[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[166] (using diethyl ether/hexane), or by flash chromatography.[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**.



281 **283**

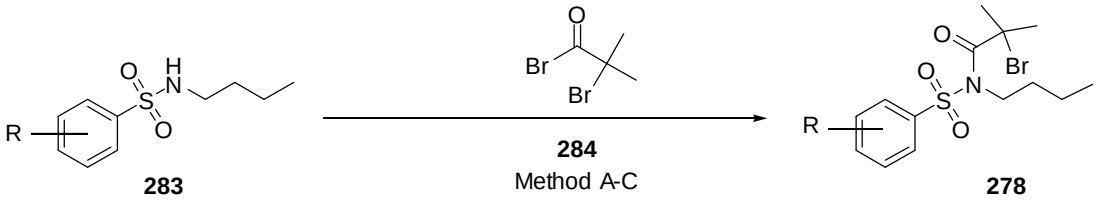
Entry	Substrate	Method	Entry	Substrate	Yield (%)
281a	H	B	**283a**	H	*99*[168]
281b	4-F	B	**283b**	4-F	*90*[169]
281c	4-Br	B	**283c**	4-Br	*77*[170]
281d	4-I	B	**283d**	4-I	*86*[171]
281e	4-CH_3	B	**283e**	4-CH_3	*89*[172]
281f	2,4,6-CH_3	A	**283f**	2,4,6-CH_3	[a]
281g	2-Naph.	A	**283g**	2-Naph.	*26*[173]
281h	4-OMe	A	**283h**	4-OMe	*90*[174]
281i	4-CN	B	**283i**	4-CN	*80*[175]
281j	4-NO_2	B	**283j**	4-NO_2	*87*[176]
281k	4-CF_3	B	**283k**	4-CF_3	*92*
281l	3,5-CF_3	A	**283l**	3,5-CF_3	*62*
281m	2-CN	A	**283m**	2-CN	*0*[177]

[a] Gift from D. Fullaway.

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

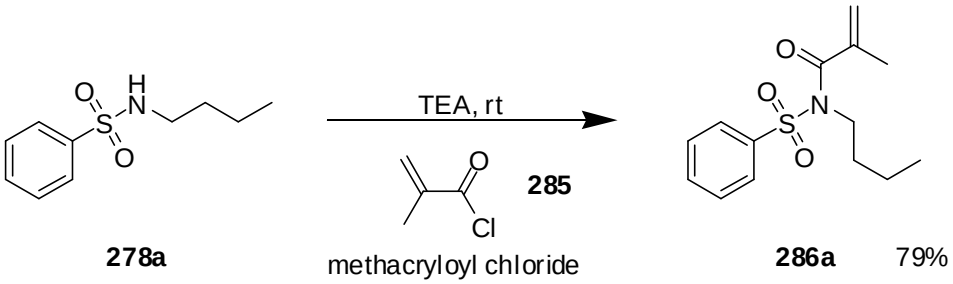
2.1 Synthesis and use of the radical precursor 278

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**).



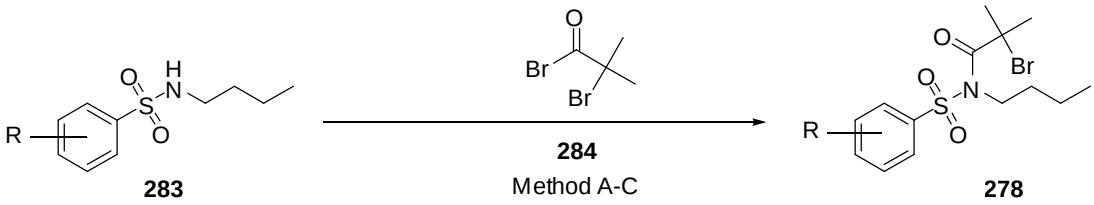
Scheme 71 Synthesis of radical precursors 278

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[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[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**).



Scheme 72 Synthesis of eliminated product 286a

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*-buytllithium to triethylamine (2.0 eq., pKa ≈ 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**).



Entry	Substrate	Method	Yield (%)
278a	H	B	*58* (48)[163]
278b	4-F	B	*52*
278c	4-Br	A	*70*
278d	4-I	B	*43*
278e	4-CH_3	B	*22* (79)[163]
278f	2,4,6-CH_3	B	*22* (7)[163]
278g	2-Naphthalene	B	*18*
278h	4-OMe	B	*48*
278i	4-CN	A	*56*
278j	4-NO_2	B	*32*
278k	4-CF_3	A	*70*
278l	3,5-CF_3	C	*67*

Table 2 Synthesis of the *N*-butyl-arylsulfonamides radical precursors 278a-l.

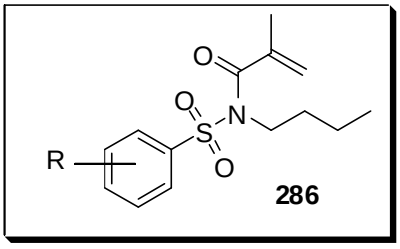


Figure 2 Structure of eliminated product 286

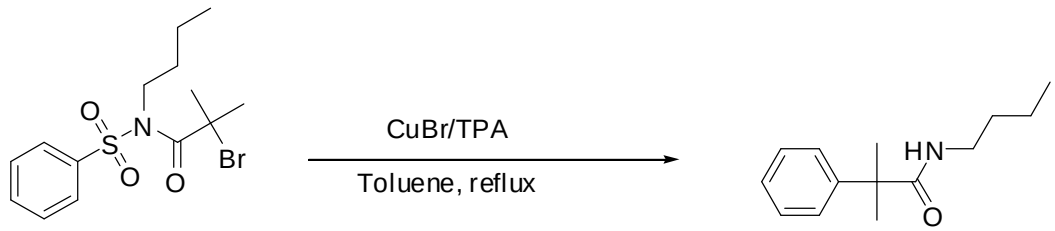
Chapter Two

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**.



278a **280a**

Scheme 73 Reaction of radical precursor with CuBr and TPA 279

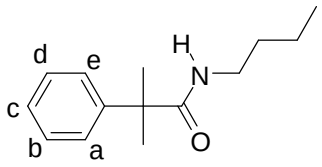
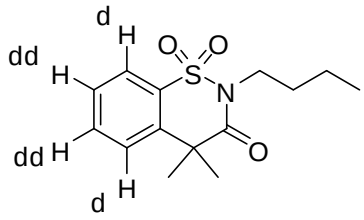


Figure 3 **^{1}H NMR assignment of phenyl rearranged amide**

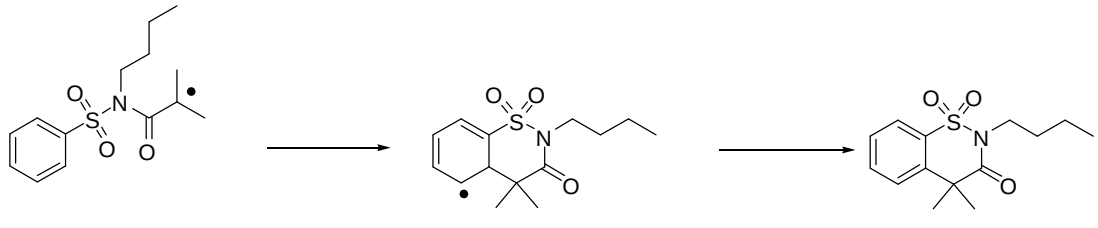
Analysis of the phenyl rearranged amide **280a** was made by ^{1}H NMR. Characteristic data involved a multiplex 7.4-7.25 (5H) for aromatics. A singlet at 1.55 for the dimethyl groups (6H), and peaks characteristic of the *n*-butyl group (2.92 (t), 1.46-1.39 (quintet), 1.33-1.23 (sextet), 0.80 (t,). 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**.



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**.



288 **289** **287**

Scheme 74

Proposed mechanism for the formation of the cyclic sulfonamide 287

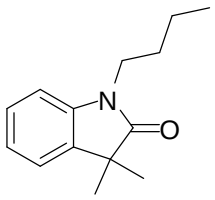
3.2 Purification of the radical products

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.[179] 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.[180-181] 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.[182] Other techniques not used but might be useful for analysis are ^{15}N NMR[183, 184] or the use of ^{17}O NMR[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 ^{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 ^{13}C NMR[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**).

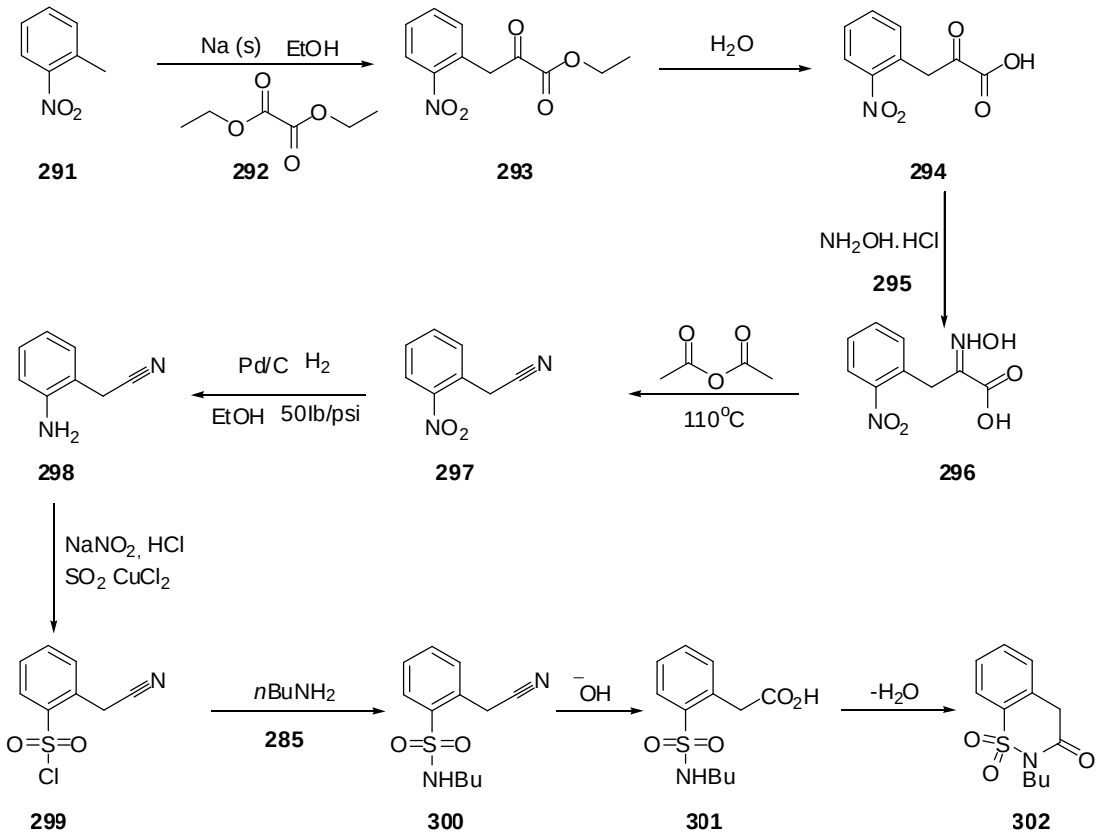


290

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.[187] Although the cyclised sulfur compound **287** is not known, the related compound **302** has been reported in the literature.[187] Treatment of *o*-nitrotoluene **291** (**Scheme 75**), with diethyl oxalate **292** in sodium ethoxide (generated *in-situ* from sodium metal and ethanol), led to *o*-nitrophenylpyruvic acid ethyl ester **293**. Hydrolysis of the ester led to the *o*-nitropyruvic acid derivative **294**. Treatment of **294** with hydroxylamine hydrochloride **295** furnished the *o*-nitropyruvic acid oxime **296**. Hydrolysis and

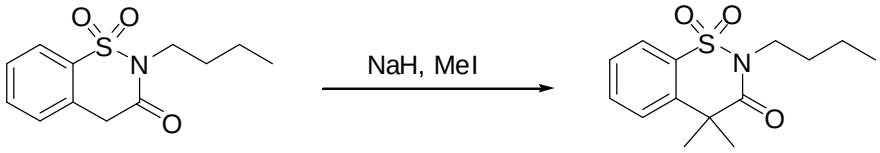
decarboxylation of the oxime **296** with acetic anhydride yield the *o*-nitrobenzylcyanide **297**. Hydrogenation of **297** with palladium on charcoal in absolute ethanol, and hydrogen gas at 50Ib/psi atmosphere furnished the *o*-aminobenzylcyanide **298**.[188] Diazoniation of **298** from sodium 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**.[189]



Scheme 75 Synthesis of the cyclic sulfonamide precursor

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)[187-189] and was not undertaken.

Consequently, the structure of the oxindole **290** has been confirmed by comparison to the literature data.[190]

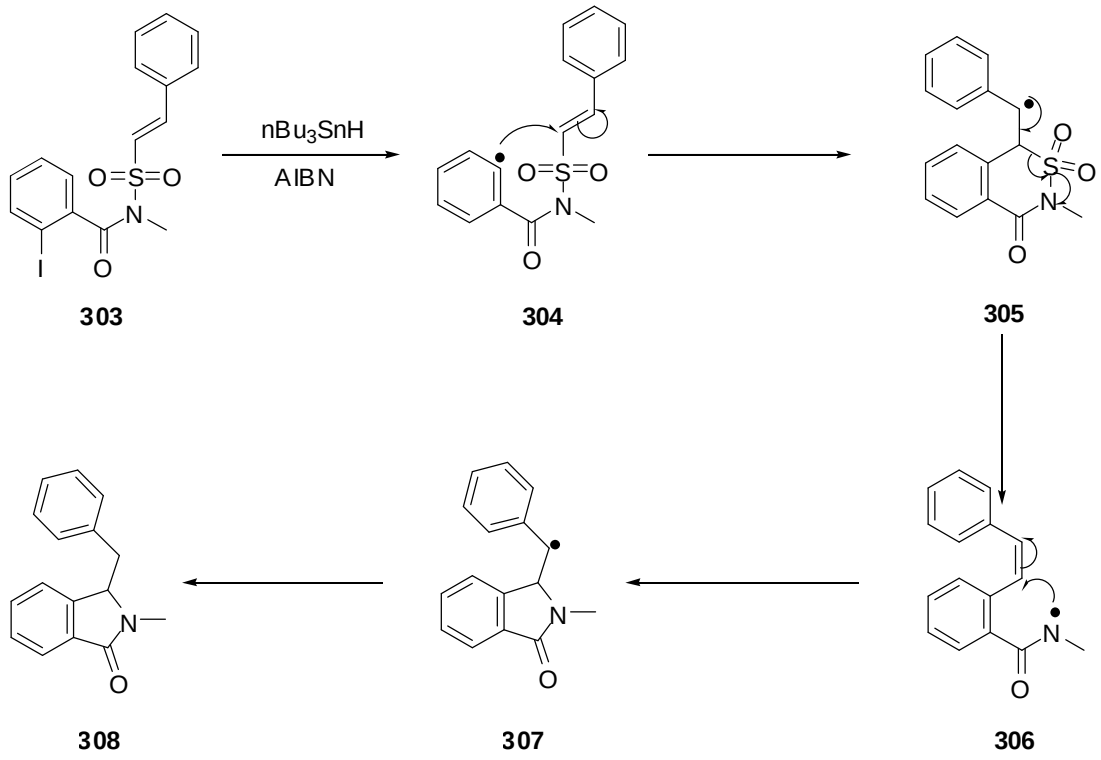


302 **287**

Scheme 76 Methylation of the sulfur precursor 287

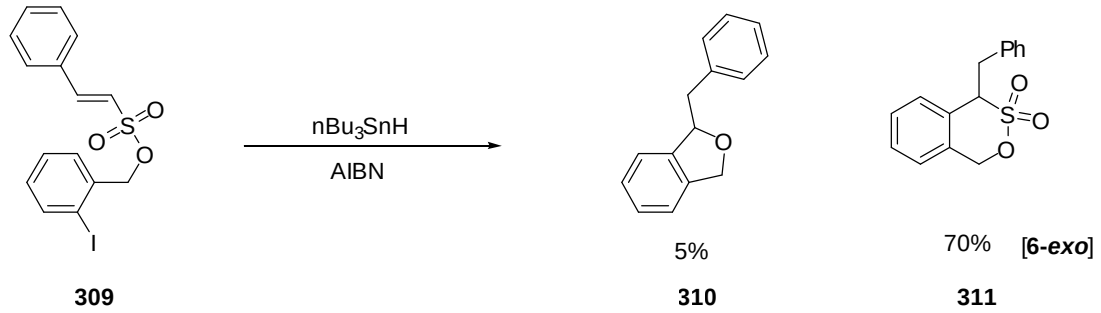
3.4 Potential mechanism for oxindole formation

Other groups have noted extrusion of SO_2[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-*exo* 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 *via* 1,5-*exo* 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

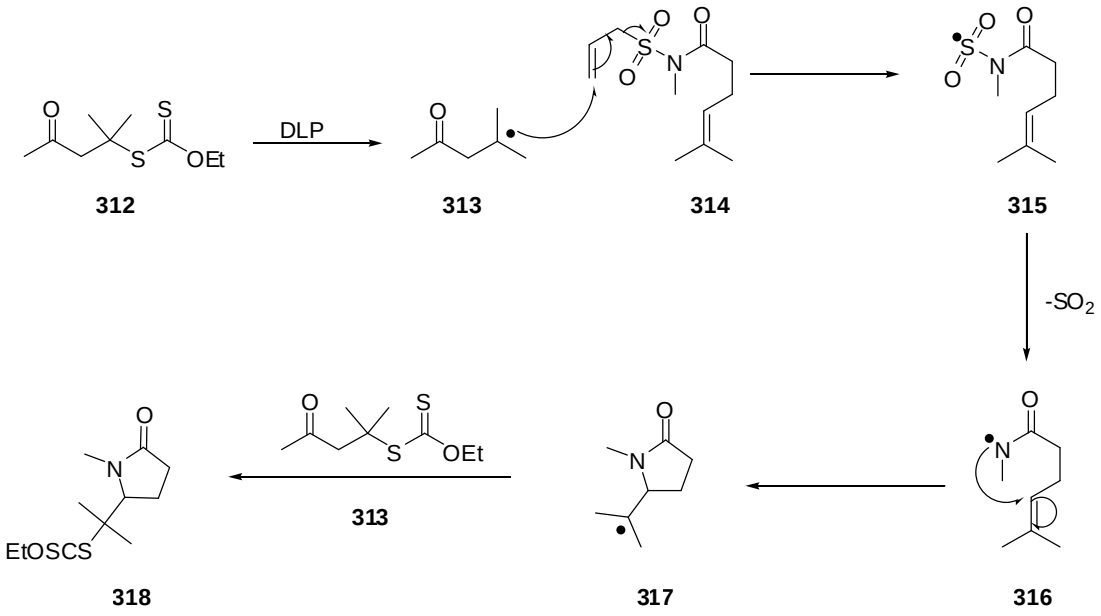
Motherwell has shown that radical cyclisation of vinylic sulfonate **309** (**scheme 78**) occurs similarly to give the 6-*exo*-product **311** in 70% yield, along with a minor amount of the ring contracted ether **310** in 5% yield *via* extrusion of SO_2.[152] However, no analogous pathway to these observations is available in the current reaction to give oxindole **290**.



Scheme 78 Motherwell's cyclic ether synthesis *via* SO_2 extrusion

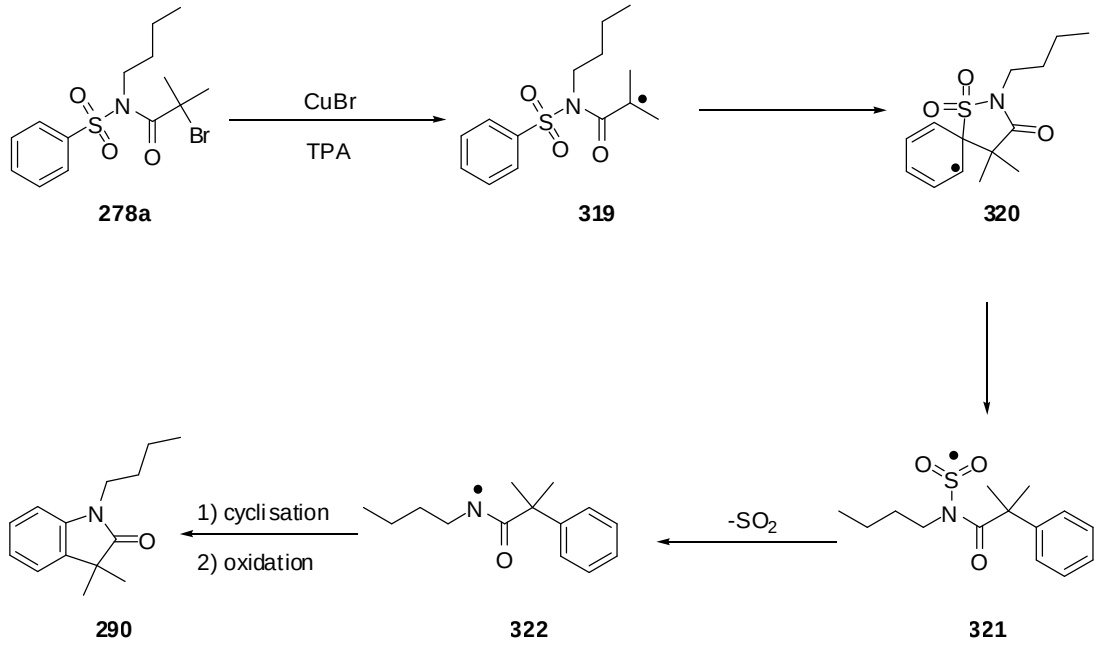
Alternatively, the oxindole **290** may be formed by direct cyclisation of the amidyl radical.[191] In the following example, xanthate **312** (**Scheme 79**) when treated with dilauroyl peroxide generated the alkyl radical **313**, which underwent an

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-*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

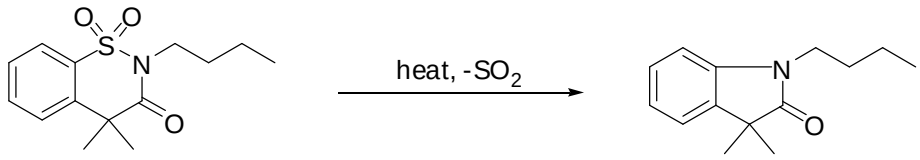
Consequently in the current reaction, the oxindole **290** (**Scheme 80**) may be formed by cyclisation of the amidyl radical **322** generated from the tertiary radical **319** *via* 1,5-*ipso* cyclisation and re-aromatisation to give **321** followed by loss of SO_2. Addition of the amidyl radical onto the aromatic ring followed by oxidation (presumably *via* $Cu(II)Br_2$) would yield the oxindole **290**.



278a 319 320 290 322 321

Scheme 80 proposed synthetic approach to oxindole

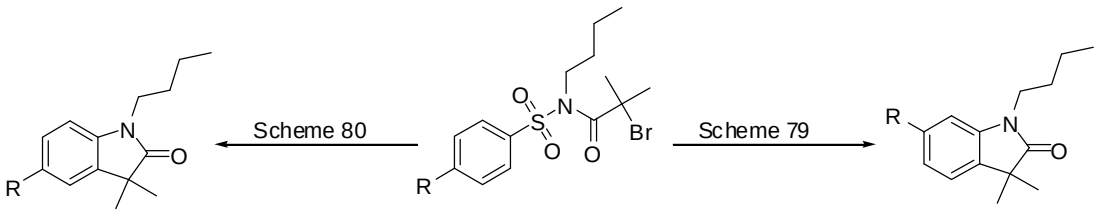
Alternatively, it may be possible that oxindole **290** forms *via* extrusion of SO_2 directly from the cyclic sulfonamide **287** as depicted in **scheme 81**.



287 290

Scheme 81 Proposed synthetic approach to oxindole

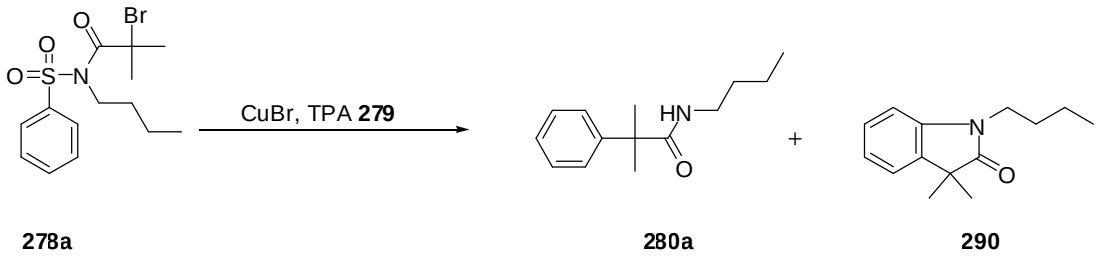
It should be possible to determine which of these two mechanisms is operating if a substitutent is appended to the aromatic ring. This is because both mechanisms lead to different regioisomeric oxindoles (**Scheme 82**).



Scheme 82 Proposed mechanisms for regioisomers

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.



278a 280a 290

Scheme 83 Phenyl sulfonamide radical reaction

Entry 278a	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 ºC, 12h	**100**	*72*	**0.3:1**
VI	PhMe, 110 ºC, 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 ^{1}H 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 ºC 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

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.

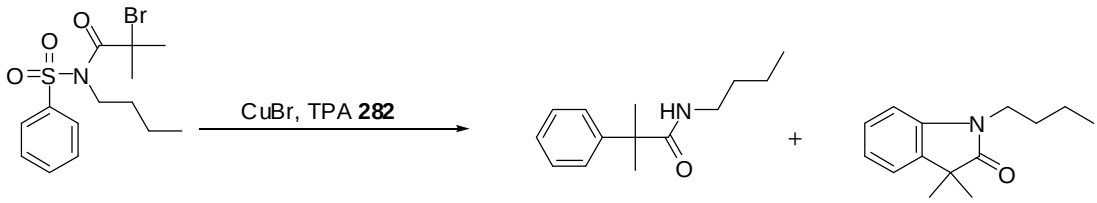
[**V**]: The previous reactions with toluene [**I**] and [**III**] showed very poor turnover and solubility of the ligand complex. When the reaction was repeated in refluxing toluene for 12 hours the reaction proceeded to completion, but now the cyclised product **290** predominated. The reaction was 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 CH_2Cl_2 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 ºC, preferentially giving rearranged amide **280a** while toluene at 110 ºC preferentially furnished oxindole **290**. This was interesting since similar work by Speckamp[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_2O, BMIM BF_4 (a common ionic liquid), all at the same temperature (**Table 4**).



278a **280a** **290**

Entry 278a	Reaction Conditions	Conversion %	Mass balance	Ratio 280a:290:X [a]
VII	MeOH, 50 ºC, 18h	**69**	*66*	**2:1:3**
VIII	THF, 50 ºC, 18h	**88**	*54*	**2:1:0**
IX	H_2O, 50 ºC, 18h	**100**	*51*	**2:1:0.2**
X	MeCN, 50 ºC, 18h	**100**	*74*	**1:0:6**
XI	BMIM BF_4, 50 ºC, 18h	**100**	*13*	**0.1:1:0.2**

[a] Significant amounts of uncharacterised by-product.

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

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.

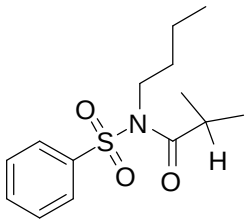
[**IX**]: Acetonitrile readily solubilised the copper ligand complex (**L**). Acetonitrile is often the choice solvent for ATRC reactions, however the reaction was not clean giving significant amounts of unidentifiable products which precluded all efforts to separate them in order to glean spectroscopic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

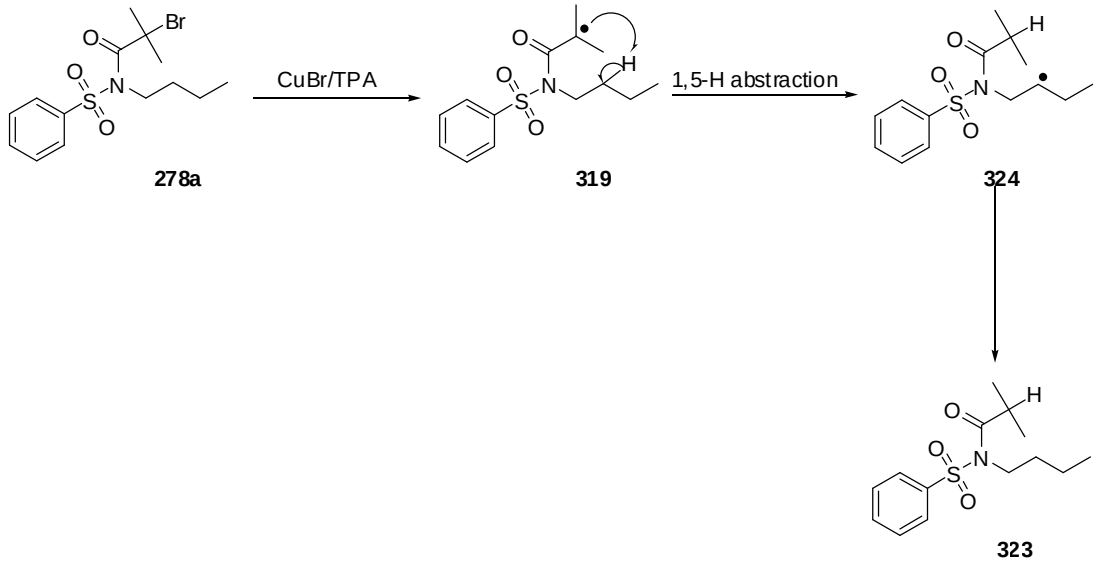
Although not fully characterised, it seems that the minor components (uncharacterised by-product) consist of **286a**, the corresponding sulfonamide **283a** and the reduced[178] product **323** (**Figure 6**). It became clear that the cleanest reactions with the best mass balance involved using either DCM or toluene.



323

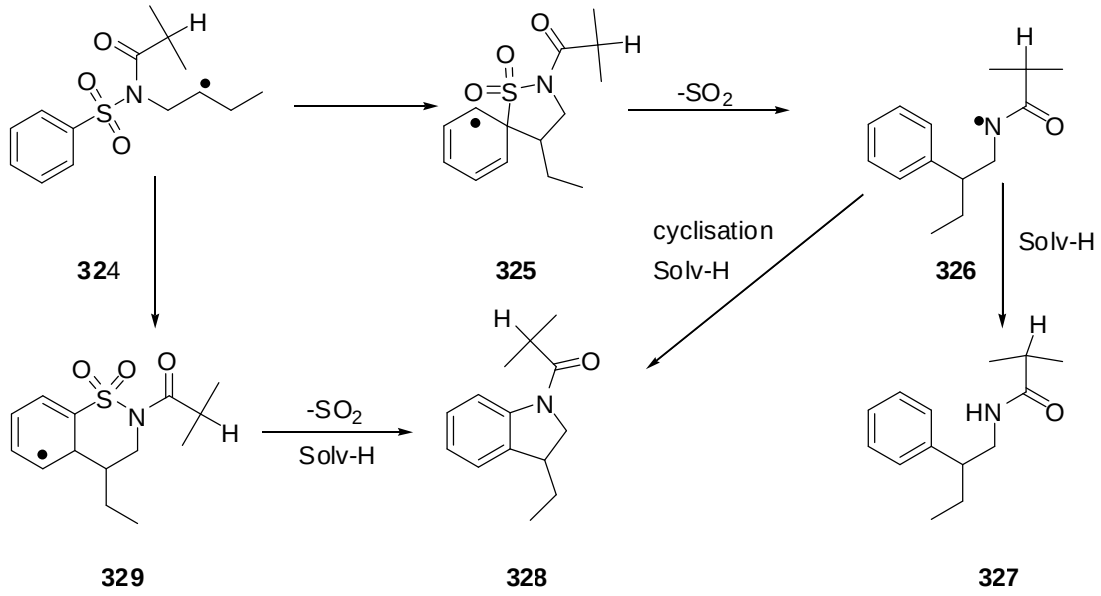
Figure 6 Phenyl reduced product 323

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-*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**.



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**).

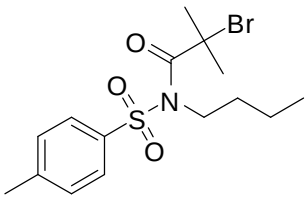
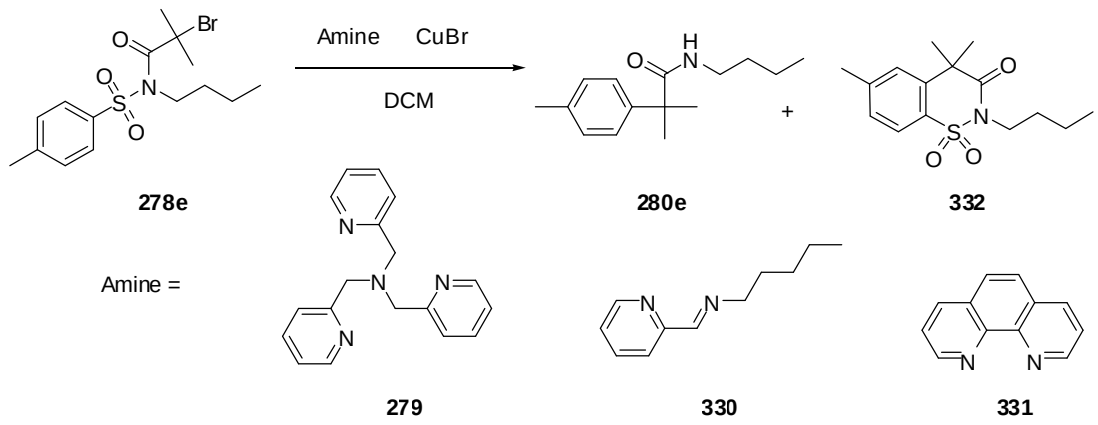


Figure 7 Structure of the tosyl radical precursor 278e

Chapter Two

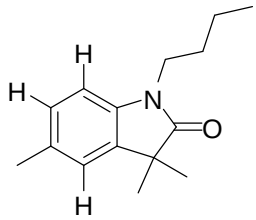
4.1 Introduction

Early work by Clark and Fullaway[163] showed reacting **278e** CuBr and various amine ligands could furnish the rearranged amide **280e** and a cyclised product initially proposed as the cyclic sulfonamide **332**. A series of amine ligands were used in conjunction with Cu(I)Br to form the ligand complex (**L**). The first experiment involved reaction of **278e**, bipyridine (2.0 eq.) and CuBr (2.0 eq.) in dichloromethane to furnish exclusively the rearranged amide **280e** but only in 26% yield. The following reaction involved using pentyl-pyridin-2-ylmethyleneamine **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 **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 **332** and the rearranged amide **280e** in 54% yield. The only difference in reaction conditions being one of concentration.



Scheme 86 Fullaway's synthesis of rearranged amide and cyclic product

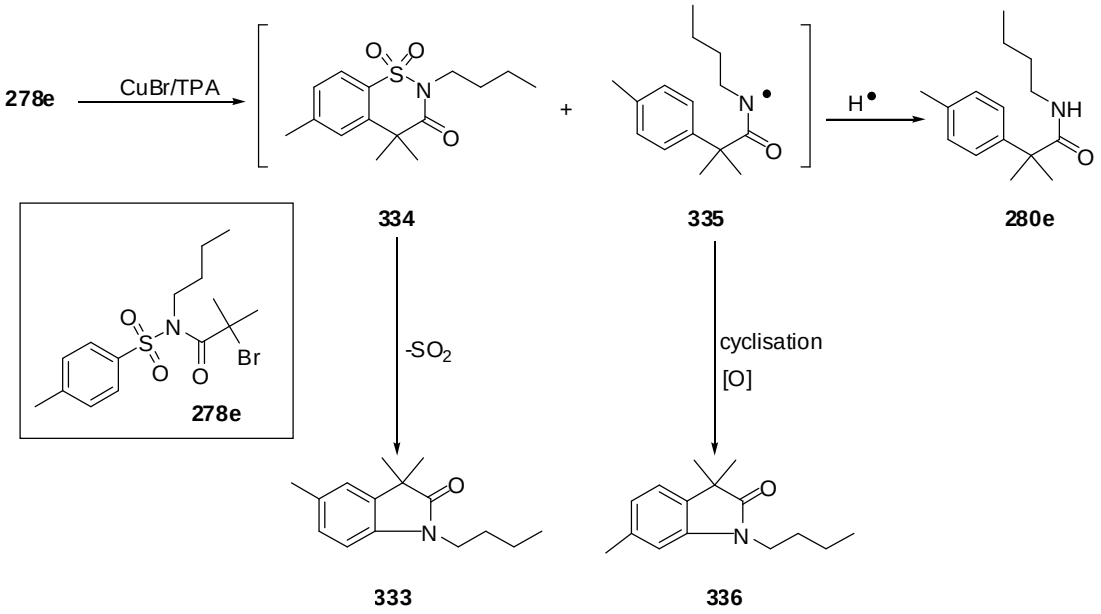
Mass Spectrometry of the cyclic compound **332** showed an M^+ (RMM = 231), which was contrary to the expected M^+ (RMM = 295). This could only occur from M-SO_2, indicating that it was most likely the oxindole **333** (**Figure 8**) and that the Clark group[165] had wrongly assigned the cyclic compound 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.



333

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 SO_2 from the cyclised compound, **334** then oxindole[190] isomer **333** would be produced, if the oxindole occurs from cyclisation of the amidyl radical **335**, the alternative oxindole isomer **336** should be detected.



Scheme 87 Proposed mechanisms for the oxindoles 333 and 336

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).

Structure determination.

- NMR spectroscopic techniques[197] for determining regioisomeric oxindoles: (1) NOE[198] (2) HMBC[198] (3) HETCOR[199] (4) INEPT[199] (5) COSY[199] INADEQUATE.[200]
- (1) X-Ray Diffraction,[201] X-Ray Crystallography[202]

Separation

- Separation techniques for isolating regioisomeric oxindoles: (1) Reverse-Phase Column Chromatography,[203] (2) HPLC-UV detector[203] (3) Reverse-Phase HPLC,[204] (4) GLC[204] (5) MPLC.[205]
- Capillary Electrophoresis[206]

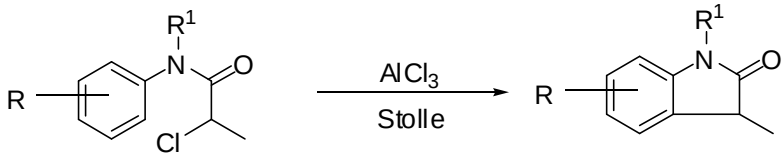
However while the methods could have been used to separate the products, ultimately an unambiguous synthesis of both of them was required.

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.

4.3 Radical reaction of tosyl precursor 278e

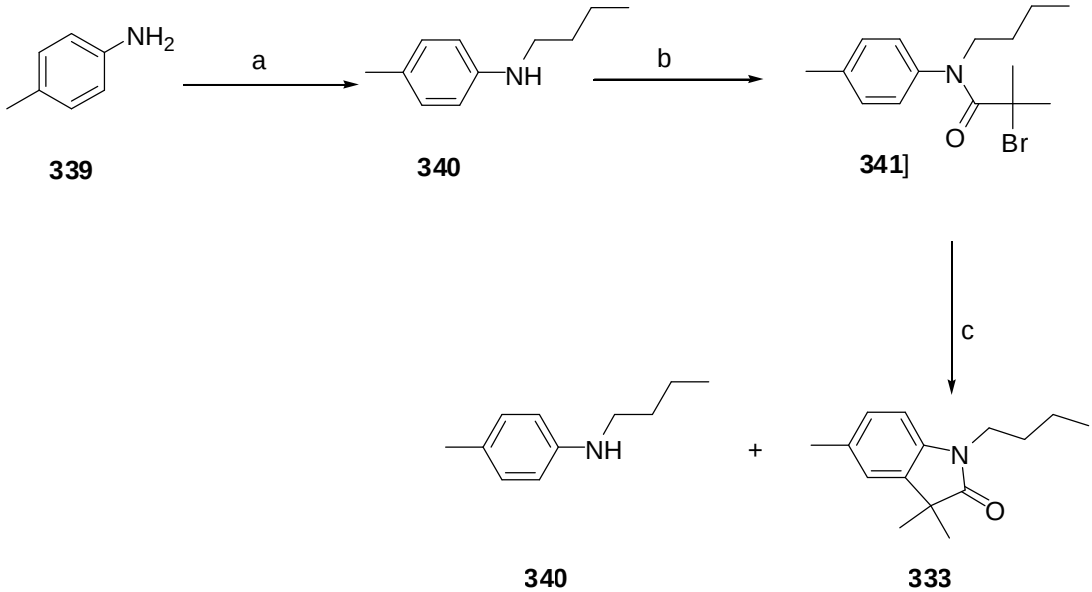
The identification of the major cyclised compound was accomplished by synthesising the oxindole **333** unambigiously. This was achieved using a modification of the Stollé synthesis (**Scheme 88**). In the original method, Stollé[207, 208] had reacted α-chlorocarboxylic acid chlorides with alkylated 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**.



337 **338**

Scheme 88 Stollé synthesis

For **333** a variation to this approach was used,[209-212] namely preparing the related bromo-analogue **341** as outlined in **Scheme 89**.



339 **340** **341**] **340** **333**

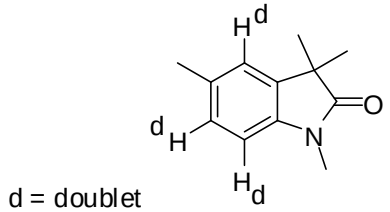
Key: (a) (i) NaH, DMF, (ii) n-BuI, RT, 24h; (b) TEA, **284**, RT, 3h; (c) $AlCl_3$ Anh. 50ºC at 10 min. then 160ºC at 60 min.

Scheme 89 Synthetic route toward the oxindole 333

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**.

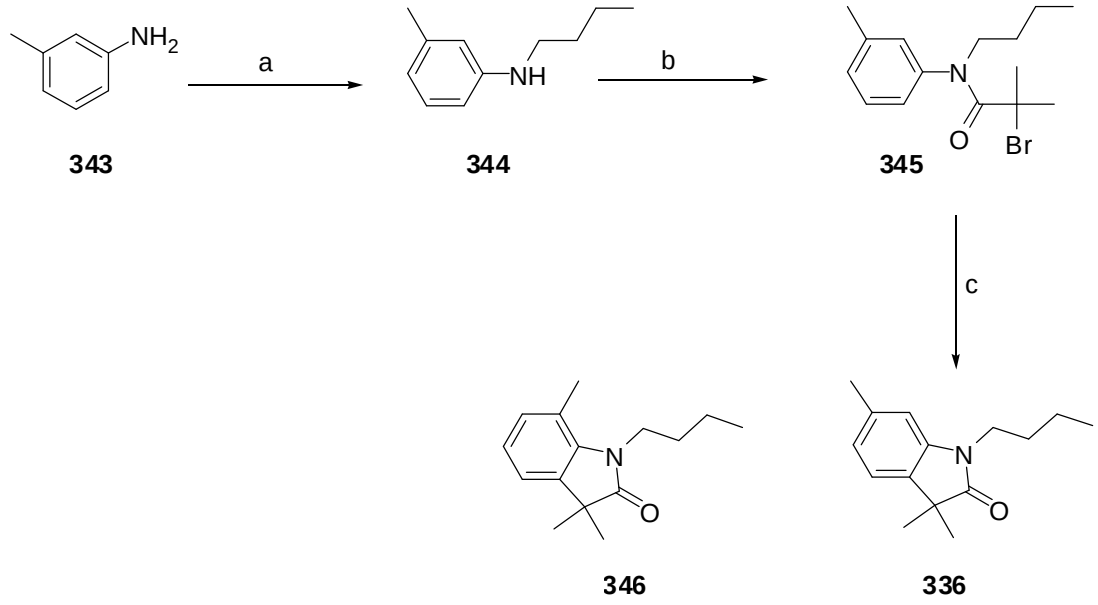
4.4 Attempted synthesis of the major oxindole 336

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's[178] group (**Figure 9**) and NMR was consistent with assignment of **336**.



342

Figure 9 Structure of Nishio oxindole 342

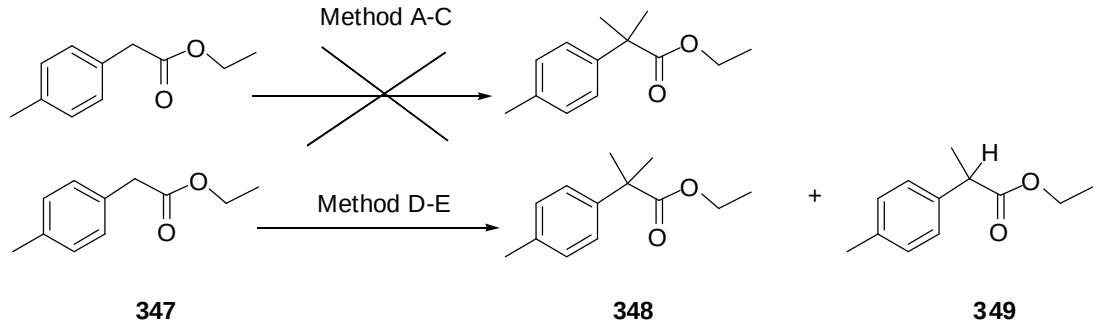


Key: (a) (i) NaH, DMF, (ii) n-BuI, RT, 24h; (b) TEA, **284**, RT, 3h; (c) $AlCl_3$ Anh. 50ºC at 10 min. then 160ºC at 60 min.

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]



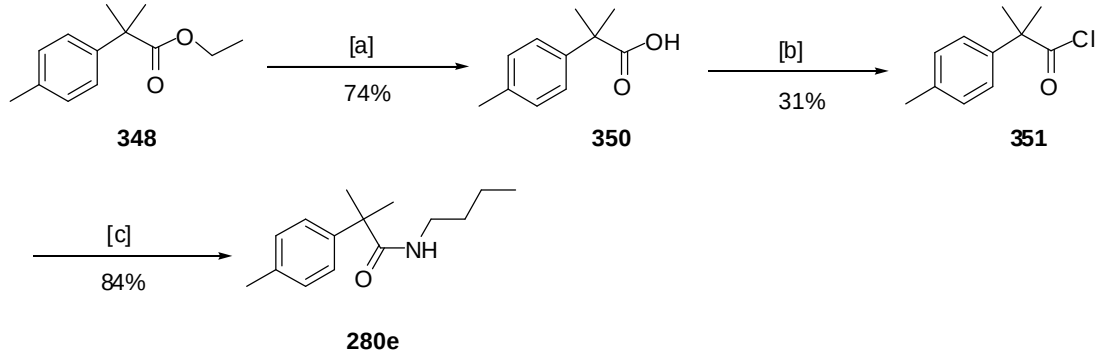
Scheme 91 Synthesis of the di-methylated product 348

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

room temperature for 48 hours (**Method A**).[216-217] 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**).[219] Again chromatography was required after initial distillation and gave the dialkylated product **347** in slightly better yield (20%).

The *gem* methylated ester **348** was next subjected to hydrolysis with ethanolic potassium hydroxide solution to give the acid **350**[220] 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** [221-222] with excess butylamine **282**. The spectroscopic details matched those of the product isolated from the copper mediated reaction (**Scheme 87**).

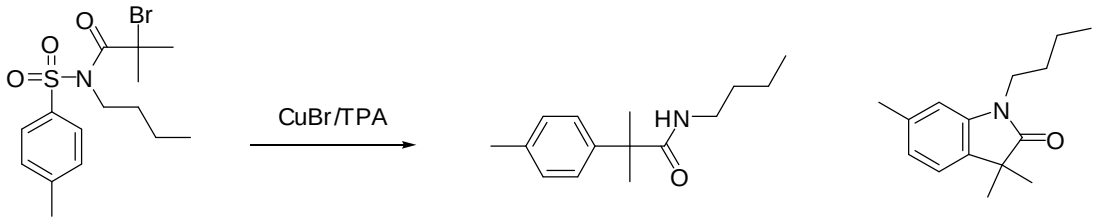


Key: (a) (i) KOH, Anh. EtOH refluxed 6d (ii) acidified with 2M HCl; (b) $(COCl)_2$ DCM 40 ºC 24h; (c) $nBuNH_2$ (3.0 eq.), RT, 2d.

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**.



278e 280e 336

Scheme 93 Radical reaction of tosyl derivative 278e

Entry 278e	Reaction Conditions	Conversion %	Mass Balance %	Ratio 280e:336/ (278e)[a]
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 °C, 18h	**85**	*65*	**1.2:1** (**1.4:1**)
IV	THF, 50 °C, 18h	**76**	*69*	**1**:**1** (**2:1**)
V	H_2O, 50 °C, 18h	**24**	*74*	**1**:**1** (**2:1**)

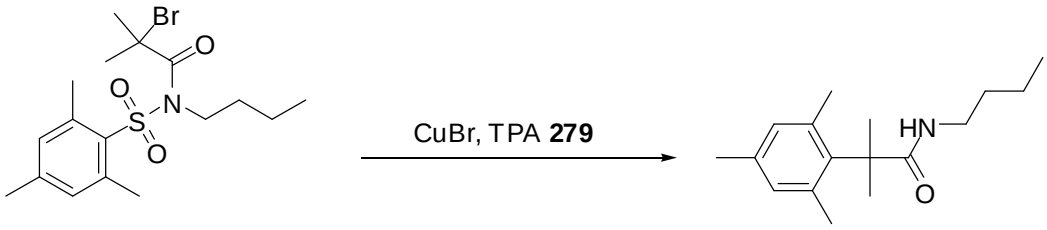
[a] Ratios for cyclisation of parent **278a** in parenthesis for comparison

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 H_2O 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.

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 *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 *ortho* methyl groups is also likely to retard the rate of formation of the rearranged amide **280f** due to increased steric hinderence for the *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.



278f **280f**

Scheme 94 Radical reaction of mesitylene sulphonamide 278f

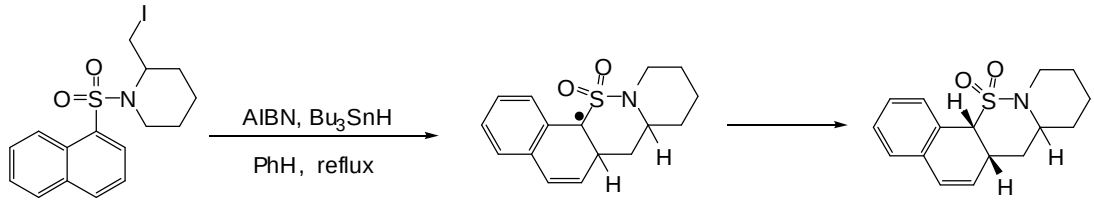
Entry 279f	Reaction Conditions	Conversion %	Mass balance	Ratio 280f
I	Toluene, 50 ºC, 18h	**0**	*100*	**0**
II	BMIM BF_4, 50 ºC, 18h	**100**	*25*	**1**

Table 6 Effects of reaction conditions on product distribution for 278f

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.[223]

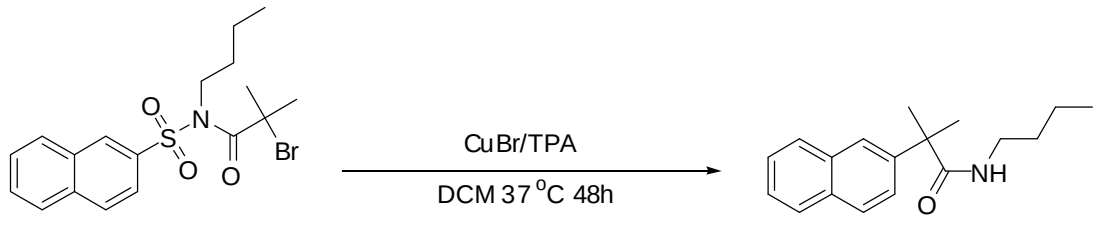
6.0 *N*-Butyl-2-naphthylsulfonamide 278g

Previous work by Speckamp[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 substates.



248 **249** **250**

Scheme 95 Speckamp's naphthalene sulfonamide radical reaction

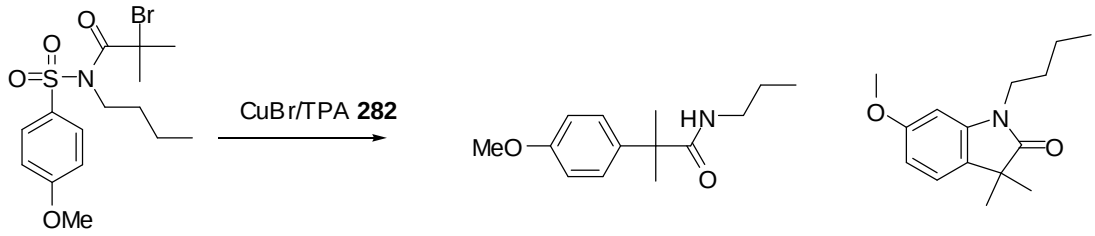


278g **280g**

Scheme 96 Radical reaction of naphthalene sulfonamide 278g

7.0 *N*-Butyl-4-methoxy-benzenesulfonamide 278h

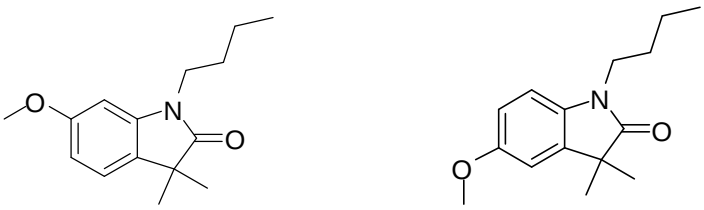
Having investigated the scope of the reaction with simple substrates, it was now decided to determine the effects of various electron donating and withdrawing aryl groups on the efficiency and selectivity of the mechanism. The first substrate to be examined involved the electron donating *para* methoxy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



278h **280h** **352**

Scheme 97 Radical reaction of 4-methoxy sulfonamide 278h

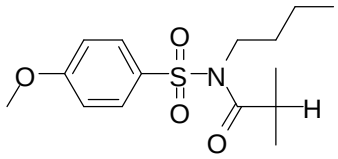
Reacting the bromo radical precursor **278h** with copper bromide/TPA in dichloromethane at 37 ºC for 18h [**II**] furnished 3 products in 73% overall yields. Chromatography separated two cyclised regioisomeric products **352** and **353** from the rearranged amide **280h** obtained from individual column 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**).



352 **353**

Figure 10 Structure of regioisomeric oxindoles 352 and 353

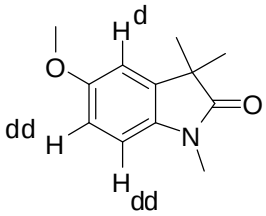
The minor cyclised product was tentatively assigned as the 5-substituted oxindole **353**[224] that was analogous to the previously synthesised oxindole **333**. This could occur *via* the extrusion of sulfur dioxide mechanism as shown in **Scheme 87**. A minor compound tentatively assigned as the reduced product **323h** was also isolated (**Figure 11**).



323h

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 **352**. An analogous compound to **353** was synthesised by Hartwig.[224] (**Figure 12**) Spectroscopic data was similar to the minor oxindole **353**[225]

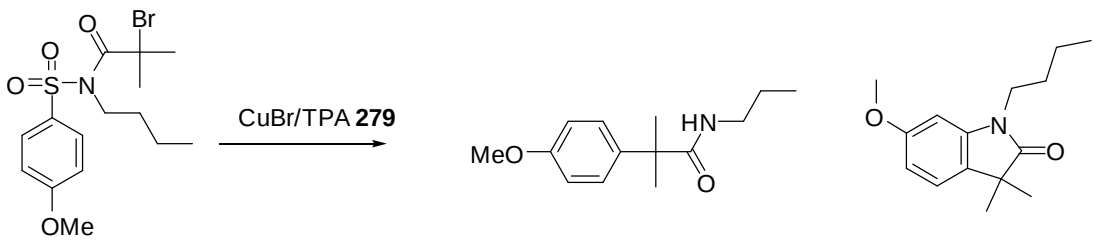


354

Figure 12 Hartwig's *N*-Me oxindole 354

An important observation was that the reaction appeared to be faster than for the tosyl derivative **278e** (85% conversion under the same conditions). This trend was explored more thoroughly (**Table 7**). Initial studies using dichloromethane at 37 ºC for 3h [**I**] showed complete conversion to products. The reaction was repeated using toluene at 50ºC [**III**] and 80ºC [**IV**] for 18h. Again, there was complete conversion to products (as a comparison **278e** proceeded to 56% conversion under identical conditions to entry **III**). The ratio of products **280h** to **352** from these reactions was

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 ºC 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.



278h **280h** **352**

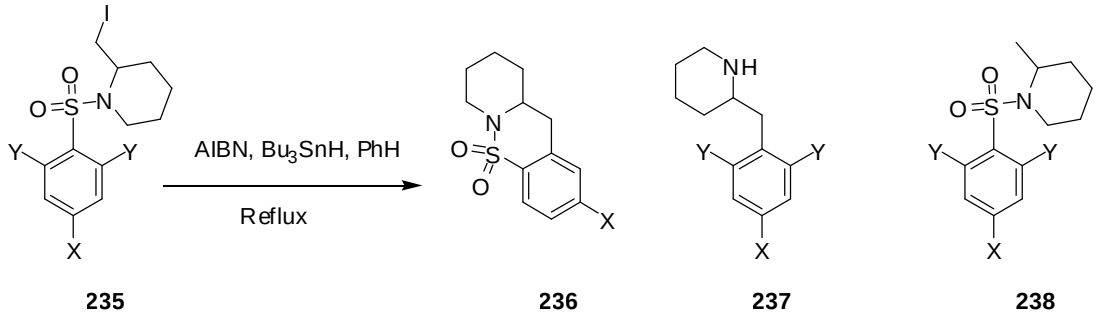
Scheme 98 Radical reaction of 4-methoxy sulphonamide 278h

Entry 278h	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 *para* position.

Speckamp[226] has investigated the effect of halogen substitution in the *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).

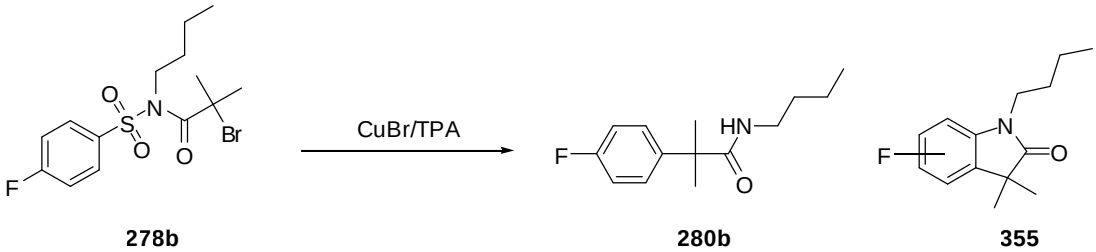


235 **236** **237** **238**

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

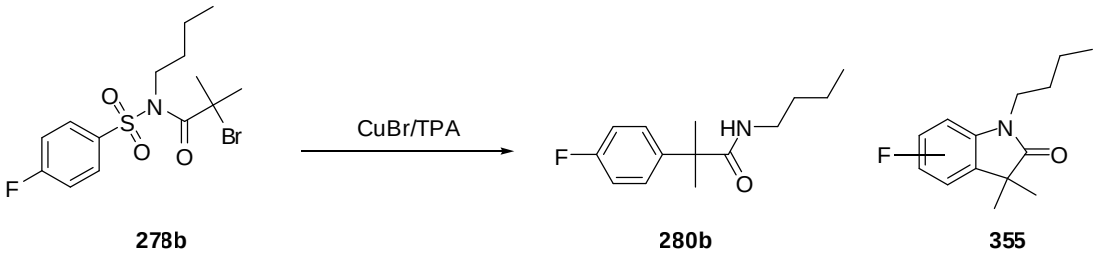


278b **280b** **355**

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**).

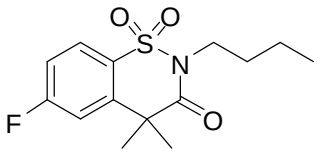


Scheme 101 Radical reaction of 4-fluoro sulfonamide 278b

Entry		Solvent/Temp./Conversion	Ratio 280b:355
I	**280a**[a]	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.



356

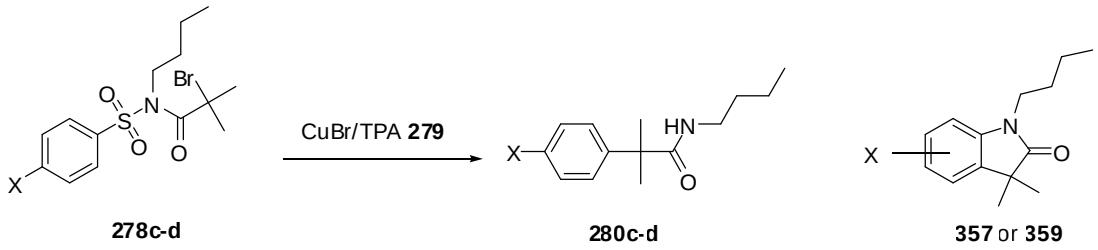
Figure 13 Structure of proposed fluoro compound 356

Due to the complex ^{1}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 = Br in dichloromethane at 37 ºC 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}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**.



278c-d **280c-d** **357** or **359**

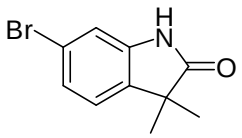
Scheme 102 Radical reaction for 4-bromo and 4-iodo sulfonamides

Entry	Reaction Conditions	Conversion %	Mass balance	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 = Br; **278d** X = I, **357** = X = Br, **359** = X = I

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

An analogous compound to **357**, namely **358** has been synthesised by Atwal *et al.*[227] as shown in **Figure 14**.



358

Figure 14 Atwal's structure of oxindole 358

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.

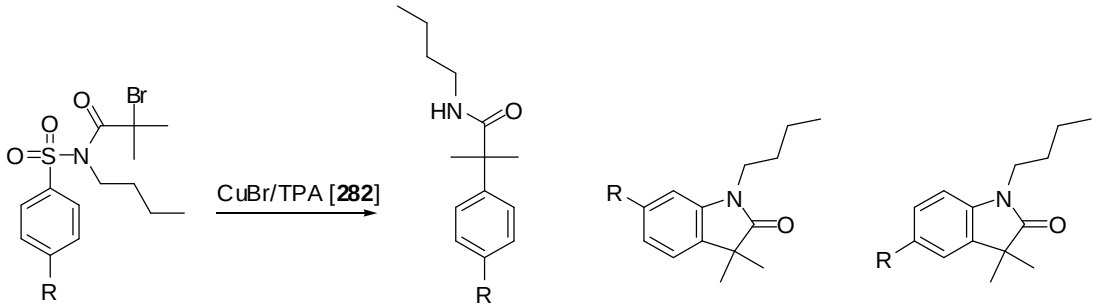
The rates of reaction between the parent sulfonamide **278a** and the halogens **278b-d** in DCM under copper(I)bromide/TPA conditions showed that the halogens reacted faster than the parent compound **278a.**

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



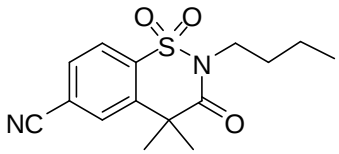
278i-j **280i-j** **360** and **361** **362** and **363**

Key: **279i** = CN; **279j** = NO_2; R = CN = **360** and **362**, R = NO_2 = **361** and **363**

Scheme 103 Radical reactions of 4-cyano and 4-nitro sulfonamides

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 ^{1}H NMR showed two products the rearranged amide **280i** and the cyclised product. Chromatography separated the rearranged amide from the cyclised product **364** with the rearranged amide **280i** being obtained pure in good yield (60%) (see **Appendix 8**). Only <u>one</u> 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**).

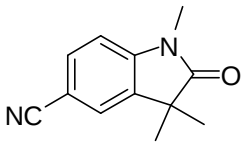


364

Figure 15 Proposed minor cyclised sulfonamide 364

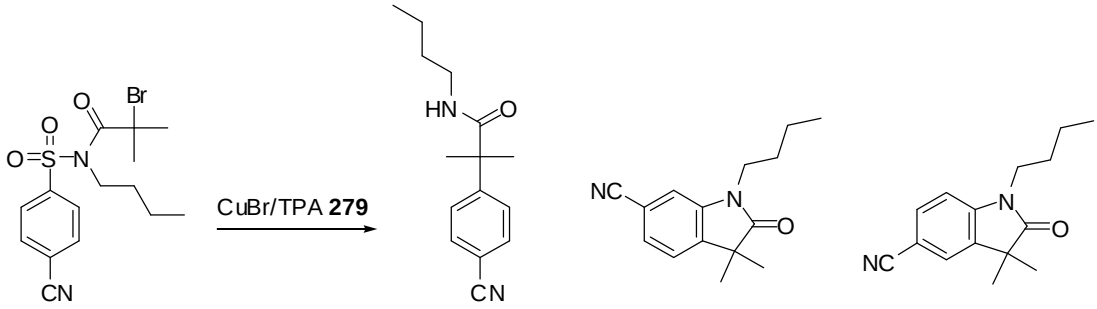
The CHN gave C, 74.3; H, 7.8; N, 11. 6, and the calculated oxindole was C, 74.1; H, 7.8; N, 11.0. It was most likely that the cyclised products were the regioisomers of the oxindoles **360** and **362**.

An analogous compound by Hartwig[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**.



365

Figure 16 Hartwig's structure 365



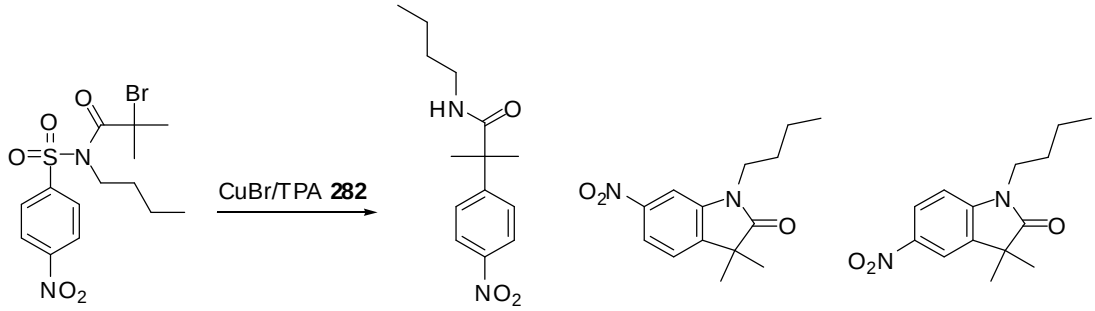
278i 280i 360 362

Scheme 104 Radical reaction of 4-cyano sulfonamide 278e

Entry 278i-j	Reaction Conditions	Conversion %	Mass Balance	Ratio 280 :360:362
I	**278i**, DCM, 37 °C, 4h	**100**	53	**4:0:1**
II	**278i**, PhMe, 110 ºC, 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 ºC 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**.



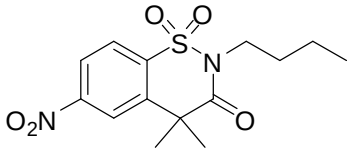
Scheme 105 Radical reaction of 4-nitro sulfonamide 278j

Entry 278i-j	Reaction Conditions	Conversion %	Mass Balance	Ratio 280 :361:363
I	**162 j**, DCM, 37 °C, 2.5h	**100**	69	**6.5:1:0**
II	**162j** DCM, 37 ℃, 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

attributed to one of the oxindoles, but it is not possible to determine which oxindole as this would be from the crude NMR.



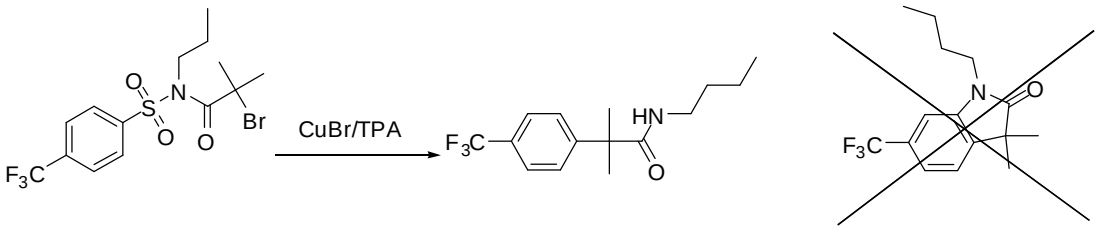
366

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

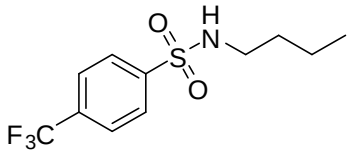
The previous compounds **278i-j** predominately led to the rearranged amides **280i-j** in dichloromethane at 37 ºC. Although only seen as a minor by-product, a significant amount of the hydrolysed sulfonamide **283i-j** (see **page 86**), was also isolated from these reactions. This maybe due to the 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**).



278k **280k** **367/368**

Scheme 106 Radical reaction of 4-trifluoromethylbenzenesulfonamide 278k

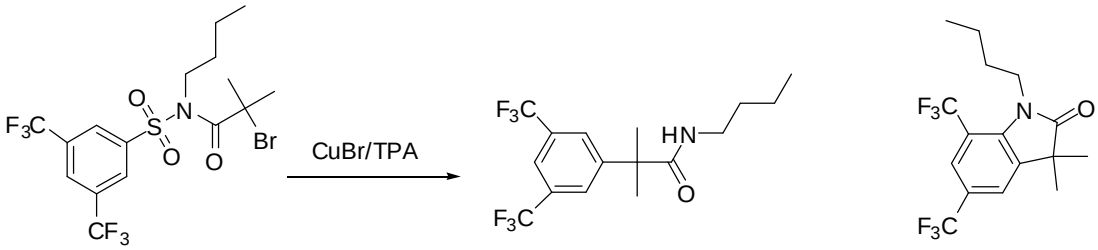
Heating the bromide **278k** in dichloromethane at 37 ºC for 4.5h led to complete disappearance of the starting material. Again the reaction was more rapid than the parent (R = H) and *p*-methoxy (R = OMe) with a similar rate to R = CN. The crude ^{1}H NMR showed two compounds which were identified as 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**.



283k

Figure 18 Structure of trifluoromethylbenzenesulfonamide

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 ºC 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**).



278l **280**] **367/368**

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 ºC, 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 ºC. 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* trifluromethyl 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

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-NO_2, 4-CN < 4-OMe, 3, 5-CF_3). The rates of reaction also seem to be influenced by the substituent with the rate following (2-naphthyl < H, 4-CH_3 < 4-I, F, 4-Br, < 4-CN, CF_3 < 4-OMe < 4-NO_2, <3,5-CF_3). The intermediate cyclohexadienyl radical **355** will be stabilised by both electron withdrawing and donating substitutents 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

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.

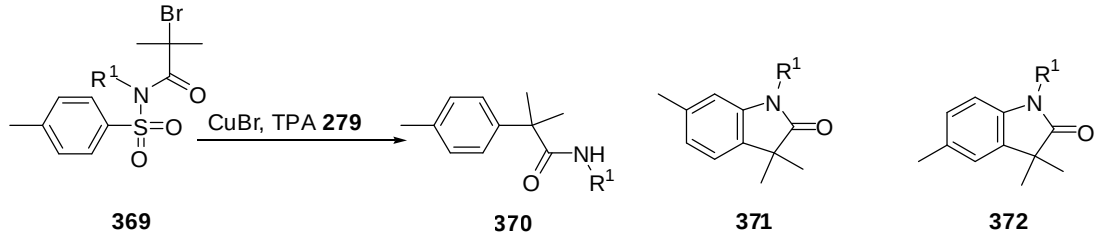
CHAPTER THREE

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, (±)-*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_2Br) were kept constant.

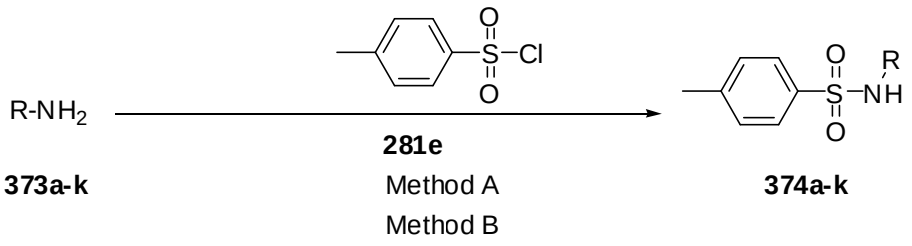


369 **370** **371** **372**

Scheme 108 General reaction scheme for *N*-alkyl substrates 369 with CuBr/TPA

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

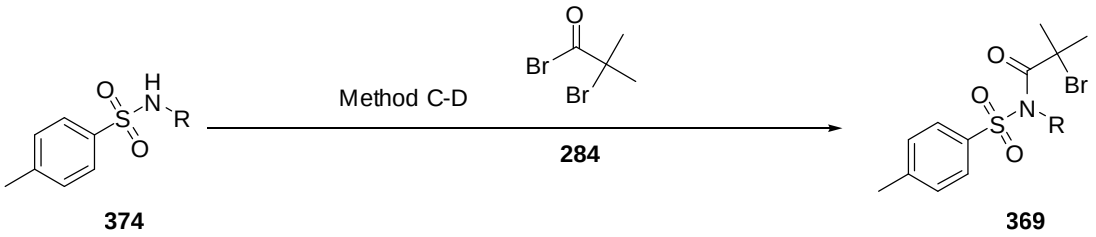
Entry	R-NH_2	Method	Entry	Yield %
373a	Ethyl	B	**374a**	*84* [228]
373b	Propyl	B	**374b**	*81* [229]
281e	*n*-Butyl[a]	B	**283e**	*89* [230]
373c	Pentyl	B	**374c**	*92* [231]
373d	Hexyl	A	**374d**	*62* [232]
373e	Docecyl	B	**374e**	*92* [233]
373f	Isopropyl	B	**374f**	*65* [234]
373g	*iso*-Butyl[a]	B	**374g**	*85* [235]
373h	(±)-*sec*-Butyl[a]	B	**374h**	*41* [236]
373i	*tert*-Butyl	B	**374i**	*76* [237]
373j	(R)-(-)-1-Cyclohexylethyl	A	**374j**	*97* [238]
373k	Adamantan-1-yl	A	**374k**	*76* [239]

Key: a = Synthesised by D. Fullaway[165] **283e** = 88%, **374g** = 95%, **374h** = 85%

Table 13 *N*-alkyl-4-methylbenzenesulfonamide

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**).



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[163]. Yield: **278e** = 79%, **379g** = 62%, **369h** = 50%

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

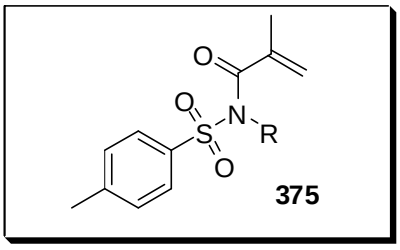


Figure 19 The structure of the acrylamide 375

Chapter Three

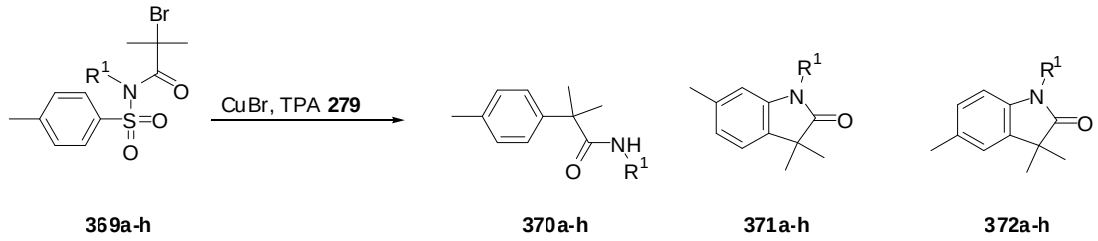
2.0 Reaction of *N*-alkyl-4-methylbenzenesulfonamide with copper (I) bromide and TPA

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 **279** 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 ºC 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.



369a-h **370a-h** **371a-h** **372a-h**

Scheme 111 General scheme for *N*-alkyl substrates 369 with CuBr/TPA

Entry 369	Reaction Conditions	Conversion %	Mass balance	Ratio 370:371/372
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]

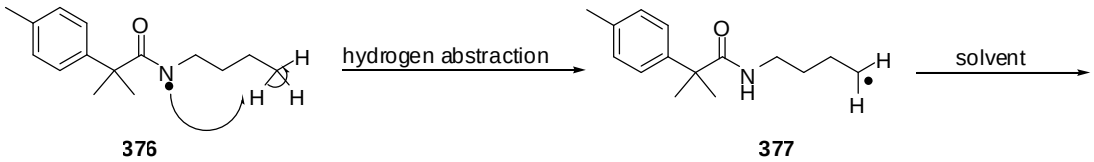
Table 15 The effects of dichloromethane on product distribution

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 substitutent **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.

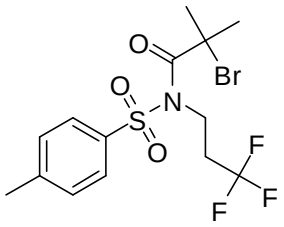
The reasons for the trends are not clear. Presumably, the product distribution is determined from the relative rates of cyclisation versus reduction of the intermediate amidyl radical **335**, (see **Chapter 2**, **Scheme 87**). The factors, which govern these rates, must be relatively complicated as 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**.



376 377

Scheme 112 Proposed mechanism for radical hydrogen translocation

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.



378

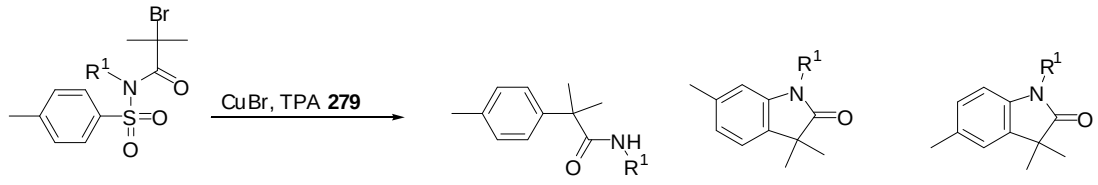
Figure 20 Structure of compound to block 1-5-H abstraction 378

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 BF_4, 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**).



369 370 371 372

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 BF_4 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.

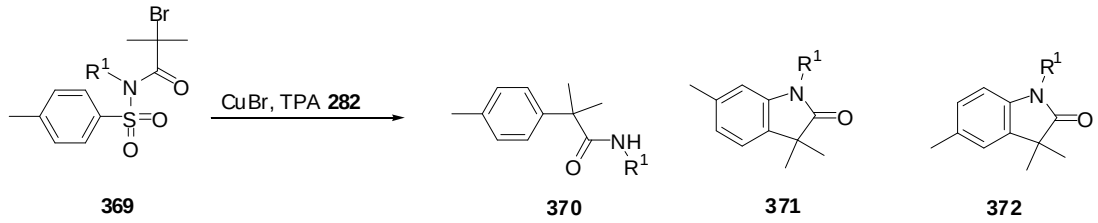
Comparing the reactions in toluene at 50 ºC and 110 °C the N-Et **369a** undergoes the fastest reaction, followed by *N*-*n*-Bu **278e** and *N*-*i*-Bu **369g**. This would be expected on steric grounds. The low conversion of *N*-*i*-Bu (**369g Entry VII**) made determining the product ratio difficult from the crude NMR and so the result of this experiment should be treated with caution.

In toluene at 110 ºC 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*-*n*Bu **281e** in the ionic liquid BMIM BF_4 at 50 ºC for 18hs as depicted in **Table 17**.



369 370 371 372

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**

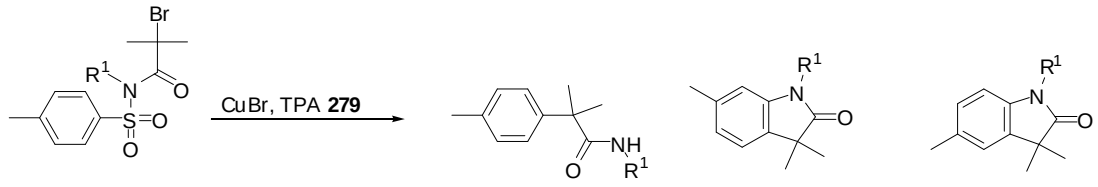
Table 17 The effects of the ionic liquid BMIM BF_4 on product distribution.

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 C_5, C_6 and C_{12} 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

(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 ^{o}C, 18hrs) are represented here as a comparison.



369 **370** **371** **372**

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

Scheme 115 General reaction scheme for *N*-alkyl substrates 369 with CuBr/TPA

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 ºC 18h) in parenthesis.

Table 18 The effects of dichloromethane at room temperature on product distribution.

Chapter Three

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 (CMe_2Br) were kept constant.

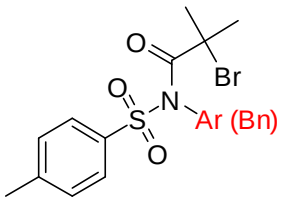
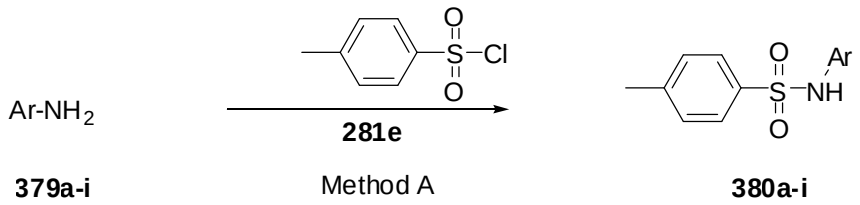


Figure 21 General structure for the (hetero)aryl derivatives 381

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**).



Scheme 116 Synthesis of *N*-hetero(aromatic) substrates 380a-i

Entry	R-NH_2	Method	Entry	Yield %
379a	*N*-*p*-Methylbenzyl	A	**380a**	*22* [240]
379b	*N*-*p*-Methoxybenzyl	A	**380b**	*33* [241]
379c	*N*-*o*-Trifluoromethylbenzyl	A	**380c**	*83* [242]
379d	*N*-Pyridin-2-ylmethyl	A	**380d**	*32* [243]
379e	*N*-Furfuryl	A	**380e**	*75* [244]
379f	*N*-Thiophenemethyl	A	**380f**	*75*
379g	*N*-Phenyl	A	**380g**	*0*
379h	*N*-Pyrid-2-yl	A	**380h**	*0*
379i	*N*-Quinucldinyl	A	**380i**	*1*

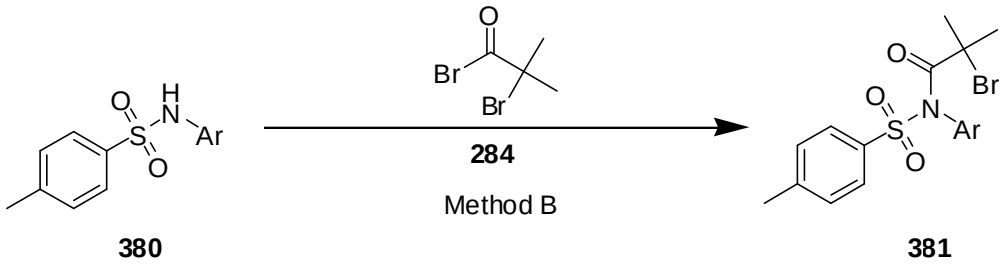
Table 19: Synthesis of *N*-(hetero)aromatic-4-methylbenzenesulfonamides

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**.

Chapter Three

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.



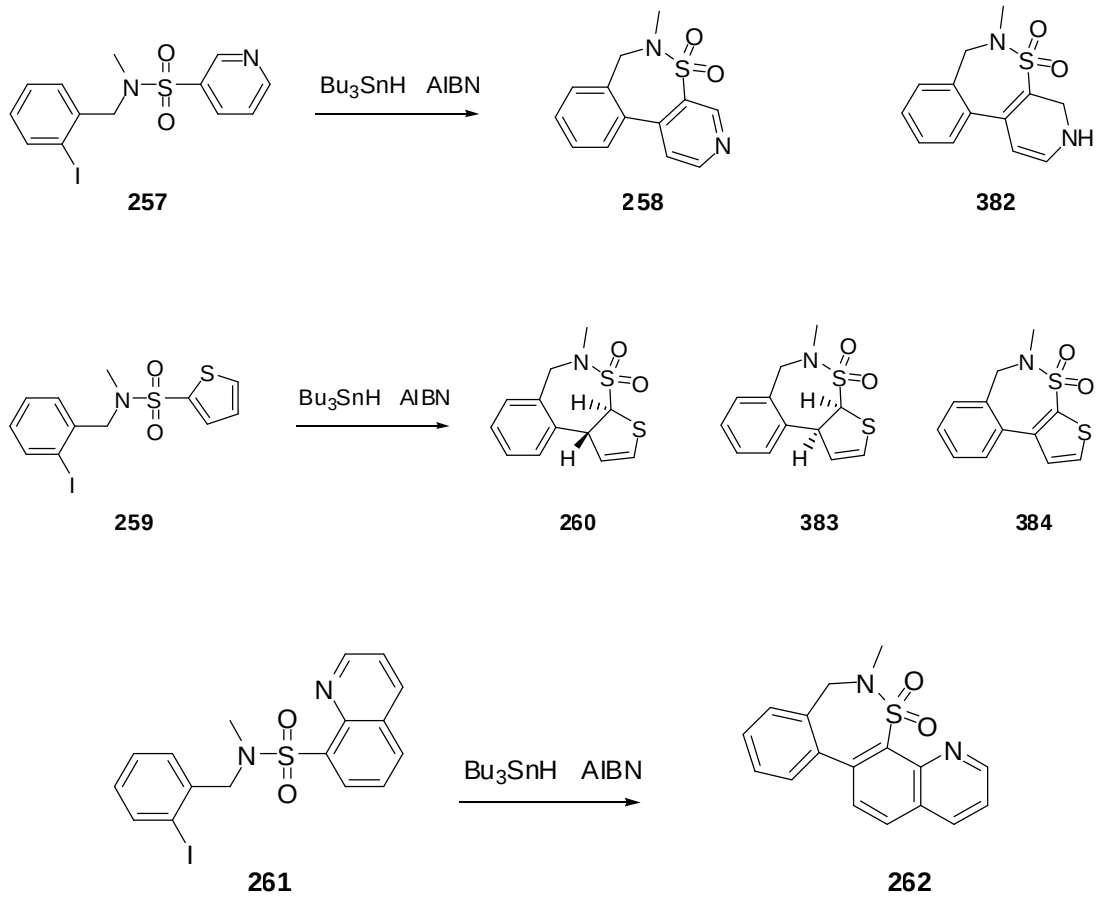
Scheme 117 Synthesis of *N*-(hetero)aromatic sulfonamide radical precursors

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.

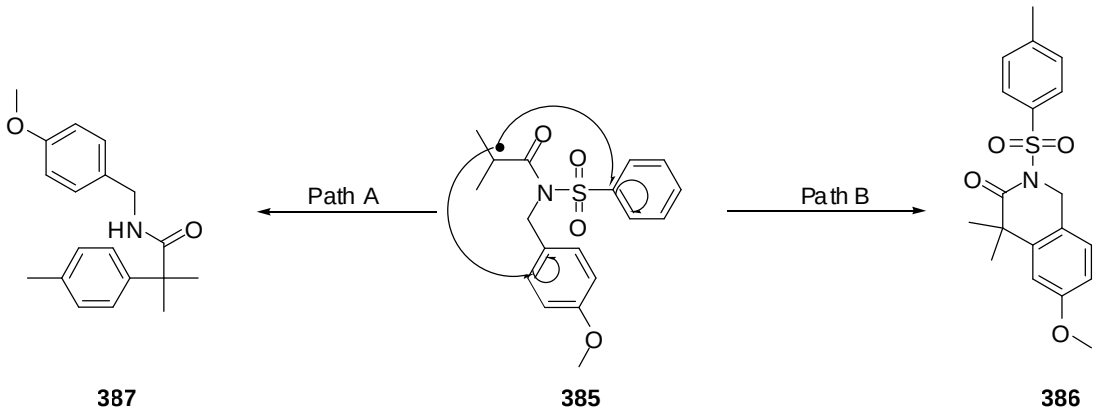
3.2 Attempted radical reactions of (hetero)aromatic sulfonamides 381

Motherwell[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.



Scheme 118 Motherwell radical cyclisation onto heteroaromatics

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[156] using the substrate **381a** furnished the rearranged amide analogous to **387**.

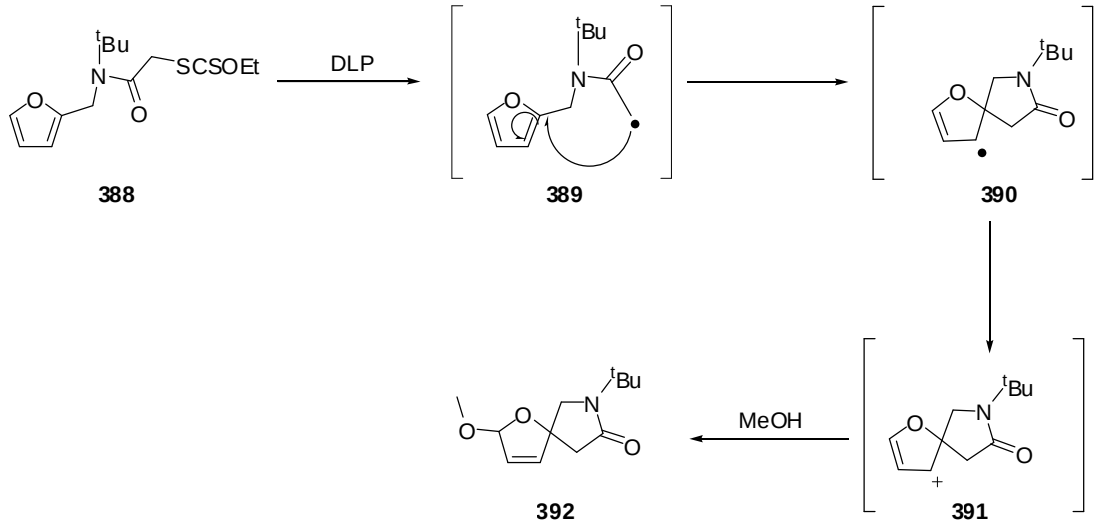


Scheme 119 Proposed radical mechanism for the substrate 387

The first experiment involved treating the benzyl bromide **381b** with CuBr/TPA in tetrahydrofuran at 50 ºC 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.

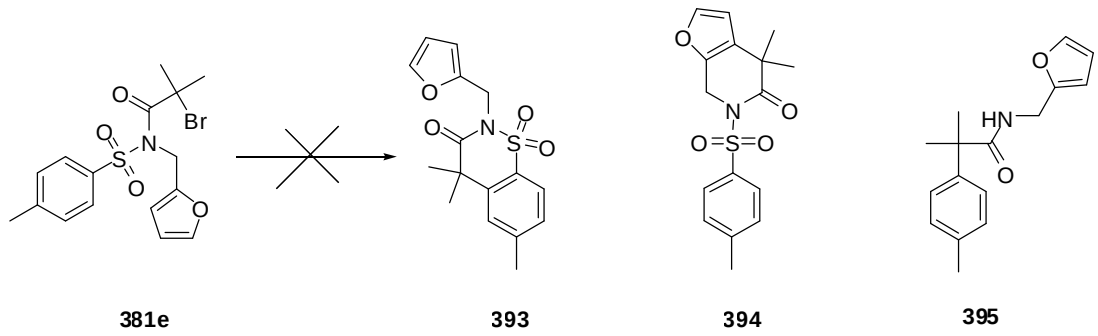
Zard[245] has recently shown that a suitably substituted furan xanthate **388** can undergo *ipso*-type radical cyclisation to furnish spirocyclised products (e.g. **392**). (**Scheme**

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

However, on heating the bromide **381e** in tetrahydrofuran at 50 ºC 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 sulfonamides 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*-docecyl. 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 BF_4). 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

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°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 α-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.[158] 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

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**.

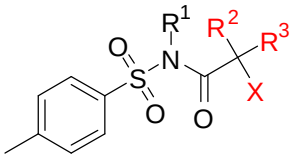
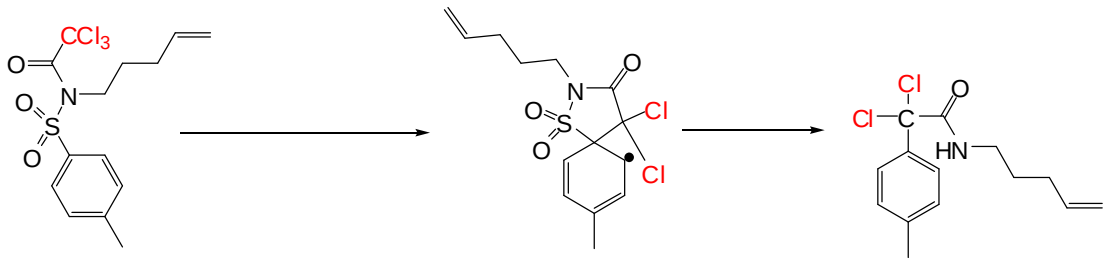


Figure 22 Structure of arylsulfonamide using various radical initiators

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 **Chaper 1 section 3.5** 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.



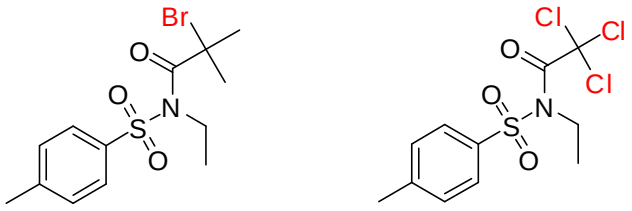
275 **276** **277**

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

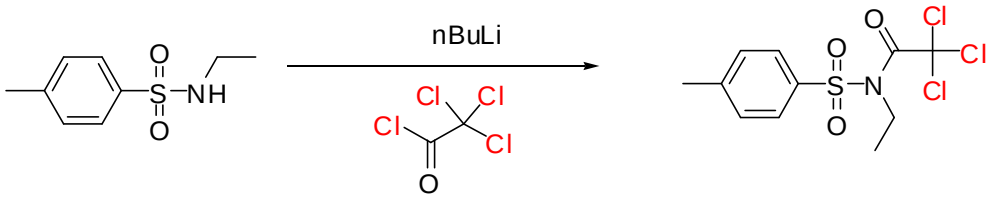
Figure 22. In this case, the unactivated bromide initiator (CMe_2Br) was substituted for an activated (CCl_3) initiator **396**.



369a **396**

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

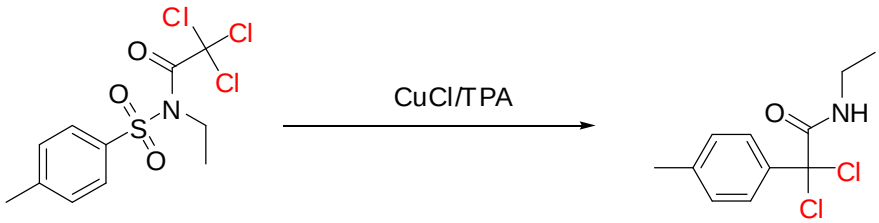
The precursor **396** was prepared from commercially pure **369a** (1.0 eq.) with trichloroacetyl chloride **397** (1.0 eq.) and *n*-butyllithium (1.0 eq.) in excellent yields in 84% yield as depicted in **Scheme 123**.



369a **397** **396**

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.

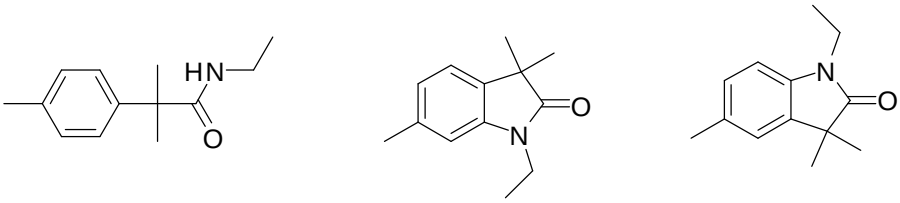


396 **398**

Scheme 124 General reaction scheme for substrate 396 with CuBr/TPA

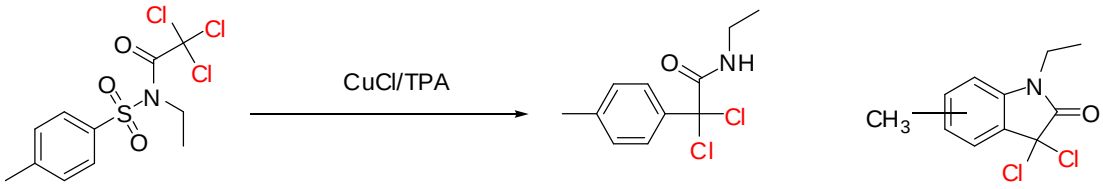
1.2 Radical reaction of the trichloroacetamide 396

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).



370a **371** **372**

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



396 **398** **399**

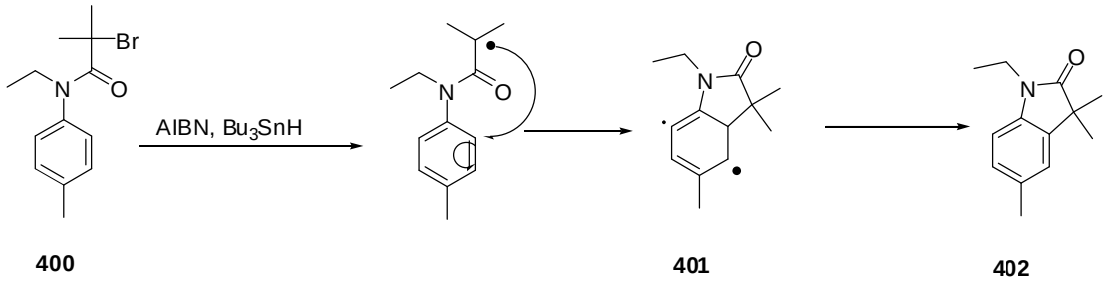
Scheme 125 Radical reaction of trichloroacetamide with CuBr/TPA

An analogous reaction by Wongtap[156] 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.

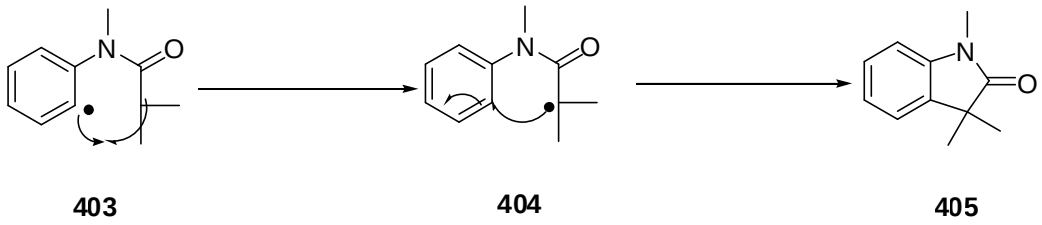
Chapter Four

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[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[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.

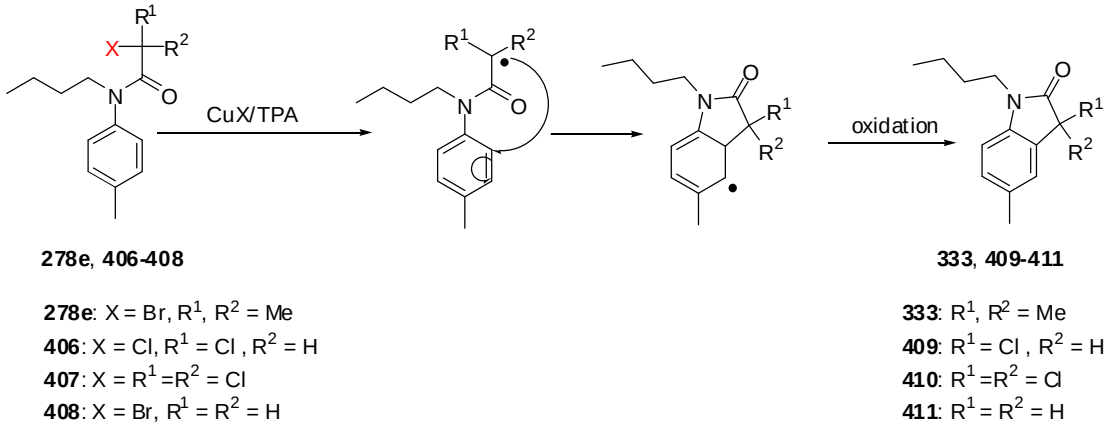


Scheme 126 Nishio's radical approach to oxindoles



Scheme 127 Storey's radical approach to oxindoles

The following investigation to determine if similar cyclisations of haloacetamides (eg. **278e**, **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**).



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**).

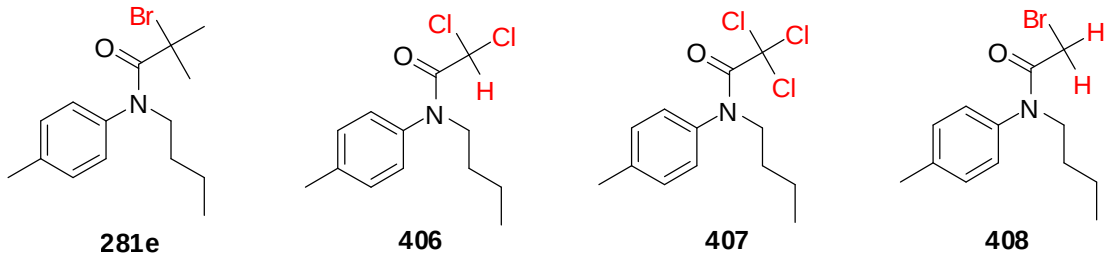
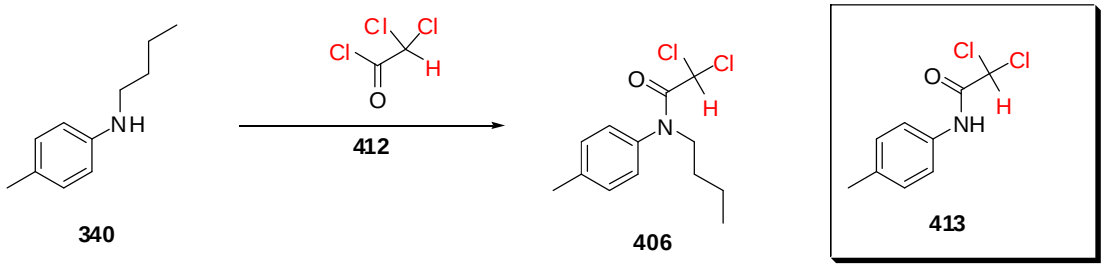


Figure 25 The functionized initiators 341 and 406-408

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**).

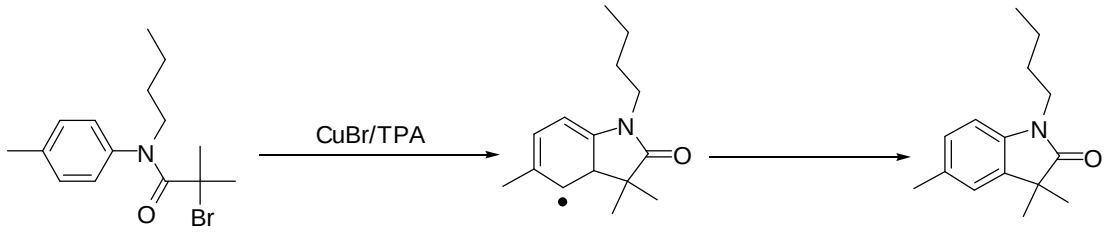


Scheme 129 Synthetic approach to dichloro precursor 406

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.



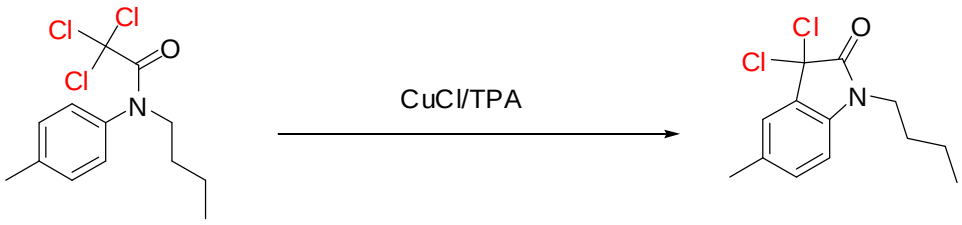
341 **414** **333**

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.



407 **415**

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 succeeed. 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 dimethylbromoacetylamides 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 *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

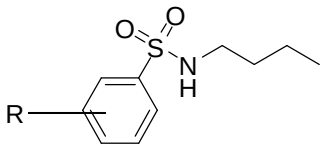
^{1}H NMR spectra were recorded at 300, 400 and 500MHz on the Bruker DPX300, DPX400 and DPX500 spectrometer respectively, and are in $CDCl_3$ unless otherwise stated. All chemical shifts (δ) are quoted in parts per million (ppm) with deuterated chloroform ($CDCl_3$, δ_H = 7.26 ppm) in tetramethylsilane ($Si(CH_3)_4$, (TMS), δ_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 polymolybdonate 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

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 quantanties 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 (**C**H), **t** = methylene carbon (**C**H_2), **q** = methyl carbon **C**H_3, app. = apparent, m. = multiplet, WAS = Warwick Analytical Service.

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



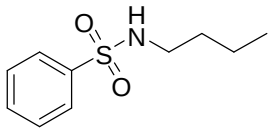
1.1.1 Method A

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).

1.1.2 Method B

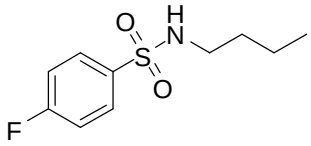
As above but arylsulfonyl chloride (1.0 eq.) **281** and amine (3.0 eq.) **282** were reacted in diethyl ether. No purification was required with this method.

_N_-Butyl-benzenesulfonamide 283a [168]



Commercially available from Aldridge [3622-84-2]. Method B: Furnished *N-butyl-benzenesulfonamide* **283a** as a clear oil (27.60g, 99%). IR (neat) ν_{max}: 3274, 2958, 2869, 1316, 1155, 795, 687 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$, δ): 7.92-7.89 (d, *J* = 7.0, 2H, ArC**H**), 7.58-7.48 (m, 3H, ArC**H**), 5.41 (bs, 1H, N**H**), 2.92 (t, *J* = 7.0, 2H, C**H₂**), 1.46-1.39 (quin., *J* = 7.0, 2H, C**H₂**), 1.33-1.23 (sxt., *J* = 7.0, 2H, C**H₂**), 0.80 (t, *J* = 7.0, 3H, C**H₃**). ^{13}C NMR (100.5MHz, $CDCl_3$, δ): 139.9 (**s**, **C**-SO_2-), 132.5 (**d**, Ar**C**H), 129.1 (2 x **d**, Ar**C**H), 127.0 (2 x **d**, Ar**C**H), 42.9 (**t**, **C**H_2), 31.4 (**t**, **C**H_2), 20.0 (**t**, **C**H_2), 13.5 (**q**, **C**H_3). LRMS (LSIMS-FAB$^+$) *m/z*: 214 (MH^+ = 100%), 154 (57), 136 (40). HRMS (LSIMS-FAB$^+$) *m/z*: calcd for $C_{10}H_{15}NO_2S$, 214.0902; found, 214.0895.

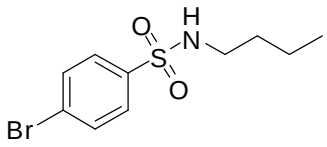
_N_-Butyl-4-fluoro-benzenesulfonamide 283b [169]



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) ν_{max}: 3280, 2958, 2929, 2868, 1325, 1155, 788 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$, δ): 7.92-7.86 (m, 2H, ArC**H**), 7.22-7.14 (app. t, *J* = 9, 2H, ArC**H**), 4.94 (bs, 1H N**H**), 2.92 (t, *J* = 7.0, 2H,

C**H₂**), 1.48-1.38 (quin. *J* = 7.0, 2H, C**H₂**), 1.34-1.21 (sxt. *J* = 7.0, 2H, C**H₂**), 0.85 (t, *J* = 7.0, 3H, C**H₃**). ^{13}C NMR (75.5MHz, $CDCl_3$, δ): 165.0 (**s**, *J* = 254.5, **C**-F), 136.4 (**s**, **C**-SO_2-), 130.1 (2 x **d**, Ar**C**H), 116.6 (2 x **d**, Ar**C**H), 43.3 (**t**, **C**H_2), 31.9 (**t**, **C**H_2), 20.0 (**t**, **C**H_2), 13.9 (**q**, **C**H_3). LRMS (EI$^+$) *m/z*: 232 (100% M^+), 188 (95), 176 (15), 159 (65). HRMS (CI) *m/z*: calcd for $C_{10}H_{14}FNO_2S$, 231.0729; found, 231.0729.

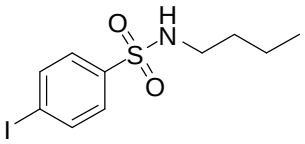
4-Bromo-*N*-butyl-benzenesulfonamide 283c [170]



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) ν_{max}: 3262, 2955, 2867, 1321, 1153, 1088, 736 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$, δ): 7.74-7.71 (d.t, *J* = 9.0 and 2.0, 2H, ArC**H**), 7.61-7.59 (d.t, *J* = 9.0 and 2.0, 2H, ArC**H**), 4.90 (bs, 1H, N**H**), 2.93, (t, *J* = 7.0, 2H, C**H₂**), 1.47-1.39 (quin., *J* = 7.0, 2H, C**H₂**), 1.31-1.22 (sxt., *J* = 7.0, 2H, C**H₂**), 0.83 (t, *J* = 7.0, 3H, C**H₃**). ^{13}C NMR (75.5MHz, $CDCl_3$, δ): 139.1 (**s**, **C**-SO_2-), 132.4 (2 x **d**, Ar**C**H), 128.6 (2 x **d**, Ar**C**H), 127.5 (**s**, **C**-Br), 42.9 (**t**, **C**H_2), 31.5 (**t**, **C**H_2), 19.7 (**t**, **C**H_2), 13.9 (**q**, **C**H_3). LRMS (EI$^+$) *m/z*: 294 (^{81}Br MH$^+$ 2%), 293 (^{81}Br M$^+$ 7), 292 (^{79}Br MH$^+$ 6), 291 (^{79}Br M$^+$ 10), 250 (^{81}Br 98), 248 (^{79}Br 96), 156 (^{81}Br 75), 154 (^{79}Br 76). HRMS (CI) *m/z*: calcd for $C_{10}H_{14}BrNO_2S$, 290.9929 (M$^+$); found, 290.9915. Elemental Analysis (WAS): Calcd for $C_{10}H_{14}BrNO_2S$: C, 41.1; H, 4.8; N, 4.7. Found: C, 41.4, H, 5.0, N, 4.8%.

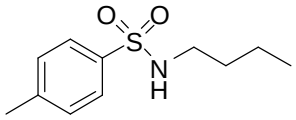
Experimental

N-Butyl-4-iodo-benzenesulfonamide 283d [171]



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) ν_{max}: 3282, 2958, 2932, 2870, 1570, 1325, 1160, 818 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$, δ): 7.91-7.86 (d.t, *J* = 9.0 and 2.0, 2H, ArC**H**), 7.62-7.58 (d.t, *J* = 9.0 and 2.0, 2H, ArC**H**), 4.91 (bs, 1H, N**H**), 2.94 (q, *J* = 7.0, 2H, C$\mathbf{H_2}$), 1.50-1.42 (quin., *J* = 7.0, 2H, C$\mathbf{H_2}$), 1.35-1.26 (sxt., *J* = 7.0, 2H, C$\mathbf{H_2}$), 0.87 (t, *J* = 7.0, 3H, C$\mathbf{H_3}$). ^{13}C NMR (100MHz, $CDCl_3$, δ): 139.7 (**s**, **C**-SO_2), 138.3 (2 x **d**, Ar**C**H), 128.5 (2 x **d**, Ar**C**H), 99.8 (**s**, **C**-I), 43.0 (**t**, **C**H_2), 31.5 (**t**, **C**H_2), 19.8 (**t**, **C**H_2), 14.0 (**q**, **C**H_3). LRMS (LSIMS-FAB^+) *m/z*: 340 (M^+ = 73%). HRMS (LSIMS-FAB^+) *m/z*: (MH^+) calcd for $C_{10}H_{15}INO_2S$, 339.9868; found, 339.9879.

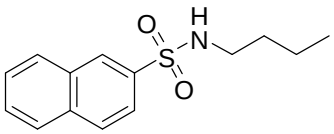
N-Butyl-4-methyl-benzenesulfonamide 283e [172]



Commercially available from ABCR GmbH KG [1907-65-9]. Previously synthesised by Fullaway.[163] Method B: Recrystallisation furnished *N-butyl-4-methyl-benzene-sulfonamide* **283e**, as a yellow crystalline solid (6.39g, 89%). mp 40-41 ºC. IR (neat) υ_{max}: 3244, 2937, 2868, 1427, 1316, 1155, 668 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$, δ): 7.68 (d, *J* = 8.0, 2H, ArC**H**), 7.19 (d, *J* = 8.0, 2H, ArC**H**), 5.26 (app.t, *J* = 6.0, 1H, N**H**), 2.80 (q, *J* = 7.0, 2H, C$\mathbf{H_2}$), 2.31 (s, 3H, ArC$\mathbf{H_3}$), 1.37-1.29 (app. quin. *J* = 7.0, 2H, C$\mathbf{H_2}$), 1.22-1.13 (app. sxt. *J* = 7.0, 2H, C$\mathbf{H_2}$), 0.72 (t, *J* = 7.0, 3H, C$\mathbf{H_3}$). ^{13}C NMR (100.5MHz,

$CDCl_3$, δ): 143.2 (**s**, **C**-Me), 137.0 (**s**, **C**-SO_2-), 129.7 (2 x **d**, Ar**C**H), 127.1 (2 x **d**, Ar**C**H), 42.9 (**t**, **C**H_2), 31.5 (**t**, **C**H_2), 21.5 (**q**, Ar**C**H_3), 20.0 (**t**, **C**H_2), 14.9 (**q**, **C**H_3). LRMS (EI^+) *m/z*: 227 (M^+ = 10), 184 (72), 154 (100). HRMS (LSIMS-FAB^+) *m/z*: calcd for $C_{11}H_{17}NO_2S$, 227.0980; found, 227.0974. Elemental Analysis (WAS): Calcd for $C_{11}H_{17}NO_2S$: C. 58.1; H. 7.5; N. 6.2. Found: C. 58.1; H. 7.4; N. 6.2%.

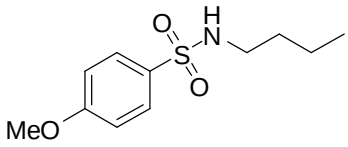
Naphthalene-2-sulfonic acid-butyramide 283g [173]



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 ºC (lit. [248] 54-55 °C). ^{1}H NMR (300MHz, $CDCl_3$, δ): 8.50 (s, 1H, ArC**H**), 7.92-7.85 (m, 4H, ArC**H**), 7.63-7.52 (m, 2H, ArC**H**), 5.57 (app t, *J* = 6.0, 1H, N**H**), 2.96 (q, *J* = 7.0, 2H, C**H₂**), 1.49-1.39 (quin., *J* = 7.0, 2H, C**H₂**), 1.31-1.19 (sxt., *J* = 7.0, 2H, C**H₂**), 0.77 (t, *J* = 7.0, 3H, C**H₃**). ^{13}C NMR (100.5MHz, $CDCl_3$, δ): 136.8 (**s**, **C**), 134.8 (**s**, **C**), 132.2 (**s**, **C**), 129.5 (**d**, Ar**C**H), 129.2 (**d**, Ar**C**H), 128.7 (**d**, Ar**C**H), 128.4 (**d**, Ar**C**H), 127.9 (**d**, Ar**C**H), 127.5 (**d**, Ar**C**H), 122.4 (**d**, Ar**C**H), 43.0 (**t**, **C**H_2), 31.6 (**t**, **C**H_2), 20.1 (**t**, **C**H_2), 14.6 (**q**, **C**H_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 $C_{14}H_{17}NO_2S$, 263.0980; found 263.0978. Elemental Analysis (WAS): Calcd for $C_{14}H_{17}NO_2S$: C, 63.8; H, 6.5; N, 5.3. Found: C, 63.5; H, 6.5; N, 5.2 %.

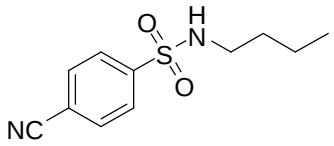
Experimental

N-Butyl-4-methoxy-benzenesulfonamide 283h [174]



Commercially available from Ambinter [35088-85-8]. Method A: Recrystallization yielded *N-butyl-4-methoxy-benzenesulfonamide* **283h** as a golden yellow solid, (5.71g, 94%). mp 39-40 °C. IR (neat) $\nu_{max:}$ 3272, 2957, 2868, 1596, 1301, 1148, 1023, 803 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$, δ): 7.80 (app. d, *J* = 9.0, 2H, ArC**H**), 6.97 (app. d, *J* = 9.0, 2H, ArC**H**), 4.43 (t, *J* = 6.0, 1H, N**H**), 3.87 (s, 3H, OC$\mathbf{H_3}$), 2.93 (q, *J* = 7.0, 2H, C$\mathbf{H_2}$), 1.49-1.39 (quin., *J* = 7.0, 2H, C$\mathbf{H_2}$), 1.35-1.23 (sxt., *J* = 7.0, 2H, C$\mathbf{H_2}$), 0.85 (t, *J* = 7.0, 3H, C$\mathbf{H_3}$): ^{13}C NMR (75.5MHz, $CDCl_3$, δ): 161.7 (**s**, **C**-OMe), 130.5 (**s**, **C**-SO_2-), 128.2 (2 x **d**, Ar**C**H), 113.2 (2 x **d**, Ar**C**H), 54.6 (**q**, O**C**H_3), 41.9 (**t**, **C**H_2), 30.5 (**t**, **C**H_2), 18.7 (**t**, **C**H_2), 12.5 (**q**, **C**H_3). LRMS (LSIMS-FAB$^+$) *m/z*: 243 (M^+ = 40), 200 (54), 171 (100), 155 (15). HRMS (LSIMS-FAB$^+$) *m/z*: calcd for $C_{11}H_{17}NO_3S$, 243.0929; found, 243.0924. Elemental Analysis (WAS): Calcd for $C_{11}H_{17}NO_3S$: C, 54.3; H, 7.0; N, 5.8. Found: C, 54.1; H, 7.0; N, 5.7%.

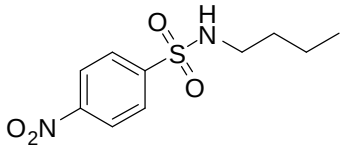
N-Butyl-4-cyano-benzenesulfonamide 283i [176]



Commercially available from Ambinter [858497-76-4]. Method A: Recrystallisation furnished *N-butyl-4-cyano-benzenesulfonamide* **283i** as a pale yellow crystalline solid (4.79g, 85%). mp 104.5-105.5 °C (lit. [176] 99 ºC). IR (neat) $\nu_{max:}$ 3282, 2959, 2931, 2870, 2237, 1329, 1158, 735cm^{-1}. ^1H NMR (300MHz, $CDCl_3$, δ): 7.98 (app. d, *J* = 8.0, 2H, ArC**H**), 7.83 (app. d, *J* = 8.0, 2H, ArC**H**), 4.5 (bs, 1H, N**H**), 3.0 (q, *J* = 7.0, 2H, C$\mathbf{H_2}$),

1.52-1.42 (quin., *J* = 7.0, 2H, C**H**$_2$), 1.36-1.24 (sxt., *J* = 7.0, 2H, C**H**$_2$), 0.87 (t, *J* = 7.0, 3H, C**H**$_3$). ^{13}C NMR (75.5MHz, $CDCl_3$, δ): 144.8 (**s**, **C**-SO_2-), 133.4 (2 x **d**, Ar**C**H), 128.1 (2 x **d**, Ar**C**H), 117.8 (**s**, C-**C**≡N), 116.6 (**s**, **C**-C≡N), 43.4 (**t**, **C**H_2), 31.9 (**t**, **C**H_2), 20.0 (**t**, **C**H_2), 13.9 (**q**, **C**H_3). LRMS (LSIMS-FAB$^+$) *m/z*: 239 (MH^+ = 28%), 154 (100), 137 (70). HRMS (LSIMS-FAB$^+$) *m/z*: calcd for $C_{11}H_{14}N_2O_2S$, 239.0854; found, 239.0857.

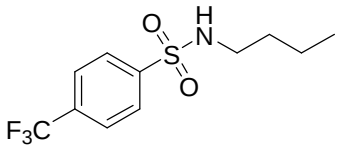
_N_-Butyl-4-nitro-benzenesulfonamide 283j [176]



Commercially available from Aurora Fine Chemicals [66473-14-1]. Method B: Furnished *N-butyl-4-nitro-benzenesulfonamide* **283j** as a pale yellow crystalline solid (20.19g, 86%). mp 80-81 °C. (Lit. mp.[176] 84 ºC). IR (neat) $\nu_{max.}$ 3294, 2939, 2860, 1522, 1345, 1305, 1151, 852 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$, δ): 8.37 (d.t, *J* = 9.0 and 2.0, 2H, ArC**H**), 8.06 (d.t, *J* = 9.0 and 2.0, 2H, ArC**H**), 4.57 (bs, 1H, N**H**), 3.02 (q, *J* = 7.0, 2H, C**H**$_2$), 1.52-1.43 (quin., *J* = 7.0, 2H, C**H**$_2$), 1.37-1.25 (sxt., *J* = 7.0, 2H, C**H**$_2$), 0.83 (t, *J* = 7.0, 3H, C**H**$_3$). ^{13}C NMR (75.5MHz, $CDCl_3$, δ): 150.4 (**s**, **C**-NO_2), 146.4 (**s**, **C**-SO_2-), 128.7 (2 x **d**, Ar**C**H), 124.8 (2 x **d**, Ar**C**H), 43.5 (**t**, **C**H_2), 32.0 (**t**, **C**H_2), 20.0 (**t**, **C**H_2), 13.9 (**q**, **C**H_3). LRMS (EI+) *m/z*: 259 (M^+ = 10), 216 (12), 210 (100), 185 (65), 122 (29); HRMS (LSIMS-FAB$^+$) *m/z*: (MH^+) calcd for $C_{10}H_{15}N_2O_4S$, 258.0674; found 258.0670.

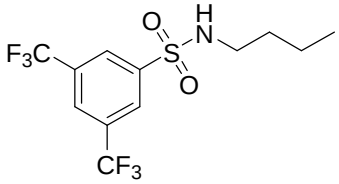
Experimental

N-Butyl-4-trifluoromethyl-benzenesulfonamide 283k



Method A: Recrystallization yielded *N-butyl-4-trifluoromethyl-benzenesulfonamide* **283k** as a beige reflective crystalline solid (3.61g, 94%). mp 76-77 °C. IR (neat) ν_{max}: 3263, 2960, 2931, 2867, 1322, 1162, 713 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$, δ): 8.01 (d, *J* = 8.5, 2H, ArC**H**), 7.79 (d, *J* = 8.5, 2H, ArC**H**), 4.68 (bs, 1H, N**H**), 2.97 (t, *J* = 7.0, 2H, C$\mathbf{H_2}$), 1.51-1.42 (m, 2H, C$\mathbf{H_2}$), 1.36-1.24 (sxt., *J* = 7.0, 2H, C$\mathbf{H_2}$), 0.87 (t, 7.0, 3H, C$\mathbf{H_3}$). ^{13}C NMR (100.5MHz, $CDCl_3$, δ): 144.0 (**s**, **C**-SO_2-), 134.5 (**s**, *J* = 286.6, C-**C**F_3), 127.6 (2 x **d**, Ar**C**H), 126.4 (2 x **d**, Ar**C**H), 124.5 (**s**, *J* = 34, Ar**C**-CF_3), 43.0 (**t**, **C**H_2), 31.5 (**t**, **C**H_2), 19.9 (**t**, **C**H_2), 13.6 (**q**, **C**H_3). LRMS (LSIMS-FAB$^+$) *m/z*: 282 (M^+ = 100%), 280 (15), 226 (26), 209 (17), 154 (43). HRMS (LSIMS-FAB$^+$) *m/z*: (MH^+) calcd for $C_{11}H_{15}F_3NO_2S$, 282.0776; found, 282.0772.

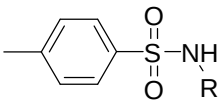
N-Butyl-(bis-3, 5-trifluoromethylbenzene)-sulfonamide 283l



Method A: Purified using column chromatography (diethyl ether/hexane; 3:1) to furnish *N-butyl-(bis-3,5-trifluoromethylbenzene)-sulfonamide* **283l** as an off-white (beige) crystalline solid (2.86, 76%). mp 83.8-84.8 °C. IR (neat) ν_{max}: 3287, 2967, 2934, 2872, 1340, 1136, 904, 689 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$, δ): 8.31 (s, 2H, ArC**H**), 8.07 (s, 1H, ArC**H**), 4.67 (t, *J* = 6.0, 1H, N**H**), 3.04 (q, *J* = 7.0, 2H, C$\mathbf{H_2}$), 1.54-1.44 (quin., *J* = 7.0, 2H, C$\mathbf{H_2}$), 1.37-1.25 (sxt., *J* = 7.0, 2H, C$\mathbf{H_2}$), 0.87 (t, *J* = 7.0, 3H, C$\mathbf{H_3}$). ^{13}C NMR

(75.5MHz, $CDCl_3$, δ): 142.1 (**s**, Ar**C**-SO-), 132.1 (2 x **s**, J = 273.4, C-**C**F_3), 126.29 (2 x **d**, Ar**C**H), 125.1 (**d**, Ar**C**H), 121.0 (2 x **s**, J = 34.4, Ar**C**-CF_3), 42.1 (**t**, **C**H_2), 30.56 (**t**, **C**H_2), 18.6 (**t**, **C**H_2), 12.3 (**q**, **C**H_3). LRMS (EI^+) *m/z*: 350 (MH^+ = 83), 213 (100), 195 (28), 145 (21) and 121 (50). HRMS (CI): calcd for $C_{12}H_{13}F_6NO_2S$, 349.0571; found, 349.0571; Elemental Analysis (WAS): Calcd for $C_{12}H_{13}F_6NO_2S$: 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

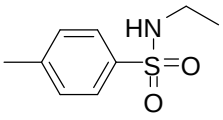
To a stirred solution of 4-methyl-benzenesulfonyl chloride **281** (1.2 eq.) in dichloromethane (DCM) (50 mL) was added the alkylamine **373** (1.0 eq.) and triethylamine (TEA) (1.36 eq.). The solution was stirred at 0 °C (ice bath) for four hours unless otherwise stated. The reaction was quenched with 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.

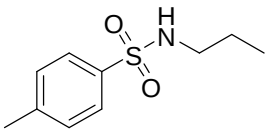
Experimental

N-Ethyl-4-methyl-benzenesulfonamide 374a [228]



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 ºC. IR (neat) ν_{max}: 3268, 2978, 2876, 2361, 1322, 1157, 814 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$, δ): 7.79 (d, *J* = 8.0, 2H, ArC**H**), 7.32 (d, *J* = 8.0, 2H, ArC**H**), 5.11 (app. t, *J* = 5.0, 1H, N**H**), 2.97 (quin., *J* = 7.0, 2H, C$\mathbf{H_2}$), 2.42 (s, 3H, ArC$\mathbf{H_3}$), 1.08 (t, *J* = 7.0, 3H, C$\mathbf{H_3}$). ^{13}C NMR (75.5MHz, $CDCl_3$, δ): 143.1 (**s**, **C**-Me), 136.7 (**s**, **C**-SO_2-), 129.4 (2 x **d**, Ar**C**H), 126.9 (2 x **d**, Ar**C**H), 37.3 (**t**, **C**H_2), 21.3 (**q**, Ar**C**H_3), 14.7 (**q**, **C**H_3). LRMS (EI^+) *m/z*: 199 (M^+ = 20%), 184 (90), 155 (100). HRMS (LSIMS-FAB^+) *m/z*: calcd for $C_9H_{14}NO_2S$ (MH^+), 200.0745; found, 200.0742. Elemental Analysis (WAS): Calcd. for $C_9H_{13}NO_2S$: C, 54.2; H, 6.6; N, 7.0. Found: C, 54.3; H, 6.5; N, 7.0%.

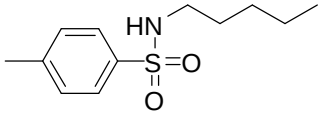
N-Propyl-4-methyl-benzenesulfonamide 374b [229]



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 ºC. IR (neat) ν_{max}: 3275, 2968, 2875, 1315, 1156 and 814 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$, δ): 7.66 (d, *J* = 8.0, 2H, ArC**H**), 7.17 (d, *J* = 8.0, 2H, ArC**H**), 5.52 (app.t, *J* = 5.0, 1H, N**H**), 2.75 (t, *J* = 7.0, 2H, C$\mathbf{H_2}$), 2.28 (s, 3H, ArC**H**), 1.40-1.31 (sxt., *J* = 7.0, 2H, C$\mathbf{H_2}$), 0.72 (t, *J* = 7.0, 3H, C$\mathbf{H_3}$). ^{13}C NMR (100MHz, $CDCl_3$, δ): 143.0 (**s**, **C**-Me), 136.8 (**s**, **C**-SO_2-), 129.4 (2 x **d**, Ar**C**H), 126.9 (2 x **d**, Ar**C**H), 44.7 (**t**, **C**H_2), 22.6 (**t**, **C**H_2), 21.1 (**q**,

Ar**C**H_3), 10.9 (**q**, **C**H_3). LRMS (CI) *m/z*: 214 MH^+ = 22%), 196 (35), 184 (67), 155 (90), 139 (15). HRMS (CI) calcd for $C_{10}H_{15}NO_2S$; 213.0823, found 213.0817. Elemental Analysis (WAS): Calcd. for $C_{10}H_{15}NO_2S$; C, 56.1; H, 7.1; N, 6.6. Found: C, 55.9; H, 7.1; N, 6.4%.

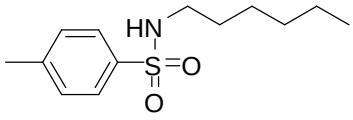
4-Methyl-*N*-pentyl-benzenesulfonamide 374d



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) ν_{max}: 3276, 2929, 1322, 1155, 813, 659 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$, δ): 7.74 (d.t, *J* = 8.0 and 2.0, 2H, ArC**H**), 7.30 (d, *J* = 8.0, 2H, ArC**H**), 4.35 (t, *J* = 6.0, 1H, N**H**), 2.92 (q, *J* = 7.0, 2H, C$\mathbf{H_2}$), 2.43 (s, 3H, ArC$\mathbf{H_3}$), 1.49-1.41 (app. quin., *J* = 7.0, 2H, C$\mathbf{H_2}$), 1.27-1.21 (m, 4H, C$\mathbf{H_2}$), 0.84 (t, *J* = 7.0, 3H, C$\mathbf{H_3}$). ^{13}C NMR (100MHz, $CDCl_3$, δ): 143.3 (**s**, **C**-Me), 137.0 (**s**, **C**-SO_2-), 129.7 (2 x **d**, Ar**C**H), 127.1 (2 x **d**, Ar**C**H), 43.2 (**t**, **C**H_2), 29.2 (**t**, **C**H_2), 28.7 (**t**, **C**H_2), 22.1 (**t**, **C**H_2), 21.5 (**q**, Ar**C**H_3), 14.3 (**q**, **C**H_3). LRMS (LSIMS-FAB$^+$) *m/z*: 242 (MH^+ 100%), 154 (22%), 137 (16%). HRMS (LSIMS-FAB$^+$) *m/z*: (MH^+) calcd for $C_{12}H_{20}NO_2S$, 242.1215; found, 242.1210. Elemental Analysis (WAS): Calcd for $C_{12}H_{19}NO_2S$: C, 59.7; H, 7.9; N, 5.8. Found: C, 59.5; H, 7.8; N, 5.7%.

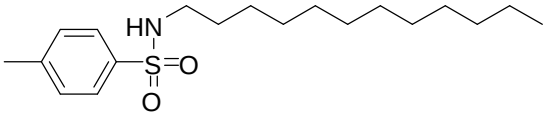
Experimental

N-Hexyl-4-methyl-benzenesulfonamide 374e [231]



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 ºC (lit. [231] DCM/Pentane 59.5 °C). IR (neat) ν_{max}: 3280, 2922, 2854, 1319, 1153, 664 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$, δ): 7.74 (d.t, *J* = 8.0 + 2.0, 2H, ArC**H**), 7.29 (d, *J* = 8.0, 2H, ArC**H**), 4.39 (app. t, *J* = 6.0, 1H, N**H**), 2.89 (t, *J* = 7.0, 2H, C$\mathbf{H_2}$), 2.42 (s, 3H, ArC$\mathbf{H_3}$), 1.48-1.36 (sxt., *J* = 7.0, 2H, C$\mathbf{H_2}$), 1.29-1.13 (m, 6H, 3 x C$\mathbf{H_2}$), 0.83 (t, *J* = 7.0, 3H, C$\mathbf{H_3}$). ^{13}C NMR (100MHz, $CDCl_3$, δ): 143.2 (**s**, **C**-Me), 137.0 (**s**, **C**-SO_2-), 129.6 (2 x **d**, Ar**C**H), 127.1 (2 x **d**, Ar**C**H), 43.2 (**t**, **C**H_2), 31.2 (**t**, **C**H_2), 29.5 (**t**, **C**H_2), 26.2 (**t**, **C**H_2), 22.4 (**t**, **C**H_2), 21.5 (**q**, Ar**C**H_3), 15.0 (**q**, **C**H_3). LRMS (CI) *m/z*: 256 (MH^+ 23%), 184 (80), 155 (100), 100 (28), 91 (80). HRMS (EI^+) calcd for $C_{13}H_{21}NO_2S$, 255.1293; found, 255.1293. Elemental Analysis (WAS): Calcd for $C_{13}H_{21}NO_2S$: C, 61.1; H, 8.3; N, 5.5. Found: C, 61.0; H, 8.1; N, 5.5%.

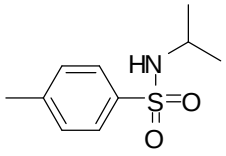
N-Docecyl-4-methyl-benzenesulfonamide 374f [232]



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 ºC. IR (neat) ν_{max}: 3284, 2914, 2845, 1324, 1157, 814, 670 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$, δ): 7.74 (d.t, *J* = 8.0 + 2.0, 2H, ArC**H**), 7.30 (d, *J* = 8.0, 2H, ArC**H**), 5.0 (bs, 1H, N**H**), 2.90 (t, *J* = 7.0, 2H, C$\mathbf{H_2}$), 2.42 (s, 3H, ArC$\mathbf{H_3}$), 1.19-1.46 (m, 20H

C**H$_2$**), 0.87 (t, *J* = 7.0, 3H, C**H$_3$**). ^{13}C NMR (75.5MHz, $CDCl_3$, δ): 143.6 (**s**, **C**-Me), 137.4 (**s**, **C**-SO_2-), 130.0 (2 x **d**, Ar**C**H), 127.5 (2 x **d**, Ar**C**H), 43.6 (**t**, **C**H$_2$), 32.3 (**t**, **C**H), 30.0 (**t**, **C**H$_2$), 29.9 (**t**, **C**H$_2$), 29.9 (**t**, **C**H$_2$), 29.8 (**t**, **C**H$_2$), 29.8 (**t**, **C**H$_2$), 29.7 (**t**, **C**H$_2$), 29.5 (**t**, **C**H$_2$), 26.9 (**t**, **C**H$_2$), 23.1 (**t**, **C**H$_2$), 21.9 (**q**, Ar**C**H$_3$), 14.5 (**q**, **C**H$_3$). LRMS (EI$^+$) *m/z*: 340 (MH$^+$ 35%), 184 (100), 172 (40), 155 (98), 91 (85%). HRMS (EI$^+$) *m/z*: calcd for $C_{19}H_{33}NO_2S$, 339.2232; found, 339.2246. Elemental Analysis (WAS): Calcd for $C_{19}H_{33}NO_2S$: C, 67.2; H, 9.8; N, 4.1. Found: C, 66.8; H, 9.6; N, 3.8%.

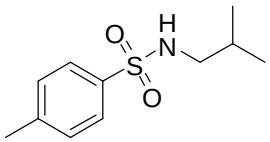
N-Isopropyl-4-methyl-benzenesulfonamide 374g[234]



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 ºC. IR (neat) υ_{max}: 3275, 2974, 1320, 1141, 1092, 729. ^{1}H NMR (400MHz, $CDCl_3$, δ): 7.76 (d.t, *J* = 8.0 and 2.0, 2H, ArC**H**), 7.29 (d, *J* = 8.0, 2H, ArC**H**), 4.26 (d, *J* = 7.0, 1H, N**H**), 3.45 (oct. *J* = 7.0, 1H, C**H**), 2.43 (s, 3H, ArC**H$_3$**), 1.07 (d, *J* = 7.0, 6H, 2 x C**H$_3$**). ^{13}C NMR (100MHz, $CDCl_3$, δ): 143.6 (**s**, **C**-Me), 138.5 (**s**, **C**-SO_2-), 130.5 (2 x **d**, Ar**C**H), 127.4 (2 x **d**, Ar**C**H), 46.4 (**d**, **C**H), 24.1 (2 x **q**, **C**H$_3$), 21.9 (**q**, Ar**C**H$_3$). LRMS (LSIMS-FAB$^+$) *m/z*: 214 (MH$^+$ 100%), 172 (30), 155 (15), 137 (13). HRMS (LSIMS-FAB$^+$) *m/z*: calcd for $C_{10}H_{16}NO_2S$, 214.0902; found, 214.0912; Elemental Analysis (WAS): Calcd for $C_{10}H_{15}NO_2S$: C, 56.3; H, 7.1; N, 6.5. Found: C, 56.1; H, 7.1; N, 6.4%.

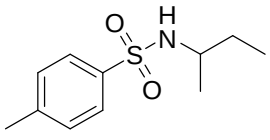
Experimental

N-Isobutyl-4-methyl-benzenesulfonamide 374h [235]



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 ºC (lit. 77-78 °C). IR (neat) ν_{max}: 3273, 2960, 2872, 1320, 1155, 729 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$, δ): 7.74 (d, *J* = 8.0, 2H, ArC**H**), 7.30 (d, *J* = 8.0, 2H, ArC**H**), 4.55 (bs, 1H, N**H**), 2.74 (t, *J* = 7.0, 2H, C$\mathbf{H_2}$), 2.43 (s, 3H, ArC$\mathbf{H_3}$), 1.71 (spt., *J* = 7.0, 1H, C**H**), 0.86 (d, *J* = 7.0, 6H, 2 x C$\mathbf{H_3}$). ^{13}C NMR (75.5MHz, $CDCl_3$, δ): 143.1 (**s**, **C**-Me), 136.8 (**s**, **C**-SO_2-), 129.5 (2 x **d**, Ar**C**H), 126.8 (2 x **d**, Ar**C**H), 50.3 (**t**, **C**H_2), 28.2 (**d**, **C**H_2), 21.9 (**q**, Ar**C**H_3), 19.7 (2 x **q**, **C**H_3). LRMS (LSIMS-FAB$^+$) *m/z*: 228 (MH^+ 100%), 154 (100), 137 (70). HRMS (LSIMS-FAB$^+$) *m/z*: (MH^+) calcd. 228.1058 for $C_{11}H_{18}NO_2S$; found, 228.1065. Elemental Analysis (WAS): Calcd for $C_{11}H_{17}NO_2S$: C, 58.1; H, 7.5; N, 6.1. Found: C, 57.8; H, 7.4; N, 6.1%.

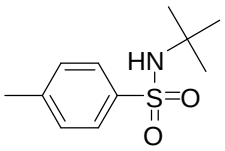
N-sec-Butyl-4-methyl-benzenesulfonamide 374i [235]



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 ºC (lit. 56-57 °C). IR ν_{max} (neat) 3274, 2969, 2875, 1313, 1157, 814, 661 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$, δ): 7.79 (d.t, *J* = 8.0 + 2.0, 2H ArC**H**), 7.29 (d, *J* = 8.0, 2H, ArC**H**),

4.99 (bs, 1H, N**H**), 3.28-3.17 (app. sxt., *J* = 7.0, 1H, C**H**), 2.42 (s, 3H, ArC**H$_3$**), 1.45-1.35 (app. quin., *J* = 7.0, 2H, C**H$_2$**), 1.00 (d, *J* = 7.0, 3H, C**H$_3$**), 0.79 (t, *J* = 7.0 , 3H, C**H$_3$**). ^{13}C NMR (75.5 (MHz, $CDCl_3$, δ) 142.8 (**s**, **C**-Me), 138.1 (**s**, **C**-SO_2), 129.4 (2 x **d**, Ar**C**H), 126.8 (2 x **d**, Ar**C**H), 51.1 (**d**, **C**H), 30.0 (**t**, **C**H_2), 21.6 (**q**, Ar**C**H_3), 21.1 (**q**, **C**H_3), 9.7 (**q**, **C**H_3). 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 $C_{11}H_{18}NO_2S$, 228.1058; found, 228.1051. Elemental Analysis (WAS): Calcd for $C_{11}H_{17}NO_2S$: C, 58.1; H, 7.5; N, 6.1. Found: C, 58.0; H, 7.4; N, 6.1%.

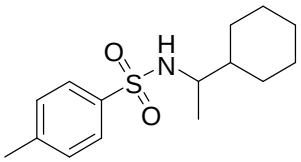
***N-tert*-Butyl-4-methyl-benzenesulfonamide 374j** [236]



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}. ^{1}H NMR (400MHz, $CDCl_3$, δ): 7.78 (d, *J* = 8.0, 2H, ArC**H**), 7.27 (d, *J* = 8.0, 2H, ArC**H**), 4.88 (bs, 1H, N**H**), 2.42 (s, 3H, ArC**H$_3$**), 1.21 (s, 9H, 3 x C**H$_3$**). ^{13}C NMR (75.5MHz, $CDCl_3$, δ): 142.5 (**s**, **C**-Me), 140.3 (**s**, **C**-SO_2-), 129.2 (2 x **d**, Ar**C**H), 126.7 (2 x **d**, Ar**C**H), 54.3 (**s**, **C**-$(CH_3)_3$), 29.9 (3 x **q**, **C**H_3), 21.26 (**q**, Ar**C**H_3). LRMS (LSIMS-FAB$^+$) *m/z*: 228 (MH$^+$ 100), 212 (35), 172 (100), 137 (58). HRMS (LSIMS-FAB$^+$) *m/z*: calcd. for $C_{11}H_{18}NO_2S$, 228.1058; found, 228.1051. Elemental Analysis (WAS): Calcd for $C_{11}H_{17}NO_2S$: C, 58.4; H, 7.6; N, 6.0. Found: C, 58.1; H, 7.5; N, 6.1%.

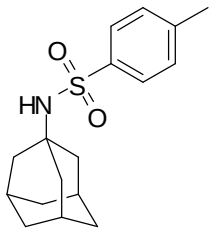
Experimental

N-(R)-(-)-(1-Cyclohexylethyl)-4-methylbenzenesulfonamide 374k [237]



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 ºC. IR (neat) ν_{max}: 3288, 2916, 2860, 1321, 1159 and 671 cm^{-1}. ^1H NMR (300MHz; $CDCl_3$, δ): 7.77-7.74 (d.t, *J* = 8.0 and 2.0, 2H, ArC**H**), 7.29 (d, *J* = 8.0, 2H, ArC**H**), 4.30 (bd, *J* = 8.0, 1H, N**H**), 3.19-3.10 (m, 1H, N**H**), 2.42 (s, 3H, ArC**H**$_3$), 1.72-1.52 (m, 6H, C**H**$_2$), 1.29-0.76 (m, 8H, C**H**$_2$ + C**H**$_3$ overlap). ^{13}C NMR (100MHz, $CDCl_3$, δ): 143.1 (**s**, **C**-Me), 138.4 (**s**, **C**-SO_2-), 129.6 (2 x **d**, Ar**C**H), 127.1 (2 x **d**, Ar**C**H), 54.4 (**d**, **C**H), 43.5 (**d**, **C**H), 28.5 (2 x **t**, **C**H_2), 26.1 (3 x **t**, **C**H_2), 21.5 (**q**, Ar**C**H_3), 19.5 (**q**, **C**H_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 $C_{15}H_{24}NO_2S$, 282.1528; found, 282.1541.

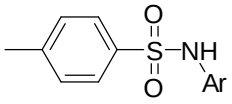
N-Adamantan-1-yl-4-methylbenzenesulfonamide 374l [238]



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) ν_{max}: 3228, 2971, 2844, 1328, 1114 `and 665 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$, δ) 7.77 (d.t, *J* = 8.0 and 2.0, 2H, ArC**H**), 7.27 (d, *J* = 8.0, 2H, ArC**H**),

4.45 (s, 1H, N**H**), 2.42 (s, 3H, ArC**H**$_3$), 2.00 (bs, 3H, C**H**), 1.78 (app. s, 6H, C**H**$_2$), 1.57 (m, 6H, C**H**$_2$). ^{13}C NMR (100MHz, $CDCl_3$, δ) 142.7 (**s**, **C**-Me), 141.1 (**s**, **C**-SO_2-), 129.4 (2 x **d**, Ar**C**H), 126.9 (2 x **d**, Ar**C**H), 55.1 (**s**, **C**-NH-), 43.1 (3 x **t**, **C**H_2), 35.9 (3 x **t**, **C**H_2), 29.5 (3 x **d**, **C**H), 21.5 (**q**, Ar**C**H). LRMS (LSIMS-FAB$^+$) *m/z*: 306 (MH^+ = 46%), 154 (32), 135 (100). HRMS (LSIMS-FAB$^+$) *m/z*: calcd for $C_{17}H_{23}NO_2S$; 304.1371, found 304.1370. Elemental Analysis (WAS): Calcd for C, 66.8, H, 7.6, N, 4.6; $C_{17}H_{23}NO_2S$, Found: C, 66.7, H, 7.5, N, 4.6%.

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



3.1 Method A

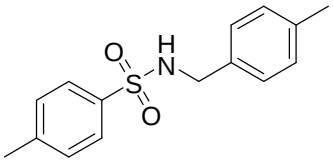
To a stirred solution of 4-methylbenzenesulfonyl chloride **281e** (1.2 eq.) in dichloromethane (DCM) (50 mL) was added the amine **379** (1.0 eq.) and triethylamine (TEA) (1.36 eq.). The solution was stirred at 0 °C (ice bath) for four hours unless otherwise stated. The reaction was quenched with distilled 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.

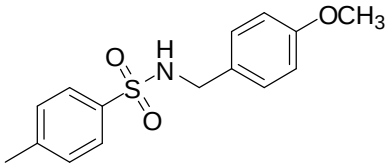
Experimental

4-Methyl-*N*-(4-methylbenzyl)-benzenesulfonamide 380a [239]



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) ν_{max}: 3270, 2916, 1324, 1152, 843, 798, 741, 657 cm^{-1}. ^1H NMR (400MHz; $CDCl_3$, δ): 7.76 (d. *J* = 8.0, 2H, ArC**H**), 7.27 (d. *J* = 8.0, 2H, ArC**H**), 7.10 (d, *J* = 8.0, 2H, ArC**H**), 7.08 (m, 2H, ArC**H**), 5.50 (t, *J* = 6.0, 1H, N**H**), 4.06 (d, *J* = 6.0, 2H, C$\mathbf{H_2}$), 2.43 (s, 3H, ArC$\mathbf{H_3}$), 2.31 (s, 3H, C$\mathbf{H_3}$). ^{13}C NMR (100MHz, $CDCl_3$, δ): 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**, Ar**C**H), 129.3 (2 x **d**, Ar**C**H), 127.9 (2 x **d**, Ar**C**H), 127.2 (2 x **d**, Ar**C**H), 46.9 (**t**, **C**H_2), 21.5 (**q**, Ar**C**H_2), 21.0 (**q**, Ar**C**H_3). LRMS (LSIMS-FAB^+) *m/z*: 276 (MH^+ = 68%), 184 (26), 154 (100), 137 (70). HRMS (LSIMS-FAB^+) *m/z*: calcd for $C_{15}H_{17}NO_2S$, 276.1058; found, 276.1050.

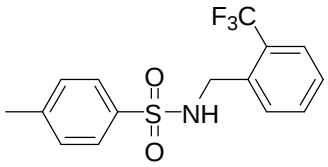
N-(4-Methoxybenzyl)-4-methylbenzenesulfonamide 380b



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 ºC. IR (neat) ν_{max}: 3245, 2974, 2837, 1251, 1319, 1154 and 815 cm^{-1}. ^1H NMR (400MHz; $CDCl_3$, δ): 7.75 (app. d., *J* = 8.0, 2H, ArC**H**), 7.31 (d, *J* = 8.0, 2H, ArC**H**), 7.10 (d.t., *J* = 8.0 and 3.0, 2H, ArC**H**), 6.79 (d.t, *J*

= 8.0 and 3.0, 2H, ArC**H**), 4.55 (app. t., *J* = 5.0, 1H, N**H**), 4.05 (d, *J* = 6.0, 2H, C**H**$_2$), 3.77 (s, 3H, OC**H**$_3$), 2.44 (s, 3H, ArC**H**$_3$). ^{13}C NMR (100MHz, $CDCl_3$, δ): 159.4 (**s**, **C**-OMe), 143.5 (**s**, **C**-Me), 136.9 (**s**, **C**-SO_2-), 129.7 (2 x **d**, Ar**C**H), 129.1 (2 x **d**, Ar**C**H), 128.3 (**s**, **C**-CH_2-), 127.2 (2 x **d**, Ar**C**H), 114.1 (2 x **d**, Ar**C**H), 55.3 (**q**, O**C**H_3), 46.8 (**t**, **C**H_2), 21.5 (**q**, Ar**C**H_3). LRMS (LSIMS) *m/z*: 291 (M^+ = 100%), 219 (20), 154 (100), 136 (100), 121 (65). HRMS (LSIMS-FAB$^+$) *m/z*: (MH^+) calcd for $C_{15}H_{18}NO_3S$, 292.1007; found, 292.1015.

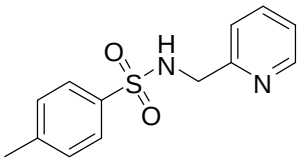
4-Methyl-*N*-(2-trifluoromethylbenzyl)-benzenesulfonamide 380c [240]



Method A: Recrystallisation furnished *4-methyl-N-(2-trifluoromethylbenzyl)-benzene-sulfonamide* **380c** as a very pale yellow crystallised solid (7.13g, 83%). IR (neat) υ_{max}: 3236, 2361, 1308, 1152, 714. mp. 98.5-99.5 °C. ^{1}H NMR (400MHz, $CDCl_3$, δ): 7.74 (d, *J* = 8.0, 2H, ArC**H**), 7.59 (t, *J* = 8.0, 2H, ArC**H**), 7.49 (t, *J* = 8.0, 1H, ArC**H**), 7.37 (t, *J* = 8.0, 1H, ArC**H**), 7.30 (d, *J* = 8.0, 2H, ArC**H**), 4.85 (app. t, *J* = 7.0, 1H, N**H**), 4.29 (d, *J* = 7.0, 2H, C**H**$_2$), 2.43 (s, 3H, ArC**H**$_3$). ^{13}C NMR (100MHz, $CDCl_3$, δ): 143.7 (**s**, **C**-Me), 136.8 (**s**, **C**-CH_2-), 134.9 (**s**, **C**-SO_2-), 132.3 (**d**, Ar**C**H), 130.8 (**d**, Ar**C**H), 129.8 (2 x **d**, Ar**C**H), 128.0 (2 x **d**, Ar**C**H), 127.1 (2 x **d**, **C**H), 125.5-123.5 (**s**, *J* = 200.0, **C**-C-F), not observed (**C**F_3), 43.7 (**t**, **C**H_2), 21.5 (**q**, Ar**C**H_3). (LSIMS-FAB$^+$) *m/z*: 330 (MH^+ = 100%), 159 (23), 137 (12). HRMS (LSIMS-FAB$^+$) *m/z*: (MH^+) calcd. for $C_{15}H_{15}F_3NO_2S$; 330.0775, found 330.0778. Elemental Analysis (WAS): Calcd for $C_{15}H_{14}F_3NO_2S$: C, 54.6; H, 4.2; N, 4.1. Found: C, 54.7; H, 4.2; N, 4.2.

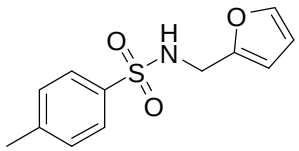
Experimental

4-Methyl-*N*-pyridin-2-ylmethylbenzenesulfonamide 380d [241]



Commercially available from Ambinter [75391-97-8]. Method A: recrystallisation furnished *4-methyl-N-pyridin-2-yl-methylbenzensulfonamide* **380d** as hydroscopic lemon-yellow crystallised solid (2.21g, 32%). IR (neat) ν_{max}: 3059, 2920, 2852, 1326, 1155 and 811 cm^{-1}. ^1H NMR (300MHz; $CDCl_3$, δ): 8.5 (app. s, 1H, ArC**H**), 7.75 (d.t, *J* = 8.0 and 2.0, 2H, ArC**H**), 7.64 (app. d.t, *J* = 8.0 and 2.0, 1H, ArC**H**), 7.26-7.18 (m, 4H, ArC**H**), 5.98 (app. t, *J* = 5.0, 1H, N**H**), 4.25 (d, *J* = 5.0, 2H, C$\mathbf{H_2}$), 2.39 (s, 3H, ArC$\mathbf{H_3}$). ^{13}C NMR (100MHz, $CDCl_3$, δ): 155.2 (**s**, **C**-*pyridine*), 148.9 (**d**, Ar**C**H), 143.8 (2 x **s**, **C**), 137.7 (**d**, Ar**C**H), 130.0 (2 x **d**, Ar**C**H), 127.6 (2 x **d**, Ar**C**H), 123.2 (**d**, Ar**C**H), 122.6 (**d**, Ar**C**H), 47.6 (**t**, **C**H_2), 21.9 (**q**, Ar**C**H_3). LRMS (LSIMS-FAB$^+$) *m/z*: 263 (MH^+ = 35%), 154 (100), 137 (67), 136 (60). HRMS (LSIMS-FAB$^+$) *m/z*: (MH^+) calcd for $C_{13}H_{14}N_2O_2S$, 263.0854; found, 263.0858.

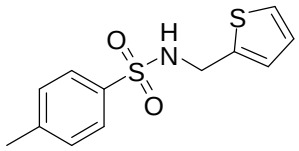
N-Furan-2-ylmethyl-4-methylbenzenesulfonamide 380e [242]



Commercially available from Ambinter [121564-33-8]. Method A: Recrystallisation furnished *N-furan-2-ylmethylbenzenesulfonamide* **380e** as an hydroscopic golden yellow crystallised solid (4.95g, 75%). IR (neat) ν_{max}: 3275, 2918, 2839, 1321, 1185, 686 cm^{-1}. ^1H NMR (400MHz; $CDCl_3$, δ): 7.72 (d.t, *J* = 8.0 and 2.0, 2H, ArC**H**), 7.27 (d, *J* = 8.0, 2H, ArC**H**), 7.24 (app. d, *J* = 2.0, 1H, ArC**H**), 6.21 (app. q., *J* = 2.0, 1H, ArC**H**), 6.09

(app. d, *J* = 3.0, 1H, ArC**H**), 4.78 (app. t, *J* = 6.0, 1H, N**H**), 4.16 (d, *J* = 6.0, 2H, C**H**$_2$), 2.42 (s, 3H, ArC**H**$_3$). ^{13}C NMR (100MHz, $CDCl_3$, δ): 149.9 (**s**, **C**-*furan*), 143.9 (**s**, **C**-Me), 142.9 (**d**, **C**H), 137.21 (**s**, **C**-SO_2-), 130.6 (2 x **d**, Ar**C**H), 127.5 (2 x **d**, Ar**C**H), 110.8 (**d**, **C**H), 108.6 (**d**, **C**H), 40.5 (**t**, **C**H_2), 21.9 (**q**, Ar**C**H_3). LRMS (LSIMS-FAB$^+$) *m/z*: 252 (MH^+ = 20%), 250 (33), 184 (64), 154 (100), 136 (96), 133 (54), 128 (25), 120 (15). HRMS (LSIMS-FAB$^+$) *m/z*: (MH^+) calcd for $C_{12}H_{14}NO_3S$, 252.0694; found, 252.0696. Elemental Analysis (WAS): Calcd. for $C_{12}H_{13}NO_3S$: C, 57.3; H, 5.2; N, 5.6. Found: C, 57.1; H, 5.2; N, 5.5%.

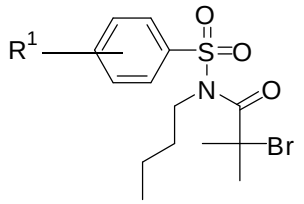
4-Methyl-*N*-(2-thienylmethyl)-benzenesulfonamide 380f



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) ν_{max}: 3286, 2977, 2862, 1320, 1117, 613 cm^{-1}. ^{1}H NMR (400MHz; $CDCl_3$, δ): 7.73 (d, *J* = 8.0, 2H, ArC**H**), 7.28 (d, *J* = 8.0, 2H, ArC**H**), 7.16 (app. d., *J* = 1.0, 1H, ArC**H**), 6.85 (app. quin., *J* = 3.0, 2H, ArC**H**), 5.00 (bs, 1H, N**H**), 4.31 (s, 2H, C**H**$_2$), 2.42 (s, 3H, ArC**H**$_3$). ^{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**, Ar**C**H), 127.8 (**d**, **C**H), 126.9 (**d**, **C**H), 126.5 (**d**, **C**H), 125.8 (2 x **d**, Ar**C**H), 42.1 (**t**, **C**H_2), 21.6 (**q**, Ar**C**H_3). LRMS (LSIMS-FAB$^+$) *m/z*: 268 (MH^+ = 28%), 219 (20), 184 (40), 154 (100), 136 (70). Elemental analysis (WAS): Calcd for $C_{12}H_{13}NO_2S_2$: 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



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) benzenelsulfonamide **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**.

Experimental

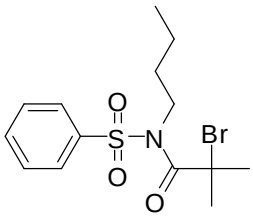
4.3 HÜNIG'S BASE METHOD

To a solution of *N*-butyl-(substituted)-benzenesulfonamide (1.0 eq.) **283** in dichloromethane, was added *N*-ethyldiisopropylamine (Hünig's base, 1.3 eq.) and 2-bromo-isobutyryl bromide (1.1 eq.) **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 *in-vacuo* to yield the crude product. Purification with petrol ether: ethyl acetate furnished the radical precursor **278**.

4.4 IMPROVED METHOD

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

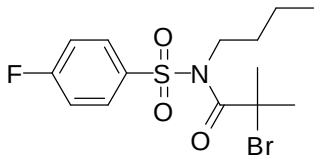
***N*- (2-Bromo-2-methyl-propionyl)-*N*-butyl-benzenesulfonamide 278a**



Flash chromatography (petrol ether/ethyl acetate, 6:1) furnished *N-(2-bromo-2-methyl-propionyl)-N-butyl-benzenesulfonamide* **278a** as a light yellow viscous solid (13.17g, 31%). IR (neat) υ_{max}: 2955, 1675, 1346, 1166, 1069, 723 cm^{-1}. ^{1}H NMR (400MHz/$CDCl_3$, δ): 7.99-7.96 (app. d.t, *J* = 8.0 and 2.0, 2H, ArC**H**), 7.61-7.59 (m, 1H, ArC**H**), 7.54-7.50 (m, 2H, ArC**H**) 4.19 (app. t, *J* = 8.0, 2H, C$\mathbf{H_2}$), 1.96-1.88 (m, 8H, C$\mathbf{H_2}$ and C (C$\mathbf{H_3}$)$_2$) 1.46-1.37 (app. sxt., *J* = 7.0, 2H, C$\mathbf{H_2}$), 0.99 (t, *J* = 7.0, 3H, C$\mathbf{H_3}$). ^{13}C NMR (75.5MHz, $CDCl_3$, δ): 170.8 (**s**, **C**=O), 139.7 (**s**, **C**-SO_2-), 133.9 (**d**, Ar**C**H),

133.0 (**d**, Ar**C**H), 128.8-128.1 (3 x **d**, Ar**C**H), 57.0 (**s**, **C**-$(CH_3)_2$), 48.8 (**t**, **C**H_2), 33.3 (2 x **q**, C(**C**$H_3)_2$), 31.7 (**t**, **C**H_2), 19.9 (**t**, **C**H_2), 13.7 (**q**, C**H**$_3$). LRMS (EI^+) *m/z*: 364 (^{81}Br MH^+ = 54%), 362 (^{79}Br MH^+ = 56), 284 (^{81}Br = 15), 282 (^{79}Br = 98), 206 (^{81}Br = 65), 204 (^{79}Br = 66), 170 (55), 141 (100). HRMS (EI^+) *m/z*: (MH^+) calcd for $C_{14}H_{21}BrNO_3S$, 362.0425; found, 362.0425.

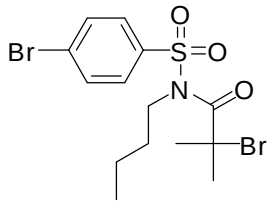
***N*-(2-Bromo-2-methyl-propionyl)-*N*-butyl-4-fluoro-benzenesulfonamide 278b**



Flash chromatography (petrol ether/ethyl acetate, 6:1) furnished *N-(2-bromo-2-methyl-propionyl)-N-butyl-4-fluoro-benzenesulfonamide* **278b** as a yellow viscous solid (2.52g, 52%). IR (neat) υ_{max}: 2955, 1669, 1350, 1156, 1068, 838 and 696 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$, δ): 8.03-7.99 (m, 2H, ArC**H**), 7.18 (app. t, *J* = 8.0, 2H, ArC**H**), 4.19 (app. t, *J* = 8.0, 2H, C**H**$_2$), 1.93-1.85 (m, 8H, C**H**$_2$ and C(C**H**$_3)_2$), 1.46-1.36 (sxt., *J* = 7.0, 2H, C**H**$_2$), 0.99 (t, *J* = 7.0, 3H, C**H**$_3$). ^{13}C NMR (100MHz, $CDCl_3$, δ): 170.5 (**s**, **C**=O), 165.0 (**s**, *J* = 256, **C**-F), 136.0 (**s**, **C**-SO_2-), 131.6 (2 x **d**, J^{CF} = 9.6, **C**H), 115.9 (2 x **d**, J^{CF} = 22.8, **C**H), 56.5 (**s**, **C**-$(CH_3)_2$), 48.9 (**t**, **C**H_3), 32.9 (**t**, **C**H_2), 31.8 (2 x **q**, C(**C**$H_3)_2$) 20.0 (**t**, **C**H_2) 14.0 (**q**, **C**H_3). LRMS (EI/CI) *m/z*: 382 (^{81}Br-M^+ = 100), 380 (^{79}Br-M^+ = 100), 159 (20), 135 (^{81}Br 68), 133 (^{79}Br 70). HRMS (EI^+) *m/z*: (MH^+) calcd for $C_{14}H_{20}BrFNO_3S$, 380.0331; found, 380.0314; Elemental Analysis (WAS): Calcd. for $C_{14}H_{19}BrFNO_3S$: C, 44.2; H, 5.0; N, 3.7. Found: C, 44.4; H, 5.0; N, 3.6.

Experimental

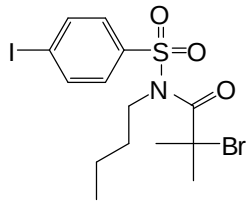
4-bromo-*N*-(2-Bromo-2-methyl-propionyl)-*N*-butyl-benzenesulfonamide 278c



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) ν_{max}: 2960, 2933, 2361, 1681, 1355, 1170 1068, 739 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$, δ): 7.85-7.81 (d.t, *J* = 8.0 and 2.0, 2H, ArC**H**), 7.66-7.61 (d.t, *J* = 8.0 and 2.0, 2H, ArC**H**), 4.17 (app. t, *J* = 7.0, 2H, C$\mathbf{H_2}$), 1.94-1.85 (m, 8H, (C$\mathbf{H_3}$)$_2$ + C$\mathbf{H_2}$), 1.39 (sxt., *J* = 7.0, 2H, C$\mathbf{H_2}$), 1.00 (t, *J* = 7.0, 3H, C$\mathbf{H_3}$). ^{13}C NMR (100MHz, $CDCl_3$, δ): 170.0 (**s**, **C**=O), 137.7 (**s**, **C**-SO_2-), 131.3 (2 x **d**, Ar**C**H), 129.5 (2 x **d**, Ar**C**H), 128.1 (**s**, **C**-Br), 56.0 (**s**, **C**$(CH_3)_2$), 48.3 (**t**, **C**H_2), 32.3 (**t**, **C**H_2), 31.1 (2 x **q**, C(**C**$H_3)_2$), 20.0 (**t**, **C**H_2), 14.5 (**q**, **C**H_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 $C_{14}H_{19}Br_2NO_3S$, 441.9510, found 441.9507.

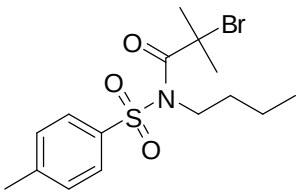
Experimental

N-(2-Bromo-2-methyl-propionyl)-*N*-butyl-4-iodo-benzenesulfonamide 278d



Flash chromatography (petrol ether: ethyl acetate, 4.1) furnished *N-(2-bromo-2-methyl-propionyl)-N-butyl-4-iodo-benzenesulfonamide* **278d** as a greyish-white viscous solid (1.82g, 43%). IR (neat) υ_{max}: 2961, 2361, 1681, 1354, 1170, 1073, 738 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$, δ): 7.89-7.85 (d.t, *J* = 9.0 and 2.0, 2H, ArC**H**), 7.68-7.66 (d.t, *J* = 9.0 and 2.0, 2H, ArC**H**), 4.18-4.14 (app.t, *J* = 8.0, 2H, C$\mathbf{H_2}$), 1.95-1.88 (m, 8H, C$\mathbf{H_2}$ and C($C\mathbf{H_3}$)$_2$), 1.37-1.47 (sxt., *J* = 7.0, 2H, C$\mathbf{H_2}$), 0.98 (t, *J* = 7.0, 3H, C$\mathbf{H_3}$). ^{13}C NMR (100MHz, $CDCl_3$, δ) 170.2 (**s**, **C**=O), 139.0 (**s**, **C**-SO_2-), 137.7 (2 x **d**, Ar**C**H), 129.7 (2 x **d**, Ar**C**H), 101.3 (**s**, **C**-I), 56.2 (**s**, **C**-$(CH_3)_2$), 48.7 (**t**, **C**H_2), 32.0 (**t**, **C**H_2), 31.3 (2 x **q**, C(**C**H_3)$_2$), 19.5 (**t**, **C**H_3), 13.4 (**q**, **C**H_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 (CI) *m/z*: (MH^+) calcd for $C_{14}H_{20}{}^{79}BrINO_3S$ 487.9392, found: 487.9390.

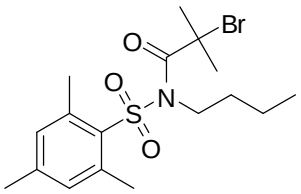
N-(2-Bromo-2-methyl-propionyl)-*N*-butyl-4-methyl-benzenesulfonamide 278e



Previously synthesised by Fullaway.[165] Flash chromatography (petrol ether/ethyl acetate, 6:1) furnished *N-(2-bromo-2-methyl-propionyl)-N-butyl-4-methyl-benzenesulfonamide* **278e** as a viscous yellow crystallised solid (2.20g, 25%). IR (neat) ν_{max}: 2979, 2361, 1710, 1173, 1071 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$, δ): 7.85 (d, *J* = 8.0, 2H, ArC**H**),

7.30 (d, *J* = 8.0, 2H, ArC**H**), 4.16 (bt, *J* = 7.0, 1H, N**H**), 2.43 (s, 3H, ArC**H₃**), 1.96-1.87 (m, 8H, C**H₂** + (C**H₃**)**₂**), 1.45-1.36 (sxt, *J* = 7.0, 2H, C**H₂**), 0.98 (t, *J* = 7.0, 3H, C**H₃**). ^{13}C NMR (100MHz, $CDCl_3$, δ) 165.7 (**s, C═**O), 144.4 (**s**, **C**-Me), 136.41 (**s**, **C**-SO_2-), 129.3 (2 x **d**, Ar**C**H), 128.6 (2 x **d**, Ar**C**H), 56.7 (**s**, **C**-$(CH_3)_2$), 48.8 (**t**, **C**H_2), 32.9 (**t**, **C**H_2), 32.9 (2 x **q**, C(**C**$H_3)_2$), 21.6 (**q**, Ar**C**H_3), 20.0 (**t**, **C**H_2), 14.5 (**q**, **C**H_3). LRMS (EI^+) *m/z*: 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/z*: (MH^+) calcd for $C_{15}H_{22}BrNO_3S$, 376.0582; found, 376.0568.

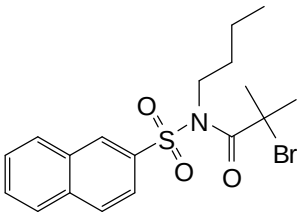
***N*-(2-Bromo-2-methyl-propionyl)-*N*-butyl-2,4,6-trimethyl-benzenesulfonamide 278f**



Previously synthesised by Fullaway.[165] Flash chromatography furnished (petrol ether/ethyl acetate, 6:1) *N-(2-bromo-2-methyl-propionyl)-n-butyl-2,4,6trimethyl-benzene-sulfonamide* **278f** as a yellow crystallised solid (2.74g, 34%). IR (Neat) υ_{max}: 2972, 2361, 1709, 1345, 1164, 1066, 811 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$, δ) 6.95 (app.s 2H, ArC**H**), 4.20 (app. t. *J* = 8.0, 2H, C**H₂**), 2.65 (s, 3H, ArC**H₃**), 2.28 (s, 3H, ArC**H₃**), 2.08-1,93 (m, 8H, C**H₂** and C(C**H₃**)**₂**), 1.87 (s, 3H, ArC**H₃**), 1.49-1.37 (sxt. *J* = 7.0, 2H, C**H₂**), 1.00 (t, *J* = 7.0, 3H, C**H₃**). ^{13}C NMR (100MHz, $CDCl_3$, δ) 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**, Ar**C**H), 131.9 (**d**, Ar**C**H), 56.9 (**s**, **C**-$(CH_3)_2$), 47.8 (**t**, **C**H_2), 33.0 (**t**, **C**H_2), 31.6 (2 x **q**, C(**C**$H_3)_2$) 22.4 (**q**, Ar**C**H_3), 21.0 (**q**, Ar**C**H_3), 20.0 (**t**, **C**H_2), 18.00 (**q**, Ar**C**H_3), 13.5 (**q**, **C**H_3).

Experimental

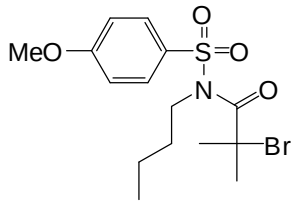
2-Naphthalene-sulfonic-acid-(2-bromo-2-methyl-propionyl)-butylamide 278g



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}. ^{1}H NMR (300MHz, $CDCl_3$, δ): 8.58 (s, 1H, ArC**H**), 8.02-7.93 (m, 1H, ArC**H**), 7.93-7.88 (m, 3H, ArC**H**), 7.69-7.59 (m, 2H, ArC**H**), 4.25 (app.t, *J* = 8.0, 2H, C$\mathbf{H_2}$), 2.02-1.92 (m, 2H, C$\mathbf{H_2}$), 1.87 (s, 6H, 2 x C$\mathbf{H_3}$), 1.43 (sxt., *J* = 7.0, 2H, C$\mathbf{H_2}$), 1.01 (t, *J* = 7.0, 3H, C$\mathbf{H_3}$). ^{13}C NMR (100MHz, $CDCl_3$, δ): 170.5 (**s**, **C**═O), 136.2 (**s**, **C**-SO_2-), 135.2 (**s**, **C**-C), 131.8 (**s**, **C**-C), 130.7 (**d**, Ar**C**H), 129.6 (**d**, Ar**C**H), 129.2 (**d**, Ar**C**H), 128.8 (**d**, Ar**C**H), 127.9 (**d**, Ar**C**H), 127.5 (**d**, Ar**C**H), 122.9 (**d**, Ar**C**H), 56.6 (**s**, **C**-$(CH_3)_2$), 49.0 (**t**, **C**H_2), 33.0 (**t**, **C**H_2), 31.8 (2 x **q**, C(**C**$H_3)_2$), 20.0 (**t**, **C**H_2), 15.0 (**q**, **C**H_3). LRMS (EI^+) *m/z*: 414 (^{81}Br MH^+ = 90%), 412 (^{79}Br MH^+ 90), 334 (^{81}Br 15), 332 (^{79}Br 33), 270 (^{81}Br 71), 268 (^{79}Br 90), 206 (^{81}Br 60), 204 (^{79}Br 54), 144 (^{81}Br 100). Elemental Analysis (WAS): Calcd $C_{18}H_{22}BrNO_3S$: C, 52.4; H, 5.3; N, 3.4. Found: C; 52.4; H, 5.4; N, 3.3.

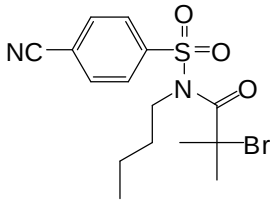
Experimental

_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) υ_{max}: 2956, 2927, 1711, 1664, 1351, 1156, 840 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$, δ): 7.91 (d.t, *J* = 9.0 and 3.0, 2H, ArC**H**); 6.96 (d.t, *J* = 9.0 and 3.0, 2H, Ar-C**H**), 4.15 (app. t, *J* = 7.0, 2H, C$\mathbf{H_2}$), 3.85 (s, 3H, OC$\mathbf{H_3}$), 1.92-1.85 (m, 8H, C$\mathbf{H_2}$ and C (C$\mathbf{H_3}$)$_2$), 1.44-1.35 (sxt., *J* = 7.0, 2H, C$\mathbf{H_2}$), 0.98 (t, *J* = 7.0, 3H, C$\mathbf{H_3}$). ^{13}C NMR (100MHz, $CDCl_3$, δ): 170.4 (**s**, **C**═O), 163.5 (**s**, **C**-OMe), 131.0 (2 x **d**, Ar**C**H), 130.5 (**s**, **C**-SO_2-), 113.7 (2 x **d**, Ar**C**H), 56.7 (**s**, **C**-$(CH_3)_2$), 55.7 (**q**, O**C**H_3), 48.7 (**t**, **C**H_2), 32.9 (**t**, **C**H_2), 31.8 (2 x **q**, C(**C**H_3)$_2$), 19.9 (**t**, **C**H_2), 13.0 (**q**, **C**H_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 $C_{15}H_{22}BrNO_4S$, 392.0531; found, 392.0523.

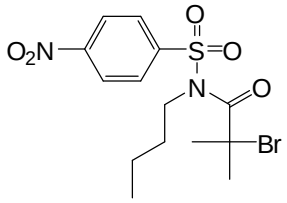
_N_-(2-Bromo-2-methyl-propionyl)-_N_-butyl-4-cyano-benzenesulfonamide 278i



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) ν_{max}: 2961, 1681, 1463, 1356, 1168, 1072, 911 and 729 cm^{-1}. ^{1}H

NMR (300MHz, $CDCl_3$, δ): 8.11 (d.t, *J* = 8.5 and 2.0, 2H, ArC**H**), 7.84 (d.t, *J* = 8.5 and 2.0, 2H, ArC**H**), 4.22 (app. t, *J* = 7.0, 2H, C**H₂**), 1.92 (m, 8H, C**H₂** and C (C**H₃**)₂), 1.49-1.38 (app. quin., *J* = 7.0, 2H, C**H₂**), 1.10-0.98 (m, 3H, C**H₃**). ^{13}C NMR (75.5MHz, $CDCl_3$, δ): 171.0 (**s**, **C**═O), 143.9 (**s**, **C**-SO_2-), 132.9 (2 x **d**, Ar**C**H), 129.4 (2 x **d**, Ar**C**H), 117.6 (**s**, **C**≡N), 117.4 (**s**, Ar**C**-C≡N), 56.7 (**s**, **C**-$(CH_3)_2$), 49.4 (**t**, **C**H_2), 32.7 (**t**, **C**H_2), 32.0 (2 x **q**, C(**C**H_3)$_2$), 20.5 (**t**, **C**H_2), 14.0 (**q**, **C**H_3). LRMS (LSIMS-FAB$^+$) *m/z*: 389 (^{81}Br M^+ = 15%), 387 (^{79}Br M^+ = 15), 154 (100), 137 (76). HRMS (LSIMS-FAB$^+$) *m/z*: (M^+) calcd for $C_{15}H_{19}BrN_2O_3S$, 387.0378; found, 387.0376.

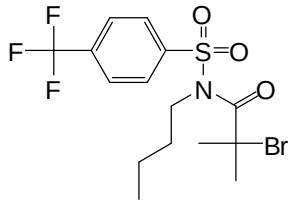
***N*-(2-Bromo-2-methyl-propionyl)-*N*-butyl-4-nitro-benzenesulfonamide 278j**



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) υ_{max}: 2936, 1671, 1350, 1170 and 742, cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$, δ): 8.65 (d, *J* = 7.0, 2H, ArC**H**), 8.16 (d.t, *J* = 7.0, 2H, ArC**H**), 4.22 (app. t, *J* = 8.0, 2H, C**H₂**), 2.06-1.87 (m, 8H, C**H₂** + C(C**H₃**)₂), 1.48-1.39 (sxt., *J* = 7.0, 2H, C**H₂**), 1.00 (t, *J* = 7.0, 3H, C**H₃**). ^{13}C NMR (100MHz, $CDCl_3$, δ): 171.0 (**s**, **C**═O), 150.4 (**s**, **C**-NO_2), 145.0 (**s**, **C**-SO_2-), 129.8 (2 x **d**, Ar**C**H), 123.9 (2 x **d**, Ar**C**H), 56.2 (**s**, **C**-$(CH_3)_2$), 49.1 (**t**, **C**H_2), 33.0 (**t**, **C**H_2), 30.5 (2 x **q**, C(**C**H_3)$_2$), 19.9 (**t**, **C**H_2), 14.0 (**q**, **C**H_3). LRMS (EI$^+$) *m/z*: 409 (^{81}Br-M, 8%), 407 (^{79}Br-M, 8%), 327 (19), 206 (40), 186 (100), 165 (50), 122 (^{81}Br, 72), 120 (^{79}Br, 75). HRMS (EI$^+$) *m/z*: (MH^+), calcd for $C_{14}H_{20}BrN_2O_5S$, 407.0276; found: 407.0267.

Experimental

_N_-(2-Bromo-2-methyl-propionyl)-_N_-butyl-4-trifluoromethyl-benzenesulfonamide 278k

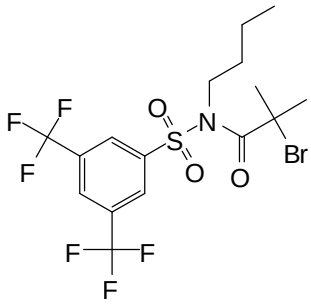


Flash chromatography (petrol ether/ethyl acetate, 4:1) furnished *N-(2-bromo-2-methyl propionyl)-N-Butyl-4-trifluoromethyl-benzenesulfonamide* **278k** as a pale yellow viscous solid (1.12g, 2.62mmol, 36.9%). IR (neat) υ_{max}: 2965, 1326, 1161, 1129, 839, cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$, δ): 8.03 (d, *J* = 8.0, 2H, ArC**H**), 7.70 (d, *J* = 8.0, 2H, ArC**H**), 4.15-4.05 (app. t, *J* = 8.0, 2H, C$\mathbf{H_2}$), 1.87-1.80 (m, 8H, C$\mathbf{H_2}$ and C (C$\mathbf{H_3}$)$_2$), 1.38-1.27 (app. sxt. *J* =7.0, 2H, C$\mathbf{H_2}$), 0.91 (m, 3H, C$\mathbf{H_3}$). ^{13}C NMR (75.5MHz, $CDCl_3$, δ): 170.9 (**s**, **C**=O), 143.4 (**s**, **C**-SO_2-), 135.0 (**s**, *J* = 33, **C**-CF_3), 127.6 (2 x **d**, Ar**C**H), 126.3 (2 x **d**, Ar**C**H), 121.7 (**s**, *J* = 273Hz, **C**F_3), 55.3 (**s**, **C**-$(CH_3)_2$) 49.3 (**t**, **C**H_3), 33.5 (**t**, **C**H_2), 31.3 (2 x **q**, C(**C**H_3)$_2$), 21.2 (**t**, **C**H_2), 12.1 (**q**, **C**H_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 $C_{15}H_{19}BrF_3NO_3S$, 430.0299; found 430.0309.

Experimental

_N_-(2-Bromo-2-methyl-propionyl)-_N_-butyl-3,5-trifluoromethyl-benzenesulfonamide

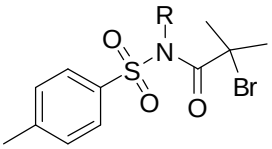
278l



Flash chromatography (petrol ether/ethyl acetate, 4:1) furnished *N-(2-bromo-2-methyl-propionyl)-N-butyl-3,5-trifluoromethyl-benzenesulfonamide* **278l** a yellow oil (2.70g, 97%). IR (neat) υ_{max}: 2964, 1685, 1360, 1279, 1142, 839 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$, δ): 8.40 (s, 2H, ArC**H**), 8.08 (s, 1H, ArC**H**), 4.20 (app.t, *J* = 8.0, 2H, C$\mathbf{H_2}$), 1.93-1.84 (m, 8H, C$\mathbf{H_2}$ and C ($C\mathbf{H_3}$)$_2$), 1.37 (sxt., *J* = 7.0, 2H, C$\mathbf{H_2}$), 0.92 (t, *J* = 7.0, 3H, ArC$\mathbf{H_3}$). ^{13}C NMR (75.5MHz, $CDCl_3$, δ): 171.2 (**s**, **C**=O), 142.5 (**s**, **C**-SO_2-), 133.0 (2 x **s**, *J* = 34.6Hz, (**C**(CF_3)$_2$), 129.3 (**d**, **C**H), 128.2 (2 x **d**, **C**H), 121.0 (2 x **q**, *J* = 273.6, (**C**F_3)$_2$), 56.5 (**s**, **C**-(CH_3)$_2$), 49.7 (**t**, **C**H_2), 32.8 (**t**, **C**H_2) 30.0 (2 x **q**, C(**C**H_3)$_2$), 20.8 (**t**, **C**H_2), 14.00 (**q**, **C**H_3). LRMS (EI^+) *m/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 (EI^+) *m/z*: (MH^+) calcd for $C_{16}H_{19}BrF_6NO_3S$, 498.0173; found 498.0169.

Experimental

5.0 General procedure for synthesis of radical procedures 369



R = alkyl

5.1 *N*-BUTYLLITHIUM METHOD:

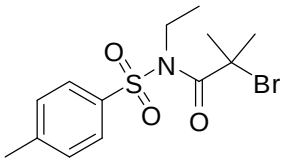
To a stirred solution of *N*-alkyl-4-methylbenzenesulfonamide **374** (1.0 eq.) in anhydrous tetrahydrofuran was added *n*-butyllithium (1.6 M in hexanes) (1.0 eq.) and 2-bromo-isobutyryl bromide **287** (1.0 eq.) at -78°C (dry ice/acetone) overnight. The reaction was quenched with saturated ammonium 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 *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*-alky-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 *in vacuo* to furnish the crude product. Purification with petrolether: ethyl acetate, yield the radical precursor **369**.

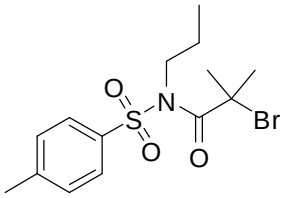
Experimental

***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) ν_{max}: 2978, 1709, 1391, 1163, 811 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$, δ): 7.86 (d, *J* = 8.0, 2H, ArC**H**), 7.30 (d, *J* = 8.0, 2H, ArC**H**), 4.33 (q, *J* = 7.0, 2H, C$\mathbf{H_2}$), 2.42 (s, 3H, ArC$\mathbf{H_3}$), 1.96 (s, 6H, C(C$\mathbf{H_3}$)$_2$), 1.51 (t, *J* = 7.0, 3H, C$\mathbf{H_3}$). ^{13}C NMR (100MHz, $CDCl_3$, δ): 171.5 (**s**, **C**=O), 144.5 (**s**, **C**-Me), 136.5 (**s**, **C**-SO_2-), 129.3 (2 x **d**, Ar**C**H), 128.6 (2 x **d**, Ar**C**H), 56.6 (**s**, **C**-$(CH_3)_2$), 44.0 (**t**, **C**H_2), 31.8 (2 x **q**, C(**C**H_3)$_2$), 21.7 (**q**, Ar**C**H_3), 17.0 (**q**, **C**H_3). LRMS (LSIMS-FAB^+) *m/z*: 350 (^{81}Br-MH^+ = 12%), 348 (^{79}Br-MH^+ = 10), 154 (100), 137 (68). HRMS (LSIMS-FAB^+) calcd for $C_{13}H_{18}BrNO_3S$, 348.0269; found, 348.0262.

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

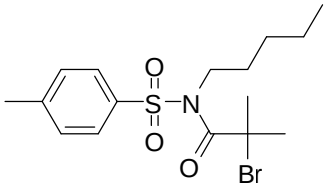


Flash chromatography (6:1 petrol ether:ethyl acetate) furnished *N-(2-bromo-2-methyl-propionyl)-N-propyl-4-methyl-benzenesulfonamide* **369b** as a viscous lemon-yellow crystallised solid (1.19g, 34%). IR (neat) ν_{max}: 2968, 1710, 1349, 1161, 814 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$, δ): 7.75 (d, *J* = 8.5, 2H, ArC**H**), 7.19 (d, *J* = 8.5, 2H, ArC**H**), 4.03 (app.t, *J* = 8.5, 2H, C$\mathbf{H_2}$), 2.31 (s, 3H, ArC$\mathbf{H_3}$), 1.88-1.82 (app. quin., *J* = 7.0, 2H,

C**H₂**), 1.78 (s, 6H, 2 x C**H₃**), 0.88 (t, *J* = 7.0, 3H, C**H₃**). ^{13}C NMR (100MHz, $CDCl_3$, δ) 169.2 (**s**, **C**=O), 143.5 (**s**, **C**-Me), 135.2 (**s**, **C**-SO_2-), 128.2 (2 x **d**, Ar**C**H), 127.5 (2 x **d**, Ar**C**H), 55.6 (**s**, **C**-$(CH_3)_2$), 49.2 (**t**, **C**H_2), 30.7 (2 x **q**, C(**C**$H_3)_2$), 23.2 (**t**, **C**H_2), 20.6 (**q**, Ar**C**H_3), 15.0 (**q**, **C**H_3). LRMS (LSIMS-FAB$^+$) *m/z*: 364 (^{81}Br MH^+ = 30%), 362 (^{79}Br MH^+ = 28), 155 (35), 154 (100), 137 (70), 136 (60). HRMS (LSIMS-FAB$^+$) *m/z*: calcd for $C_{14}H_{20}BrNO_3S$, 362.0425; found, 362.0434.

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

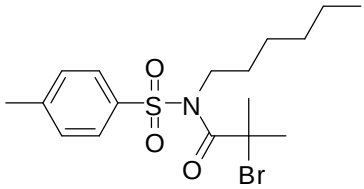
Discernible data:



Flash chromatography (6:1 petrol ether:ethyl acetate) furnished *N-(2-bromo-2-methyl-propionyl)-N-pentyl-4-methyl-benzenesulfonamide* **369d** as a yellow oil (0.54g, 22%). IR (neat) ν_{max}: 2929, 1598, 1494, 1321, 1155, 1092, 1019, 813 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$, δ): 7.85 (d, *J* = 8.0, 2H, ArC**H**), 7.30 (d, *J* = 8.0, 2H, ArC**H**), 4.16 (app. t. *J* = 8.0, 2H, C**H₂**), 2.41 (s, 3H, ArC**H₃**), 1.96-1.88 (m, 8H, C**H₂** + C(C**H₃**)**₂**), 1.44-1.30 (m, 4H, 2 x C**H₂**), 0.92 (t, *J* = 7.0, 3H, C**H₃**). LRMS (LSIMS-FAB$^+$) *m/z*: 392 (^{81}Br-MH^+ = 100), 390 (^{79}Br-MH = 98), 310 (43), 154 (32), 136 (32). HRMS (LSIMS-FAB$^+$) calcd for $C_{16}H_{24}BrNO_3S$, 390.0738; found, 390.0735.

Experimental

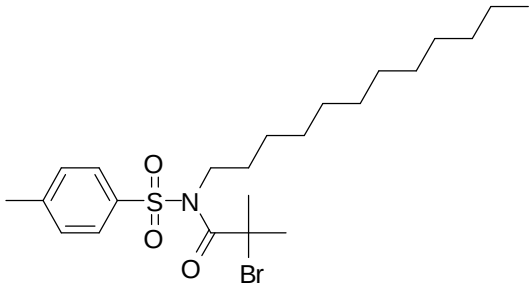
_N_-(2-Bromo-2-methyl-propionyl)-_N_-hexyl-4-methyl-benzenesulfonamide 369e



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) ν_{max}: 2927, 1679, 1348, 1163, 1072, 811 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$, δ): 7.85 (d.t, *J* = 8.0 and 2.0, 2H, ArC**H**), 7.30 (d, *J* = 8.0, 2H, ArC**H**), 4.15 (app. t. *J* = 8.0, 2H, CH_2), 2.43 (s, 3H, ArC$\mathbf{H_3}$), 1.93-1.89 (m, 8H, C$\mathbf{H_2}$ + (C$\mathbf{H_3}$)$\mathbf{_2}$), 1.38-1.26 (m, 6H, 3 x C$\mathbf{H_2}$), 0.90 (t, *J* = 7.0, 3H, C$\mathbf{H_3}$). ^{13}C NMR (100MHz, $CDCl_3$, δ): "not observed" (**C**=O), 145.0 (**s**, **C**-Me), 135.0 (**s**, **C**-SO_2-), 129.0 (2 x **d**, Ar**C**H), 128.3 (2 x **d**, Ar**C**H), 56.4 (**s**, **C**$(CH_3)_2$), 48.8 (**t**, **C**H_3), 31.6 (2 x **q**, **C**H_3), 31.0 (**t**, **C**H_2), 30.7 (**t**, **C**H_2), 26.1 (**t**, **C**H_2), 22.4 (**t**, **C**H_2), 21.4 (**q**, Ar**C**H_3), 13.8 (**q**, **C**H_2). LRMS (LSIMS-FAB$^+$) *m/z*: 406 (^{81}Br MH^+ = 60%), 404 (^{79}Br MH^+ 60), 324 (30), 256 (31), 170 (20), 154 (100), 137 (81). HRMS (LSIMS-FAB$^+$) *m/z*: (MH^+) calcd for $C_{17}H_{27}{}^{79}BrNO_3S$, 404.0895; found, 404.0909.

Experimental

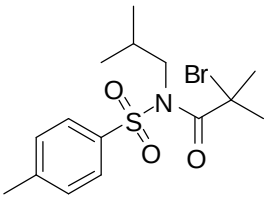
_N_-(2-Bromo-2-methyl-propionyl)-_N_-dodecyl-4-methyl-benzenesulfonamide 369f



Flash Chromatography (6:1 petrol ether:ethyl acetate) furnished *N-(2-bromo-2-methyl-propionyl)-N-dodecyl-4-methyl-benzenesulfonamide* **369f** as a white crystallised solid (1.79g, 41%). IR (neat) ν_{max}: 2915, 1679, 1345, 1159, 1066, 886 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$, δ): 7.78 (d, *J* = 8.0, 2H, ArC**H**), 7.19 (d, *J* = 8.0, 2H, ArC**H**), 4.09 (t, *J* = 8.0, 2H, C$\mathbf{H_2}$), 2.30 (s, 3H, ArC$\mathbf{H_3}$), 1.86-1.79 (m, 8H, C$\mathbf{H_2}$ + (C$\mathbf{H_3}$)$_2$), 1.29-1.22 (m, 18H, 9 x C$\mathbf{H_2}$), 0.83 (t, *J* = 7.0, 3H, C$\mathbf{H_3}$). ^{13}C NMR (100MHz, $CDCl_3$, δ): 170.2 (**s**, **C**=O), 144.2 (**s**, **C**-Me), 136.5 (**s**, **C**-SO_2-), 129.1 (2 x **d**, Ar**C**H), 128.6 (2 x **d**, Ar**C**H), 56.7 (**s**, **C**-$(CH_3)_2$), 49.9 (**t**, **C**H_2), 32.5 (**t**, **C**H_2), 31.7 (**t**, **C**H_2), 31.7 (2 x **q**, C(**C**H_3)$_2$), 29.3-29.1 (6 x **t**, **C**H_2), 26.6 (**t**, **C**H_2), 22.7 (**t**, **C**H_2), 21.5 (**q**, Ar**C**H_3), 14.7 (**q**, **C**H_3). LRMS (LSIMS-FAB$^+$) *m/z*: 490 (^{81}Br MH^+ = 95%), 489 (^{81}Br M^+ = 94), 408 (41), 340 (48), 155 (45), 154 (100), 138 (48), 137 (100). HRMS (LSIMS-FAB$^+$) *m/z*: (MH^+) calcd for $C_{23}H_{39}{}^{81}BrNO_3S$, 488.1834; found 488.1814.

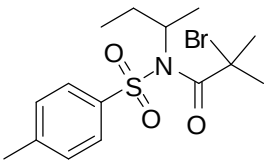
Experimental

_N_-(2-Bromo-2-methyl-propionyl)-_N-iso_-butyl-4-methyl-benzenesulfonamide 369h



Previously synthesised by Fullaway.[163] Flash Chromatography (6:1 petrol ether:ethyl acetate) furnished *N-(2-bromo-2-methyl-propionyl)-N-iso-butyl-4-methyl-benzene-sulfonamide* **369h** as pale yellow crystallised solid (3.06g, 90%). mp 91.3-91.5 ºC. IR (neat) ν_{max}: 2964, 1813, 1323, 1159, 1040 and 812 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$, δ): 7.74 (d, *J* = 8.0, 2H, ArC**H**), 7.30 (d, *J* = 8.0, 2H, ArC**H**), 3.90 (d, *J* = 8.0, 2H C$\mathbf{H_2}$), 2.42 (s, 3H, ArC$\mathbf{H_3}$), 1.96 (s, 6H, (C$\mathbf{H_3}$)$_\mathbf{2}$), 1.74-1.68 (spt., *J* = 7.0, 1H, C**H**), 1.07 (d, *J* = 7.0, 6H, (C$\mathbf{H_3}$)$_\mathbf{2}$). ^{13}C NMR (100MHz, $CDCl_3$, δ): 176.00 (**s**, **C**=O), 165.76 (**s**, **C**-Me), 143.32 (**s**, **C**-SO_2-), 129.70 (2 x **d**, Ar**C**H), 127.07 (2 x **d**, Ar**C**H), 55.01 (**s**, **C**-$(CH_3)_2$), 50.55 (**t**, **C**H_2), 30.01 (2 x **q**, C(**C**H_3)$_2$), 19.88 (2 x **q**, C(**C**H_3)$_2$), 28.44 (**d**, **C**H) 20.25 (**q**, Ar**C**H_3). LRMS (LSIMS) *m/z*: 378 (^{81}Br M^+ = 19%), 376 (^{79}Br M^+ = 20%), 296 (25), 228 (^{79}Br 100), 154 (30), 137 (35).

_N_-(2-Bromo-2-methyl-propionyl)-_N_-sec-butyl-4-methyl-benzenesulfonamide 369i

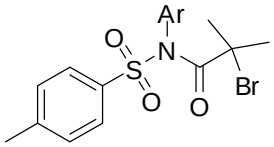


Previously synthesised by Fullaway.[163] Flash chromatography (6:1 petrol ether:ethyl acetate) furnished *N-(2-bromo-2-methyl-propionyl)-N-sec-butyl-4-methyl-benzene-sulfonamide* [**369i**] as a pale yellow crystallised solid (2.88g, 85%). mp 105.4-105.5 ºC.

Experimental

IR (neat) ν_{max}: 2971, 1712, 1297, 1157, 1090, 663 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$, δ): 7.86 (d.t, *J* = 8.0 and 2.0, 2H, ArC**H**), 7.29 (d, *J* = 8.0, 2H, ArC**H**), 4.61 (app. spt. *J* = 7.0, 1H, C**H**), 2.42 (s, 3H, ArC$\mathbf{H_3}$), 2.40-2.30 (m, 1H, C**H**), 2.13-2.03 (m, 1H, C**H**), 1.90 (s, 6H, (C$\mathbf{H_3})_2$), 1.69 (d, *J* = 7.0, C$\mathbf{H_3}$), 1.03 (t, *J* = 7.0Hz, C$\mathbf{H_3}$). ^{13}C NMR (100MHz, $CDCl_3$, δ): 176.6 (**s**, **C**═O), 143.2 (**s**, **C**-Me), 138.2 (**s**, **C**-SO_2-), 129.5 (2 x **d**, **C**H), 127.0 (2 x **d**, **C**H), 55.3 (**s**, **C**-$(CH_3)_2$), 51.4 (**d**, **C**H), 30.6 (2 x **q**, **C**$H_3)_2$), 30.2 (**t**, **C**H_2) 21.6 (2 x **q**, **C**H_3), 15.0 (**q**, **C**H_3).

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

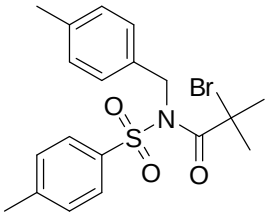


6.1 TRIETHYLAMINE METHOD

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

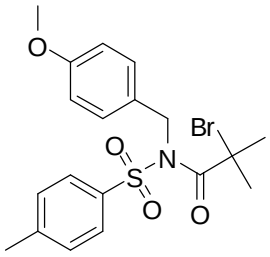
_N_-(2-Bromo-2-methyl-propionyl)-4-methyl-_N_-(4-methyl-benzyl)benzene-sulfonamide 381a



N-(2-bromo-2-methyl-propionyl)-4-methyl-N-(4-methyl-benzyl)-benzenesulfonamide **381a** obtained as a light brown crystallised solid (3.14g, 100%). IR (neat) ν_{max}: 2919, 1690, 1320, 1165, 725 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$, δ): 7.64 (d.t, *J* = 7.0 and 2.0, 2H, ArC**H**), 7.18 (app. t. *J* = 8.0, 4H, ArC**H**), 7.12 (app. d., *J* = 8.0, 2H, ArC**H**), 5.51 (bs, 2H, C$\mathbf{H_2}$), 2.39 (s, 3H, ArC$\mathbf{H_3}$), 2.34 (s, 3H, ArC$\mathbf{H_3}$), 1.86 (s, 6H, C$\mathbf{H_3})_2$). ^{13}C NMR (100MHz, $CDCl_3$, δ): 170.94 (**s**, **C**═O), 144.39 (**s**, **C**-Me), 137.38 (**s**, **C**-Me), 133.32 (**s**, **C**-SO_2-), 128.80 (**d**, Ar**C**H), 128.78 (**d**, Ar**C**H), 128.31 (**d**, Ar**C**H), 128.21 (**d**, Ar**C**H), 127.93 (**d**, Ar**C**H), 127.66 (**d**, Ar**C**H), 127.38 (**d**, Ar**C**H), 126.99 (**d**, Ar**C**H), 60.00 (**s**, **C**-$(CH_3)_2$), 51.72 (**t**, **C**H_3), 31.84 (2 x **q**, C(**C**$H_3)_2$), 21.47 (**q**, Ar**C**H_3), 21.34 (**q**, Ar**C**H_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

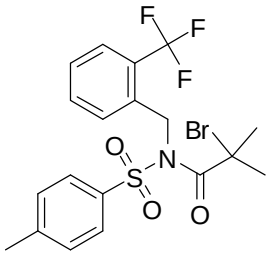


N-(2-bromo-2-methyl-propionyl)-4-methyl-N-(4-methoxy-benzyl)-benzene-sulfonamide **381b** obtained pure as a light brown solid (2.72g, 91%). IR (neat) ν_{max}: 2928, 1676, 1336, 1168, 1088 and 811 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$, δ): 7.61 (d., *J* = 8.0, 2H, ArC**H**), 7.21 (app. t., *J* = 8.0, 4H, ArC**H**), 6.85 (d.t, *J* = 8.0 and 3.0, 2H, ArC**H**), 5.47 (s, 2H, C$\mathbf{H_2}$), 3.80 (s, 3H, OC$\mathbf{H_3}$), 2.40 (s, 3H, ArC$\mathbf{H_3}$), 2.95 (s, 6H, C(C$\mathbf{H_3}$)$_2$). ^{13}C NMR (100MHz, $CDCl_3$, δ): 171.34 (**s**, **C**=O), 159.11 (**s**, **C**-OMe), 144.59 (**s**, **C**-Me), 128.45 (**s**, **C**-SO_2-), 129.04 (2 x **d**, Ar**C**H), 129.01 (2 x **d**, Ar**C**H), 128.45 (**d**, Ar**C**H), 128.40 (**d**, Ar**C**H), 114.37 (**d**, Ar**C**H), 114.04 (**d**, Ar**C**H), 57.20 (**s**, **C**-$(CH_3)_2$), 55.38 (**q**, O**C**H_3), 51.70 (**t**, **C**H_2), 32.08 (2 x **q**, C(**C**H_3)$_2$), 21.70 (**q**, Ar**C**H_3). LRMS (LSIMS-FAB$^+$) *m/z*: 442 (MH^+ = 5%), 154 (100), 137 (65), 121 (38).

Experimental

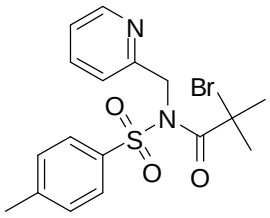
_N_-(2-bromo-2-methyl-propionyl)-4-methyl-_N_-(2-trifluoromethyl-benzyl)-benzene-sulfonamide 381c

Discernible data



N-(2-bromo-2-methyl-propionyl)-4-methyl-N-(2-trifluoromethyl-benzyl)-benzene-sulfonamide **381c** as a light brownish-yellow crystallised solid (2.31g, 79%). IR (neat) ν_{max}: 2361, 1681, 1311, 1165, 1036, 775 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$, δ): 7.87 (d.t, *J* = 8.0 and 2.0, 2H, ArC**H**), 7.71 (d, *J* = 8.0, 1H, ArC**H**), 7.65 (d, *J* = 8.0, 1H, ArC**H**), 7.58 (t, *J* = 8.0, 1H, ArC**H**), 7.41 (t, *J* = 8.0, 1H, ArC**H**), 7.32 (d, *J* = 8.0, 2H, ArC**H**), 5.83 (s, 2H, C$\mathbf{H_2}$), 2.46 (s, 3H, ArC$\mathbf{H_3}$), 1.73 (s, 6H, 2 x C$\mathbf{H_3}$). LRMS (LSIMS-FAB$^+$) *m/z*: 480 (^{81}Br MH^+ = 20%), 477 (^{79}Br MH^+ = 18), 154 (100), 136 (74), 120 (12). HRMS (LSIMS-FAB$^+$) *m/z*: (MH^+) calcd for $C_{19}H_{20}BrF_3NO_3S$, 478.0299; found, 478.0305.

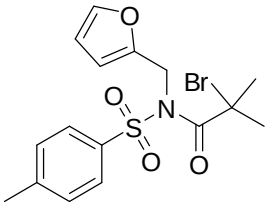
_N_-(2-bromo-2-methyl-propionyl)-4-methyl-_N_-pyridin-2-yl-methyl-benzene-sulfonamide 381d



N-(2-bromo-2-methyl-propionyl)-4-methyl-N-pyridin-2-yl-methyl-benzenesulfonamide **381d** as a light brown crystallised solid (3.14g, 100%). IR (neat) ν_{max}: 2923, 1682, 1346, 1168, 1112, 1086 and 782 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$, δ): 8.59 (app. d. *J* = 5.0,

1H, ArC**H**), 7.81-7.76 (app. d., *J* = 8.0, 3H, ArC**H**), 7.55 (d, *J* = 8.0, 1H, ArC**H**), 7.27 (app.d, *J* = 8.0, 3H, ArC**H**), 5.71 (s, 2H, C**H**$_2$), 2.43 (s, 3H, ArC**H**), 1.97 (s, 6H, (C**H**$_3$)$_2$). ^{13}C NMR (100MHz, $CDCl_3$, δ): 170.29 (**s**, **C**=O), 156.13 (**s**, **C**-pyridine), 148.23 (**d**, Ar**C**H), 144.73 (**s**, **C**-Me), 137.77 (**d**, Ar**C**H), 135.31 (**s**, **C**-SO_2-), 129.10 (2 x **d**, Ar**C**H), 128.75 (2 x **d**, Ar**C**H), 122.60 (**d**, Ar**C**H), 121.33 (**d**, Ar**C**H), 56.73 (**s**, **C**-$(CH_3)_2$), 52.50 (**t**, **C**H_2), 30.64 (2 x **q**, C(**C**H_3)$_2$), 21.50 (**q**, Ar**C**H_3). LRMS (LSIMS-FAB$^+$) *m/z*: 412 (^{81}Br M^+ = 18%), 410 (^{79}Br M^+ = 18), 331 (16), 219 (20), 165 (20), 154 (100), 136 (36). HRMS (LSIMS-FAB$^+$) calcd for $C_{17}H_{19}BrN_2O_3S$, 411.0378; found, 411.0371.

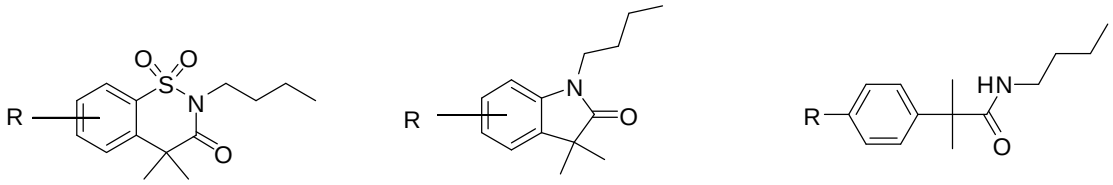
***N*-(2-Bromo-2-methyl-propionyl)-*N*-(furan-2-ylmethyl)-4-methyl-benzene-sulfonamide 381e**



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) ν_{max}: 2977, 1709, 1348, 1161, 1087, 811 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$, δ): 7.58 (d, *J* = 8.0, 2H, ArC**H**), 7.30 (app s., 1H, furan-**H**), 7.21 (d, *J* = 8.0, 2H, ArC**H**), 6.45 (app. d, *J* = 3.0, 1H, furan-**H**), 6.38 (app.q. *J* = 3.0, 1H, furan-**H**), 5.47 (s, 2H, C**H**$_2$), 2.40 (s, 3H, ArC**H**$_3$), 1.95 (app d. *J* = 4.0, 6H, (C**H**$_3$)$_2$). ^{13}C NMR (100MHz, $CDCl_3$, δ): 176.8 (**s**, **C**=O), 149.6 (**s**, **C**-furan), 144.5 (**s**, **C**-Me), 142.3 (2 x **d**, Ar**C**H), 135.9 (**s**, **C**-SO_2-), 129.1 (**d**, Ar**C**H), 128.9 (**d**, Ar**C**H), 110.7 (**d**, **C**H), 109.7 (**d**, **C**H) 57.4 (**s**, **C**-$(CH_3)_2$), 45.2 (**t**, **C**H_2), 32.3 (2 x **q**, **C**H_3), 30.5 (**q**, C(**C**H_3)$_2$), 21.7 (**q**, Ar**C**H_3). LRMS (LSIMS) *m/z*: 402 (^{81}Br-M^+ = 13%), 400 (^{79}Br-M^+ = 15), 244 (20), 219 (15), 154 (100), 136 (76).

Experimental

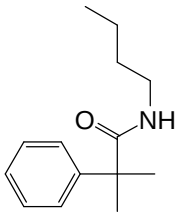
7.0 Synthesis of cyclised and rearranged amides from radical precursors 278



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.

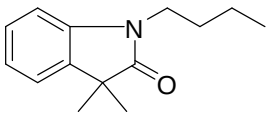
2-(Phenyl)-*N*-butyl-isobutyramide 280a



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_2Cl_2) ν_{max}: 3359, 2928, 1643, 1525, 1365, 1164, 762 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$, δ): 7.36 (s, 4H, ArC**H**), 7.29-7.24 (m, 1H, ArC**H**), 5.18 (s, 1H, N**H**), 3.15 (q, *J* = 7.0, 2H, C$\mathbf{H_2}$), 1.56 (s, 6H, C(C$\mathbf{H_3}$)$_2$), 1.40-1.30 (quin., *J* = 7.0, 2H, C$\mathbf{H_2}$), 1.26-1.14 (sxt., *J* = 7.0, 2H,

C**H$_2$**), 0.84 (t, *J* = 7.0Hz, 3H, C**H$_3$**). ^{13}C NMR (100MHz, $CDCl_3$, δ): 177.4 (**s**, **C**=O), 145.3 (**s**, **C**-SO_2-), 128.6 (**d**, Ar**C**H), 127.0 (2 x **d**, Ar**C**H), 126.4 (2 x **d**, Ar**C**H), 47.0 (**s**, **C**$(CH_3)_2$), 39.4 (**t**, **C**H_2), 31.5 (**t**, **C**H_2), 29.7 (2 x **q**, C(**C**$H_3)_2$), 20.00 (**t**, **C**H_2), 14.00 (**q**, **C**H_3). LRMS (EI$^+$) *m/z*: 220 (100 = M^+), 120 (100), 119 (90), 105 (95). HRMS (EI$^+$) *m/z*: (M^+) calcd for $C_{14}H_{21}NO$, 219.1623; found, 219.1624.

_N_-Butyl-3,3-dimethyl-1,3-dihydro-indol-2-one 290 [190]

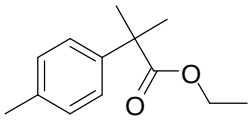


Previously synthesised. Purification by flash chromatography furnished *1-butyl-3,3-dimethyl-1,3-dihydro-indol-2-one* **290** as a transparent spherical film (0.14g, 59%). IR (CH_2Cl_2) ν_{max}: 2962, 2928, 2868, 1357, 1133, 749 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$, δ): 7.21 (app. q., *J* = 7.5, 2H, ArC**H**), 7.04 (m, 1H, ArC**H**), 6.87 (d, *J* = 7.0, 1H, ArC**H**), 3.71 (t, *J* = 7.0, 2H, C**H$_2$**), 1.71-1.61 (app. quin., *J* = 7.0, 2H, C**H$_2$**), 1.44-1.31 (m, 8H, C**H$_2$** + (C**H$_3$)$_2$**), 0.95 (t, *J* = 7.0, 3H, C**H$_3$**). ^{13}C NMR (75.5MHz, $CDCl_3$, δ) 181.3 (**s**, **C**=O), 142.1 (**s**, **C**-N-), 136.0 (**s**, **C**-$C(CH_3)_2$), 127.6 (2 x **d**, Ar**C**H), 122.2 (**d**, Ar**C**H), 108.3 (**d**, Ar**C**H), 44.1 (**s**, **C**-$(CH_3)_2$), 39.6 (**t**, **C**H_2), 29.5 (**t**, **C**H_2), 24.5 (2 x **q**, C(**C**$H_3)_2$), 20.1 (**t**, **C**H_2), 14.1 (**q**, **C**H_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 [219]

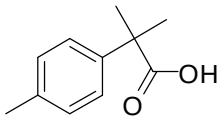


Synthesised according to Küntzel *et al*. procedure. To a solution of anhydrous dimethylformamide (DMF) (25 mL), was added ethyl-p-tolylacetate (10g, 9.9 mL, 56 mmol) (Flask A). In a separate flask (B) was added sodium hydride in mineral oil (60%) (7.85g, 196 mmol) which was thrice washed in pentane 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).

^{1}H NMR (300MHz, $CDCl_3$, δ): 7.24-7.15 (app. d.t. *J* = 8.0 and 2.0, 2H, ArC**H$_3$**), 7.09 (app. d, *J* = 8.0, 2H, ArC**H$_2$**), 4.14-4.05 (app. q, *J* = 7.0, 2H, C**H$_2$**), 2.15 (s, 3H, ArC**H$_3$**), 1.54 (s, 6H, (C(C**H$_3$**)$_2$), 1.21-1.12 (t *J* = 7.0, 3H, C**H$_3$**). ^{13}C NMR (100MHz, $CDCl_3$, δ): 176.9 (**s**, **C**=O), 141.2 (**s**, **C**-Me), 136.2 (**s**, **C**-C(CH_3)$_2$), 129.0 (2 x **d**, Ar**C**H), 125.5 (2 x **d**, Ar**C**H), 60.7 (**t**, **C**H_2), 29.7 (2 x **q**, C-(**C**H_3)$_2$), 20.9 (**q**, Ar**C**H_3), 15.0 (**q**, **C**H_3).

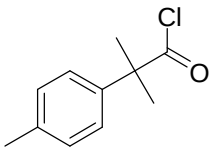
Experimental

α,α, 4-Trimethylbenzeneacetic acid 350 [222]



Commercially available from Interchim [20430-18-6]. Previously synthesised by Smith III *et. al.*[220] 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, COO**H**), 7.10 (d.t, *J* = 8.0 and 2.0, 2H, ArC**H**), 6.99 (t, *J* = 8.0, 2H, ArC**H**), 2.19 (s, 3H, ArC**H$_3$**), 1.44 (s, 6H, (C**H$_3$**)$_2$). ^{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**, Ar**C**H), 125.7 (2 x **d**, Ar**C**H), 46.2 (**s**, **C**-(CH$_3$)$_2$), 26.6 (2 x **q**, C(**C**H$_3$)$_2$), 21.0 (**q**, Ar**C**H$_3$).

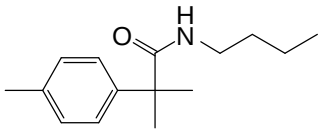
2-Methyl-2-*p*-tolyl-propionyl chloride 351 [222]



Previously synthesised by Buckle *et. al*.[247] 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, ArC**H**), 2.32 (s, 3H, ArC**H$_3$**), 1.58 (s, 6H, (C(C**H$_3$**)$_2$).

Experimental

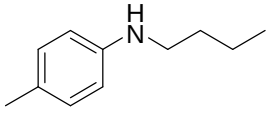
Authentic Synthesis *N*-Butyl-2-*p*-tolyl-isobutyramide 280e [222]



To a stirred solution of 2-methyl-2-phenyl-propionyl chloride **351** (0.02g, 0.1mmol) in diethyl ether (2 mL), was added *n*-butylamine (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, $CDCl_3$, δ): 7.18 (d.t, *J* = 8.0 and 2.0, 2H, ArC**H**), 7.08 (d, *J* = 8.0, 2H, ArC**H**), 5.05 (bs, 1H, N**H**), 3.07 (q, *J* = 7.0, 2H, C$\mathbf{H_2}$), 2.27 (s, 3H, ArC$\mathbf{H_3}$), 1.47 (s, 6H, 2 x C$\mathbf{H_3}$), 1.31-1.24 (quin. *J* = 7.0, 2H, C$\mathbf{H_2}$), 1.19-1.09 (app. sxt., *J* = 7.0, 2H, C$\mathbf{H_2}$), 0.78 (t, *J* = 7.0, 3H, C$\mathbf{H_3}$). ^{13}C NMR (100MHz, $CDCl_3$, δ): 177.6 (**s**, **C**=O), 142.3 (**s**, **C**-Me), 136.6 (**s**, **C**-C$(CH_3)_2$), 129.3 (2 x **d**, Ar**C**H), 126.4 (2 x **d**, Ar**C**H), 46.7 (**s**, **C**-$(CH_3)_2$), 39.4 (**t**, **C**H_2), 31.6 (**t**, **C**H_2), 27.2 (2 x **q**, C(**C**$H_3)_2$), 20.9 (**q**, Ar**C**H_3), 20.0 (**t**, **C**H_2), 14.8 (**q**, **C**H_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

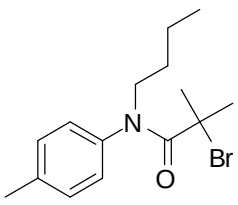
N-*n*-Butyl-*p*-toluidine 340 [209]



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

oil decanted. In a separate flask (B) was added *p*-toluidine **339** (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 effervensing 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* **340**. ^{1}H NMR (400MHz, $CDCl_3$, δ): 6.90 (d, *J* = 8.0, 2H, ArC**H**), 6.45 (d.t, *J* = 8.0 and 2.5, 2H, ArC**H**), 3.01 (t, *J* = 7.0, 2H, C$\mathbf{H_2}$), 2.16 (s, 3H, ArC$\mathbf{H_3}$), 1.55-1.48 (q, *J* = 7.0, 2H, C$\mathbf{H_2}$), 1.40-1.30 (sxt. *J* = 7.0, 2H, C$\mathbf{H_2}$), 0.88 (t, *J* = 7.0, 3H, C$\mathbf{H_3}$). ^{13}C NMR (100MHz, $CDCl_3$, δ): 146.3 (**s**, **C**-N-), 129.7 (2 x **d**, Ar**C**H), 126.3 (**s**, **C**-Me), 122.9 (2 x **d**, Ar**C**H), 44.1 (**t**, **C**H_2), 31.8 (**t**, **C**H_2), 20.4 (**t**, **C**H_2), 20.4 (**q**, Ar**C**H_3), 15.0 (**q**, **C**H_3).

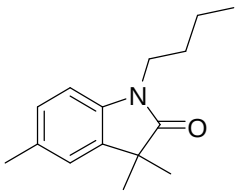
2-Bromo-*N*-butyl-2-methyl-*N*-p-tolyl-propionamide 341 [210]



To a flask containing *N*-butyl-*p*-toluidine **340** in diethyl ether (50 mL) was added triethylamine (1.41g) and 2-bromo-2-isobutyryl bromide (5.5 mL). The reaction mixture

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 (1.65g). Flash chromatography (petrol ether:ethyl acetate 6:1) furnished *2-bromo-N-butyl-2-methyl-N-p-tolyl-propionamide* **341** as a yellow oil (0.39g, 31%). ^{1}H NMR (300MHz, $CDCl_3$, δ): 7.29-7.12 (m, 4H, ArC**H**), 3.65 (t, *J* = 7.0, 2H, C$\mathbf{H_2}$), 2.39 (s, 3H, ArC**H**), 1.70 (s, 6H, (C$\mathbf{H_3}$)$_2$), 1.57-1.51 (app. quin., *J* = 7.0, 2H, C$\mathbf{H_2}$), 1.37-1.25 (app. sxt., *J* = 7.0, 2H, C$\mathbf{H_2}$), 0.89 (t, *J* = 7.0, 3H, C$\mathbf{H_3}$). ^{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**, Ar**C**H), 59.0 (**s**, **C**-$(CH_3)_2$), 53.2 (**t**, **C**H_2), 29.8 (2 x **q**, C(**C**H_3)$_2$), 28.9 (**t**, **C**H_2), 20.9 (**q**, Ar**C**H_3), 19.8 (**t**, **C**H_2), 13.7 (**q**, **C**H_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]

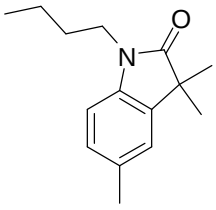


Anhydrous aluminium chloride was kept under a stream of nitrogen and to a single necked flask was added (0.54g) and the precursor **341** (0.50g). An air condenser was attached and the mixture was heated to 50 °C for 10 min, then maintained at 160 °C for 1h. A black viscous solid was obtained upon cooling.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

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 *1-butyl-3,3,5-trimethyl-1,3-dihydroindol-2-one* **333** as a light yellow oil (0.17g, 46%). IR (CH_2Cl_2) ν_{max}: 2927, 1641, 1510, 1108 and 822 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$, δ) 6.94 (d, *J* = 7.0, 2H, ArC**H**), 6.64 (app. d, *J* = 7.0, 1H, ArC**H**), 3.60 (t, *J* = 7.0, 2H, C$\mathbf{H_2}$), 2.24 (s, 3H, ArC$\mathbf{H_3}$), 1.59-1.52 (quin., *J* = 7.0, 2H, C$\mathbf{H_2}$), 1.32-1.22 (m, 8H, C$\mathbf{H_2}$ + (C$\mathbf{H_3}$)$_2$), 0.85 (t, *J* = 7.0, 3H, C$\mathbf{H_3}$). ^{13}C NMR (100MHz, $CDCl_3$, δ) 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**, Ar**C**H), 122.2 (**d**, Ar**C**H), 107.0 (**d**, Ar**C**H), 43.0 (**s**, **C**-(CH_3)$_2$), 38.5 (**t**, **C**H_2), 28.5 (**t**, **C**H_2), 23.4 (2 x **q**, C(**C**H_3)$_2$), 20.0 (**q**, Ar**C**H_3), 19.7 (**t**, **C**H_2), 13.5 (**q**, **C**H_3); *m/z* (LSIMS) 232 (MH^+ = 32%), 207 (27), 165 (11), 154 (100), 136 (80), 120 (27).

1-Butyl-3,3,5-trimethyl-1,3-dihydroindol-2-one 333

Copper-mediated radical reaction

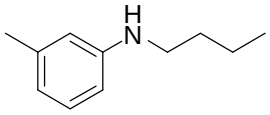


To a three necked RB flask was added **341** (0.58g, 1.0 eq.), tris-(2-pyridylmethyl)-amine **279** (0.67g, 1.1 eq) and copper bromide (0.39g, 1.1 eq.) in toluene (16 mL) and the reaction mixture stirred under nitrogen at 120 °C for 24 h. The crude product was filtered through a silica plug with ethyl acetate to yield a pale yellow oil (0.42g, 98%) as *1-butyl-3,3,5-trimethyl-1,3-dihydroindol-2-one* **333**. IR (CH_2Cl_2) ν_{max} 2927, 1706, 1494, 1192, 803cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) 6.93 (d, *J* = 7.0, 2H, ArC**H**), 6.65 (d, *J* =

7.0, 1H, ArC**H**), 3.59 (t, *J* = 7.0, 2H, C**H**$_3$), 2.24 (s, 3H, ArC**H**$_3$), 1.59-1.51 (quin. *J* = 7.0, 2H, C**H**$_2$), 1.29-1.21 (m, 8H, C**H**$_2$ + (C**H**$_3$)$_2$), 0.84 (t, *J* = 7.0, 3H, C**H**$_3$). ^{13}C NMR (100MHz, $CDCl_3$, δ) "not observed" (**s**, **C**=O), 139.90 (**s**, **C**-N-), 136.1 (**s**, **C**-Me), 131.7 (**s**, **C**-C$(CH_3)_2$), 127.7 (**d**, Ar**C**H), 123.3 (**d**, Ar**C**H), 108.0 (**d**, Ar**C**H), 68.2 (**s**, **C**-$(CH_3)_2$), 39.6 (**t**, **C**H_2), 29.5 (**t**, **C**H_2), 24.5 (2 x **q**, C(**C**$H_3)_2$), 22.5 (**q**, Ar**C**H_3), 20.09 (**t**, **C**H_2), 14.75 (**q**, **C**H_3).

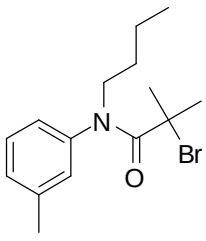
Discernible data for butyl-3,3,6-trimethyl-1,3-dihydroindol-2-one 336

Butyl-*m*-tolylamine 343 [212]



Procedure same as above for **340**. Distilled at 114 ºC/10Torr to furnish green mobile oil (3.0g, 20%). ^{1}H NMR (300MHz, $CDCl_3$, δ): 7.14-7.06 (m, 1H, ArC**H**), 6.55 (app. d. *J* = 7.0, 1H, ArC**H**), 6.46 (app. d. *J* = 7.0, 2H, ArC**H**), 3.56 (bs, 1H, N**H**), 3.14 (t, *J* = 7.0, 2H, C**H**$_2$), 2.31 (s, 3H, ArC**H**$_3$), 1.68-1.59 (m, 2H, C**H**$_3$), 1.50-1.40 (m, 2H, C**H**$_2$), 1.00 (app. t, *J* = 7.0, 3H, C**H**$_3$).

2-Bromo-*N*-butyl-2-methyl-*N*-*m*-tolyl-propionamide 345 [210]

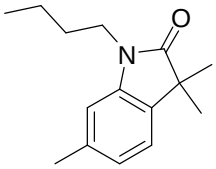


Same procedure as for **341**. Flash chromatography (petrol ether: ethyl acetate 6:1) furnished *2-bromo-N-butyl-2-methyl-N-m-tolyl-propionamide* **345** as yellow oil (1.65g). ^{1}H NMR (300MHz, $CDCl_3$, δ) 7.35-7.13 (m, 4H, ArC**H**), 3.67 (t, *J* = 7.5, 2H, C**H**$_3$),

2.35 (s, 3H, ArC**H**$_3$), 2.00 (s, 6H, C(C**H**$_3$)$_2$), 1.61-1.50 (m, 2H, C**H**$_2$), 1.38-1.32 (m, 2H, C**H**$_2$), 0.90 (t, *J* = 7.5, 3H, C**H**$_3$).

Butyl-3,3,6-trimethyl-1,3-dihydroindol-2-one 336 [210]

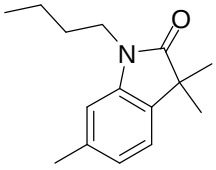
$AlCl_3$ anhydrous reaction



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). ^{1}H NMR (400MHz, $CDCl_3$, δ) 7.08 (d, *J* = 7.5, 1H, ArC**H**), 6.85 (d, *J* = 7.5, 1H, ArC**H**), 6.68 (s, 1H, ArC**H**), 3.69 (t, *J* = 7.5, 2H, C**H**$_3$), 2.38 (s, 3H, ArC**H**$_3$), 1.69-1.60 (m, 2H, C**H**$_2$), 1.40-1.30 (m, 8H, C**H**$_2$ + (C**H**$_3$)$_2$), 0.94 (t, *J* = 7.5, 3H, C**H**$_3$).

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

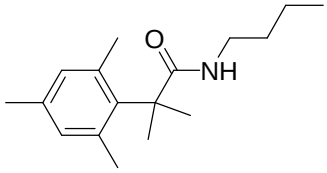
Copper (I) bromide/TPA reaction



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}. ^{1}H NMR (300MHz, $CDCl_3$, δ) 7.08 (d, *J* = 7.5, 1H, ArC**H**), 6.85 (d, *J* = 7.5, 1H, ArC**H**), 6.68 (s, 1H, ArC**H**), 3.69 (t, *J* = 7.5, 2H, C**H**$_2$), 2.38 (s, 3H, ArC**H**$_3$), 1.69-1.61 (m, 2H, C**H**$_2$), 1.42-1.31 (m, 8H, C**H**$_2$ + (C**H**$_3$)$_2$), 0.95 (t, *J* = 7.5, 3H, C**H**$_3$); ^{13}C NMR (100MHz, $CDCl_3$, δ) 182.5 (**s**, **C**=O), 142.1 (**s**, **C**-N-),

137.6 (**s**, **C**-Me), 133.2 (**s**, **C**-C$(CH_3)_2$), 122.7 (**d**, Ar**C**H), 122.1 (**d**, Ar**C**H), 109.3 (**d**, Ar**C**H), 43.9 (**s**, **C**-$(CH_3)_2$), 39.5 (**t**, **C**H_2), 31.8 (**t**, **C**H_2), 29.6 (**t**, **C**H_2), 21.8 (2 x **q**, C(**C**$H_3)_2$), 20.0 (**q**, Ar**C**H_3), 14.9 (**q**, **C**H_3).

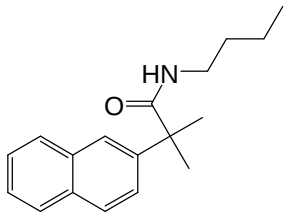
***N*-Butyl-2,4,6-trimethyl-phenyl-isobutryramide 280f**



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 (CH_2Cl_2) ν_{max}: 3316, 2958, 1736, 1521, 1161, 850 cm^{-1}. ^{1}H NMR (400MHz; $CDCl_3$, δ) 6.80 (s, 2H, ArC**H**), 5.28 (s, 1H, N**H**), 3.18 (q, *J* = 7.0Hz, 2H, C**H$_2$**), 2.35 (s, 6H, 2 x ArC**H$_3$**), 2.23 (s, 3H, ArC**H$_3$**), 1.62 (s, 6H, (C**H$_3$)$_2$**), 1.46-1.37 (quin., *J* = 7.0, 2H, C**H$_2$**), 1.30-1.21 (sxt, *J* = 7.0, 2H, C**H$_2$**), 0.88 (t, *J* = 7.0, 3H, C**H$_3$**). ^{13}C NMR (100MHz, $CDCl_3$, δ) 180.3 (**s**, **C**=O), 138.2 (**s**, **C**-C$(CH_3)_2$), 137.8 (2 x **s**, **C**-Me), 135.8 (**s**, **C**-Me), 131.9 (**d**, Ar**C**H), 131.9 (**d**, Ar**C**H), 49.7 (**s**, **C**-$(CH_3)_2$), 39.8 (**t**, **C**H_2), 31.4 (**t**, **C**H_2), 30.9 (**q**, Ar**C**H_3), 28.7 (**q**, Ar**C**H_3), 23.4 (2 x **q**, C(**C**$H_3)_2$), 20.3 (**q**, Ar**C**H_3), 20.0 (**t**, **C**H_2), 14.7 (**q**, **C**H_3). LRMS (LSIMS-FAB$^+$) *m/z*: 262 (MH^+ = 100%), 161 (33), 154 (51), 136 (43). HRMS (LSIMS-FAB$^+$) *m/z*: calcd for $C_{17}H_{28}NO$, 262.2171; found, 262.2170.

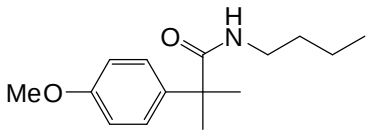
Experimental

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_2Cl_2) ν_{max}: 3347; 2960. 2930, 1649, 1527, 748 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$, δ): 7.82 (m 3H, ArC**H**), 7.41-7.51 (m, 4H, ArC**H**), 5.19 (bs, 1H, N**H**), 3.15 (q, *J* = 7.0, 2H, C$\mathbf{H_2}$), 1.64 (s, 6H, C(C$\mathbf{H_3}$)$_2$), 1.12-1.34 (m, 4H, C$\mathbf{H_2}$), 0.83 (t, *J* = 7.0, 3H, C$\mathbf{H_3}$). ^{13}C NMR (125.8MHz, $CDCl_3$, δ) 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**, Ar**C**H), 128.5 (**d**, Ar**C**H), 127.7 (**d**, Ar**C**H), 126.4 (**d**, Ar**C**H), 126.1 (**d**, Ar**C**H), 125.5 (**d**, Ar**C**H), 124.4 (**d**, Ar**C**H), 47.2 (**s**, **C**-(CH_3)$_2$), 39.5 (**t**, **C**H_2), 31.6 (**t**, **C**H_2), 27.0 (2 x **q**, C(**C**H_3)$_2$), 19.9 (**t**, **C**H_2), 13.6 (**q**, **C**H_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.

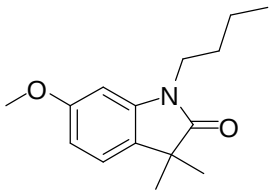
N-Butyl-2- (4-methoxy-phenyl)-isobutyramide 280h



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_2Cl_2) ν_{max}: 3349, 2960, 1645, 1511, 1249, 1182, 1017, 839 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$, δ): 7.27 (d.t, *J* = 9.0 and 3.0, 2H, ArC**H**), 6.88 (d.t, *J* = 9.0 and 3.0, 2H, ArC**H**) 5.13 (bs, 1H, N**H**), 3.82 (s, 3H, OC$\mathbf{H_3}$), 3.15 (q, *J* = 7.0, 2H, C$\mathbf{H_2}$), 1.54 (s, 6H, C(C$\mathbf{H_3}$)$_2$), 1.40-

1.30 (quin., *J* = 7.0, 2H, C**H**$_2$), 1.27-1.15 (sxt, *J* = 7.0, 2H, C**H**$_2$), 0.87 (t, *J* = 7.0, 3H, C**H**$_3$). ^{13}C NMR (75.5MHz, $CDCl_3$, δ) 177.5 (**s**, **C**=O), 158.2 (**s**, **C**-OMe), 137.1 (**s**, **C**-Me), 127.4 (2 x **d**, Ar**C**H), 113.7 (2 x **d**, Ar**C**H), 55.1 (**q**, O**C**H$_3$), 46.1 (**s**, **C**-(CH$_3$)$_2$), 39.2 (**t**, **C**H$_2$), 31.3 (**t**, **C**H$_2$), 27.0 (2 x **q**, C(**C**H$_3$)$_2$), 19.7 (**t**, **C**H$_2$), 13.5 (**q**, **C**H$_3$). LRMS (LSIMS-FAB$^+$) *m/*z 250 (MH$^+$ = 100), 154 (22), 149 (42), 136 (15). HRMS (LRMS-FAB$^+$) *m/z*: (MH$^+$) calcd for $C_{15}H_{24}NO_2$, 250.1807; found, 250.1811.

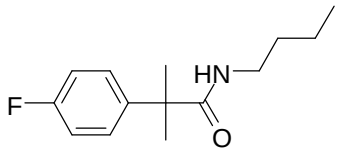
Butyl-5-methoxy-3,3-dimethyl-1,3-dihydro-indol-2-one 352



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 (CH_2Cl_2) ν_{max}: 2966, 2203, 1712, 1624, 1504, 1384, 750 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$, δ): 7.00 (app. d., *J* = 8.0, 1H, ArC**H**), 6.55 (m, 1H, ArC**H**), 6.45 (app. d, *J* = 2.0, 1H, ArC**H**), 3.81 (s, 3H, OC**H**$_3$), 3.68 (t, *J* = 7.0, 2H, C**H**$_2$), 1.70-1.61 (quin., *J* = 7.0, 2H, C**H**$_2$), 1.42-1.31 (m, 8H, C**H**$_2$ + (C**H**$_3$)$_2$), 0.94 (t, *J* = 7.0, 3H, C**H**$_3$). ^{13}C NMR (100MHz, $CDCl_3$, δ): 182.1 (**s**, **C**=O), 159.8 (**s**, **C**-OCH$_3$), 143.1 (**s**, **C**-N-), 128.2 (**s**, **C**-C(CH$_3$)$_2$), 122.8 (**d**, Ar**C**H), 105.8 (**d**, Ar**C**H), 96.7 (**d**, Ar**C**H), 55.5 (**q**, O**C**H$_3$), 43.7 (**s**, **C**(CH$_3$)$_2$), 39.6 (**t**, **C**H$_2$), 30.8 (**t**, **C**H$_2$), 24.4 (2 x **q**, C(**C**H$_3$)$_2$), 20.0 (**t**, **C**H$_2$), 13.50 (**q**, **C**H$_3$). LSRM (LSIMS-FAB$^+$) *m/z*: 248 (MH$^+$ = 100%), 232 (25), 176 (25), 154 (78), 136 (67). HRMS (LSIMS-FAB$^+$) *m/z*: calcd for $C_{15}H_{21}NO_2$, 247.1572; found, 247.1577.

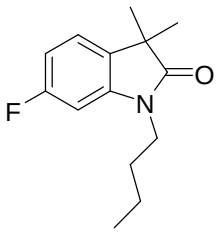
Experimental

N-Butyl-2-(4-fluorophenyl)-isobutyramide 280b



Purification by flash chromatography (petrol ether/ethyl acetate 6:1) furnished *N-butyl-2-(4-fluorophenyl)-isobutyramide* **280b** as an apple white oil (0.12g, 41%). IR (CH_2Cl_2) ν_{max}: 3345, 2960, 1641, 1508, 1229, 1164, 833 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$, δ): 7.36-7.30 (m, 2H, ArC**H**), 7.06-7.00 (m, 2H, ArC**H**), 5.10 (s, 1H, N**H**), 3.16 (q, *J* = 7.0, 2H, C$\mathbf{H_2}$), 1.55 (s, 6H, C(C$\mathbf{H_3}$)$_2$), 1.40-1.33 (quin., *J* = 7.0, 2H, C$\mathbf{H_2}$), 1.27-1.17 (sxt., *J* = 7.0, 2H, C$\mathbf{H_2}$), 0.86 (t, *J* = 7.0, 3H, C$\mathbf{H_3}$). ^{13}C NMR (100MHz, $CDCl_3$, δ): 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**, Ar**C**H), 115.5 (2 x **d**, Ar**C**H), 46.5 (**s**, **C**-$(CH_3)_2$), 39.5 (**t**, **C**H_2), 31.5 (**t**, **C**H_2), 27.2 (2 x **q**, C(**C**H_3)$_2$), 19.9 (**t**, **C**H_2), 14.5 (**q**, **C**H_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.

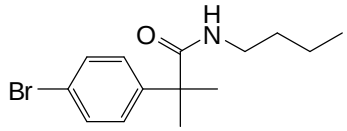
1-Butyl-(6)-fluoro-3,3-dimethyl-1,3-dihydroindol-2-one 355b



Purification by flash chromatography (petrol ether/ethyl acetate 10:1) furnished *1-butyl-(6)-fluoro-3,3-dimethyl-1,3-dihydroindol-2-one* **355b** as a clear oil (0.16g, 53%). IR (CH_2Cl_2) ν_{max}: 3292, 2960, 1667, 1514, 1284, 1127, 812 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$, δ): 7.03 (app q. *J* = 8.0, 1H, ArC**H**), 6.62 (app. d.t *J* = 8.0 and 2.0, 1H, ArC**H**),

6.50 (app. d.d *J* = 9.0 and 2.0, 1H, ArC**H**), 3.60 (t, *J* = 7.0, 2H, C**H₂**), 1.61-1.53 (quin. *J* = 7.0, 2H, C**H₂**), 1.34-1.24 (m, 8H, C**H₂** + (C**H₃**)**₂**), 0.87 (t, *J* = 7.0, 3H, C**H₃**). ^{13}C NMR (100MHz, $CDCl_3$, δ): 182.0 (**s**, **C**=O), 163.9-161.5 (**d**, *J* = 242, **C**-F), 145.0 (**s**, **C**-N-), 131.2 (**s**, **C**-$C(CH_3)_2$), 123.2 (**d**, Ar**C**H), 108.1 (**d**, Ar**C**H), 97.1 (**d**, Ar**C**H), 43.7 (**s**, **C**-$(CH_3)_2$), 39.7 (**t**, **C**H_2), 29.4 (**t**, **C**H_2), 24.5 (2 x **q**, C(**C**$H_3)_2$), 20.0 (**t**, **C**H_2), 13.0 (**q**, **C**H_3). LRMS (EI^+) *m/z*: 235 (M^+ = 80%), 192 (55), 164 (100), 148 (20). HRMS (EI^+) *m/z*: calcd for $C_{14}H_{18}FNO$, 235.1372; found, 235.1370.

2-(4-bromo-phenyl)-*N*-butyl-isobutyramide 280c

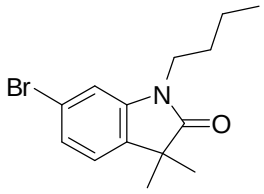


Purification by column petrol ether/ethyl acetate (4:1) furnished *2-(4-bromo-phenyl)-n-butyl-isobutyramide* **280c** (0.41g, 58%) as a clear oil. IR (CH_2Cl_2) ν_{max}: 3357, 2933 1651, 1519, 1169, 853 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$, δ): 7.45 (app. d.t, *J* = 8.5 and 2.0, 2H, ArC**H**), 7.23 (app. d.t, *J* = 8.5 and 2.0, 2H, ArC**H**), 5.16 (bs, 1H, N**H**), 3.15 (t, *J* = 7.0, 2H, C**H₂**), 1.53 (s, 6H, C(C**H₃**)**₂**), 1.40-1.32 (quin., *J* = 7.0, 2H, C**H₂**), 1.26-1.19 (app. sxt., *J* = 7.0, 2H, C**H₂**), 0.86 (t, *J* = 7.0, 3H, C**H₃**). ^{13}C NMR (75.5MHz, $CDCl_3$, δ): 175.7 (**s**, **C**=O), 151.1 (**s**, **C**-$C(CH_3)_2$), 132.3 (2 x **d**, Ar**C**H), 127.1 (2 x **d**, Ar**C**H), 110.5 (**s**, **C**-Br), 47.2 (**s**, **C**-$(CH_3)_2$), 39.5 (**t**, **C**H_2), 31.4 (**t**, **C**H_2), 26.8 (2 x **q**, C(**C**$H_3)_2$), 20.0 (**t**, **C**H_2), 13.5 (**q**, **C**H_3). LRMS (EI^+) *m/z*: 299 (^{81}Br-M^+ = 7%), 297 (^{79}Br-M^+ 8), 218 (69), 199 (^{81}Br 98), 197 (^{79}Br 97), 183 (20), 170 (24), 169 (25), 119 (72). HRMS (EI^+) *m/z*: calcd for $C_{14}H_{20}{}^{81}BrNO_2$, 299.0708; found, 299.0710.

Experimental

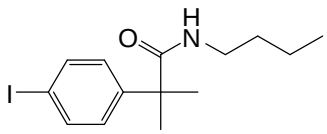
6-Bromo-1-butyl-3,3-dimethyl-dihydro-indol-2-one 357b

Discernible data for major oxindole:



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_2Cl_2) $\nu_{max:}$ 2961, 1712, 1603, 1485, 1360, 1123 and 808 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$, δ): 7.19 (d, *J* = 8.0, 1H, ArC**H**), 7.07 (d, *J* = 8.0, 1H, ArC**H**), 7.03 (s, 1H, ArC**H**), 3.70 (t, *J* = 7.0, 2H, C**H₂**), 1.70-1.62 (app. quin., *J* = 7.0, 2H, C**H₂**), 1.43-1.36 (m, 8H (C**H₃**)**₂**) + C**H₂**), 0.98 (t, *J* = 7.0, 3H C**H₃**).

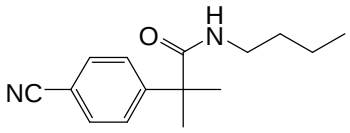
N-Butyl-2- (4-iodo-phenyl)-isobutyramide 280d



Purification by column (petrol ether/ethyl acetate 4:1), furnished *2-(4-iodo-phenyl)-n-butyl-isobutyramide* **280d** as clear oil (0.16g, 28%). IR (CH_2Cl_2) ν_{max}: 3332, 2932, 1718, 1276, 1130, 895 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$, δ): 7.67 (d.t, *J* = 9.0 and 3.0, 2H, ArC**H**), 7.11 (d.t, *J* = 9.0 and 3.0, 2H, ArC**H**), 5.12 (bs, 1H, N**H**), 3.16 (q, *J* = 7.0, 2H, C**H₂**), 1.53 (s, 6H, C(C**H₃**)**₂**), 1.41-1.38 (quin., *J* = 7.0, 2H, C**H₂**), 1.27-1.18 (sxt., *J* = 7.0, 2H, C**H₂**), 0.87 (t, *J* = 7.0, 3H, C**H₃**). ^{13}C NMR (100MHz, $CDCl_3$, δ): 175.7 (**s**, **C**=O), 144.1 (**s**, **C**-C$(CH_3)_2$), 136.7 (2 x **d**, Ar**C**H), 127.5 (2 x **d**, Ar**C**H), 91.5 (**s**, **C**-I), 45.8 (**s**, **C**-$(CH_3)_2$), 38.6 (**t**, **C**H_2), 30.5 (**t**, **C**H_2), 25.9 (2 x **q**, C(**C**$H_3)_2$), 19.8 (**t**, **C**H_2), 13.5 (**q**, **C**H_3). LRMS (LSIMS-FAB$^+$) *m/z*: 346 (MH^+ = 100%), 244.96 (20), 136 (15),

133 (10). HRMS (LSIMS-FAB$^+$) *m/z*: (MH$^+$) Calc for $C_{14}H_{21}INO$ 346.0668, found 346.0738.

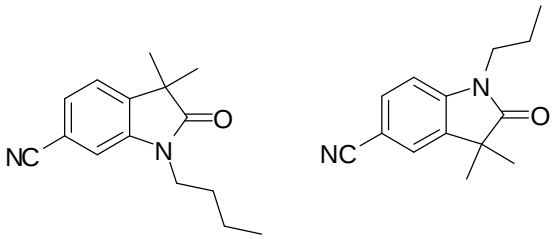
_N_-Butyl-2- (4-cyano-phenyl)-isobutyramide 280i



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 (CH_2Cl_2) ν_{max}: 2928, 2867, 1685, 1509, 1399, 1205, 804 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$, δ): 7.56 (d.t, *J* = 8.5 and 2.0, 2H, ArC**H**); 7.41 (d.t, *J* = 8.5 and 2.0, 2H, ArC**H**), 5.28 (bs, 1H, N**H**), 3.11 (q, *J* = 7.0, 2H, C**H$_2$**), 1.50 (s, 6H, C(C**H$_3$**)$_2$), 1.37-1.27 (app. quin., *J* = 7.0, 2H, C**H$_2$**), 1.20-1.11 (app. sxt, *J* = 7.0, 2H, C**H$_2$**), 0.80 (t, *J* = 7.0, 3H, C**H$_3$**). ^{13}C NMR (100MHz, $CDCl_3$, δ): 176.6 (**s**, **C**=O), 144.5 (**s**, **C**-C(CH$_3$)$_2$), 131.7 (2 x **d**, Ar**C**H), 128.2 (2 x **d**, Ar**C**H), 120.9 (**s**, C-**C**≡N), 111.1 (**s**, **C**-C≡N) 46.7 (**s**, C(**C**H$_3$)$_2$), 39.7 (**t**, **C**H$_2$), 31.5 (**t**, **C**H$_2$), 27.0 (2 x **q**, C(**C**H$_3$)$_2$), 20.0 (**t**, **C**H$_2$), 14.1 (**q**, **C**H$_3$). LRMS (LSIMS-FAB$^+$) *m/z*: 245 (30), 154 (100), 136 (70). HRMS (LSIMS-FAB$^+$) *m/z*: (MH$^+$) calcd for $C_{15}H_{21}N_2O$, 245.1654; found 245.1647.

Experimental

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

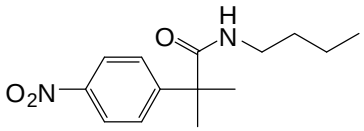


Purification by column (petrol ether/ethyl acetate 4:1), furnished *1-butyl-3,3-dimethyl-2-oxo-2,3-dihydro-1H-indol-6-carbonitrile* **360** and *1-butyl-3,3-dimethyl-2-oxo-2,3-dihydro-1H-indole-5-carbonitrile* **362** as a yellow translucent oil (0.05g, 30%). Discernible data for **360**: ^{1}H NMR (400MHz, $CDCl_3$, δ): 7.59 (app. d, *J* = 8.0, 1H, ArC**H**), 7.45 (app. s, 1H, ArC**H**), 6.92 (d, *J* = 8.0, 1H, ArC**H**), 3.73 (t, *J* = 7.5, 2H, C$\mathbf{H_2}$), 1.69-1.61 (app.quin., *J* = 7.5, 2H, C$\mathbf{H_2}$), 1.41-1.35 (m, 8H, C$\mathbf{H_2}$ and (($\mathbf{CH_3}$)$_2$), 0.96 (t, *J* = 7.5, 3H, C$\mathbf{H_3}$). ^{13}C NMR (100MHz, $CDCl_3$, δ): 180.9 (**s**, **C**=O), 142.9 (**s**, **C**-N-), 133.1 (**d**, Ar**C**H), 136.0 (**s**, **C**-C(CH$_3$)$_2$), 125.9 (**d**, Ar**C**H), 119.5 (**s**, **C**≡N), 111.4 (**s**, **C**-C≡N), 108.7 (**d**, Ar**C**H), 44.0 (**s**, C(**C**H$_3$)$_2$), 39.8 (**t**, **C**H$_2$), 29.4 (**t**, **C**H$_2$), 24.2 (2 x **q**, C(**C**H$_3$)$_2$), 20.0 (**t**, **C**H$_2$), 14.7 (**q**, **C**H$_3$).

Discernible data for **362**: ^{1}H NMR (400MHz, $CDCl_3$, δ): 7.39 (app. d, *J* = 7.0, 1H, ArC**H**), 7.29 (d, *J* = 7.0, 1H, ArC**H**), 7.08 (s, 1H, ArC**H**), 3.73 (t, *J* = 7.5, 2H, C$\mathbf{H_2}$), 1.69-1.61 (app.quin., *J* = 7.5, 2H, C$\mathbf{H_2}$), 1.41-1.35 (m, 8H, C$\mathbf{H_2}$ + (($\mathbf{CH_3}$)$_2$), 0.97 (t, *J* = 7.5, 3H, C$\mathbf{H_3}$). ^{13}C NMR (100MHz, $CDCl_3$, δ): 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**, Ar**C**H), 123.1 (**d**, Ar**C**H), 110.8 (**d**, Ar**C**H), 44.3 (**s**, **C**(CH$_3$)$_2$), 39.8 (**t**, **C**H$_2$), 29.3 (**t**, **C**H$_2$), 24.1 (2 x **q**, C(**C**H$_3$)$_2$), 20.0 (**t**, **C**H$_2$), 14.7 (**q**, **C**H$_3$). LRMS (EI$^+$) **360** and **362** 242 (M = 81%), 204 (27), 199 (71), 186 (34), 171 (100), 155 (26), 141 (96), 121 (18). HRMS (LSIMS-FAB$^+$) **362**

calcd for $C_{15}H_{18}N_2O$, 242.1419; found, 242.1423. Data for **360**/**362**. Elemental Analysis (WAS) Calcd for $C_{15}H_{18}N_2O$: 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%.

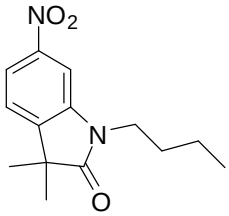
_N_-Butyl-2-(4-nitro-phenyl)-isobutyramide 280j

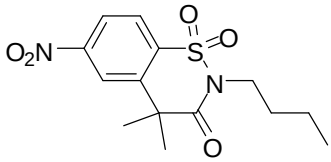


Purification by column (petrol ether/ethyl acetate 4:1), furnished *2-(4-nitro-phenyl)-n-butyl-isobutyramide* **280j** as a yellow oil (0.14g, 43%). IR (CH_2Cl_2) ν_{max}: 3346, 2961, 1648, 1600, 1518, 1466, 1344, 1279, 855 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$, δ): 8.17 (d.t, *J* = 7.0 and 2.0, 2H, ArC**H**), 7.54 (d.t, *J* = 7.0 and 2.0, 2H, ArC**H**), 5.40 (bs, 1H, N**H**), 3.20 (q, *J* = 7.0, 2H, C$\mathbf{H_2}$), 1.61 (s, 6H, C(C$\mathbf{H_3}$)$_2$), 1.47-1.37 (quin., *J* = 7.0, 2H, C$\mathbf{H_2}$), 1.16-1.31 (sxt, *J* = 7.0, 2H, C$\mathbf{H_2}$), 0.88 (t, *J* = 7.0, 3H, C$\mathbf{H_3}$). ^{13}C NMR (75.5MHz, $CDCl_3$, δ): 175.2 (**s**, **C**=O), 152.8 (**s**, **C**-NO_2), 146.5 (**s**, **C**-C(CH_3)$_2$), 127.0 (2 x **d**, Ar**C**H), 123.5 (2 x **d**, Ar**C**H), 47.1 (**s**, **C**(CH_3)$_2$), 39.4 (**t**, **C**H_2), 31.3 (**t**, **C**H_2), 26.7 (2 x **q**, C(**C**H_3)$_2$), 19.7 (**t**, **C**H_2), 13.5 (**q**, **C**H_3). LRMS (EI^+) *m/z*: 266 (MH^{2+} = 31%), 265 (MH^+ = 37), 206 (31), 204 (36), 165 (100), 149 (52), 135 (36). HRMS (LSIMS-FAB^+) *m/z*: (MH^+) calcd for $C_{14}H_{21}N_2O$, 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-2*H*-1λ^6-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-1λ^6-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 $C_{14}H_{18}N_2O_5S$ and $C_{14}H_{19}N_2O_3$ [3:1].

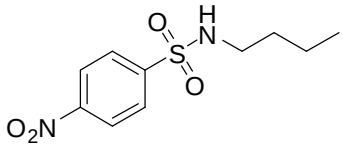
Data for *2-butyl-4,4-dimethyl-6-nitro-1,1-dioxo-1,4-dihydro-2H-1λ^6-benzo-[e][1,2]-thiazin-3-one* **366**. IR (CH_2Cl_2) mixture ν_{max}: 2960, 2361, 1722, 1527, 1385, 1269, 1124, 1070, 885 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$, δ): 7.95 (app. d, *J* = 8.0, 1H, ArC**H**), 7.64 (app. s, 1H, ArC**H**), 7.31 (d, *J* = 8.0, 1H, ArC**H**), 3.75 (t, *J* = 7.0, 2H, C**H$_2$**), 1.71-1.61 (m, 2H, C**H$_2$**), 1.43-1.30 (m, 8H, C**H$_2$** + (C**H$_3$**)$_2$), 0.95 (t, *J* = 7.0, 3H, C**H$_3$**). ^{13}C 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**-$C(CH_3)_2$), 124.1 (**d**, Ar**C**H), 117.4 (**d**, Ar**C**H), 102.16 (**d**, Ar**C**H), 43.3 (**s**, **C**$(CH_3)_2$), 38.9 (**t**, **C**H_2), 28.4 (**t**, **C**H_2), 23.1 (2 x **q**, C(**C**$H_3)_2$), 19.5 (**t**, **C**H_2), 13.7 (**q**, **C**H_3). LRMS (EI^+) *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**

^{1}H NMR (300MHz, $CDCl_3$, δ): 8.23 (app. d, *J* = 8.5, 1H, ArC**H**), 8.08 (app. s, 1H, ArC**H**), 6.90 (d, *J* = 8.5, 1H, ArC**H**), 3.76 (t, *J* = 7.0, 2H, C**H$_2$**), 1.73-1.63 (m, 2H, C**H$_2$**),

1.45-1.35 (m, 8H, C**H₂** + ((C**H₃**)₂), 0.81 (t, *J* = 7.0, 3H, C**H₃**). ^{13}C NMR (75.5MHz, $CDCl_3$, δ): 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**, Ar**C**H), 117.4 (**d**, Ar**C**H), 106.8 (**d**, Ar**C**H), 43.3 (**s**, **C**$(CH_3)_2$), 39.0 (**t**, **C**H_2), 28.7 (**t**, **C**H_2), 23.1 (2 x **q,** C(**C**$H_3)_2$), 19.5 (**t**, **C**H_2), 13.7 (**q**, **C**H_3). *m/z* 264 (M^+ = 40%), 154 (100), 137 (65). HRMS (LSIMS-FAB$^+$) *m/z*: (MH^+) Calcd for 263.1396, $C_{14}H_{19}N_2O_3$; 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 $C_{14}H_{18}N_2O_5S$, 263.1396; found, 263.1399.

_N_-Butyl-(4-nitrobenzene)-sulphonamide 283j [280]

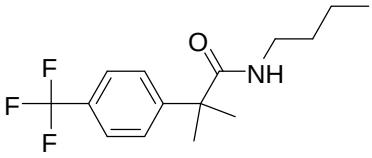


Purification by flash chromatography (petrol ether/ethyl acetate 6:1) from radical reaction furnished *N-butyl-(4-nitrobenzene)-sulphonamide* as a pale yellow crystalline solid **283j**. ^{1}H NMR (300MHz, $CDCl_3$, δ): 8.34 (app. d, *J* = 9.0, 2H, ArC**H**), 8.06 (app d, *J* = 9.0, 2H, ArC**H**), 4.96 (bs, 1H, N**H**), 3.03 (app. q, *J* = 7.0, 2H, C**H₂**), 1.52-1.43 (app. quin., *J* = 7.0, 2H, C**H₂**), 1.37-1.25 (app. sxt, *J* = 7.0, 2H, C**H₂**), 0.83 (t, *J* = 7.0, 3H, C**H₃**).

Experimental

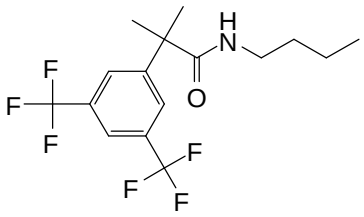
N-Butyl-2-(4-trifluoromethylphenyl)isobutyramide 280k

Discernible data:



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 ($CDCl_3$) ν_{max}: 3332, 2962, 1643, 1328, 1125 and 840 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$, δ) 7.60 (d, *J* = 8.0, 2H, ArC**H**), 7.48 (d, *J* = 8.0, 2H, ArC**H**), 5.16 (bs, 1H, N**H**), 3.18 (q, *J* = 7.0, 2H, C$\mathbf{H_2}$), 1.58 (s, 6H, C(C$\mathbf{H_3}$)$_2$), 1.43-1.35 (app. quin., *J* = 7.0, 2H, C$\mathbf{H_2}$), 1.28-1.18 (app. sxt, *J* = 7.0, 2H, C$\mathbf{H_2}$), 0.87 (t, *J* = 7.0, 3H, C$\mathbf{H_3}$); ^{13}C NMR (100MHz, $CDCl_3$, δ) 176.6 (**s**, **C**=O), 149.9 (**s**, **C**-C$(CH_3)_2$), 129.9-129.4 (**s**, *J* = 44, **C**(CF_3), 126.7 (2 x **d**, Ar**C**H), 125.6 (2 x **d**, Ar**C**H), 125.3-122.5 (**s**, *J* = 277, C(**C**F_3), 47.1 (**s**, **C**$(CH_3)_2$), 39.6 (**t**, **C**H_2), 31.5 (**t**, **C**H_2), 27.0 (2 x **q**, C(**C**$H_3)_2$), 20.0 (**t**, **C**H_2), 14.7 (**q**, **C**H_3). (LSIMS) *m/z*: 273 (M^+ = 6%), 154 (100), 136 (70), 120 (14).

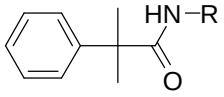
N-Butyl-2-(3,5-bis-trifluoromethyl-phenyl)-isobutyramide 280l



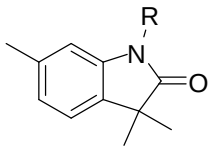
Purification by column chromatography furnished *N-butyl-2-(3,5-bis-trifluoromethyl-phenyl)-isobutyramide* **280l.** As a clear crystalline solid (0.01g, 26%). IR (CH_2Cl_2) ν_{max}: 3301, 2933, 1644, 1281, 1130, 896 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$, δ): 7.81 (s, 2H, ArC**H**), 7.79 (s, 1H, ArC**H**), 5.42 (bs, 1H, N**H**), 3.23 (q, *J* = 7.0, 2H, C$\mathbf{H_2}$), 1.62 (s, 6H,

($C\mathbf{H_3})_2$), 1.46-1.39 (app. quin., J = 7.0, 2H, $C\mathbf{H_2}$), 1.29-1.20 (app. sxt, J = 7.0, 2H, $C\mathbf{H_2}$), 0.88 (t, J = 7.0, 3H, $C\mathbf{H_3}$). ^{13}C NMR (125MHz, $CDCl_3$, δ): 175.1 (**s**, **C**=O), 148.3 (**s**, **C**-$C(CH_3)_2$), 132.0-131.8 (2 x **s**, J = 33.1, **C**(CF_3), 126.5 (2 x **d**, Ar**C**H), 124.3-122.2 (2 x **d**, J = 271.5, C(**C**F_3), 121.0 (**d**, Ar**C**H), 47.1 (**s**, **C**$(CH_3)_2$), 39.7 (**t**, **C**H_2), 31.5 (**t**, **C**H_2), 27.0 (2 x **q**, ($\mathbf{C}H_3)_2$), 20.0 (**t**, **C**H_2), 13.6 (**q**, **C**H_3). LRMS (LSIMS-FAB$^+$) *m/z*: 355 (M^+ = 10%), 220 (15), 154 (15), 147 (100), 136 (30) HRMS (LSIMS-FAB$^+$) *m/z*: (MH^+) calcd for $C_{16}H_{20}F_6NO$, 356.1449; found 356.1463.

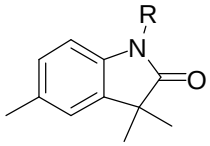
8.0 Synthesis of cyclised and rearranged amides from radical precursors 369



370



371



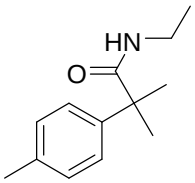
372

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

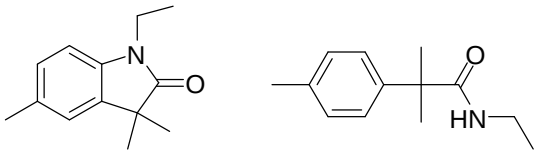
Authentic synthesis of *N*-ethyl-2-tolyl-isobutyramide 370a [222]



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 (CH_2Cl_2) ν_{max}: 3370, 2971, 1706, 1513, 1130, 820 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$, δ): 7.24 (d, *J* = 8.0, 2H, ArC**H**), 7.16 (d, *J* = 8.0, 2H, ArC**H**), 5.14 (bs, 1H, N**H**), 3.20 (quin., *J* = 7.0, 2H, C**H**), 2.34 (s, 3H, ArC$\mathbf{H_3}$), 1.54 (s, 6H, (C$\mathbf{H_3}$)$_2$), 1.02 (t, *J* = 7.0, 3H, C$\mathbf{H_3}$). ^{13}C NMR (100MHz, $CDCl_3$, δ) 177.6 (**s**, **C**=O), 142.3 (**s**, **C**-Me), 136.6 (**s**, **C**-$C(CH_3)_2$), 129.4 (2 x **d**, Ar**C**H), 126.4 (2 x **d**, Ar**C**H), 46.6 (**s**, **C**-$C(CH_3)_2$), 34.6 (**t**, **C**H_2), 27.2 (2 x **q**, C(**C**H_3)$_2$), 21.0 (**q**, Ar**C**H_3), 13.0 (**q**, **C**H_3). LRMS (LSIMS-FAB^+) *m/z*: 206 (M^+ = 57%), 204 (100), 154 (87), 136 (62), 124 (10). HRMS (LSIMS-FAB^+) *m/z*: (MH^+) calcd for $C_{13}H_{20}NO$, 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

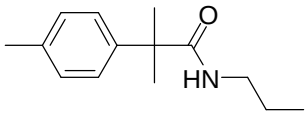


Purification by flash chromatography (petrol ether/ethyl acetate 6:1) furnished an inseparable mixture (3:1) of *1-ethyl-3,3,5-trimethyl-1,3-dihydro-indol-2-one* **372a** and *N-ethyl-2-p-tolyl-isobutyramide* **370a** as a yellow oil (0.57g). Data for **372a**. IR (CH_2Cl_2) ν_{max}: 2968, 1646, 1515, 1462, 1352, 1169, 819 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$, 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$\mathbf{H_2}$), 2.28 (s, 3H, ArC$\mathbf{H_3}$), 1.21 (s, 6H, (C$\mathbf{H_3}$)$_2$), 1.15 (t, *J* = 7.0, 3H, C$\mathbf{H_3}$). ^{13}C NMR (100MHz, $CDCl_3$, δ): 181.2 (**s**, **C**=O), 141.7 (**s**, **C**-N-), 136.4 (**s**, **C**-Me), 133.0 (**s**, **C**-$(CH_3)_2$), 122.7 (**d**, Ar**C**H), 122.2 (**d**, Ar**C**H), 109.1 (**d**, Ar**C**H), 43.8 (**s**, **C**-$(CH_3)_2$), 41.9 (**t**, **C**H), 24.4 (2 x **q**, **C**H_3)$_2$), 21.0 (**q**, Ar**C**H_3), 13.5 (**q**, **C**H_3). LRMS (LSIMS-FAB$^+$) *m/z*: 270 (M^+ + SO_2) 206 (M^+- SO_2 = 57%), 188 (15), 154 (86), 139 (55), 133 (35).

Data for *N-ethyl-2-p-tolyl-isobutyramide* **370a**. IR (CH_2Cl_2) ν_{max}: 3370, 2971, 1706, 1513, 1130, 820 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$, δ): 7.14 (d, *J* = 8.0, 2H, ArC**H**), 7.04 (d, *J* = 8.0, 2H, ArC**H**), 5.23 (bs, 1H, N**H**), 3.09 (quin., *J* = 7.0, 2H, C**H**), 2.23 (s, 3H, ArC$\mathbf{H_3}$), 1.44 (s, 6H, (C$\mathbf{H_3}$)$_2$), 1.13 (t, *J* = 7.0, 3H, C$\mathbf{H_3}$). ^{13}C NMR (100MHz, $CDCl_3$, δ): 177.8 (**s**, **C**=O), 143.3 (**s**, **C**-Me), 136.1 (**s**, **C**-$(CH_3)_2$), 129.3 (2 x **d**, Ar**C**H), 126.3 (2 x **d**, Ar**C**H), 47.2 (**s**, **C**-$(CH_3)_2$), 34.6 (**t**, **C**H), 27.1 (2 x **q**, C(**C**H_3)$_2$), 21.8 (**q**, Ar**C**H_3), 13.3 (**q**, **C**H_3). LRMS (LSIMS-FAB$^+$) *m/z*: 203 (M^+ = 30%), 154 (100), 136 (70), 120

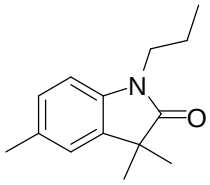
(10). HRMS (LSIMS) *m/z*: for **370a** (MH^+) calcd for $C_{13}H_{20}NO$ 206.1545; found, 206.1552.

_N_-Propyl-2-_p_-tolyl-isobutyramide 370b



Data for *N-propyl-2-p-tolyl-isobutyramide* **370b** furnished as a partially separated mixture with *3,3,5-trimethyl-1-propyl-1,3-dihydroindol-2-one* **372b** (4:1) as a colourless oil, 0.13g. Data for **370b**. IR (CH_2Cl_2) ν_{max}: 3351, 2924, 2360, 1644, 1512 and 816 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$, δ) 7.25 (d, *J* = 8.0, 2H, ArC**H**), 7.15 (d, *J* = 8.0, 2H, ArC**H**), 5.20 (bs, 1H, N**H**), 3.11 (q, *J* = 7.0, 2H, C**H₂**), 2.38 (s, 3H, ArC**H₃**), 1.55 (s, 6H, (C**H₃**)**₂**), 1.44-1.36 (quin., *J* = 7.0, 2H, C**H₂**), 0.81 (t, *J* = 7.0, 3H, C**H₃**). ^{13}C NMR (125MHz, $CDCl_3$, δ) 178.0 (**s**, **C**=O), 142.7 (**s**, **C**-Me), 137.0 (**s**, **C**-$C(CH_3)_2$), 129.7 (2 x **d**, Ar**C**H), 126.8 (2 x **d**, Ar**C**H), 47.1 (**s**, **C**-$(CH_3)_2$), 41.7 (**t**, **C**H_2), 28.4 (2 x **q**, C(**C**$H_3)_2$), 23.1 (**t**, **C**H_2), 21.3 (**q**, Ar**C**H_3), 11.6 (**q**, **C**H_3); LRMS (LSIMS) *m/z* 220 (MH^+ = 15%), 154 (100), 138 (38), 137 (64), 136 (70), 120 (15); HRMS (LSIMS) *m/z*: (MH^+) calcd for $C_{14}H_{22}NO$; 220.1701, found, 220.1708.

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

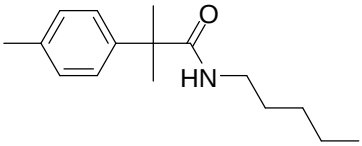


Purification by flash chromatography furnished *3,3,5-trimethyl-1-propyl-1,3-dihydroindol-2-one* **372b** and a minor tentatively assigned reduced product **375b** (7:1) as a mixture (yellow oil, 0.19g); Data for **372b** IR (CH_2Cl_2) ν_{max}: 2966, 1720, 1618, 1457,

1384, 1360, 1131, 810 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$, δ) 7.08 (d, *J* = 7.5, 1H, ArC**H**), 6.85 (d, *J* = 7.5, 1H, ArC**H**), 6.68 (s, 1H, ArC**H**), 3.66 (t, *J* = 7.0, 2H, C$\mathbf{H_2}$), 2.38 (s, 3H, ArC$\mathbf{H_3}$), 1.76-1.66 (sxt. *J* = 7.0, 2H, C$\mathbf{H_2}$), 1.34 (s, 6H, C$\mathbf{H_3})_2$), 0.95 (t, *J* = 7.0, 3H, C$\mathbf{H_3}$); ^{13}C NMR (100MHz, $CDCl_3$, δ) 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**, Ar**C**H), 122.1 (**d**, Ar**C**H), 109.2 (**d**, Ar**C**H), 48.2 (**s**, **C**$(CH_3)_2$), 41.3 (**t**, **C**H_2), 24.6 (2 x **q**, C(**C**$H_3)_2$), 21.8 (**q**, Ar**C**H_3), 20.5 (**t**, **C**H_2), 11.0 (**q**, **C**H_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

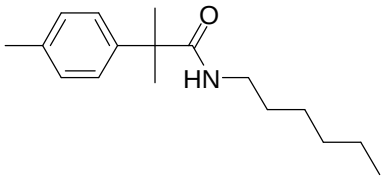
Discernible data:



Purification from flash chromatography (petrol ether/ethyl acetate 6:1) furnished *N-pentyl-2-p-tolyl-isobutramide* **370c** as a colourless globular film (0.14g, 57%). IR (neat) ν_{max}: 3354, 2928, 1620, 1513, 1161 and 816 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$, δ) 7.25 (d, *J* = 8.0, 2H, ArC**H**), 7.15 (d, *J* = 8.0, 2H, ArC**H**), 5.20 (bs, 1H, N**H**), 3.13 (q, *J* = 7.0, 2H, C$\mathbf{H_2}$), 2.34 (s, 3H, ArC$\mathbf{H_3}$), 1.54 (s, 6H, (C$\mathbf{H_3})_2$), 1.40-1.33 (app. quin., *J* = 7.0, 2H, C$\mathbf{H_2}$), 1.28-1.22 (app. sxt, *J* = 7.0, 2H, C$\mathbf{H_2}$), 1.19-1.13 (app. quin., *J* = 7.0, 2H, C$\mathbf{H_2}$), 0.84 (t, *J* = 7.0, 3H, C$\mathbf{H_3}$). ^{13}C NMR (100MHz, $CDCl_3$, δ) 177.6 (**s**, **C**=O), 142.3 (**s**, **C**-Me), 136.5 (**s**, **C**-$C(CH_3)_2$), 129.4 (2 x **d**, Ar**C**H), 126.4 (2 x **d**, Ar**C**H), 46.6 (**s**, **C**$(CH_3)_2$), 39.6 (**t**, **C**H_2), 29.1 (**t**, **C**H_2), 28.9 (**t**, **C**H_2), 27.1 (2 x **q**, C(**C**$H_3)_2$), 22.3 (**t**, **C**H_2), 20.9 (**q**, Ar**C**H_3), 14.7 (**q**, CH_3).

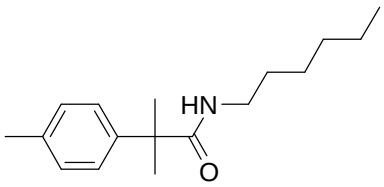
Experimental

N-Hexyl-2-*p*-tolyl-isobutyramide 370d



Data for *N-hexyl-2-p-tolyl-isobutyramide* **370d** as a colourless oil (0.14g, 57%). IR (neat) ν_{max}: 3344, 2926, 1620, 1513 and 815 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$, δ) 7.25 (d, *J* = 8.0, 2H, ArC**H**), 7.15 (d, *J* = 8.0, 2H, ArC**H**), 5.19 (bs, 1H, N**H**), 3.13 (q, *J* = 7.0, 2H, C$\mathbf{H_2}$), 2.34 (s, 3H, ArC$\mathbf{H_3}$), 1.54 (s, 6H, (C$\mathbf{H_3}$)$_2$), 1.39-1.32 (app. quin., *J* = 7.0, 2H, C$\mathbf{H_2}$), 1.28-1.14 (m, 6H, 3 x C$\mathbf{H_2}$), 0.85 (t, *J* = 7.0, 3H, ArC$\mathbf{H_3}$). ^{13}C NMR (100MHz, $CDCl_3$, δ) 177.5 (**s**, **C**=O), 142.3 (**s**, **C**-Me), 136.5 (**s**, **C**-C$(CH_3)_2$), 129.3 (2 x **d**, Ar**C**H), 126.3 (2 x **d**, Ar**C**H), 46.6 (**s**, **C**$(CH_3)_2$), 39.7 (**t**, **C**H_2), 31.4 (**t**, **C**H_2), 29.4 (**t**, **C**H_2), 27.1 (2 x **q**, C(**C**$H_3)_2$), 26.4 (**t**, **C**H_2), 22.5 (**t**, **C**H_2), 20.9 (**q**, **C**H_3), 14.0 (**q**, **C**H_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.

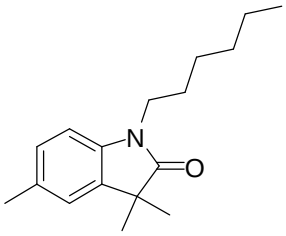
Authentic synthesis of *N*-hexyl-2-*p*-tolyl-isobutyramide 370d



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

furnish a yellow viscous solid (0.015g) as *N-hexyl-2-p-tolyl-isobutyramide* **370d**; ^{1}H NMR (400MHz, $CDCl_3$, δ) 7.25 (d, *J* = 8.0, 2H, ArC**H**), 7.15 (d, *J* = 8.0, 2H, ArC**H**), 5.12 (bs, 1H, N**H**), 3.13 (q, *J* = 7.0Hz, 2H, C$\mathbf{H_2}$), 2.34 (s, 3H, ArC$\mathbf{H_3}$), 1.55 (s, 6H, 2 x C$\mathbf{H_3}$), 1.39-1.30 (quin., *J* = 7.0Hz, 2H, C$\mathbf{H_2}$), 1.26-1.15 (m, 6H, 3 x C$\mathbf{H_2}$), 0.85 (t, *J* = 7.0Hz, 3H, C$\mathbf{H_3}$); ^{13}C NMR (100MHz, $CDCl_3$, δ) 177.5 (**s**, **C**=O), 142.3 (**s**, **C**-Me), 136.6 (**s**, **C**-$C(CH_3)_2$), 129.6 (2 x **d**, Ar**C**H), 126.4 (2 x **d,** Ar**C**H), 46.7 (**s**, **C**$(CH_3)_2$), 39.4 (**t**, **C**H_2), 31.4 (**t**, **C**H_2), 29.4 (**t**, **C**H_2), 27.1 (2 x **q**, C(**C**$H_3)_2$), 26.4 (**t**, **C**H_2), 22.5 (**t**, **C**H_2), 21.0 (**q**, **C**H_3), 14.8 (**q**, **C**H_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.

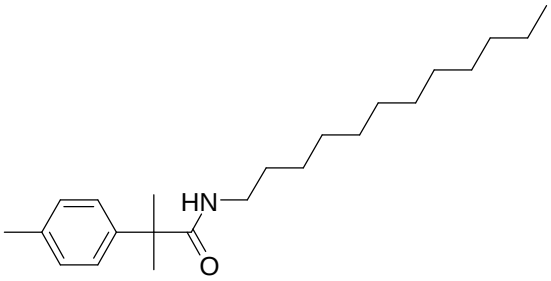
1-Hexyl-3,3,5-trimethyl-1,3-dihydroindole-2-one 372d



Purification by flash chromatography furnished *1-hexyl-3,3,5-trimethyl-1,3-dihydroindole-2-one* **372d** as a colourless oil (8%); IR (CH_2Cl_2) ν_{max}: 2928, 1720, 1620, 1458, 1384, 1132 and 809 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$, δ) 7.08 (d, *J* =7.0, 1H, ArC**H**), 6.85 (d, *J* = 7.0, 1H, ArC**H**), 6.67 (s, 1H, ArC**H**), 3.68 (t, *J* = 7.0, 2H, C$\mathbf{H_2}$), 2.38 (s, 3H, ArC$\mathbf{H_3}$), 1.68-1.64 (m, 2H, C$\mathbf{H_2}$), 1.37-1.21 (m, 12H, 3 x C$\mathbf{H_2}$ and 2 x C$\mathbf{H_3}$), 0.87 (t, *J* = 7.0, 3H, C$\mathbf{H_3}$). ^{13}C NMR (100MHz, $CDCl_3$, δ) 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**, Ar**C**H), 122.1 (**d**, Ar**C**H), 109.2 (**d**, Ar**C**H), 43.8 (**s**, **C**$(CH_3)_2$), 39.8 (**t**, **C**H_2), 31.5 (**t**, **C**H_2), 27.4 (**t**, **C**H_2), 24.5 (2 x **q**, C(**C**$H_3)_2$), 22.6 (**t**, **C**H), 21.8 (**q**, (**C**H_3), 22.5 (**t**, **C**H_2), 14.7 (**q**, **C**H_3). LRMS (LSIMS-

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.

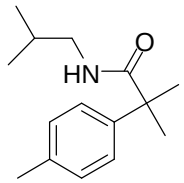
***N*-Dodecyl-2-*p*-tolyl-isobutyramide 370e**



Data for *N-dodecyl-2-p-tolyl-isobutyramide* **370** as colourless globular oil (0.55g, 79%). IR (neat) ν_{max}: 3351, 2900, 1644, 1514, 1465 and 816 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$, δ) 7.24 (d.t, *J* = 8.0 and 2.0, 2H, ArC**H**), 7.14 (d, *J* = 8.0, 2H, ArC**H**), 5.20 (s, 1H, N**H**), 3.13 (t, *J* = 7.0, 2H, C$\mathbf{H_2}$), 2.03 (s, 3H, ArC$\mathbf{H_3}$), 1.54 (s, 6H, (C$\mathbf{H_3}$)$\mathbf{_2}$), 1.39-1.12 (m, 20H, 10 x C$\mathbf{H_2}$), 0.90-0.82 (m, 3H, C$\mathbf{H_3}$). ^{13}C NMR (100MHz, $CDCl_3$, δ) 172.3 (**s**, **C**=O), 144.6 (**s**, **C**-Me), 140.9 (**s**, **C**-$C(CH_3)_2$), 129.5 (2 x **d**, Ar**C**H), 122.6 (2 x **d**, Ar**C**H), 43.8 (**s**, **C**-$(CH_3)_2$), 39.7 (**t**, **C**H_2), 31.9 (**t**, **C**H_2), 29.6 (**t**, **C**H_2), 29.5 (**t**, **C**H_2), 29.5 (**t**, **C**H_2), 29.3 (**t**, **C**H_2), 27.3 (2 x **t**, **C**H_2), 27.0 (**t**, **C**H_2), 27.0 (**t**, **C**H_2), 24.9 (2 x **q**, C(**C**H_3)$_2$), 23.0 (**t**, **C**H_2), 22.5 (**q**, Ar**C**H_3), 14.7 (**q**, **C**H_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[222] 370g



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, $CDCl_3$, δ) 7.19 (d.t, *J* = 8.0 and 3.0, 2H, ArC**H**), 7.09 (d, *J* = 8.0, 2H, ArC**H**), 5.10 (bs, 1H, N**H**), 2.90 (t, *J* = 7.0, 2H, C$\mathbf{H_2}$), 2.27 (s, 3H, ArC$\mathbf{H_3}$), 1.61-1.52 (spt., *J* = 7.0, 1H, C**H**), 1.48 (s, 6H, (C$\mathbf{H_3})_2$), 0.70 (d, *J* = 7.0, 6H, (C$\mathbf{H_3})_2$); ^{13}C NMR (100MHz, $CDCl_3$, δ) 177.9 (**s**, **C**=O), 142.5 (**s**, **C**-Me), 136.9 (**s**, **C**-C$(CH_3)_2$), 129.9 (2 x **d**, Ar**C**H), 126.7 (2 x **d**, Ar**C**H), "not observed" (**C**$(CH_3)_2$), 47.2 (**t**, **C**H_2), 28.7 (**s**, **C**H), 27.4 (2 x **q**, C(**C**$H_3)_2$), 20.2 (**q**, Ar**C**H_3), 19.5 (2 x **q**, **C**H_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.

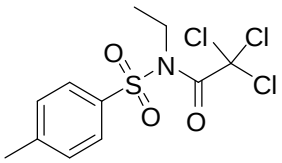
9.0 Synthesis of radical precursors **396**, **407**, **408**, **406** and **413**

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

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_-Ethyl-4-methyl-_N_-trichloromethylbenzenesulfonamide 396



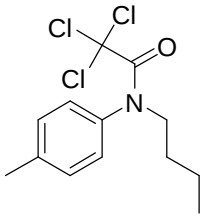
Flash chromatography (6:1 petrol ether/ethyl acetate) furnished *N-ethyl-4-methyl-N-trichloromethylbenzenesulfonamide* **396** as a white crystallised solid (2.5g, 84%).

^{1}H NMR (400MHz, $CDCl_3$, δ) 7.91 (d.t, *J* = 8.0 and 2.0, 2H, ArC**H**), 7.33 (d, *J* = 8.0, 2H, ArC**H**), 4.33 (q, *J* = 7.0, 2H, C**H$_2$**), 2.45 (s, 3H, ArC**H$_3$**), 1.55 (t, *J* = 7.0, 3H, C**H$_3$**). ^{13}C NMR (100MHz, $CDCl_3$, δ) 158.8 (**s**, **C**=O), 145.6 (**s**, **C**-Me), 134.9 (**s**, **C**-SO_2-), 129.5 (2 x **d**, Ar**C**H), 129.1 (2 x **d**, Ar**C**H), 92.5 (**s**, **C**Cl_3) 44.8 (**t**, **C**H_2), 21.7 (**q**, Ar**C**H_3), 15.5 (**q**, **C**H_3); LRMS (LSIMS-FAB$^+$) *m/z* 343 (M^+ = 10%), 155 (100), 137 (72), 136 (66), 120 (13). HRMS (LSIMS-FAB$^+$) *m/z*: (M^+) calcd for $C_{11}H_{12}Cl_3NO_3S$; 343.9681, found 343.9671.

Experimental

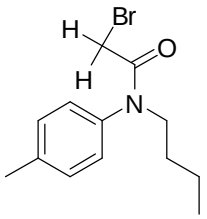
N-Butyl-2,2,2-trichloro-*N*-tolyl-acetamide 407

Discernible data:



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, $CDCl_3$, δ) 7.12 (s, 4H, ArC**H**), 3.67 (bs, 2H, C**H$_2$**), 2.31 (s, 3H, ArC**H$_3$**), 1.57-1.46 (quin. *J* = 7.0, 2H, C**H$_2$**), 1.31-1.17 (sxt, *J* = 7.0, 2H, C**H$_2$**), 0.83 (t, *J* = 7.0, 3H, C**H$_3$**). 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.

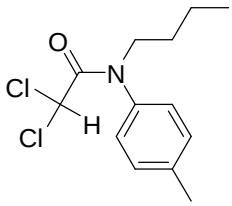
2-Bromo-*N*-butyl-*N*-*p*-tolyl-acetamide 408

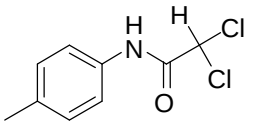


Flash chromatography (6:1 petrol ether:EtOAc) furnished *2-bromo-N-butyl-N-p-tolyl-acetamide* **408** as a yellow oil (3.08g, 31%). ^{1}H NMR (300MHz, $CDCl_3$, δ) 7.15 (d, *J* = 8.0, 2H, ArC**H**), 7.05 (d.t, *J* = 8.0 and 2.0, 2H, ArC**H**), 3.59 (t, *J* = 7.0, 2H, C**H$_2$**), 3.53 (s, 2H, C**H$_2$**), 2.30 (s, 3H, ArC**H$_3$**), 1.45-1.35 (quin., *J* = 7.0, 2H, C**H$_2$**), 1.28-1.15 (sxt., *J* = 7.0, 2H, C**H$_2$**), 0.79 (t, *J* = 7.0, 3H, C**H$_3$**). ^{13}C NMR (100MHz, $CDCl_3$, δ) 165.9 (**s**, **C**=O), 138.6 (**s**, **C**-N-), 138.3 (**s**, **C**-Me, 130.2 (2 x **d**, Ar**C**H), 127.5 (2 x **d**, Ar**C**H), 51.5

(**t**, **C**H_2), 29.2 (**t**, **C**H_2), 27.3 (**t**, **C**H_2), 20.8 (**q**, Ar**C**H_3), 19.6 (**t**, **C**H_2), 13.5 (**q**, **C**H_3). *m/z* (LSIMS) 286 (^{81}Br MH^+ = 98%), 284 (^{79}Br MH^+ = 100), 204 (24), 154 (54), 136 (41), 120 (26). HRMS (LSIMS) *m/z*: (MH^+) calcd for $C_{13}H_{19}BrNO$, 284.0650; found 284.0652.

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





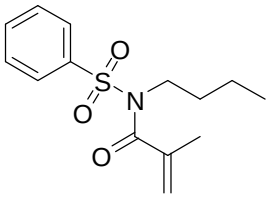
Purification by flash chromatography (6:1 petrol ether:ethyl acetate) furnished *N-butyl-2,2-dichloro-N-p-tolyl acetamide* **409** as a yellow oil (0.78g, 46%); IR ν_{max} (neat) 2960, 1728, 1385, 1269, 1124, 1070 and 744 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$, δ) 7.28 (d, *J* = 8.0, 2H, ArC**H**), 7.12 (app. d, *J* = 8.0, 2H, ArC**H**), 5.83 (s, 1H, C**H**), 3.70 (app. t. *J* = 7.0, 2H, C**H₂**), 2.42 (s, 3H, ArC**H₃**), 1.56-1.49 (app. quin., *J* = 7.0, 2H, C**H₂**), 1.38-1.26 (app. sxt., *J* = 7.0, 2H, C**H₂**), 0.90 (t, *J* = 7.0, 3H, ArC**H₃**). ^{13}C NMR (100MHz, $CDCl_3$, δ) 164.0 (**s**, **C**=O), 139.4 (**s**, **C**-N-), 137.5 (**s**, **C**-Me), 130.8 (2 x **d**, Ar**C**H), 127.7 (2 x **d**, Ar**C**H), 64.0 (**d**, **C**H), 50.3 (**t**, **C**H_2), 29.3 (**t**, **C**H_2), 21.1 (**q**, Ar**C**H_3), 20.0 (**t**, **C**H_2), 19.5 (**q**, **C**H_3). 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}. ^{1}H NMR (400MHz, $CDCl_3$, δ) 8.24 (s, 1H, N**H**), 7.45 (app. d, *J* = 8.0, 2H, ArC**H**), 7.17 (d, *J* = 8.0, 2H, ArC**H**), 6.08 (s, 1H, C**H**), 2.34 (s, 3H, ArC**H₃**). ^{13}C NMR (100MHz, $CDCl_3$, δ) 161.1 (**s**, **C**=O), 135.0 (**s**,

C-N-), 133.9 (**s**, **C**-Me), 129.7 (2 x **d**, Ar**C**H), 120.3 (2 x **d**, Ar**C**H), 67.0 (**d**, **C**H), 21.0 (**q**, Ar**C**H). 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**

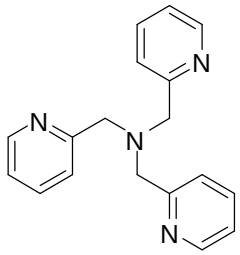


To a stirred solution of *N*-butyl benzenesulfonamide **283a** (0.21g, 0.97 mmol) in anhydrous dichloromethane (DCM) (10 mL) was added via syringe methacryloyl chloride **285** 0.09 mL, 0.94 mmol) followed by triethylamine (TEA) (0.13 mL, 0.94%). The solution became turbid and was stirred at room temperature 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 yelow 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) ν_{max} 2959, 1686, 1353, 1168, 1026 and 686 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$, δ) 7.89 (d, *J* = 7.0, 2H, ArC**H**), 7.61 (app. t, *J* = 7.0, 1H, ArC**H**), 7.52 (t, *J* = 7.0, 2H, ArC**H**), 5.26 (brs, 1H, C=C**H**H), 5.09 (s, 1H, C=CH**H**), 3.74 (t, *J* = 7.0, 2H, C**H**$_2$), 1.92 (s, 3H, C**H**$_3$), 1.69-1.59 (quin. *J* = 7.0, 2H, C**H**$_2$), 1.36-1.24 (sxt., *J* = 7.0, 2H, C**H**$_2$), 0.90 (t, *J* = 7.0, 3H, C**H**$_3$). ^{13}C NMR (100MHz, $CDCl_3$, δ) 172.7 (**s**, **C**=O), 141.2 (**s**, **C**-SO_2-), 139.8 (**s**, **C**=CH_2), 134.0 (**d**, Ar**C**H), 129.3 (2 x **d**, Ar**C**H), 128.5 (2 x **d**, Ar**C**H), 119.5 (**t**, C=**C**H_2), 47.7 (**t**, **C**H_2), 32.2 (**t**, **C**H_2), 20.3 (**t**, **C**H_2), 20.0 (**q**, Ar**C**H_3), 14.0 (**q**,

CCH_3). LRMS (LSIMS) *m/z*: 282 (MH^+ = 100%), 165 (12), 154 (91), 136 (100), 115 (20). HRMS (LSIMS-FAB$^+$) *m/z*: (MH^+) calcd for $C_{14}H_{20}NO_3S$; 282.1164, found 282.1166.

Tris-(2-pyridylmethyl)-amine[162] **279**



To a three necked RB flask was added 2-picoloyl chloride HCl (38.97g, 234 mmol, 2.0 eq.) and 2-picoloylamine (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 (10M, 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 t*ris-(2-pyridylmethyl)-amine* **279** (12.68g, 71%). IR (neat) ν_{max}: 2823, 1589, 1433, 1366, 1147 and 766 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$, δ) 8.54 (s, 3H, Ar**H**), 7.68-7.57 (m, 6H, Ar**H**), 7.15 (m, 3H, Ar**H**), 3.89 (s, 6H, (C$\mathbf{H_3}$)$_2$). ^{13}C NMR (100MHz, $CDCl_3$, δ) 159.4 (3 x **s**, **C**-***py***), 149.1 (3 x **d**, Ar**C**H), 136.4 (3 x **d**, Ar**C**H), 123.0 (3 x **d**, Ar**C**H), 122.0 (3 x **d**, Ar**C**H), 60.1 (3 x

t, **C**H_2); LRMS (EI^+) *m/z*: 291 (MH^+ = 100%), 198 (100), HRMS (EI^+) Calc. 290.1531 for $C_{18}H_{18}N$ Found 290.1525.

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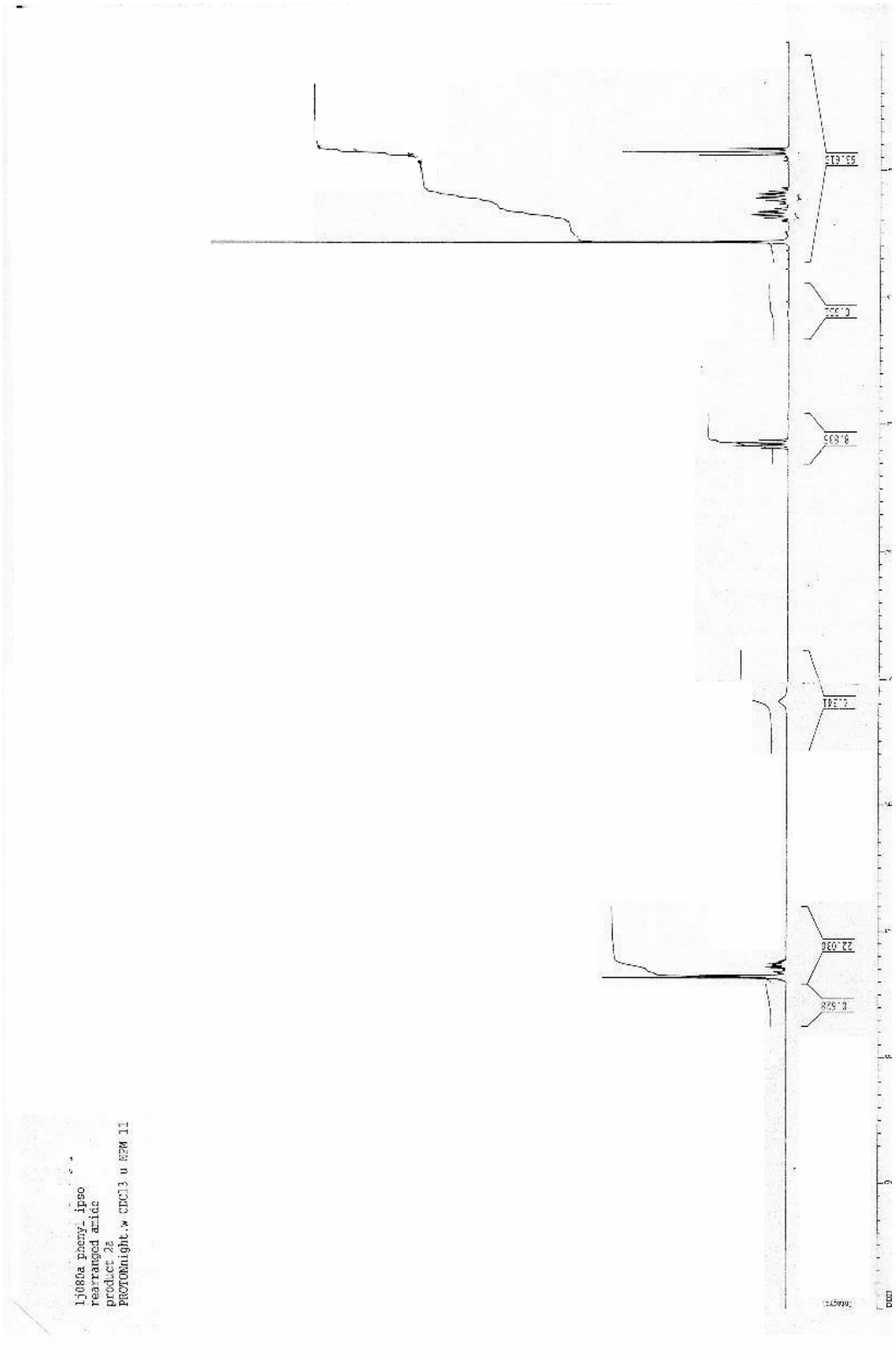
APPENDICES

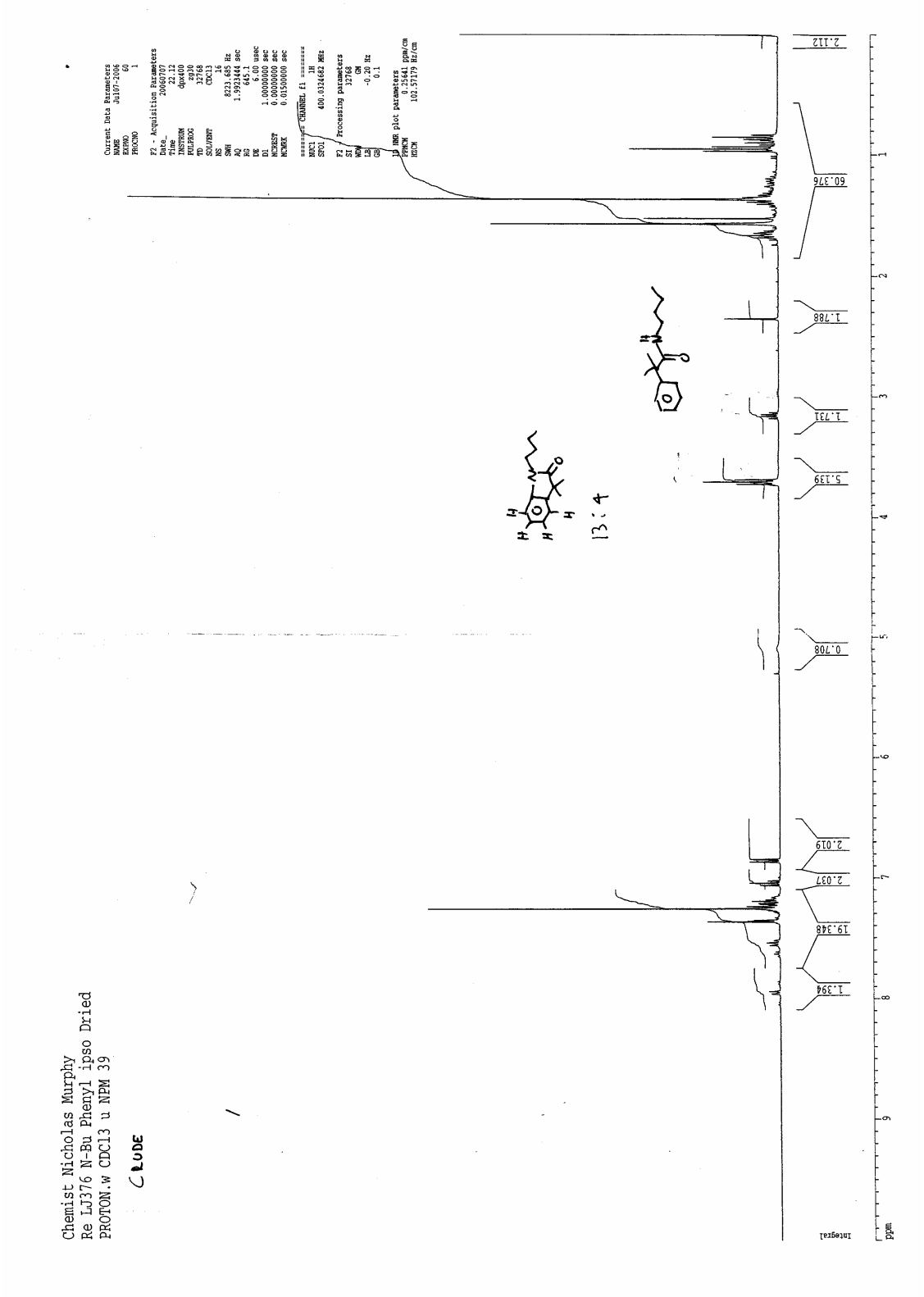
PROTON NMR SPECTRA

APPENDICES



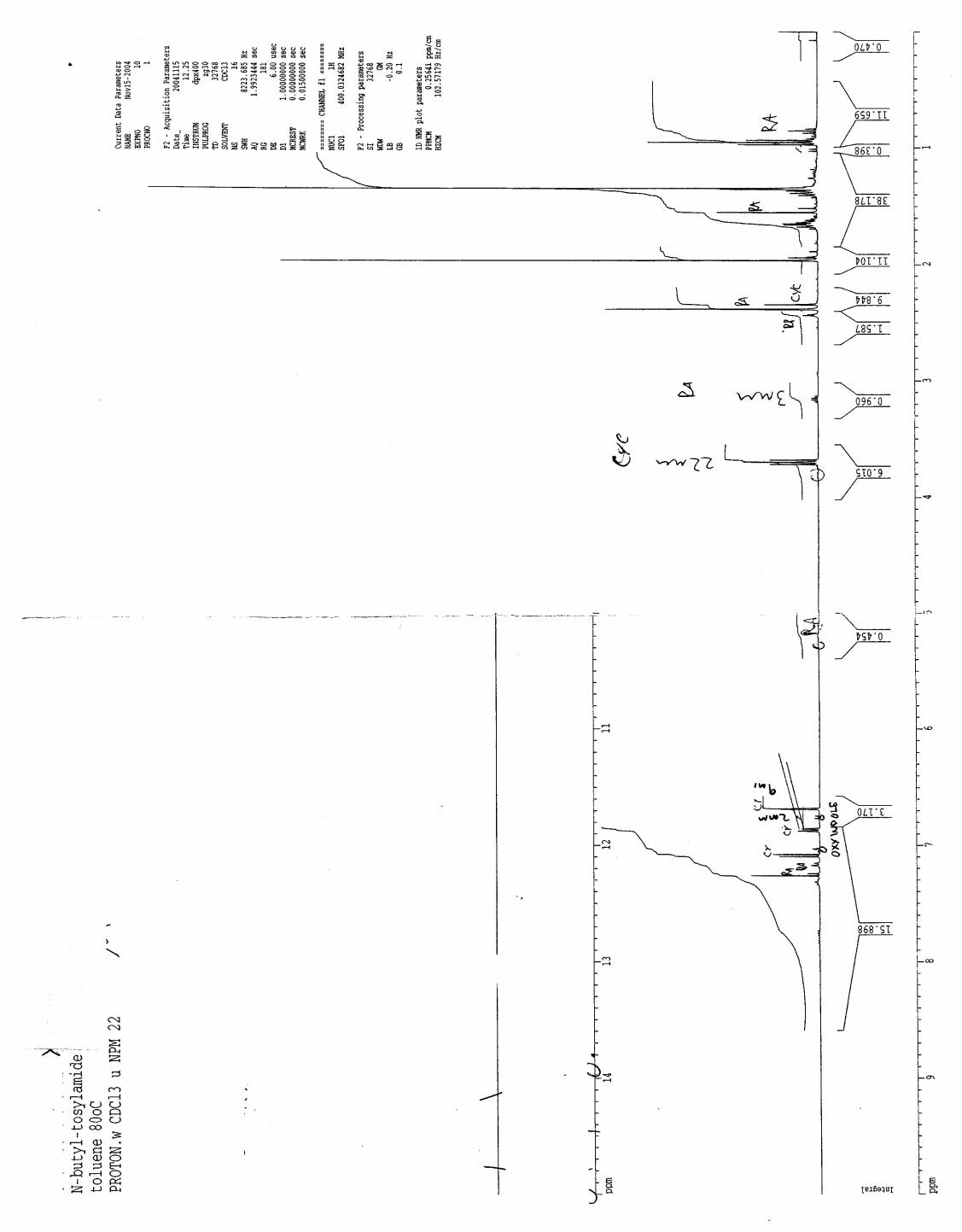
Appendix 1 ^{1}H NMR of phenyl rearranged amide 280a

Appendix 2 ^{1}H NMR of phenyl cyclised product 290

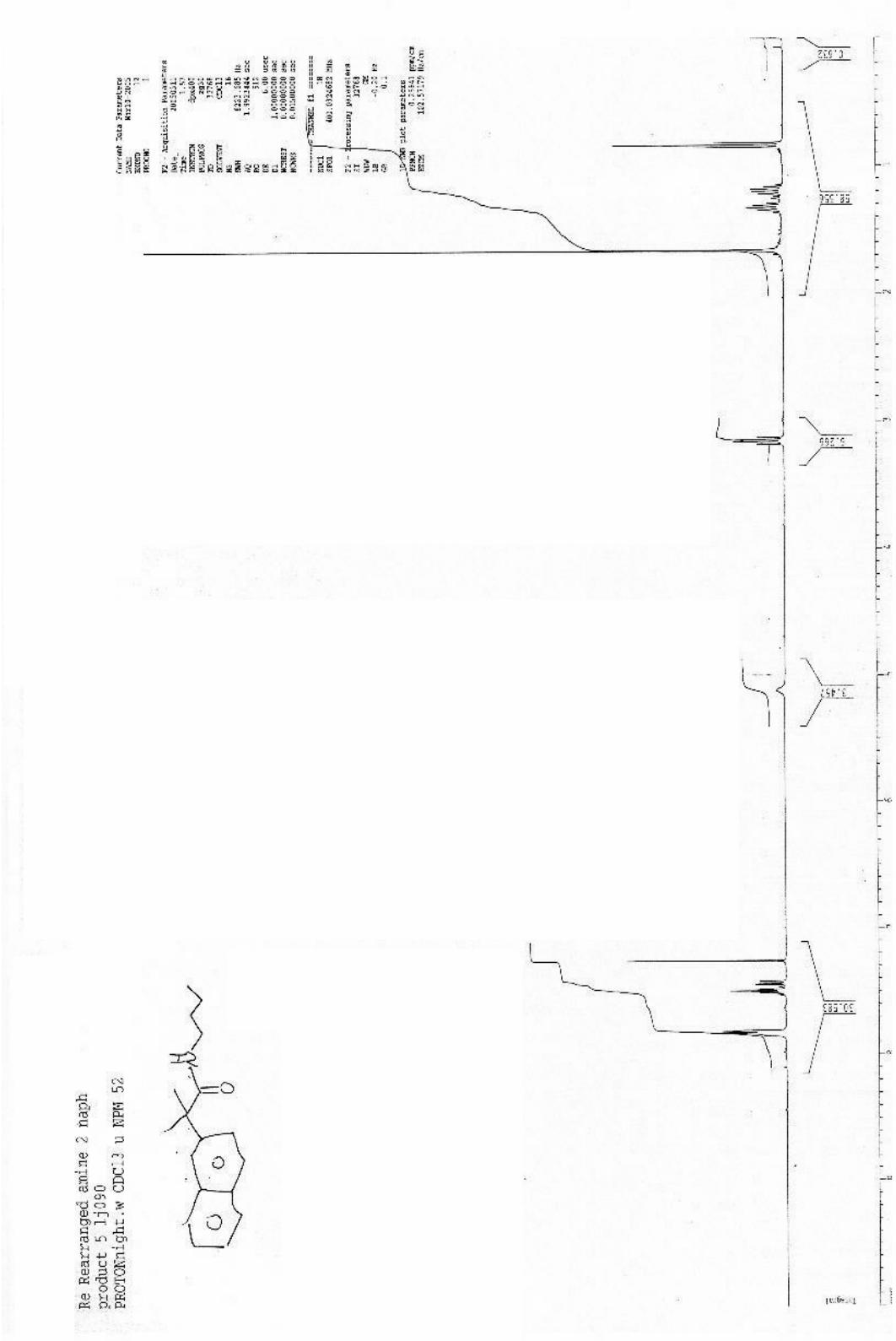


Appendix 3 Crude NMR of the phenyl radical products 280a and 290

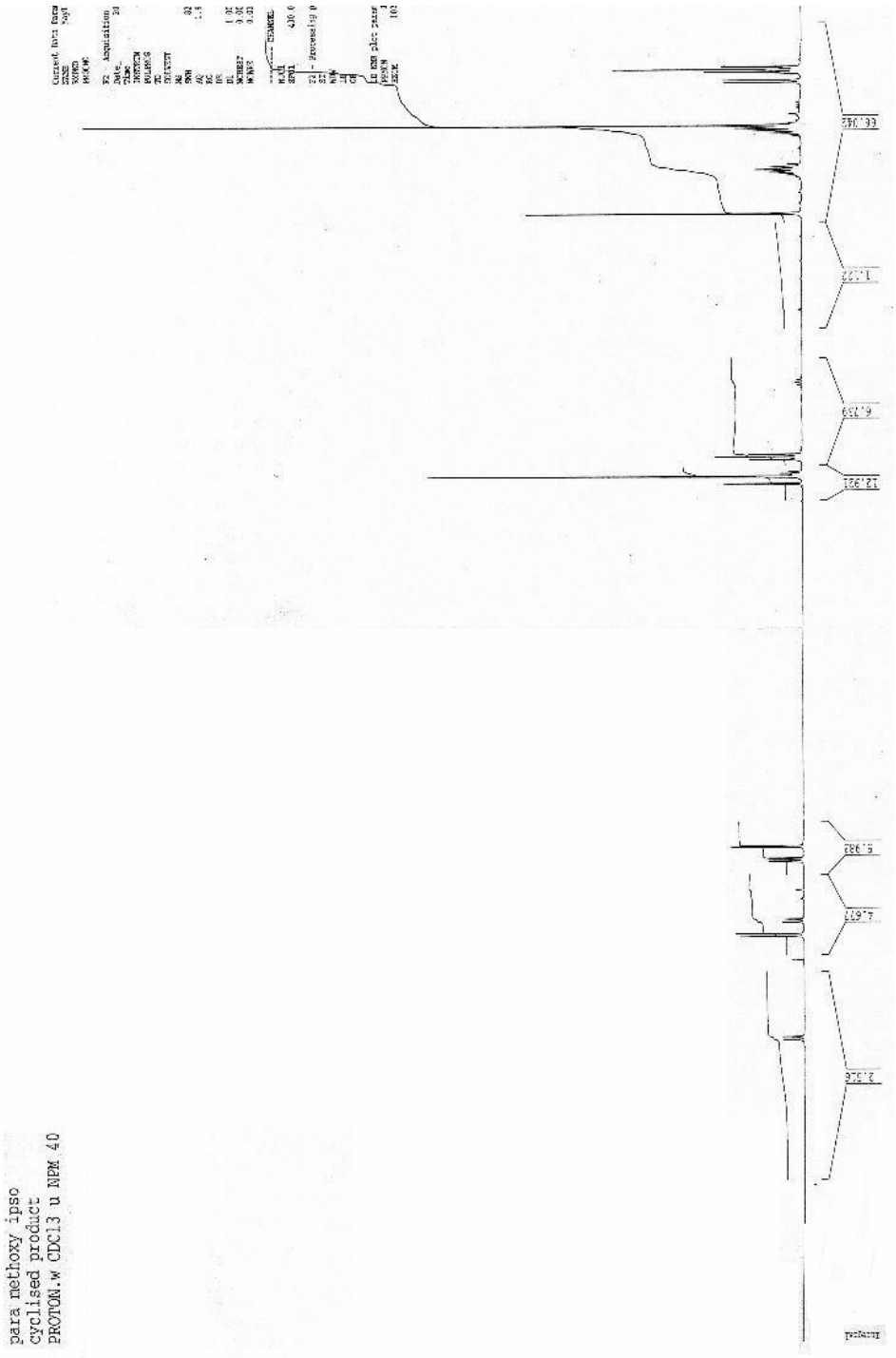
APPENDICES



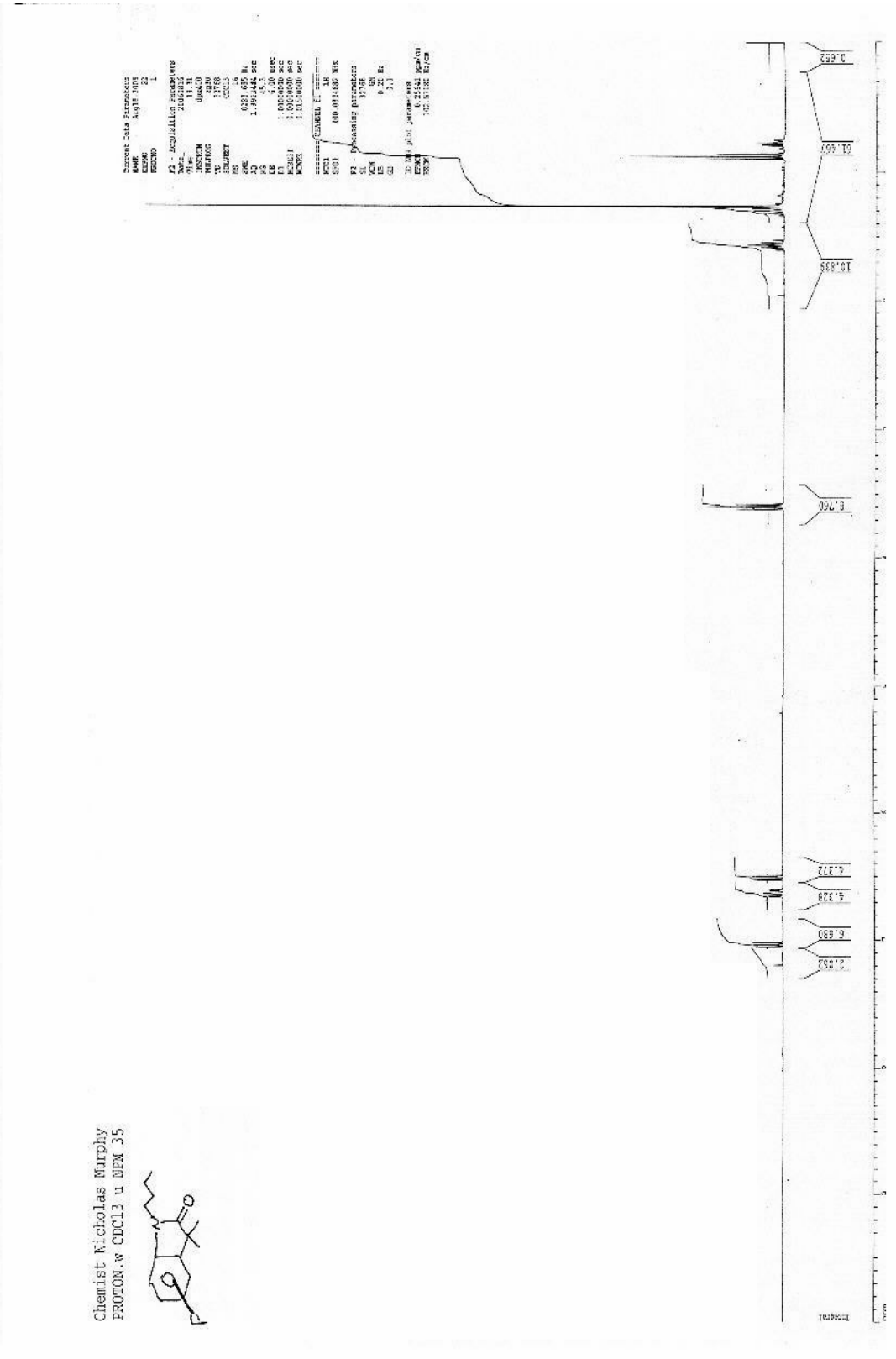
Appendix 4 The Proton NMR for the cyclised products from the tosyl derivative 278e



Appendix 5 ^{1}H NMR of naphthalene rearranged amide 280g

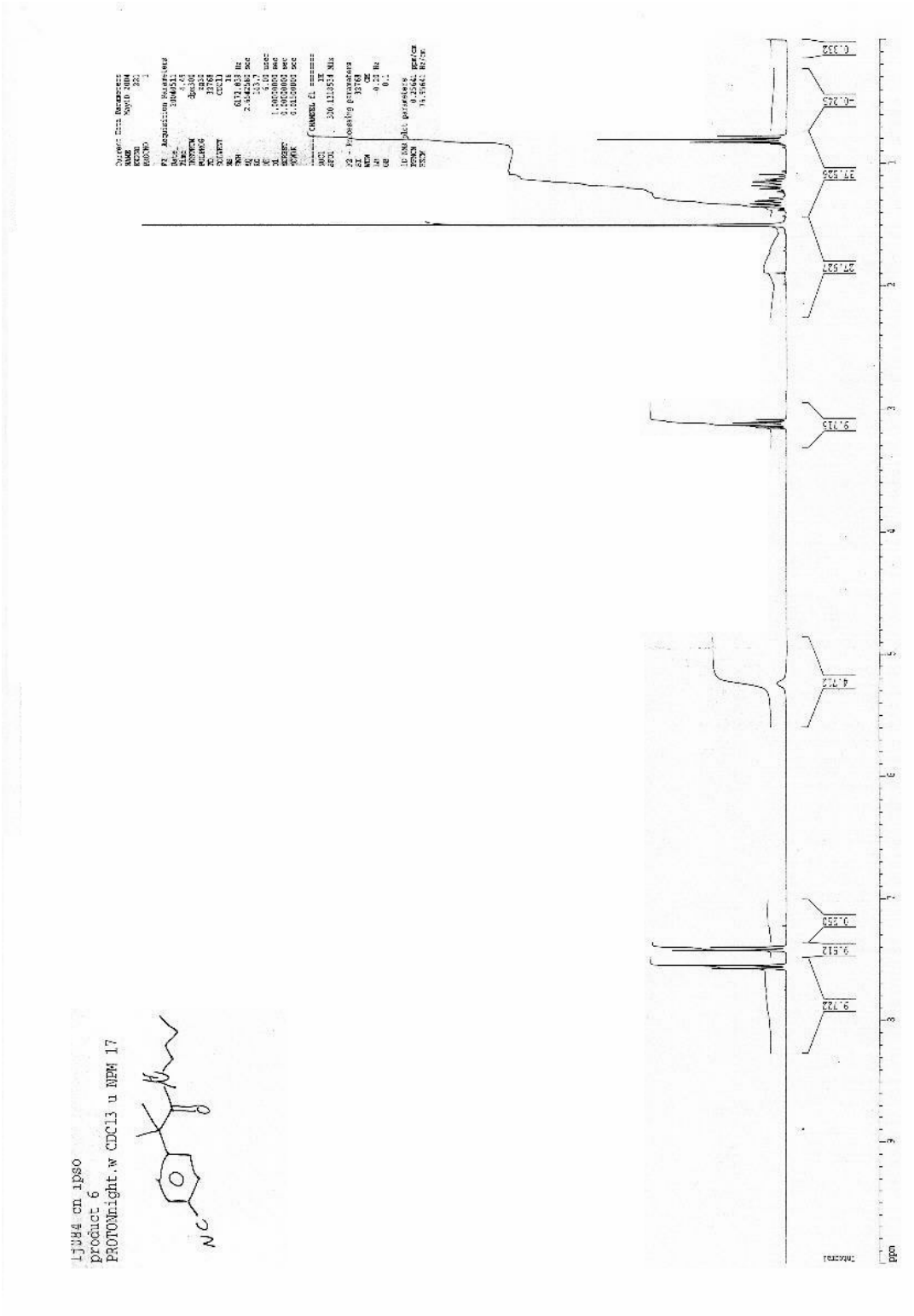


Appendix 6 ^{1}H NMR of *p*-methoxy cyclised products



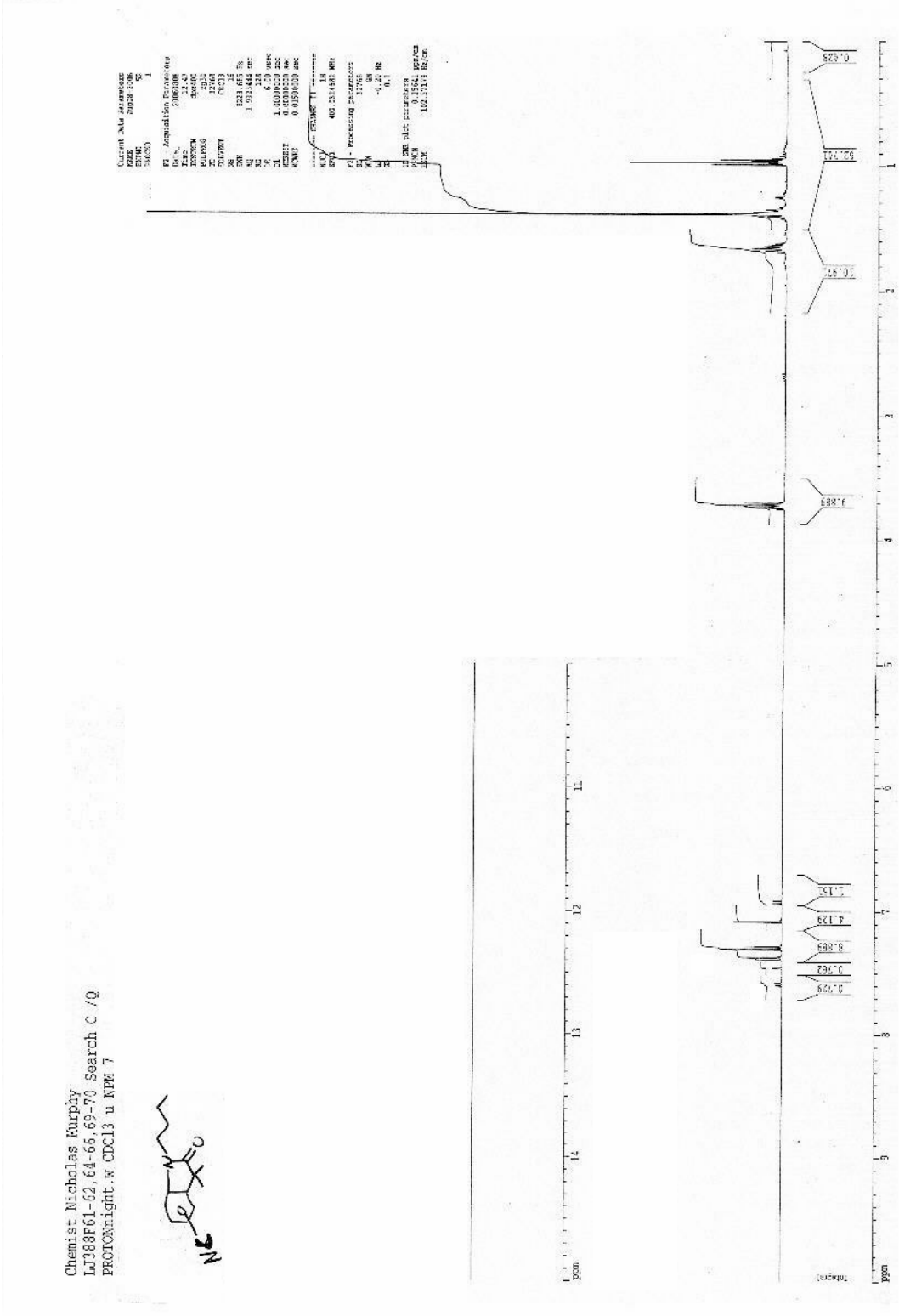
Appendix 7 ^{1}H NMR of fluoro cyclised product(s) 355

APPENDICES



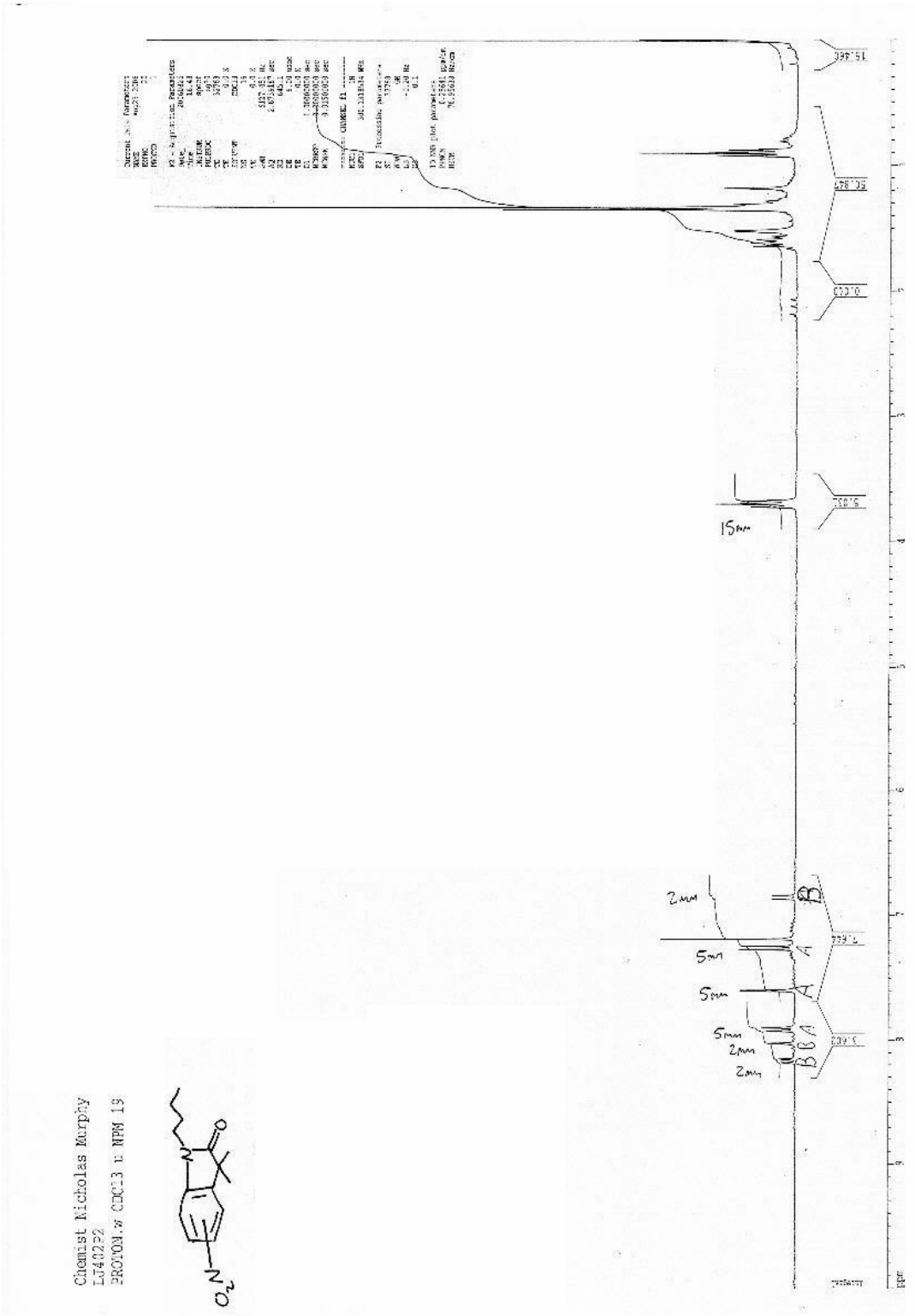
Appendix 8 ^{1}H NMR of *p*-cyano rearranged amide 280i

APPENDICES

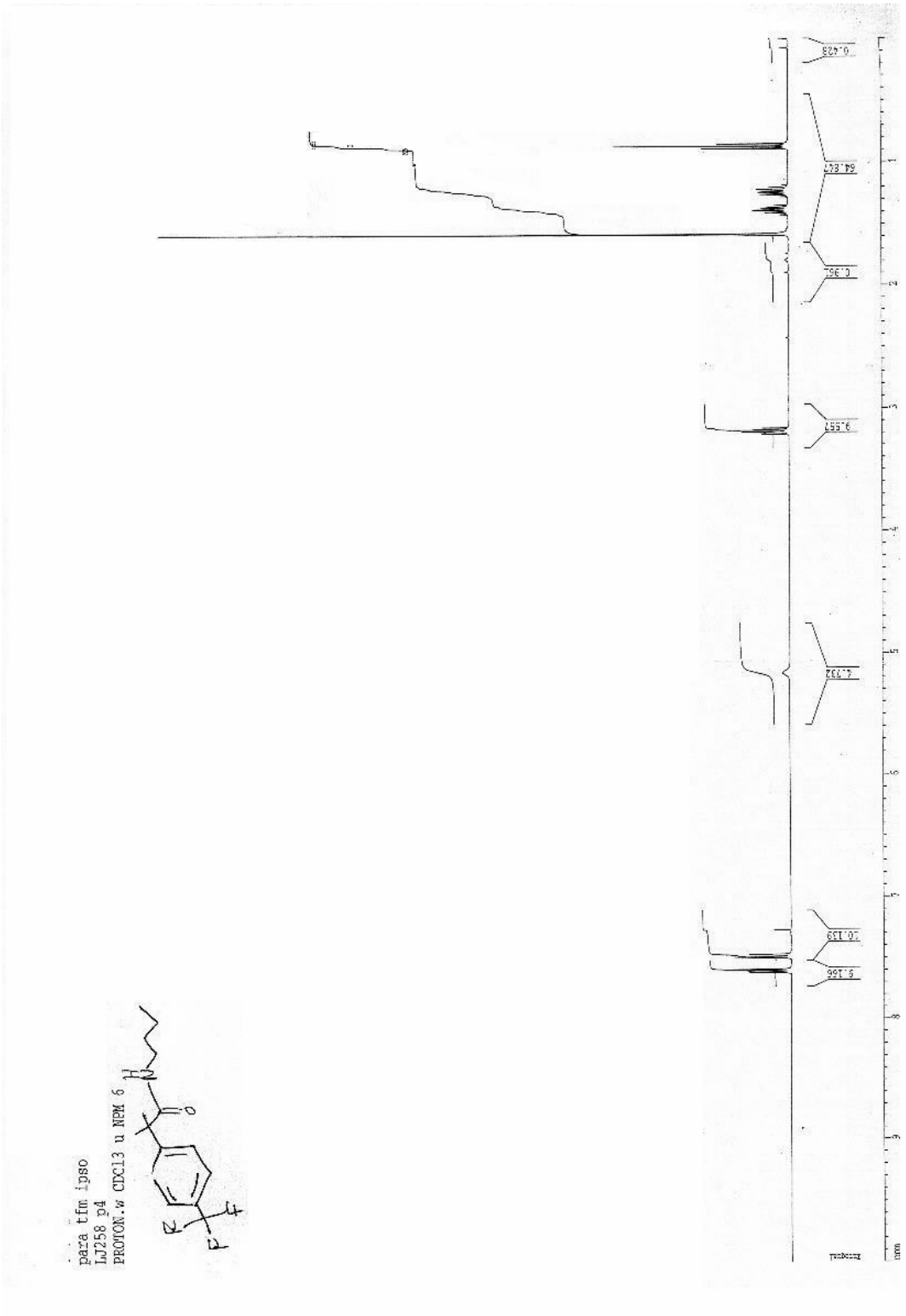


Appendix 9 ^{1}H NMR of *p*-cyano cyclised products 360/362

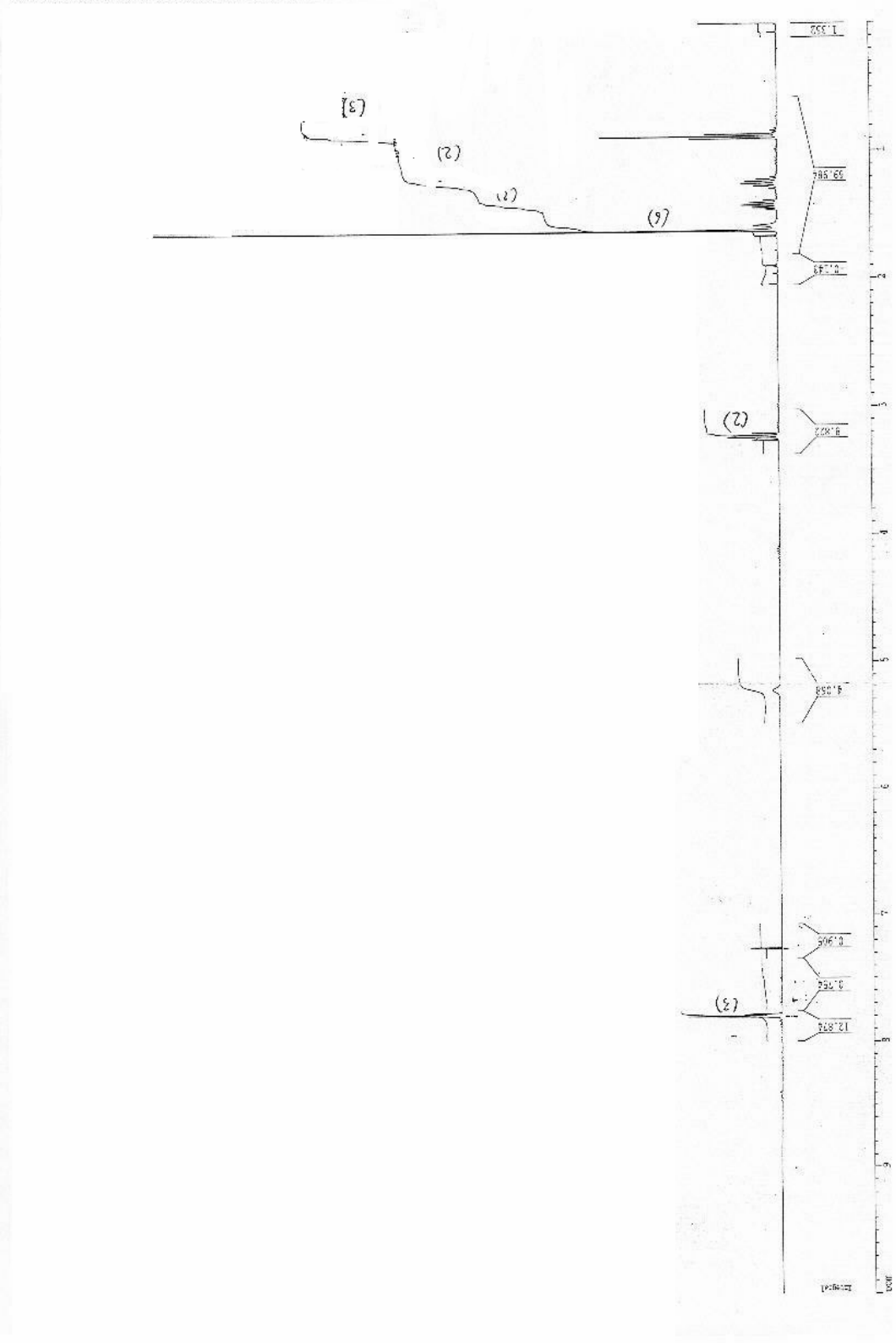
APPENDICES



Appendix 10 ^{1}H NMR of *p*-nitro cyclised products 361/363 or 366

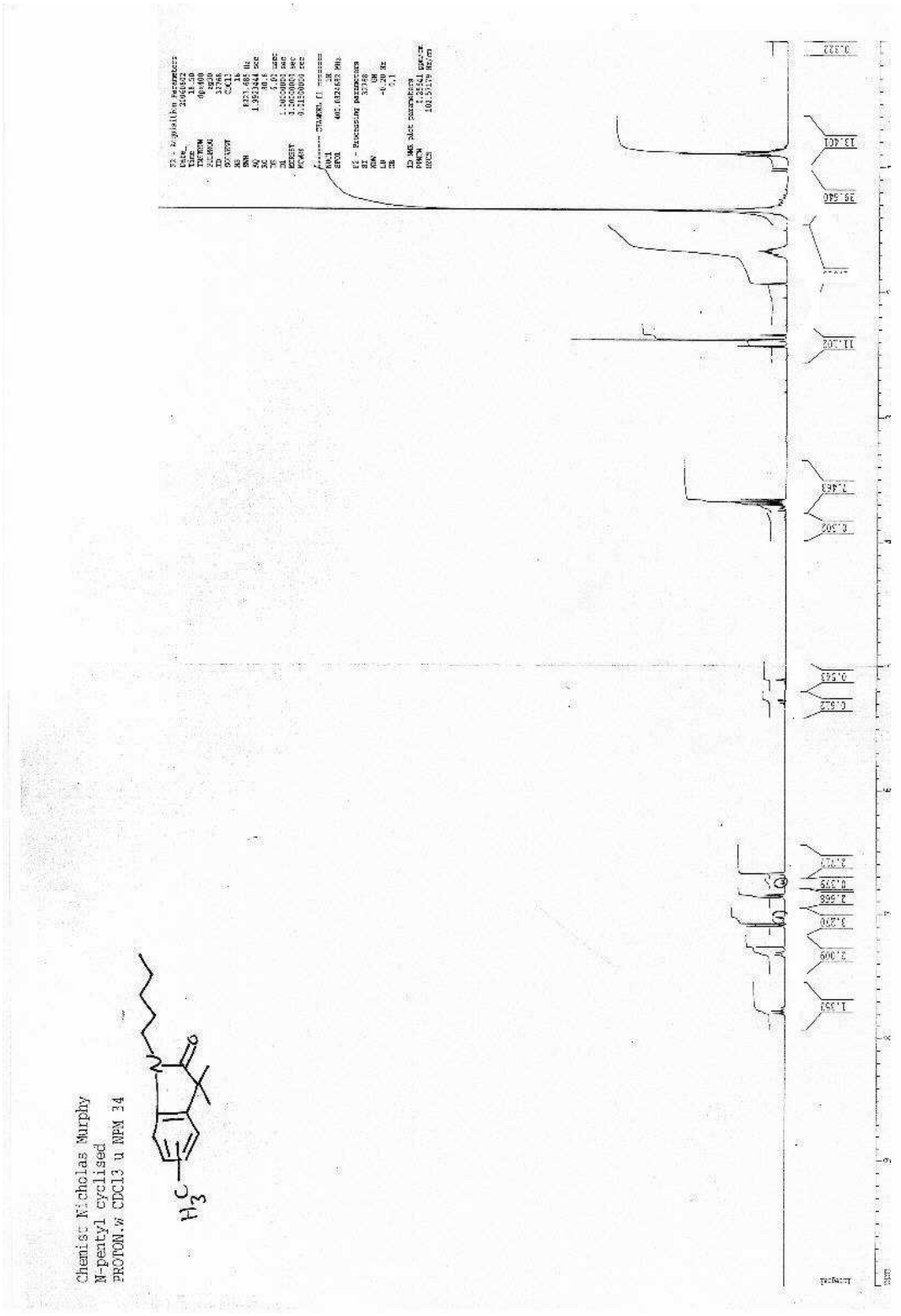


Appendix 11 ^{1}H NMR of *p*-TFM rearranged amide 280k



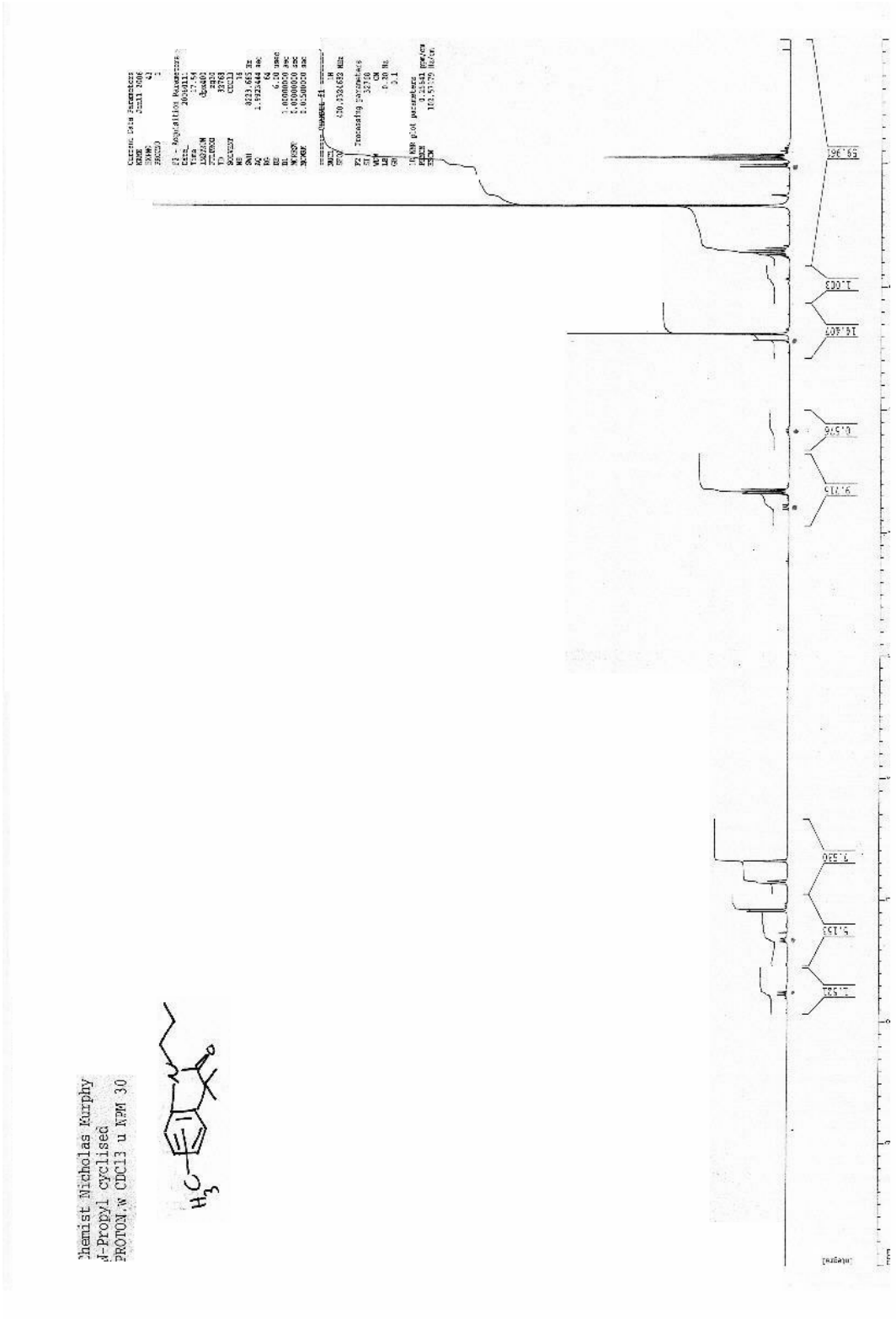
Appendix 12 ^{1}H NMR of *bis*-TFM rearranged amide 280l

APPENDICES



Appendix 13 ^{1}H NMR of *N*-pentyl cyclised product 369c

APPENDICES



Appendix 14 ^{1}H NMR of the *N*-propyl cyclised and reduced 375b product