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Generation of aminyl radicals and use in the synthesis of nitrogen heterocycles

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Generation of aminyl radicals and use in the
synthesis of nitrogen heterocycles

D.N. CLARK

A Doctoral Thesis. Submitted in partial fulfilment of the
requirements for the award of Doctor of Philosophy at
Loughborough University of Technology.

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Generation of Aminyl Radicals and use in the Synthesis of Nitrogen Heterocycles.

An Abstract.

The purpose of this project was to show that aminyl radicals (nitrogen atoms with one unpaired electron) could be generated from the radical reactions between tri-*n*-butyltin hydride and sulfenamides. Sulfenamides are defined as a divalent sulfur atom bonded to a trivalent nitrogen atom.

A wide range of sulfenamides were prepared in good yield using two methods. Benzenesulfonyl chloride and primary or secondary amines were reacted at room temperature with triethylamine as base to yield sulfenamides. Sulfenamides were also synthesised in good yield from the reaction between amines and *N*-(benzenesulfonyl)phthalimide. Initially, reactions were performed to show that aminyl radicals could be formed by reacting selected sulfenamides with tri-*n*-butyltin hydride in refluxing solvent. When these reactions proved to be successful, experiments were carried out to cyclise the intermediate aminyl radicals intramolecularly onto an olefin. The studies have led to a new method for the formation of nitrogen containing heterocycles.

The reluctance of aminyl radicals to cyclise onto alkenes was overcome by three methods; the use of alkenes which gave a stabilised radical on cyclisation, strained alkenes in favoured proximity, and trapping of the cyclised radical by tandem cyclisation. The latter route was developed for the synthesis of pyrrolizidines and indolizidines. The methods of cyclisation led to the facile synthesis of a wide range of polycyclic amines, including some natural product analogues.

Further studies were performed to determine whether aminyl radicals could be formed sequentially from the action of tri-*n*-butyltin hydride on disulfenamides [RN(SAr)₂] for use in bicyclisation reactions. Disulfenamides were synthesised by two routes; reaction between primary amines and two equivalents of benzenesulfonyl chloride, and reaction between alkyl bromides and the anion of *N,N*-di(benzenesulfonyl)amine [(PhS)₂NH]. Early work showed that aminyl radicals could be formed from disulfenamides, but attempts at forming precursors for cyclisation studies were incomplete due to shortage of time.

To conclude, this project has shown that nitrogen heterocycles can be formed from aminyl radicals generated from sulfenamides. This work represents an efficient route to many natural product analogues. However, further work needs to be performed to determine whether the same could be true when using disulfenamides.

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Cheers

**Special Thanks to Mum, Dad, Richard, Philippa, Beth and Adam, Alison
and Jason, Anne and Adam, Sarah, Mark and Jade**

Thanks also to Susan, David and Mark

Woof to Rufus

for Jane,
for ever

All I wanted in the end
Was world domination and a whole lot of money to spend
Everything I touch, everything I see
Fame and fortune, immortality
Well that's not too much to ask, it's really not
It's not much to ask, just the same as everybody else

Great Expectations, New Model Army

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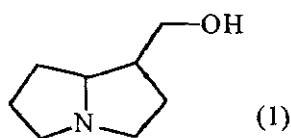
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Introduction

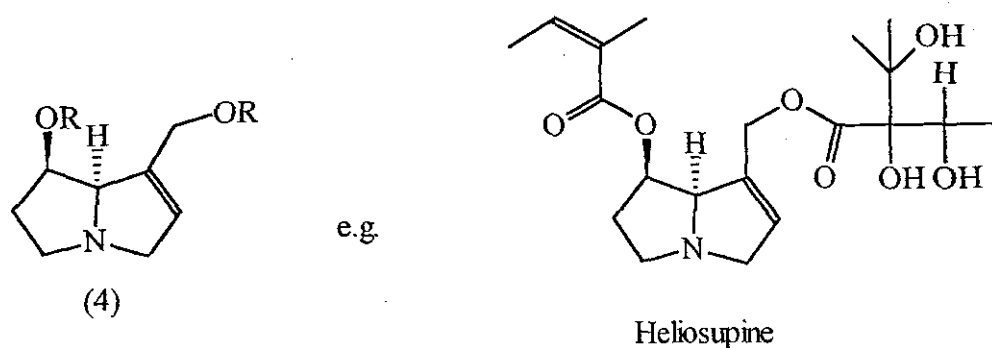
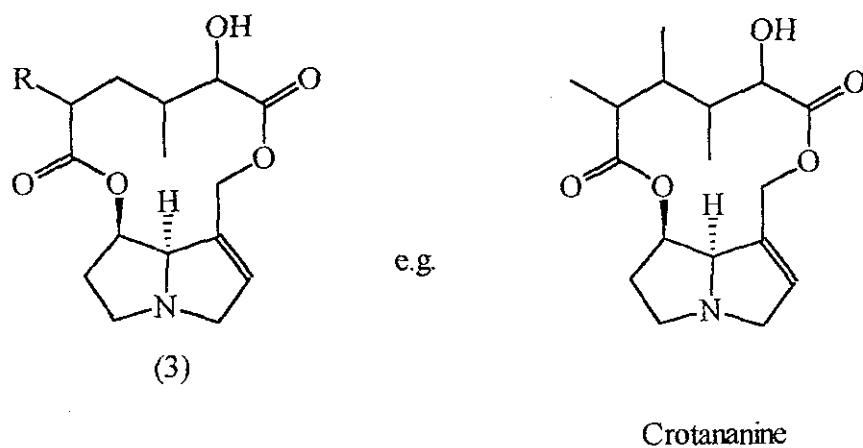
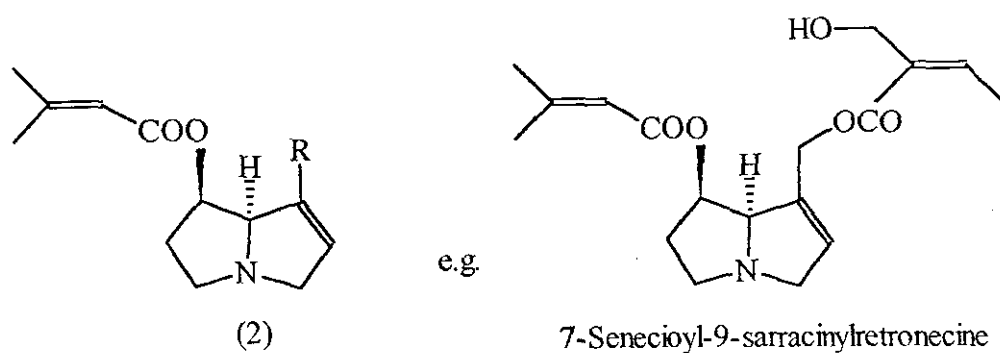
The development of methods for synthesising nitrogen heterocycles has occupied organic chemists since the early days of organic chemistry and continues unabated. The aim of the project was to apply the use of nitrogen centered radicals (aminyl $R^1R^2N\cdot$) to the synthesis of nitrogen heterocycles. Five and six-membered ring saturated heterocycles lend themselves best to radical cyclisation reactions. Since the discovery by Gomberg¹ in 1900 of single electron species, termed radicals, much work has been performed on the reactions of radicals, and in recent years has centered on regio- and stereospecific syntheses involving radicals. However, much of the work has concentrated on carbon centered radicals and the formation of carbon-carbon bonds, either through intermolecular addition or intramolecular cyclisation reactions.² In relation, not a great deal of work has been dedicated to the formation of carbon-nitrogen bonds and nitrogen-centred radicals. This fact is doubly surprising when considering the amount of naturally occurring compounds and pharmaceutically active compounds that contain nitrogen heterocycles. These nitrogen heterocycles should be easily obtained from the cyclisation of various nitrogen centred radicals onto alkenes.

1.1) Pyrrolizidines and Indolizidines

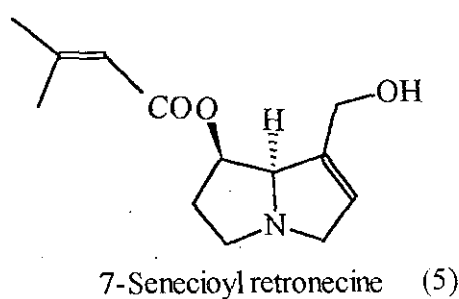
There are a vast number of biologically active and natural product nitrogen heterocycles present in the world today. Our interests lay particularly in developing new radical methods of synthesis for pyrrolizidines and indolizidines. Pyrrolizidines,³ characterised by the presence of the ring system (1) are the most widely distributed alkaloid type.



The word pyrrolizidine is a chemical description that refers to the two-fused-membered ring with a nitrogen atom at the bridgehead. Plants containing these alkaloids are found all over the world and they include mainly botanical families such as the *Compositae*, *Boraginaceae*, and *Leguminosae*. There are several main families of pyrrolizidine alkaloids, the genera exhibiting the greatest toxicity to livestock and humans include *Senecio* (2), *Crotalaria* (3), and *Heliotropium* (4).



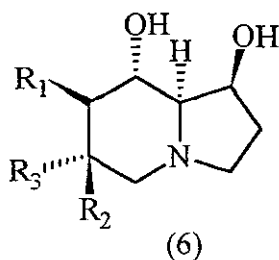
Members of this family exhibit quite remarkable biological properties.⁴ These include antitumor, anti-inflammatory, carcinogenic and hepatotoxic activities. In places such as South Africa, Jamaica, and Mexico, herbal teas are prepared from Senecio alkaloids, *e.g.* (5) for their medicinal and hallucinogenic effects.



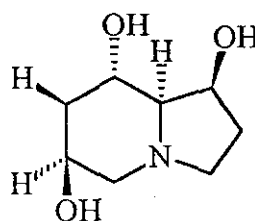
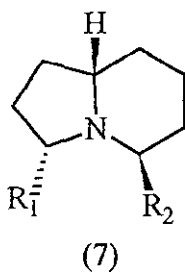
Even in some European countries, pyrrolizidine alkaloid-containing plants are still available for medical treatment. For example, the leaves of Russian comfrey (*Symphytum x uplandicum*) are eaten as a salad and drunk as a blended 'green drink', or, in infusion form, as a tea.⁵ This plant, which has been also recommended by herbalists as a medicinal plant, was found to contain toxic pyrrolizidine alkaloids.⁶

Unsaturated pyrrolizidine alkaloids are converted by hepatic microsomal enzymes to both *N*-oxides and pyrrolic metabolites.^{7,8} They are noted for their acute and chronic hepatotoxicity, pneumotoxicity, and a nucleotoxicity that includes mutagenesis, carcinogenesis, and long lasting antimitotic effects.⁵ Many of these alkaloids are of considerable veterinary and medical interest and economic importance, because of their toxic action on grazing animals and humans where they may find their way into foods, herbal medicine, or bush teas.⁹

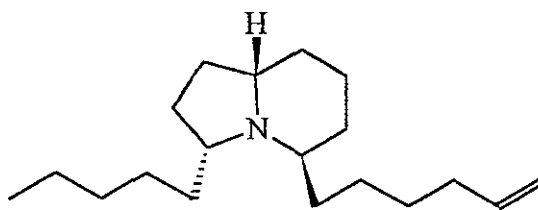
Like pyrrolizidines, indolizidine alkaloids exhibit many biological properties, including inhibition of glycoprotein processing, the inhibition of plant and intestinal glycosidases, insect antifeedant properties, and effects on cancer and the immune response.¹¹ They have also been found to exhibit anti viral activity, a field which is receiving a great deal of attention in recent years. A number of indolizidines have been detected in the seeds of the Moreton Bay Chestnut [*Castanospermum australe* (6)],¹² the venom of the New Zealand ant *Monomorium smithii* (7),¹³ Australian myobatrachid frogs (8)¹⁴ and the New Caledonian tree *Cryptocarya phyllostemon* (9)¹⁵ to cite just a very few examples.

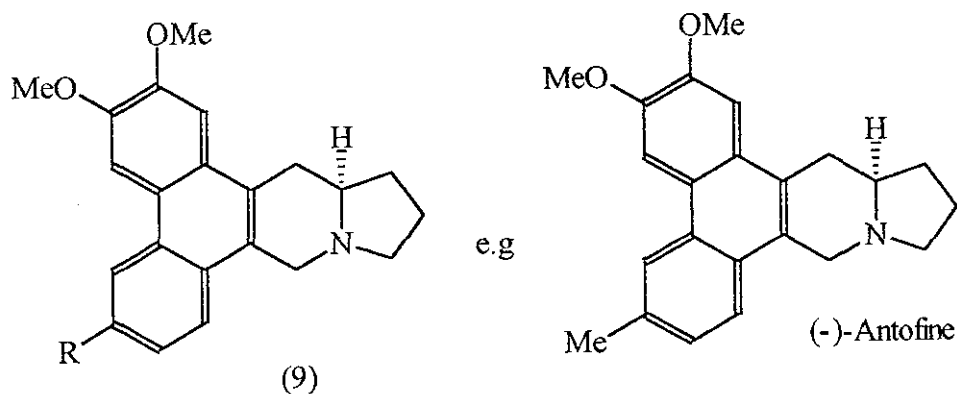
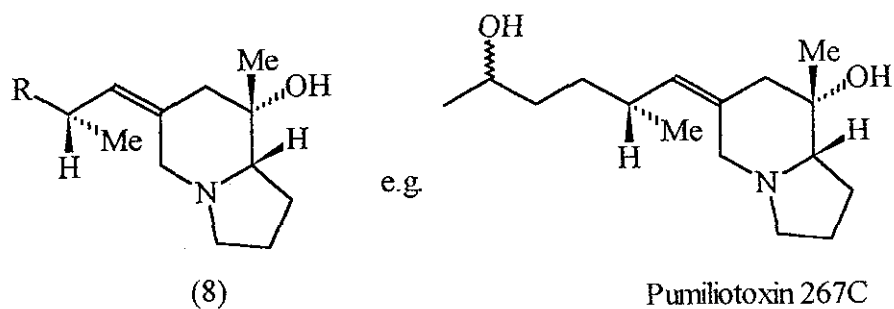


e.g

7-Deoxy-6-*epi*-castanospermine

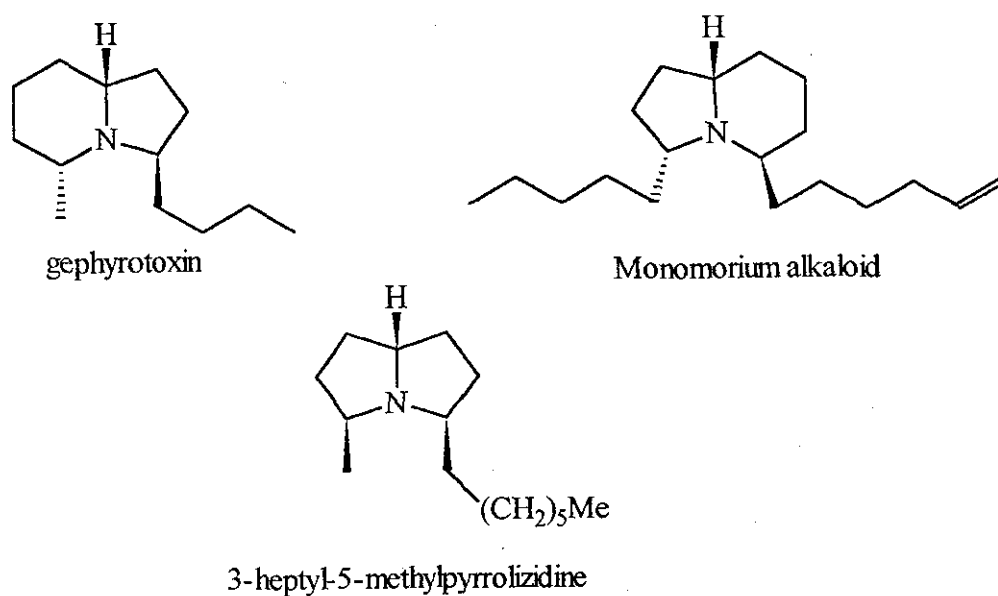
e.g

An example of a *Monomorium* Alkaloid

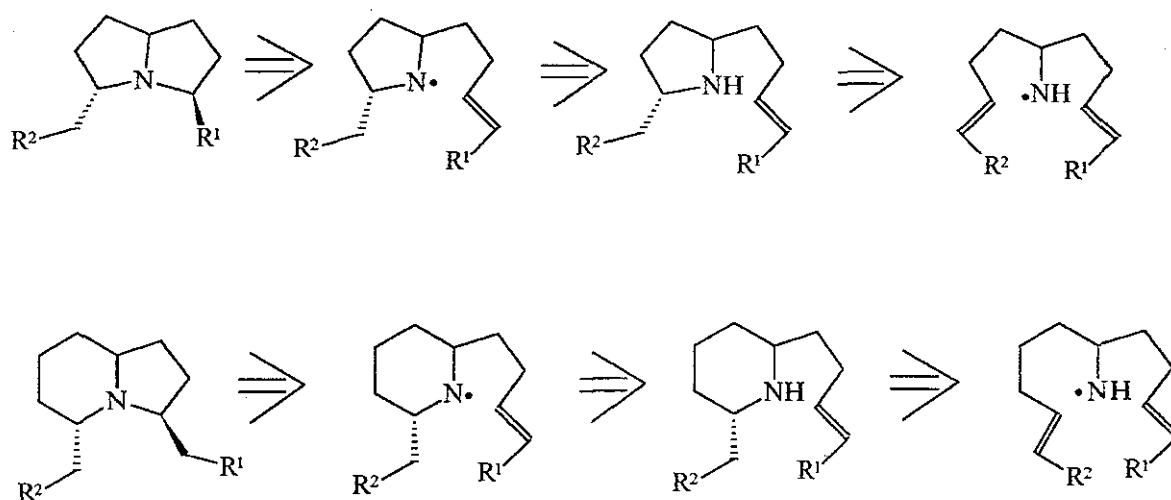


Pyrrolizidines and indolizidines were chosen as targets for developing new synthetic strategies using aminyl radicals. For example, one particular group of pyrrolizidines and indolizidines of interest were those substituted in the 3,5- positions *e.g.* (Scheme 1). The use of aminyl radicals could be envisaged as follows (Scheme 2). Note that the 3,5-alkyl groups are well-placed to allow cyclisation onto alkenes.

Scheme 1



Scheme 2

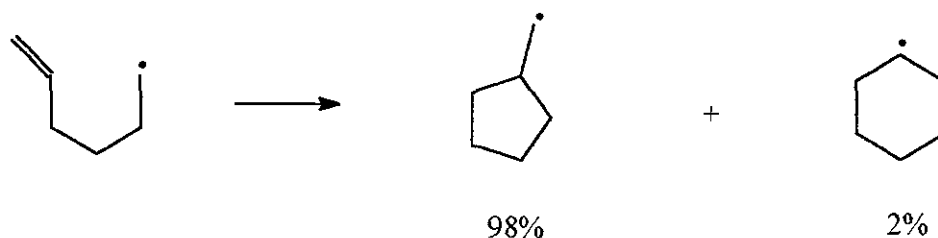


The following sections will consider several facets of radical cyclisation relevant to our intended work.

1.2) Regioselectivity and Stereoselectivity of Radical Cyclisation Reactions

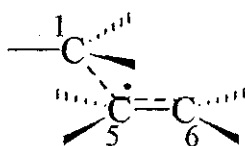
In Baldwin's 'Rules for Ring Closure', the author discusses the various types of ring closure that can occur in organic synthesis. He concludes that,¹⁶ in the cyclisation of a hexenyl radical onto an unactivated double bond, the less stable 5-*exo* product will be formed over the more stabilised 6-*endo* product (Scheme 3).¹⁷ In a normal ionic reaction, however, the more stable six-membered ring is formed.

Scheme 3



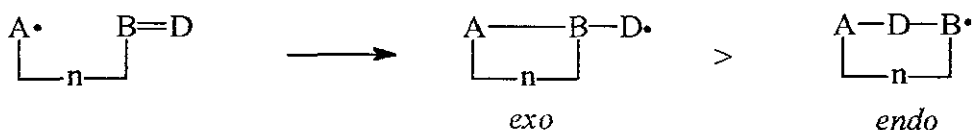
Beckwith¹⁸ has investigated this anomaly and found the answer to lie in transition state calculations. He found that the entropy change associated with formation of the transition structure for 1,5 ring closure will be less unfavourable than the entropy change associated with the 1,6 ring closure. Force field calculations gave the difference between these two entropies to be 2.8 kcal mol⁻¹. For cyclisation to take place, the bond-lengths and bond-angles had to be as follows: C(1)-C(5) = 2.40Å, C(5)-C(6) = 1.35Å, C(1),C(5),C(6) = 107° (Scheme 4).

Scheme 4



Thus it seems that stereoelectronic effects, *i.e.* the way in which the requirement for overlap of frontier orbitals affects the energy of the transition structure, is the deciding factor in radical reactions. This preference for the formation of the smaller possible ring is true for a large number of substituted hexenyl radicals and related systems (Scheme 5).

Scheme 5



B=D represents C=C, C=O, N=N, C=N etc

A represents C, Si, S, O, N etc

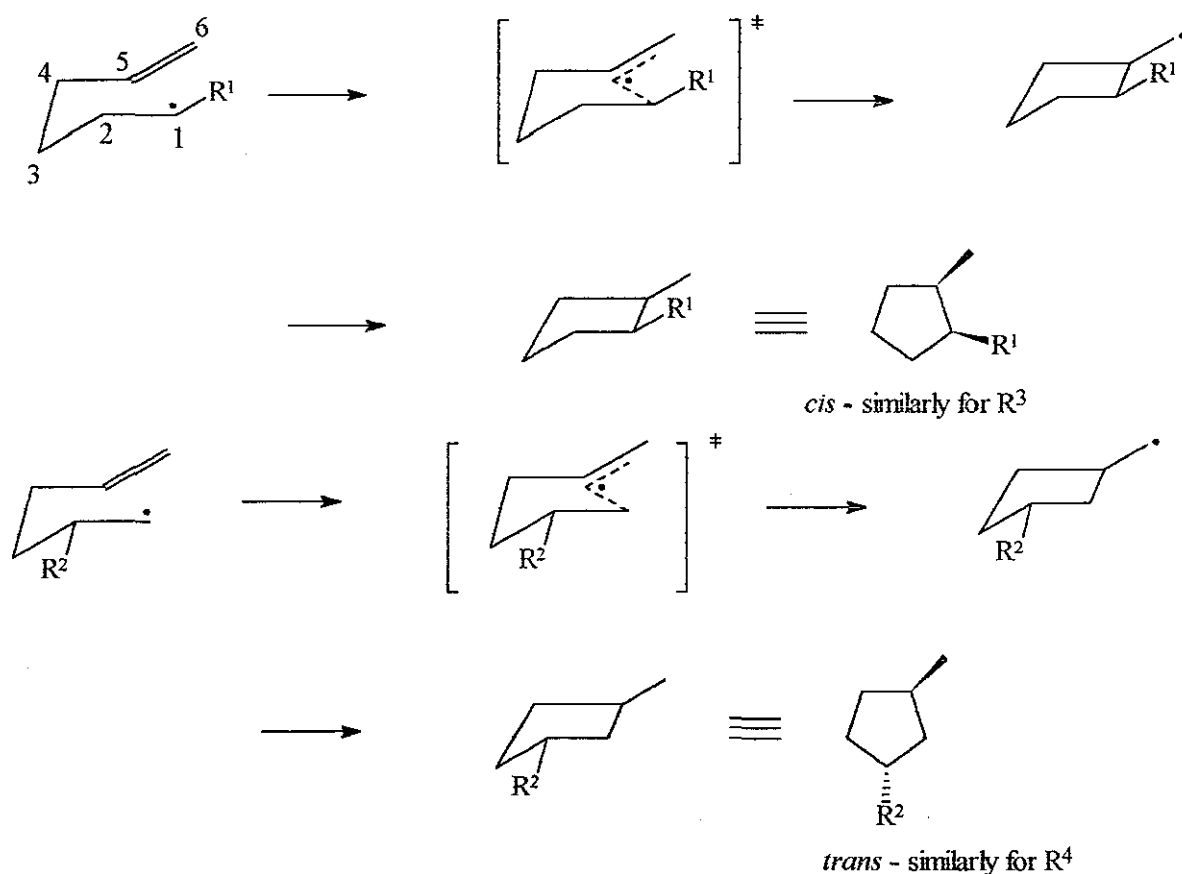
n represents a chain of 1-5 atoms

The stereoselective outcome of the cyclisation of an hexenyl radical can also be predicted from its transition state. The calculated transition structure for *exo*-cyclisation resembles cyclohexane in its chair form. For a typical monosubstituted system like the 4-methylhex-5-enyl radical, there are two possible diastereomeric transition structures; one in which the substituent is pseudo-axial, and the other where the substituent is pseudo-equatorial. The latter case has the lowest energy transition state; therefore it can be predicted that cyclisation of 4-substituted hexenyl radicals preferentially forms the *trans*-product. Similarly, cyclisation of 2-substituted hexenyl systems will yield the *trans*-product, whereas 1- or 3-substituted systems will preferentially form the *cis*-product (Scheme 6).

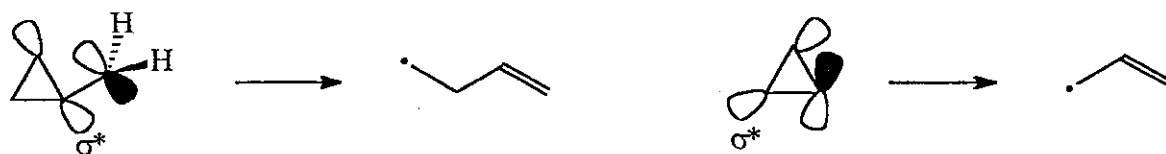
In the case of ring-opening of systems through radicals, it appears that stereoelectronic effects play a major role. It is assumed that the transition structure for β -scission comprises a triangular array of centres arising from interaction of the SOMO orbital with the σ^* orbital of the bond undergoing fission. This arrangement is readily attained in cycloalkylcarbinyl radicals, where rotation about the exocyclic bond allows coplanarity between the SOMO and σ^* orbitals to be reached. However, in cyclopropyl radicals, the orbitals involved are essentially orthogonal. Therefore, even though β -scission of the cyclopropyl radical to give the allyl radical is highly exothermic, the rate constant is at least six orders of magnitude less than the mildly exothermic ring opening of the cyclopropylcarbinyl radical. Similarly, cyclobutylcarbinyl radicals undergo fast ring-

opening, whereas the corresponding cyclobutyl radicals do not undergo ring-opening quite so rapidly (Scheme 7).

Scheme 6



Scheme 7

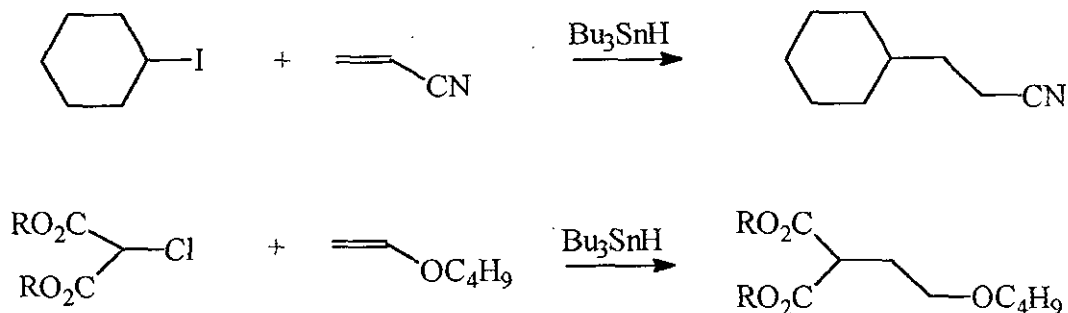


1.3) Reactivity of Aminyl Radicals

In order to discuss the reactivity of aminyl radicals, we first need to address the philicity of the radical. Alkyl radicals substituted with electron releasing groups² (alkyl, alkoxy, amino etc) behave like nucleophiles and react very fast with alkenes substituted by electron-withdrawing groups (nitrile, ketone, ester). Alternatively, radicals with electron withdrawing substituents behave as electrophiles, and react very fast with electron-rich alkenes. For example, reaction of cyclohexyl iodide with acrylonitrile in the presence of tri-*n*-butyltin hydride occurs in 95% yield, due to the formation of the nucleophilic cyclohexyl

radical (Scheme 8). This is also true for the reaction between chloromalonic ester and butoxyethene.

Scheme 8



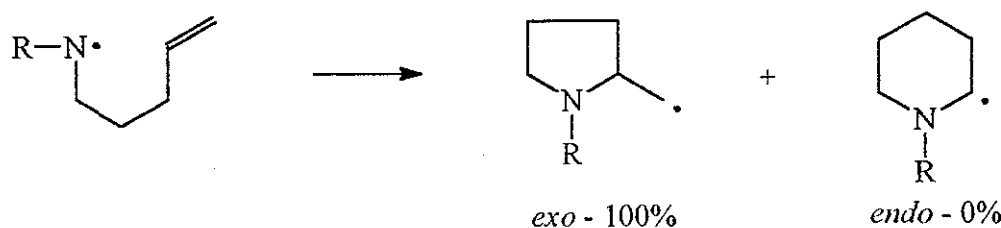
Radicals centred on atoms more electronegative than carbon are regarded as electrophilic.²⁰ This behaviour has been shown to be true for alkoxy radicals. An example of this property is the faster cyclisation of the electrophilic alkoxy radical onto an unactivated olefin, than the more nucleophilic alkyl radical. Alkenes are weakly nucleophilic and react faster with electrophilic radicals than nucleophilic radicals. These considerations suggest that the rate of cyclisation of an aminyl radical will be faster than the nucleophilic alkyl radical, but not so rapid as the strongly electrophilic alkoxy radical, *i.e.* $k_{\text{c(O)}} > k_{\text{c(N)}} > k_{\text{c(C)}}$

Similarly, the abstraction of hydrogen from tri-*n*-butyltin hydride should be in a similar order; *i.e.* the more electrophilic the radical, the faster the $\text{S}_{\text{H}}2$ rate to yield nucleophilic tin radicals. In fact, measurements²¹ show that $k_{\text{H(O)}} >> k_{\text{H(C)}} > k_{\text{H(N)}}$. This therefore suggests that aminyl radicals are more nucleophilic than alkyl radicals. One explanation is that the strongly basic lone pair has a significant effect on the reactivity of aminyl radicals and overrides predicted polarisation effects. This means that the nucleophilic aminyl radical will not preferentially cyclise onto a slightly nucleophilic olefin.

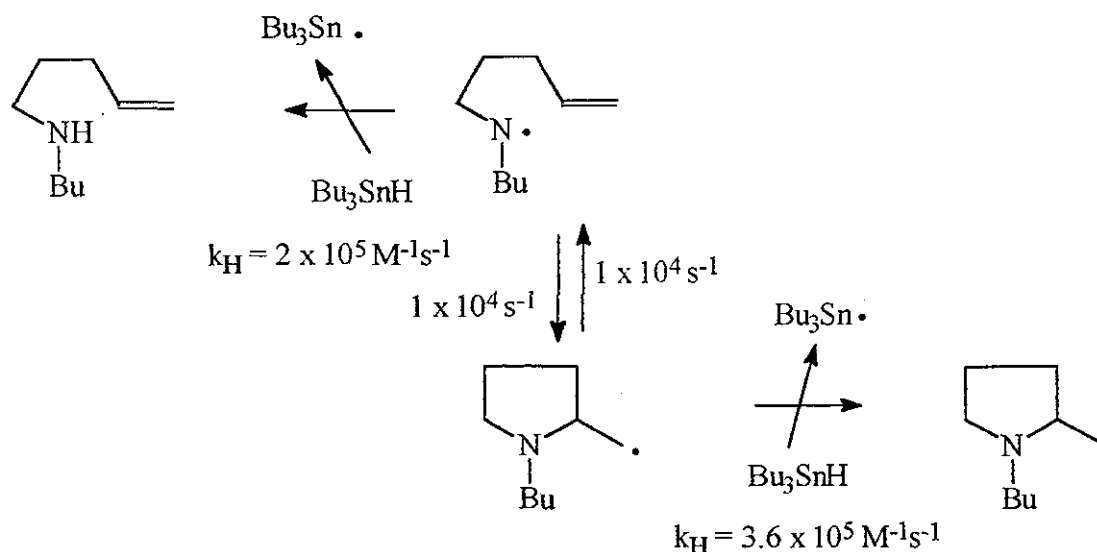
The previous section indicates that we should expect aminyl radicals to undergo cyclisation in a 5-*exo-trig* manner, and that cyclisation of 4-substituted pentylaminyl radicals should yield the *trans* product predominantly. Indeed, work by Newcomb and co-workers²¹ has shown that for the simple case of the cyclisation of 5-pentenylaminyl radical, cyclisation occurs to give exclusively the pyrrolidine (*i.e.* the 5-*exo-trig* product), with no piperidine being observed from the reaction (Scheme 9).

However, the yield of cyclised material in this reaction is very small. Rate studies performed on this reaction²² indicate that the cyclisation of aminyl radicals is reversible, with the rate of cyclisation being approximately equal to the rate of ring-opening of the initially formed alkyl radical. Also the rate of hydrogen abstraction from tri-*n*-butyltin hydride by the aminyl radical is similar to that of the primary carbinyl radical (Scheme 10).

Scheme 9



Scheme 10



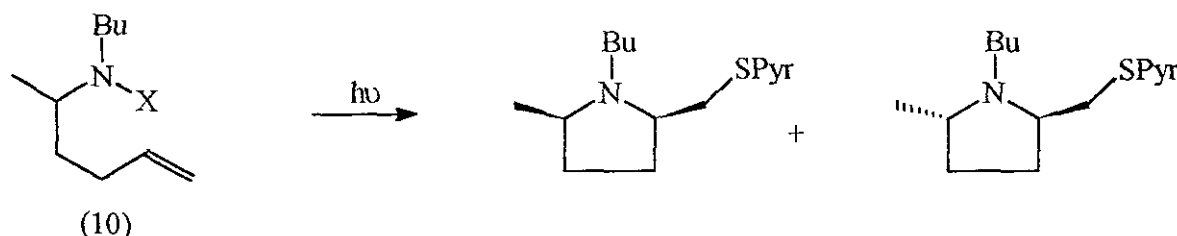
It seems that aminyl radicals, once formed, will be expected to cyclise to typically yield 5-membered nitrogen heterocycles. This rate of cyclisation will be increased if the nitrogen radical is made more electrophilic. The presence of the lone pair on aminyl radicals appears to play a critical role in their reactivity. When these electrons are delocalised *e.g.* aminium²³ and amidyl²⁴ radicals, the behaviour changes dramatically. The rate of cyclisation of aminium and amidyl radicals is very rapid²⁵ and the radicals exhibit electrophilic behaviour as expected. Indeed, a far greater amount of cyclised material is observed when the initially formed aminyl radical is protonated prior to reaction with an intramolecular olefin (see Section 1.4.7).



The stereochemistry of the aminyl radical cyclisation reaction can be investigated using the *N*-butyl-2-methyl-4-pentenaminyl radical (10). Cyclisation of this radical under

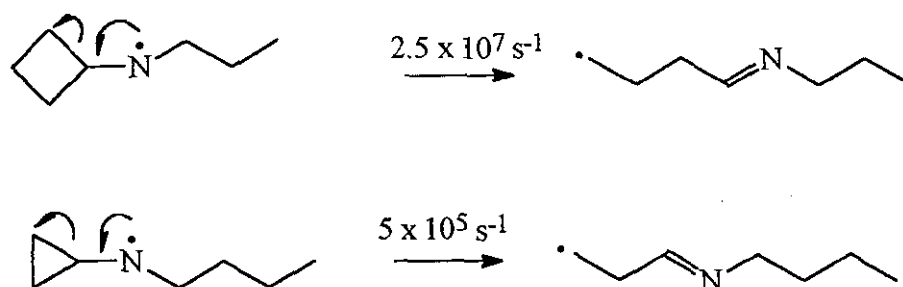
standard conditions²⁶ gave a *trans:cis* ratio of 3:1, showing that this reaction seems to obey the rules for radical cyclisation reactions (Scheme 11).

Scheme 11



Similarly, the ring-opening of aminyl radicals seems to obey the same rules as for the ring-opening of cycloalkylcarbinyl radicals. It can be seen that the rate of ring-opening²⁷ of the *N*-propylcyclobutylaminyl and *N*-butylcyclopropylaminyl radicals is fast ($2.5 \times 10^7 \text{ s}^{-1}$ and $5 \times 10^5 \text{ s}^{-1}$ respectively) (Scheme 12).

Scheme 12



From the above data, it seems that aminyl radicals undergo all of the same reactions that carbinyl radicals do. However, work is required to increase the efficiency of the cyclisation reaction to make the synthesis of nitrogen-containing heterocycles a viable procedure. Below it is intended to discuss the various methods used to generate aminyl radicals available up to now, with a description of their respective advantages and disadvantages.

1.4) Previous methods of generating Aminyl Radicals

Over the years, a number of methods have been formulated for the generation of aminyl radicals. These methods include the photolysis or thermolysis of *N*-chloramines, *N*-nitrosamines, tetrazenes, *N*-hydroxypyridine-2-thione carbamates or aminodiethoxyphosphines, as well as an electron-transfer reaction of the amidate anion to tetracyanoethylene, by anodic oxidation of dialkylamines, or by anodic oxidation of metal

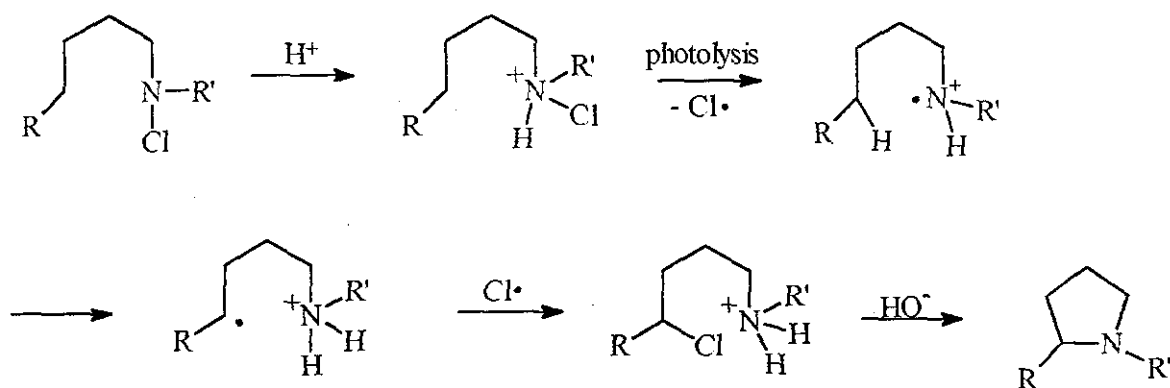
dialkylamides. It is proposed to summarise the main methods of aminyl radical generation in this introduction, and to indicate the more noteworthy reactions from these sequences.

The first method, initially studied some 20-30 years ago, involved the photolysis of *N*-chloramines.

1.4.1) *N*-Chloramines as Precursors for Aminyl Radicals

The first method to be extensively used for the generation of aminyl radicals involved *N*-chloramines and a 1,5-hydrogen abstraction, *i.e.* the Hoffman-Löffler-Freytag reaction which is shown in Scheme 13.

Scheme 13



Generation of radicals from *N*-chloramines has been the most widely used system but suffers from a number of disadvantages. The early work on the use of *N*-chloramines as precursors to aminyl radicals was first pioneered by Surzur and Stella at Marseilles²⁸ in the 1960's. The first method that they used involved the photolysis of *N*-chloramines and strong acidic solution, *e.g.* as shown in Scheme 14 below.

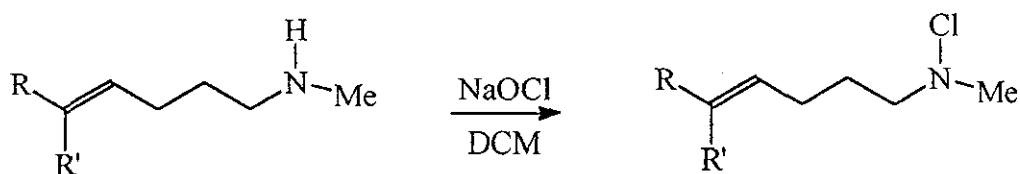
Scheme 14



However, this method proved unsuitable for general application to synthesis because of the requirement of up to 4M sulfuric acid or hydrochloric acid, and the generation of chlorine radicals, which interfered with the final cyclised products. Further work showed that by reacting chloramines in the presence of metallic salts, regioselective aminyl radical cyclisations could be achieved.²⁹ The chloramines themselves were readily prepared from the action of sodium hypochlorite in dichloromethane on secondary amines as shown below

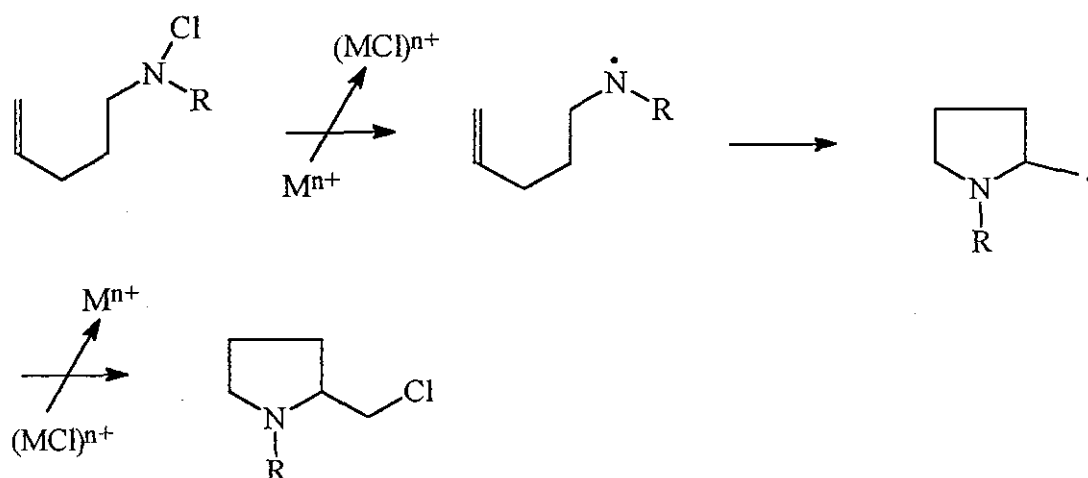
(Scheme 15).^{30, 31, 32} Later methods of forming chloramines involved the action of *N*-chlorosuccinimide on primary or secondary amines.³³

Scheme 15



Cyclisation was achieved through the reductive elimination of the nitrogen-chlorine bond, giving rise to the metal complexed aminyl radical. The aminyl radical is then free to cyclise onto the olefin in an *exo* manner, leaving a primary alkyl radical to propagate the radical sequence by combining with a "chlorine radical", e.g. by oxidative addition (Scheme 16).

Scheme 16



The reaction of the *N*-chloramines (13a, 13b) with a reducing metallic salt in acetic acid - water solution gave rise to a mixture of the regenerated amine (14), unreacted *N*-chloramine (13) and cyclised pyrrolidine (15) (Scheme 17).

Various different metallic salts were tried, with the results as summarised below (Table 1). As can be seen, the best stereospecificity was obtained when the metallic salt was copper or cobalt, although on the whole these did not lead to the best yield of cyclised material.

Scheme 17

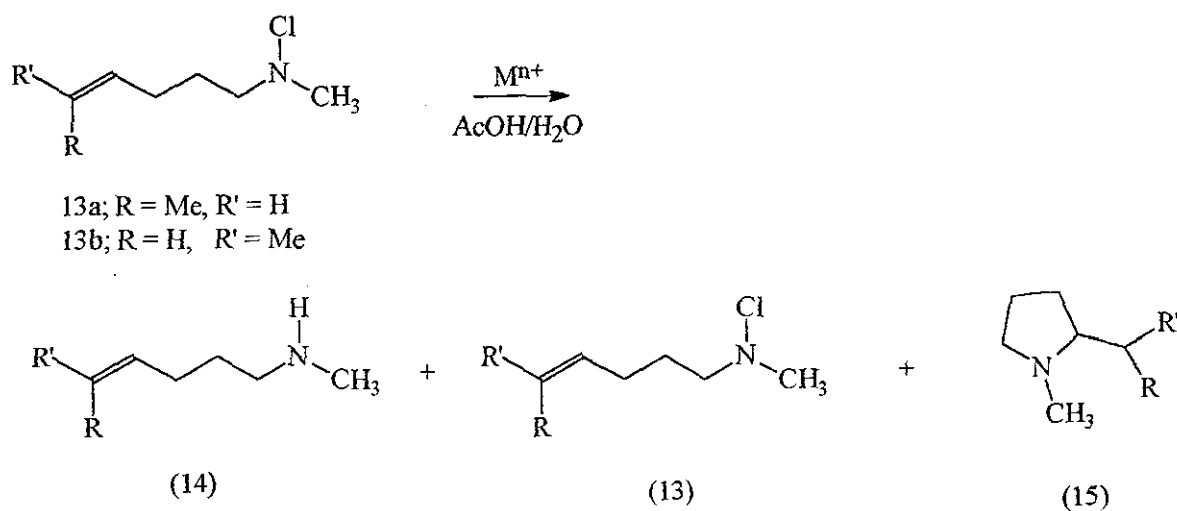
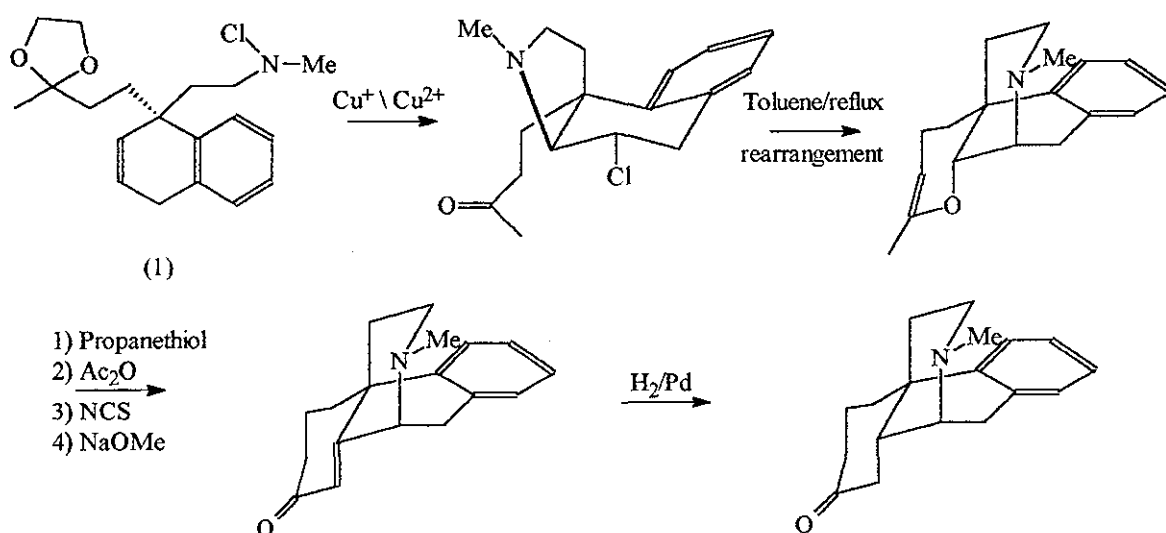


Table 1. Radical Cyclisation of *N*-Chloramines (13a) and (13b) by means of Metallic Salts

Substrate	ML _n	Yield (13)+(14)+(15)	Molar (13)	Ratio (14)	(15)	Diastereomeric <i>ethyro</i>	Purity <i>threo</i>
b	TiCl ₃	74	5	0	95	58	42
a	TiCl ₃	79	18	0	82	42	58
b	CuCl	79	16	0	84	55	45
a	CuCl	72	35	0	65	44	56
b	CuCl/CuCl ₂	81	4	0	96	100	0
a	CuCl/CuCl ₂	79	7	0	93	9	91
b	FeSO ₄	74	0	54	46	100	0
a	FeSO ₄	93	2	45	54	0	100
b	FeCl ₂	78	0	33	67	100	0
a	FeCl ₂	76	0	38	62	0	100
b	Co(C ₁₀ H ₁₄ O ₄)	57	45	0	55	100	0
a	Co(C ₁₀ H ₁₄ O ₄)	67	43	0	57	0	100

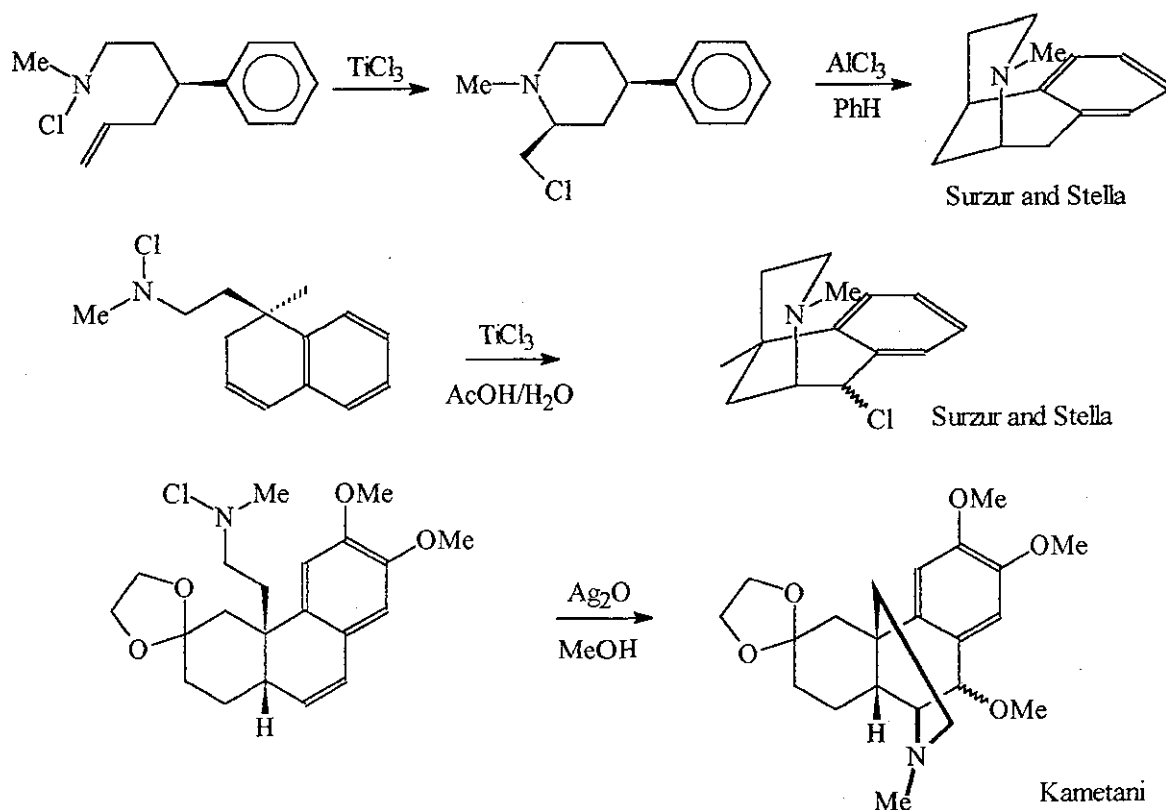
Since the early pioneering work, much use has been made of aminyl radicals generated through the cleavage of chloramines in the synthesis of naturally occurring nitrogen heterocycles. Broka³⁴ at Illinois formed the morphinan below using this methodology to form the crucial 5-membered heterocyclic ring (Scheme 18). Upon reaction of the chloramine with copper (I) chloride/copper (II) chloride in THF/AcOH/H₂O, the required cyclised product was obtained in 44% yield. The *syn* isomer was also formed in 5% yield. Repeat reactions using different metallic salts didn't give such good overall yields or high stereospecificity.

Scheme 18



Both Surzur and Stella,³⁵ and Kametani³⁶ have used this type of cyclisation to form morphinan ring systems (Scheme 19).

Scheme 19

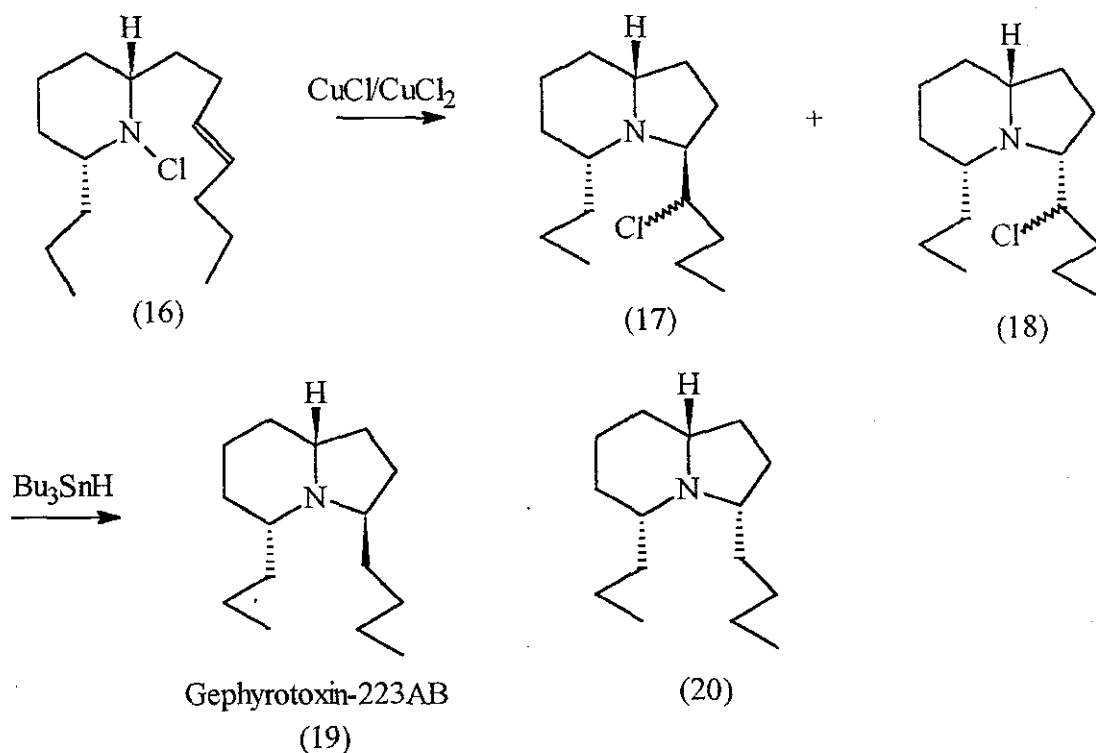


Finally, in a recent example, Broka has also used this system to aid the complete synthesis of Gephyrotoxin-223AB.³⁷ Once again, reaction of the chloramine (16) in the

presence of copper salts lead to the diastereomeric products (17) and (18) in 66% overall yield. Simple reduction of the alkyl chlorides with tributyltin hydride gave the required alkaloids (19) and (20) which were easily separated by chromatography (Scheme 20).

It can be seen that reactions between reducing metal salts and chloramines provide a quick and efficient method of forming aminyl radicals as precursors to nitrogen-containing heterocycles, and their use has provided useful routes to many alkaloids. However, the generation of an active C-Cl bond β to the amine often leads to rearrangements via aziridinium salts, and this has limited their efficient use in organic synthesis.

Scheme 20



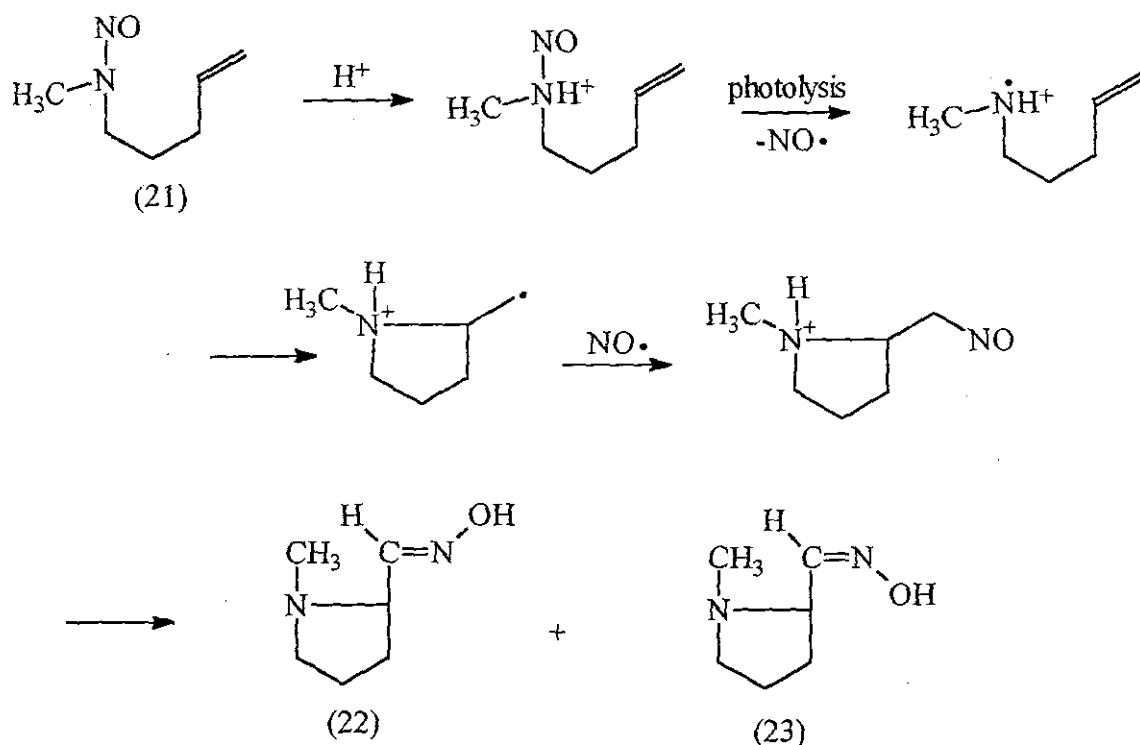
1.4.2) *N*-Nitrosamines as Precursors for Aminyl Radicals

Early work by Chow and Perry at Simon Fraser University, British Columbia,³⁸ has shown that aminyl and aminium cation radicals can be formed from the photolysis of *N*-nitrosamines. *N*-Nitrosamines are, unfortunately, very toxic and are known carcinogens. Also, although some *N*-nitrosamines can be purified, most of the compounds studied are unstable to conventional purification techniques, and are reacted in their crude state. In spite of their obvious disadvantages, cyclisation reactions have been performed *via* aminium cation radicals derived from the photolysis of *N*-nitrosamines.

The alkenyl *N*-nitrosamines studied were all prepared from the action of either sodium nitrite and acid or a modified procedure involving nitrogen tetroxide on the equivalent alkenylamine. The aminium cation radicals were generated by the photolysis of the *N*-nitrosamines in methanol in the presence of a dilute solution of hydrochloric acid. When the reactions were repeated without the hydrochloric acid solution, no cyclised

product was observed, due, presumably, to the nucleophilicity of the aminyl radicals formed in this way. Photolysis of *N*-nitrosamine (21) under standard conditions lead to a mixture of the *syn* (22) and *anti* (23) oxime in an approximate ratio of 4:1, as illustrated (Scheme 21). As can clearly be seen, the aminium cation radicals thus formed cyclise predominantly in an *exo* rather than *endo* fashion, as predicted by the rules for radical cyclisation.

Scheme 21

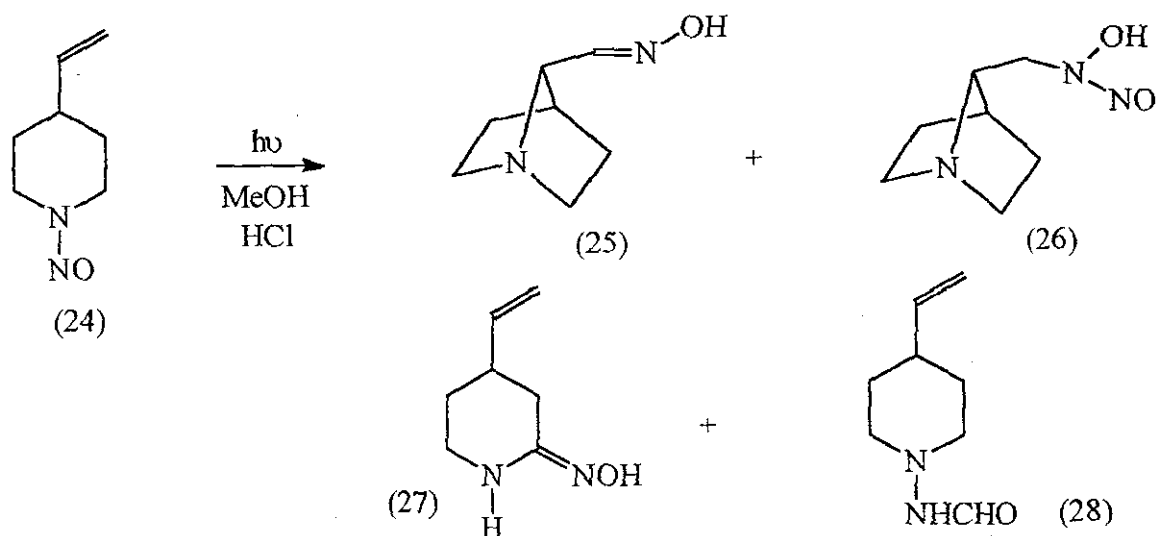


Cyclisation of *N*-nitrosamine (24) gave a mixture of products, the expected oxime (25), the hydroxylamine (26), the oxime (27), the formamide (28) and the parent amine (29) (Scheme 22).

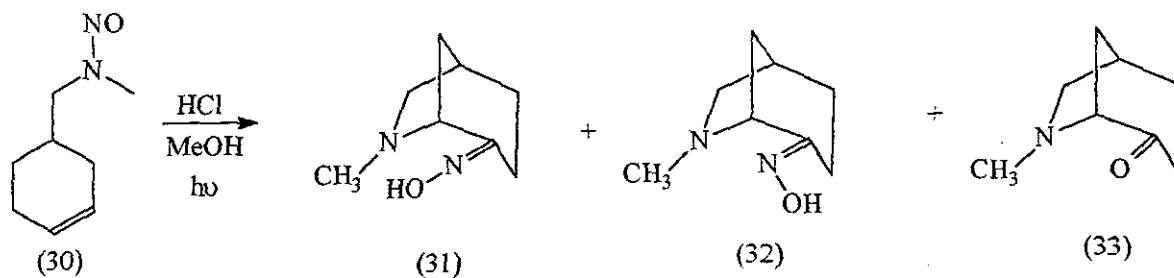
This mixture of products obtained upon photolysis of *N*-nitrosamines is quite common, due to the nitrosyl radicals reacting with the cyclised material. Therefore, this technique has the further disadvantage of requiring copious purification after work-up of the reaction mixture. Despite these disadvantages, this method has been used for the synthesis of azabicyclics.³⁹ Photolysis⁴⁰ of the *N*-nitrosamine (30) lead to a mixture of the ketone (31),⁴¹ the *anti* oxime (32) and the *syn* oxime (33), with only 5% of the purified mixture being the ketone (Scheme 23).

Similarly, photolysis of the *N*-nitrosamine (34) lead to predominantly a mixture of the *syn* (35) and *anti* (36) oxime being produced (Scheme 24).

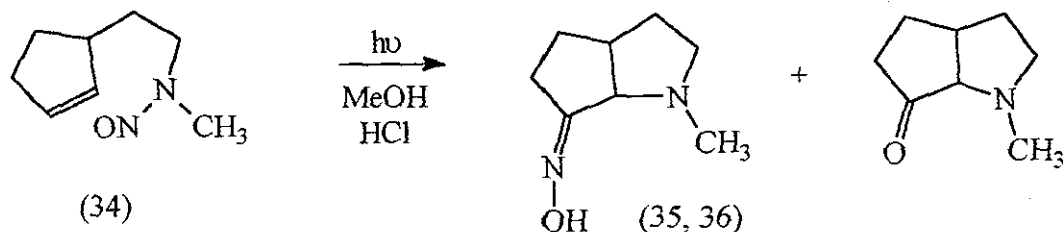
Scheme 22



Scheme 23



Scheme 24



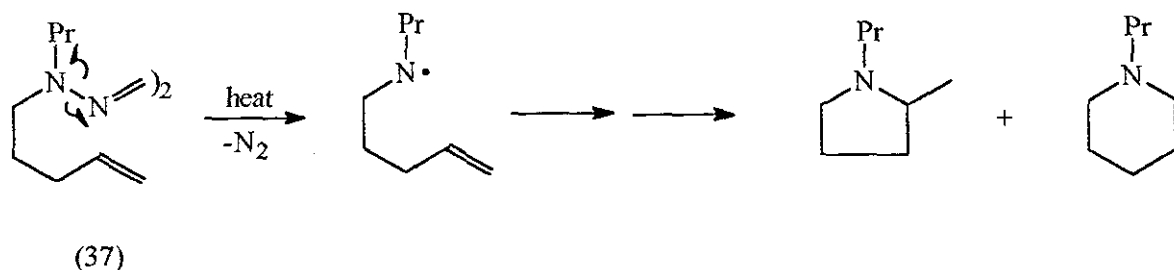
To conclude, the disadvantages of using *N*-nitrosamines to generate aminium radical cations outweigh the synthetic usefulness of this technique. To illustrate this, this field of work has largely ceased, with aminyl and aminium radical cations being produced from safer and more readily available materials.

1.4.3) Tetrazenes as Precursors of Aminyl Radicals

Michjeda⁴² reported that aminyl radicals can be formed from the decomposition of tetrazenes, *e.g.* by using the tetrazenes (37), decomposition leads to a mixture of the 5-*exo*

cyclised material, and the 6-*endo* cyclised material. This is surprising when considering that in radical cyclisations it is normally the 5-*exo* product that predominates, often to the point of their being no 6-*endo* product being detected at all (Scheme 25).

Scheme 25



To further investigate this phenomena, Newcomb⁴³ studied the decomposition products of tetrazene (38). Table 2 shows the distribution of the four products detected from the decomposition (Scheme 26).

Scheme 26

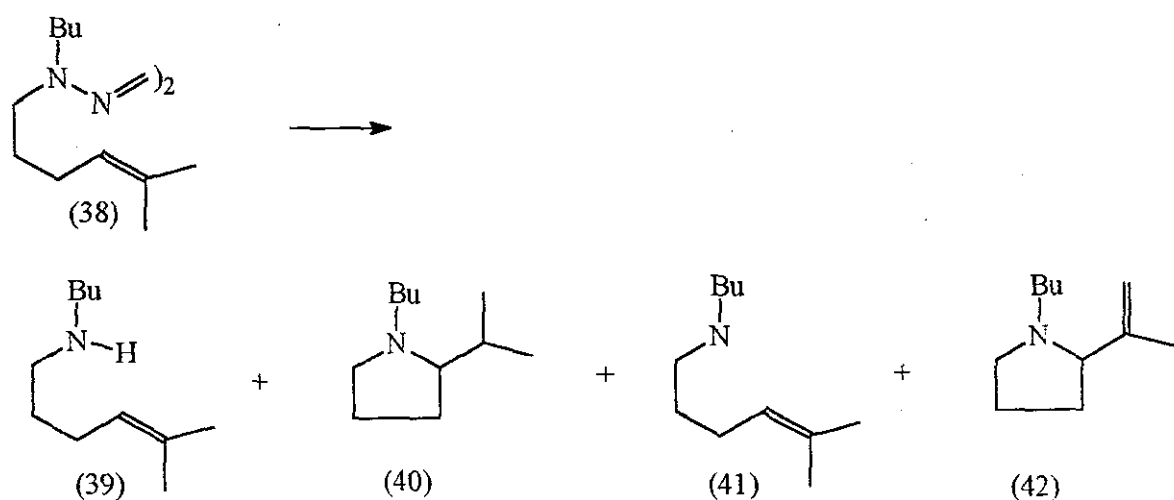


Table 2. Product Yields from Decomposition of Tetrazene (38).

Method	Temp °C	Solvent	Time h	(39)	% Yield (40)	(41)	(42)
Thermolysis	160	THF	8	30	36	9	3
" "	160	c-C ₆ H ₁₂	8	30	33	9	4
Photolysis	25	THF	5	31	15	14	18
" "	25	Ether	5	32	10	18	14
" "	25	c-C ₆ H ₁₂	5	32	12	20	16

All of the four products were found to result from the radical reaction itself, with no ionic reactions occurring after the radical initiated products had been formed. It is also notable that no 6-*endo* cyclised product was detected from this reaction. It would therefore suggest that the aminyl radical cyclisation reaction is reversible, and that the piperidine product observed by Michjeda was the result of a partially equilibrated radical cyclisation reaction. Therefore it can be concluded that in aminyl radical cyclisation reactions, it is the kinetic *i.e.* the *exo* product that is most favoured. The tetrazenes themselves are difficult to prepare and are potentially explosive. The method also yields a mixture of products which are difficult to separate. Therefore, tetrazenes do not provide a suitable precursor for synthesis via aminyl radicals.

1.4.4) Lithium Dialkylamides as Precursors to Aminyl Radicals

A considerable amount of work has been carried out into the generation of aminyl radicals through the anodic oxidation of lithium dialkylamides. The process, believed to operate by single electron transfer, forms aminyl radicals that can be detected by their subsequent cyclisation reactions. Newcomb⁴³ has used this method, along with other methods for the generation of aminyl radicals, to investigate the rate of cyclisation of a model aminyl radical. Tokuda,⁴⁴ meanwhile, has concentrated on using this method to create a stereospecific synthesis of pyrrolidines. By taking the related alkenylamines (43a-e) and reacting them with *n*-butyllithium at -78°C, the required lithium dialkylamides can be formed. These lithium dialkylamides were then typically electrolysed in a 30:1 mixture of THF/HMPA containing lithium perchlorate with a platinum anode (Scheme 27). The products from the reaction of the newly formed aminyl radicals (45a-e) with the intramolecular olefin were then analysed by GLC (Table 3).

As can clearly be seen, only the *cis*-2,5-disubstituted pyrrolidines were formed, with apparently no evidence of the *trans* product being formed in this reaction. This stereoselectivity is surprising when considering that it is the *trans* product that is predicted by the transition state models for radical cyclisation as proposed by Beckwith and Houk. It seems that in the case of lithium dialkylamides, the electrode surface might have an effect on the stereoselectivity.⁴⁵ However, the reversible nature of the aminyl radical cyclisation might also have an effect on this particular preference of conformation. It also appears that when the reaction is performed at a lower temperature, as in the case of (43a) when the reaction was performed at -50°C, the yield of pyrrolidine was decreased. It is also useful to note that the 5-*exo* cyclisation is still favoured over the 6-*endo* cyclisation in all the systems tested in this procedure. This agrees with the transition state models and the rate data available for radical cyclisation reactions.

Scheme 27

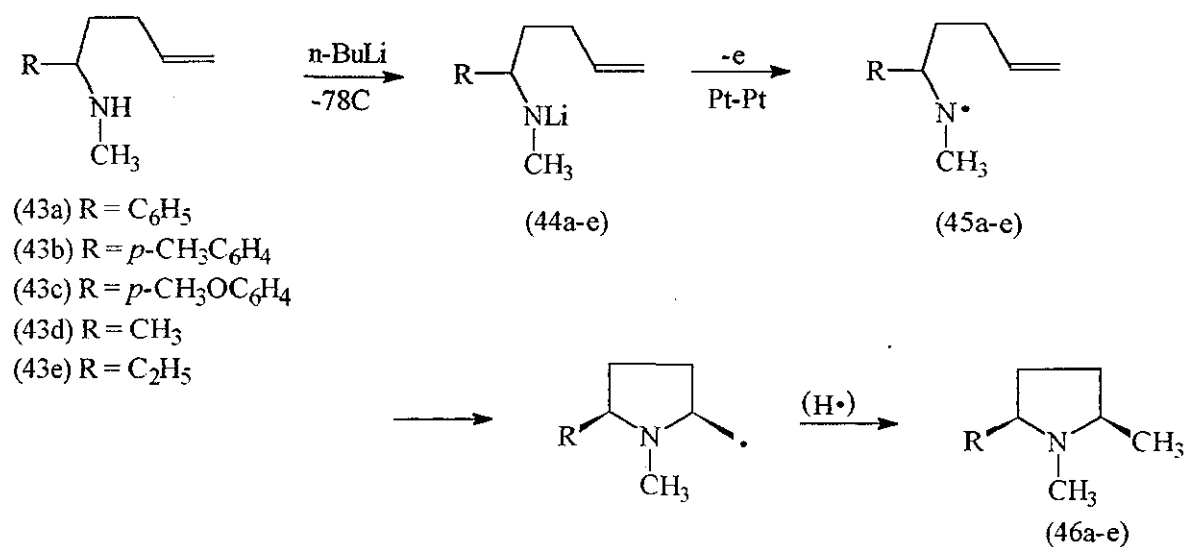
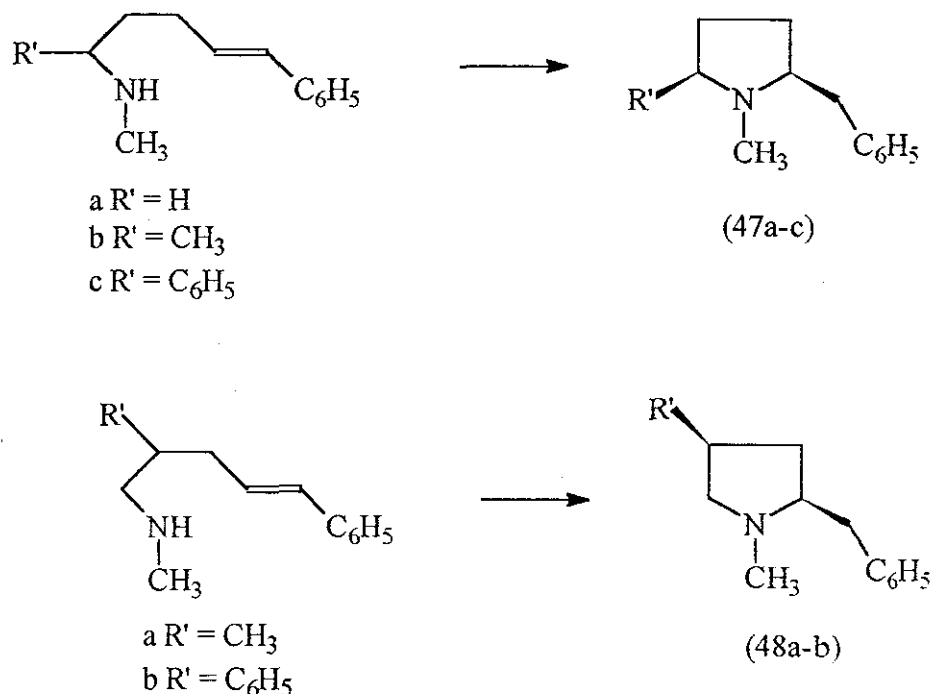


Table 3. Cyclisation of 43a-43e by anodic oxidation

Amine	Temp. (°C)	Product	Yield of (46) (%)	Recovered (43) (%)
43a	-10	46a	52	29
43a	-50	46a	41	52
43b	-10	46b	48	44
43c	-10	46c	46	50
43d	-10	46d	31	9
43e	-10	46e	34	4

Tokuda has further used this approach to synthesise *cis*-5-substituted-2-benzylmethylpyrrolidines (47a-c) and *cis*-4-substituted-2-benzyl-1-methylpyrrolidines (48a,b) (Scheme 28)⁴⁶

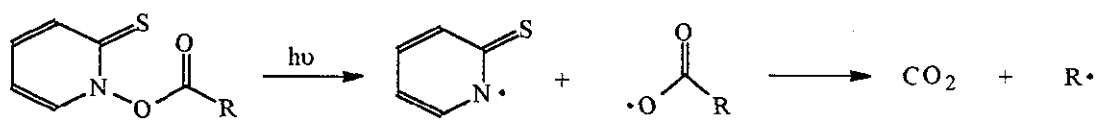
Scheme 28



1.4.5) Photolysis of *N*-Hydropyridine-2-thione (PTOC) Carbamates as Precursors for Aminyl Radicals

Recent work by Barton and co-workers has shown that alkyl radicals can be readily achieved through the photolysis of *N*-hydroxypyridine-2-thione esters (Barton's Esters).⁴⁷ Initial cleavage of the thiyl carbonyl bond leads to re-aromatisation of the pyridine molecule. Subsequent loss of carbon dioxide gives the required alkyl radical (Scheme 29).

Scheme 29

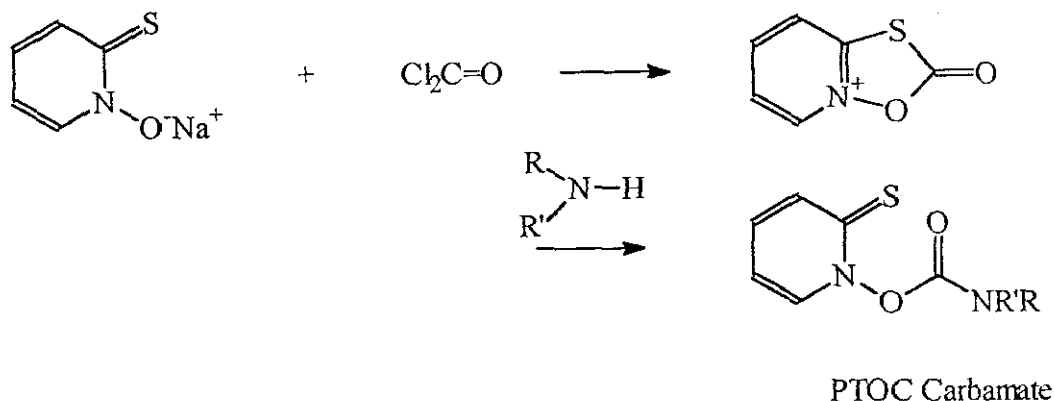


Martin Newcomb, formerly of Texas A&M University, now at Wayne State University, Detroit, has utilised this methodology to lead to the facile generation of aminyl radicals. By forming the analogous *N*-hydroxypyridine-2-thione carbamates (PTOC carbamates), a whole range of dialkyl aminyl radicals can be generated.⁴⁸ Reaction through the photolysis of the PTOC carbamate, leading eventually to the required aminyl radical, provides one of several routes using these compounds.

PTOC carbamates can be readily formed from one of two facile syntheses; the first involves the reaction of the sodium salt of *N*-hydroxypyridine-2-thione with phosgene.⁴⁷ Subsequent reaction with a dialkylamine gives the required aminyl radical precursor.⁴⁹ (Scheme 30). Alternatively, the PTOC carbamates can be formed from the

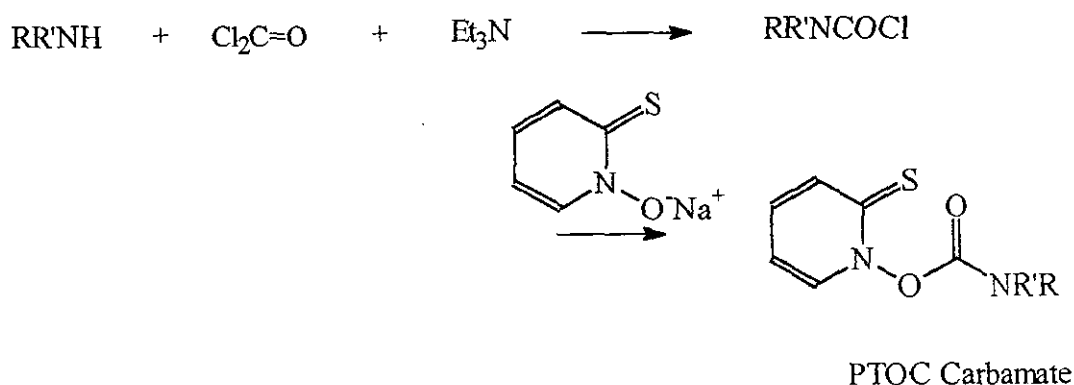
reaction of a dialkylamine with phosgene, followed by reaction with the sodium salt of *N*-hydroxypyridine-2-thione⁴⁹ (Scheme 31).

Scheme 30



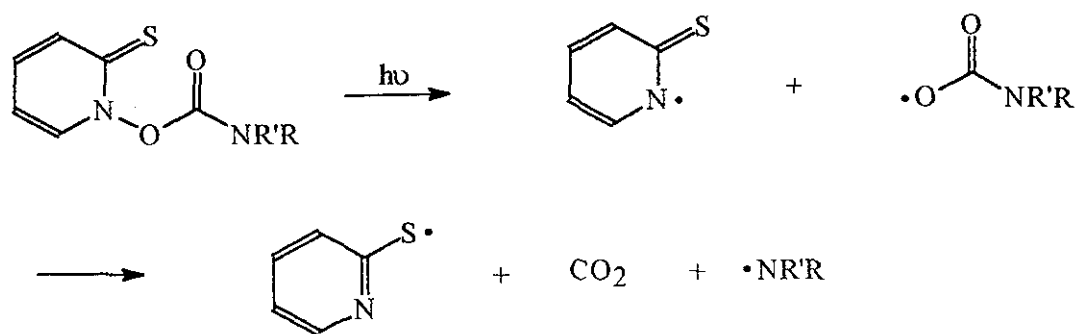
In general, the first method involves the more facile synthesis and is therefore the most readily used. The PTOC carbamates are yellow, photo-sensitive compounds which absorb visible light and are stable at room temperature only if kept in bottles shielded from light. They are also stable enough to be chromatographed on silica gel, or even through purification by re-crystallisation. Once formed, the weak N-O bond of the PTOC carbamates can be homolytically cleaved in photolysis using tungsten filament lamps to form initially short-lived carbamoyloxy radicals. These radicals readily decarboxylate to give the aminyl radicals (Scheme 32).

Scheme 31

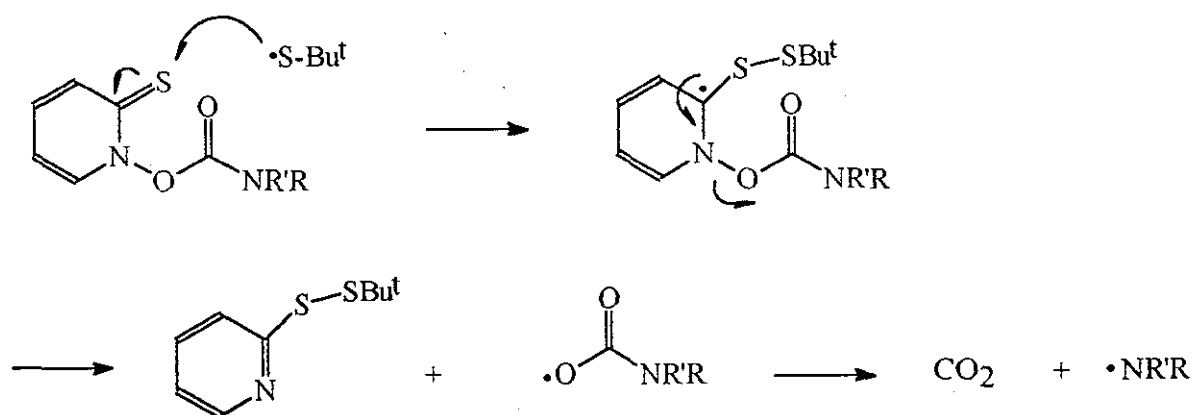


Once the reaction has been initiated through photolysis, a hydrogen atom donor, *e.g.*, *t*-butylthiol, can be added to propagate the radical sequence (Scheme 33).

Scheme 32

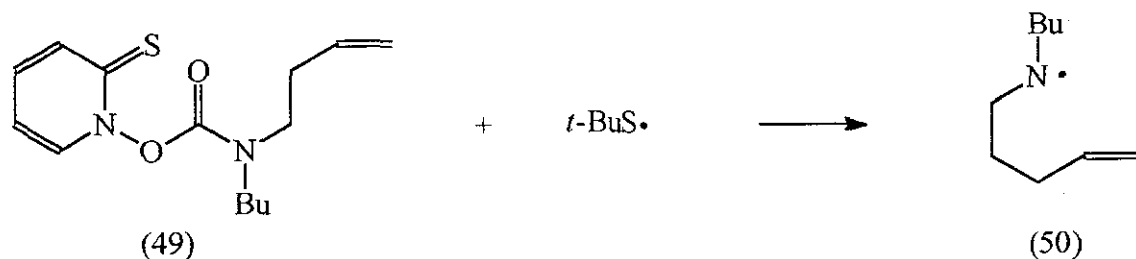


Scheme 33



The bulk of Newcomb's studies have concentrated on the formation and subsequent cyclisation of aminyl radicals to form nitrogen heterocycles. Initial work was concerned with the 5-*exo* trig cyclisation of aminyl radicals to form substituted pyrrolidines. For this purpose, PTOC carbamate (49) was formed and reacted under standard conditions to give aminyl radical (50) (Scheme 34).

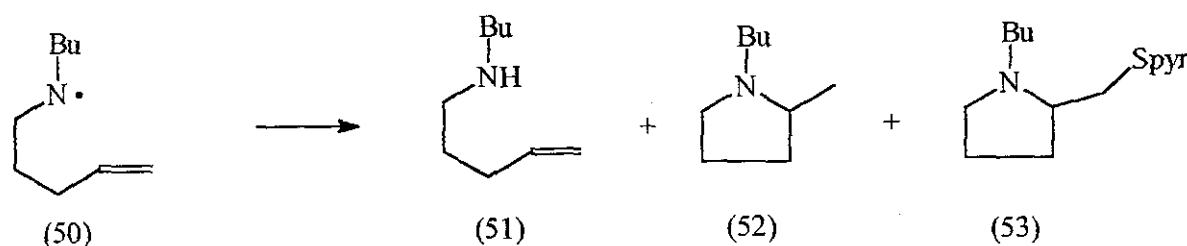
Scheme 34



The aminyl radical (50) once formed is free to react in one of three different ways: reduction with a hydrogen atom donor to give the acyclic amine (51); cyclisation to the pyrrolidine followed by reduction with a hydrogen atom donor (52); or cyclisation to the

pyrrolidine followed by reaction with the PTOC carbamate (49) in a chain propagating step (53) (Scheme 35).

Scheme 35



In general, the results have shown that, in the presence of a nucleophilic hydrogen atom donor such as tri-*n*-butyltin hydride, cyclisation to the pyrrolidine (52) occurs to a greater extent than in the presence of an electrophilic hydrogen atom donor, such as *t*-butylthiol. Condensation with a further molecule of PTOC carbamate (49) only becomes apparent in the absence of any good hydrogen atom donors (Table 4). These results would confirm that the aminyl radicals formed are nucleophilic, since reaction with an electrophilic hydrogen atom donor occurs more readily than with a nucleophilic hydrogen atom donor. Therefore, cyclisation occurs to a greater extent when tri-*n*-butyltin hydride is present, than when *t*-butylthiol is present.

Table 4. Products of Reactions of PTOC Carbamate in the Presence of Hydrogen Atom Donors

Donor	Conc. (M)	Relative (51)	Yield % (52)	(53)	Total Yield %
<i>t</i> -BuSH	0.02	100			80
Bu ₃ SnH	0.10	81	19		85
	0.104	73	27		65
	0.204	90	10		85
	0.25	90	10		90
	0.52	93	6		75
	0.76	95	5		75
	0.94	96	4		38
	1.02	100	<1		81
Ph ₃ SiH	0.11-1.12	37	63		74
Et ₃ SiH	0.1	67	<1	33	48
	0.5	67	<1	33	66
	1.0	45	7	48	76

Recent rate studies conducted by Newcomb on the above cyclisation reaction indicate that the reaction to form the pyrrolidine is reversible. By using laser flash methods²², it can be shown that the rate of cyclisation is roughly equivalent to the rate of ring-opening of the newly formed carbinyl radical, and that the rate of hydrogen abstraction from tri-*n*-butyltin hydride of the aminyl radical is similar to that of the carbinyl radical (see Section 1.3).

1.4.6) Cyclisation using aminium cation radicals

Assuming that aminyl radicals are nucleophilic, cyclisation onto the nucleophilic carbon of an olefin would appear to be unfavourable. This theory is borne out by the rate data (see Section 1.3), and the yields of cyclisation products when cyclisation onto an unactivated double bond is performed. In order to overcome this problem, Newcomb and co-workers formed the aminium cation radical, through protonation of the aminyl radical with a suitable acid. The aminium radical is electrophilic, and should be more inclined to cyclise onto a nucleophilic olefin. With this in mind, Newcomb repeated the cyclisation reaction with a trace of acetic acid.²³ Further experiments with other acid sources showed that the best conditions generally to involve addition of trifluoroacetic acid. Reaction of the PTOC carbamate (49) under various conditions gave various mixtures of the three amines (51), (52), or (53) (Table 5).

Table 5. Products from reactions of PTOC Carbamate in the presence of acids and *t*-BuSH

Solvent	Acid	Relative (51)	Yield % (52)	(53)	Total Yield %
benzene	CH ₃ CO ₂ H	97	2	1	91
THF	" "	94	4	3	99
CH ₃ CN	" "	49	36	15	98
benzene	CH ₂ (CO ₂ H) ₂	100	0	0	98
THF	" "	31	39	30	97
CH ₃ CN	" "	0	43	57	100
benzene	CF ₃ CO ₂ H	8	23	69	87
CH ₃ CN	" "	4	33	62	90

The electrophilic hydrogen atom donor *t*-butylthiol was used because its use led to lower yields of acyclic amine (51) and higher yields of the cyclic pyrrolizidine (52). An electrophilic source of hydrogen was used to minimise reaction between the hydrogen source and the strongly acidic uncyclised aminium radicals. The weakly nucleophilic carbon-centered radicals on (52) react rapidly with the electrophilic source of hydrogen. When the

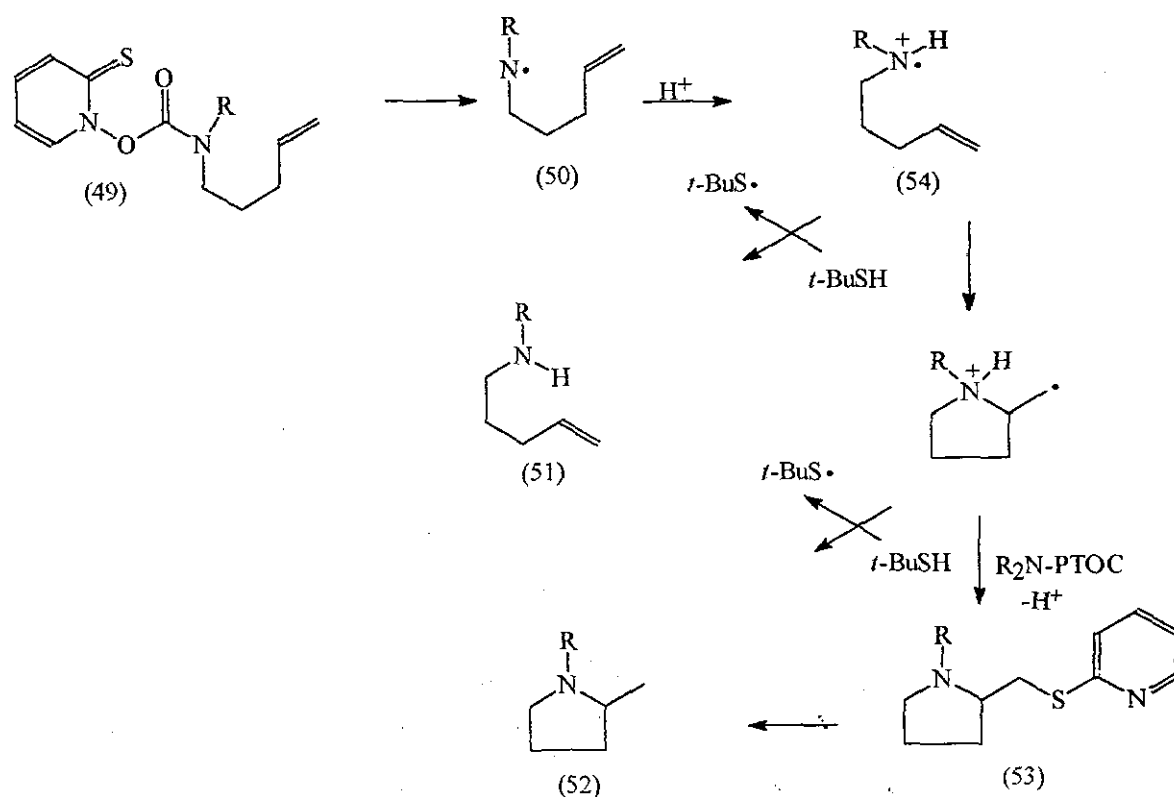
reaction was repeated in the absence of *t*-butylthiol, the self-condensation product became apparent (Table 6).

Table 6. Products from Reactions of PTOC Carbamate in the Presence of Acids

Solvent	Acid	Relative (51)	Yield % (52)	(53)	Total Yield %
benzene	CH ₃ CO ₂ H	19	0	81	69
CH ₃ CN	" "	15	1	84	69
benzene	CH ₂ (CO ₂ H) ₂	0	0	100	97
THF	" "	0	0	100	96
CH ₃ CN	" "	0	0	100	98
benzene	CF ₃ CO ₂ H	6	0	94	85

Later studies showed that a system containing acetonitrile as solvent and malonic acid as the proton source yielded the best results for aminium cation radical cyclisation reactions. The reactions were all initiated using a tungsten filament lamp and run at room temperature. Typically, the scheme for cyclisation of aminium cation radicals is as shown below (Scheme 36). This general method was found to be suitable for a wide range of cyclisations with secondary aminyl radicals.

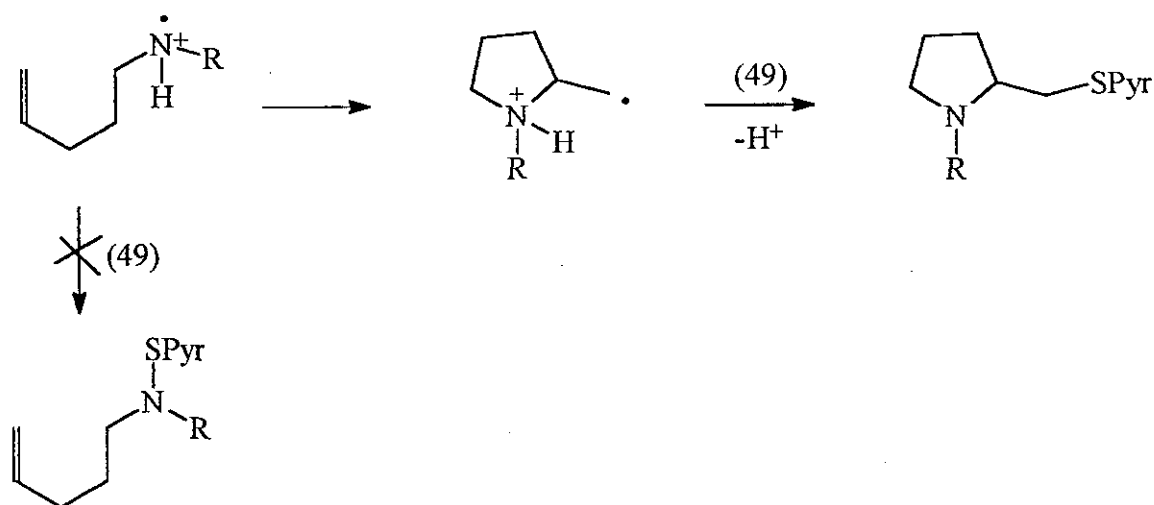
Scheme 36



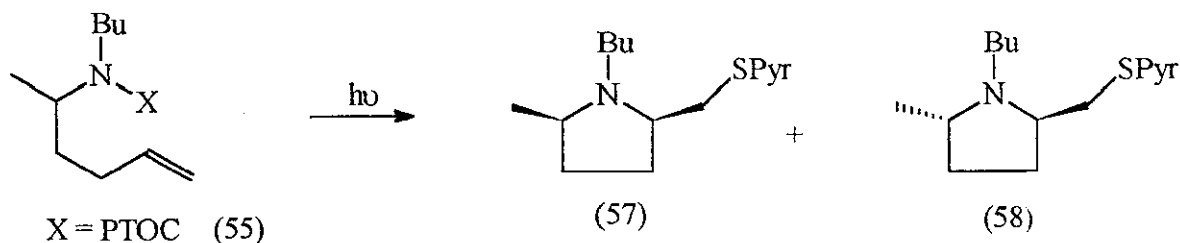
Extensive studies have shown that, when cyclisation was not too efficient in the presence of a hydrogen atom donor, the yields of cyclisation can be improved by the self trapping reaction with a further molecule of PTOC carbamate, with the reaction being performed in the absence of any hydrogen atom donor. This can be explained by noting that the PTOC carbamates readily react with the newly formed alkyl radical formed on cyclisation to the heterocycle, but not at all with the initially formed aminium cation radical⁴⁹ (Scheme 37).

The stereochemistry of the cyclisation reaction was investigated using the *N*-butyl-2-methyl-4-penten-aminium cation radical (55).²⁶ Reaction of the PTOC carbamate (56) in benzene in the presence of *t*-butylthiol and trifluoroacetic acid at 25°C gave an isomeric mixture of the expected pyrrolidines in the ratio 3:1 of *trans* to *cis* (57) and (58). The predominance of the *trans* product is in agreement with transition state models for radical cyclisations (Scheme 38).^{50, 51}

Scheme 37



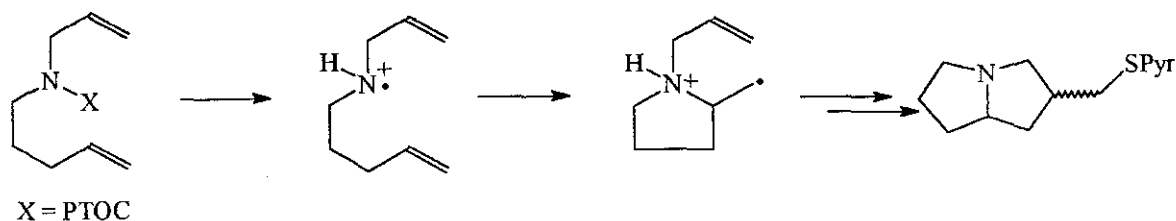
Scheme 38



1.4.7) Syntheses of Pyrrolizidines

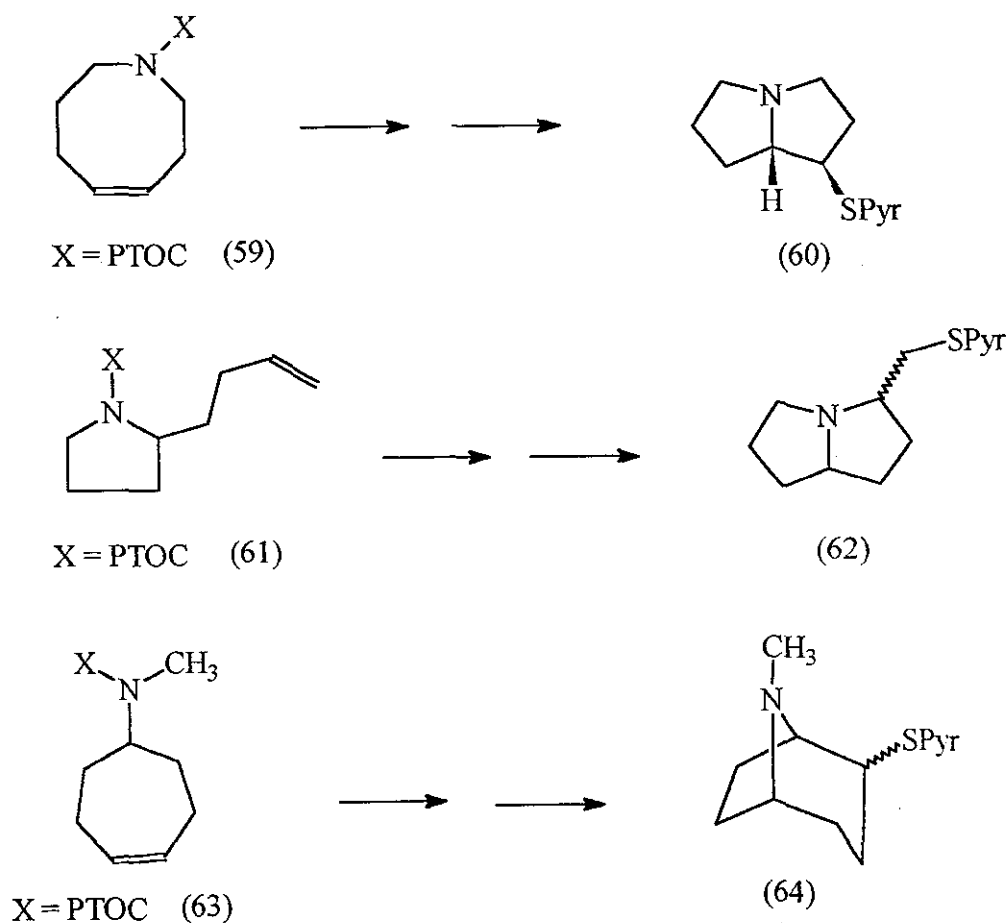
Pyrrolizidines can be easily prepared by placing an allyl group on the amine prior to cyclisation. The initially formed alkyl radical can now be intramolecularly trapped by the allyl group in a tandem reaction to form a range of pyrrolizidines (Scheme 39).

Scheme 39



Other pyrrolizidines could be formed by altering the original PTOT carbamate. Reaction of PTOT carbamate (59) under cyclisation conditions gave the pyrrolizidine (60); likewise, reaction of (61) under similar conditions gave a good yield of (62) (Scheme 40). This methodology has also been adapted to the synthesis of aza-bridged bicycles. Formation⁵² and subsequent reaction of PTOT carbamate (63) under standard cyclisation conditions gave good yields of the tropane (64).⁵³

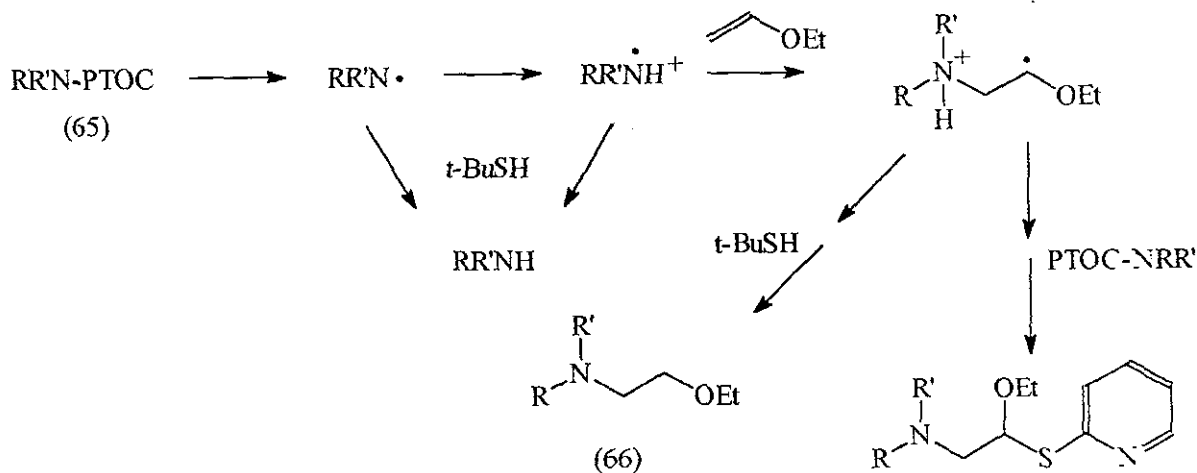
Scheme 40



By careful manipulation of the reaction conditions, intermolecular addition and cyclisation reactions can be accomplished.⁵⁴ The first stage was to successfully react PTOT carbamate (65) with ethyl vinyl ether. The strongly nucleophilic alkene reacts rapidly with

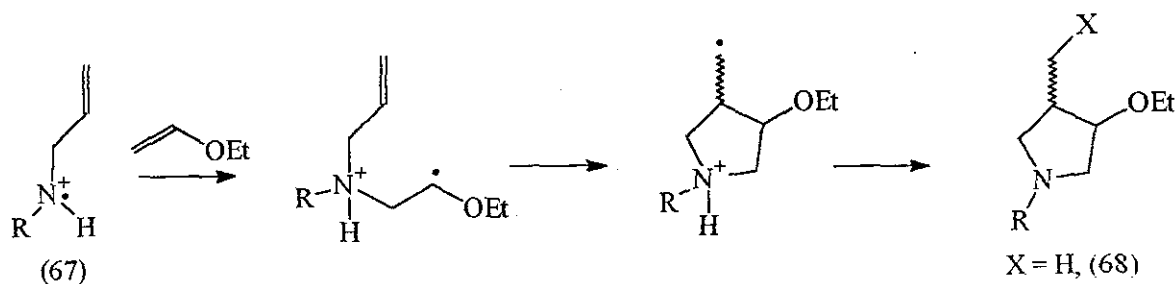
the electrophilic aminium radical intermediate. Reaction using malonic acid and *t*-butylthiol in acetonitrile with an excess of ethyl vinyl ether gave the best results of the addition product (66) (Scheme 41).

Scheme 41



Reacting *N*-allylamminium cation radical (67) with ethyl vinyl ether as solvent lead to a [3 + 2]cycloaddition giving the substituted pyrrolidine (68). Clearly, this sequence could lead to be very important when planning syntheses (Scheme 42).

Scheme 42

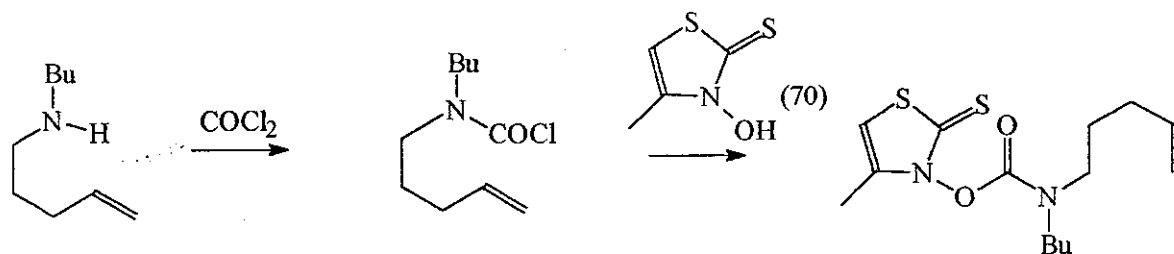


1.4.8) TTOC Carbamates as Precursors of Aminyl Radicals

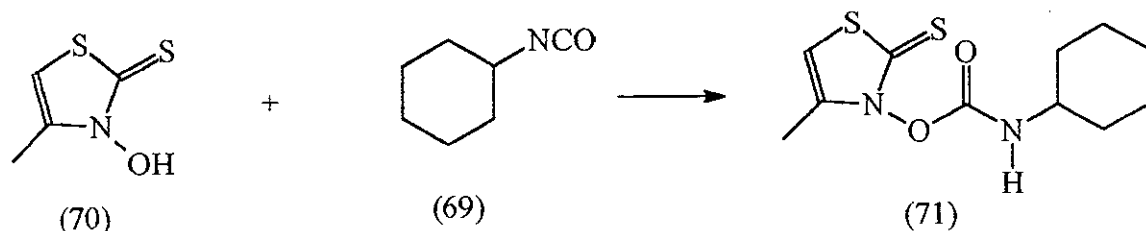
Although PTOC carbamates have proved to be very useful precursors of dialkylaminyl radicals,⁴⁸ the equivalent PTOC carbamate precursors to primary aminyl radicals are too unstable to use in radical reactions. TTOC carbamates⁵⁵ [3-hydroxy-4-methylthiazole-2(3H)-thione carbamates] can be readily formed by reaction of an amine with phosgene, followed by reaction with 3-hydroxy-4-methylthiazole-2(3H)-thione (70) (Scheme 43).

The reaction of cyclohexyl isocyanate (69) with thione (70) gave the model TTOC carbamate (71). When this carbamate was reacted in acetonitrile in the presence of malonic acid and *t*-butylthiol, cyclohexylamine was produced in good yield (Scheme 44).

Scheme 43

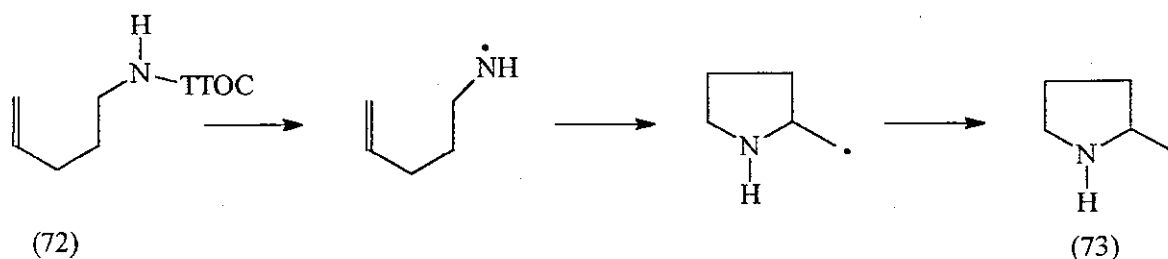


Scheme 44



This result was used as evidence that a monoalkylamminium radical cation was generated and reduced with the hydrogen atom donor. The alkenyl TTOC carbamate (72) precursor was also formed and reacted under standard cyclisation conditions. As expected, a good yield of the pyrrolidine (73) was obtained (Scheme 45).

Scheme 45

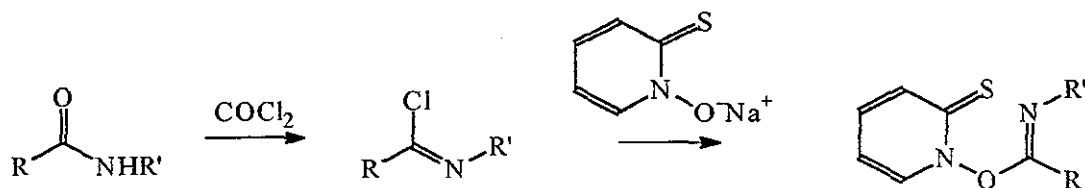


These results show that methods are now available to form both monoalkyl and dialkyl aminyl and aminium cation radicals, and that these can be readily cyclised to form a wide range of *N*-containing heterocycles.

1.4.9) Generation and Cyclisation of Amidyl Radicals

Amidyl radicals have already been formed from Chow and co-workers work on *N*-amidonitrosamides,⁵⁶ and from *N*-amidochloramides.⁵⁷ *N*-Hydroxypyridine-2-thione imidate esters, formed by the reaction of secondary amides with phosgene in benzene/toluene followed by subsequent reaction with *N*-hydroxypyridine-2-thione sodium salt in ether (Scheme 46), provide possibly a more facile route to the generation of amidyl radicals.⁵⁸

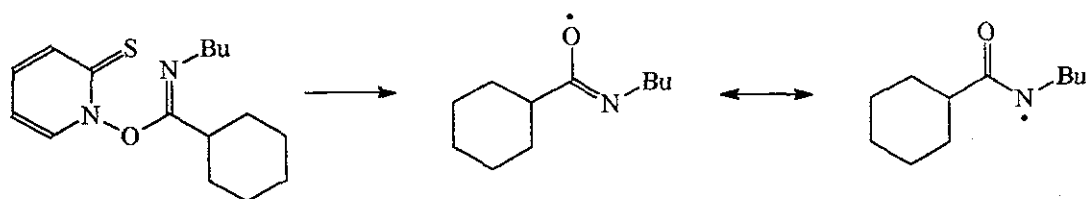
Scheme 46



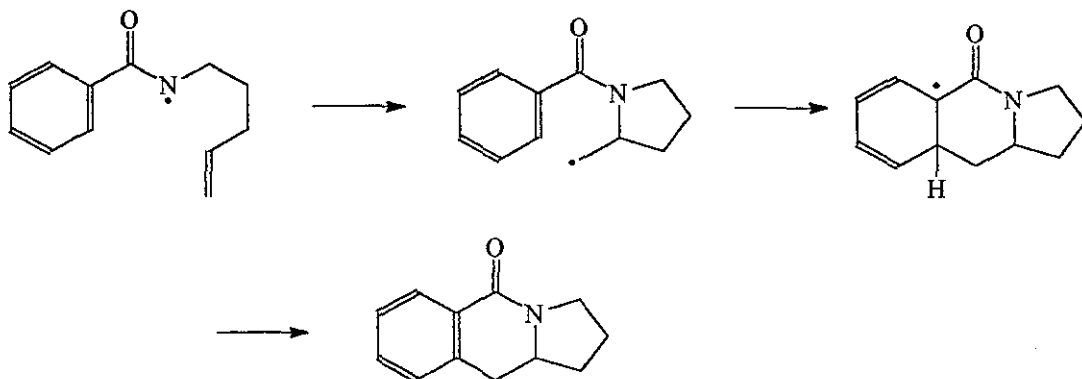
Upon irradiation with visible light in the presence of *t*-butylthiol, the weak N-O bond was cleaved, in a similar sequence to that of PTOC carbamates, to give eventually the amidyl radical (Scheme 47).

The amidyl radicals have been shown to cyclise to give substituted pyrrolidines (74), and have also been reacted in a tandem cyclisation to give tricyclic *N*-containing heterocycles (Scheme 48).

Scheme 47



Scheme 48



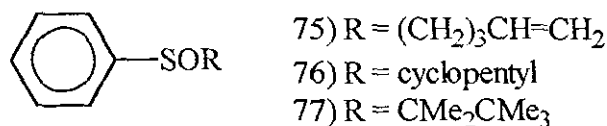
Clearly, the use of carbamates and their analogues have proven to be very versatile and consequently a number of natural product analogues have been synthesised using this method.

1.5) Functional Groups Abstracted by Tri-*n*-butyltin Radicals

The use of tri-*n*-butyltin hydride is probably the most common and favoured method to generate radicals, especially carbon-centered radicals. Tin is a polarisable (soft) metal and prefers to abstract other polarisable groups, *e.g.* iodine is more polarisable than bromine (*i.e.*

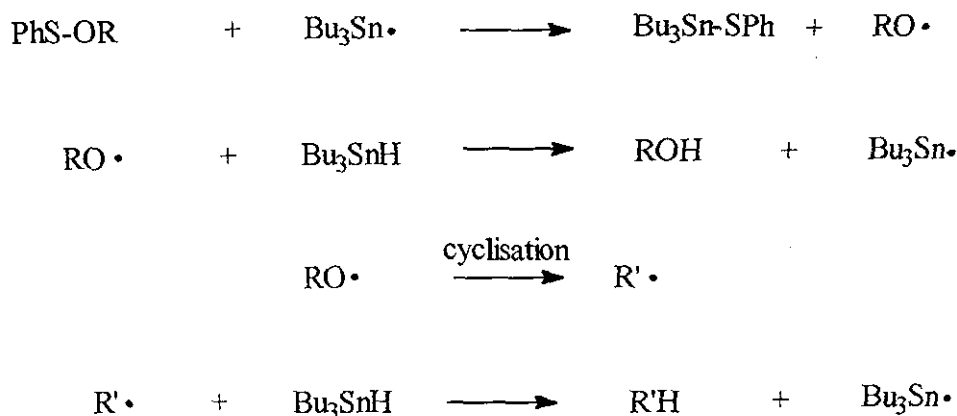
it is softer) which is more polarisable than chlorine *etc.* Other groups that fall into this category include oxythiones and PTOC carbamates (see section 1.4.5). Sulfur and selenium are also "soft" metals that will combine with tin in a radical cleavage reaction, though the action of tin hydride on the C-S bond is a rather slow method for the generation of carbinyl radicals. One of the aims of the project was to use sulfenamides (R_2N-SPh) as precursors for aminyl radicals. The radicals would hopefully be generated using tri-*n*-butyltin hydride. Therefore it is instructive to look at the use of -SPh as a leaving group in radical S_H2 abstraction reactions.

The recent work of Beckwith⁵⁹ shows that alkoxy radicals can be generated from the action of tri-*n*-butyltin hydride on *O*-alkylbenzenesulfenates. The *O*-alkylbenzenesulfenates (75-77) were prepared in 60-70% yield by the addition of benzenesulfonyl chloride to the appropriate lithium alkoxide in tetrahydrofuran.⁶⁰



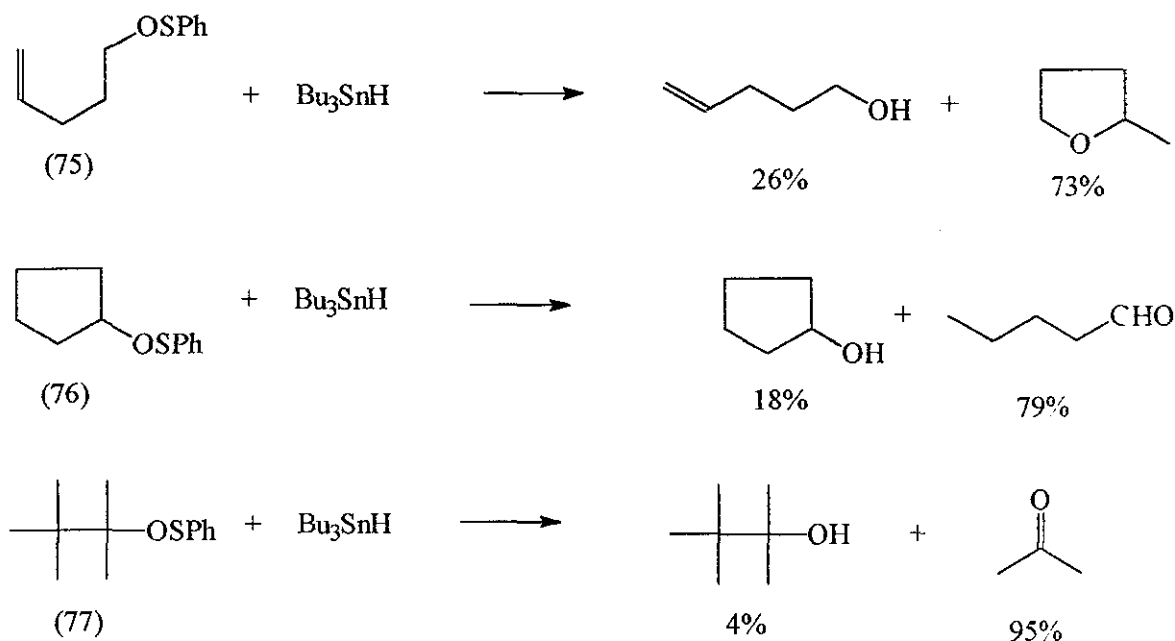
The reaction of these substrates with tri-*n*-butyltin hydride in the presence of AIBN as radical initiator was believed to follow the radical pathway as shown in Scheme 49.

Scheme 49

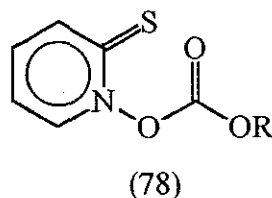


The products obtained from these reactions were: pent-4-en-1-ol (26%) and 2-methyltetrahydrofuran (73%) from (75); cyclopentanol (18%) and pentanal (79%) from (76); and 1,1,2,2-tetramethylpropan-1-ol (4%) and acetone (95%) from (77) (Scheme 50). The formation of all of these products cannot be explained by any ionic mechanism, and so the above radical pathway would seem to be the true mechanism of this type of reaction.

Scheme 50



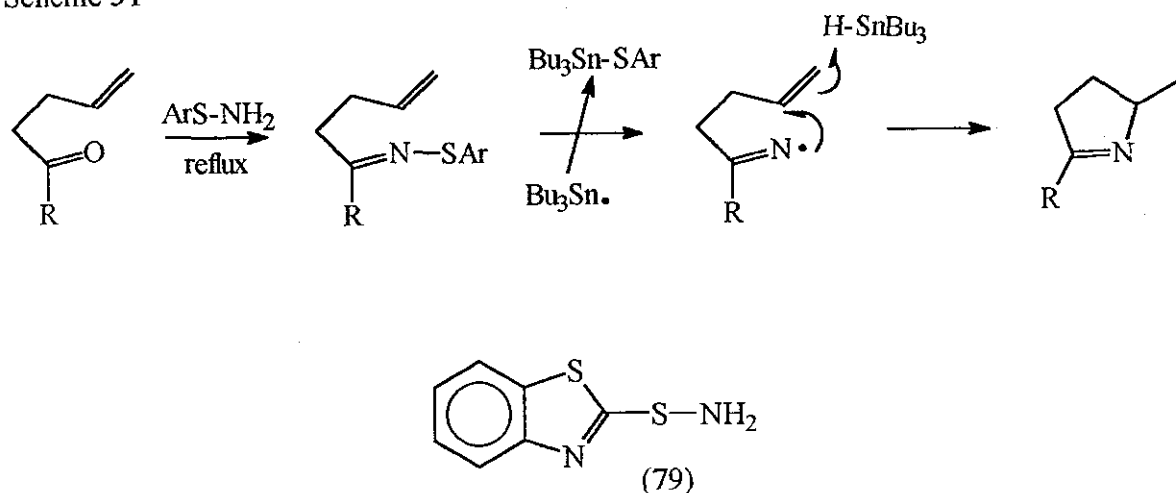
Finally, in comparison to the use of *N*-alkoxy-pyridine-2-thiones (78)⁵⁰ for the formation of alkoxy radicals, it would appear that primary, secondary and tertiary *O*-alkylbenzenesulfenates can all be readily prepared in reasonable yields. The corresponding *N*-alkoxy-pyridine-2-thiones can only be prepared in poor or modest yields, even under carefully selected and controlled conditions.⁶¹ Therefore, a clear advantage exists for the use of *O*-alkylbenzenesulfenates in synthesis.



Zard has investigated the use of -SPh as a leaving group to form iminyl radicals using sulfonylimines.⁶² Upon reaction with tri-*n*-butyltin hydride and AIBN as initiator, the sulfonylimines form synthetically useful iminyl radicals. The sulfonylimines themselves are readily prepared by a number of methods,⁶³ usually from the corresponding carbonyl derivative. Once formed, they are stable to purification by chromatography or recrystallisation, and react to form the iminyl radical (Scheme 51).

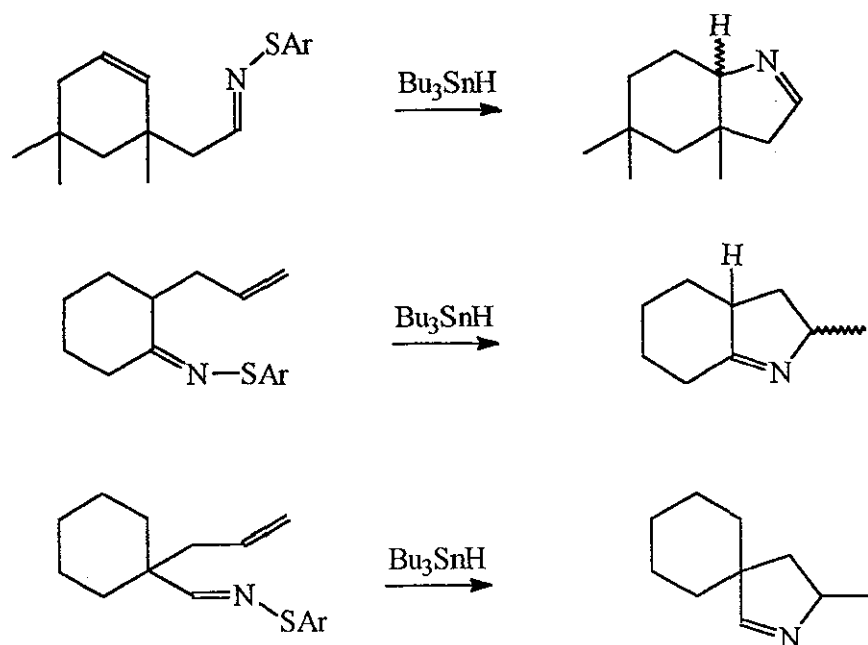
The sulfonylimines originally studied were prepared from the reaction between the corresponding carbonyl derivatives, and sulfenamide (79) which is a stable crystalline solid.⁶⁴

Scheme 51



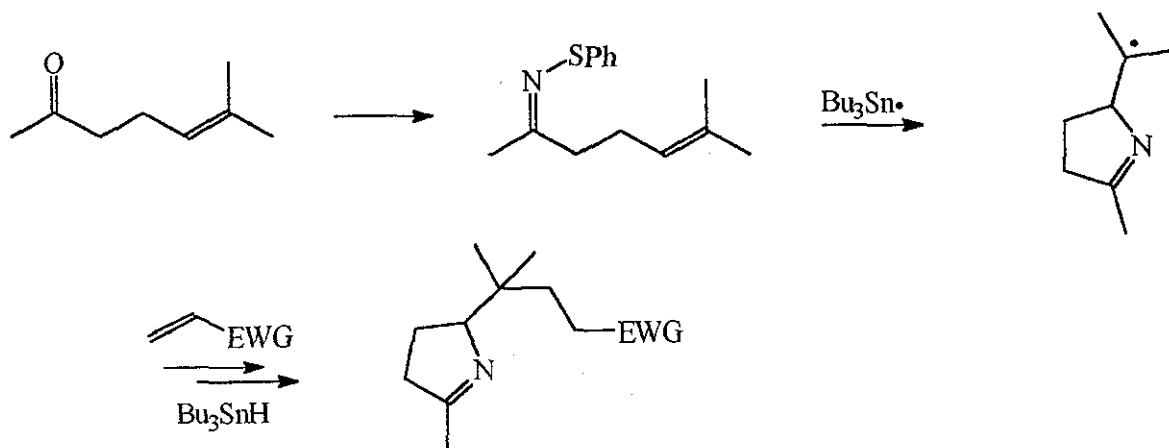
The sulfenylimines are reacted with tri-*n*-butyltin hydride and AIBN in refluxing cyclohexane. It is necessary to add the tin hydride slowly over a period of 5 hours to ensure that no reduction of the iminyl radical by tin hydride occurs. Using this method, a number of pyrrolidines, bicyclic pyrrolidines and spiro pyrrolidines were readily formed (Scheme 52). All of the following cyclised products were obtained predominantly as the *trans*, 5-*exo*-cyclised products, agreeing with the rules for radical cyclisation reactions.

Scheme 52



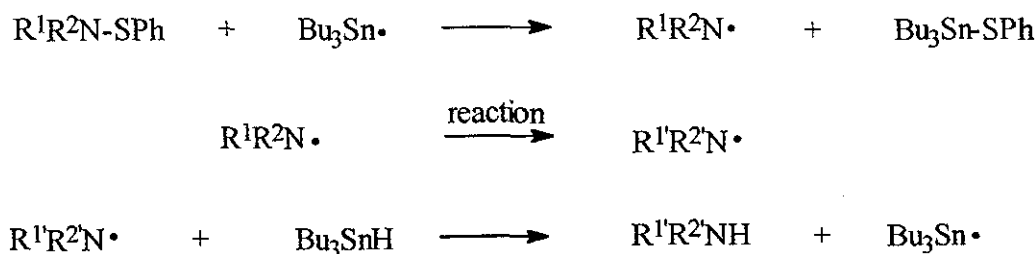
Recently, Zard⁶⁵ has also mirrored Newcombs work by performing radical cyclisation followed by intermolecular trapping with an electron poor olefin using iminyl radicals (Scheme 53). Again, these reactions were very successful, leading to great advances for the use of iminyl radicals in organic synthesis.

Scheme 53



Both of the above examples show that radicals can be easily prepared by the action of tri-*n*-butyltin hydride on a SPh group attached to a heteroatom. It would therefore be reasonable to suggest that aminyl radicals can be formed from the action of tin hydride on sulfenamides in the following radical pathway (Scheme 54).

Scheme 54



1.6) The Properties and Reactions of Sulfenamides

Sulfenamides are defined as compounds that contain trivalent nitrogen attached to divalent sulfur. They are derived from sulfinic acids (RSOH), as sulfonamides and sulfinamides are derived from sulfonic and sulfinic acids respectively. Sulfenamides have long been known, both as herbicides in the agrochemical industries,⁶⁶ and as accelerators for the vulcanisation of rubber.⁶⁷ They are also used for treating the after-effects of radiation sickness,⁶⁸ as polymerisation initiators,⁶⁹ and even in rocket technology as spontaneously igniting fuels.⁷⁰

Sulfenamides and their derivatives exist as liquids or crystalline compounds with clearly defined melting points. They have an unpleasant smell and are readily soluble in non-polar solvents (benzene, chloroform, dichloromethane or hexane). They are also very readily hydrolysed by aqueous acids. However, they are relatively stable in cold aqueous and basic aqueous media.

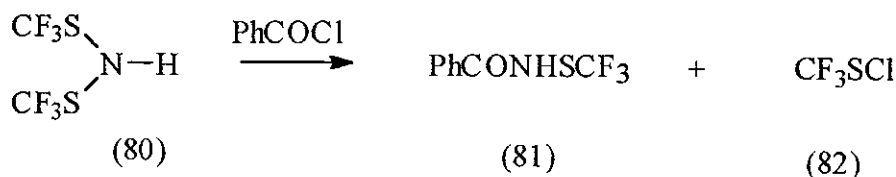
Because of the polarisation of the N-S bond, sulfenamides can be attacked by nucleophiles at the sulfur atom, and by electrophiles at the nitrogen atom. They can be

oxidised at nitrogen or sulfur, and they can be reductively cleaved. It is intended to summarise the reactions of sulfenamides into two main types; (1) reaction with electrophiles, and (2) reaction with nucleophiles.

1.6.1) Reaction of Sulfenamides with Electrophiles

The reaction of sulfenamides with electrophiles involves the coordination of the electrophile with nitrogen, and the subsequent nucleophilic attack on sulfur. For example, disulfenylamine (80) reacts with benzoyl chloride to give the sulfenamide (81) and the sulfenyl chloride (82)⁷¹ (Scheme 55).

Scheme 55



Similarly, acylation of alkene- and arenesulfenamides with acetic anhydride yields disulfenylamines and acetamides⁷² (Scheme 56).

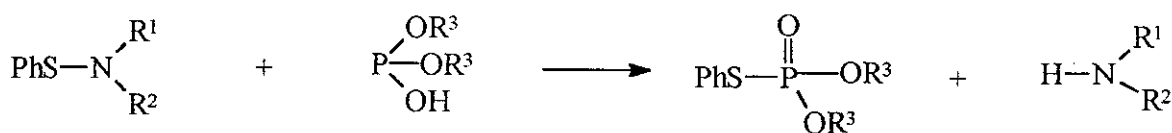
Scheme 56



1.6.2) Reaction of Sulfenamides with Nucleophiles

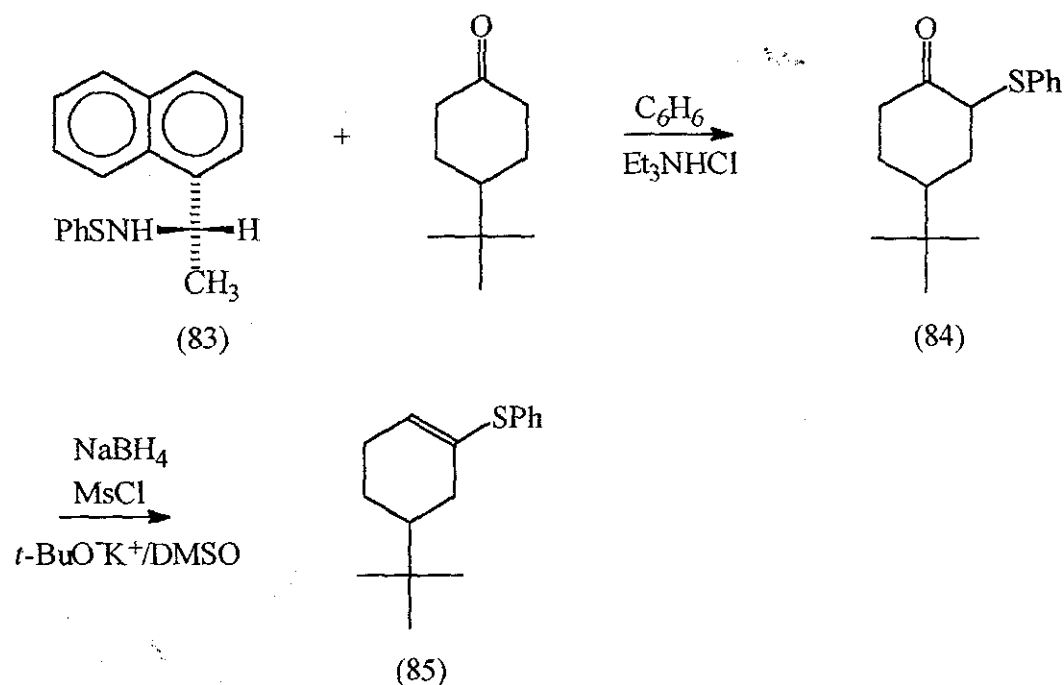
In reactions with nucleophiles, the sulfenamide bond is usually attacked at the more electropositive sulfur. In the below scheme (Scheme 57), phenylsulfenamides are attacked at sulfur by dialkyl and trialkyl phosphites to form phosphorothiolates.⁷³

Scheme 57



Sulfenamides react with active methylene compounds such as malononitrile, acetylacetone, ethyl acetoacetate, enamines and ketones to give sulfides. Asymmetric sulfenylation has also been achieved⁷⁴ with the reaction of (S)-(-)-*N*-(phenylthio)- α -naphthylamine (83) with 4-*t*-butylcyclohexanone in the presence of a catalytic amount of triethylamine hydrochloride to give a diastereomeric mixture of the sulfide (84). Reduction of the ketone, followed by mesylation and elimination gave the alkene (85), in which the S absolute configuration was dominant (Scheme 58).

Scheme 58



As has been shown, the configuration of sulfenamides allows for a whole range of reactions to be performed. However, the homolytic radical cleavage of the S-N bond has not until now been investigated. The purpose of this project is to show that the sulfenamide bond can be cleaved using tri-*n*-butyltin hydride, and that the resulting aminyl radical be made to react to yield a variety of nitrogen-containing heterocycles. Below, the findings of this work shall be discussed, with an insight into the reactivity of aminyl radicals formed from the reaction of sulfenamides with tri-*n*-butyltin hydride.

Chapter 2. Synthesis of Sulfenamides.

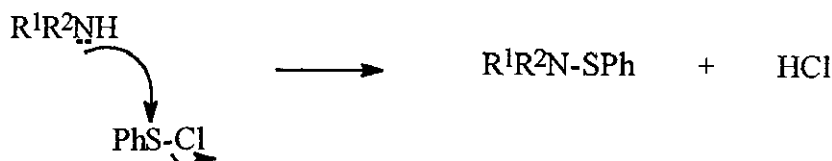
2.1) Traditional Methods of Preparing Sulfenamides

The first part of the project was to develop facile methods for the synthesis of sulfenamides for use in the generation of aminyl radicals. The chapter describes the synthesis of the first group of sulfenamide precursors used in the studies to provide evidence for the intermediacy of aminyl radicals and the initial studies of aminyl radical cyclisation. As has already been noted (see Section 1.8), sulfenamides have long been known in the chemical literature, and over the years several methods have been found to synthesise them. A brief summary of some of the methods available are detailed below.

2.1.1) Sulfenyl Halides as Precursors to Sulfenamides

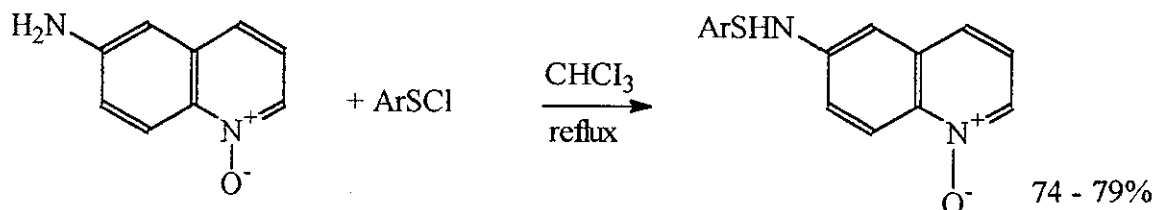
Perhaps the most common method for the preparation of sulfenamides involves the use of primary or secondary amines with sulfenyl halides.^{75, 76, 77} The reaction proceeds via nucleophilic attack of the amine on the sulfenyl halide (Scheme 59). When an acid acceptor such as excess amine, triethylamine or pyridine⁷⁸ is employed in the reaction, the acid initially formed can be neutralised.

Scheme 59



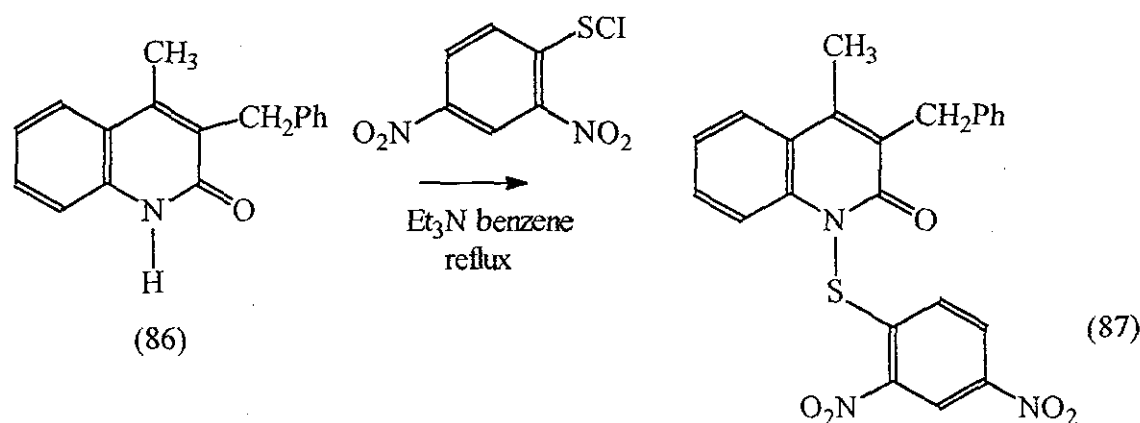
The yields for this type of reaction are usually high, especially for those reactions where an arenesulfenyl halide reacts with aliphatic amines. The reaction of arenesulfenyl halides with aromatic amines can also be achieved in high yields. For example, yields of 74-79% are recorded for the reaction of 6-aminoquinoline-*N*-oxide with 2-nitro- and 2,4-dinitrobenzenesulfenyl chloride (Scheme 60).⁷⁹

Scheme 60



Similarly, 3-benzyl-4-methylcarbostyryl (86) reacts with 2,4-dinitrobenzenesulfenyl chloride and triethylamine to form the sulfenamide (87) (Scheme 61).⁸⁰

Scheme 61



Although it is predominantly arenesulfonyl chlorides that are used in this type of reaction, examples show that sulfonyl bromides can be used to form sulfenamides. For example, organophosphorus sulfenamides can be prepared from the action of secondary amines on sulfonyl bromides (Scheme 62).⁸¹

Scheme 62



There are, however, no examples given of sulfenamides prepared from the reaction of sulfonyl fluorides or sulfonyl iodides with amines. It is assumed that whereas the sulfonyl fluorides will so stable as to be unreactive with amines, the sulfonyl iodides will be far too unstable for this type of reaction.

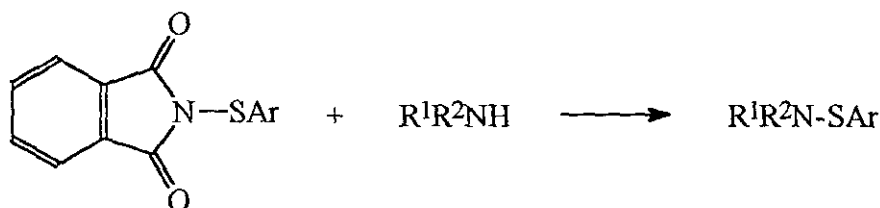
Due to their reactivity, sulfonyl halides will react with hydroxyl groups, active methylene groups and multiple bonds. Therefore, sulfenamides bearing these functional groups cannot on the whole be prepared using this method and a less active form of sulfur must be employed.

2.1.2) Thiophthalimides as Precursors to Sulfenamides

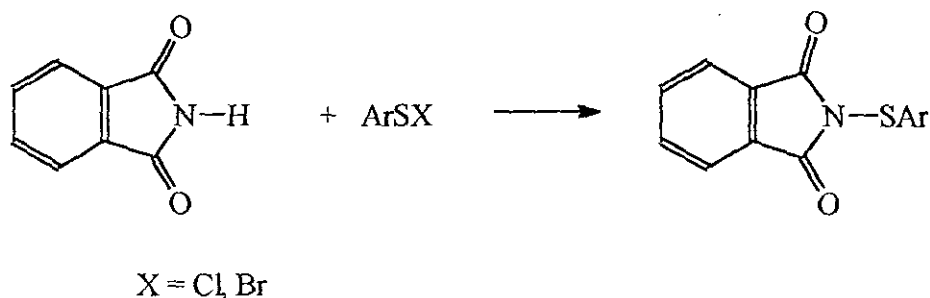
Thiophthalimides have been shown to undergo displacement of phthalimide when treated with a variety of nucleophiles. When the nucleophiles in question are primary or secondary amines, a wide range of sulfenamides can be generated (Scheme 63).⁸²

Thiophthalimides themselves can be readily prepared from the reaction of phthalimide with sulfonyl halides (Scheme 64).⁸³

Scheme 63



Scheme 64



The main advantage of this method over the use of sulfenyl halides on amines is the mild conditions employed. Generally, reaction can be achieved merely by stirring the thiophthalimide with an equivalent of the amine in a non-polar solvent, either at room temperature or under reflux conditions. The phthalimide by-product precipitates out of the solvent to leave a crude solution of the required sulfenamide. In this way, a range of alkyl- and aryl sulfenamides can be readily prepared in high yields (Table 7).

Table 7. Products Derived from the Reaction of Amines with Thiophthalimides

Thiophthalimide	Amine	Solvent	Yield (%)
$\text{C}_6\text{H}_5\text{CH}_2\text{S-PHL}$	morpholine	benzene	90
EtS-PHL	<i>N</i> -methyl- <i>n</i> -butylamine	diethyl ether	91
<i>n</i> -BuS-PHL	piperidine	diethyl ether	100
$\text{C}_6\text{H}_5\text{CH}_2\text{S-PHL}$	cyclohexylamine	dichloromethane	87
$\text{C}_6\text{H}_5\text{S-PHL}$	aniline	ethanol	82
EtS-PHL	piperazine	benzene	90
$\text{C}_6\text{H}_5\text{CH}_2\text{S-PHL}$	piperazine	benzene	81
<i>i</i> -PrS-PHL	benzylamine	diethyl ether	73

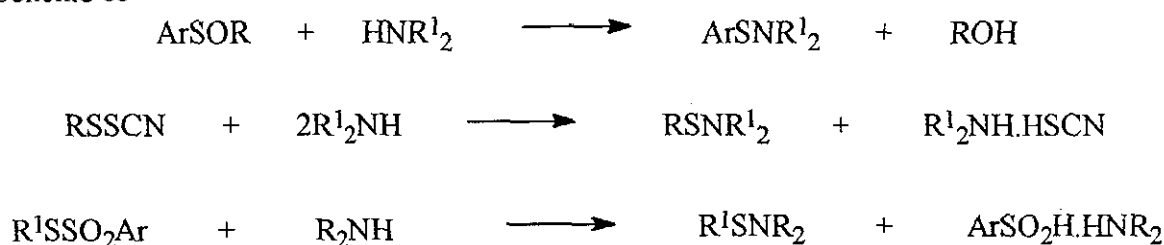
PHL = phthalimide

2.1.3) Arenesulfenate Esters, Sulfenyl Thiocyanates, and Thiosulfonates as Precursors of Sulfenamides

Arenesulfenate esters react with amines in the same manner as sulfenyl halides to yield sulfenamides, though reaction times are longer.⁸⁴ Also in reaction with primary

amines, the amine must be present in excess in order to prevent the formation of diaryl sulfenamides $(\text{ArS})_2\text{NR}$. Similarly, moderate yields of *N,N*-dialkylalkanesulfenamides have been achieved from the addition of alkanesulfonyl thiocyanates to dialkylamines⁸⁵. A few examples are available where sulfenamides have been prepared from primary and secondary amines and thiosulfonates.⁸⁶ However, in the case of aromatic amines, only the 2-nitrophenyl benzenethiosulfonate has been used successfully (Scheme 65).

Scheme 65



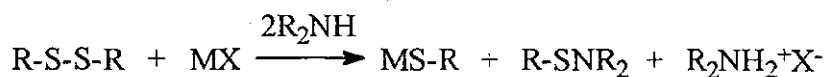
2.1.4) Disulfides as Precursors of Sulfenamides

Davis and co-workers⁸⁷ have developed an effective one-step synthesis of sulfenamides from disulfides and amines in the presence of silver or mercuric salts (Scheme 66). It is believed that the mechanism involves the complexation of the metal ion with one sulfur atom in the disulfide, followed by nucleophilic attack on the other sulfur atom by the amine. Unlike sulfonyl halides, the disulfide reaction can be used with amines containing hydroxyl groups and carbon-carbon double bonds. However, an excess of the amine is required which means that this reaction is limited to readily available amines. The best yields of sulfenamides are formed when aromatic, as opposed to aliphatic disulfides, are used (Table 8).

Table 8. The Generation of Sulfenamides from Disulfides

Disulfide	Amine	Conditions	Yield (%)
<i>p</i> -tolyl	piperidine	$\text{AgNO}_3\text{-MeOH}$	60
phenyl	allylamine	" "	88
"	aniline	" "	75-80
4-chlorophenyl	aniline	" "	75
3-nitrophenyl	ethylamine	" "	90
2-benzothiazoyl	isopropylamine	" "	90
methyl	piperidine	AgOAc-EtOAc	43
ethyl	piperidine	" "	30
isopropyl	piperidine	" "	45

Scheme 66



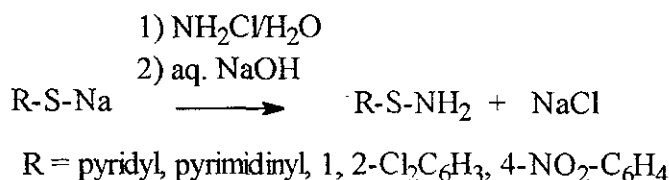
R = alkyl, aryl

MX = AgNO₃, AgOAc, HgCl₂

2.1.5) Thiols as Precursors of Sulfenamides

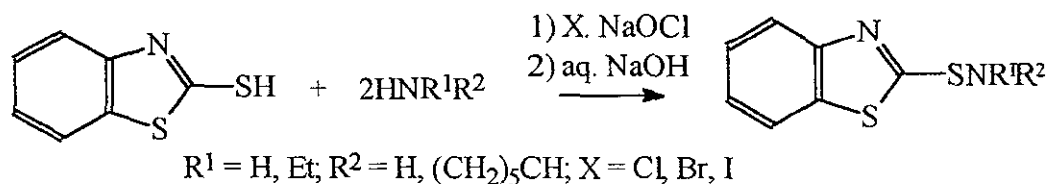
Sulfenamides with a free amino group are obtained in yields of up to 50% when mercaptides are reacted with chloramines (Scheme 67).⁸⁸

Scheme 67



Sulfenamides can also be generated from the reaction of aromatic mercaptans with ammonia, or with primary or secondary amines in the presence of an oxidising agent, such as hypochlorites, halogens or potassium ferricyanide in aqueous solution (Scheme 68).⁸⁹ This method is similar to the chloramine route since mercaptans react with chlorine or hypochlorite with formation of sulfenyl chlorides and chloramines, following which the former will interact with the amines and the latter with the mercaptans. The main disadvantage of this reaction is the oxidation of the thiol to form the corresponding disulfide. In extreme cases, the only product that can be isolated from this reaction is the equivalent disulfide.

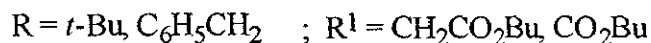
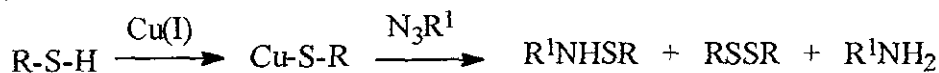
Scheme 68



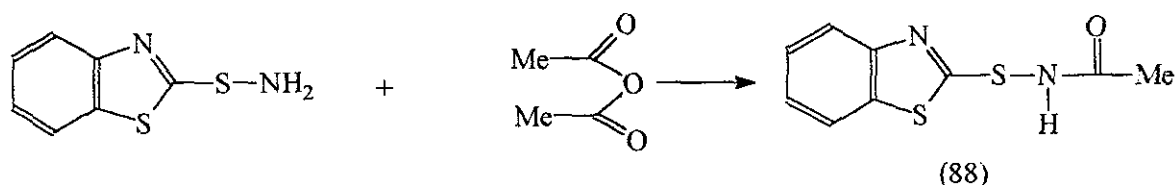
2.1.6) Other Methods of Sulfenamide Formation

Sulfenamides have also been generated from the amination of mercaptides with azides (Scheme 69). In this way, sulfenamides have been formed from the treatment of *t*-butyl or benzyl mercaptan with butyl azidoacetate or azidoformate in the presence of cuprous oxide or cuprous chloride.⁹⁰

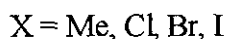
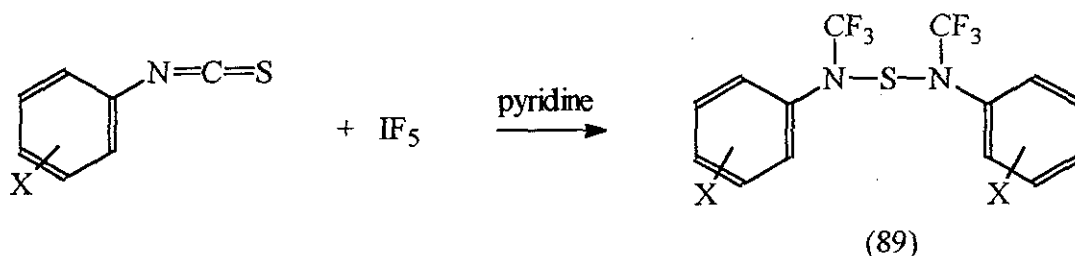
Scheme 69



2-Benzothiazoylsulfenamides have been prepared from the acylation of sulfenamides with free amino groups.⁹¹ Sulfenamide (88) was prepared using this method in the presence of sodium acetate in 30% yield.



Finally, iodine pentafluoride has been shown to react with phenyl thiocyanates in dichloromethane to yield sulfenamides, in this example leading to the formation of thiobis[*N*-(*p*-chlorophenyl)-*N*-(trifluoromethyl)amine] (89) in 94% yield.⁹²



2.2) Synthesis of Sulfenamides

In collaboration with Dr R Marmon, three of the above methods for the generation of sulfenamides were investigated in order to determine the most efficient method of forming the precursors for our studies into the generation of aminyl radicals. Below it is intended to detail each method tried, with examples of the sulfenamides formed in order to demonstrate the various advantages and disadvantages of each method.

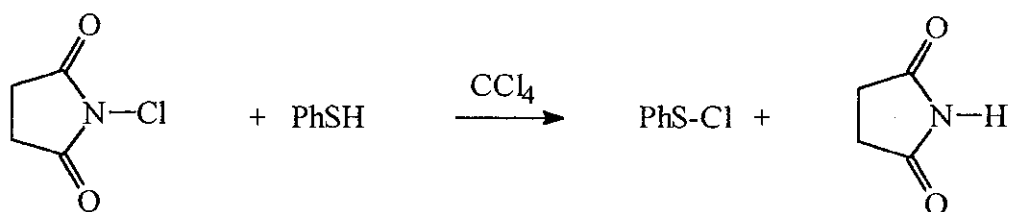
2.2.1) Arenesulfenyl Chlorides as Precursors to Sulfenamides

The use of sulfenyl chlorides as precursors to sulfenamides has been fully investigated and found to be a reliable method for the generation of sulfenamides (see Section 2.1.1). It was decided for the purpose of this project to concentrate on the aromatic sulfenyl chlorides as it was considered that these would lead to the more stable

sulfenamides. Aromatic sulfenyl chlorides themselves tend to be coloured (usually red) and unpleasant smelling compounds which are readily hydrolysed to the appropriate disulfide. In spite of these disadvantages, three methods for the formation of aromatic sulfenyl chlorides were investigated.

The first method was researched prior to the commencement of this research project and involved the action of *N*-chlorosuccinimide on benzenethiol in the presence of carbon tetrachloride (Scheme 70).⁹³ This method, although very easy in theory to perform, led to large amounts of diphenyl disulfide impurity. The impurity was present to such an extent that it was not feasible to attempt to separate the small amount of benzenesulfenyl chloride present. It was decided to abandon this method for the formation of benzenesulfenyl chloride and it was subsequently not investigated in this research project.

Scheme 70

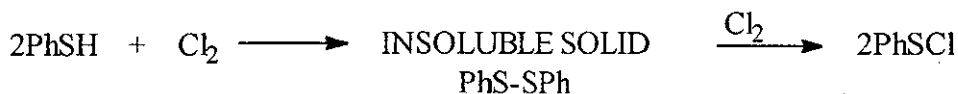


The method initially studied for the formation of benzenesulfenyl chloride was through the action of chlorine gas on benzenethiol in light petroleum (Scheme 71).⁹⁴ The chlorine gas was bubbled through a solution of benzenethiol in light petroleum until a red solution of benzenesulfenyl chloride was observed. A white solid, insoluble in light petroleum, was formed midway through the addition of chlorine (Scheme 72). On addition of more chlorine gas, this white solid dissolved to form the required red solution. This observed white solid was found to be diphenyl disulfide, presumably formed from the initial oxidation of the thiol by the chlorine gas.

Scheme 71



Scheme 72

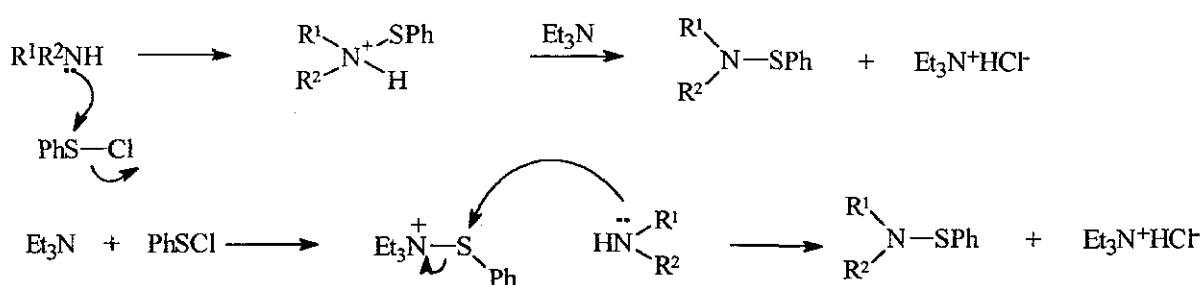


Since diphenyl disulfide has numerous advantages over benzenethiol, namely it is an odourless solid, the final method adopted for the formation of benzenesulfenyl chloride involved suspending diphenyl disulfide in light petroleum and bubbling chlorine gas through this suspension until a red solution had been formed. This final method led to good yields of benzenesulfenyl chloride, free from any diphenyl disulfide impurities.

2.2.1.1) Formation of Sulfenamides using Benzenesulfonyl Chloride (90)

The sulfenamides were formed by the addition of benzenesulfonyl chloride dropwise to a stirred solution of an amine and triethylamine in diethyl ether. Formation was through nucleophilic attack of the amine on the sulfur. The triethylamine was present as an acid acceptor in order to drive the reaction to completion. A possible alternative mechanism is initial attack by the more nucleophilic triethylamine followed by reaction of this intermediate with the amine. (Scheme 73). The reactions were all performed at room temperature and usually required only two hours stirring at this temperature to effect full conversion of starting materials to the required sulfenamide. Some reactions proceeded rapidly and were complete in minutes.

Scheme 73



When the reaction was complete, the triethylamine hydrochloride was filtered off, the solvent was removed *in vacuo* and the oily residue purified on a dry flash alumina column. Attempts at purifying the sulfenamides on a silica column lead to degradation (hydrolysis) of the sulfenamide to give the amine and diphenyl disulfide. Sulfenamides are susceptible to rapid hydrolysis in aqueous acid and had to be chromatographed on alumina and not silica gel. The sulfenamides thus prepared were stable for several weeks when refrigerated, but tended to decompose rapidly when left open to the air at room temperature. Using the above method, a number of sulfenamides were readily prepared (Table 9). As can be seen, the yields for all of these reactions were high but some loss of product occurred in the purification stage. The purity of sulfenamides immediately after work-up was good but some diphenyl disulfide impurity occurred in most reactions.

Benzenesulfonyl chloride is known to react with alkenes but the reaction is obviously much slower than with amines. We observed no evidence of competition by the alkene over the amine for the sulfonyl chloride.

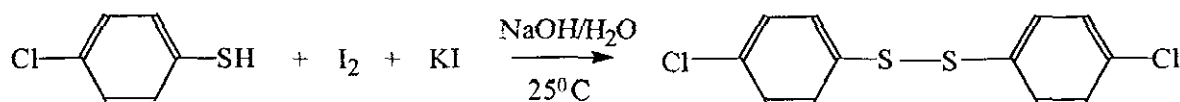
Table 9. Sulfenamides Generated from Benzenesulfenyl Chloride

Amine (R ¹)	Amine (R ²)	% Yield of Sulfenamide
methyl	cyclohexyl	100 (91)
<i>p</i> -methylbenzyl	cyclopentyl	70 (92)
<i>p</i> -methylbenzyl	cyclobutyl	73 (93)
<i>p</i> -methylbenzyl	cyclopropyl	96 (94)
butyl	4-pentenyl	95 (95)
2,2-diphenylethyl	3-phenylpropyl	50 (96)
4- <i>t</i> -butylphenylethyl	cyclohex-2-enyl	90 (97)
prop-2-enyl	cyclohex-2-enylphenylethyl	81 (98)
cyclohex-2-enyl	cyclohex-2-enylphenylethyl	71 (99)
4-isopropylphenylpentenyl	but-3-enyl	93 (100)
4-isopropylphenylpentenyl	cyclohex-2-enyl	88 (101)
butyl	3-phenylpropyl	69 (102)
phthalimide		53 (103)

2.2.1.2) Formation of Sulfenamides using *p*-Chlorophenylsulfenyl Chloride (104)

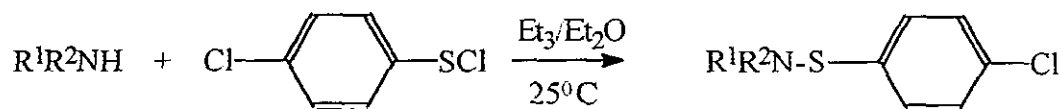
In a bid to make the sulfenamides more stable, the use of *p*-chlorobenzenesulfenyl was attempted in a limited number of cases. *p*-Chlorobenzenesulfenyl chloride can be synthesised in the same manner as benzenesulfenyl chloride, either from direct addition of chlorine gas to the thiol or to the disulfide. Though the thiol can be obtained commercially from Aldrich Chemical Co., the disulfide had to be synthesised from the thiol and iodine (Scheme 74).⁹⁵ The disulfide was then subjected to treatment by chlorine to give the required sulfenyl chloride in 89% yield.

Scheme 74



The *p*-chlorobenzenesulfenamides were generated by direct addition of sulfenyl chloride to a stirred solution of the amine and triethylamine in diethyl ether. Two sulfenamides were obtained in this way (Scheme 75) in good overall yield.

Scheme 75

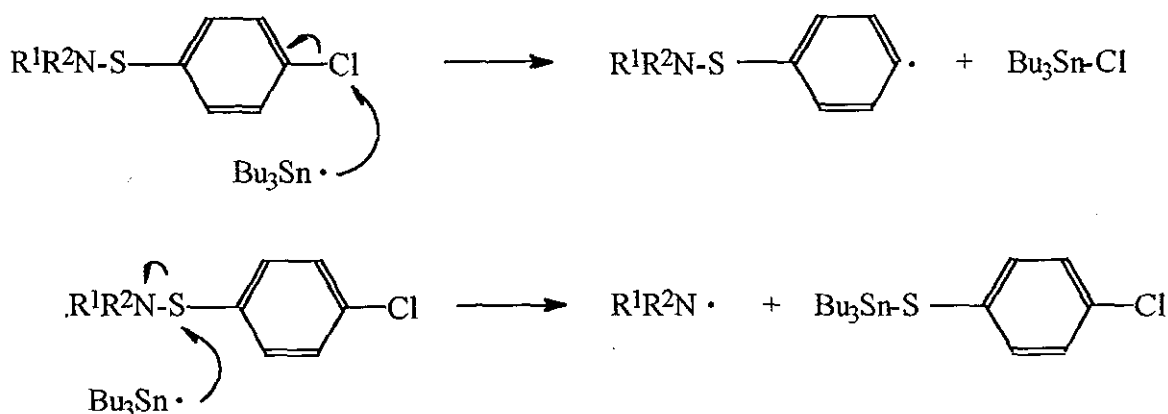


$R^1 = \text{butyl}$, $R^2 = \text{pent-5-enyl}$, 95%

$R^1 = p\text{-methylbenzyl}$, $R^2 = \text{cyclopropyl}$ 96%

Although the *p*-chlorobenzenesulfenamides obtained were more stable than the corresponding benzenesulfenamides, problems were encountered when reacting these sulfenamides with tri-*n*-butyltin hydride. It appears that the *p*-chloro substituent may also react with the tin molecule, resulting in an intractable mixture being obtained from the radical step (Scheme 76). The reaction between tributyltin hydride and chloroarenes is slow and reactions of this type were not expected. For this reason, only the benzenesulfenamides were used for the investigations into the generation of aminyl radicals.

Scheme 76



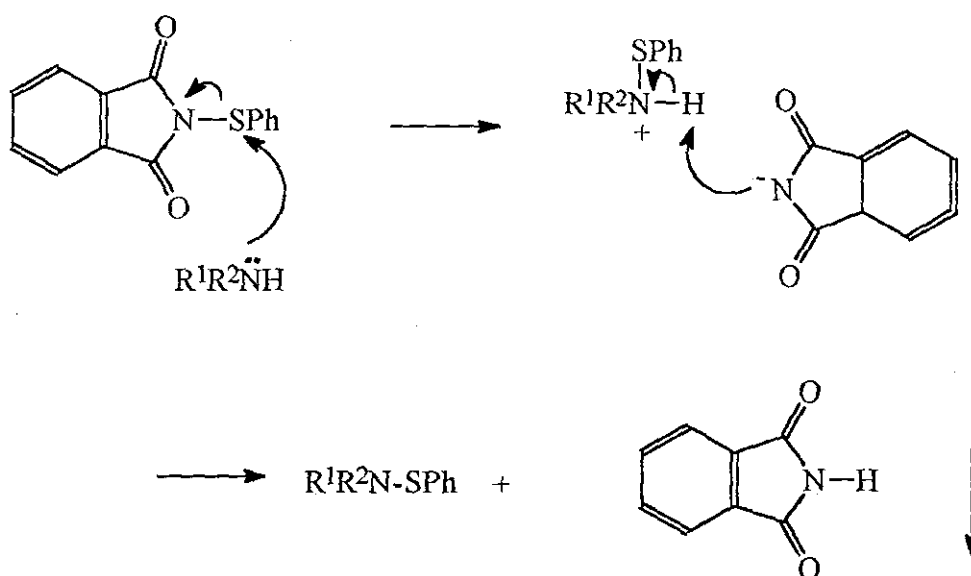
2.2.2) *N*-(Benzenesulfonyl)phthalimide as a Precursor to Sulfenamides

The obvious disadvantages of using benzenesulfonyl chloride to synthesise sulfenamides, namely the unpleasantness of the starting materials and the instability of the sulfonyl chloride due to hydrolysis, led us to seek a better method for forming sulfenamides. The use of *N*-(benzenesulfonyl)phthalimide seemed a far more suitable method for the formation of sulfenamides. This molecule was easily prepared by the action of previously formed benzenesulfonyl chloride on phthalimide, following the method as outlined above (see Section 2.2.1). On removal of the solvent, an off-white solid remained which on recrystallisation from absolute ethanol gave pure crystals of *N*-(benzenesulfonyl)phthalimide. This material could be prepared in 50 g scale, and appeared to be completely stable to air at room temperature. Furthermore, it was an odourless solid.

which made handling it far easier than benzenesulfonyl chloride. Following our work, it has become commercially available from Aldrich Chemicals Co.

The sulfenamides were formed by adding an equimolar amount of *N*-benzenesulfonyl phthalimide to a stirred solution of the amine in a non-polar solvent, typically dichloromethane. The resulting solution was either stirred for a period of hours at room temperature, or heated to reflux and maintained at this temperature until the end-point of the reaction. Phthalimide was formed as a by-product of this reaction, and a precipitate of phthalimide could clearly be seen towards the end of each reaction. In the mechanism the electrophilic sulfur atom is attacked by the nucleophilic amine, leaving the phthalimide ion to pick-up a proton and precipitate out of the reaction mixture (Scheme 77).

Scheme 77



Due to its ease of preparation and stability, *N*-(benzenesulfonyl)phthalimide was used to form a large number of the required sulfenamides. Typically, the reactions were stirred at room temperature for 17 hours, though in some cases, a week long reflux was required (Table 10). The sulfenamides formed from this method also appeared to be more stable than the corresponding sulfenamides formed from benzenesulfonyl chloride, due, presumably, to the absence of traces of hydrogen chloride from this reaction.

In two cases, no reaction was observed with *N*-(benzenesulfonyl)phthalimide even after prolonged reflux and it was assumed that the starting amines were too sterically hindered to allow reaction with the the phthalimide molecule. The sulfenamides of both of these amines were successfully formed from the action of benzenesulfonyl chloride on the amines. It seems that in the majority of cases, the use of *N*-(benzenesulfonyl)phthalimide is far superior to that of benzenesulfonyl chloride. Although the yields of the two methods are comparable, with some low yields encountered in the purification steps, the reaction involving *N*-(benzenesulfonyl)phthalimide is the more facile one. Only when the starting

amines are particularly hindered does the use of benzenesulfonyl chloride become the optimum method.

Table 10. Generation of Sulfenamides using *N*-(Benzenesulfonyl)phthalimide

Amine (R ¹)	Amine (R ²)	Method	% Yield Sulfenamide
<i>p</i> -methylbenzyl	cyclopropyl	17 h, r.t	72 (105)
methyl	cyclohexyl	17 h, r.t	93 (106)
<i>p</i> -methylbenzyl	cyclohexyl	168 h, reflux	67 (107)
2,2-diphenylethyl	3-phenylpropyl	1 h, reflux	34 (108)
<i>p</i> -methylbenzyl	cyclobutyl	1 h, reflux	44 (109)
<i>p</i> -methylbenzyl	cyclopentyl	2 h, reflux	20 (110)
<i>p</i> -methylbenzyl	bicyclo[2.2.1]hept-2-yl	1 h, reflux	43 (111)
H	bicyclo[2.2.1]hept-2-yl	2 h, reflux	90 (112)
methyl	bicyclo[2.2.1]hept-5-en-2-yl	2 h, reflux	41 (113)
phenylethyl	cyclohex-2-enyl	17 h, reflux	0
4- <i>t</i> -butylphenylethyl	cyclohex-2-enyl	17 h, reflux	0
4- <i>t</i> -butylphenylhexenyl	prop-2-enyl	4 h, reflux	49 (114)
H	4-isopropylphenylpent-4-enyl	3 h, reflux	72 (115)

2.2.3) Diphenyl Disulfide as a Precursor to Sulfenamides

The action of metallic salts on disulfides was investigated as a means of forming sulfenamides. A solution of the amine, silver nitrate and diphenyl disulfide in dry methanol was stirred at room temperature for 12 h (Scheme 78).

Scheme 78



R¹ = methyl, R² = cyclohexyl, 86%

R¹ = allyl, R² = 4-pentenyl, 87%

Although clean samples of the required sulfenamides were formed from this reaction, 5 equivalents of the amine was required to ensure that all of the disulfide reacted. While this may not be a major problem when dealing with readily available amines, it is not feasible to waste a valuable amine using this method. Therefore, this method was not used as a major source of sulfenamides.

2.3) New Methods for the Formation of Sulfenamides

While this project was taking place, a new method for generating sulfenamides was reported. Work by Barton and co-workers⁹⁶ has shown that sulfenamides can be formed from the reaction between thiolates and *N*-chloramines. It appears that this synthesis of sulfenamides proceeds through an S_N2 attack of the thiolate of the *N*-chloramine (formed *in situ*) (Scheme 79). Using this method, the authors have successfully formed a number of sulfenamides from morpholine amines (Table 11).

Scheme 79

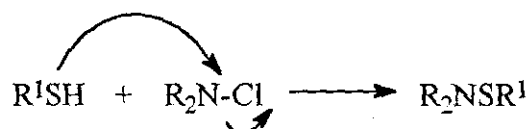


Table 11. The Generation of Sulfenamides from Chloramines

Thiol	Amine	Isolated Yield
		97%
		40%
		96%
		84%

The reactions were all performed in a basic media (generated by using an excess of the amine) in a non-polar solvent (normally chloroform). The method generates sulfenamides free from disulfide impurities, and leads to a good method of forming sulfenamides where the corresponding sulfenyl halide is not available. Obviously, this will

prove to be an important method for generating sulfenamides in the future, particularly those sulfenamides that are difficult to synthesise using traditional methods.

2.4) The Use of Sulfenamides to Generate Aminyl Radicals

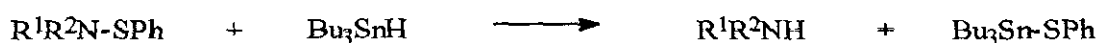
Our studies have shown that sulfenamides can be readily synthesised using benzenesulfonyl chloride and *N*-(benzenesulfonyl)phthalimide in good yield. A wide variety of sulfenamides have been prepared and the presence of an alkene or arene does not interfere, even though these groups are known to react with benzenesulfonyl chloride. The reaction of the amino groups is selective in the presence of alkenes and arenes. In the next chapter we show that aminyl radicals can be readily formed from the action of tri-*n*-butyltin hydride on sulfenamides. Chapter 3 concentrates on the evidence obtained to prove the intermediacy of aminyl radicals, together with blank experiments that show the reactions performed must have proceeded through a radical pathway. Chapter 4 shows that the methodology can be used for the synthesis of polycyclic amines, many of which are natural product analogues.

Chapter 3. The Generation of Aminyl Radicals using Sulfenamides

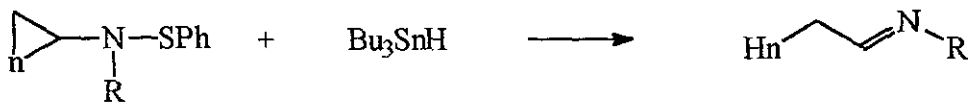
It is well known that alkoxy and iminyl radicals can be generated by the action of tri-*n*-butyltin hydride on the corresponding sulfenyl derivative (see Section 1.) By analogy, it should be possible to generate aminyl radicals from the action of tri-*n*-butyltin hydride on sulfenamides. In order to determine whether this was true, a number of sulfenamides were generated using the methods listed above (See Chapter 2), and reacted under radical conditions *i.e.* using tri-*n*-butyltin hydride and AIBN radical initiator in refluxing solvent. The investigation covered three types of reaction; a straight reduction reaction to give the parent amine, ring-opening reactions and a β -scission reaction (Scheme 80). Each of these reactions will be covered in turn, in each case detailing proofs to indicate that the reactions occurred through a radical pathway.

Scheme 80

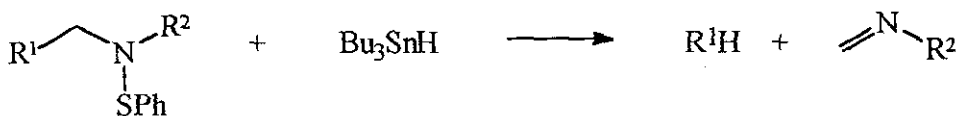
i) Reduction



ii) Ring-Opening



iii) β -Scission

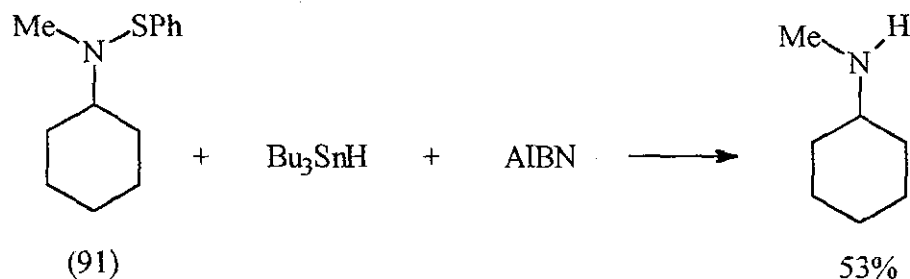


3.1) Reduction Reactions Involving Aminyl Radicals

N-(Benzenesulfonyl)-*N*-methylcyclohexylamine (91) was chosen for initial studies to show that aminyl radicals could be generated from sulfenamides. The sulfenamide was reacted with tri-*n*-butyltin hydride and AIBN in refluxing cyclohexane for 15 min. At the end of this time, the reaction was allowed to cool to room temperature, and extracted into 2M hydrochloric acid solution. The organic layer was evaporated to dryness to yield tributylstannyl phenylsulfide, whilst the aqueous layer was basified using saturated sodium carbonate solution and sodium hydroxide pellets and extracted into diethyl ether. The ether extracts were evaporated to dryness to yield *N*-methylcyclohexylamine in 53% yield

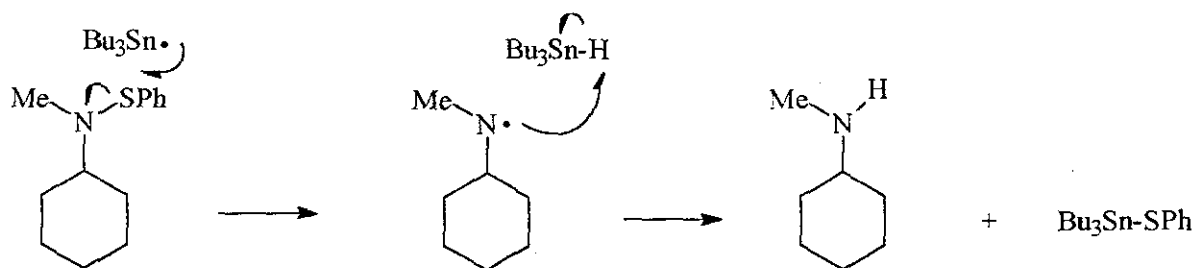
(Scheme 81). The identity of this product was checked against a pure sample of the authentic *N*-methylcyclohexylamine purchased from Aldrich Chemical Co.

Scheme 81



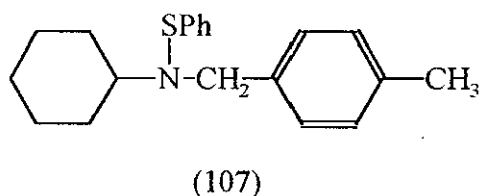
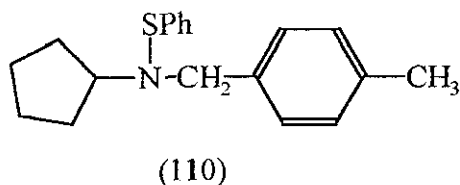
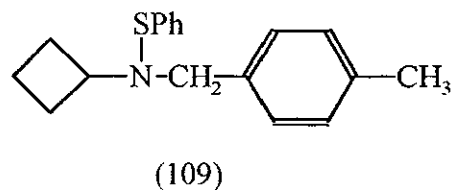
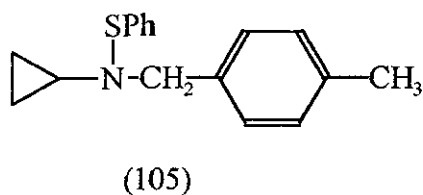
Clearly, the evidence of reduced amine from this reaction could be due to an ionic reaction taking place, and not through the intermediacy of aminyl radicals. Therefore blank reactions were carried out using this molecule. Firstly, the reaction was carried out in refluxing cyclohexane but in the absence of tri-*n*-butyltin hydride. GLC analysis of this reaction after refluxing for 2 h showed 100% recovery of starting sulfenamide. Therefore, the sulfenamide was stable to refluxing solvent. The reaction was then performed under an atmosphere of oxygen, in the absence of AIBN radical initiator and in the dark. These conditions would completely hinder any radical reaction that might take place. GLC analysis of the reaction mixture after refluxing in cyclohexane for 15 min showed 100% recovery of starting sulfenamide. From these reactions, it is clear that the presence of reduced amine in the reaction flask could only have been due to the tributyltin radical reacting with the sulfenamide to form an aminyl radical, since the sulfenamide had been shown to be stable both to refluxing solvent and any ionic interaction with tin hydride. The isolation of a sample of tributylstannyl phenylsulfide from this reaction also indicates the intermediacy of aminyl radicals (Scheme 82).

Scheme 82



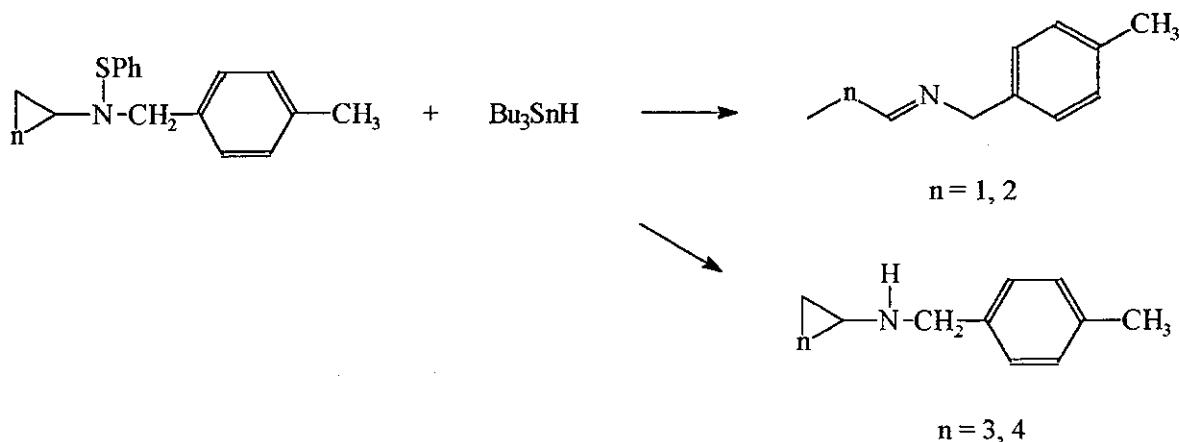
3.2) Ring-Opening Reactions involving Aminyl Radicals

A series of 3-, 4-, 5- and 6-membered ring cycloalkyl sulfenamides were chosen to further prove the intermediacy of aminyl radicals (105, 109, 110 and 107).



Earlier research has shown that the ring-opening of *N*-propylcyclobutylaminyl and *N*-butylcyclopropylaminyl radicals is fast ($2.5 \times 10^7 \text{ s}^{-1}$ and $5 \times 10^5 \text{ s}^{-1}$ respectively). Therefore, it would be expected to observe the radical induced ring-opening of sulfenamides (105) and (109). However, the sulfenamides (110) and (107) would not be expected to undergo ring-opening as the five and six membered rings do not have as much ring-strain as the equivalent three and four membered rings (Scheme 83).

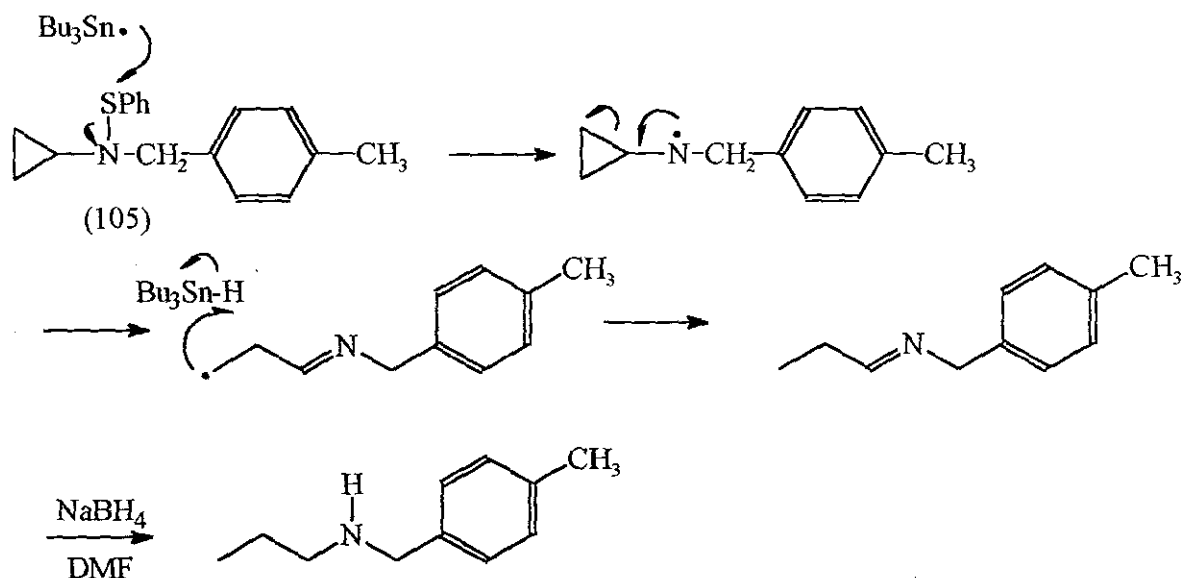
Scheme 83



Initial experiments concentrated on *N*-(benzenesulfonyl)-*N*-(*p*-methylbenzyl)cyclopropylamine (105) as a precursor to radical-induced ring-opening. The sulfenamide was mixed with an equivalent amount of tributyltin hydride and a catalytic amount of AIBN radical initiator in a suitable solvent (usually toluene) and refluxed for typically 2 h. After this time TLC analysis indicated complete conversion of starting sulfenamide. However, if ring-opening had occurred, the primary product would be an imine. Therefore, standard work-up at this stage would lead to hydrolysis of the imine resulting in problems isolating the products of the reaction. The imine, therefore, had to be reduced 'in situ', using a suitable hydride reducing agent. Sodium borohydride in DMF was

chosen as it was believed that more conventional solvents, namely methanol, may react with the initially formed imine. Therefore, when the reaction was seen to have gone to completion, a solution of three equivalents of sodium borohydride in a small volume of DMF was added and the resulting solution stirred at room temperature for 2 h. Standard work-up of the reaction at this stage lead to the isolation of a product believed to be *N*-(*p*-methylbenzyl)propylamine in 73% yield (Scheme 84). No evidence of *N*-(*p*-methylbenzyl)cyclopropylamine was detected in the final product.

Scheme 84

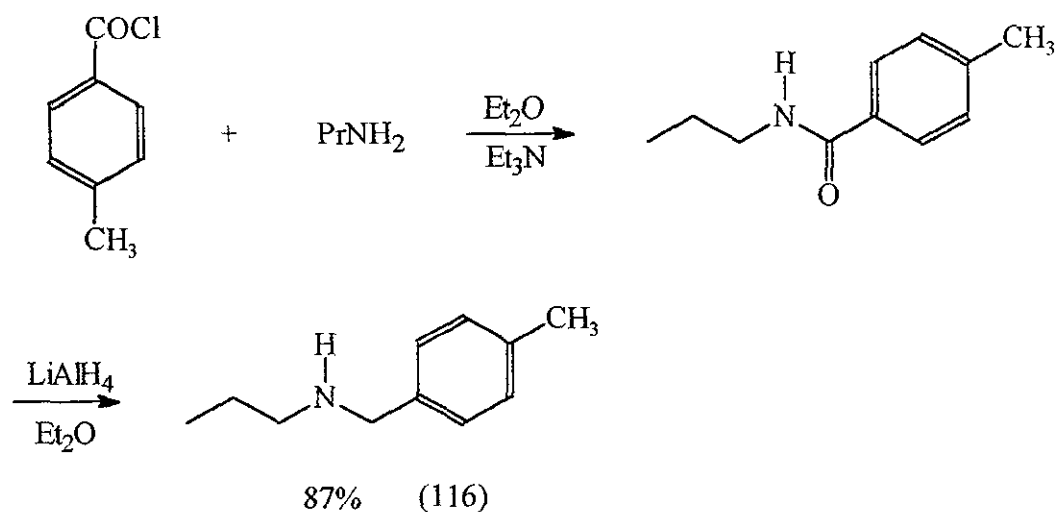


The identity of this expected product was confirmed by the more conventional synthesis of *N*-(*p*-methylbenzyl)propylamine (116), through the action of propylamine on *p*-toluyl chloride. The initially formed amide was then reduced using lithium aluminium hydride to give the required amine (Scheme 85).

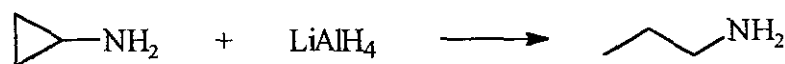
As expected, the physical data and the physical properties of the two samples of *N*-(*p*-methylbenzyl)propylamine were found to be identical. However, this experiment did not fully prove that the ring-opening of the cyclopropyl ring was occurring through a radical-induced pathway, as work has shown that lithium aluminium hydride is capable of ring-opening a cyclopropyl ring in an ionic fashion (Scheme 86). Therefore, as a hydride reducing agent itself, tributyltin hydride could theoretically cleave the cyclopropyl ring ionically, and not through the mediation of aminyl radicals. To investigate this query, a blank reaction was performed whereby *N*-(benzenesulfonyl)-*N*-(*p*-methylbenzyl)cyclopropylamine was refluxed with tributyltin hydride in the absence of AIBN radical initiator, under an oxygen atmosphere and in the dark. As has already been noted, these conditions hinder a radical reaction. After refluxing in toluene for two hours, GLC analysis of the reaction mixture showed a complete recovery of the starting

sulfenamide, with no ring-opened amine being observed. The conclusion to be drawn was that the tributyltin radical combined with the sulfur molecule to form an aminyl radical, which rapidly underwent ring-opening according to the observed rate data.

Scheme 85

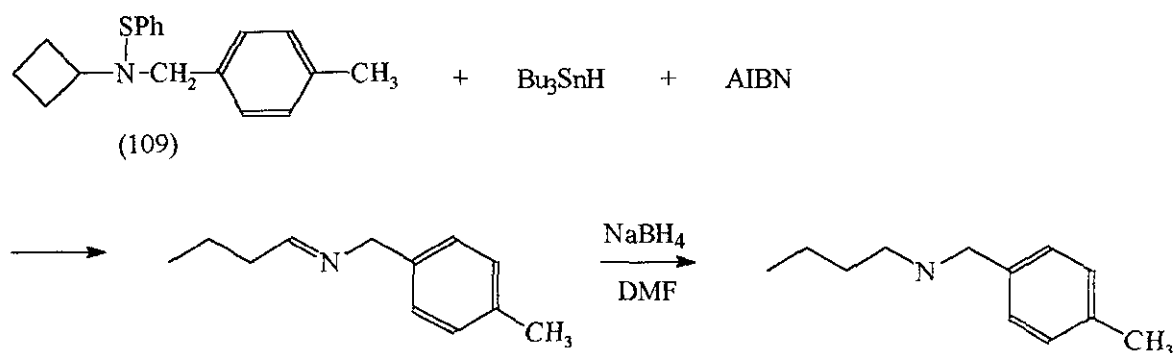


Scheme 86



The next stage of the investigation was to show that the equivalent cyclobutylaminyl radical could be generated, and once generated would undergo rapid ring-opening to give the imine (Scheme 87).

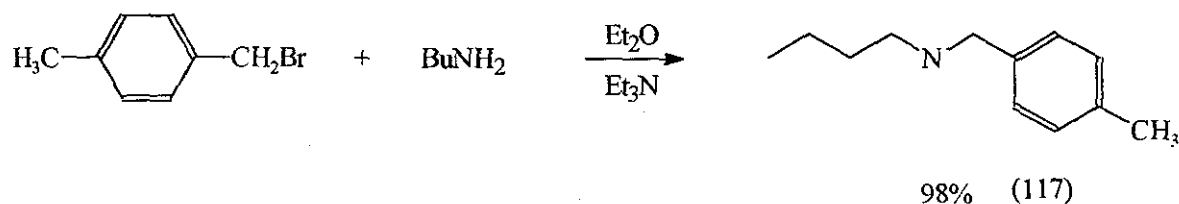
Scheme 87



N-(Benzenesulfonyl)-*N*-(*p*-methylbenzyl)cyclobutylamine (109) was generated in the usual manner and reacted with an equivalent of tributyltin hydride under the standard radical conditions. Once more, when TLC had indicated complete conversion of starting

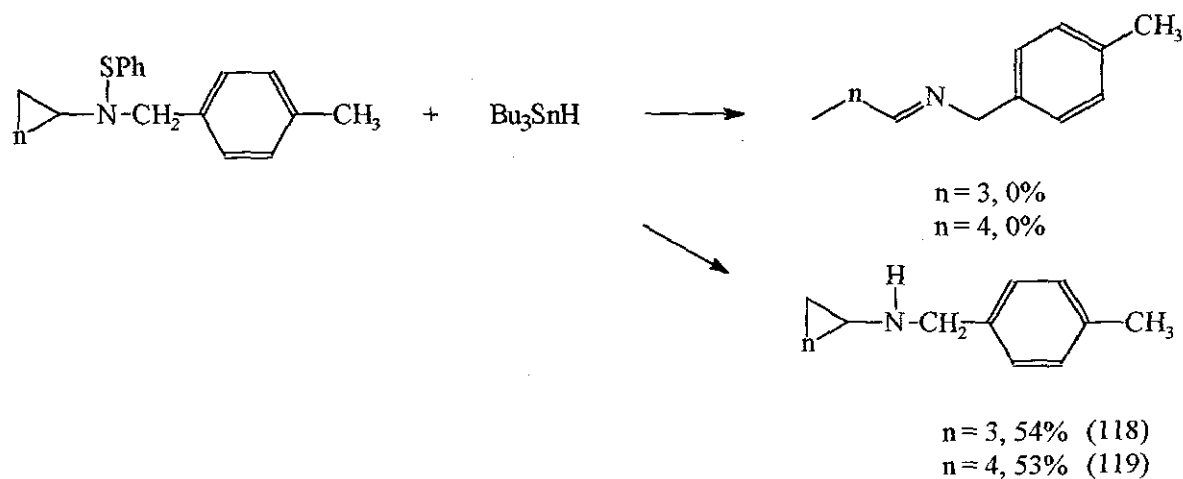
sulfenamide, the reaction was allowed to cool to room temperature and a solution of sodium borohydride in DMF added. Work-up of this reaction after stirring at room temperature gave a product that was believed to be *N*-(*p*-methylbenzyl)butylamine in 42% yield. This was subsequently confirmed by the synthesis of an authentic sample of *N*-(*p*-methylbenzyl)butylamine (117) (Scheme 88). No products relating to the ring closed amine were evident in the final product.

Scheme 88



It was expected that the *N*-(benzenesulfonyl)-*N*-(*p*-methylbenzyl)cyclopentyl- and cyclohexylamines would not undergo radical induced ring-opening when reacted with tin hydride and AIBN. It was of no surprise, therefore, when the only products resulting from the reaction of these sulfenamides under radical conditions were *N*-(*p*-methylbenzyl)cyclopentylamine (118) and *N*-(*p*-methylbenzyl)cyclohexylamine (119) in 54% and 53% yields respectively. In both of these cases, no evidence of ring-opened product was observed (Scheme 89).

Scheme 89



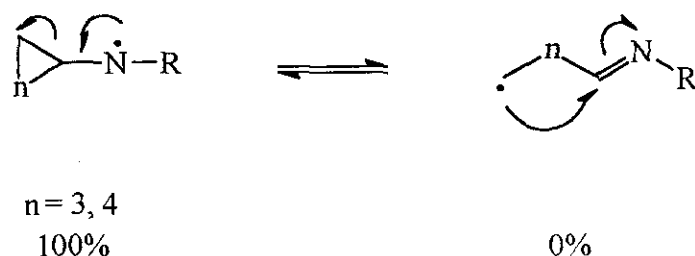
Since this work has been completed, research work by A. Young of Loughborough University⁹⁷ on the cyclisation of alkyl radicals onto imines has shown that the radical, once generated, cyclises rapidly to give the cyclopentylaminyl radical (Scheme 90). This work proves that, even if ring-opening of the cyclopentyl- and cyclohexyl rings occur initially in

the generation of the appropriate aminyl radicals, the ring-closure of these iminyl radicals is the more favoured process (Scheme 91).

Scheme 90

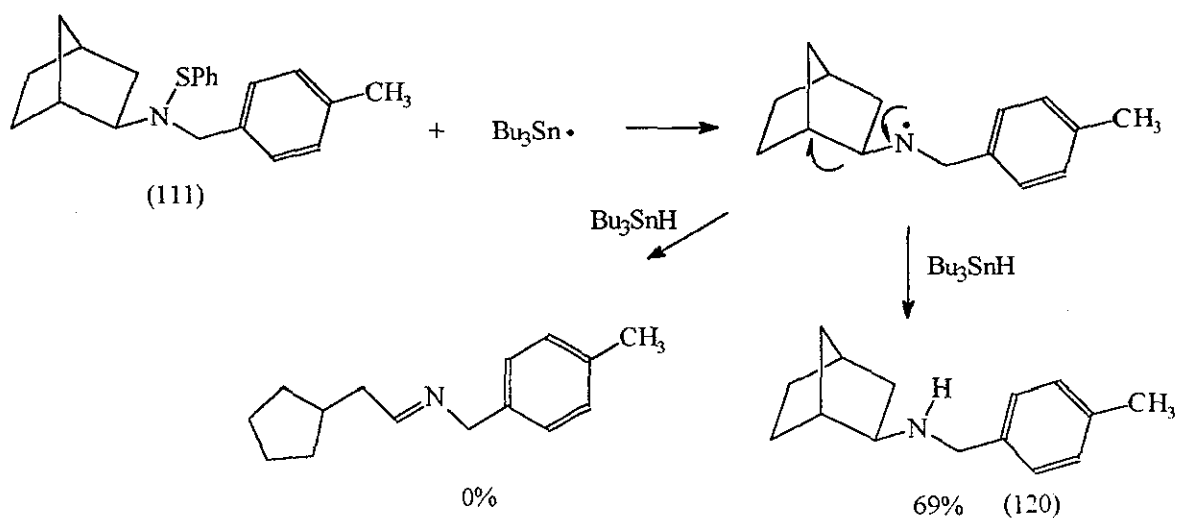


Scheme 91



Another example tried was the attempted ring-opening of a strained bicyclic ring, in this case, *exo-N*-(benzenesulfonyl)-*N*-(*p*-methylbenzyl)-bicyclo[2.2.1]heptylamine (111). However, reaction of this sulfenamide under standard radical conditions generated merely *exo-N*-(*p*-methylbenzyl)-bicyclo[2.2.1]heptylamine (120) in 69% yield. No ring-opened product was isolated from this reaction (Scheme 92).

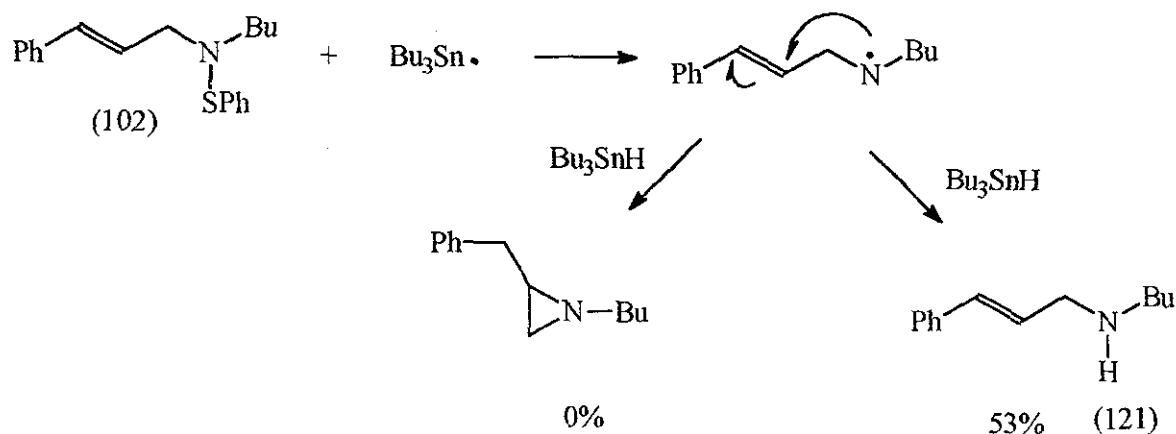
Scheme 92



Finally, an attempt was made to overcome the ring-strain of the cyclopropyl ring by stabilising the cyclised aminyl radical through a benzylic substituent. For this purpose, *N*-(benzenesulfonyl)-*N*-(3-phenylprop-1-enyl)-*N*-butylamine (102) was formed using standard procedures and reacted under standard radical conditions (Scheme 93). However, in spite of

using a syringe pump to deliver a solution of tributyltin hydride and AIBN in toluene to a refluxing solution of the sulfenamide in toluene (to ensure a low concentration of tin radicals in the reaction mixture) no evidence of *N*-butyl-2-benzylaziridine was detected in the final product. *N*-butyl-(3-phenylprop-1-enyl)amine (121) was generated in 53% yield, indicating that benzylic stabilisation of the cyclised radical is not sufficient to overcome the effects of ring strain of the ring system.

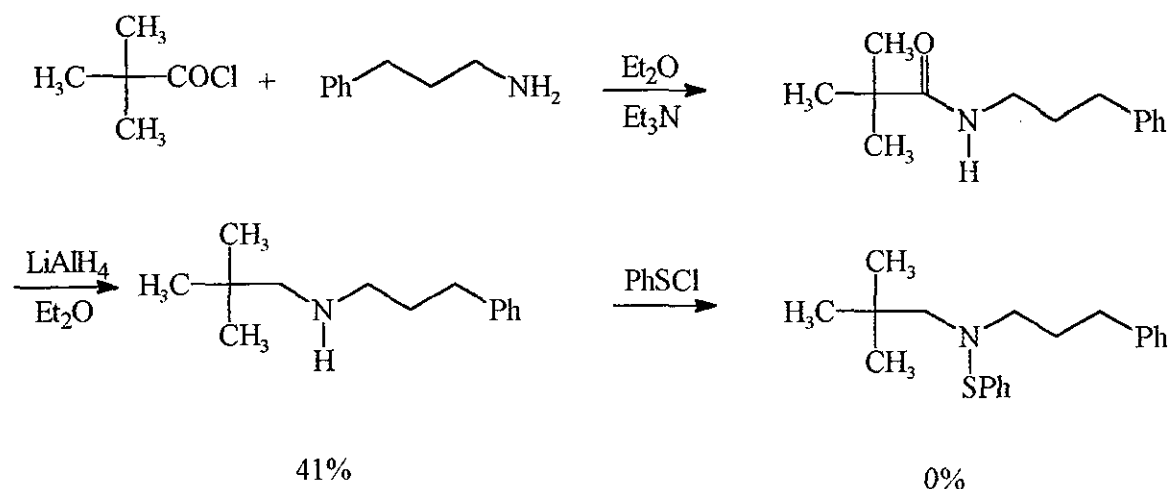
Scheme 93



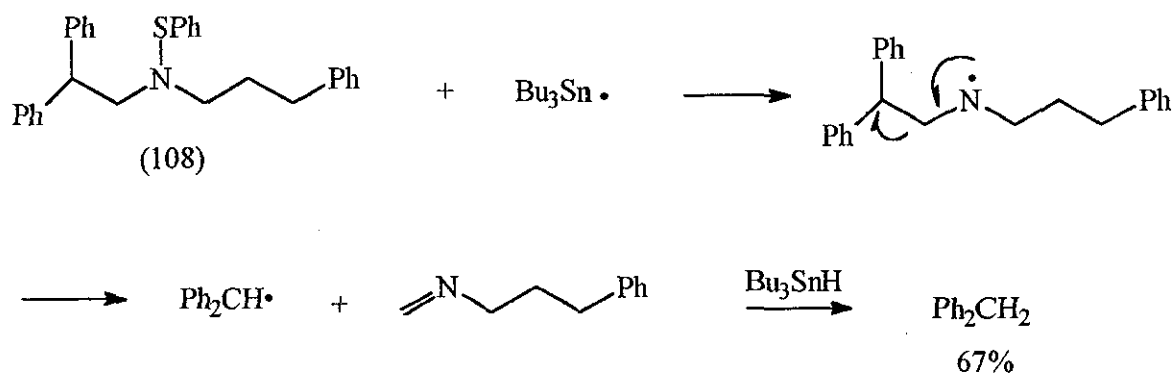
3.3) β -Scission Reactions Involving Aminyl Radicals

Although β -scission reactions through using aminyl radicals has been illustrated in the above ring-opening of cyclopropyl- and cyclobutyl-ring systems, a further system was set up to illustrate this area of aminyl radical reactivity. After attempts at forming *N*-(benzenesulfonyl)-*N*-(1,1-dimethylpropyl)-3-phenylpropylamine had met with limited success, due to the failure to generate the sulfenamide (Scheme 94), the sulfenamide *N*-(benzenesulfonyl)-*N*-(2,2-diphenylethyl)-3-phenylpropylamine (108) was successfully synthesised and reacted under standard radical conditions. Upon work-up, the only product obtained from this reaction was shown to be diphenylmethane in 67% yield, confirmed by comparison with an authentic sample bought from Aldrich Chemical Co. This can only be explained by β -scission of the initially formed aminyl radical to give the very stable diphenylmethyl radical, and the very unstable primary imine. This imine was presumably lost through the work-up procedure (Scheme 95).

Scheme 94



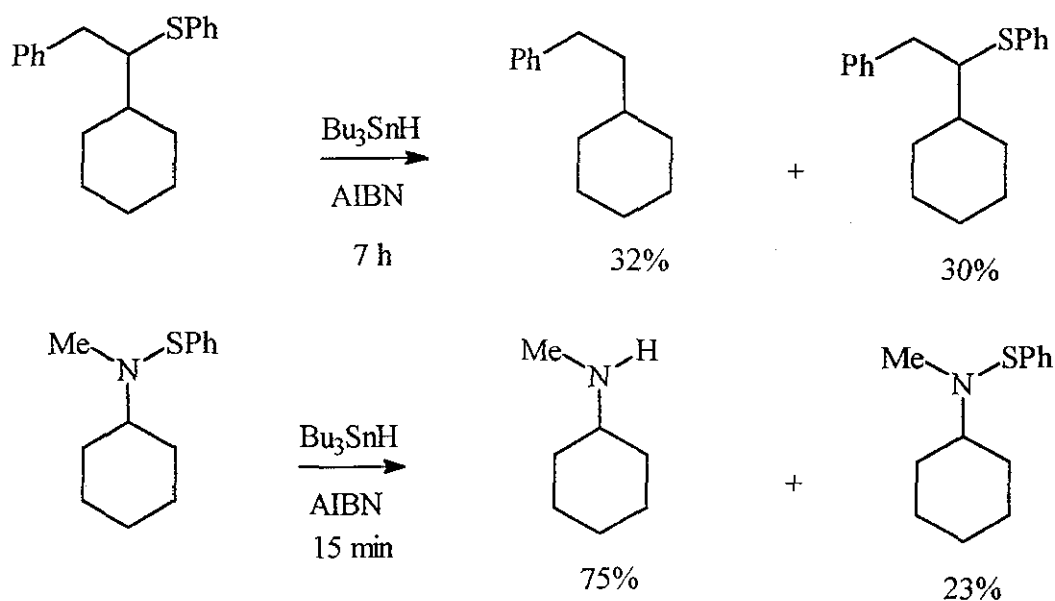
Scheme 95



3.4) Comparison of the Rate Abstraction by Tin Radicals on Alkylsulfides and Sulfenamides

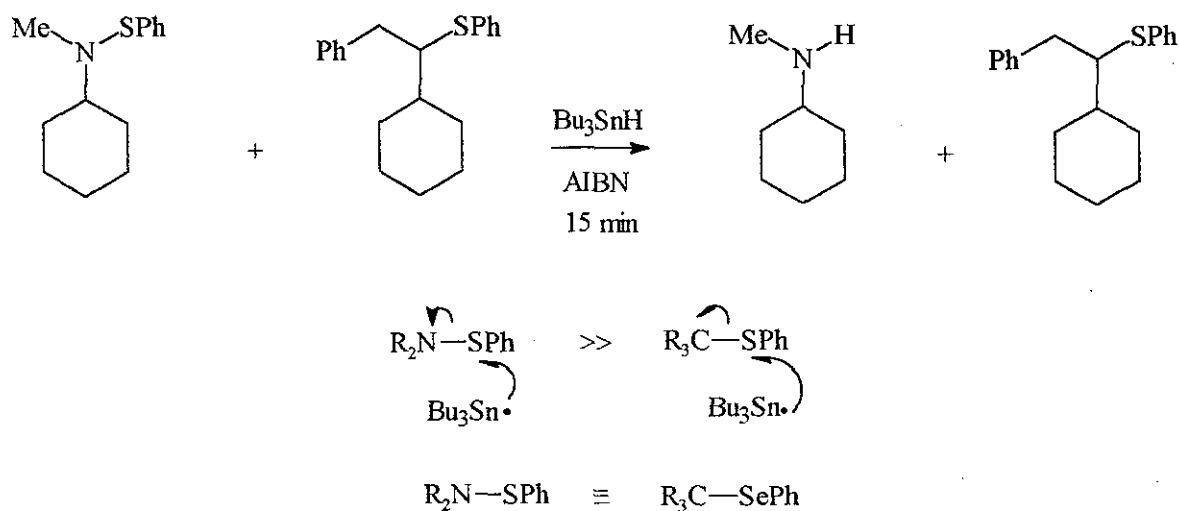
Work was conducted by Dr R Marmon to investigate whether the $\text{S}_{\text{H}}2$ abstraction by $\text{Bu}_3\text{Sn}\cdot$ radicals of PhS from sulfenamides (N-SPh bond fission) would be far faster than the abstraction from sulfides (C-SPh bond fission). Comparison reactions were carried out on two equivalent substrates under standard radical conditions to determine this. It was found that when the sulfide, 1-cyclohexyl-3-phenyl-1-propyl phenyl sulfide was reacted, a mixture of the alkane, 1-cyclohexyl-3-phenylpropane (32%) and the starting sulfide (30%) were recovered after 7 h reflux. However, the equivalent reaction on a similar sulfenamide, *N*-(benzenesulfonyl)-*N*-methylcyclohexylamine gave a mixture of *N*-methylcyclohexylamine (75%) and unreacted sulfenamide (23%) after 15 min reflux (Scheme 96).

Scheme 96



Further, when a mixture of the sulfide and sulfenamide were reacted together under standard radical conditions for 15 min, only PhS abstraction from the sulfenamide was observed. This proves that the $\text{S}_{\text{H}}2$ abstraction of PhS by tin radicals is faster from sulfenamides than sulfides, and that the sulfenamides are in fact the nitrogen counterparts of selenides ($\text{C}-\text{SePh}$) in radical reactions (Scheme 97).

Scheme 97



The studies above have shown that aminyl radicals can be successfully generated by the action of tin hydride on sulfenamides. Also, these radicals are stable enough to undergo various reactions. The next stage of the project was to show that the initially formed aminyl

radicals could be made to cyclise onto intramolecular olefins to give a range of nitrogen heterocycles. The results of these studies will be covered in detail in the following chapter.

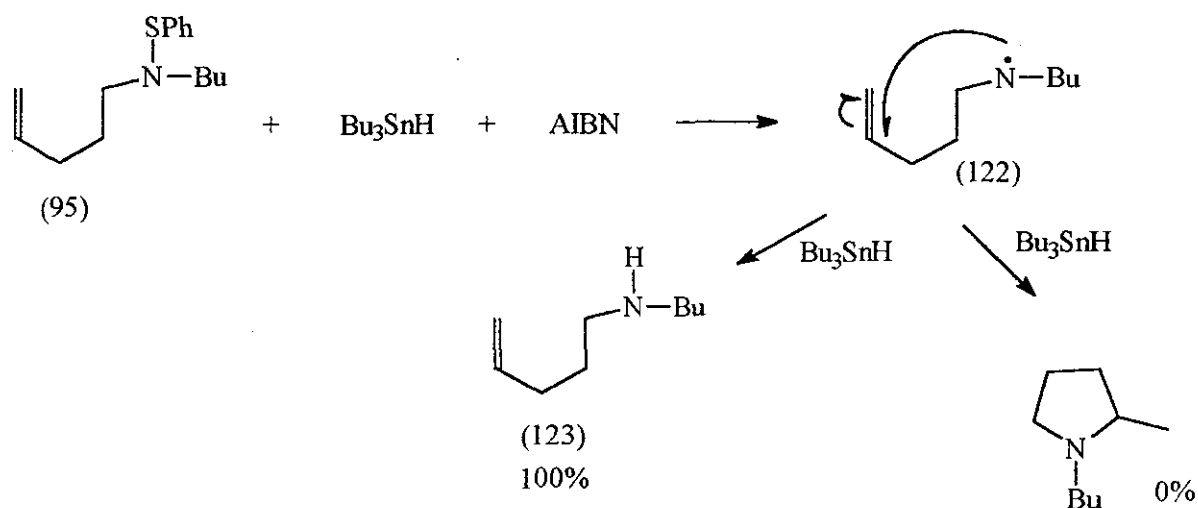
Chapter 4. Cyclisation Reactions using Aminyl Radicals

In this chapter, it is intended to show that aminyl radicals can be generated and made to cyclise onto intramolecular olefins to form nitrogen containing heterocycles. As has already been stated in Section 1.3, the cyclisation of aminyl radicals onto olefins is essentially a reversible process, with the predominant product from such a reaction being the uncyclised material. Below will be detailed the ways we have discovered of aiding the cyclisation process, leading to the facile synthesis of a whole range of nitrogen containing heterocycles. These ways include cyclisation to form a stable benzylic radical, the use of aminyl radicals that cyclise rapidly and forcing tandem cyclisation reactions. Each of these methods will be outlined below with a detailed account of their use for general synthetic reactions.

4.1) Attempted Cyclisation of Aminyl Radicals onto an Unactivated Olefin

Our initial investigations into the possibility of cyclising aminyl radicals onto intramolecular olefins concentrated on the cyclisation of the *N*-butylpent-5-enyl system (122). The sulfenamide *N*-(benzenesulphenyl)-*N*-butylpent-5-enylamine (95) was synthesised in the usual manner and reacted with tri-*n*-butyltin hydride and AIBN radical initiator in refluxing solvent. Upon standard work-up of the reaction mixture, it became apparent that none of the product was cyclised material. The only isolatable product from the reaction mixture was *N*-butylpent-5-enylamine (123) (Scheme 98).

Scheme 98



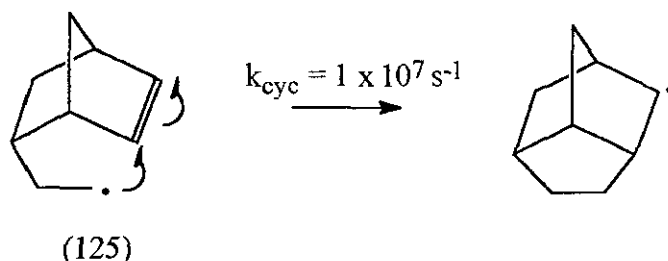
At the same time that this work was being performed, a paper by Newcomb *et al*²⁴ was published claiming that the rate of cyclisation of this system was roughly equivalent to the rate of ring-opening of the cyclised radical and that the rate of hydrogen abstraction from tributyltin hydride by the aminyl radical was similar to that of the primary carbinyl radical (See Section 1.3). Although Newcomb's results suggest that some cyclised amine should

have been formed, none was observed. For this reason, it was decided to discover more favourable methods for cyclising aminyl radicals and this reaction was not further investigated.

4.2) Cyclisation of the Bicyclo[2.2.1]hept-5-en-2-methylaminy Radical

In an attempt to create more favourable conditions for cyclising aminyl radicals, the cyclisation of the *endo*-(bicyclo[2.2.1]hept-5-en-2-yl)methylaminy radical (124) was investigated. This particular system was investigated because the buttressed aminyl radicals are correctly orientated to react rapidly with the strained alkene. The carbiny radical equivalent of this system have been found to cyclise very rapidly, *e.g.* the rate of *exo*-cyclisation of *endo*-2-(bicyclo[2.2.1]hept-5-en-2-yl)ethyl radicals (125) is $1 \times 10^7 \text{ s}^{-1}$ (Scheme 99).⁹⁸

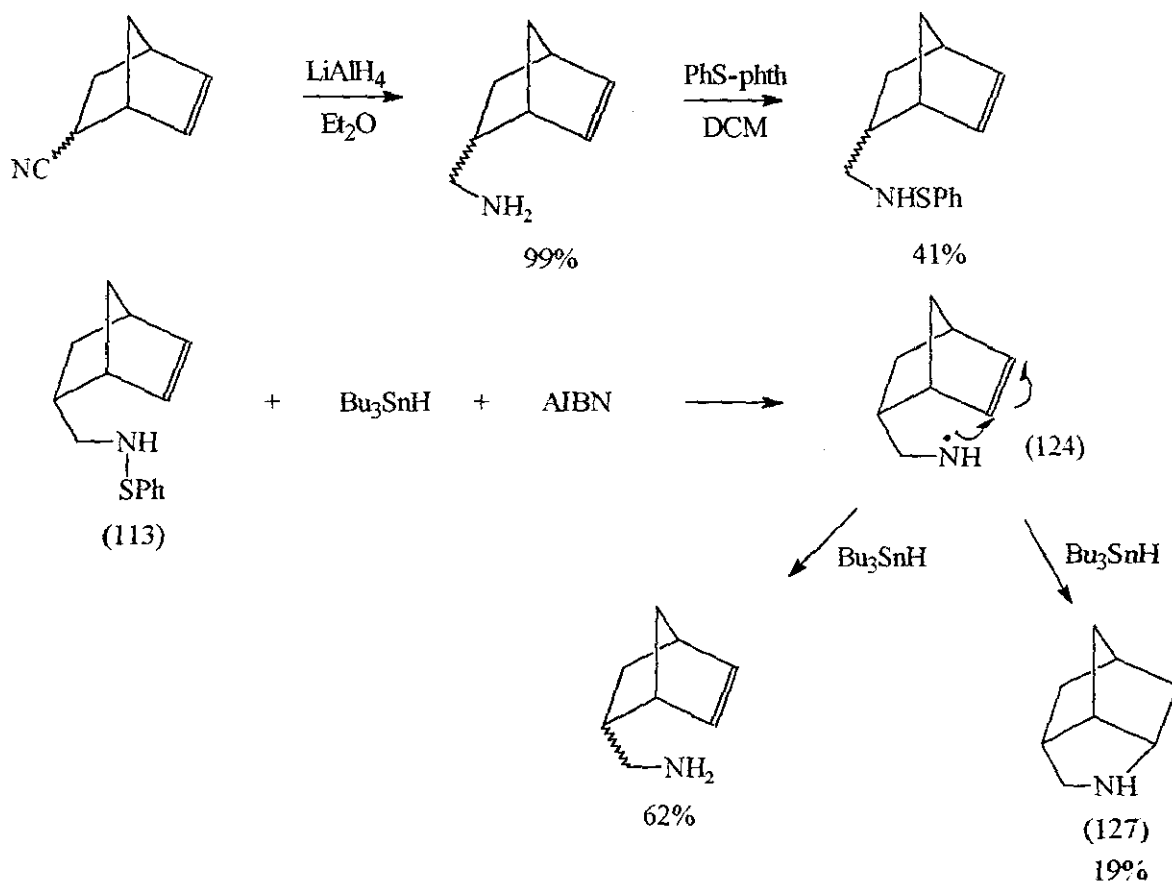
Scheme 99



A mixture of *endo*- and *exo*-(bicyclo[2.2.1]hept-5-en-2-yl)methylamines (126) were synthesised by reduction of 5-cyanobicyclo[2.2.1]hept-2-ene (*exo:endo* 50:50) using lithium aluminium hydride. The *exo*- and *endo*-amines were not separated and were reacted throughout as a mixture. The sulfenamide *exo*- and *endo*-*N*-(benzenesulfonyl)-(bicyclo[2.2.1]hept-5-en-2-yl)methylamine (114) was prepared in the usual manner from the parent amine, and reacted under standard radical conditions with tributyltin hydride and AIBN radical initiator. As predicted, only the *endo*-isomer cyclised, with the products from the reaction being a mixture of *endo*- and *exo*-(bicyclo[2.2.1]hept-5-en-2-yl)methylamine and a small amount of cyclised material (127) (Scheme 100).

Further reactions carried out by Dr R. Marmon using *N*-methyl and *N*-propyl substituents on this molecule led to slightly better yields of cyclisation, due, presumably, to the extra buttressing effects afforded this molecule from the additional alkyl chains. In the case of the *N*-propyl substituent, analysis of the reaction mixture showed a ratio of cyclised to uncyclised material to be 4:1. This clearly shows that the rate of cyclisation of the aminyl radical is greater than the rate of ring-opening of the cyclised radical in this case.

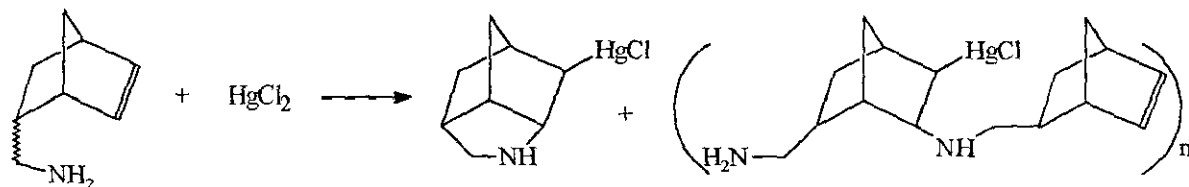
Scheme 100



4.2.1) Ionic Methods of Cyclising *endo*-(Bicyclo[2.2.1]hept-5-en-2-yl)methylamine

In an attempt to generate a sample of fully cyclised material (127) to compare with the products obtained from the radical cyclisation reaction, the reaction between *endo*- and *exo*-(bicyclo[2.2.1]hept-5-en-2-yl)methylamine and mercury(II) chloride was carried out. Unfortunately, it appeared that the *exo*-isomer of the amine was interfering with the reaction to form a polymeric mess. No cyclised material was obtained from this reaction and this approach was discontinued (Scheme 101).

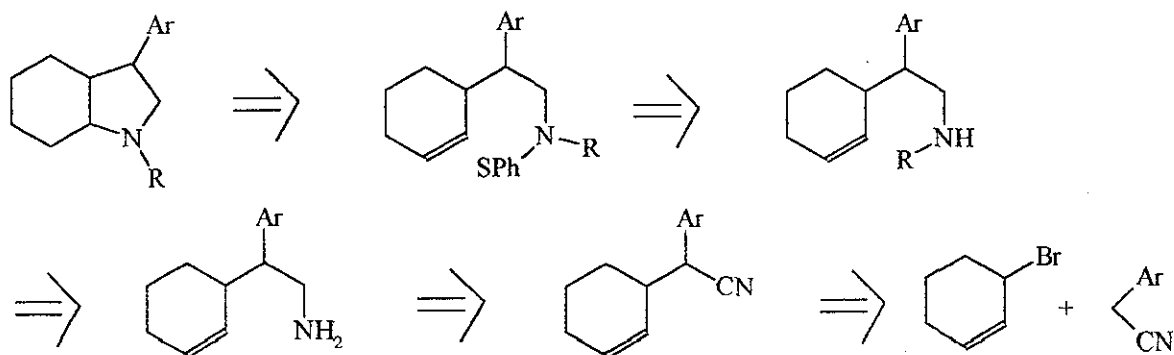
Scheme 101



4.3) Attempted Cyclisation onto an Unactivated Cyclohexene Ring

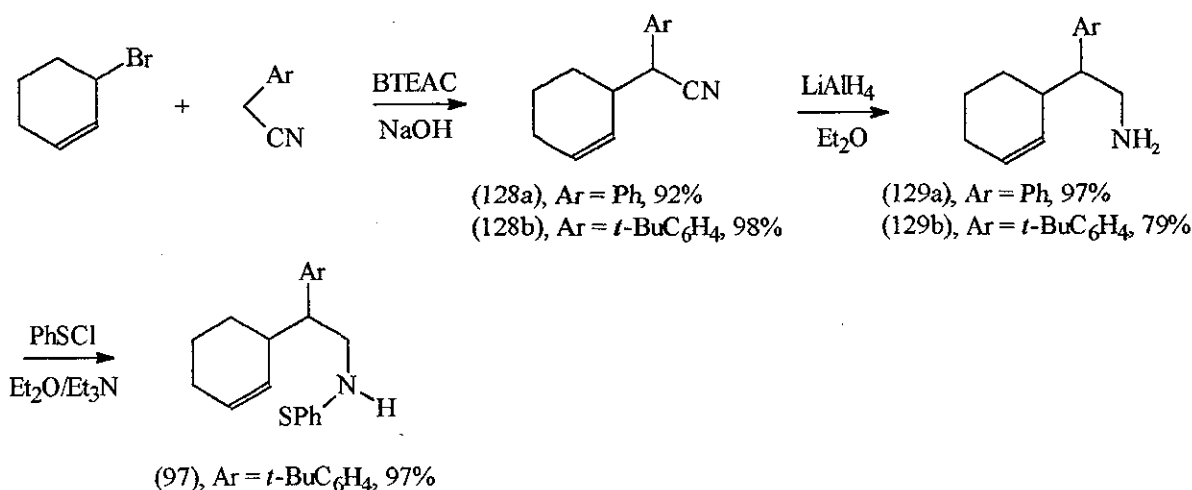
Due to the requirements of our sponsors, it was decided to synthesise a number of perhydroindoles through aminyl radical cyclisation reactions. The retro-synthesis of such a scheme was believed to be the following (Scheme 102).

Scheme 102



The sulfenamide precursors to this scheme were synthesised without any major problems. Benzyl cyanide (or *t*-butylbenzylcyanide) was reacted with cyclohexene in the presence of a phase transfer catalyst to give the nitriles (128a,b). Reduction with lithium aluminium hydride gave the amines (129a,b) and reaction with benzenesulfonyl chloride gave the sulfenamide (97) (Scheme 103). Attempts to synthesise the sulfenamide (97) using *N*-(benzenesulfonyl)phthalimide failed, possibly due to steric hindrance in the reaction.

Scheme 103



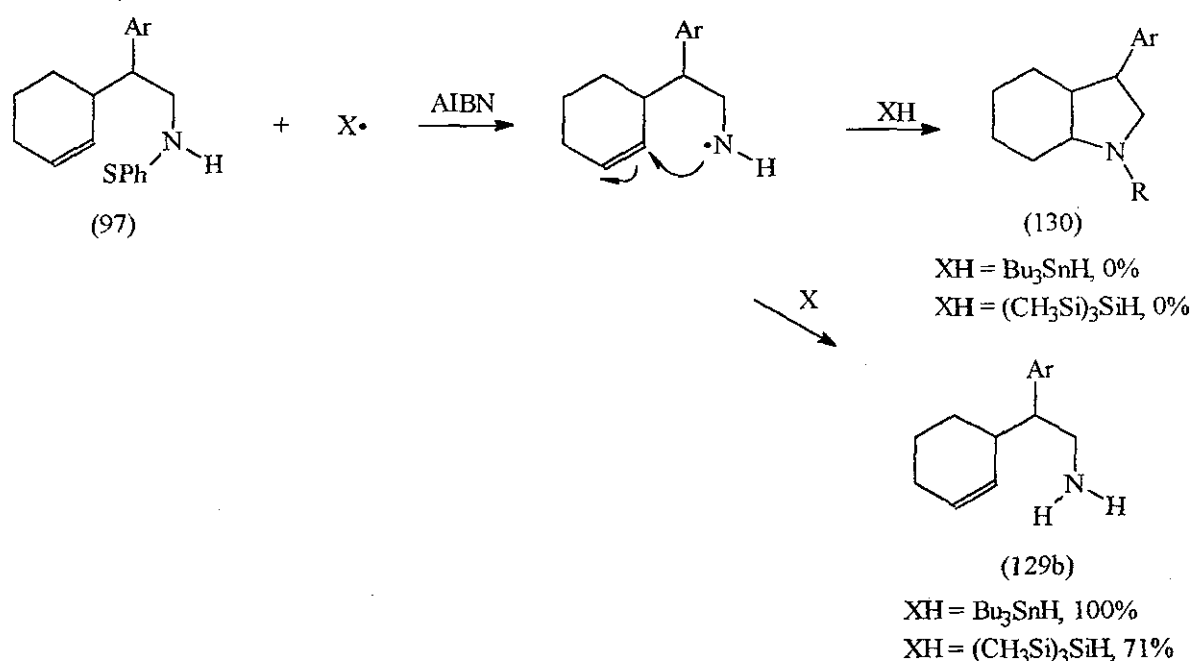
The decision was taken to employ a syringe pump for all aminyl radical cyclisation reactions. In this way, a steady concentration of tributyltin hydride and AIBN could be delivered to a refluxing solution of the sulfenamide. This ensures a low concentration of tin hydride in the reaction flask at all times, leading to less chance of reduction reactions with tin hydride. However, in the above case, in spite of adding the tin hydride and AIBN in THF over 5 h to a refluxing solution of the sulfenamide (97) in THF, work-up of the reaction yielded no expected cyclised material (130). This reaction was repeated using tris(trimethylsilyl)silane as hydrogen source, in place of tin hydride.

Tris(trimethylsilyl)silane reacts more slowly than tributyltin hydride with intermediate radicals, and is therefore more useful for cyclisation reactions. Unfortunately, reaction of

sulfenamide (97) with tris(trimethylsilyl)silane also led to only uncyclised amine (129b) being recovered from the reaction (Scheme 104).

It appears that cyclisation of an aminyl radical onto the cyclohexene ring is unfavoured, due presumably to the intermediate perhydroindoline radical not being stabilised in any way and therefore undergoing immediate ring-opening to the uncyclised amine. In this case, the rate of ring-opening is still greater than the rate of cyclisation of the aminyl radical, *i.e.* in keeping with other unactivated alkenylaminyl radical systems.

Scheme 104



4.3.1) Ionic Cyclisation Reactions onto an Unactivated Cyclohexene Ring

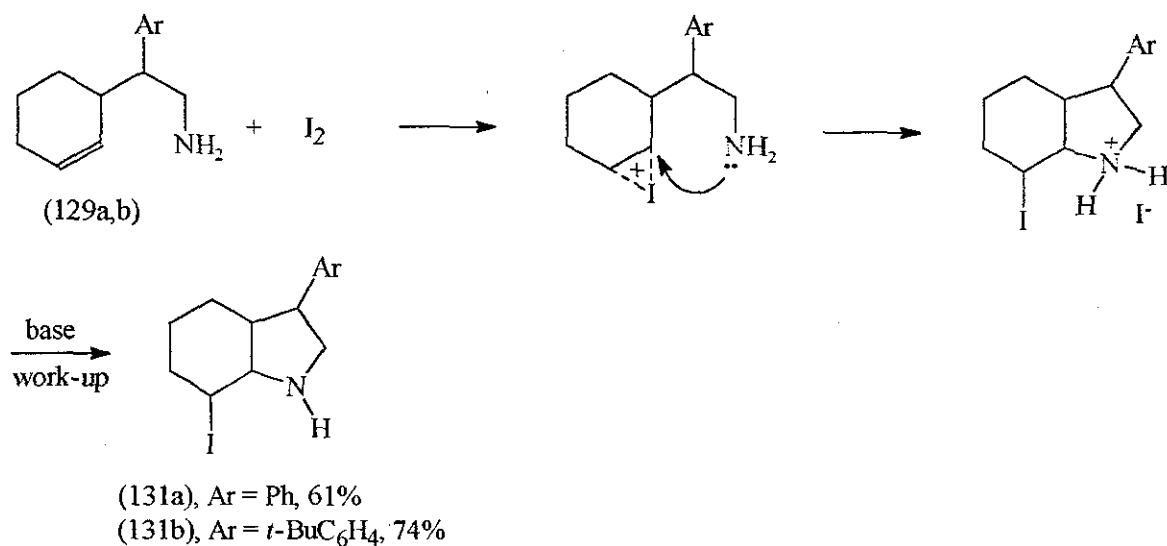
In order to synthesise the required perhydroindoles, reactions involving the amines (129a,b) and either iodine⁹⁹ or mercury(II) chloride¹⁰⁰ were performed. The reaction between amines (129a,b) and iodine resulted in good yields of 7-iodoperhydroindoles (131a,b) being generated. It is assumed that the slightly electropositive iodine atom coordinates to the double bond. Attack on the activated double bond by the nucleophilic amine then gives cyclisation. Excess iodine was destroyed by reduction to iodide by sodium thiosulfate solution (Scheme 105).

Further work on this molecule, replacing the iodide atom with nucleophilic species, and by substituting molecules on the amine, were proposed. However, initial attempts at *N*-methylating this molecule using paraformaldehyde in trifluoroacetic acid failed,¹⁰¹ and time did not allow for any further research into this area.

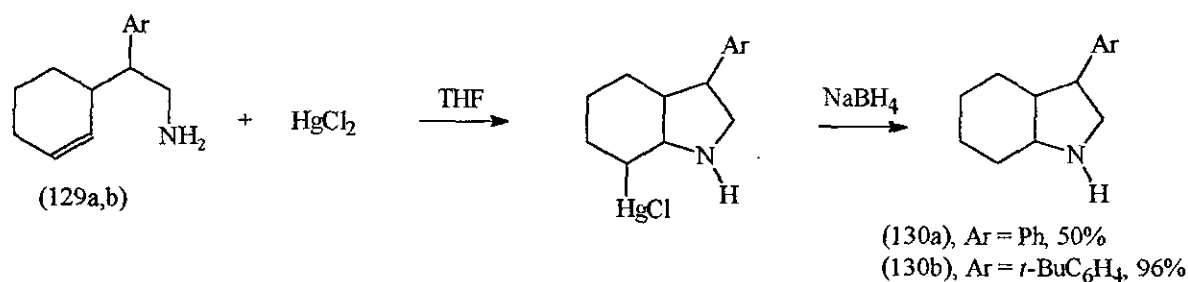
Cyclisation to form perhydroindoles was also performed using mercury(II) chloride. The intermediate mercury adducts were not purified prior to reduction with sodium

borohydride, and good overall yields of perhydroindoles (130a,b) were formed from this process (Scheme 106).

Scheme 105

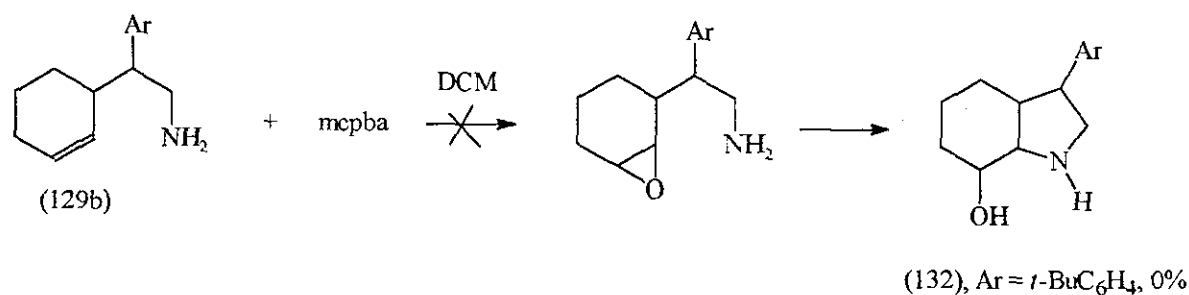


Scheme 106



Finally, attempts were made to form 7-hydroxyperhydroindoles (132) through reaction of amine (129b) with *m*-chloroperbenzoic acid in dichloromethane¹⁰² (Scheme 107). Unfortunately, upon work-up of the reaction mixture, none of the expected perhydroindole (132) could be isolated and this approach was subsequently discontinued.

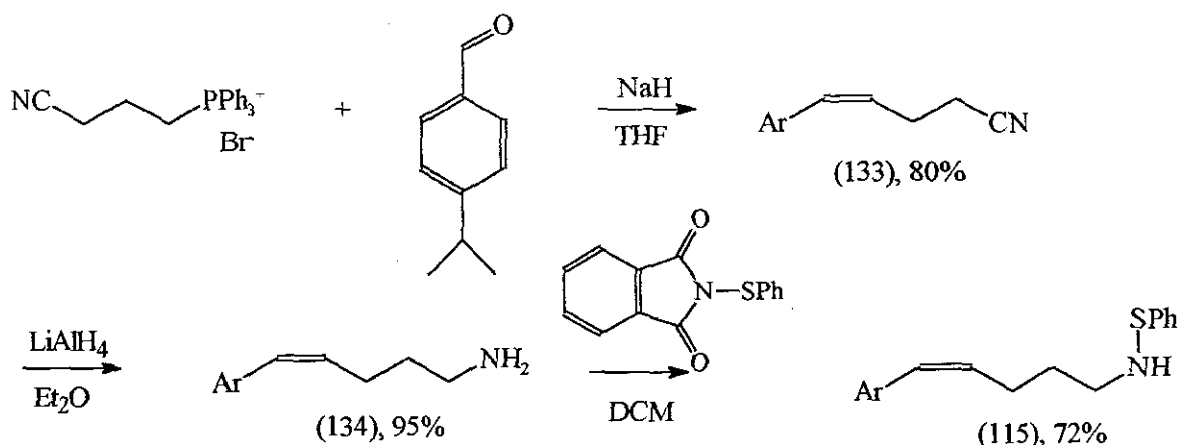
Scheme 107



4.4) Cyclisation of Aminyl Radicals to form Stable Benzylic Radicals

In order to overcome this lack of cyclisation, it was postulated that cyclisation of aminyl radicals could be achieved if the initial cyclised radical was stabilised in some way *e.g.* through conjugation with an aromatic ring. For this purpose, the sulfenamide *cis-N*-(benzenesulfenyl)-5-(4-isopropylphenyl)pent-4-enylamine (115) was synthesised and reacted under radical conditions. The nitrile (133) was formed from a Wittig reaction between 4-isopropylbenzaldehyde and 3-cyanopropylphosphonium bromide. Reduction of this nitrile with lithium aluminium hydride gave the amine (134), which upon reaction with *N*-(benzenesulfenyl)phthalimide gave the required sulfenamide (115) in good overall yield (Scheme 108). It is interesting to note that the initial Wittig reaction gave selectively the *cis*-isomer, with none of the *trans*-isomer being observed. It is believed that it is the use of the polar solvent tetrahydrofuran that gives this selectivity, as use of different solvents such as dichloromethane tend to give more of the *trans*-isomer (See Section 4.6).

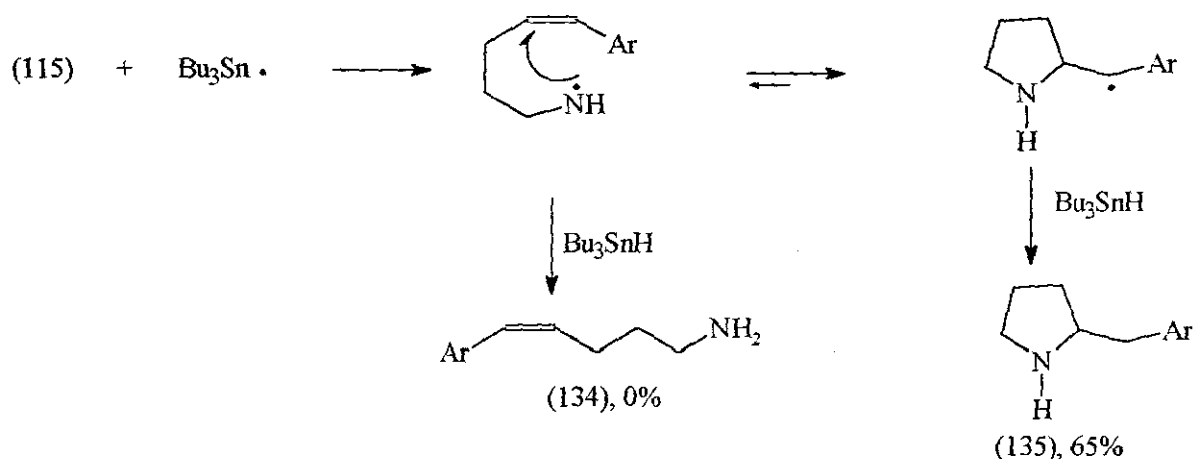
Scheme 108



Reaction of sulfenamide (115) with tributyltin hydride and AIBN using the syringe pump method lead to the formation of 2-(4-isopropylbenzyl)pyrrolidine (135) in 65% yield. Clearly, the initial cyclised radical is stabilised through conjugation with the aromatic ring (Scheme 109). This provides a strong driving force for the cyclisation reaction and results, in this case, of selective cyclised material. No uncyclised amine (134) was recovered from this reaction.

This method provided a facile route to a number of substituted pyrrolidines. Further work was undertaken to widen the scope of nitrogen heterocycle synthesis, the results of which are detailed below.

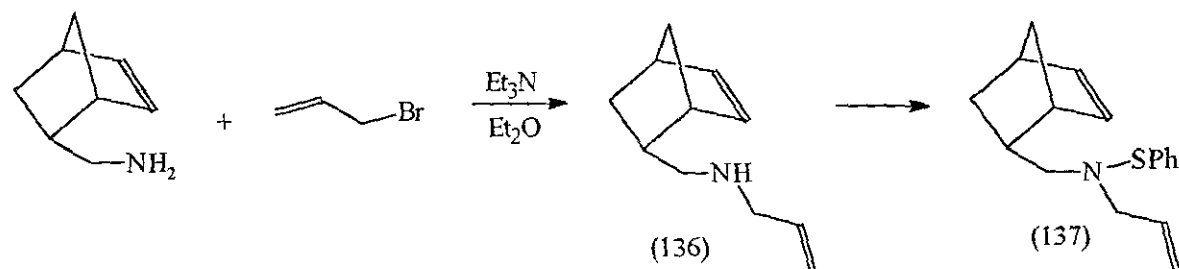
Scheme 109

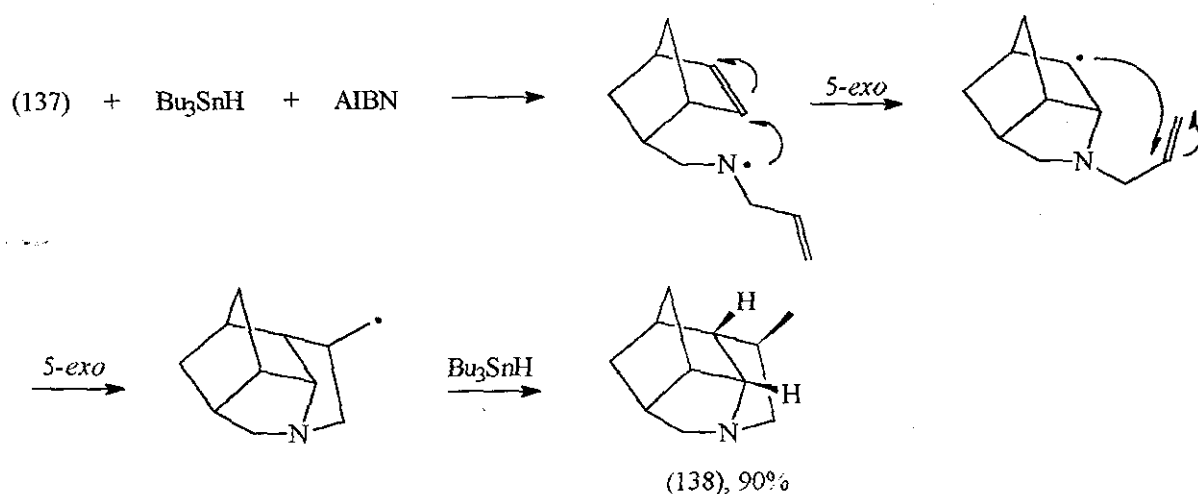


4.5) Cyclisation of Aminyl Radicals using a Tandem Cyclisation Process

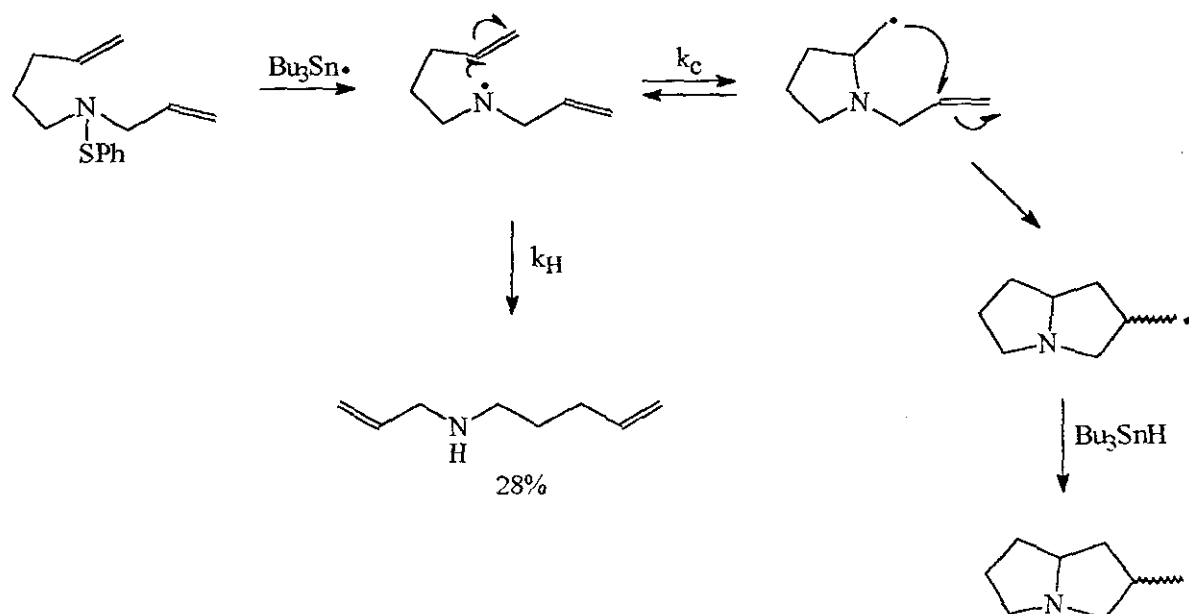
So far two methods have been used to overcome the reversible cyclisation of aminyl radicals; kinetically fast cyclisation onto a strained bicycloheptenyl alkene and cyclisation to yield stabilised intermediate radicals. A third method considered was to trap the cyclised carbonyl radical in an irreversible tandem cyclisation, thereby preventing ring-opening back to the aminyl radical. Cyclisations of pent-5-enyl radical systems are not reversible and therefore a tandem reaction of this system should force aminyl radical cyclisation. Work by Dr. R. Marmon on the *endo*-(bicyclo[2.2.1]hept-5-en-2-yl)methylaminyl radical series illustrated that good yields of cyclised material could be obtained through a tandem radical cyclisation reaction. *endo*-(Bicyclo[2.2.1]hept-5-en-2-yl)methylamine was reacted with allyl bromide in the presence of triethylamine to form *endo*-(bicyclo[2.2.1]hept-5-en-2-yl)-*N*-allyl-methylamine (136). The sulfenamide (137) was then formed and reacted with tributyltin hydride under standard radical conditions. Analysis of the reaction mixture showed that the tandem cyclised product (138) was formed selectively in 90% yield, with no evidence of uncyclised or monocyclised material being present (Scheme 110).

Scheme 110



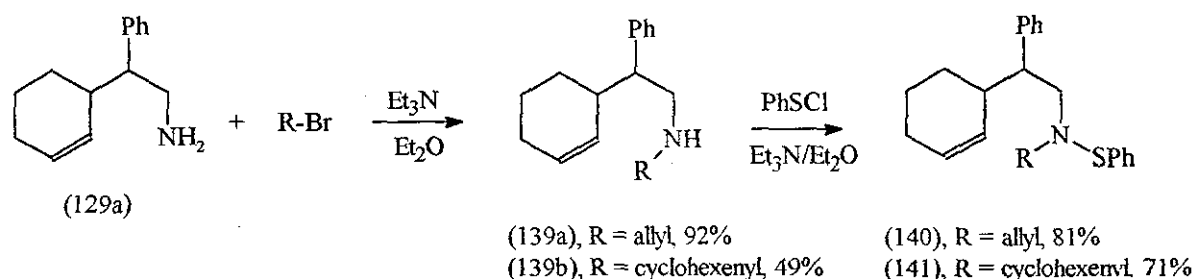


Obviously, the initial cyclised radical was intramolecularly trapped by the extra allyl group, leading to exclusive tandem cyclisation taking place. This indicated a clear route to the synthesis of many nitrogen heterocycles. The method was further illustrated at a later stage by Dr R. Marmon, by the successful tandem cyclisation of the simplest system *N*-allylpent-5-enylaminyl radicals.



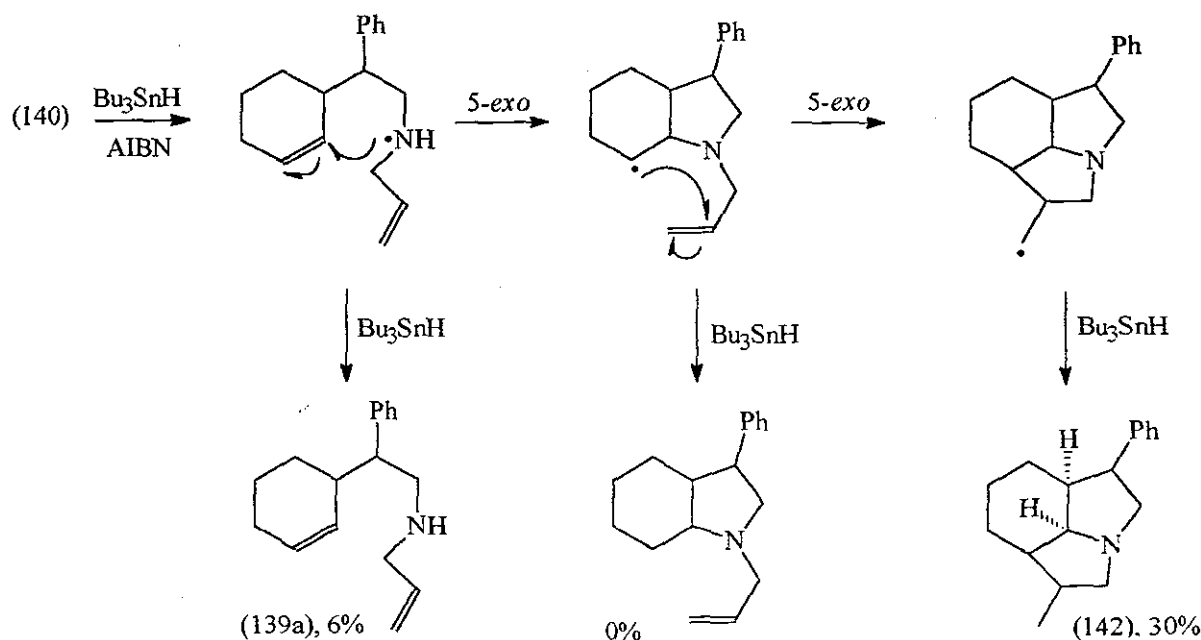
We sought to use the methodology to overcome the lack of cyclisation to perhydroindoles. To this end the amine (129a) was reacted with both allyl bromide and in a separate experiment, 3-bromocyclohexene, in the presence of triethylamine to form the secondary amines (139a,b). The sulfenamides (140, 141) were then formed by reaction with benzenesulfonyl chloride (Scheme 111).

Scheme 111



Sulfenamide (140) was reacted with tributyltin hydride using the syringe pump method. Work-up of the reaction after a 5 h addition of the tin hydride gave a mixture of fully bicyclic amine (142) and uncyclised amine (139a) in a ratio of 5:1 (Scheme 112). This is compared to the attempted cyclisation of the sulfenamide (97) when only uncyclised material was recovered from the reaction (See Section 4.3). The bicyclic material was obtained as a mixture of 3 diastereoisomers in the ratio 2:2:1. The first ring closure should give a *cis* stereochemistry at the ring-junction, but this could not be determined from ^1H NMR spectroscopic studies. Interestingly, no monocyclised perhydroindole was observed, indicating that all of the initially cyclised intermediate was rapidly trapped in the tandem cyclisation.

Scheme 112



Sulfenamide (141) was also reacted with tributyltin hydride using the syringe pump method. However, in this case, work-up of the reaction gave a mixture of monocyclised amine (143) and uncyclised amine (139b), with none of the expected bicyclic amine (144) being observed (Scheme 113). This unusual behaviour could be explained by molecular model studies on this reaction. It appeared that the monocyclised radical (145) may be able

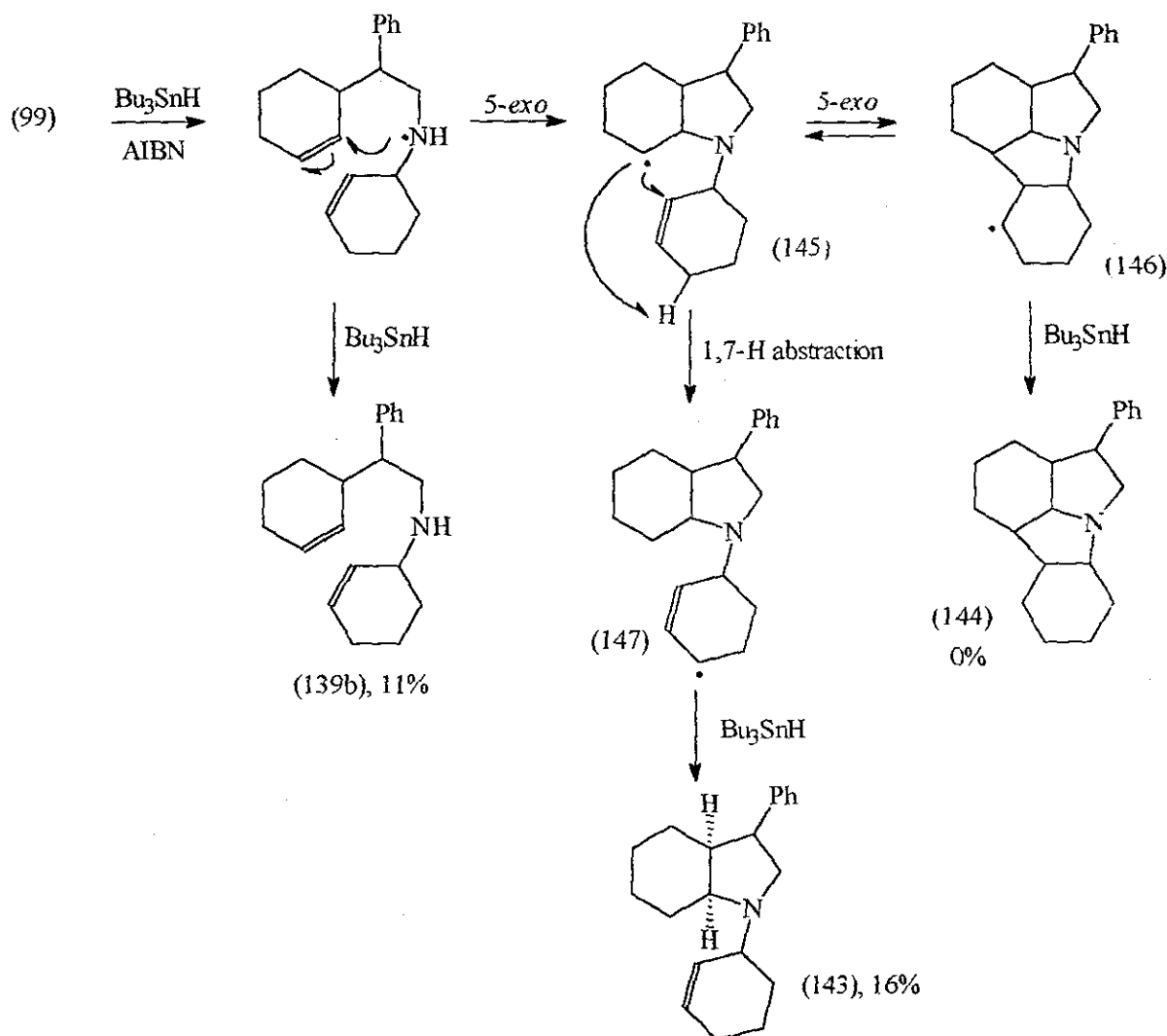
to perform a 1,7-H abstraction from the allylic position of the cyclohexyl ring, to leave the stabilised allylic radical (147). An alternative explanation is that a bimolecular hydrogen abstraction takes place to trap the monocyclised perhydroindole radical intermediate. One of these processes was more favoured than the trapping of the radical (145) by the cyclohexene olefin, to give radical (146).

4.6) Cyclisation of Aminyl Radicals using a Stabilised Benzylic Radical together with a Tandem Cyclisation Process

At this stage, it had been successfully proved that aminyl radical cyclisation could be aided by formation of stabilised radicals (See Section 4.4) and through tandem cyclisation reactions (See Section 4.5). By combining these two methods of cyclisation reactions, the synthesis of a wide range of substituted pyrrolizidines and indolizidines could be envisaged. In order to investigate this, Dr. R. Marmon synthesised the sulfenamide (148) and reacted it with tributyltin hydride using the syringe pump method. The products from this reaction were found to be the pyrrolizidine (152) present as a mixture of three diastereoisomers in the ratio 2.8:1.2:1, and the indolizidine (153). Two of the diastereoisomers of the pyrrolizidine were identified by ^1H NMR spectroscopic studies, though the structure of the third diastereoisomer remained elusive. It is believed that the aminyl radical (149) undergoes cyclisation to form the stabilised benzylic radical. This then cyclises in a 5-*exo* or 6-*endo* manner to give either alkyl radical (150) or radical (151). Abstraction of hydrogen from tributyltin hydride by these radicals gives the pyrrolizidine and indolizidine observed from the reaction (Scheme 114).

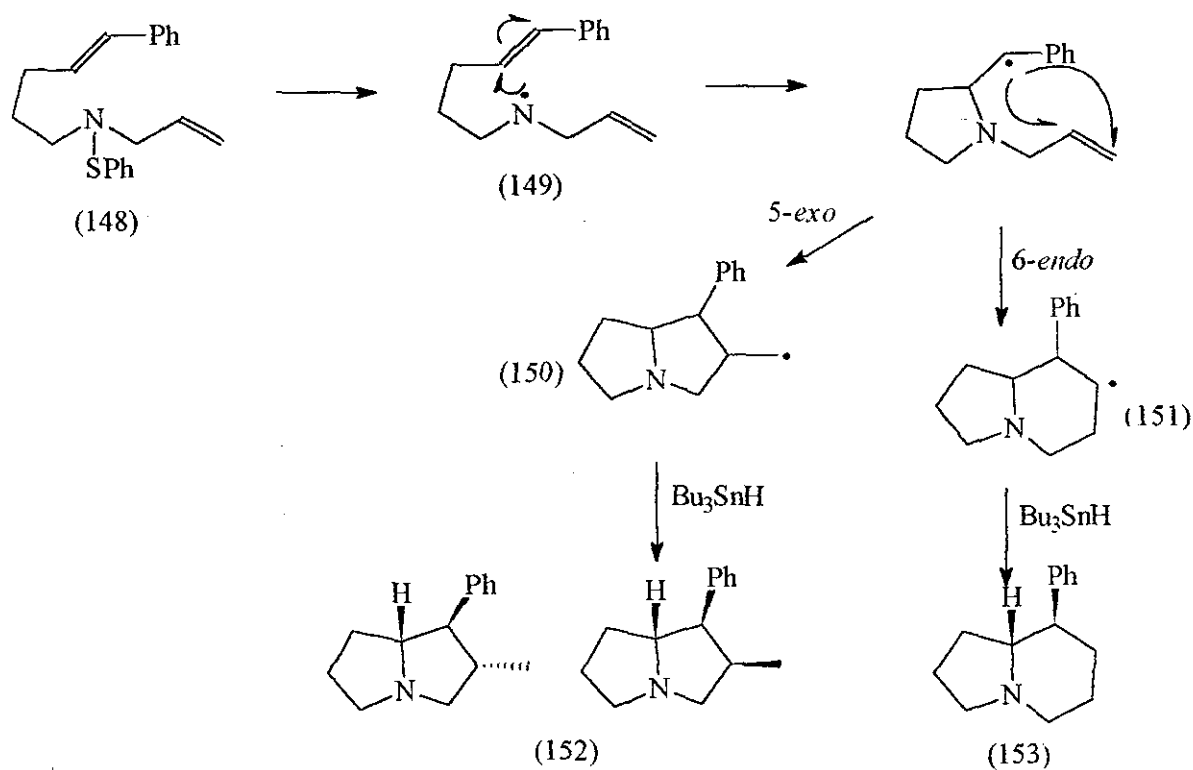
The potential of this system was extended by investigating the cyclohexenyl analogue (101). The precursor amine (154) was synthesised from the amine (134) reacting with 3-bromocyclohexene in the presence of triethylamine. The sulfenamide (101) was then formed by reacting this newly-formed amine with benzenesulfonyl chloride (Scheme 115).

Scheme 113

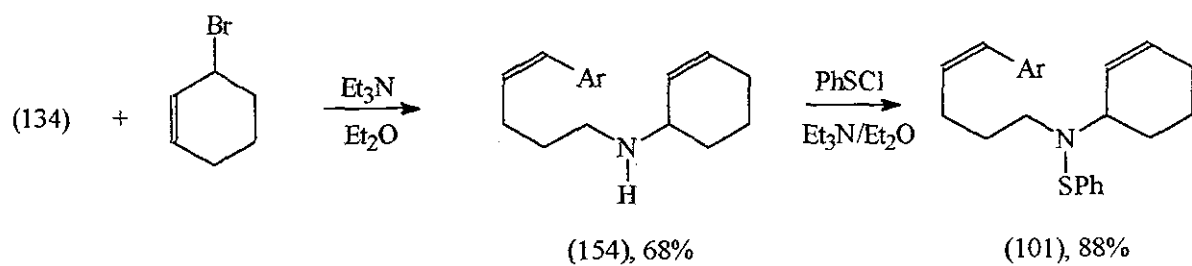


Reaction of sulfenamide (101) under standard radical conditions led to a mixture of the bicyclic amine (157) and the uncyclised amine (154) in the ratio 2.4:1 being formed (Scheme 116). The stereochemistry of the alkene in the uncyclised amine remained *cis*, indicating that it was formed from direct reduction of the radical (155). If isomerisation to the *trans* alkene was observed, this would suggest equilibration via radical (155). This has therefore been shown not to be the case. The tricyclic amine (157) was found to be one diastereoisomer. Model studies on this molecule suggest one favourable diastereoisomer [as shown for (157)] though NMR spectroscopic studies could not confirm that this was indeed the diastereoisomer that had been observed. The second cyclisation is predicted to give a *cis* ring junction as is observed for cyclisation onto cycloalkenes. Although the yields were low, shortage of time precluded optimisation of yields and radical conditions.

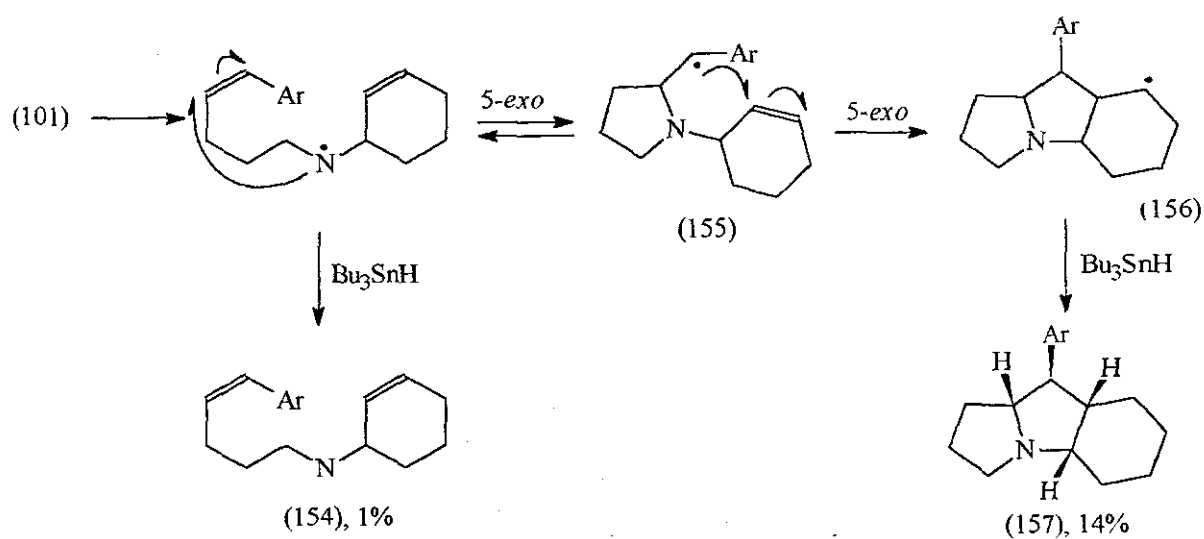
Scheme 114



Scheme 115



Scheme 116



The synthesis of substituted indolizidines was also approached using this method with the attempted synthesis *via* a 6-*exo*, 5-*exo* cyclisation. The precursor sulfenamide (161) was synthesised from the Wittig-formed nitrile (158) as shown in Scheme 117. It was found that the reaction formed selectively the *cis*-isomer if performed in tetrahydrofuran as solvent. When identical reactions were performed in different solvents, the product nitrile was formed as a mixture of *cis*- and *trans*-isomers (Table 12). When the reaction was performed in the presence of 18-Crown-6, the nitrile (158) was formed in a ratio 1:4 *cis:trans*. Reduction of the nitrile with lithium aluminium hydride gave amine (159) and reaction with allyl bromide in the presence of triethylamine gave amine (160). The sulfenamide (161) was formed by reacting amine (160) with *N*-(benzenesulfonyl)phthalimide under standard conditions (Scheme 117).

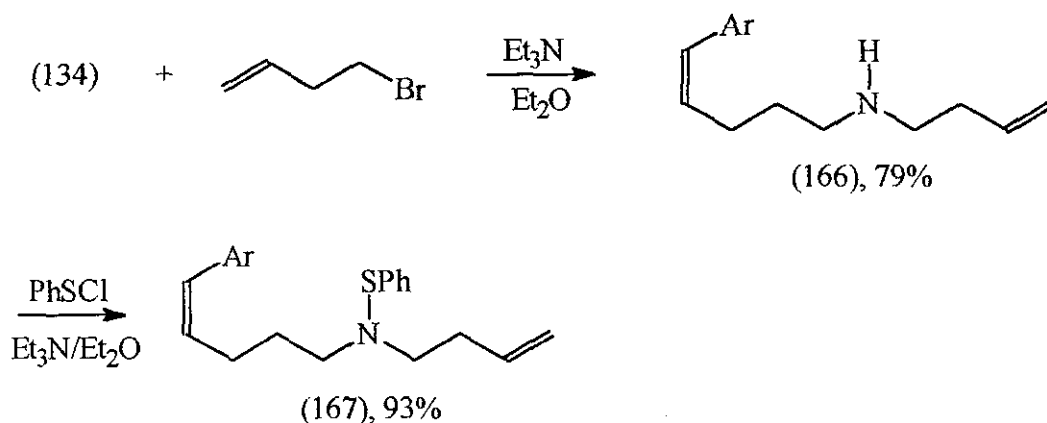
Table 12. Isomeric ratio of nitrile (156) formed from the Wittig Reaction between 4-*t*-butylbenzaldehyde and the phosphonium salt of valeronitrile

Solvent	<i>cis:trans</i>	Yield (%)
Tetrahydrofuran	exclusively <i>cis</i>	84
Diethyl ether	1:3	72
Dichloromethane	3:1	56

The sulfenamide (161) was reacted under standard radical conditions using a syringe pump. Upon work-up of the reaction, however, none of the expected indolizidine (164) was observed. The only product to be isolated from this reaction was the *trans*-isomer of the uncyclised amine (160) (Scheme 118). By conducting model studies on this reaction, it became clear that the aminyl radical (162) was perfectly placed to undergo a 1,5-H abstraction to give the extremely stable radical (163). This would rapidly isomerise to give the more stable *trans*-radical, which would lead to the observed product. This reaction was repeated using tris(trimethylsilyl)silane in place of tributyltin hydride, though this gave the same product as before. Further evidence was provided by repeating the reaction using tributyltin deuteride. This gave the only product as the amine (160) with a deuterium at 4-C, proving the radical sequence as outlined. It is useful to note that this reaction only occurred due to the formation of the very stable phenylallylic radical. Under normal conditions, cyclisation would probably have occurred to give the required product.

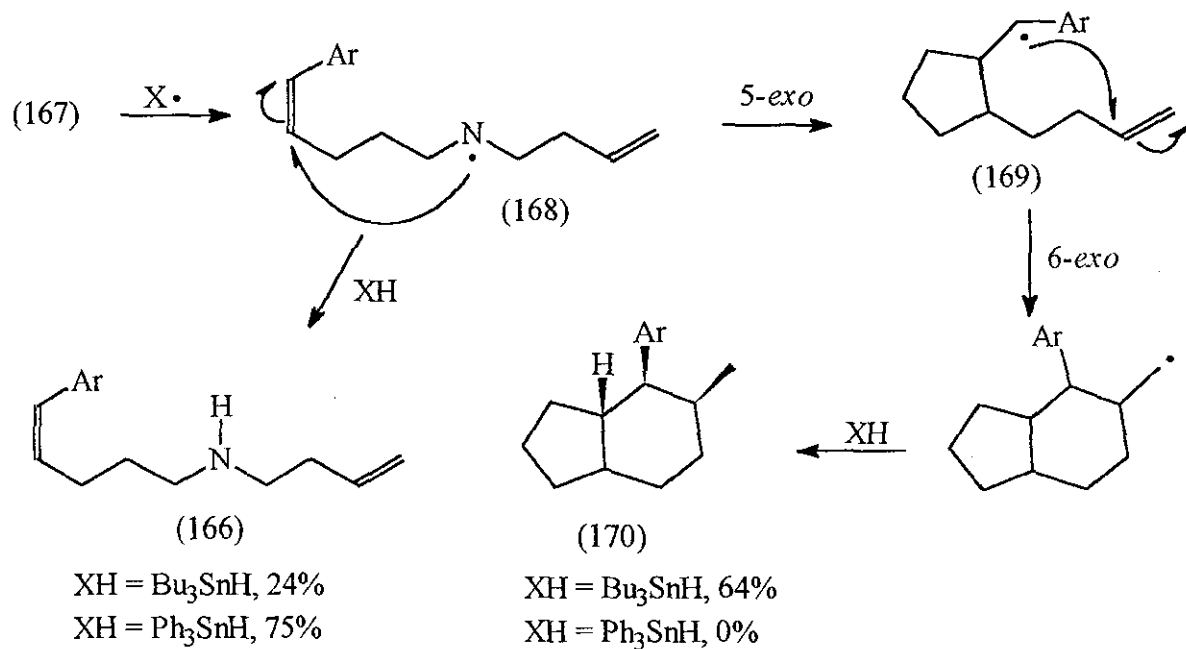
However, the isomeric indolizidine (170) was formed by a 5-*exo*, 6-*exo* cyclisation from the reaction of sulfenamide (167) under standard radical conditions. The sulfenamide was synthesised as before by reacting the amine (134) with 4-butenyl bromide in the presence of triethylamine, followed by reaction with benzenesulfonyl chloride (Scheme 119).

Scheme 119



The sulfenamide (167) was reacted by the normal method with tri-*n*-butyltin hydride and the indolizidine (170) was formed as the major product, though a small amount of uncyclised amine (166) was also observed (Scheme 120). Two isomers of indolizidine (170) were formed, though difference nOe and COSY45 techniques indicated that they were in fact invertomers in the ratio 55:45. The major invertomer is as shown for (170). When this reaction was repeated using triphenyltin hydride in place of tributyltin hydride, only a trace of indolizidine (170) was observed, with the major product being the uncyclised amine (166). Triphenyltin hydride is known to react more rapidly with nucleophilic radicals than tributyltin hydride, and in this case was able to trap the aminyl radical (168) prior to cyclisation. This result illustrates the small difference in rate between cyclisation and ring-opening.

Scheme 120



To conclude, it has been shown that a variety of pyrrolizidines, indolizidines and perhydroindoles can be formed using the sulfenamide tandem methodology. By careful choice of the precursors, it should also be possible to synthesise indolizidines by 6-*exo*, 5-*exo* cyclisation and quinolizidines by 6-*exo*, 6-*exo* cyclisation. This work could lead to the rapid and facile synthesis of a whole range of natural product analogues. Shortage of time preclude further investigation into the synthesis of these other ring systems.

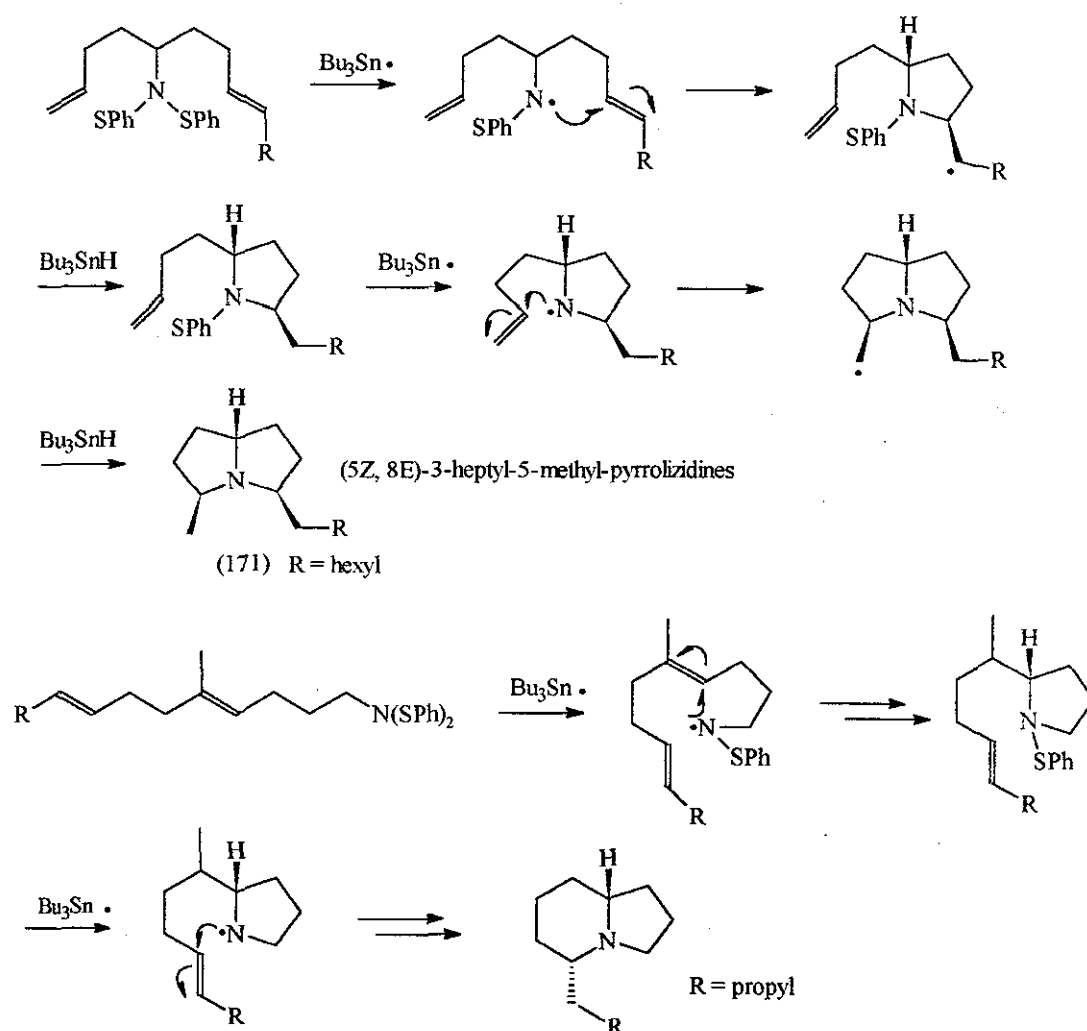
Chapter 5. Synthesis and Reactivity of Disulfenamides

5.1) The Use of Disulfenamides in forming Aminyl Radicals

Aminyl radical cyclisations have a potential, and as yet unexploited, advantage over alkoxy and alkyl radical cyclisations in that two consecutive aminyl radicals can be generated at the same centre. Using our sulfenamide/tri-*n*-butyltin hydride methodology, this process could be achieved using the action of tributyltin radical on disulfenamides.¹⁰³ Disulfenamides are known, stable compounds which can be easily prepared. Sequential cyclisation using disulfenamides as the precursors could lead to a wide range of natural product analogues. Examples to illustrate the effectiveness of disulfenamides in synthetic strategies include the synthesis of the pyrrolizidine alkaloid, (5*Z*,8*E*)-3-heptyl-5-methyl-pyrrolizidine (171)¹⁰⁴ found in the venom of Thief Ants (*selenopsis*) and the newly isolated Dendrobatid alkaloids,¹⁰⁵ a poisonous extract from frogs (Scheme 121).

The second part of this project was designed to show that a variety of disulfenamides could be synthesised and reacted to form aminyl radicals. At first, only reduction and ring-opening reactions involving aminyl radicals generated from disulfenamides were carried out, as detailed below, though various attempts at cyclising aminyl radicals from disulfenamides were achieved and these are detailed in Chapter 6.

Scheme 121



5.2) Synthesis of Disulfenamides

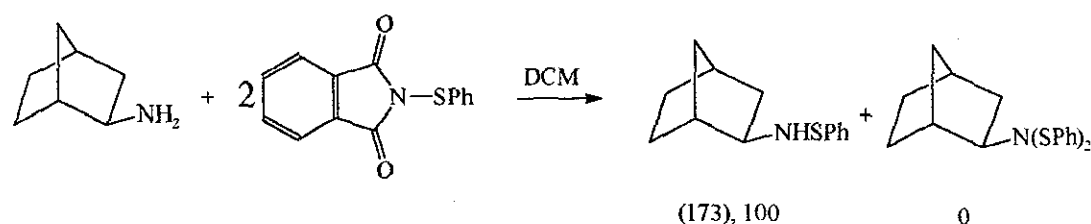
Disulfenamides have been used in the literature mainly as precursors to amines which are difficult to prepare from other methods¹⁰⁶. The main preparation of disulfenamides seems to be through the action of bis(benzenesulfonyl)amine¹⁰⁷ (172) on alkyltosylates or bromides. Below it is intended to detail our attempts at forming disulfenamides through the standard methods of sulfenamide formation, namely through using benzenesulfonyl chloride and *N*-(benzenesulfonyl)phthalimide and our later attempts at disulfenamide formation using bis(benzenesulfonyl)amine.

5.2.1) Attempted Synthesis of Disulfenamides using *N*-(Benzenesulfonyl)-phthalimide

Initial attempts at forming disulfenamides were through the reaction between primary amines and two equivalents of *N*-(benzenesulfonyl)phthalimide. *exo*-2 Aminobicyclo[2.2.1]heptane was reacted with 2 equivalents of *N*-

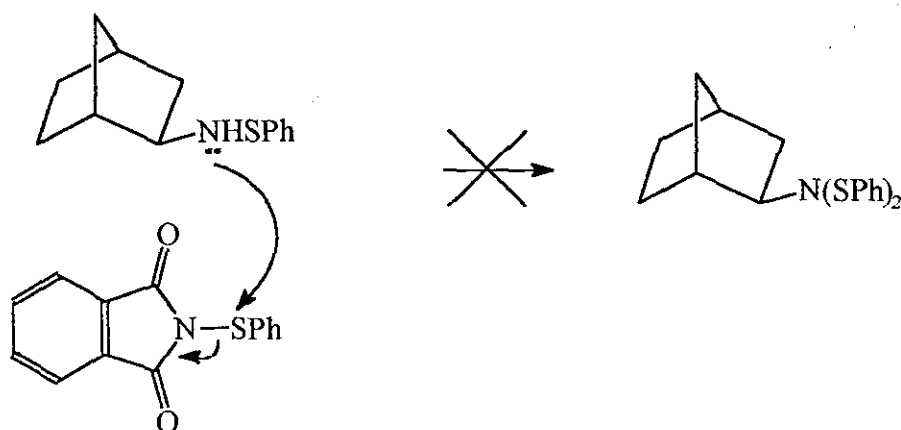
(benzenesulfonyl)phthalimide in benzene. Despite refluxing the mixture for a period of 5 hours, the only product obtained from this reaction was the monosulfenamide (173) (Scheme 122).

Scheme 122



A similar result was noticed when the amine to be reacted was (bicyclo[2.2.1]hept-5-en-2-yl)methylamine. Once more, the only product isolated from this reaction was the monosulfenamide. It was evident from these two results that *N*-(benzenesulfonyl)phthalimide could not be used to form disulfenamides. The most likely reason is that *N*-(benzenesulfonyl)phthalimide is not active enough to donate a sulfenating group onto the already formed monosulfenamide (Scheme 123). The monosulfenamide is only weakly basic because of the -I inductive effects of the adjacent sulfur.

Scheme 123

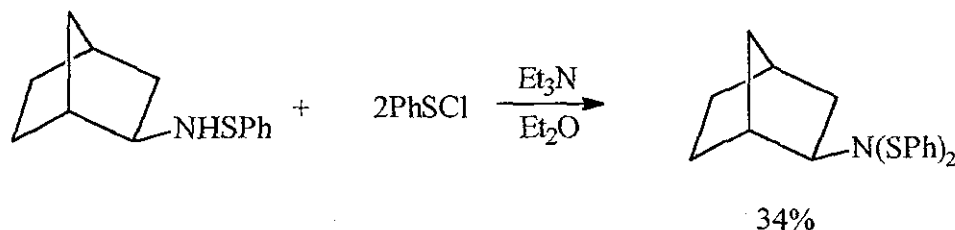


5.2.2) Formation of Disulfenamides using Arenesulfonyl chlorides

When it became clear that *N*-(benzenesulfonyl)phthalimide could not be used to form disulfenamides, the reaction between primary amines and two equivalents of an arenesulfonyl chloride was investigated. The reactions were performed in the same manner as for the formation of monosulfenamides, using diethyl ether as solvent and triethylamine as an acid acceptor. In this way, *N,N*-di(benzenesulfonyl)-

(bicyclo[2.2.1]hept-*exo*-2-ylamine was formed in 34% yield after purification on a dry alumina column (Scheme 124).

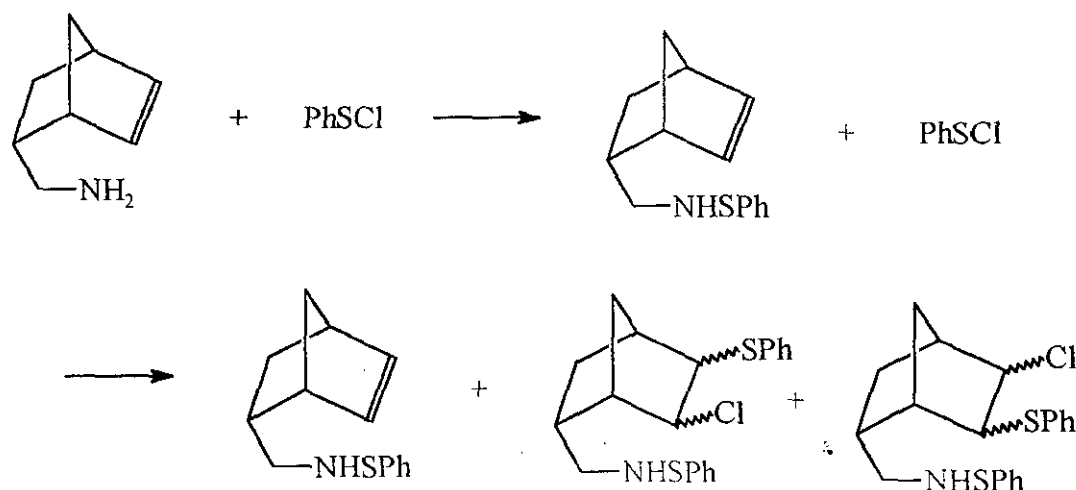
Scheme 124



N,N-di(Benzenesulfonyl)cyclohexylamine was also formed using this method, though problems encountered during purification led to a minimal yield of product.

In an attempt to form a precursor for cyclisation studies using disulfenamides, two equivalents of benzenesulfonyl chloride were reacted with (bicyclo[2.2.1]hept-5-en-2-yl)methylamine. However, standard work-up of the reaction led to a mixture of products being observed. NMR spectroscopic analysis showed that one of the products was the equivalent monosulfenamide. However, the evidence also showed saturation of the double bond. Since sulfonyl halides are known to react with double bonds,¹⁰⁸ it was reasoned that this had occurred. Therefore, even though reaction to form monosulfenamides is much faster than the reaction of benzenesulfonyl chloride with the olefin, the reaction to form the disulfenamide from the monosulfenamide is not. ¹H NMR spectroscopy of the crude products indicated addition of benzenesulfonyl chloride onto the alkene (Scheme 125). These products were of no interest and further purification was not carried out. These results show that ω -alkenyl-disulfenamides required for cyclisation studies could not be prepared from ω -alkenylamine and benzenesulfonyl chloride.

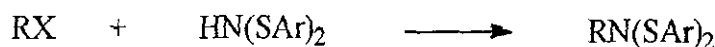
Scheme 125



5.2.3) *N,N*-di(Benzenesulfonyl)amine as a Precursor to Disulfenamides

According to literature methods, the most facile way of forming disulfenamides is through the action of the anion of *N,N*-di(benzenesulfonyl)amine on alkyl halides or tosylates¹⁰⁷ (Scheme 126).

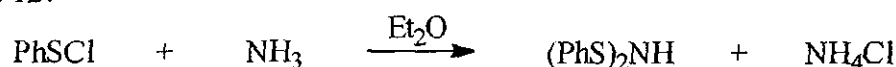
Scheme 126



X = halide, tosylate

N,N-di(Benzenesulfonyl)amine itself can be formed by reacting benzenesulfonyl chloride with diethyl ether saturated with ammonia gas. According to literature preparations, this method leads to good yields of the required product (Scheme 127).

Scheme 127



Unfortunately, when we repeated the reaction, the amine was only obtained in low yield, requiring a vast excess of benzenesulfonyl chloride to be synthesised for this reaction. *N,N*-di(Benzenesulfonyl)amine was found to be a crystalline compound that was stable only if kept refrigerated. In this way, the amine could be kept for up to two months, with no sign of degradation to diphenyl disulfide.

In an attempt to improve the yield for the formation of this amine, the 4-chlorophenyl analogue was formed (174). Synthesis was the same as for the *N,N*-di(benzenesulfonyl)amine, the yield was slightly improved, and the final product appeared to be more stable than the former product (Scheme 128).

Scheme 128



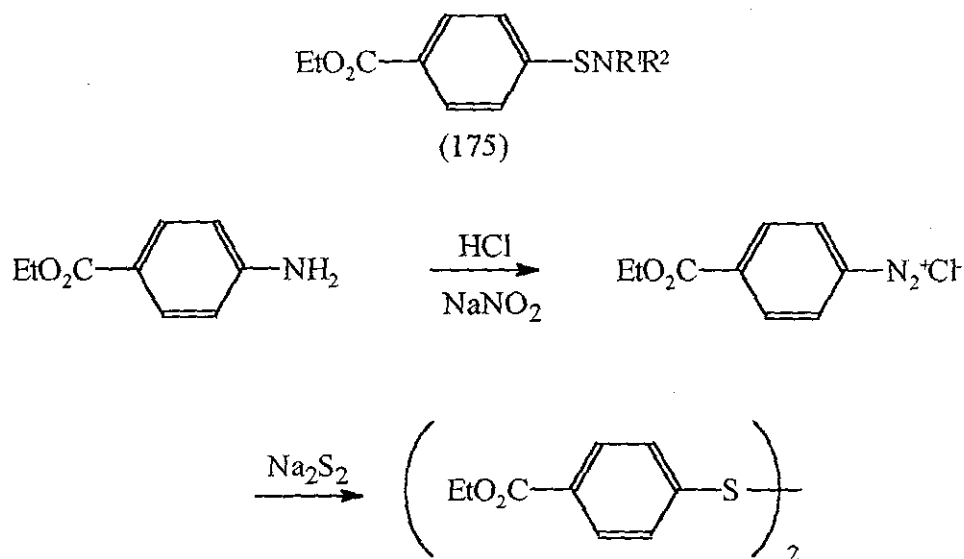
Ar = phenyl, 19% (172)

Ar = 4-Cl-phenyl, 29% (174)

Finally, work performed by Beckwith *et al*²² had concentrated on the formation of 4-ethoxycarbonylphenyl sulfenamides (175). It was believed that this group would lead to more stable disulfenamides and so the formation of the disulfide (176) was attempted following a known literature preparation.¹⁰⁹ Unfortunately, none

of the expected disulfide was formed from this method, and so the synthesis of the equivalent, *N,N*-di(arylsulfenyl)amine could not be attempted (Scheme 129).

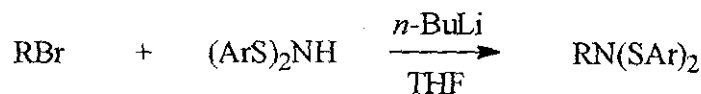
Scheme 129



5.3) Formation of Disulfenamides for use in Reduction reactions

As has already been noted, the disulfenamide *N,N*-di(benzenesulfenyl)-cyclohexylamine was formed from the action of cyclohexylamine on two equivalents of benzenesulfenyl chloride. Further disulfenamides were formed from the action of alkyl bromides on *N,N*-di(arylsulfenyl)amine. These included *N,N*-di(benzenesulfenyl)-4-methylbenzylamine (177), *N,N*-di(benzenesulfenyl)methylamine (178) and *N,N*-di(*p*-chlorophenylsulfenyl)benzylamine (179) (Scheme 130). All of the disulfenamides were purified by dry flash chromatography using alumina and all were formed in reasonable yield.

Scheme 130



R = 4-methylbenzyl, Ar = phenyl, 92% (177)

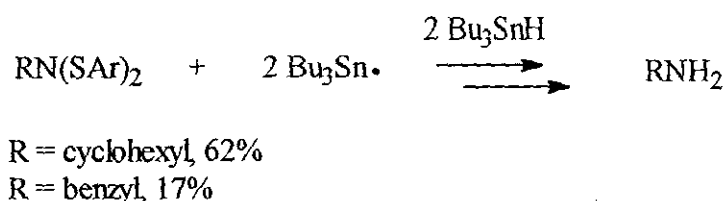
R = Me, Ar = phenyl, 48% (178)

R = benzyl, Ar = *p*-Cl-phenyl, 23% (179)

To determine whether disulfenamides could be used to generate aminyl radicals, the disulfenamides *N,N*-di(benzenesulfenyl)cyclohexylamine and *N,N*-di(*p*-chlorophenylsulfenyl)benzylamine were reacted with tri-*n*-butyltin hydride in

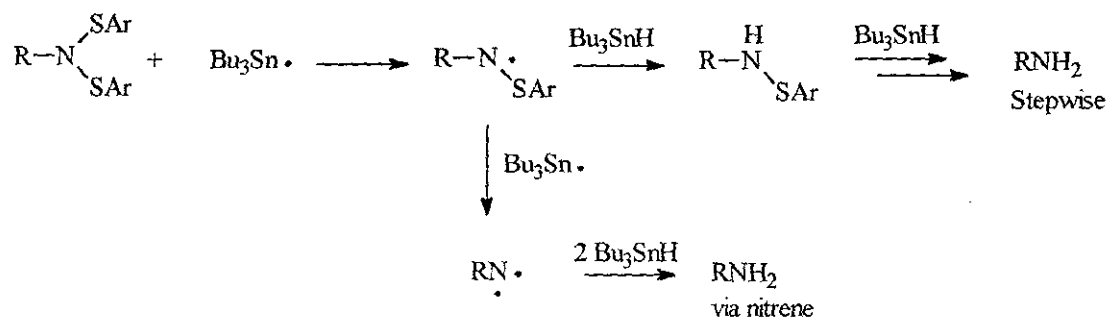
refluxing solvent using standard radical procedures. After two hours, TLC analysis had indicated that all of the starting disulfenamide had been converted. The reactions were then worked-up to give cyclohexylamine and benzylamine respectively (Scheme 131). Both of these products were compared with authentic samples obtained from Aldrich Chemical Co. The yields for these reactions were not optimised.

Scheme 131



These simple experiments showed that disulfenamides could be used as precursors to aminyl radicals, though there was no proof to say whether the reaction proceeded in a step-wise manner, *i.e.* the sulfenylaryl groups were removed one-by-one by the tin hydride to yield the triplet nitrene, or whether each abstraction was followed by H-abstraction from tin hydride (Scheme 132). Obviously, further experiments needed to be performed to solve this problem. If a nitrene was an intermediate, the lower energy triplet nitrene would be expected which would react as a di-radical and may achieve the same aim of sequential bicyclisation onto alkenes.

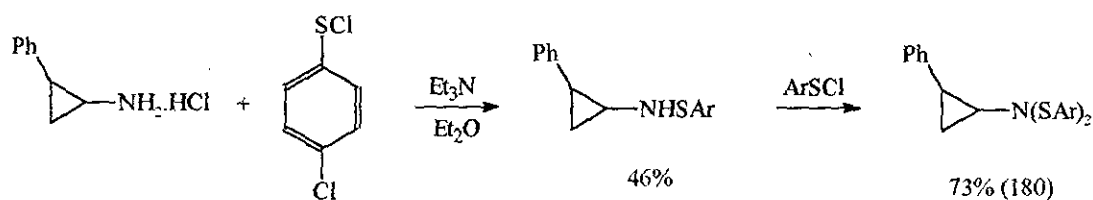
Scheme 132



5.4) Formation of Disulfenamides for use in Ring-Opening reactions

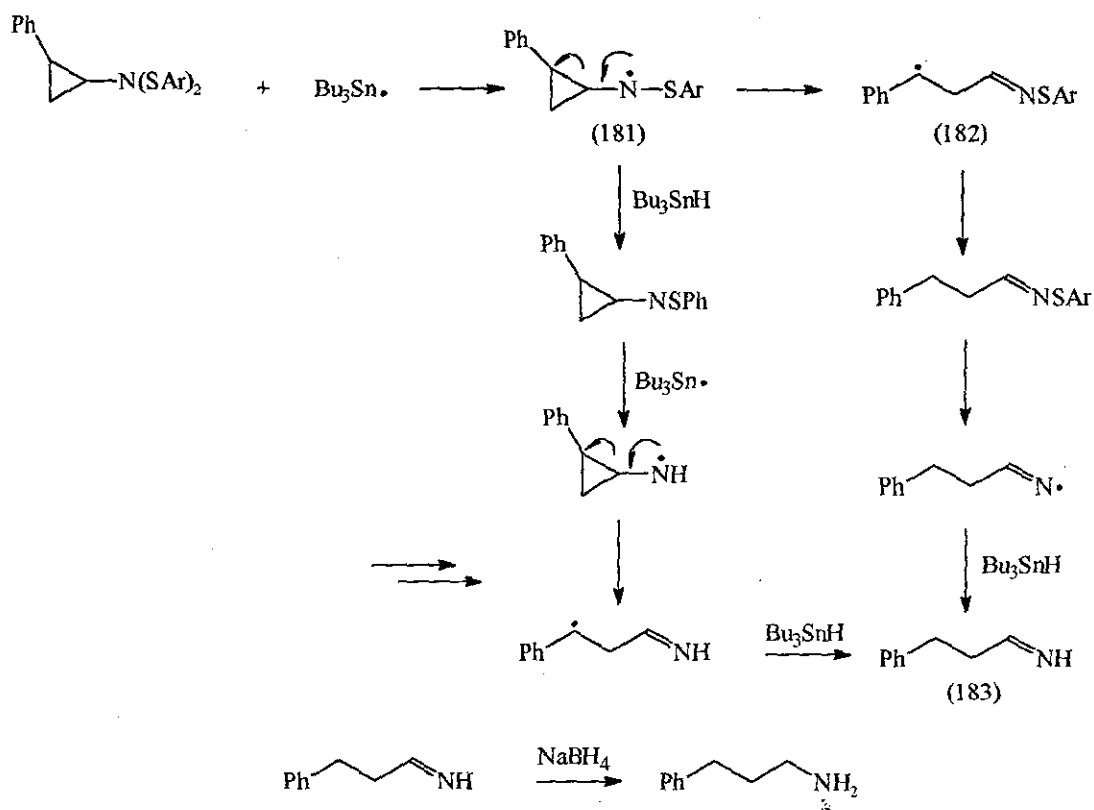
Further proof to illustrate the intermediacy of aminyl radicals from the reaction of disulfenamides with tri-*n*-butyltin hydride was gained from performing a ring-opening reaction. The disulfenamide *N,N*-di(*p*-chlorophenylsulfenyl)-2-phenylcyclopropylamine (180) was formed in a step-wise manner from the hydrochloride salt of 2-phenylcyclopropylamine (Scheme 133).

Scheme 133



This disulfenamide was reacted under standard radical conditions with tin hydride. It was believed that the aminyl radical (181) initially formed would force a ring-opening reaction to give the stabilised benzylic radical (182). This would then abstract a hydrogen from tri-*n*-butyltin hydride to give the imine (183) which could be reduced *in situ* using sodium borohydride to give 3-phenylpropylamine (Scheme 134). Alternative routes via ring-opening of the second intermediate aminyl radical or via a nitrene were also possible and would yield the same product. Because of the extremely fast ring-opening of 2-arylcyclopropylaminyl radicals, ring-opening of the intermediate (*N*-benzenesulfonyl)aminyl intermediate is most likely. The reduction of *N*-(benzenesulfonyl)-imines with tri-*n*-butyltin hydride via iminyl radicals to yield imines has been extensively studied by Zard and co-workers.⁶⁵

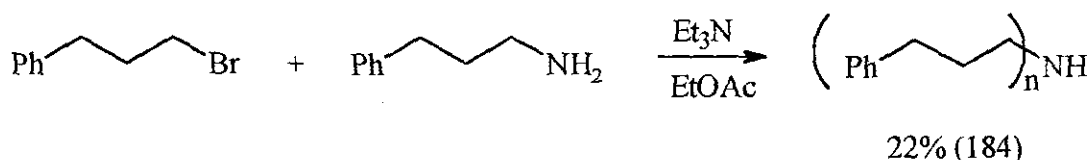
Scheme 134



However, upon work-up of the reaction, a product was isolated that was that shown not to be the expected 3-phenylpropylamine. Further, reaction of *N*-(*p*-chlorophenylsulfenyl)cyclopropylamine under the same conditions led to the isolation of the same product. Both reactions were repeated using lithium aluminium hydride in place of sodium borohydride, though no product was isolated in each of these cases.

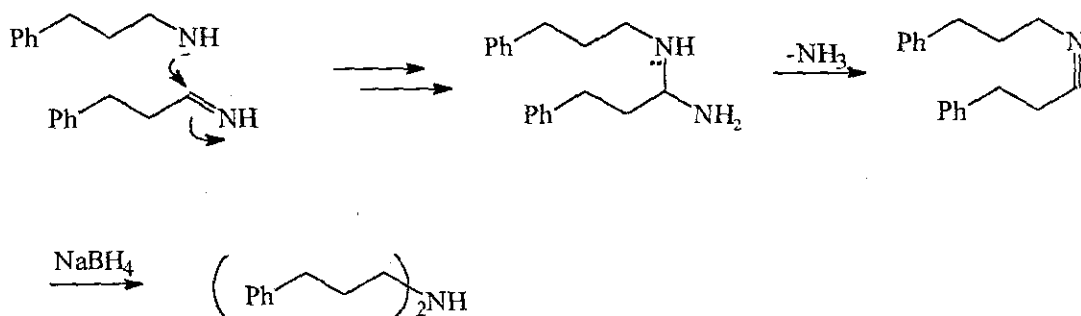
The products obtained from these radical reactions were analysed and were shown to be probably the dimer di(3-phenylpropyl)amine (184). In order to confirm this, an authentic sample of (184) was formed from the reaction between 3-phenylpropylamine and 3-phenylpropyl bromide (Scheme 135). Comparison between the authentic sample and the products obtained from the radical reactions showed that the products were indeed di(3-phenylpropyl)amine.

Scheme 135



These products can be explained by a hydride-induced dimerisation of the initially formed imine (Scheme 136). The evidence of this product in no way deters from the intermediacy of the aminyl radical, as the initially formed imine (183) could only have been formed from a radical reaction taking place.

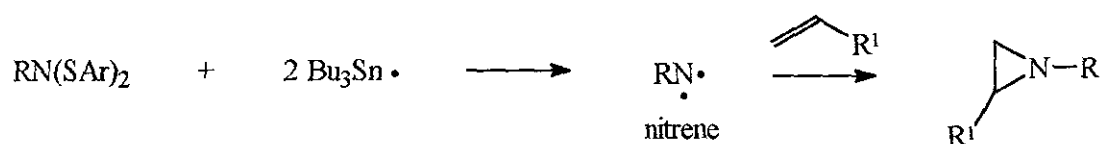
Scheme 136



In summary, we have shown that disulfenamides can be readily formed by a variety of methods. Further, the disulfenamides react with tin hydride in a process similar to monosulfenamides, to give aminyl radicals. However, the above experiments do not show if the disulfenamides react with the tin hydride in a step-

wise manner to give the aminyl radical, or if both arylsulfenyl groups are abstracted to yield a nitrene. If the latter case is true, the nitrene which would be formed which could be trapped in some manner (Scheme 137). The following chapter details the attempts at cyclising aminyl radicals formed from disulfenamides, in order to provide another synthetic route to nitrogen-containing heterocycles. It was hoped that these studies would also show whether a nitrene had been formed as an intermediate or whether the reaction proceeded in two stages.

Scheme 137



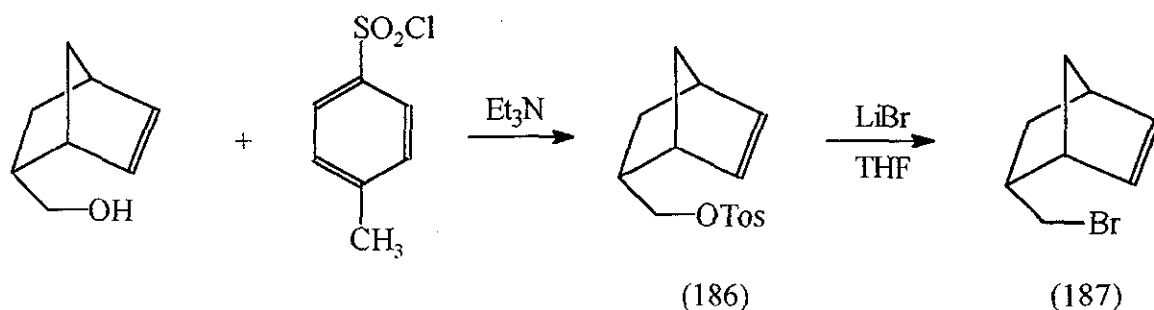
Chapter 6. Cyclisation Studies using Disulfenamides

Earlier studies have shown that aminyl radicals can be generated from monosulfenamides and made to cyclise onto intramolecular olefins using a variety of methods (see Chapter 4). If the same types of reactions could be achieved using aminyl radicals generated from disulfenamides, a greater range of natural product analogues could be synthesised using aminyl radical reactions. For this reason, systems were set up so that aminyl radicals generated from disulfenamides could cyclise intramolecularly onto olefins. The studies involving monosulfenamides have shown that cyclisation is best achieved when cyclisation of the aminyl radical is onto a strained olefin, or when the initially cyclised alkyl radical could be stabilised *i.e.* through an aromatic ring. Therefore, equivalent precursors containing the disulfenamide group were synthesised and reacted under standard radical conditions. The results of these studies are detailed below.

6.1. Cyclisation reactions using Strained Ring Systems

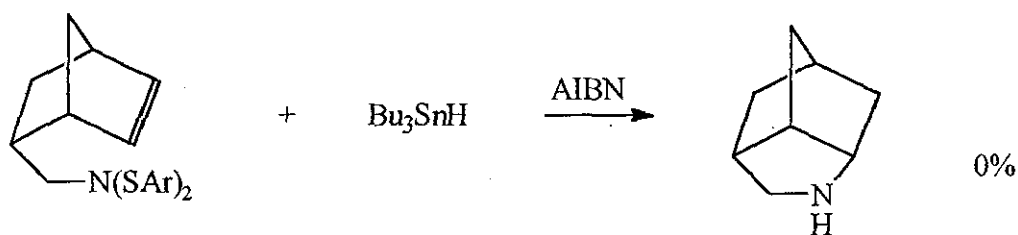
Cyclisation of an aminyl radical onto a strained bicyclo[2.2.1]hept-5-enyl ring-system was achieved in moderate yield using monosulfenamides (see Section 4.). To investigate whether the same result could be achieved using disulfenamides, it was required to synthesise *N,N*-di(arylsulphenyl)-*exo*-(bicyclo[2.2.1]hept-5-en-2-yl)methylamine (185). Since it has been shown that the only way of forming disulfenamides containing a double bond was through the action of *N,N*-di(arylsulphenyl)amine on alkyl halides or tosylates, the required tosylate and bromide were prepared. Initially, the alkyl tosylate (186) was formed from the action of tosyl chloride on *exo*-(bicyclo[2.2.1]hept-5-en-2-yl)methanol. The bromide (187) was then prepared by reacting the tosylate with lithium bromide in refluxing tetrahydrofuran for a period of three days (Scheme 138).

Scheme 138



Both the tosylate (186) and the bromide (187) were reacted with *N,N*-di(*p*-chlorophenylsulphenyl)amine in the presence of *n*-butyl lithium. However, when both of these reactions were worked-up, it was shown that the disulfenamide (185) was only formed from the reaction between the bromide and the disulfenamide. Only starting materials were recovered from the reaction using the tosylate precursor (Scheme 139). It appears that

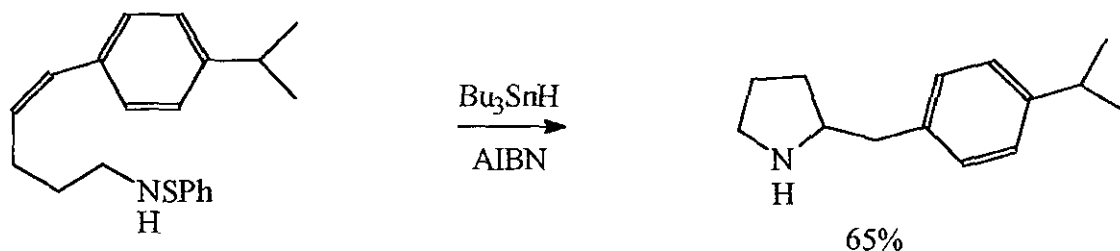
Scheme 141.



6.2. Cyclisation Reactions using Stabilised Alkyl radicals

Previous work has shown that cyclisation of aminyl radicals could be achieved by reacting *N*-(benzenesulfonyl)-5-(4-isopropylphenyl)pent-4-enylamine with tin hydride to give 2-(4-isopropylbenzyl)pyrrolidine (Scheme 142).

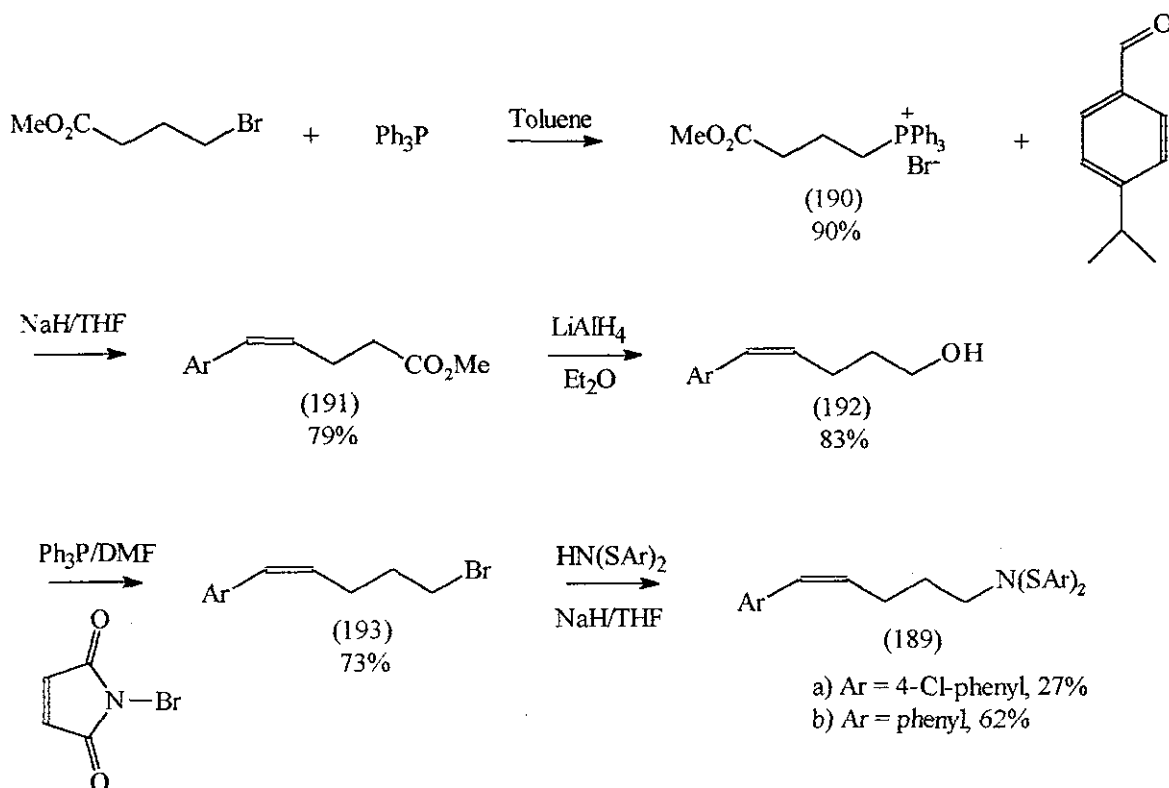
Scheme 142



By synthesising the equivalent disulfenamide (189), comparison studies could be carried out to determine whether cyclisation using disulfenamides could be achieved in as good a yield as cyclisation reactions using monosulfenamides. The disulfenamides (189a,b) were synthesised using reactions already investigated in the synthesis of monosulfenamide precursors (Scheme 143). The phosphonium salt (190) was reacted with 4-isopropylbenzaldehyde in a Wittig reaction to give the ester (191), which was reduced to the alcohol (192) using lithium aluminium hydride. Conversion of the alcohol to the bromide (193) was achieved once more using triphenylphosphine and *N*-bromosuccinamide¹¹⁰. Finally, the disulfenamides (189a,b) were synthesised by reacting the bromide (193) with the equivalent di(arylsulfonyl)amine in the presence of sodium hydride.

Both of the disulfenamides (187a,b) were reacted under standard radical conditions using the syringe pump method. When both reactions were worked up, it could be seen that the expected cyclised pyrrolidine was only present in the *N,N*-di(benzenesulfonyl)-5(4-isopropylphenyl)pent-4-enylamine reaction. no recognisable product was isolated when the equivalent *p*-chlorophenyl disulfenamide was reacted with tin hydride (Scheme 144).

Scheme 143

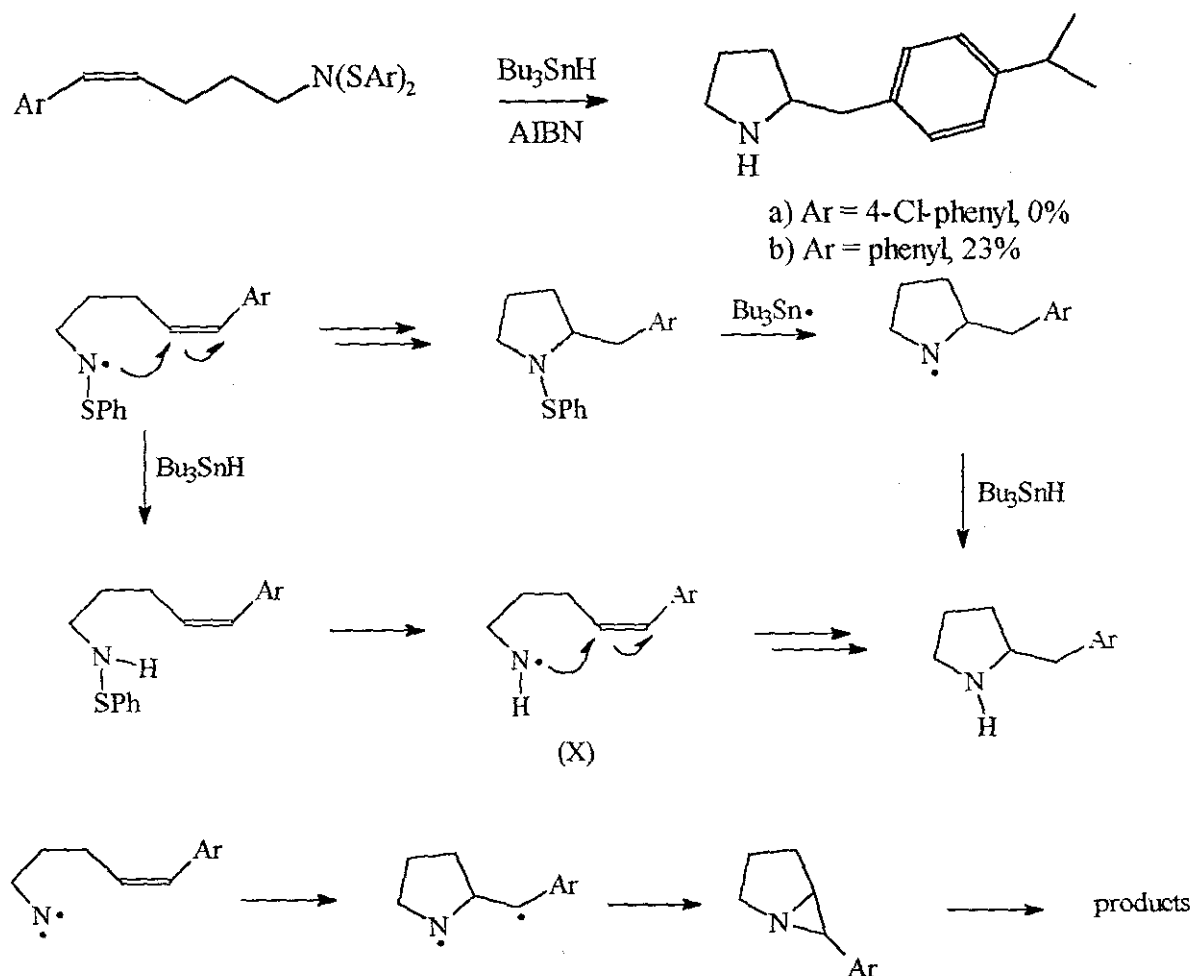


It is clear from the results obtained from these reactions, and from the results obtained in Section 6.1, that the *p*-chloro substituent on the disulfenamides does interfere with the cyclisation reactions. The tin hydride must interact with the chlorine in some manner to give a range of unrecognisable products. This was suspected from our earlier studies on monosulfenamides, but it is proved here with the different results from similar systems.

The above work does show that aminyl radicals can be generated from disulfenamides and made to cyclise in a similar manner to those generated from monosulfenamides. The yield of cyclisation of (189b) was low because of purification and no other products appeared to have been formed. The yield was not optimised because of shortage of time. Again, the cyclisation does not indicate which intermediate aminyl radical undergoes cyclisation (Scheme 144) but does indicate that a nitrene intermediate is unlikely. The intermediate (X) has been shown to cyclise in good yield (see page 68) but this does not necessarily indicate that this is the intermediate in this reaction.

The next stage of the project was to show that novel systems could be generated from aminyl radical cyclisation reactions. These systems would offer a clear advantage of disulfenamides over monosulfenamides, as a new range of natural product analogues could be generated in this way.

Scheme 144



6.3. Bicyclisation Reactions using Sequential Removal of SAr Molecules

As has been illustrated in Chapter 5, the proposed synthesis of natural product analogues such as (5Z, 8E)-3-heptyl-5-methylpyrrolizidines rely on the sequential removal of SAr molecules by tin hydride to give two separate aminyl radicals. Studies were conducted to form precursor disulfenamides to ascertain whether these types of reactions could be achieved, or whether competing reactions would lead to other products being obtained.

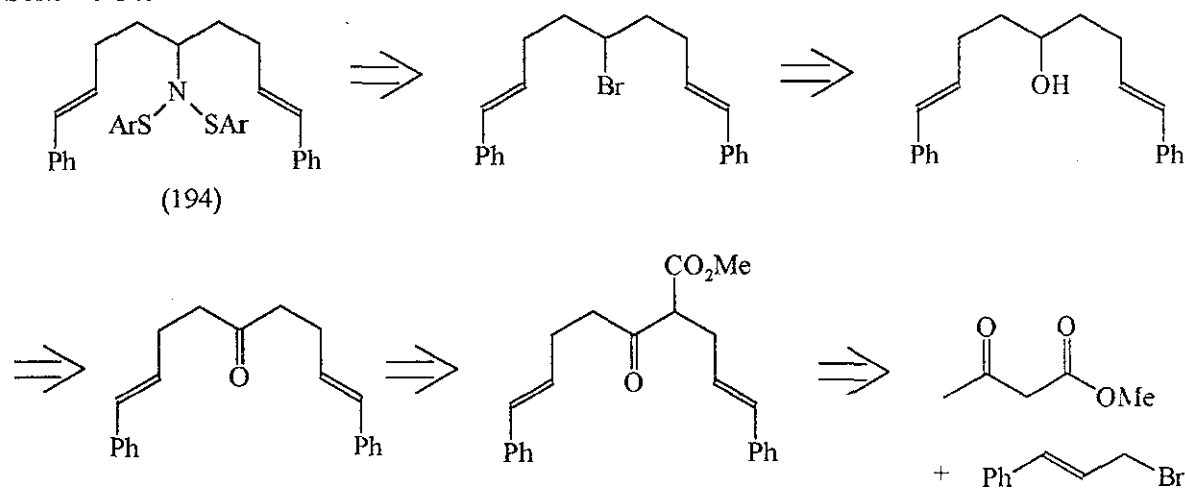
6.3.1. Attempted Synthesis Through Dianion Formation

Our initial aim was to synthesise the distyryl analogue to ensure that potential cyclisation was most likely. A route to the disulfenamide *N,N*-di(benzenesulfonyl)-1,9-diphenyl-4-methylcarboxy-nona-1,8-dienyl-5-amine (194) was formulated from methyl acetoacetate and cinnamyl bromide (Scheme 145).

Unfortunately, problems were encountered from the first step of this synthesis. The reaction to form 1,9-diphenyl-4-methylcarboxy-5-oxo-nona-1,8-diene (195) by reacting methyl acetoacetate with two equivalents of cinnamyl bromide gave methyl 3-oxo-7-phenylhept-6-enoate (196). The reaction proceeded by formation of the monoanion (197) with sodium hydride followed by formation of the dianion (198) with *n*-butyllithium.

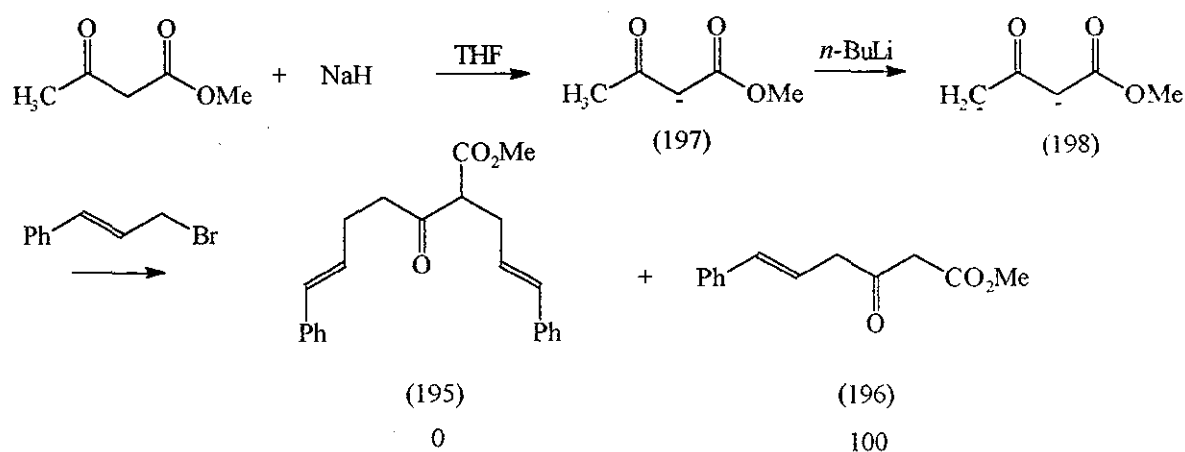
Evidently, the cinnamyl bromide was only reacting at the terminal anion to give the observed product (Scheme 146).

Scheme 145

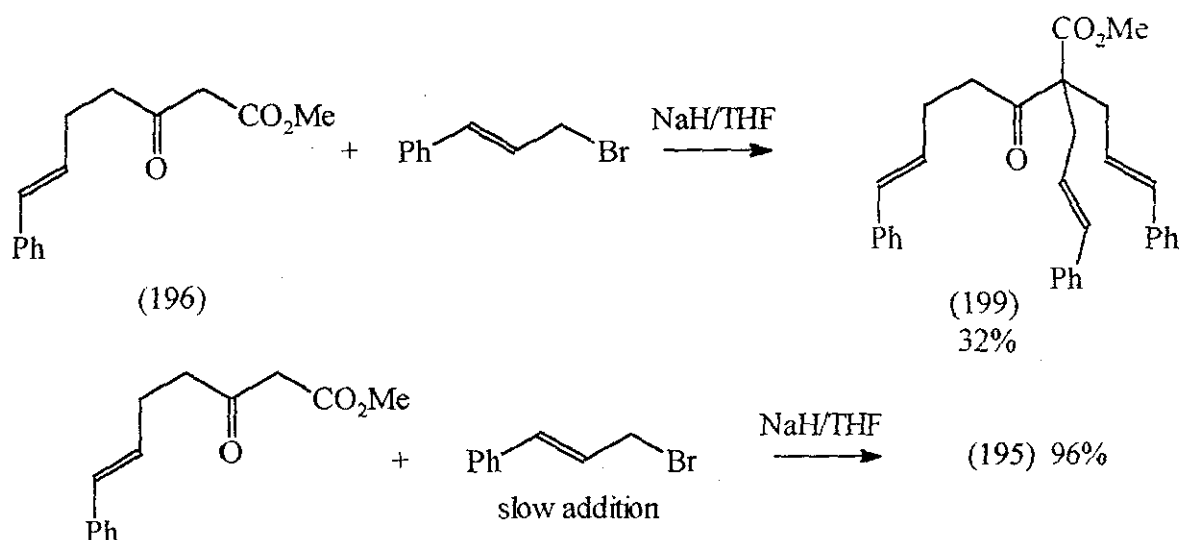


The ester (196) was then reacted with sodium hydride and one equivalent of cinnamyl bromide in order to form the required ketone (195). However, a product was recovered from this reaction that was shown to be the diaddition product 1,9-diphenyl-4-methylcarboxy-5-oxo-4-(3-phenylprop-2-enyl)nona-1,8-diene (199). In this case, the cinnamyl bromide had reacted twice at the anion to give the observed product (Scheme 147). This problem could be overcome by slow addition of the cinnamyl bromide to a refluxing solution of the monoanion. When this reaction was repeated using a syringe pump for the addition of the cinnamyl bromide, the required ester (195) was formed in 96% yield.

Scheme 146

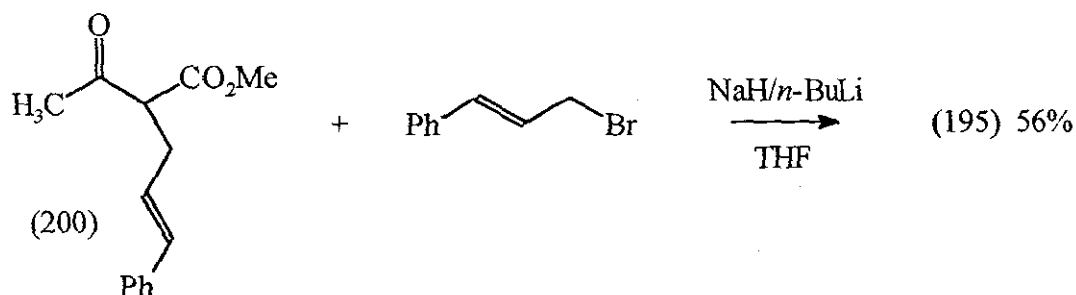


Scheme 147



The ester (195) was also formed in reasonable yield using the reverse route; the monoadduct ester (200) was first formed, followed by slow addition of cinnamyl bromide to give (195) (Scheme 148).

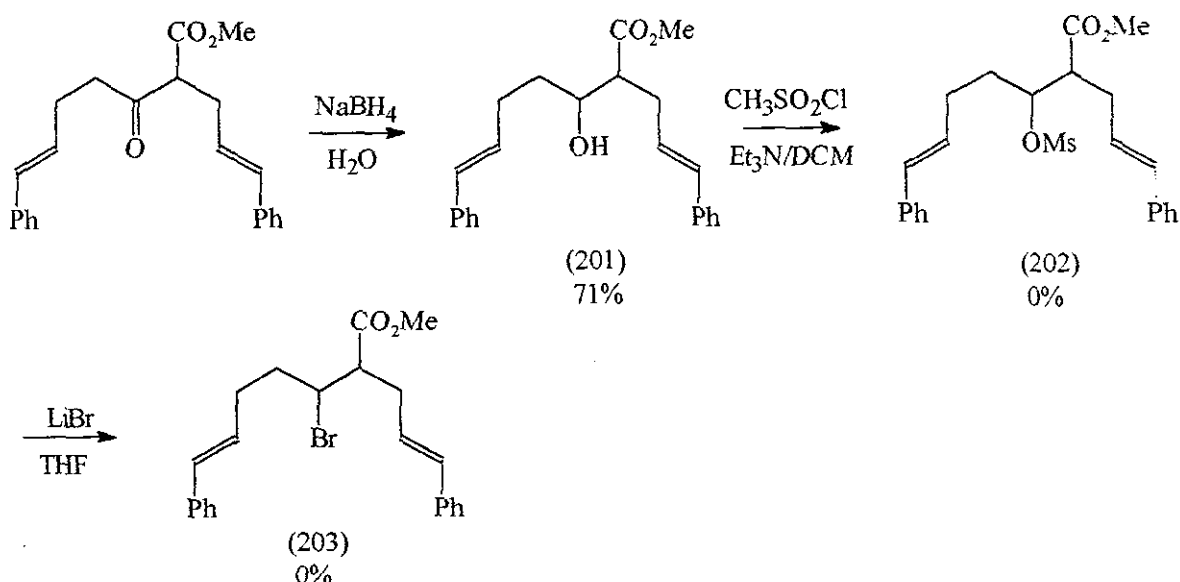
Scheme 148



We decided at this stage not to remove the methoxycarbonyl group and to proceed on with the synthesis. Reduction of (195) using sodium borohydride in methanol to give 1,9-diphenyl-4-methylcarboxy-5-hydroxy-nona-1,8-diene (201) provided no difficulties, though attempted formation of 1,9-diphenyl-4-methylcarboxy-5-mesylnona-1,8-diene (202) using mesyl chloride provided no confirmation of the required product. Not surprisingly, further reaction of (202) with lithium bromide yielded no trace of the bromide (203) (Scheme 149). This scheme was discontinued at this point as time did not allow for further research into this work.

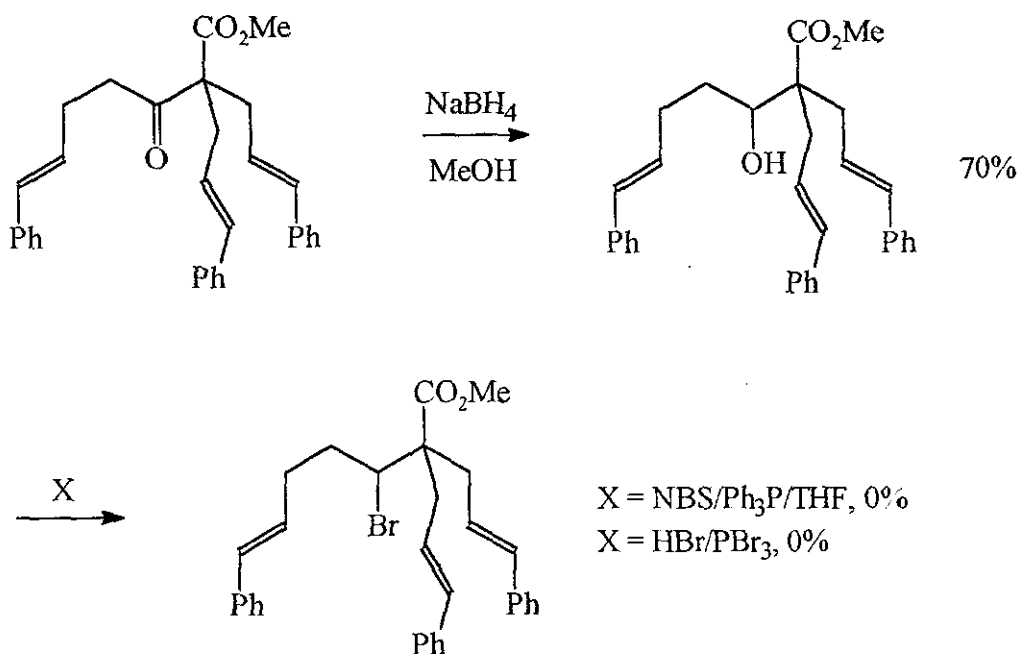
In order to provide a substrate for bicyclisation studies, the diaddition product (199) was reduced using sodium borohydride. Attempts were then made to form the bromide (205) directly from the alcohol (204) using firstly triphenylphosphine and N-bromosuccinamide and then 48% hydrobromic acid with phosphorus tribromide¹¹¹ (Scheme 150). Both of these approaches failed and a disulfenamide precursor was not formed from this work.

Scheme 149

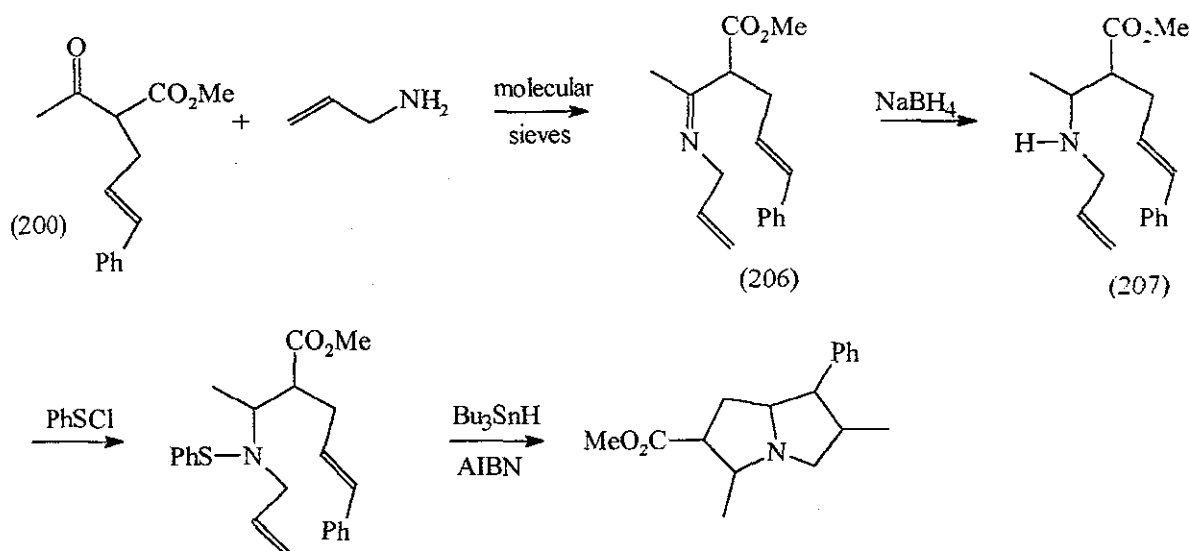


Finally, the monoadduct product (200) was reacted under dehydrating conditions with allylamine in an attempt to form the imine (206). It was postulated that reduction of this imine to the amine (207) would give an additional aminyl radical cyclisation precursor (Scheme 151). Unfortunately, no imine (206) was isolated from this reaction and this approach was discontinued.

Scheme 150



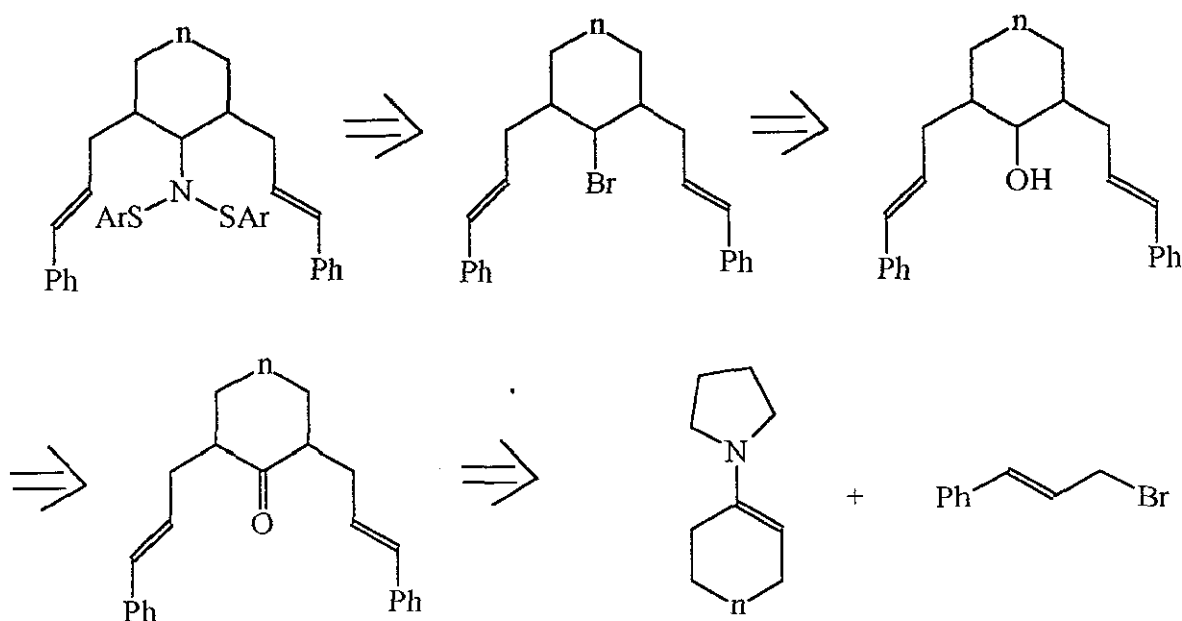
Scheme 151



6.3.2. Attempted Synthesis Through Enamines

The failure of the previous system led us to investigate alternative routes to a disulfenamide precursor for bicyclisation studies. Early publications¹¹³ have shown that enamines can be dialkylated and hydrolysed to give a disubstituted cycloalkanone. By utilising this procedure, a suitable precursor could be formed for our further studies using a range of simple reactions (Scheme 152).

Scheme 152

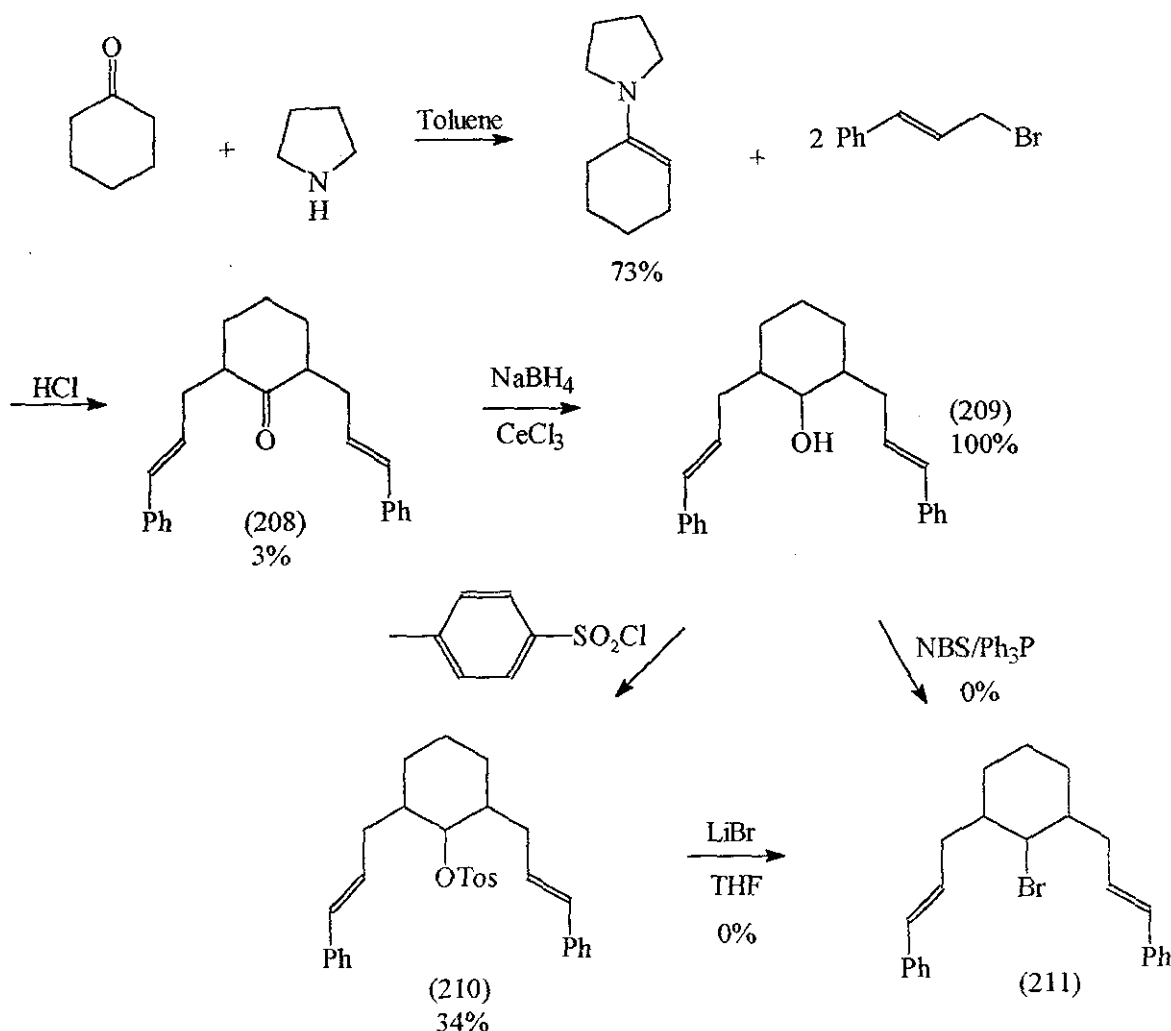


The pyrrolidine enamine of cyclohexanone was formed in good yield using a known procedure.¹¹² Reaction of this enamine with two equivalents of *cinnamyl* bromide with *N*-ethylcyclohexylamine as base followed by hydrolysis with hydrochloric acid gave 2,6-di(3-

phenylprop-2-enyl)cyclohexanone¹¹³ (208) in a disappointing yield. Reduction using sodium borohydride and cerium chloride in methanol gave the expected alcohol (209). When this reaction was repeated in the absence of cerium chloride, the yield was reduced from quantitative to 56%. Attempts to form the bromide (211) directly from the alcohol using triphenylphosphine and *N*-bromosuccinamide¹¹⁴ in tetrahydrofuran failed, though the tosylate (210) was formed in reasonable yield. However, reaction of the tosylate with lithium bromide in refluxing tetrahydrofuran failed and time was not available for any further studies (Scheme 153).

Finally, the pyrrolidine enamine of cycloheptanone was formed, though initial attempts at formation of 2,7-di(3-phenylprop-2-enyl)cycloheptanone failed. No further time was available for our studies into bicyclisation reactions involving disulfenamides, and these approaches were discontinued.

Scheme 153



The work in this final chapter has shown that aminyl radicals generated from disulfenamides do undergo simple cyclisation reactions. However, it is inconclusive whether disulfenamides can be used as precursors to more sophisticated natural product analogues, as

there was difficulty in generating the starting materials required. Judging by the success of the monosulfenamide cyclisation reactions, it would be reasonable to presume that if the starting materials had been prepared, successful cyclisation reactions could have been achieved. Unfortunately, time did not allow for any further research into this field and the work had to be finished incomplete.

Conclusion

The research project was undertaken to investigate various parameters concerning aminyl radical reactions. The first is that aminyl radicals can be easily generated from the action of tri-*n*-butyltin hydride on sulfenamides. The sulfenamides themselves are synthesised from any one of three methods, all involving readily available starting materials. The aminyl radicals, once formed can be reacted in a number of different ways, including reductive reactions, ring-opening reactions, β -scission reactions, and perhaps most importantly, cyclisation reactions. Past work has indicated difficulty in cyclising nucleophilic aminyl radicals onto unactivated olefins, since it has been found that the rate of cyclisation of such a reaction is roughly equivalent to the rate of ring-opening of the reversible reaction. However, this project has shown that this problem can be overcome by encouraging the initially formed aminyl radical to cyclise, through kinetic means, stabilisation effects, and tandem cyclisation reactions. Various reactions have been performed to show that these methods of cyclisation can lead to a wide range of polycyclic amines, including natural product analogues.

The latter part of this project has concentrated on the formation of aminyl radicals from disulfenamides. Once more, it has been found that disulfenamides can be easily prepared from known literature procedures and reacted with tin hydride to form the required aminyl radicals. However, even though reduction and ring-opening reactions involving aminyl radicals have been successfully performed, only simple cyclisation reactions have been achieved. Time was not available to fully research bicyclisation reactions involving disulfenamides leading to pyrrolizidines and this work had to be finished incomplete.

Since completing our studies, Newcomb and co-workers have shown that sulfenamides of amides can be reacted with tri-*n*-butyltin hydride to yield intermediate electrophilic amidyl radicals which readily cyclise.¹¹⁵ Further studies by Tsanaktisidis¹¹⁶ have shown that adding tri-*n*-butyltin oxide, $(\text{Bu}_3\text{Sn})_2\text{O}$, improves the yield of cyclisation of aminyl radicals generated from sulfenamides.

Chapter 7. Experimental

General

All solvents were dried and distilled before use: methanol from magnesium and iodine; dichloromethane, cyclohexane and acetonitrile from phosphorus pentoxide; DMF from calcium hydride; toluene, benzene and di-*iso*-propylamine from sodium hydride; THF from sodium/benzophenone ketyl; light petroleum, diethyl ether and ethyl acetate from calcium chloride. The light petroleum used was the boiling fraction 40-60°C unless otherwise stated. Starting materials were obtained predominantly from Aldrich Chemical Co. Ltd. or from Lancaster Synthesis Ltd. Tungsten 'white light' fluorescence lamps (2 x 150 W) (mercury blended) were used for irradiation studies. TLC was performed on aluminium plates coated with Merck silica gel 60F254 or on aluminium plates coated with aluminium oxide. IR spectra were recorded as liquid films on a Pye Unicam PU 516 spectrometer and a Nicolet 205 FT-IR spectrometer unless otherwise stated. Elemental analyses were provided by the service at the University of Brunel and by Mr Alaister Daley at Loughborough University of Technology. 400 MHz, nOe difference spectra and cosy 45 spectra were provided by the SERC High Field NMR Service at the University of Warwick. 300 MHz NMR spectra were provided by Rhone-Poulenc Agriculture, Ongar Site. 250 MHz NMR spectra were obtained using a Bruker AC250 spectrometer. ^1H NMR spectra referred to in the text were run at 250 MHz and ^{13}C NMR spectra at 62.5 MHz unless otherwise stated. *d*-Chloroform was used as the NMR solvent with tetramethylsilane as internal standard. ^1H NMR spectra were determined at 60 MHz on a Varian EM 360A spectrometer. *p*-Dimethoxybenzene was used as an internal standard to measure yields of products in mixtures by ^1H NMR spectroscopy. Mass spectra were provided by the SERC Mass Spectrometry Service at University College, Swansea. For a number of compounds, especially those which are oils, the data for elemental analyses were unsatisfactory. These unsatisfactory data are not quoted, However, the spectroscopic data obtained from other techniques permitted unambiguous characterisation of the compounds in question.

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Preparation of the benzenesulfenyl chlorides

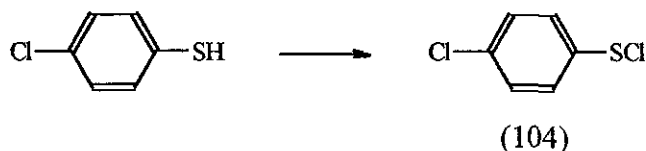
1. Benzenesulfenyl chloride (90)



Chlorine gas was bubbled through carbon tetrachloride (200 ml) with stirring until the solution turned yellow (usually about 15 min) in a 500 ml round bottomed flask. Benzenethiol (10.0 g, 91 mmol) in carbon tetrachloride (100 ml) was added over a period of 20 min, and the chlorine gas bubbled through the mixture for a further 2 h. The orange solution formed was neutralised with anhydrous sodium carbonate (30 g) and the solution was distilled to yield the sulfenyl chloride (b.p. 94-96°C at 1 mm) as an orange liquid (6.2 g, 47%). The TLC analysis (light petroleum/silica gel) showed the sulfenyl chloride as the only product, and it was not further purified; $\nu_{\text{max}}(\text{neat})$ 3060 (aromatic C-H str.), 1578 and 1474 (aromatic C=C str.), and 748 cm^{-1} (monosubst. aromatic). δ_{H} 7.15 (s, Ph-H).

Repeat experiments produced yields between 35 and 47%.

2. *p*-Chlorobenzenesulfenyl chloride (104)



p-Chlorobenzenethiol (14.0 g, 0.11 mol) was reacted with chlorine gas using the same procedure as experiment 1. Distillation at reduced pressure yielded the *p*-chlorobenzenesulfenyl chloride as a red oil (12.5 g, 71%). TLC analysis (light petroleum/silica gel) indicated the sulfenyl chloride as the only product, and it was not further purified.

Repeat experiments produced yields between 27 and 45%.

The synthesis of 2-benzothiazolesulfenyl chloride from 2-mercaptobenzothiazole and 2,2'-di(benzothiazole) disulfide were both attempted in this way; unfortunately problems were encountered with the solubilities of the products and the starting materials, and so the experiments were discontinued.

The sulfenyl chloride of benzenethiol was also prepared using benzenethiol and *N*-chlorosuccinamide, but this method produced a large amount of diphenyl disulfide impurity.

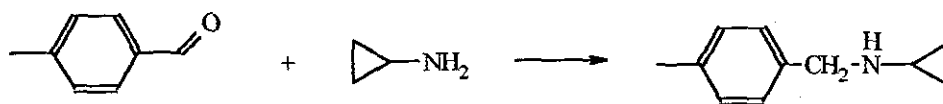
Synthesis of Amines

3. *N*-Butyl-5-penten-1-ylamine (123)



Butylamine (100 ml) and dry diethyl ether (50 ml) were stirred in a round-bottomed flask, to which was added dropwise 5-bromopent-1-ene (3.0 g, 0.02 mol) in dry ether (50 ml). The mixture was refluxed overnight and evaporated to dryness to yield brown crystals of the hydrobromide. The crystals were neutralised by addition of aqueous sodium carbonate (100 ml) and the product amine extracted with ether. Evaporation to dryness yielded a brown oil of *N*-butyl-5-penten-1-ylamine (2.5 g, 89%); ν_{\max} 3284 and 3076 (N-H and C=C str.), and 1638 cm^{-1} (C=C str.); δ_{H} 1.30 (3H, t, $J = 10.3$ Hz, CH_2CH_3), 1.63 (4 H, m, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2.35 (3 H, q, CH_2CHCH_2 and -NH), 2.92 (4 H, t, $J = 8.2$ Hz, $\text{CH}_2\text{-NH-CH}_2$), 5.10 (2 H, m, $\text{CH}_2=\text{CH}$), and 5.95 (1 H, m, $\text{CH}_2=\text{CH}$). Analysis using TLC (chloroform/methanol/silica gel) showed the amine as the only product. It was not further purified.

4. *N*-(*p*-Methylbenzyl)cyclopropylamine

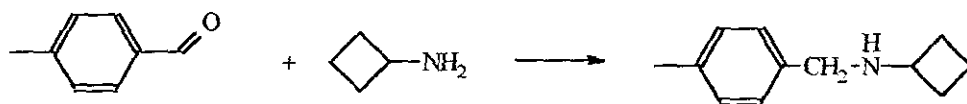


A solution of tolualdehyde (4.2 g, 35 mmol) and a crystal of *p*-toluenesulphonic acid as catalyst in toluene (50 ml) was added dropwise to cyclopropylamine (2.0 g, 35 mmol) in toluene (50 ml). A Dean-Stark water separator was attached to the flask and the mixture was refluxed for 2 h, in which time approximately 1 ml of water had been liberated. Removal of the solvent yielded *N*-(*p*-methylbenzylidene)cyclopropylamine as a brown oil; ν_{\max} 3088 and 3008 cm^{-1} (C=CH and arom C-H str.); δ_{H} 0.92 (4 H, d, CH_2 's of cyclopropyl ring), 2.25 (3 H, s, CH_3), 2.93 (1 H, m, CH of cyclopropyl ring), 7.00 and 7.57 (4 H, ABq, $J = 16.2$ Hz, Ar-H), and 8.23 (1 H, s, N=CH). TLC (ethyl acetate/alumina) showed the imine as the only product. It was not further purified.

Reduction of the imine was achieved by refluxing for 2 h with sodium borohydride (2.0 g, 1.5 equiv.) in dry methanol (100 ml). At the end of 2 h, the mixture was diluted with water (100 ml) and the amine extracted into dichloromethane (150 ml). The solvent was evaporated to dryness to yield *N*-(*p*-methylbenzyl)cyclopropylamine as a brown oil (4.8 g, 85%); ν_{\max} 3312 and 3084 (N-H and aromatic C-H str.), 1612 and 1512 (aromatic C=C str.), and 804 cm^{-1} (1,4-disubst. aromatic); δ_{H} 0.46 (4 H, d, CH_2 's of cyclopropyl ring), 1.95 (1 H, s, CH of cyclopropyl ring), 2.23 (3 H, s, CH_3), 3.68 (2H, s, NH- CH_2), and 6.90 (4 H, s, Ar-

H). TLC (ethyl acetate/alumina) showed the amine as the only product. The amine was not further purified.

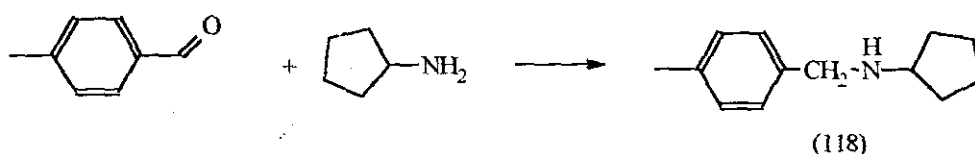
5. *N*-(*p*-Methylbenzyl)cyclobutylamine



Cyclobutylamine (2.8 g, 39 mmol) and *p*-tolualdehyde (4.7 g, 39 mmol) were reacted together by the same method as experiment 4 to yield the corresponding imine as a yellow oil; ν_{\max} 3020 (aromatic CH), 1636 (imine C=N), 1610 and 1510 (aromatic C=C), and 814 cm^{-1} (1,4-disubst. aromatic); δ_{H} 2.03 (6 H, m, cyclobutyl CH_2 's), 2.21 (3 H, s, CH_3), 4.15 (1 H, q, $J = 6.2$ Hz, cyclobutyl CH), 7.34 (4 H, ABq, $J = 15.9$ Hz, Ar-H), and 8.07 (1 H, s, N=CH).

Reduction of the imine using NaBH_4 (4.5 g, 0.117 mol, 3 equiv.) in methanol (75 ml) gave *N*-(*p*-methylbenzyl)cyclobutylamine as a brown liquid (5.9 g, 86 % overall); ν_{\max} 3292 and 3044 (amine NH and aromatic CH), 1614 and 1512 (aromatic C=C), and 806 cm^{-1} (aromatic 1,4-disubst.); δ_{H} 1.65 (6 H, m, cyclobutyl CH_2 's), 2.24 (3 H, s, CH_3), 3.28 (1 H, m, cyclobutyl CH), 3.65 (2 H, s, NHCH_2), and 7.02 (4 H, s, Ar-H); m/z 175.1361 [M^+ (18%)]. $\text{C}_{12}\text{H}_{17}\text{N}$ requires 175.1361, 147 (50), 105 (100), 77 (10), 51 (4), 39 (5), and 27 (6). TLC analysis [light petroleum / alumina] showed one product (the amine) and it was not further purified.

6. *N*-(*p*-Methylbenzyl)cyclopentylamine (118)

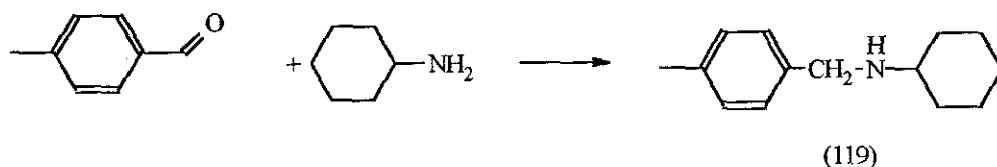


Cyclopentylamine (3.0 g, 35 mmol) and *p*-tolualdehyde (4.2 g, 35 mmol) in toluene (100 ml) were reacted together by the same method as for experiment 4 to yield the corresponding imine as a brown oil; ν_{\max} 3020 (aromatic CH), 1638 (imine N=CH), 1610 and 1510 (aromatic C=C), and 814 cm^{-1} (1,4-disubst. aromatic); δ_{H} 1.84 (8 H, m, cyclopentyl CH_2 's), 2.23 (3 H, s, CH_3), 3.85 (1 H, m, CH-N), 7.32 (4 H, ABq, $J = 16.5$ Hz, Ar-H), and 8.25 (1 H, s, CH=N).

Reduction of the imine using NaBH_4 (3.9 g, 0.105 mol, 3 equiv.) in methanol (100 ml) yielded *N*-(*p*-methylbenzyl)cyclopentylamine as a red liquid (6.5 g, 98% overall); ν_{\max} 3044 (aromatic CH), 1512 (aromatic C=C), and 806 cm^{-1} (1,4-disubst. aromatic); δ_{H} 1.73 (9 H, m, cyclopentyl CH_2 's), 2.26 (3 H, s, CH_3), 3.14 (1 H, m, CHNH), 3.72 (2 H, s, NHCH_2), 7.10 (4

H, s, Ar-H); m/z 189.1517 [M^+ (82%). $C_{13}H_{19}N$ requires 189.1517], 160 (40), 105 (100), 84 (11), and 41 (6). TLC analysis [light petroleum / alumina] revealed the amine as the only product, and it was not further purified.

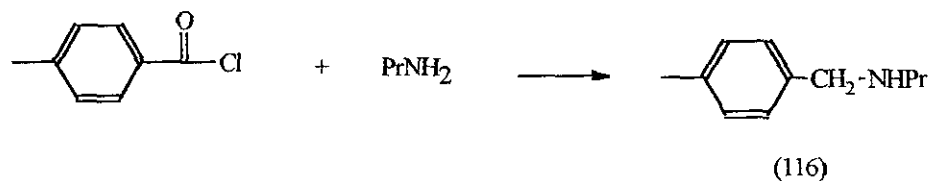
7. *N*-(*p*-Methylbenzyl)cyclohexylamine (119)



Cyclohexylamine (5.0 g, 0.05 mol) and *p*-tolualdehyde (6.1 g, 0.05 mol) were reacted by the same procedure as experiment 4 to yield the corresponding imine as a pure yellow oil; ν_{\max} 3084 (CH=N str.), 3020 (aromatic C-H str.), 1640 (C=N str.), 1610 and 1510 (aromatic C=C str.), and 814 and 694 cm^{-1} (1,4 disubstituted aromatic); δ_{H} 1.57 (10 H, m, cyclohexyl CH_2 's), 2.23 (3 H, s, CH_3), 3.15 (1 H, m, cyclohexyl CH), 7.02 (4 H, ABq, $J = 16.1$ Hz, 1,4 disubstituted aromatic), and 8.14 (1 H, s, CH=N). TLC showed the imine as the only product.

The imine was reduced using sodium borohydride (3 equiv) to generate *N*-(*p*-methylbenzyl)cyclohexylamine as a yellow oil (7.0 g, 69% overall); ν_{\max} 3308 (N-H str.), 3016 (aromatic C-H str.), 1512 (aromatic C=C str.), and 804 and 698 cm^{-1} (1,4 disubstituted aromatic); δ_{H} 1.54 (11 H, m, cyclohexyl and NH), 2.24 (3 H, s, CH_3), 3.86 (2 H, s, CH_2NH), and 7.03 (4 H, s, Ar-H). TLC (ethyl acetate / light petroleum ether / alumina) showed the amine as the only product. The amine was not further purified.

8. *N*-(*p*-Methylbenzyl)propylamine (116)

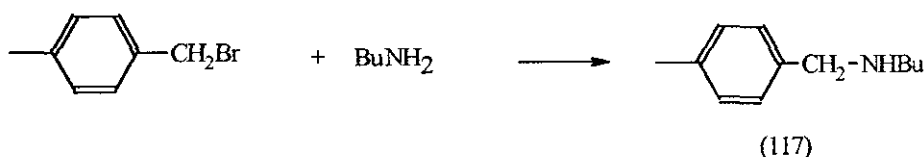


p-Toluoyl chloride (3.0 g, 19 mmol) and propylamine (25.0 g, 0.42 mol, 22 equiv.) were reacted together by the same procedure as experiment 10 to yield the corresponding amide as a colourless, crystalline solid; ν_{\max} 3348 (sec. amide N-H str.), 1646 (sec. amide C=O str.), 1612 and 1498 (aromatic C=C str.), and 834 cm^{-1} (1,4-disubst. aromatic); δ_{H} 0.92 (3 H, t, $J = 7.0$ Hz, CH_2CH_3), 1.55 (3 H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$ and NH), 2.10 (3 H, s, CH_3), 3.46 (2 H, q, $J = 7.1$ Hz, NHCH_2), and 7.45 (4 H, ABq, Ar-H). TLC (ethyl acetate/alumina) showed the amide as the only product.

N-(*p*-Methylbenzyl)propylamide (1.0 g, 5.65 mmol) and lithium aluminium hydride (0.4 g, 10 mmol, 2 equiv.) were reacted together by the same procedure as in experiment 10 to produce *N*-(*p*-methylbenzyl)propylamine as a pure yellow oil (0.8 g, 87% overall); ν_{\max} 3312 (amine NH str.), 3016 (aromatic CH str.), 1612 and 1512 (aromatic C=C str.), and 804 cm^{-1} (1,4-disubst. aromatic); δ_{H} 0.97 (3 H, t, $J = 7.1$ Hz, CH_3CH_2), 1.52 (2 H, m, $\text{CH}_3\text{CH}_2\text{CH}_2$), 2.26 (3 H, s, CH_3), 2.65 (2 H, t, $J = 6.8$ Hz, $\text{CH}_2\text{CH}_2\text{NH}$), 3.78 (2 H, s, NHCH_2Ar), and 7.02 (4 H, s, Ar-H); m/z 163.1361 [M^+ (58%)]. $\text{C}_{11}\text{H}_{17}\text{N}$ requires 163.1361], 134 (22), 105 (100), 84 (12), 77 (8), and 39 (3). TLC (ethyl acetate/alumina) showed the amine as the only product. The amine was not further purified.

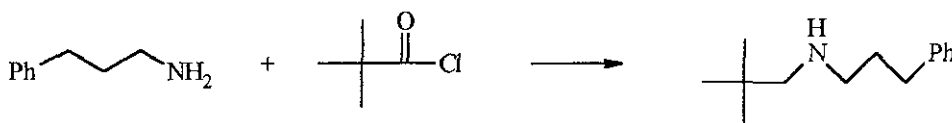
The generation of this amine was attempted using molecular sieves and by using titanium tetrachloride. Unfortunately the yields for both these experiments were unsatisfactory.

9. *N*-(*p*-Methylbenzyl)butylamine (117)



Butylamine (50 ml, excess) and *p*-methylbenzyl bromide (1.0 g, 5.40 mmol) in diethyl ether (100 ml) were reacted together by the same procedure as in experiment 3 to yield *N*-(*p*-methylbenzyl)butylamine as a brown oil (941 mg, 98 %); ν_{\max} 3304 (amine NH), 3016 (aromatic CH), 1512 (aromatic C=C), and 804 cm^{-1} (aromatic 1,4-disubst.); δ_{H} 0.84 (3 H, d, CH_3CH_2), 1.32 (4 H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 2.23 (3 H, s, CH_3), 2.50 (2 H, m, CH_2NH), 3.71 (2 H, s, NHCH_2Ph), and 7.16 (4 H, s, Ar-H). TLC analysis (light petroleum / alumina) showed the amine as the only product. The amine was not further purified prior to subsequent reaction.

10. *N*-(1,1-Dimethylpropyl)-3-phenylpropylamine



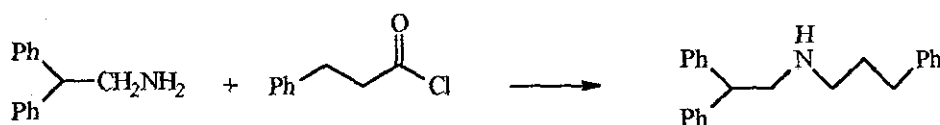
Trimethylacetyl chloride (0.9 g, 7.39 mmol) in light petroleum (50 ml) was added dropwise over a period of 30 min to 3-phenylpropylamine (1.0 g, 7.39 mmol) in triethylamine (50 ml, excess). The mixture was stirred for 1 h after which a precipitate of triethylamine hydrochloride [m.p. 226-229°C] could clearly be seen. The precipitate was filtered off and dried. The filtrate was washed with aqueous hydrochloric acid (100 ml) and aqueous sodium carbonate solution (100 ml), and the solution was evaporated to dryness to

yield *N*-(3-phenylpropyl)trimethylacetamide as a white crystalline solid (1.4 g, 86%); ν_{\max} 1660 cm^{-1} (secondary amide C=O str.); δ_{H} 1.16 (9 H, s, $(\text{CH}_3)_3$), 1.93 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.78 (2 H, t, $J = 6.2$ Hz, CH_2Ph), 3.25 (2 H, q, $J = 6.5$ Hz, HNCH_2), and 7.12 (5 H, s, Ar-H). TLC (ethyl acetate/alumina) showed the amide as the only product. The amide was not further purified prior to reduction.

The amide was reduced by slowly adding the amide (1.6 g, 7.30 mmol) in dry diethyl ether (15 ml) to a stirred suspension of LiAlH_4 (0.7 g, 2 equiv.) in dry diethyl ether (10 ml). The mixture was refluxed for 1 h and left to stand overnight. Water (7 ml) was slowly added to form the inorganic salts, which precipitated out. The precipitate was filtered off and the solution evaporated to dryness to leave *N*-(1,1-dimethylpropyl)-3-phenylpropylamine as a clear liquid (0.6 g, 41%); ν_{\max} 3420 (amine N-H str.), 3060 (aromatic C-H str.), 1602 and 1494 (aromatic C=C str.), and 736 cm^{-1} (monosubst. aromatic); δ_{H} 0.90 (9 H, s, $(\text{CH}_3)_3$), 1.18 (2 H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.85 (2 H, m, CH_2Ph), 2.65 (4 H, dt, CH_2NHCH_2), and 7.18 (5 H, s, Ar-H). TLC (ethyl acetate/alumina) showed the amine as the only product. The amine was not further purified.

This amine was also generated by using trimethylacetaldehyde and 3-phenylpropylamine to form the initial imine, which was subsequently reduced using sodium borohydride. Unfortunately, unsatisfactory yields were obtained for these two steps.

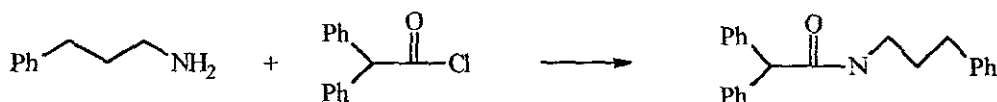
11. *N*-2,2(Diphenylethyl)-3-phenylprop-1-ylamine



2,2-Diphenylethylamine (4.0 g, 20 mmol) and 3-phenylpropionyl chloride (3.4 g, 20 mmol) in dry diethyl ether (50 ml) were reacted together by the same procedure as experiment 10 to form the corresponding amide as orange crystals (m.p. 89.2-90.8°C); ν_{\max} 3436 and 3320 (amide NH), 3060 and 3024 (aromatic CH), 1656 (amide C=O), 1600 and 1510 (aromatic C=C), and 784 cm^{-1} (monosubst. aromatic); δ_{H} 1.05 (1 H, m, NH), 2.23 (2 H, t, $J = 9.18$ Hz, $\text{CH}_2\text{CH}_2\text{Ph}$), 2.86 (2 H, t, $J = 9.2$ Hz, CH_2NH), 3.92 (2 H, m, CH_2Ph), 5.85 (1 H, m, Ph_2CH), and 7.13 (15 H, s, Ar-H).

Reduction of the amide using LiAlH_4 (0.9 g, 0.024 mol, 2 equiv.) in THF (40 ml) yielded *N*-2,2(diphenylethyl)-3-phenylprop-1-ylamine as a yellow oil (2.9 g, 78 % overall); ν_{\max} 3324 (amine NH), 3056 and 3024 (aromatic CH), 1600 and 1492 (aromatic C=C), and 744 cm^{-1} (monosubst. aromatic); δ_{H} 1.11 (1 H, m, NH), 1.74 (2 H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.63 (4 H, tt, $J = 4.5$ Hz, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{Ph}$), 3.15 (2 H, d, $J = 9.0$ Hz, $\text{Ph}_2\text{CHCH}_2\text{N}$), 4.12 (1 H, t, $J = 8.8$ Hz, Ph_2CH), and 7.12 (15 H, s, Ar-H). TLC analysis (light petroleum / alumina) showed the amine as the only product. The amine was not further purified.

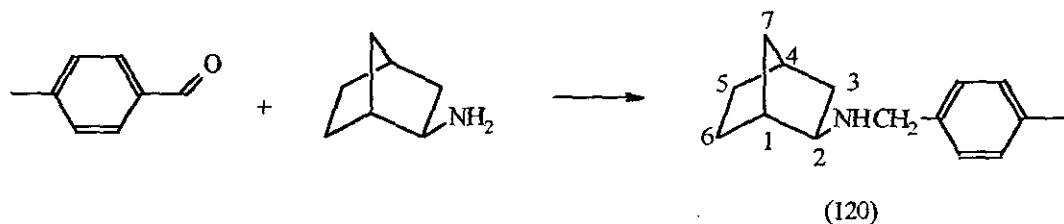
12. *N*-(3-Phenylpropyl)-diphenylacetamide



3-Phenylpropylamine (5.0 g, 37 mmol) and diphenylacetyl chloride (8.5 g, 37 mmol) in dry diethyl ether (100 ml) were reacted together by the same procedure as experiment 10 to yield the corresponding amide as off-white crystals (7.9 g, 65%), m.p. 136–138°C (recrystallised from ethyl acetate); ν_{\max} 3428 and 3324 (amide NH), 3060 and 3024 (aromatic CH), 1672 (amide C=O), 1600, 1582 and 1510 (aromatic C=C), and 728 cm^{-1} (aromatic monosubst.); δ_{H} 1.84 (2 H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.42 (2 H, t, $J = 6.0$ Hz, CH_2Ph), 3.22 (2 H, q, $J = 7.5$ Hz, NHCH_2), 3.95 (1 H, m, NH), 4.91 (1 H, s, Ph_2CH), and 7.10 (15 H, s, Ar-H).

Attempted reduction of this amide to *N*-(2,2-diphenylethyl)-3-phenylprop-1-ylamine using LiAlH_4 (0.3 g, 2 equiv.) in THF (20 ml) was unsuccessful, possibly due to steric hindrance. The synthesis of *N*-(2,2-diphenylethyl)-3-phenylprop-1-ylamine was therefore carried out by a different route.

13. *exo-N*-(*p*-Methylbenzyl)bicyclo[2.2.1]hept-2-ylamine (120)

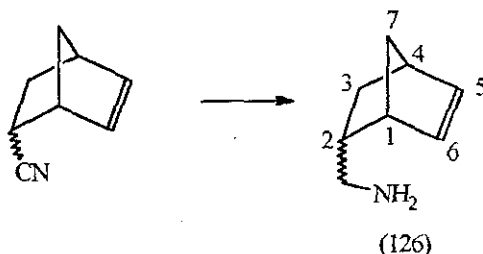


exo-2-Aminobicyclo[2.2.1]heptane (10.0 g, 89 mmol) and *p*-tolualdehyde (10.8 g, 0.089 mol) in toluene (100 ml) were reacted by the same procedure as experiment 4 to yield the corresponding imine as a brown oil; ν_{\max} 3024 (aromatic CH), 1638 (imine C=N), 1606 and 1508 (aromatic C=C), and 812 cm^{-1} (1,4-disubst. aromatic); δ_{H} 1.13 (4 H, m, 5-H and 6-H), 1.50 (4 H, m, 7-H and 3-H), 2.23 (3 H, s, CH_3), 2.90 (2 H, s, 1-H and 4-H), 3.21 (1 H, m, 2-H), 7.43 (4 H, ABq, $J = 13.6$ Hz, Ar-H), and 8.14 (1 H, s, $\text{N}=\text{CH}$).

The imine was reduced using NaBH_4 (5.1 g, 0.134 mol, 1.5 equiv.) in methanol (100 ml) to yield *exo-N*-(*p*-methylbenzyl)bicyclo[2.2.1]hept-2-ylamine as a yellow liquid (18.3 g, 95% overall); ν_{\max} 3532 (amine NH), 3044 (aromatic CH), 1512 (aromatic C=C), and 806 cm^{-1} (1,4-disubst. aromatic); δ_{H} 1.07 (4 H, m, 5-H and 6-H), 1.50 (4 H, m, 3-H and 7-H), 2.06 (2 H, s, 1-H and 4-H), 2.31 (3 H, s, CH_3), 2.60 (1 H, m, 2-H), 3.68 (2 H, ABq, $J = 9.1$ Hz, NHCH_2), and 7.22 (4 H, ABq, $J = 13.8$ Hz, Ar-H); δ_{C} 21.08 (CH_3), 26.91 (6-C), 28.62 (5-C), 34.94 (7-C), 35.67 (4-C), 40.19 (3-C), 40.68 (1-C), 51.61 (NHCH_2), 61.11 (2-C), and 125.23–136.28 (aromatic); m/z 215.1674 [M^+ (23%). $\text{C}_{15}\text{H}_{21}\text{N}$ requires 215.16739], 105

(100), 77 (12), 41 (10), and 30 (8). TLC analysis [light petroleum / alumina] showed the amine as the only product. The amine was not further purified.

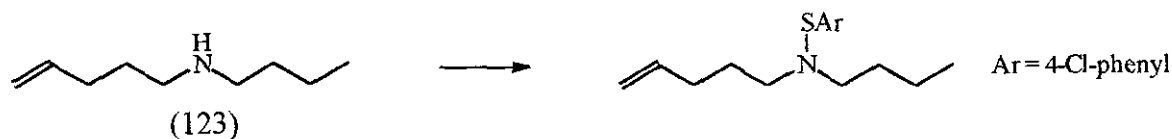
14. (Bicyclo[2.2.1]hept-5-en-2-yl)methylamine (126)



2-Cyanobicyclo[2.2.1]hept-5-ene (3.0 g, 0.025 mol) in dry diethyl ether (10 ml) was added very slowly to a cooled suspension of LiAlH_4 (1.0 g, 0.027 mol, 1.1 equiv.) in dry diethyl ether (10 ml). After stirring for 30 min, water (8 ml) was added, the subsequent lithium salts were removed by filtration, and the solution evaporated to dryness to yield (bicyclo[2.2.1]hept-5-en-2-yl)methylamine as a yellow oil (3.1 g, 99%); ν_{max} 3368 and 3056 (amine and alkene), and 1660 cm^{-1} (alkene $\text{C}=\text{C}$); δ_{H} 0.53 (1 H, ddd, *endo*-2-H), 1.12-1.45 (3 H, m, 7-H and *exo*-2-H), 1.52 (2 H, s, NH_2), 1.84 (1 H, ddd, *endo*-3-H), 2.08 (1 H, ddd, *exo*-3-H), 2.36-2.42 (2 H, m, CH_2NH_2), 2.64-2.87 (4 H, m, *exo* and *endo*-1-H and *exo* and *endo*-4-H), 5.92 (1 H, dd, 6-H), 6.11 (1 H, dd, $J = 10.1$ Hz, 5-H); δ_{C} 30.21 (2-C), 41.86 (3-C), 42.75 (4-C), 45.61 (1-C), 46.73 (7-C), 49.52 (CH_2NH_2). TLC analysis (light petroleum / alumina) showed the amine as the only product, and it was not further purified. The amine was obtained as a mixture of the *endo*- and *exo*-isomers (*endo*:*exo* = 50:50).

Synthesis of sulfenamides using *p*-chlorobenzenesulfonyl chloride

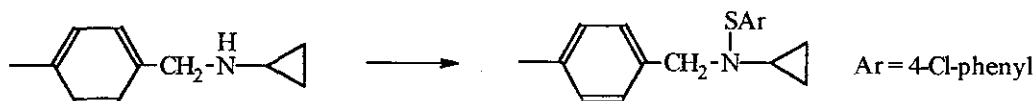
15. *N*-Butyl-*N*-(*p*-chlorobenzenesulfonyl)pent-5-en-1-amine



p-Chlorobenzenesulfonyl chloride (1.4 g, 1.5 equiv.) in diethyl ether (100 ml) was added dropwise over a period of 20 min to a solution of the amine (0.8 g, 5.67 mmol) and triethylamine (2.9 g, 5 equiv.). The precipitate (triethylamine hydrochloride) which was formed was filtered off and the solution evaporated to dryness to yield the crude product as a brown oil. Further extraction yielded *N*-butyl-*N*-(*p*-chlorobenzenesulfonyl)pent-5-en-1-amine as an orange oil (1.4 g, 95%); ν_{max} 3076 (aromatic $\text{C}-\text{H}$ str.), 1638 ($\text{C}=\text{C}$ str.), 1570 and 1472 (aromatic $\text{C}=\text{C}$ str.), and 810 cm^{-1} (1,4-disubst. aromatic); δ_{H} 0.89 (3 H, t, $J = 8.2$ Hz, CH_2CH_3), 1.29 (2 H, m, CH_2CH_3), 1.51 (2 H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.63 (2 H, q, $J = 7.2$ Hz, $\text{CH}_2=\text{CHCH}_2\text{CH}_2$), 2.04 (2 H, q, $J = 7.5$ Hz, $\text{CH}_2=\text{CHCH}_2$), 2.93 (4 H, t, $J = 7.2$ Hz,

CH_2NCH_2), 4.98 (2 H, t, $J = 10.2$ Hz, $\text{CH}_2=\text{CH}$), 5.80 (1 H, m, $\text{CH}_2=\text{CH}$), and 7.22 (4 H, m, Ar-H); δ_{C} 13.88 (CH_2CH_3), 19.98 (CH_2CH_3), 27.40 ($\text{CH}_2\text{CH}_2\text{CH}_3$), 30.62 ($\text{CH}_2=\text{CHCH}_2\text{CH}_2$), 31.11 ($\text{CH}_2=\text{CHCH}_2$), 57.73 (CH_2N), 58.32 (CH_2N), 114.79 ($\text{CH}_2=\text{CH}$), 139.75 ($\text{CH}_2=\text{CH}$), and 128.98-131.83 (Ar-C). TLC (light petroleum / ethyl acetate / alumina) showed the sulfenamide as the only product. No further purification was performed on this compound.

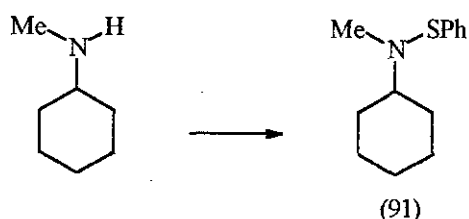
16. *N*-(*p*-Chlorobenzenesulfenyl)-*N*-(*p*-methylbenzyl)cyclopropylamine



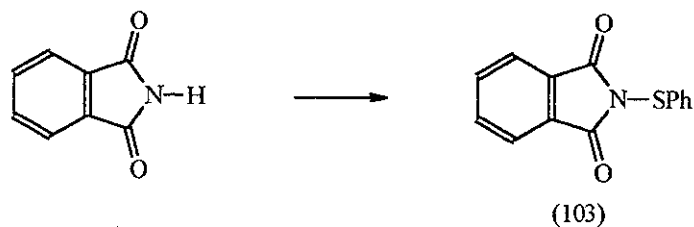
N-(*p*-methylbenzyl)cyclopropylamine (0.5 g, 3.10 mmol) and *p*-chlorobenzenesulfonyl chloride (0.6 g, 3.10 mmol) were reacted by the same procedure as experiment 15 to yield *N*-(*p*-chlorobenzenesulfenyl)-*N*-(*p*-methylbenzyl)cyclopropylamine as a pure yellow oil (0.9 g, 96%); ν_{max} 3084 (aromatic C-H str.), 1570 and 1472 (aromatic C=C str.), 808 (1,4-disubst. aromatic) and 738 and 692 cm^{-1} (monosubst. aromatic); δ_{H} 0.62 (4 H, d, cyclopropyl CH_2 's), 2.34 (3 H, s, CH_3), 2.47 (1 H, m, CHNS), 4.08 (2 H, s, NCH_2), and 7.21 (9 H, m, Ar-H); δ_{C} 9.80 (cyclopropyl CH_2 's), 21.16 (CH_3), 39.43 (CHNS), 61.61 (CH_2NS), and 126.94-132.61 (Ar-C). TLC (light petroleum / ethyl acetate / alumina) showed the sulfenamide as the only product. No further purification was performed on this compound.

Synthesis of sulfenamides using benzenesulfonyl chloride

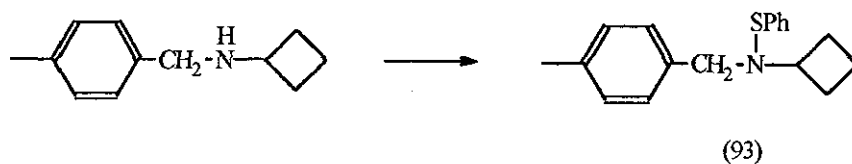
17. *N*-(Benzenesulfenyl)-*N*-methylcyclohexylamine (91)



N-Methylcyclohexylamine (0.8 g, 6.92 mmol) and benzenesulfonyl chloride (1.0 g, 6.92 mmol) were reacted by the same procedure as experiment 15 to yield *N*-(benzenesulfenyl)-*N*-methylcyclohexylamine (1.5g, 100%); ν_{max} 3060 (aromatic C-H str.), 1582 and 1474 (aromatic C=C str.), and 728 and 692 cm^{-1} (monosubst. aromatic); δ_{H} 1.50 (10 H, m, cyclohexyl protons), 2.83 (3 H, s, CH_3), and 7.01 (5 H, s, Ar-H). TLC (light petroleum / alumina) showed the sulfenamide as the only product. The data are detailed in a later preparation.

18. *N*-(Benzenesulfonyl)phthalimide (103)

Phthalimide (45.6 g, 0.31 mol), triethylamine (37.6 g, 0.37 mol) and benzenesulfonyl chloride (34.6 g, 0.31 mol) were reacted by the same procedure as experiment 15 to yield *N*-(benzenesulfonyl)phthalimide as off-white crystals. Recrystallisation from ethanol yielded pure *N*-(benzenesulfonyl)phthalimide (41.9 g, 53%). [m.p. 158-160°C (lit.⁸³ 160-161°C)]; ν_{\max} 1605 and 1465 (aromatic C=C str.), and 715 and 685 cm^{-1} (monosubst. aromatic); δ_{H} 7.23 (5 H, d, monosubst. Ph-H), and 7.81 (4 H, d, phthalimide aryl-H). TLC (light petroleum / alumina) showed the sulfenamide as the only product. No further purification was performed on this sulfenamide.

19. *N*-(Benzenesulfonyl)-*N*-(*p*-methylbenzyl)cyclobutylamine (93)

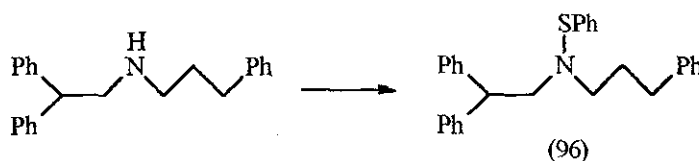
N-(*p*-Methylbenzyl)cyclobutylamine (1.0 g, 57 mmol), triethylamine (20 ml) and benzenesulfonyl chloride (0.8 g, 57 mmol) in diethyl ether (30 ml) were reacted together by the same procedure as experiment 15 to yield *N*-(benzenesulfonyl)-*N*-(*p*-methylbenzyl)cyclobutylamine as a red liquid. Purification by column chromatography on alumina gave *N*-(benzenesulfonyl)-*N*-(*p*-methylbenzyl)cyclobutylamine as a clear oil (1.2 g, 73%); ν_{\max} 3052 (aromatic CH), 1580 and 1474 (aromatic C=C), and 808 cm^{-1} (1,4-disubst. aromatic); δ_{H} 1.54 (2 H, m, cyclobutyl apex CH_2), 1.93 (4 H, m, cyclobutyl CH_2 's), 2.18 (3 H, s, CH_3), 3.54 (1 H, m, CHNSPh), 3.92 (2 H, s, CH_2N), and 7.10 (9 H, m, Ar-H); δ_{C} 13.49 (1-C), 21.16 (2-C), 29.24 (Me), 59.14 (CH_2N), 59.46 (CHN), and 125.76-131.24 (Ar-C); m/z 284.1473 [MH^+ (12%). $\text{C}_{18}\text{H}_{21}\text{NS}$ requires 284.1473], 218 (7), 176 (15), 147 (38), 105 (100), 77 (9), 65 (11), and 39 (10). TLC (light petroleum / alumina) showed the sulfenamide as the only product. No further purification was performed on this sulfenamide.

20. Attempted Synthesis of *N*-(Benzenesulfenyl)-*N*-(3-phenylpropyl)diphenyl-acetamide



N-(3-Phenylpropyl)diphenylacetamide (1.4 g, 42 mmol), triethylamine (30 ml) and benzenesulfonyl chloride (0.7 g, 42 mmol) in diethyl ether (50 ml) were reacted together by the same procedure as experiment 15. Unfortunately, only the starting material was recovered, with no evidence of product. This experiment was discontinued.

21. *N*-(Benzenesulfenyl)-*N*-(2,2-diphenylethyl)-3-phenylprop-1-ylamine (96)



N-(2,2-Diphenylethyl)-3-phenylprop-1-ylamine (1.0 g, 32 mmol), triethylamine (30 ml) and benzenesulfonyl chloride (0.5 g, 32 mmol) in diethyl ether (30 ml) were reacted together by the same procedure as experiment 15 to form *N*-(benzenesulfenyl)-*N*-(2,2-diphenylethyl)-3-phenylprop-1-ylamine as a brown oil. The *N*-(benzenesulfenyl)-*N*-(2,2-diphenylethyl)-3-phenylprop-1-ylamine was purified by column chromatography on alumina to yield the sulfenamide as a clear oil (670 mg, 50%); ν_{\max} 3060 and 3024 (aromatic CH), 1600 and 1492 (aromatic C=C), and 740 cm^{-1} (monosubst. aromatic); δ_{H} 1.84 (2 H, m, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 2.41 (2 H, t, $J = 7.1\text{ Hz}$, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{Ph}$), 2.87 (2 H, t, $J = 6.6\text{ Hz}$, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{Ph}$), 3.54 (2 H, d, $J = 8.1\text{ Hz}$, CHCH_2N), 4.43 (1 H, t, $J = 8.2\text{ Hz}$, Ph_2CH), and 7.24 (20 H, m, Ph-H); δ_{C} 31.45 (CH_2Ph), 33.49 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{Ph}$), 49.18 (NCH_2CH_2), 51.16 (Ph_2CH), 54.49 (CHCH_2N), and 125.62-132.90 (Ph-C). TLC (light petroleum / alumina) showed the sulfenamide as the only product. Attempts to perform an accurate mass on this compound resulted in its degradation. No further purification was therefore performed.

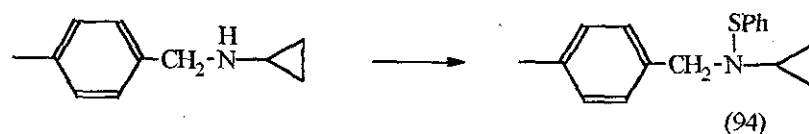
22. *N*-(Benzenesulfenyl)-*N*-(*p*-methylbenzyl)cyclopentylamine (92)



N-(*p*-Methylbenzyl)cyclopentylamine (1.0 g, 5.3 mmol), triethylamine (30 ml) and benzenesulfonyl chloride (769 mg, 5.3 mmol) in diethyl ether (30 ml) were reacted together

by the same procedure as experiment 15 to form *N*-(benzenesulfenyl)-*N*-(*p*-methylbenzyl)cyclopentylamine as a clear oil (1.1 g, 70%); ν_{\max} 3052 and 3000 (aromatic CH), 1612, 1580, 1512 and 1472 (aromatic C=C), and 808 and 738 cm^{-1} (1,4-disubst. and monosubst. aromatic); δ_{H} 1.44 (8 H, m, cyclopentyl CH_2 's), 2.17 (3 H, s, Me), 3.49 (1 H, q, $J = 9.2$ Hz, CHN), 4.18 (2 H, s, NCH_2), and 7.32 (9 H, m, Ar-H); δ_{C} 21.16 (1-C), 24.07 (2-C), 30.71 (Me), 62.44 (NCH_2), 65.67 (CHN), and 124.95-130.61 (Ar-C).

23. *N*-(Benzenesulfenyl)-*N*-(*p*-methylbenzyl)cyclopropylamine (94)



N-(*p*-Methylbenzyl)cyclopropylamine (1.0 g, 6.2 mmol), triethylamine (30 ml) and benzenesulfonyl chloride (897 mg, 6.2 mmol) in diethyl ether (30 ml) were reacted together by the same procedure as experiment 15 to form *N*-(benzenesulfenyl)-*N*-(*p*-methylbenzyl)cyclopropylamine as a clear oil (1.61 g, 96%); ν_{\max} 3052 and 3004 (aromatic C-H str.), 1612 and 1512 (aromatic C=C str.), 730 and 692 (monosubst. aromatic), and 808 cm^{-1} (1,4-disubst. aromatic); δ_{H} 0.61 (4 H, d, cyclopropyl CH_2 's), 2.31 (3 H, s, CH_3), 2.43 (1 H, m, CHNS), 4.08 (2 H, s, NCH_2), and 7.19 (9 H, m, Ar-H); δ_{C} 9.81 (cyclopropyl CH_2 's), 21.15 (CH_3), 39.33 (CHNS), 61.75 (NCH_2), and 126.34-131.73 (Ar-C).

24. *N*-(Benzenesulfenyl)-*N*-butylpent-4-enylamine (95)



N-Butylpent-4-enylamine (1.0 g, 7.1 mmol), triethylamine (30 ml) and benzenesulfonyl chloride (1.02 g, 7.1 mmol) in diethyl ether (30 ml) were reacted together by the same procedure as experiment 15 to form *N*-(benzenesulfenyl)-*N*-butylpent-4-enylamine as a clear oil (1.6 g, 95%); ν_{\max} 3076 (aromatic C-H str.), 1638 (C=C str.), 1570 and 1472 (aromatic C=C str.), and 732 and 691 cm^{-1} (monosubst. aromatic); δ_{H} 0.89 (3 H, t, $J = 7.2$ Hz, CH_2CH_3), 1.29 (2 H, m, CH_2CH_3), 1.51 (2 H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.63 (2 H, q, $J = 7.7$ Hz, $\text{CH}_2=\text{CHCH}_2\text{CH}_2$), 2.04 (2 H, q, $J = 7.6$ Hz, $\text{CH}_2=\text{CHCH}_2$), 2.93 (4 H, t, $J = 7.3$ Hz, CH_2NCH_2), 4.98 (2 H, t, $J = 10.3$ Hz, $\text{CH}_2=\text{CH}$), 5.80 (1 H, m, $\text{CH}_2=\text{CH}$), and 7.22 (4 H, m, Ar-H); δ_{C} 13.88 (CH_2CH_3), 19.98 (CH_2CH_3), 27.40 ($\text{CH}_2\text{CH}_2\text{CH}_3$), 30.62 ($\text{CH}_2=\text{CHCH}_2\text{CH}_2$), 31.11 ($\text{CH}_2=\text{CHCH}_2$), 57.73 (CH_2N), 58.32 (CH_2N), 114.79 ($\text{CH}_2=\text{CH}$), 139.75 ($\text{CH}_2=\text{CH}$), and 128.98-131.83 (Ar-C).

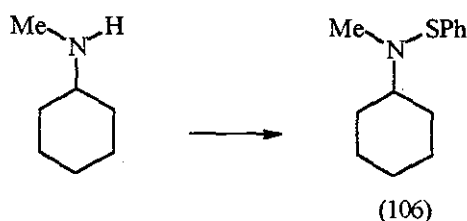
Synthesis of sulfenamides using *N*-(benzenesulfonyl)phthalimide

25. *N*-(Benzenesulfonyl)-*N*-(*p*-methylbenzyl)cyclopropylamine (105)

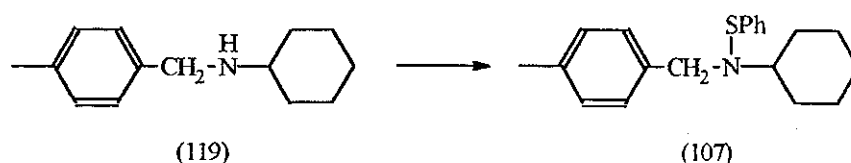


N-(*p*-Methylbenzyl)cyclopropylamine (1.0 g, 6.2 mmol) and *N*-(benzenesulfonyl)phthalimide (1.6 g, 6.2 mmol) were placed in a round-bottomed flask, together with dichloromethane (50 ml), and left to stir overnight. A precipitate of phthalimide was observed and subsequently filtered off. The product was taken up in light petroleum (100 ml) to yield *N*-(benzenesulfonyl)-*N*-(*p*-methylbenzyl)cyclopropylamine as a pure brown oil (1.2 g, 72%); ν_{\max} 3052 and 3004 (aromatic C-H str.), 1612 and 1512 (aromatic C=C str.), 730 and 692 (monosubst. aromatic), and 808 cm^{-1} (1,4-disubst. aromatic); δ_{H} 0.61 (4 H, d, cyclopropyl CH_2 's), 2.31 (3 H, s, CH_3), 2.43 (1 H, m, CHNS), 4.08 (2 H, s, NCH_2), and 7.19 (9 H, m, Ar-H); δ_{C} 9.81 (cyclopropyl CH_2 's), 21.15 (CH_3), 39.33 (CHNS), 61.75 (NCH_2), and 126.34-131.73 (Ar-C); m/z 270.1316 [MH^+ (23%)]. $\text{C}_{17}\text{H}_{19}\text{NS}$ requires 270.1316, 160 (31), 105 (100), 77 (14), 65 (9), 51 (6), and 39 (12). TLC (light petroleum / alumina) showed the sulfenamide as the only product. No further purification was performed on this sulfenamide.

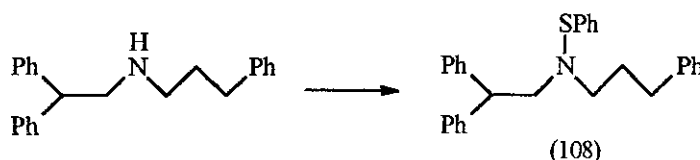
26. *N*-(Benzenesulfonyl)-*N*-methylcyclohexylamine (106)



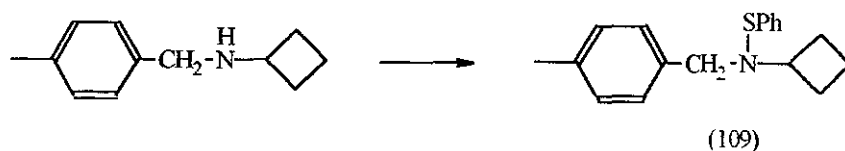
N-Methylcyclohexylamine (2.0 g, 18 mmol) and *N*-(benzenesulfonyl)phthalimide (4.5 g, 18 mmol) were reacted together by the same procedure as experiment 22 to yield *N*-(benzenesulfonyl)-*N*-methylcyclohexylamine as a pure yellow oil (3.7 g, 93%); (Found: C, 70.62; H, 8.61; N, 6.03; $\text{C}_{13}\text{H}_{19}\text{NS}$ requires: C, 70.54; H, 8.65; N, 6.33%); ν_{\max} 3060 (aromatic C-H str.), 1582 and 1474 (aromatic C=C str.), and 728 and 692 cm^{-1} (monosubst. aromatic); δ_{H} 1.53 (10 H, m, cyclohexyl protons), 2.82 (3 H, s, CH_3), and 7.06 (5 H, s, Ph-H). TLC [light petroleum / alumina] showed the sulfenamide as the only product.

27. *N*-(Benzenesulfenyl)-*N*-(*p*-methylbenzyl)cyclohexylamine (107)

N-(*p*-methylbenzyl)cyclohexylamine (3.0 g, 15 mmol) and *N*-(benzenesulfenyl)phthalimide (3.8 g, 15 mmol) were reacted together by the same procedure as experiment 22. However, refluxing for one week only caused a mixture of the amine and the sulfenamide to be formed. Separation on an alumina column using light petroleum as eluent produced *N*-(benzenesulfenyl)-*N*-(*p*-methylbenzyl)cyclohexylamine as a yellow oil (2.8 g, 67%); (Found: C, 76.67; H, 8.38; N, 4.58; $C_{20}H_{25}NS$ requires: C, 77.17; H, 8.04; N, 4.50%); ν_{\max} 3056 (aromatic C-H str.), 1580 and 1474 (aromatic C=C str.), 738 and 690 (monosubst. aromatic), and 808 cm^{-1} (1,4-disubst. aromatic); δ_H 1.53 (10 H, m, cyclohexyl protons), 2.26 (3 H, s, CH_3), 2.87 (1 H, m, NCH), 4.13 (2 H, s, NCH_2), and 7.17 (9 H, m, Ar-H); m/z 312.1786 [MH^+ (57%). $C_{20}H_{25}NS$ requires 312.1786], 204 (11), 160 (12), 105 (100), 77(11), 55 (13), and 41 (18). TLC (light petroleum / alumina) showed the sulfenamide as the only product.

28. *N*-(Benzenesulfenyl)-*N*-(2,2-diphenylethyl)-3-phenylprop-1-ylamine (108)

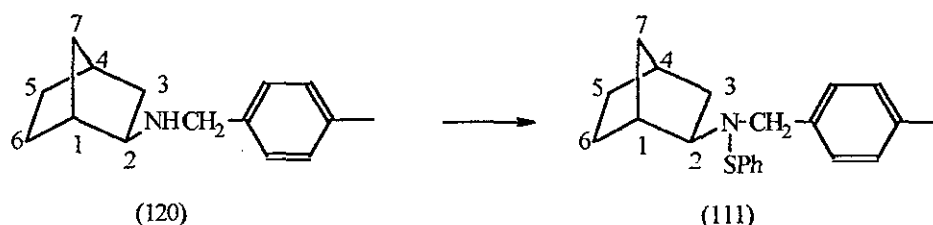
N-(2,2-Diphenylethyl)-3-phenylprop-1-ylamine (1.0 g, 32 mmol) in toluene (100 ml), and *N*-(benzenesulfenyl)phthalimide (1.6 g, 64 mmol, 2 equiv.) were reacted together by the same procedure as experiment 22. After refluxing for 1 h, the sulfenamide was formed as a brown oil. Purification by column chromatography on alumina yielded *N*-(benzenesulfenyl)-*N*-(2,2-diphenylethyl)-3-phenylprop-1-ylamine as a clear oil (451 mg, 34%); ν_{\max} 3060 and 3024 (aromatic CH), 1600 and 1492 (aromatic C=C), and 740 cm^{-1} (aromatic monosubst.); δ_H 1.84 (2 H, m, $NCH_2CH_2CH_2$), 2.41 (2 H, t, $J = 5.1$ Hz, $NCH_2CH_2CH_2Ph$), 2.87 (2 H, t, $J = 6.1$ Hz, $NCH_2CH_2CH_2Ph$), 3.54 (2 H, d, $J = 8.1$ Hz, $CHCH_2N$), 4.43 (1 H, t, $J = 8.1$ Hz, Ph_2CH), and 7.24 (20 H, m, Ph-H); δ_C 29.76 ($NCH_2CH_2CH_2$), 33.15 ($NCH_2CH_2CH_2Ph$), 50.25 ($NCH_2CH_2CH_2Ph$), 58.27 ($CHCH_2N$), 63.39 (Ph_2CH), and 122.21-131.27 (Ar-C). TLC (light petroleum / alumina) showed the sulfenamide as the only product.

29. *N*-(Benzenesulfenyl)-*N*-(*p*-methylbenzyl)cyclobutylamine (109)

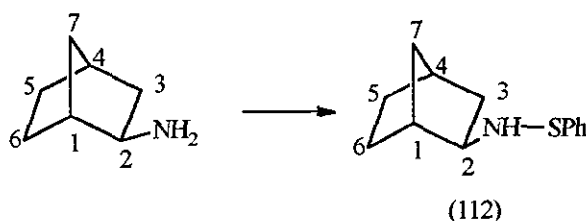
N-(*p*-Methylbenzyl)cyclobutylamine (0.9 g, 51 mmol, 1.3 equiv.) in toluene (50 ml), and *N*-(benzenesulfenyl)phthalimide (1.0 g, 39 mmol) were reacted together by the same procedure as experiment 22. Refluxing for 1 h gave the corresponding sulfenamide as an orange oil. Purification by column chromatography on alumina gave *N*-(benzenesulfenyl)-*N*-(*p*-methylbenzyl)cyclobutylamine as a clear oil (468 mg, 44%); ν_{\max} 3052 (aromatic CH), 1612, 1580, 1512 and 1474 (aromatic C=C), and 808 and 738 cm^{-1} (1,4-disubst. and monosubst. aromatic); δ_{H} 1.59 (2 H, m, apex cyclobutyl CH_2), 2.22 (4 H, m, cyclobutyl CH_2 's), 2.33 (3 H, s, CH_3), 3.26 (1 H, q, $J = 8.2$ Hz, CHNS), 3.99 (2 H, s, NCH_2), and 7.26 (9 H, m, Ar-H); δ_{C} 13.54 (1-C), 29.24 (2-C), 31.26 (2-C), 53.58 (Me), 59.22 (CHNS), 59.54 (NCH_2), and 125.37-131.73 (Ar-C); m/z 284.1473 [MH^+ (89%)]. $\text{C}_{18}\text{H}_{21}\text{NS}$ requires 284.1473], 218 (7), 176 (15), 147 (38), 105 (100), 77 (9), 65 (11), and 39 (10). TLC (light petroleum / alumina) showed the sulfenamide as the only product.

30. *N*-(Benzenesulfenyl)-*N*-(*p*-methylbenzyl)cyclopentylamine (110)

N-(*p*-Methylbenzyl)cyclopentylamine (1.0 g, 53 mmol) in toluene (100 ml) and *N*-(benzenesulfenyl)phthalimide (2.7 g, 110 mmol, 2 equiv.) were reacted together by the same procedure as experiment 22. Refluxing for 2 h yielded the sulfenamide as a brown oil. Purification by column chromatography on alumina gave *N*-(benzenesulfenyl)-*N*-(*p*-methylbenzyl)cyclopentylamine as a pale yellow oil (300 mg, 20%); ν_{\max} 3052 and 3000 (aromatic CH), 1612, 1580, 1512 and 1472 (aromatic C=C), and 808 and 738 cm^{-1} (1,4-disubst. and monosubst. aromatic); δ_{H} 1.44 (8 H, m, cyclopentyl CH_2 's), 2.17 (3 H, s, Me), 3.49 (1 H, q, $J = 9.2$ Hz, CHN), 4.18 (2 H, s, NCH_2), and 7.32 (9 H, m, Ar-H); δ_{C} 21.16 (1-C), 24.07 (2-C), 30.71 (Me), 62.44 (NCH_2), 65.67 (CHN), and 124.95-130.61 (Ar-C); m/z 297.1551 [M^+ (76%)]. $\text{C}_{19}\text{H}_{23}\text{NS}$ requires 297.1551], 218 (13), 192 (23), 105 (100), 77 (11), and 41 (11). TLC (light petroleum / alumina) showed the sulfenamide as the only product.

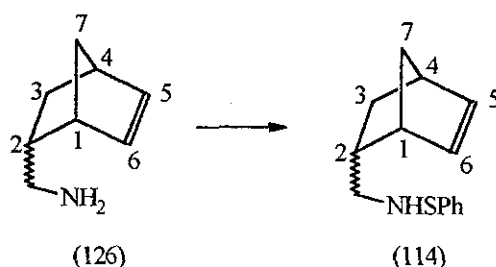
31. *exo-N*-(Benzenesulfonyl)-*N*-(*p*-methylbenzyl)bicyclo[2.2.1]hept-2-ylamine (111)

exo-N-(*p*-Methylbenzyl)bicyclo[2.2.1]hept-2-ylamine (1.2 g, 56 mmol) in toluene (30 ml), and *N*-(benzenesulfonyl)phthalimide (1.4 g, 56 mmol) were reacted together by the same procedure as experiment 22. Refluxing for 1 h gave the crude sulfenamide as a brown oil. Purification by column chromatography on alumina yielded *exo-N*-(benzenesulfonyl)-*N*-(*p*-methylbenzyl)bicyclo[2.2.1]hept-2-ylamine as an orange oil (767 mg, 43%); (Found: C, 77.84; H, 7.84; N, 4.56; $C_{21}H_{25}NS$ requires: C, 77.97; H, 7.79; N, 4.33%); ν_{\max} 3056 and 3016 (aromatic CH), 1604, 1578, 1510 and 1474 (aromatic C=C), and 808 and 740 cm^{-1} (1,4-disubst. and monosubst. aromatic); δ_H 1.05 (4 H, m, 5-H & 6-H), 1.48 (3 H, m, 7-H and 3-H), 2.24 (2 H, s, 1-H & 4-H), 2.35 (3 H, s, CH_3), 2.58 (1 H, s, 3-H), 2.95 (1 H, m, 2-H), 4.08 (2 H, ABq, $J = 10.2$ Hz, NCH_2), 7.23 (5 H, m, *SPh*), and 7.30 (4 H, ABq, $J = 18.1$ Hz, *Ph*-H); δ_C 21.16 (CH_3), 27.33 (6-C), 28.44 (5-C), 35.48 (7-C), 35.74 (4-C), 39.61 (3-C), 40.77 (1-C), 59.61 (NCH_2), 67.71 (C_2), and 125.86-130.44 (Ar-C); m/z 323.1708 [M^+ (21%). $C_{21}H_{25}NS$ requires 323.1708], 216 (21), 105 (100), 95 (15), 77 (20), 67 (22), and 39 (18). TLC (light petroleum / alumina) showed the sulfenamide as the only product.

32. *exo-N*-(Benzenesulfonyl)-*N*-bicyclo[2.2.1]hept-2-amine (112)

exo-2-Aminobicyclo[2.2.1]heptane (0.5 g, 45 mmol) in benzene (40 ml), and *N*-(benzenesulfonyl)phthalimide (2.3 g, 90 mmol, 2 equiv.) were reacted together by the same procedure as experiment 22. Refluxing for 2 h yielded the crude sulfenamide as a yellow oil. Purification by column chromatography on alumina gave *exo-N*-(benzenesulfonyl)-*N*-bicyclo[2.2.1]hept-2-amine as a clear oil (883 mg, 90%); ν_{\max} 3056 (aromatic CH), 3300 (amine), 1580 and 1474 (aromatic CC), and 742 and 688 cm^{-1} (monosubst. aromatic); δ_H 2.25 (2 H, s, 2-H and *NH*), 2.71 (1 H, m, 4-H), 2.89 (1 H, m, 1-H), 7.25 (5 H, m, *Ph*-H); δ_C 26.21 (6-C), 28.53 (5-C), 34.74 (7-C), 36.05 (4-C), 40.00 (3-C), 42.64 (1-C), 63.64 (2-C), and 125.12-129.34 (*Ph*-C).

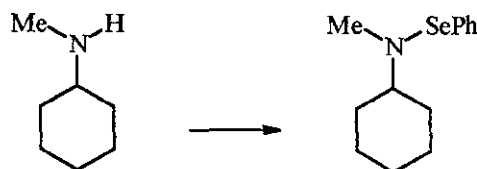
33. *N*-(Benzenesulfonyl)-(bicyclo[2.2.1]hept-5-en-2-yl)methylamine (114)



The procedure for this experiment was the same as for experiment 22. Work-up and subsequent purification of the reaction mixture on a dry alumina column yielded *N*-(benzenesulfonyl)-(bicyclo[2.2.1]hept-5-en-2-yl)methylamine as a clear oil (776 mg, 41%); ν_{\max} 3328 (amine), 3056 (aromatic CH), 1580 and 1476 (aromatic CC), and 738 and 692 cm^{-1} (monosubst. aromatic); δ_{H} 0.52 (1 H, ddd, *endo*-3-H), 1.28 (3 H, m, 7-H and 3-H), 1.83 (1 H, ddd, 2-H), 2.76 (2 H, m, 1-H and 4-H), 3.19 (2 H, m, CH_2NH), 5.91 (1 H, dd, 6-H), 6.11 (1 H, dd, 5-H), and 7.35 (5 H, m, Ar-H); δ_{C} 31.00 (3-C), 39.61 (4-C), 41.85 (1-C), 44.15 (2-C), 47.53 (7-C), 57.15 (8-C), 135.58 (olefin), and 125.67-130.20 (Ar-C).

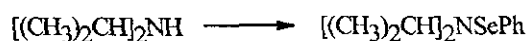
Attempted Synthesis of Selenamides

34. *N*-(Benzeneseleno)-*N*-methylcyclohexylamine

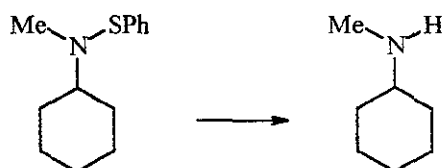


N-(Benzeneseleno)phthalimide (0.3 g, 99 mmol) was added to a stirred solution of *N*-methylcyclohexylamine (0.2 g, 149 mmol, 1.5 equiv.) in dichloromethane (50 ml). The solution was left to stir overnight, after which the solution was evaporated to dryness. This reaction was repeated and the conditions varied but unfortunately no product was obtained in either case. Therefore this approach was discontinued.

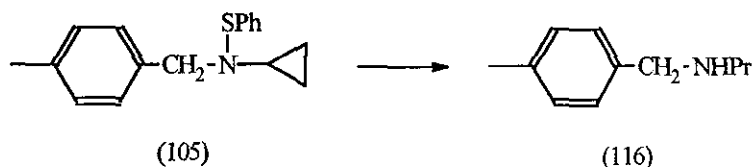
35. *N*-(Benzeneseleno)-diisopropylamine



Benzeneselenenyl bromide (0.5 g, 21 mmol) in hexane (20 ml) was added to a stirred solution of di-isopropylamine (0.42 g, 2 equiv.) in hexane (30 ml) and the mixture stirred at 50°C for 4h. The solution was evaporated to dryness to yield a yellow solid, which was mainly starting benzeneselenenyl bromide. The experiment was discontinued.

Reactions between Bu_3SnH and sulfenamides36. *N*-(Benzenesulfonyl)-*N*-methylcyclohexylamine

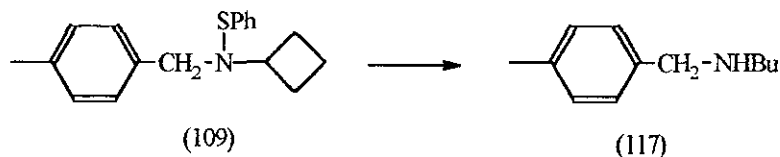
A solution of the sulfenamide (0.3 g, 1.36 mmol) in cyclohexane (30 ml), triphenyltin hydride (0.8 g, 2.31 mmol, 1.7 equiv.) and AIBN (0.07 g, 4 mmol) were all placed in a round-bottomed flask and purged with nitrogen for 30 min. The flask was then placed in a pre-heated oil bath and the contents refluxed. The reaction was followed by TLC. After 30 min TLC analysis showed that no sulfenamide was present. The *N*-methylcyclohexylamine was back-extracted into 1M hydrochloric acid (50 ml), neutralised with sodium carbonate solution and then sodium hydroxide until pH 14, and re-extracted into dichloromethane (3 x 50 ml). The solution was evaporated to dryness to yield a yellow oil of *N*-methylcyclohexylamine (81 mg, 53%); ν_{max} 3296 (amine N-H str.), and 2920 and 2852 cm^{-1} (methyl and methylene str.); δ_{H} 1.53 (10 H, m, cyclohexyl protons), and 2.42 (3 H, s, N- CH_3). TLC (light petroleum / alumina) showed the amine as the only product. Furthermore, the IR and NMR spectra were identical to authentic *N*-methylcyclohexane.

37. *N*-(Benzenesulfonyl)-*N*-(*p*-methylbenzyl)cyclopropylamine

N-(Benzenesulfonyl)-*N*-(*p*-methylbenzyl)cyclopropylamine (0.2 g, 0.74 mmol) and tributyltin hydride (0.4 g, 1.89 mmol) were reacted together by the same procedure as in experiment 36. In this case, after the reaction had been refluxing for 2.5 h, TLC showed that no sulfenamide remained. Sodium borohydride (0.3 g, 7.43 mmol, 10 equiv.) in dimethylformamide (20 ml) was added and the mixture stirred at room temperature for 60 min. Standard work-up produced *N*-(*p*-methylbenzyl)propylamine as a yellow liquid (88 mg, 73%). The hydrochloride salt was formed by adding two drops of methanolic hydrochloric acid to the amine, m.p. 177-179°C; ν_{max} 3308 (amine N-H str.), 1614 and 1512 (aromatic C=C str.), 3092 (aromatic C-H str.), and 806 cm^{-1} (1,4-disubst. aromatic); δ_{H} 0.93 (3 H, t, $J = 6.0$ Hz, $\text{CH}_3\text{CH}_2\text{CH}_2$), 1.45 (2 H, m, $\text{CH}_2\text{CH}_2\text{NH}$), 2.13 (1 H, m, NH), 2.21 (3 H, s, CH_3), 2.72 (2 H, t, $J = 7.5$ Hz, $\text{CH}_2\text{CH}_2\text{NHCH}_2$), 3.85 (2 H, s, NH- CH_2), and 7.10 (4 H, s, Ar-H).

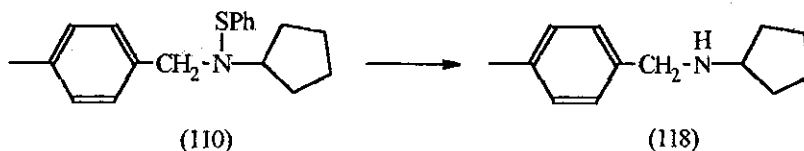
TLC (light petroleum / alumina) showed the amine as the only product. Furthermore, the IR and NMR spectra of authentic material were identical to the above.

38. *N*-(Benzenesulfonyl)-*N*-(*p*-methylbenzyl)cyclobutylamine

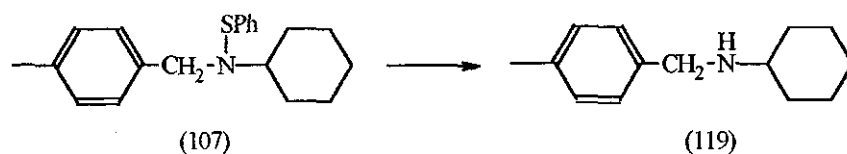


N-(Benzenesulfonyl)-*N*-(*p*-methylbenzyl)cyclobutylamine (400 mg, 14 mmol) and tributyltin hydride (520 mg, 24 mmol, 1.7 equiv.) in cyclohexane (30 ml) were reacted together by the same procedure as experiment 36 to generate the open chain imine, after refluxing for 2 h. The imine was reduced using sodium borohydride (160 mg, 42 mmol, 3 equiv.) in DMF (50 ml) to form *N*-(*p*-methylbenzyl)butylamine as a clear oil (106 mg, 42%); ν_{\max} 3304 and 3016 (amine NH and aromatic CH), 1512 (aromatic C=C), and 804 cm^{-1} (1,4-disubst. aromatic); δ_{H} 0.83 (3 H, d, $J = 6.3$ Hz, CH_3CH_2), 1.35 (4 H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 2.24 (3 H, s, CH_3), 2.57 (2 H, m, $\text{CH}_2\text{CH}_2\text{NH}$), 3.71 (2 H, s, NHCH_2Ar), and 7.12 (4 H, s, Ar-H). TLC (light petroleum / alumina) showed the amine as the only product. The IR and NMR spectra were identical to authentic *N*-(*p*-methylbenzyl)butylamine.

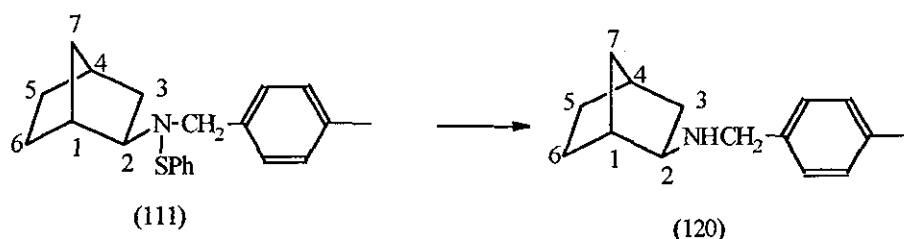
39. *N*-(Benzenesulfonyl)-*N*-(*p*-methylbenzyl)cyclopentylamine



N-(Benzenesulfonyl)-*N*-(*p*-methylbenzyl)cyclopentylamine (288 mg, 9 mmol) and tributyltin hydride (360 mg, 16 mmol, 1.7 equiv.) in cyclohexane (30 ml) were reacted together by the same procedure as experiment 36 to yield *N*-(*p*-methylbenzyl)cyclopentylamine as a clear oil (99 mg, 54%). No ring opened product [*N*-(*p*-methylbenzyl)pentylamine] was detected; ν_{\max} 3044 (aromatic CH), 1512 (aromatic C=C), and 806 cm^{-1} (1,4-disubst. aromatic); δ_{H} 1.75 (9 H, m, cyclopentyl CH_2 's and NH), 2.23 (3 H, s, CH_3), 3.18 (1 H, m, CHNH), 3.72 (2 H, s, NHCH_2), and 7.13 (4 H, s, Ar-H). TLC (light petroleum / alumina) showed the amine as the only product. The IR and NMR spectra of the amine were identical with authentic *N*-(*p*-methylbenzyl)cyclopentylamine.

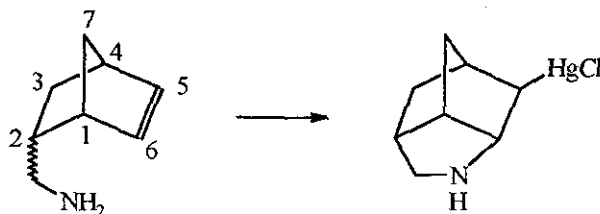
40. *N*-(Benzenesulfonyl)-*N*-(*p*-methylbenzyl)cyclohexylamine

N-(Benzenesulfonyl)-*N*-(*p*-methylbenzyl)cyclohexylamine (300 mg, 0.96 mmol) and tributyltin hydride (350 mg, 1.5 equiv) were reacted together by the same procedure as experiment 36. Standard work-up after refluxing the mixture for 2 h yielded the *N*-(*p*-methylbenzyl)cyclohexylamine as a clear liquid, (61 mg, 31%). The spectral data of the amine was found to be identical with authentic *N*-(*p*-methylbenzyl)cyclohexylamine.

41. *exo-N*-(Benzenesulfonyl)-*N*-(*p*-methylbenzyl)bicyclo[2.2.1]hept-2-ylamine

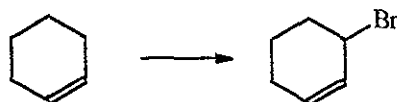
exo-N-(Benzenesulfonyl)-*N*-(*p*-methylbenzyl)bicyclo[2.2.1]hept-2-ylamine (350 mg, 11 mmol) and tributyltin hydride (400 mg, 18 mmol, 1.7 equiv.) in cyclohexane (30 ml) were reacted together by the same procedure as experiment 36 to yield *exo-N*-(*p*-methylbenzyl)bicyclo[2.2.1]hept-2-ylamine as a pale yellow oil (162 mg, 69%) after 1 h reflux. No evidence of the ring opened product was detected, even though the experiment was repeated using a syringe pump to add the tributyltin hydride; ν_{\max} 3532 (amine NH), 3044 (aromatic CH), 1512 (aromatic C=C), and 806 cm^{-1} (1,4-disubst. aromatic); δ_{H} 1.07 (4 H, m, 5-H & 6-H), 1.50 (4 H, m, 3-H & 7-H), 2.06 (2 H, s, 1-H & 4-H), 2.31 (3 H, s, CH_3), 2.60 (1 H, m, 2-H), 3.68 (2 H, ABq, $J = 9.1$ Hz, NHCH_2), and 7.22 (4 H, ABq, $J = 11.8$ Hz, Ar-H). TLC (light petroleum / alumina) showed the amine as the only product. IR and NMR spectra were identical with those of authentic *exo-N*-(*p*-methylbenzyl)bicyclo[2.2.1]hept-2-ylamine.

44. Reaction between (Bicyclo[2.2.1]hept-5-en-2-yl)methylamine and Mercury (II) chloride



A solution of *exo*- and *endo*-(bicyclo[2.2.1]hept-5-en-2-yl)methylamine (512 mg, 4.16 mmol) in dried THF (5 ml) was added in one portion to a stirred solution of mercury (II) chloride (1.13 g, 4.16 mmol) in THF (20 ml). The resulting suspension was stirred at room temperature for 1 h, when the white precipitate (cyclised organo-mercury salt) was filtered off. The precipitate was washed with THF (2 x 20 ml) and dried. Unfortunately, on reduction of the salt with first sodium borohydride and then lithium aluminium hydride, a thick oil of polymeric material was obtained. It appears that the *endo*-isomer interfered with the reaction to form an inseparable polymeric product. The experiment was discontinued.

45. 3-Bromocyclohexene



A suspension of cyclohexene (20.0 g, 0.253 mol), N-bromosuccinamide (52.0 g, 0.292 mol) and benzoyl peroxide (60 mg) in carbon tetrachloride (350 ml) was refluxed for 2 h, after which time a precipitate of succinamide could clearly be seen to be floating on top of the reaction mixture. The precipitate was filtered off and the solvent removed to leave a brown liquid. The spectra obtained from this reaction were identical with those of authentic 3-bromocyclohexene. The 3-bromocyclohexene was used without further purification.

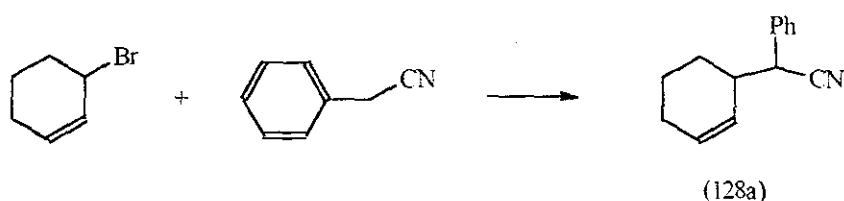
46. 4-*t*-Butylbenzyl cyanide



Sodium cyanide (4.02 g, 82 mmol) was added in one portion to a stirred solution of 4-*t*-butylbenzyl chloride (15.0 g, 82 mmol) in absolute ethanol (105 ml) and water (35 ml). The reaction was heated to reflux and maintained at this temperature for 4.5 h, when TLC indicated that all starting material had been converted. The solvent was evaporated to

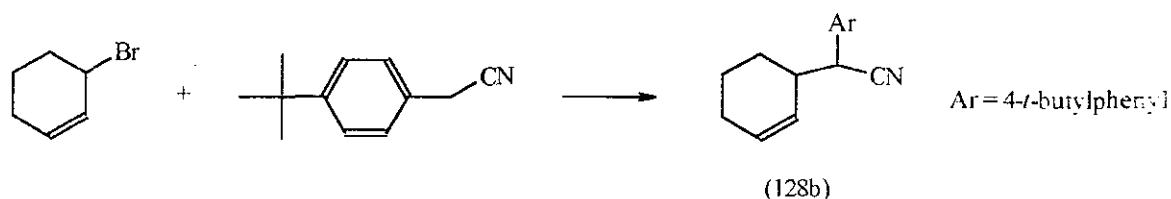
dryness and the solid residue taken up in water (50 ml) and extracted with diethyl ether (3x50 ml). The ether extracts were combined and washed once with water (50 ml), before being dried over anhydrous MgSO_4 and the solution evaporated to dryness to yield (14.0 g, 98%) of the crude product, Purification on a dry silica column using hexane and diethyl ether as eluent yielded 4-*t*-butylbenzyl cyanide as a clear liquid (10.0 g, 70%). δ_{H} (300 MHz) 1.33 (9H, s, *t*-Bu), 3.71 (2 H, s, CH_2CN), and 7.32 (4 H, ABq, $J = 19.6$ Hz, Ar-H); δ_{C} 23.12 (CH_2CN), 31.32 (*t*-Bu), 34.59 (CMe_3), 120.54 (Ar-C), and 151.16 (CN).

47. 2-(Cyclohex-2-en-1-yl)-2-phenylacetonitrile (128a)



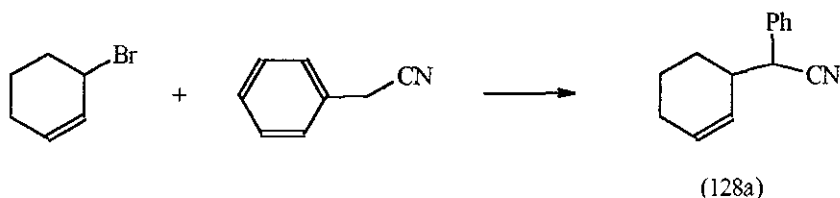
Phenylacetonitrile (12.0 g, 0.102 mol) and benzyltriethylammonium chloride (1.1 g, 4.65 mmol) were both added to a stirred solution of sodium hydroxide (100 ml, 50% w/v). The resulting two phase system was cooled to 25°C when 3-bromocyclohexene was added dropwise. The suspension was stirred at 40°C for 6 h, and at room temperature overnight. After this time, the reaction was diluted with water (100 ml) and acidified to pH 2 using concentrated hydrochloric acid (10 ml). The mixture was transferred to a separating funnel and extracted using diethyl ether (3 x 50 ml). The ether extracts were combined and washed with water (50 ml), dried over magnesium sulfate and the solution evaporated to dryness to yield a crude brown oil. Purification on a dry silica column using diethyl ether and hexane as eluent yielded 2-(cyclohex-2-en-1-yl)-2-phenylacetonitrile as a light brown oil (16.8 g, 92%); ν_{max} 3029 (aromatic CH), 2240 (CN), 1496 (aromatic CH), and 676 cm^{-1} (monosubst. aromatic); δ_{H} 1.35 (2 H, m, 5'-H), 1.67 (2 H, m, 6'-H), 1.88 (2 H, d, $J = 6.0$ Hz, 4'-H), 2.55 (1 H, m, 1'-H), 3.68 (1 H, dd, $J = 7.7$ Hz, 2-H), 5.32 (0.5 H, d, $J = 8.9$ Hz, 3'-H), 5.69 (0.5 H, d, $J = 8.9$ Hz, 3'-H), 5.76 (1 H, m, 2'-H), and 7.23 (5 H, m, Ph-H); δ_{C} 21.01 (5'-C), 25.01 (6'-C), 26.28 (4'-C), 40.45 (1'-C), 43.38 (2-C), 125.96-132.49 (Ar-C and 2'-C and 3'-C), and 134.51 (CN); m/z 197 (14%), 117 (100), and 105 (26).

48. 2-(4-*t*-Butylphenyl)-2-(cyclohex-2-en-1-yl)acetonitrile (128b)



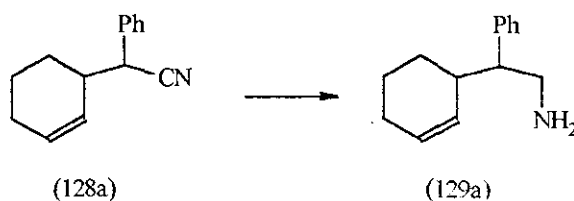
The procedure for this experiment was the same as experiment 47, except in this case, 4-*t*-butylbenzyl cyanide (3.3 g, 19 mmol) was used. Reaction and work-up in the usual manner yielded 2-(4-*t*-butylphenyl)-2-(cyclohex-2-en-1-yl)acetonitrile as a clear oil after purification (4.7 g, 98%); (Found C: 85.07, H: 8.95, N: 5.58; $C_{18}H_{23}N$ expects C: 85.32, H: 9.15, N: 5.53); δ_H (300 MHz) 1.35 (9 H, s, *t*-Bu), 1.52 (2 H, m, 5'-H), 1.73 (2 H, m, 6'-H), 2.01 (2 H, m, 4'-H), 2.59 (1 H, m, 1'-H), 3.71 (1 H, dd, $J = 7.7$ Hz, 2-H), 5.48 (1 H, d, $J = 6.9$ Hz, 3'-H), 5.76 (1 H, d, $J = 6.9$ Hz, 2'-H), and 7.32 (4 H, ABq, Ar-H); δ_C 18.72 (5'-C), 20.66 (6'-C), 27.40 (4'-C), 31.23 (*t*-Bu), 34.49 (quart), 40.45 (1'-C), 42.92 (2-C), 120.25 and 130.74 (CM_{E_3}), 123.72-131.44 (Ar-C and 2'-C and 3'-C), and 151.00 (CN); m/z 253 (19%), 173 (70), 158 (100), and 130 (26).

49. Attempted Synthesis of 2-(Cyclohex-2-en-1-yl)-2-phenylacetonitrile using Sodium Hydride

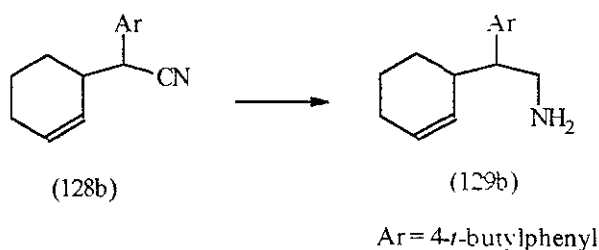


Sodium hydride (60% dispersion in mineral oils, 373 mg, 9.31 mmol, 1.5 equiv.) was first washed free of the mineral oils by stirring in hexane (2 x 20 ml). The hexane washings were decanted off and replaced with dry tetrahydrofuran (50 ml). The benzyl cyanide (800 mg, 6.83 mmol) was added dropwise over 10 min to this stirred suspension and the resulting solution stirred at room temperature for 1 h. The reaction was cooled to -78°C when the 3-bromocyclohexene (1.0 g, 6.21 mmol) was added dropwise. The temperature was maintained for a further 30 min and allowed to warm up to room temperature for 3 h, when TLC indicated that no starting material remained. The reaction was poured onto ice-water (50 ml) and acidified to pH 2 using concentrated hydrochloric acid. The product was extracted with diethyl ether (3 x 50 ml); the ether extracts were combined and washed with water (50 ml) before being dried over magnesium sulfate, and evaporated to dryness to yield a yellow oil. Unfortunately, none of the expected product was found in this mixture. This approach was therefore discontinued.

50. 2-(Cyclohex-2-en-1-yl)-2-phenylethylamine (129a)



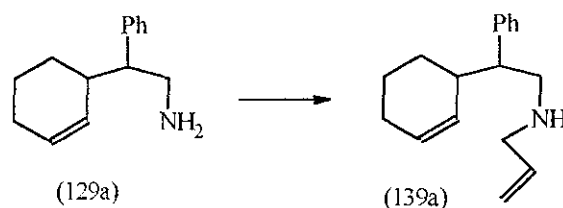
A solution of 2-(cyclohex-2-en-1-yl)-2-phenylacetonitrile (700 mg, 3.55 mmol) in dry diethyl ether (10 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (386 mg, 2.8 equiv.) in dry diethyl ether (20 ml) at room temperature. The reaction was stirred at this temperature for a further hour, when TLC indicated that no starting material remained. The reaction flask was then cooled to 0°C and 2M aqueous NaOH solution added dropwise to precipitate the inorganic lithium salts. The precipitate was filtered off and washed with dry diethyl ether (20 ml). The ether washings were combined and evaporated to dryness to yield pure 2-(cyclohex-2-en-1-yl)-2-phenylethylamine as a clear oil (690 mg, 97%); ν_{\max} 3372.8 and 3284.1 (NH₂), 3060.8 (aromatic CH), 1648.0 (C=C), 1583.3 and 1494.6 (aromatic CC), and 680.10 cm⁻¹ (monosubst. aromatic); δ_{H} 1.24 (2 H, m, 5'-H), 1.48 (2 H, m, 6'-H), 1.75 (2 H, m, 4'-H), 1.97 (2 H, s, NH₂), 2.49 (2 H, m, 1-H), 2.91 (1 H, t, J = 8.6 Hz, 1'-H), 3.15 (1 H, dt, J = 8.4 Hz, 2-H), 5.32 (0.5 H, d, J = 7.7 Hz, 3'-H), 5.64 (0.5 H, d, J = 7.7 Hz, 3'-H), 5.82 (1 H, dd, J = 9.4 Hz, 2'-H), and 7.32 (5 H, m, Ph-H); δ_{C} 21.90 (5'-C), 25.39 (6'-C), 27.35 (4'-C), 38.46 (1'-C), 39.03 (1-C), 44.86 (2-C), 124.35-132.90 (Ph-C and 2'-C and 3'-C), and 142.54 (quart); m/z 201 (20%), 184 (100), 120 (66), and 103 (42).

51. 2-(4-*t*-Butylphenyl)-2-(cyclohex-2-en-1-yl)ethylamine (129b)

The procedure for this experiment was the same as that in experiment 50, except that in this case 2-(4-*t*-butylphenyl)-2-(cyclohex-2-en-1-yl)acetonitrile (2.0 g, 7.89 mmol) was used. Reaction and work up in the usual manner yielded 2-(4-*t*-butylphenyl)-2-(cyclohex-2-en-1-yl)ethylamine as a clear oil, (1.6 g, 79%); (Found C: 83.62, H: 10.52, N: 5.55; C₁₈H₂₇N requires C: 83.98, H: 10.57, N: 5.44); δ_{H} (300 MHz) 1.32 (9 H, s, *t*-Bu), 1.63 (6 H, m, 4'-H, 5'-H and 6'-H), 1.96 (2 H, s, NH₂), 2.51 (2 H, m, 1-H), 2.93 (1 H, t, J = 7.7 Hz, 1'-H), 3.13 (1

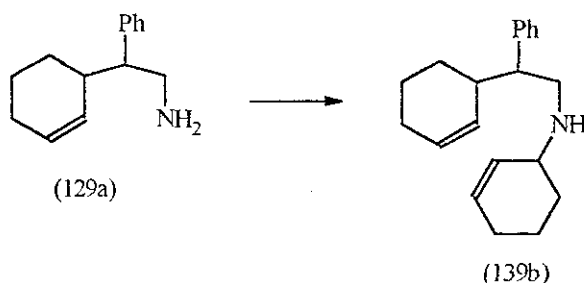
H, dt, $J = 6.0$ Hz, 2-H), 5.37 (0.5 H, d, $J = 7.3$ Hz, 3'-H), 5.62 (0.5 H, d, $J = 7.3$ Hz, 3'-H), 5.84 (1 H, dd, 2'-H), and 7.24 (4 H, ABq, Ar-H); δ_C 21.97 (5'-C), 25.23 (6'-C), 27.25 (4'-C), 31.41 (*t*-Bu), 34.37 (CMe₃), 39.08 (1'-C), 44.52 (1-C), 54.45 (2-C), 127.48-130.21 (Ar-C), 139.26 (3'-C), and 149.09 (2'-C); m/z 257 (7%), 240 (38), 183 (66), 176 (100), 147 (96), 133 (90), and 105 (61).

52. 2-(Cyclohex-2-en-1-yl)-2-phenyl-*N*-(prop-2-enyl)ethylamine (139a)



2-(Cyclohex-2-en-1-yl)-2-phenylethylamine (2.0 g, 9.9 mmol) was reacted with allylbromide (1.2 g, 9.9 mmol) using the same procedure as experiment 77. Work-up of the reaction mixture after refluxing for 15 h yielded the 2-(cyclohex-2-en-1-yl)-2-phenyl-*N*-(prop-2-enyl)ethylamine as a clear oil, (2.2 g, 92%); ν_{\max} 3025 (aromatic CH), 1453 (aromatic C=C), and 701 cm⁻¹ (monosubst. aromatic); δ_H 1.56 (6 H, m, 4'-H, 5'-H and 6'-H), 2.39 (1 H, m, 1'-H), 2.95 (5 H, m, 1-H, 2-H and 3-H), 5.03 (2 H, dt, $J = 8.2$ Hz, 2'-H and 3'-H), 5.79 (3 H, m, 4-H and 5-H), and 7.27 (5 H, m, Ph-H); δ_C 21.88 (5'-C), 25.22 (6'-C), 27.26 (4'-C), 38.96 (1'-C), 51.29 (1-C), 52.44 (3-C), 57.36 (2-C), 115.79 (4-C), 136.81 (5-C), 125.65-130.20 (Ar-C and 2'-C and 3'-C), and 142.24 (quart. aromatic); m/z 242.1909 [MH⁺ (100%). C₁₇H₂₃N requires 242.1909], 202 (53), 102 (17), and 70 (43).

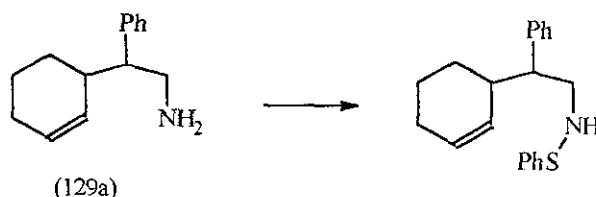
53. 2, *N*-di-(Cyclohex-2-en-1-yl)-2-phenylethylamine (139b)



2-(Cyclohex-2-en-1-yl)-2-phenylethylamine (1.25 g, 6.2 mmol) was reacted with 3-bromocyclohexene (0.7 ml, 6.2 mmol) using the same procedure as experiment 77. Work up of the reaction mixture after refluxing for 15 h yielded the 2, *N*-di(cyclohex-2-enyl)-2-phenylethylamine as a clear oil, (861 mg, 49%) after purification on a dry alumina column using diethyl ether/ethyl acetate as eluent; ν_{\max} 3402 (NH), 3024 (aromatic CH), 1452 (aromatic C=C), and 700 cm⁻¹ (monosubst. aromatic); δ_H 1.51 (15 H, m, 4'-H, 5'-H, 6'-H, 1'-

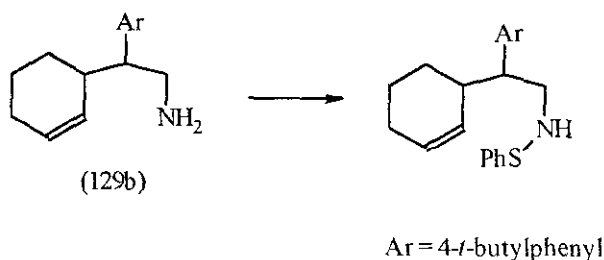
H, 2-H, NH, 6'-H, 5'-H, and 4'-H), 2.76 (2 H, d, $J = 8.2$ Hz, 1-H), 3.46 (1 H, m, 1'-H), 5.80 (4 H, dd, $J = 9.1$ Hz, 2'-H, 3'-H, 2'-H and 3'-H), and 7.19 (5 H, m, Ar-H); δ_c 22.33 (5'-C), 25.28 (6'-C), 27.99 (4'-C), 37.86 (1'-C), 49.22 (1-C), 50.59 (2-C), 55.02 (1'-C), 125.86-131.69 (Ar-C and 2'-C and 3'-C), and 143.84 (quart. aromatic); m/z 282.2222 [MH^+ (100%)]. $C_{20}H_{27}N$ requires 282.2222], 202 (15), 190 (23), and 110 (17).

54. Attempted Synthesis of *N*-(Benzenesulfenyl)-2-(cyclohex-2-en-1-yl)-2-phenylethylamine using *N*-(Benzenesulfenyl)phthalimide

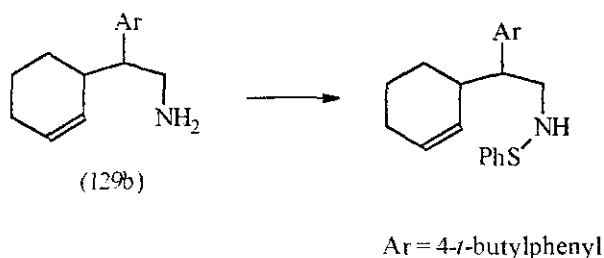


A solution of 2-(cyclohex-2-en-1-yl)-2-phenylethylamine (700 mg, 3.48 mmol) in dry dichloromethane (10 ml) was added to a stirred solution of *N*-(benzenesulfenyl)phthalimide (900 mg, 3.5 mmol) in dry dichloromethane (50 ml). The reaction was heated to reflux and maintained at this temperature for 3 days. In spite of these forcing conditions, TLC showed that no reaction had occurred after this time. The reaction was therefore discontinued on the assumption that there was too much steric hindrance for this reaction to work.

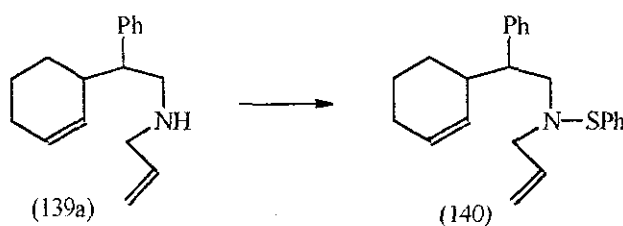
55. Attempted Synthesis of *N*-(Benzenesulfenyl)-2-(4-*t*-butylphenyl)-2-(cyclohex-2-en-1-yl)ethylamine using *N*-(Benzenesulfenyl)phthalimide



The procedure for this was the same as experiment 54, except that a solution of 2-(4-*t*-butylphenyl)-2-(cyclohex-2-en-1-yl)ethylamine (1.5 g, 5.83 mmol) in dry dichloromethane (10 ml) was used. Again, no reaction was observed after refluxing the mixture for three days. This can be explained by the steric hindrance involved in this reaction.

56. *N*-(Benzenesulfonyl)-2-(4-*t*-butylphenyl)-2-(cyclohex-2-en-1-yl)ethylamine (97)

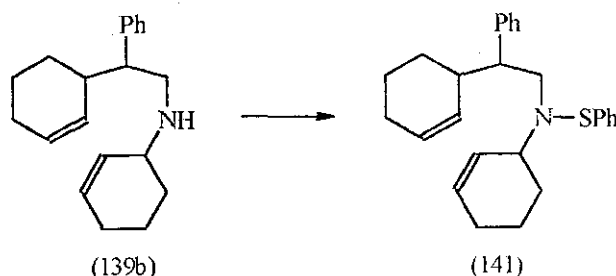
A solution of benzenesulfonyl chloride (1.4 g, 9.71 mmol) in dry diethyl ether (10 ml) was added dropwise to a stirred solution of 2-(4-*t*-butylphenyl)-2-(cyclohex-2-en-1-yl)ethylamine (2.5 g, 9.71 mmol) and dry triethylamine (15 ml, excess) in dry diethyl ether (100 ml) at room temperature under an atmosphere of nitrogen. Immediately a precipitate of triethylamine hydrochloride was observed, though the reaction was stirred at room temperature for a further 2 h before the reaction had gone to completion. The precipitate was filtered off, washed once with diethyl ether (20 ml), and the ether washings combined and evaporated to dryness to yield a crude brown oil. Purification on a dry alumina column using hexane and diethyl ether as eluent yielded the *N*-(benzenesulfonyl)-2-(4-*t*-butylphenyl)-2-(cyclohex-2-en-1-yl)ethylamine as a light yellow oil (3.2 g, 90%); δ_{H} (300 MHz) 1.31 (2 H, m, 5'-H), 1.35 (9 H, s, *t*-Bu), 1.42 (2 H, m, 6'-H), 1.64 (2 H, m, 4'-H), 1.89 (1 H, s, NH), 3.11 (1 H, m, 1'-H), 3.62 (2 H, m, 1-H), 3.95 (1 H, m, 2-H), 5.42 (1 H, d, 3'-H, $J = 9.4$ Hz), 5.63 (1 H, d, 2'-H, $J = 8.5$ Hz), 7.25 (9 H, m, Ar-H); δ_{C} 22.09 (5'-C), 25.32 (6'-C), 27.00 (4'-C), 31.51 (*t*-Bu), 34.60 (CMe₃), 38.71 (1'-C), 49.46 (2-C), 67.52 (1-C), 124.02-129.53 (Ar-C and 2'-C and 3'-C), 139.13 (C₉), and 149.01 (C₁₀); m/z 366 (15%), 351 (52), 271 (56), 258 (90), and 126 (100).

57. *N*-(Benzenesulfonyl)-*N*-(prop-2-enyl)-2-(cyclohex-2-en-1-yl)phenylethylamine (140)

N-(Prop-2-enyl)-2-(cyclohex-2-en-1-yl)-phenylethylamine (800 mg, 3.32 mmol) was reacted with benzenesulfonyl chloride (0.48 ml, 3.32 mmol) using the procedure in experiment 56 to yield 1.8 g of the crude sulfenamide. Subsequent purification on a dry alumina column using diethyl ether/light petroleum as eluent yielded the *N*-(benzenesulfonyl)-*N*-(prop-2-enyl)-2-(cyclohex-2-en-1-yl)-phenylethylamine as a clear oil (935 mg, 81%); ν_{max} 3028 (aromatic CH), 1580, 1476 and 1454 (aromatic C=C), and 691 and 689 cm⁻¹ (monosubst. aromatic); δ_{H} 1.54 (6 H, m, 4'-H, 5'-H and 6'-H), 2.41 (1 H, m, 1'-

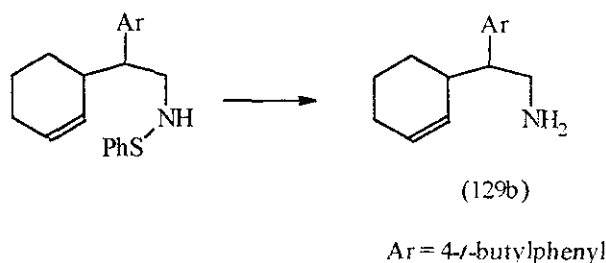
H), 3.03 (1 H, m, 2-H), 3.23 (2 H, m, 1-H), 3.52 (2 H, d, $J = 6.1$ Hz, 3-H), 5.08 (2 H, dt, $J = 9.1$ Hz, 2'-H and 3'-H), 5.71 (3 H, m, 4-H and 5-H), and 7.31 (10 H, m, Ar-H); δ_C 21.89 (5'-C), 25.23 (6'-C), 27.24 (4'-C), 39.05 (1'-C), 49.49 (2-C), 59.41 (1-C), 62.23 (3-C), 117.42 (5-C), 135.40 (4-C), and 125.57-133.62 (Ar-C and 2'-C and 3'-C); m/z 350.1942 [MH^+ (100%)]. $C_{23}H_{27}NS$ requires 350.1942], 270 (81), 218 (38), 178 (25), and 109 (10).

58. *N*-(Benzenesulfonyl)-*N*-2-di(cyclohex-2-en-1-yl)phenylethylamine (141)



N-2-di(Cyclohex-2-en-1-yl)phenylethylamine 800 mg, 2.85 mmol) was reacted with benzenesulfonyl chloride (411 mg, 2.85 mmol) using the procedure in experiment 56 to yield the *N*-(benzenesulfonyl)-*N*-2-di(cyclohex-2-en-1-yl)phenylethylamine as a clear oil after purification on a dry alumina column using diethyl ether/light petroleum as eluent (788 mg, 71%); δ_H 1.31-1.98 (12 H, m, 4'-H, 5'-H and 6'-H), 2.59 (1 H, m, 1'-H), 3.14 (1 H, m, 2-H), 3.40 (2 H, m, 1-H), 3.67 (1 H, m, 1'-H), 5.70 (4 H, m, 2'-H and 3'-H), and 6.99-7.29 (5 H, m, Ar-H); δ_C 21.39 (5'-C), 22.29 (6'-C), 25.24 (4'-C), 28.91 (1'-C), 32.13 (2-C), 46.12 (1-C), 55.03 (1'-C), and 125.57-136.58 (Ar-C and 2'-C and 3'-C); m/z 390.2255 [MH^+ (72%)]. $C_{26}H_{31}NS$ requires 390.2255], 362 (69), 282 (93), 179 (100), and 110 (28).

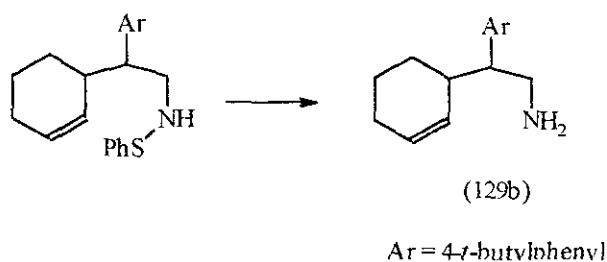
59. Reaction between *N*-(Benzenesulfonyl)-2-(4-*t*-butylphenyl)-2-(cyclohex-2-en-1-yl)ethylamine and Tri-*n*-butyltin hydride



A solution of *N*-(benzenesulfonyl)-2-(4-*t*-butylphenyl)-2-(cyclohex-2-en-1-yl)ethylamine (100 mg, 0.27 mmol) in dry tetrahydrofuran (30 ml) was placed in a round-bottomed flask and purged with nitrogen for 30 min. Simultaneously, a solution of tri-*n*-butyltin hydride (135 mg, 0.46 mmol) and AIBN (30 mg) in dried tetrahydrofuran (20 ml) was purged with nitrogen for 30 min. The tin hydride solution was transferred to a syringe

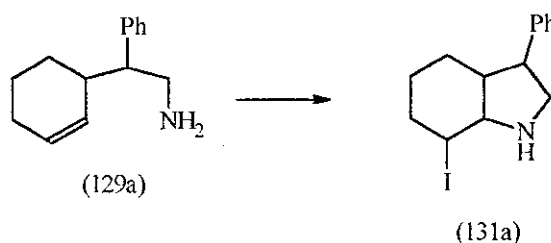
pump where it was added over 6 h to a refluxing solution of the sulfenamide in tetrahydrofuran. After this time, TLC showed complete conversion of the sulfenamide. The reaction was allowed to cool to room temperature and the solvent evaporated to dryness. The solid residue was taken up in diethyl ether (50 ml) and the solution back-extracted into 2M hydrochloric acid (3 x 50 ml). The acidic washings were neutralised with saturated sodium carbonate solution and basified to pH 14 using sodium hydroxide pellets. The aqueous layer was washed with diethyl ether (3 x 30 ml); the ether extracts were combined and washed with water (50 ml) before being dried over magnesium sulfate. Evaporation to dryness yielded pure 2-(4-*t*-butylphenyl)-2-(cyclohex-2-enyl)ethylamine (90 mg, >100%) with none of the expected cyclised product observed.

60. Reaction between *N*-(Benzenesulphenyl)-2-(4-*t*-butylphenyl)-2-(cyclohex-2-en-1-yl)ethylamine and Tris(trimethylsilyl)silane



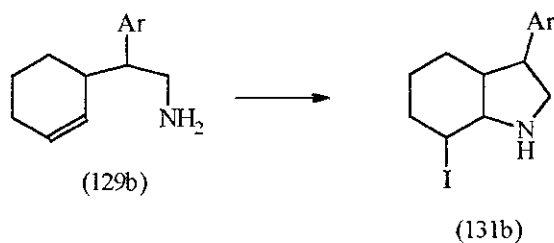
A solution of *N*-(benzenesulphenyl)-2-(4-*t*-butylphenyl)-2-(cyclohex-2-en-1-yl)ethylamine (200 mg, 0.55 mmol), tris(trimethylsilyl)silane (0.16 ml, 0.55 mmol) and AIBN (20 mg) in dry tetrahydrofuran (100 ml) was refluxed under an atmosphere of nitrogen for 3 h. After this time, TLC indicated complete conversion of sulfenamide. The reaction was allowed to cool to room temperature and the solvent was evaporated to dryness. The solid residue was taken up into diethyl ether (50 ml) and washed with 2M hydrochloric acid (3 x 30 ml). The acidic washings were then neutralised with saturated sodium carbonate solution, and basified to pH 14 using sodium hydroxide pellets. The aqueous layer was washed with diethyl ether (3 x 50 ml); the ether washings were combined, washed once with water (50 ml), dried over magnesium sulfate and evaporated to dryness to yield entirely 2-(4-*t*-butylphenyl)-2-(cyclohex-2-en-1-yl)ethylamine as a clear oil (100 mg, 71%) with no evidence of any expected cyclised product.

61. 3a,4,5,6,7,7a-hexahydro-7-iodo-3-phenylindoline (131a)



A solution of iodine (5.1 g, 19 mmol) in dry tetrahydrofuran (15 ml) was added to a stirred solution of 2-(cyclohex-2-en-1-yl)phenylethylamine (2.0 g, 9.95 mmol) in dry tetrahydrofuran (10 ml) and saturated sodium bicarbonate solution (15 ml) and stirred for 24 h. After this time, a saturated solution of sodium thiosulfate (50 ml) was added and the product was extracted with ethyl acetate (2 x 50 ml). The ethyl acetate extracts were combined and dried over magnesium sulfate, before being evaporated to dryness to yield the 3a,4,5,6,7,7a-hexahydro-7-iodo-3-phenylindoline as a brown oil (2.0 g, 61%) after purification on a dry alumina column using hexane and diethyl ether as eluent; δ_{H} (300 MHz) 1.87 (6 H, m, 4-H, 5-H and 6-H), 2.41 (1 H, m, NH), 3.08 (1 H, t, $J = 9.4$ Hz, 3a-H), 3.62 (1 H, t, $J = 7.7$ Hz, 3-H), 3.85 (1 H, m, 7a-H), 4.18 (2 H, m, 2-H), 4.85 (1 H, m, 7-H), and 7.29 (5 H, m, Ar-H); δ_{C} (75 MHz) 14.11 (5-C), 16.53 (6-C), 26.05 (4-C), 41.83 (3a-C), 47.77 (2-C), 50.35 (3-C), 62.26 (7a-C), 72.80 (7-C), and 124.59-132.31 (Ar-C); m/z 329 (32%), 261 (97), and 244 (100).

62. 3-(4-*t*-Butylphenyl)-3a,4,5,6,7,7a-hexahydro-7-iodoindoline (131b)

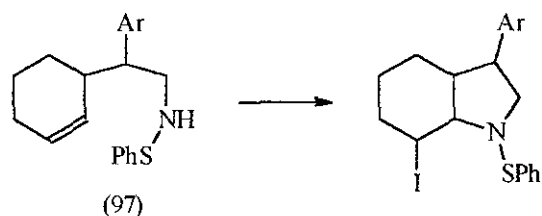


Ar = 4-*t*-butylphenyl

2-(4-*t*-Butylphenyl)-2-(cyclohex-2-en-1-yl)ethan-1-amine (100 mg, 0.38 mmol) was reacted with iodine (3 equiv) using the same procedure as experiment 61. Reaction and work up in the usual manner yielded 3-(4-*t*-butylphenyl)-3a,4,5,6,7,7a-hexahydro-7-iodoindoline as a brown oil, (110 mg, 74%) after purification on a dry alumina column using hexane and diethyl ether as eluent; δ_{H} (300 MHz) 1.21 (9 H, s, *t*-Bu), 1.48 (6 H, m, 4-H, 5-H and 6-H), 2.40 (1 H, m, NH), 2.73 (1 H, ddd, 3a-H), 3.60 (1 H, dt, $J = 6.5$ Hz, 3-H), 3.82 (1 H, m, 7a-H), 4.15 (2 H, m, 2-H), 4.87 (1 H, m, 7-H), and 7.19 (4 H, dd, Ar-H); δ_{C} (75 MHz) 14.14 (5-C), 17.18 (6-C), 25.06 (4-C), 31.33 (*t*-Bu), 34.45 ($\text{C}(\text{CH}_3)_3$), 41.87 (3a-C),

50.13 (2-C), 49.78 (3-C), 59.92 (7a-C), 72.86 (7-C), and 124.28-130.52 (Ar-C); m/z 383 (69%), 299 (100), 231 (85), and 145 (81).

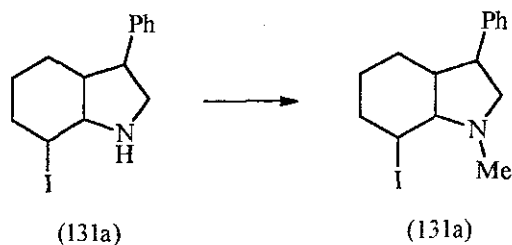
63. Attempted Synthesis of *N*-(Benzenesulfonyl)-3-(4-*t*-butylphenyl)-3a,4,5,6,7,7a-hexahydro-7-iodoindoline



Ar = 4-*t*-butylphenyl

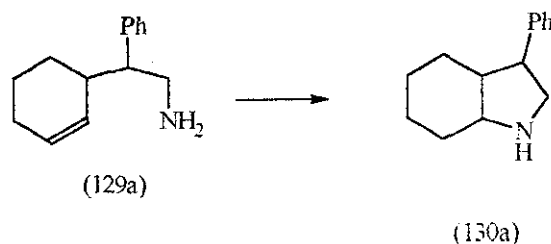
N-(Benzenesulfonyl)-2-(4-*t*-butylphenyl)-2-(cyclohex-2-en-1-yl)ethanamine (100 mg, 0.27 mmol) was reacted with iodine (3 equiv) using the same procedure as experiment 61. Unfortunately, upon standard work-up of the reaction mixture, no expected product was retrieved. This experiment was discontinued.

64. Attempted Synthesis of 3a,4,5,6,7,7a-Hexahydro-7-iodo-*N*-methyl-3-phenylindoline



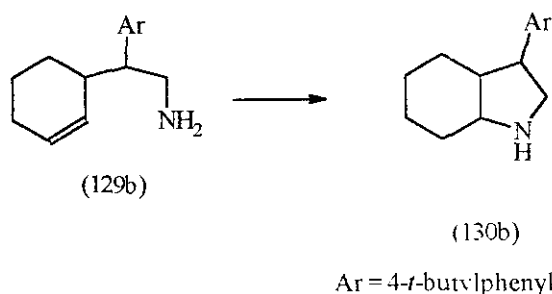
Trifluoroacetic acid (5 ml) was slowly added dropwise to a stirred solution of 3a,4,5,6,7,7a-hexahydro-7-iodo-3-phenylindoline (120 mg, 0.37 mmol), paraformaldehyde (110 mg, 3.66 mmol) and sodium borohydride (69 mg, 1.83 mmol) in dry tetrahydrofuran at room temperature. The solution was then stirred at room temperature for 24 h, after which time a solution of 25% sodium hydroxide (50 ml) was added. The reaction was diluted with saturated brine (50 ml) and extracted with ethyl acetate (3 x 50 ml). The ethyl acetate extracts were combined, dried over magnesium sulfate and evaporated to dryness. Unfortunately, no expected product was obtained from the crude material.

65. 3a,4,5,6,7,7a-Hexahydro-3-phenylindoline through reaction with Mercuric (II) Chloride (130a)



A solution of 2-(cyclohex-2-en-1-yl)-2-phenylethylamine (100 mg, 0.49 mmol) in dried tetrahydrofuran (10 ml) was added to a stirred solution of mercuric (II) chloride (203 mg, 0.75 mmol) in dried tetrahydrofuran (15 ml). The reaction was then stirred at room temperature under an atmosphere of nitrogen for 2 h. The white precipitate which formed, m.p. 224-227°C (dec.) was filtered off and suspended in tetrahydrofuran (4 ml). To this suspension was then added a solution of sodium borohydride (19 mg, 0.5 M solution) in 3 M sodium hydroxide (1 ml) and the resulting suspension stirred for 2 h. After this time, a drop of mercury could be observed in the bottom of the reaction flask. The organic solution was therefore decanted off, dried with magnesium sulfate and evaporated to dryness to yield 3a,4,5,6,7,7a-hexahydro-3-phenylindoline as a clear oil, (30 mg, 50%). No further purification was necessary on this molecule; δ_{H} (300 MHz) 1.35 (9 H, m, 4-H, 5-H, 6-H, 7-H, and NH), 3.17 (1 H, ddd, 3a-H), 3.34 (1 H, m, 3-H), 3.71 (2 H, m, 2-H), 4.13 (1 H, m, 7a-H), and 7.18 (5 H, m, Ar-H).

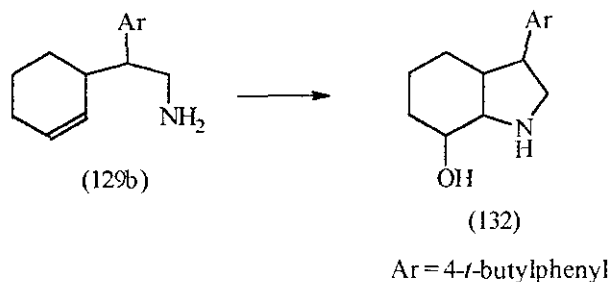
66. 3-(4-*t*-Butylphenyl)-3a,4,5,6,7,7a-hexahydroindoline through reaction with Mercuric (II) chloride (130b)



2-(4-*t*-butylphenyl)-2-(cyclohex-2-en-1-yl)ethylamine (200 mg, 0.78 mmol) was reacted with mercuric (II) chloride (1.5 equiv) using the same procedure as experiment 65. The white precipitate was duly formed, mp 243-250°C (dec.), and reduced to generate 3-(4-*t*-butylphenyl)-3a,4,5,6,7,7a-hexahydroindoline as a brown oil (120 mg, 96%); δ_{H} (300 MHz) 1.25 (9 H, s, *t*-Bu), 1.38 (9 H, m, 4-H, 5-H, 6-H, 7-H, and NH), 3.08 (2 H, m, 3a-H, and 3-H), 3.42 (2 H, dd, $J = 7.7$ Hz, 2-H), 3.71 (1 H, m, 7a-H), and 7.34 (4 H, dd, Ar-H); δ_{C}

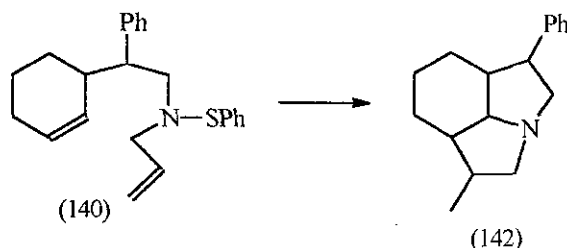
(75 MHz) 20.88 (5-C), 23.19 (6-C), 25.12 (4-C), 27.03 (7-C), 31.32 (*t*-Bu), 34.36 (C(CH₃)₃), 46.46 (3a-C), 60.06 (3-C), 65.35 (7a-C), 66.81 (2-C), and 124.78-130.63 (Ar-C).

67. Attempted Synthesis of 3-(4-*t*-Butylphenyl)-3a,4,5,6,7,7a-hexahydro-7-hydroxyindoline (132)



A solution of 2-(4-*t*-butylphenyl)-2-(cyclohex-2-en-1-yl)ethan-1-amine (200 mg, 0.78 mmol) in dry dichloromethane (2 ml) was added to a solution of *m*-chloroperbenzoic acid (370 mg, 2.14 mmol) in dry dichloromethane (10 ml) at 3°C. The mixture was stirred at this temperature for 30 min, after which time it was allowed to warm up to room temperature. 1.2 N hydrochloric acid was added (3 ml) and the reaction was stirred at room temperature for a further 2 h before dichloromethane (50 ml) was added. The organic layer was decanted off, washed with saturated sodium bicarbonate solution (2 x 50 ml), dried over magnesium sulfate and evaporated to dryness. Unfortunately, none of the expected product could be observed in the crude material.

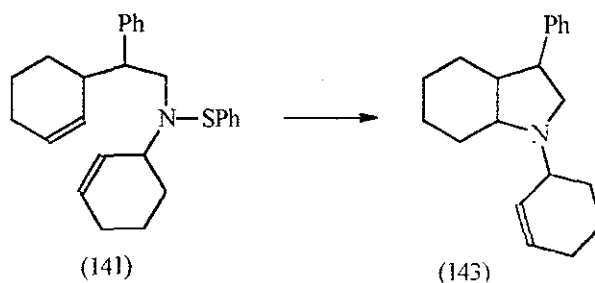
68. Reaction between *N*-(Benzenesulfonyl)-2-(cyclohex-2-en-1-yl)-2-phenyl-*N*-(prop-2-enyl)ethan-1-amine and Tri-*n*-butyltin hydride



N-(Benzenesulfonyl)-2-(cyclohex-2-en-1-yl)-2-phenyl-*N*-(prop-2-enyl)ethan-1-amine (300 mg, 0.9 mmol) was reacted with tri-*n*-butyltin hydride (0.5 ml, 1.7 equiv) using the same procedure as experiment 59 except that benzene was used for the solvent in this case. Work-up of the reaction mixture after refluxing for 6 h yielded (78 mg, 38%) of an approximate 5:1 mixture of bicyclic material (142) to *N*-(prop-2-enyl)-2-(cyclohex-2-en-1-yl)-2-phenylethan-1-amine. Purification on a dry alumina column using diethyl ether/light petroleum as eluent yielded the bicyclic material as a clear oil (60 mg, 30%); δ_{H} (400 MHz) 0.91-

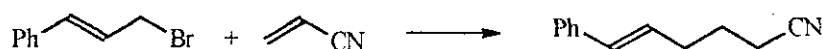
1.16 (3xd, $J = 5.0$ Hz, methyl), 1.44-1.76 (6 H, m, 4-H, 5-H, 6-H), 2.29 (3H, m, 3a-H, 7-H, 9-H), 2.73-3.06 (4H, m, 2-H, 8-H), 3.19 (1H, m, 3-H), 3.87 (1H, m, 7a-H), and 7.10-7.38 (aromatic); δ_C (100 MHz) 12.03, 16.12, 19.49 (methyl), 21.87, 23.69, 24.46, 24.55, 25.10, 25.23, 25.54 and 30.18 (4-C, 5-C, 6-C), 37.73, 40.18, 41.13, 42.81, 43.99, and 44.98 (3a-C, 7-C, 9-C), 49.49, 51.08, and 51.24 (3-C), 54.71, 55.16, 65.59, and, 66.12 (2-C and 8-C), 64.53, 65.98 and 66.84 (7a-C), and 125.85-128.84 (aromatic); m/z 242.1909 [MH^+ (89%), $C_{17}H_{23}N$ requires 242.1909], 162 (100), and 70 (22).

69. Reaction between *N*-(Benzenesulfonyl)-*N*-2-di(cyclohex-2-en-1-yl)-2-phenylethylamine and Tri-*n*-butyltin hydride



N-(Benzenesulfonyl)-*N*-2-di(cyclohex-2-en-1-yl)-2-phenylethylamine (300 mg, 0.8 mmol) and tri-*n*-butyltin hydride (0.3 ml, 1.5 equiv) were reacted by the same procedure as experiment 59 except that benzene was used for the solvent in this case. Work-up of the reaction mixture after refluxing for 6 h yielded the monocyclised material (143) as a clear oil (16%). Some uncyclised material was discovered (11%), though there was no evidence of bicyclised material. A 1,7-H abstraction has possibly occurred to yield a stable allylic radical; δ_H (400 MHz) 0.95 (2 H, dt, $J = 9.2$ Hz, 5-H), 1.19 (2 H, m, 6-H), 1.36 (2 H, m, 10-H), 1.43 (2 H, m, 4-H), 1.51 (2 H, m, 7-H), 1.78 (2 H, m, 9-H), 1.93 (1 H, dt, $J = 5.1$ Hz, 3-H), 1.95 (2 H, m, 11-H), 2.41 (1 H, m, 3a-H), 2.70-2.92 (2 H, m, 2-H), 3.04 (1 H, m, 7a-H), 3.42 (1 H, m, 8-H), 5.60-5.76 (2 H, m, olefin), and 7.05-7.26 (5 H, m, aromatic); δ_C (100 MHz) 22.00 (5-C), 25.52 (6-C), 28.00 (4-C), 28.61 (10-C), 37.83 (9-C), 38.01 (3a-C), 48.40 (11-C), 49.00 (2-C), 55.43 (3-C), 57.09 (7a-C), 69.49 (8-C), and 125.61-132.49 (aromatic and olefin); m/z 282.2222 [MH^+ (100%), $C_{20}H_{27}N$ requires 282.2222], 202 (18), 190 (19), and 110 (32).

70. Attempted Synthesis of 5-Cyano-1-phenylpent-1-ene



A solution of tributyltin hydride (1.7 g, 7.61 mmol) in dried diethyl ether (20 ml) was added to a stirred solution of cinnamyl bromide (1.0 g, 5.07 mmol) and acrylonitrile (2.7 g,

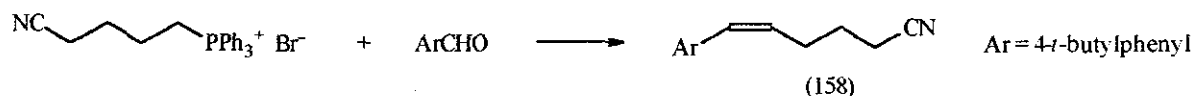
5 mmol) in diethyl ether (80 ml) at room temperature under an atmosphere of nitrogen. The solution was then heated to reflux using a Tungsten filament lamp and maintained at this temperature for 6.5 h, when it was shown that no starting material remained. The solution was allowed to cool to room temperature and the solvent evaporated to dryness. Unfortunately, no expected product was obtained from the crude material.

71. 4-Cyanobutylphosphonium Bromide



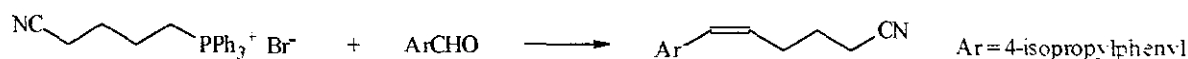
5-Bromovaleronitrile (25.0 g, 0.154 mol) and triphenylphosphine (37.0 g, 0.140 mol) in toluene (500 ml) were placed in a flask and refluxed for 72 h. At the end of this time, the colourless crystals of the product were filtered off and dried to yield 4-cyanobutylphosphonium bromide (46.3 g, 78%) m.p. 231-233°C; δ_{H} 1.68 (2 H, m, NCCH_2CH_2), 2.05 (2 H, dt, $J = 8.3$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), 2.57 (2 H, t, $J = 9.5$ Hz, NCCH_2), 3.91 (2 H, m, CH_2PPh_3), and 7.75 (15 H, m, Ar-H).

72. *cis*-1-(4-*t*-Butylphenyl)-5-cyanopent-1-ene (158) through Sodium Hydride in Tetrahydrofuran



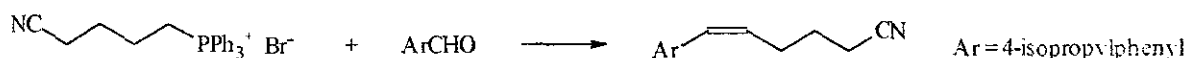
4-Cyanobutylphosphonium bromide (45.0 g, 16 mmol) was added over a period of 20 min to a stirred solution of sodium hydride (4.24 g, 0.106 mol) in dry tetrahydrofuran (200 ml) at room temperature under an atmosphere of nitrogen. The solution was stirred at this temperature for 1 h when a solution of 4-*t*-butylbenzaldehyde (6.88 g, 0.042 mol) in tetrahydrofuran (10 ml) was added dropwise. The resulting solution was stirred at room temperature for 20 h under an atmosphere of nitrogen. After this time, the solution was poured onto ice/water (200 ml) and acidified to pH 2 using 2M hydrochloric acid. The product was extracted using diethyl ether (3 x 50 ml); the ether extracts were combined, dried over magnesium sulfate and evaporated to dryness to yield the crude product. Purification on a dry silica column using hexane and diethyl ether as eluent yielded the *cis*-1-(4-*t*-butylphenyl)-5-cyanopent-1-ene as a clear oil, (8.0 g, 84%); δ_{H} (300 MHz) 1.31 (9 H, s, *t*-Bu), 1.83 (2 H, q, $J = 7.7$ Hz, 4-H), 2.35 (2 H, t, $J = 7.7$ Hz, 5-H), 2.49 (2 H, dq, $J = 6.9$ Hz, 3-H), 5.58 (1 H, m, 2-H), 6.51 (1 H, d, $J = 10.3$ Hz, 1-H), and 7.31 (4 H, ABq, Ar-H); δ_{C} (75 Mhz) 16.68 (4-C), 25.79 (5-C), 27.62 (3-C), 31.24 (*t*-Bu), 34.76 (CMe_3), 119.64 (Ar-C), 124.01-133.82 (Ar-C and 1-C and 2-C), and 150.42 (Ar-C); m/z 227 (24%), 212 (100), 131 (45), and 115 (23).

73. *cis*- and *trans*-6-(4-Isopropylphenyl)-5-cyanopent-1-ene through Sodium Hydride in Diethyl Ether



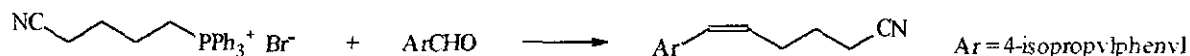
4-Cyanobutylphosphonium bromide (1.0 g, 2.35 mmol) and 4-isopropylbenzaldehyde (873 mg, 5.89 mmol) were reacted together using the same procedure as experiment 72, except that dry diethyl ether was used as solvent in this case. Work up in the usual manner yielded *cis*- and *trans*-6-(4-isopropylphenyl)-5-cyanopent-1-ene as a clear oil (72%) with an approximate *cis:trans* ratio of 1:3.

74. *cis*- and *trans*-1-(4-Isopropylphenyl)-5-cyanopent-1-ene through Sodium Hydride in Dichloromethane

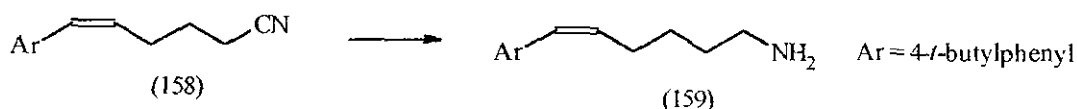


4-Cyanobutylphosphonium bromide (1.0 g, 2.35 mmol) and 4-isopropylbenzaldehyde (873 mg, 5.89 mmol) were reacted together using the same procedure as experiment 72, except that dry dichloromethane was used as solvent in this case. Work up in the usual manner yielded *cis*- and *trans*-1-(4-isopropylphenyl)-5-cyanopent-1-ene as a clear oil (56%) with an approximate *cis:trans* ratio of 3:1.

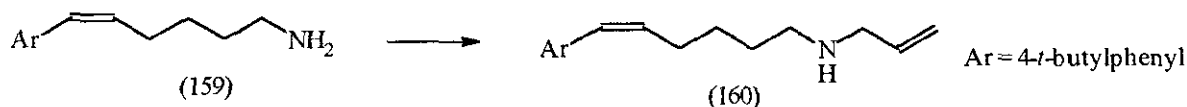
75. *cis*- and *trans*-1(4-*t*-Butylphenyl)-5-cyanopent-1-ene through Crown Ether Catalysis



A solution of *t*-butylbenzaldehyde (1.0 g, 6.16 mmol) and 18-crown-6 (30 mg) in dry dichloromethane (50 ml) was added to a stirred solution of 4-cyanobutylphosphonium bromide (5.2 g, 12 mmol) and potassium carbonate (1.7 g, 12 mmol) in dry dichloromethane (50 ml) at room temperature. The reaction was refluxed for 17 h when TLC indicated that all of the starting material had been converted. The solution was evaporated to dryness to yield a solid residue which was taken up in light petroleum (50 ml). The insoluble 18-crown-6 was removed by filtration and the petroleum evaporated to dryness to yield *cis*- and *trans*-1(4-*t*-butylphenyl)-5-cyanopent-1-ene as a clear oil (53%) in an approximate *cis:trans* ratio of 1:4.

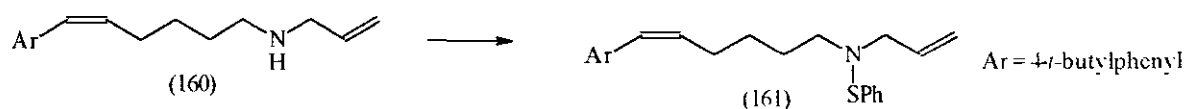
76. *cis*-6-(4-*t*-Butylphenyl)hex-5-enylamine (159)

cis-1-(4-*t*-butylphenyl)-5-cyanopent-1-ene (8.4 g, 0.037 mol) and lithium aluminium hydride (2 equiv) were reacted together by the same procedure as experiment 50. Work up in the usual manner yielded *cis*-6-(4-*t*-butylphenyl)hex-5-enylamine as a clear oil, (8.5 g, 99%). No further purification was necessary; δ_{H} (300 MHz) 1.36 (9 H, s, *t*-Bu), 1.35 (4 H, m, 2-H and 3-H), 1.49 (2 H, s, NH₂), 2.41 (2 H, t, *J* = 6.9 Hz, 4-H), 2.73 (2 H, m, 1-H), 5.64 (1 H, m, 5-H), 6.40 (1 H, d, *J* = 9.5 Hz, 6-H), and 7.30 (4 H, ABq, Ar-H); δ_{C} (75 MHz) 27.34 (3-C), 28.56 (2-C), 31.59 (*t*-Bu), 33.51 (4-C), 34.49 (CMe₃), 42.10 (1-C), 125.05-132.17 (Ar-C and 5-C and 6-C), and 135.06 and 149.72 (Ar-C); *m/z* 231 (90%), 214 (31), 199 (85), 188 (100), 129 (95), and 115 (84).

77. *cis*-6-(4-*t*-Butylphenyl)-*N*-(prop-2-enyl)hex-5-enylamine (160)

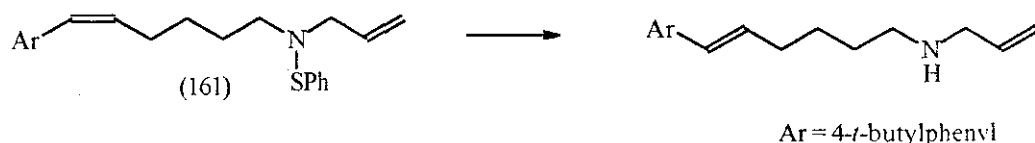
A solution of allyl bromide (3.7 g, 0.031 mol) in dried ethyl acetate (10 ml) was added dropwise to a stirred solution of *cis*-6-(4-*t*-butylphenyl)hex-5-enylamine (8.5 g, 37 mmol) and triethylamine (40 ml) in dry ethyl acetate (90 ml) at room temperature under an atmosphere of nitrogen. The resulting solution was refluxed for 4 h, when TLC indicated that all of the starting material had been converted. The precipitate (triethylamine hydrobromide, m.p. 206-214°C (dec.)) was filtered off and the solution evaporated to dryness to yield the *cis*-6-(4-*t*-butylphenyl)-*N*-(prop-2-enyl)hex-5-enylamine as a clear oil (9.8 g, 98%); δ_{H} (300 MHz) 1.19 (9 H, s, *t*-Bu), 1.36 (4 H, m, 2-H and 3-H), 2.27 (2 H, m, 4-H), 2.36 (1 H, m, NH), 2.45 (2 H, t, *J* = 7.7 Hz, 1-H), 3.09 (2 H, dd, *J* = 7.7 Hz, 7-H), 5.05 (2 H, m, 9-H), 5.48 (1 H, m, 5-H), 5.78 (1 H, m, 8-H), 6.27 (1 H, d, *J* = 10.3 Hz, 6-H), and 7.28 (4 H, ABq, Ar-H); δ_{C} (75 MHz) 28.59 (3-C), 29.29 (2-C), 31.37 (*t*-Bu), 34.51 (CMe₃), 49.08 (4-C), 52.36 (1-C), 56.84 (7-C), 116.17 (9-C), 136.52 (8-C), 124.94-133.28 (Ar-C and 5-C and 6-C), and 134.86 and 149.34 (Ar-C); *m/z* 272 (88%), 232 (71), 126 (17), and 112 (16).

78. *cis*-*N*-(Benzenesulfenyl)-6-(4-*t*-butylphenyl)-1-*N*-(prop-2-enyl)hex-5-enylamine (161)



A solution of *cis*-6-(4-*t*-butylphenyl)-*N*-(prop-2-enyl)-hex-5-enylamine (1.9 g, 6.99 mmol) in dry dichloromethane (10 ml) was added to a stirred solution of *N*-(benzenesulfenyl)phthalimide (1.8 g, 6.99 mmol) in dry dichloromethane (90 ml) at room temperature under an atmosphere of nitrogen. The solution was refluxed for 4 h when TLC indicated that all of the starting material had been converted. The colourless precipitate (phthalimide, m.p. 234-238°C; lit 232-234°C) was filtered off and washed with dichloromethane (2 x 20 ml). The dichloromethane washings were combined and evaporated to dryness to yield the crude product. Purification on a dry alumina column using hexane and diethyl ether as eluent yielded *cis*-*N*-(benzenesulfenyl)-6-(4-*t*-butylphenyl)-1-*N*-(prop-2-enyl)hex-5-enylamine as a clear oil (1.3 g, 49%); (Found C: 79.00, H: 8.75, N: 3.76. $C_{25}H_{31}NS$ requires C: 79.10, H: 8.76, N: 3.69); δ_H (300 MHz) 1.19 (9 H, s, *t*-Bu), 1.35 (2 H, m, 3-H), 1.58 (2 H, m, 2-H), 2.15 (2 H, m, 4-H), 3.81 (2 H, t, $J = 6.9$ Hz, 1-H), 3.35 (2 H, dd, $J = 7.1$ Hz, NCH_2CHCH_2), 5.02 (2 H, m, $CHCH_2$), 5.49 (1 H, m, 5-H), 5.78 (1 H, m, $CHCH_2$), 6.28 (1 H, d, $J = 10.3$ Hz, 6-H), and 7.21 (9 H, m, Ar-H); δ_C (75 MHz) 27.38 (3-C), 28.54 (2-C), 31.39 (*t*-Bu), 34.54 (CMe_3), 53.14 (4-C), 56.87 (1-C), 62.06 (NCH_2CHCH_2), 117.31 ($CHCH_2$), 135.89 ($CHCH_2$), 141.84 (Ar-C), and 123.91-135.88 (Ar-C and 5-C and 6-C); m/z 380.2412 [MH^+ (45%). $C_{26}H_{33}NS$ requires 380.2412], 312 (100), 270 (27), 123 (21), and 110 (39).

79. Reaction between *cis*-*N*-(Benzenesulfenyl)-6-(4-*t*-butylphenyl)-*N*-(prop-2-enyl)-hex-5-enylamine and Tri-*n*-butyltin Hydride



cis-*N*-(Benzenesulfenyl)-6-(4-*t*-butylphenyl)-*N*-(prop-2-enyl)-hex-5-enylamine (300 mg, 0.78 mmol) and tri-*n*-butyltin hydride (1.5 equiv) were reacted together using the same procedure as experiment 59. Reaction (THF, syringe pump, 5 h reflux) and work up in the usual manner yielded *trans*-6-(4-*t*-butylphenyl)-*N*-(prop-2-enyl)hex-5-enylamine (120 mg, 56%). This can be explained by noting that a 1,5-hydrogen abstraction can occur once the aminyl radical has been generated, and this would very rapidly lead to isomerisation. The 1H

NMR spectrum was identical to that of *cis*-6-(4-*t*-butylphenyl)-*N*-(prop-2-enyl)hex-5-enylamine except for δ_{H} 6.18 (1H, m, 6-H).

80. Reaction between *cis*-*N*-(Benzenesulfonyl)-6-(4-*t*-butylphenyl)-*N*-(prop-2-enyl)hex-5-enylamine and Tri-*n*-butyltin Deuteride



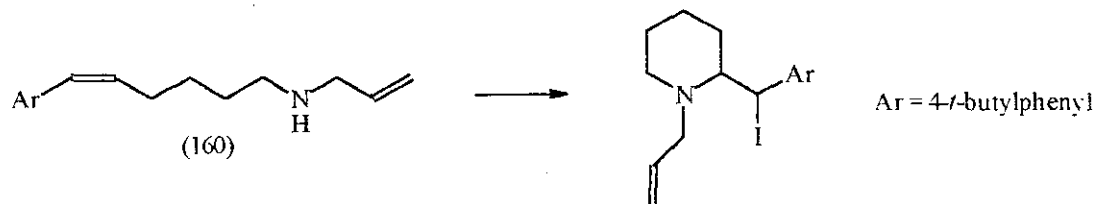
cis-*N*-(Benzenesulfonyl)-6-(4-*t*-butylphenyl)-*N*-(prop-2-enyl)-hex-5-enylamine (300 mg, 0.78 mmol) and tri-*n*-butyltin deuteride (1.5 equiv) were reacted together using the same procedure as experiment 59, except that benzene was used for the solvent in this case. Work-up of the reaction mixture after refluxing for 5 h yielded the expected *cis*-6-(4-*t*-butylphenyl)-*N*-(prop-2-enyl)hex-4-deutero-5-enylamine as a clear oil (138 mg, 38%). The ^1H NMR spectrum indicated a deuterium at 4-H; m/z 272.2392 [MH^+ (98%)]. $\text{C}_{19}\text{H}_{28}\text{DN}$ requires 272.2392], 258 (63), 172 (61), and 155 (100).

81. Reaction between *cis*-*N*-(Benzenesulfonyl)-6-(4-*t*-butylphenyl)-*N*-(prop-2-enyl)hex-6-enylamine and Tris(trimethylsilyl)silane



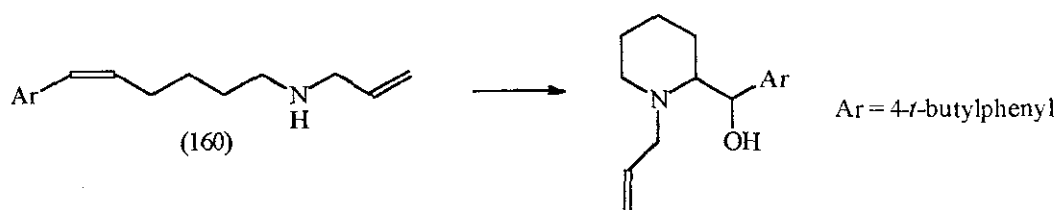
cis-*N*-(Benzenesulfonyl)-6-(4-*t*-butylphenyl)-*N*-(prop-2-enyl)hex-5-enylamine (200 mg, 0.53 mmol) and tris(trimethylsilyl)silane (equimolar) were reacted together using the same procedure as experiment 60. Reaction and work up yielded *trans*-6-(4-*t*-butylphenyl)-*N*-(prop-2-enyl)hex-5-enylamine (120 mg, 84%), with no evidence of any expected cyclised product.

82. Attempted Cyclisation of 2-[(4-*t*-Butylphenyl)iodomethyl]-*N*-(prop-2-enyl)piperidine



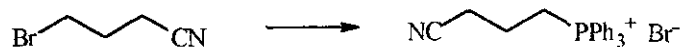
6(4-*t*-Butylphenyl)-*N*-(prop-2-enyl)hex-5-enylamine (1.0 g, 3.68 mmol) and iodine (3 equiv) were reacted together using the same procedure as experiment 61. Unfortunately, upon work-up, no expected product was retrieved. This experiment was discontinued.

83. Attempted Synthesis of 2-[(4-*t*-Butylphenyl)hydroxymethyl]-*N*-(prop-2-enyl)piperidine



6(4-*t*-Butylphenyl)-*N*-(prop-2-enyl)hex-5-enylamine (500 mg, 1.84 mmol) and *m*-chloroperbenzoic acid (3 equiv) were reacted together using the same procedure as experiment 67. Unfortunately, upon work-up, no expected product was retrieved. This experiment was discontinued.

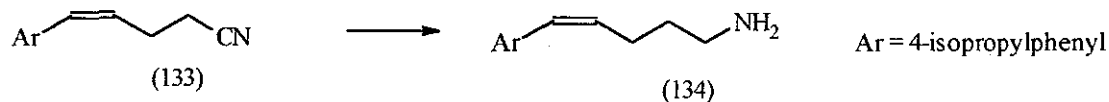
84. 3-Cyanopropylphosphonium Bromide



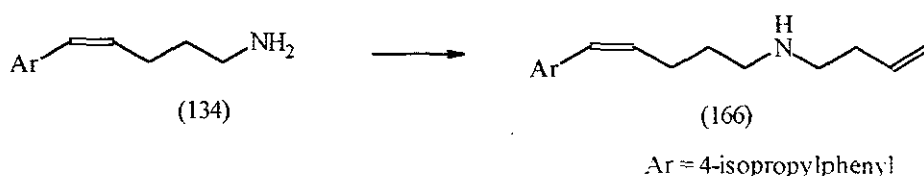
3-Cyanopropyl bromide (25 g, 0.17 mol) was reacted with triphenylphosphine (equimolar) using the same procedure as experiment 71. Work-up of the reaction mixture after 72 h reflux yielded the 3-cyanopropylphosphonium bromide as colourless crystals (55 g, 79%), (m.p. 215-217°C); δ_{H} 1.96 (2 H, dt, $J = 9.2$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_2$), 3.11 (2 H, t, $J = 9.2$ Hz, NCCH_2), 4.14 (2 H, m, CH_2PPh_3), and 7.85 (15 H, m, Ar-H); δ_{C} 17.94 (2-C), 19.79 (1-C), 21.85 (3-C), 119.19 (CN), 117.53 (Ar-C), and 132.86 (Ar-C).

85. *cis*-1-(4-Isopropylphenyl)-4-cyanobut-1-ene (133)

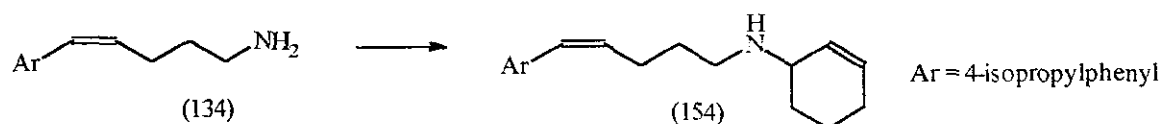
3-Cyanopropylphosphonium bromide (50 g, 0.12 mol) was reacted with 4-isopropylbenzaldehyde (6 g, 0.04 mol) using the same procedure as experiment 72. Work-up of the reaction mixture after stirring at room temperature for 17 h, and subsequent purification on a dry silica column using diethyl ether/light petroleum as eluent yielded the *cis*-1-(4-isopropylphenyl)-4-cyanobut-1-ene as a clear oil (6.4 g, 80%); ν_{max} 3017 (aromatic CH), 2246 (nitrile), 1512 and 1461 (aromatic CC), and 847 cm^{-1} (1,4-disubst. aromatic); δ_{H} 1.25 (6 H, d, $J = 9.2$ Hz, isoprop), 2.41 (2 H, t, $J = 8.2$ Hz, CH_2CN), 2.65 (2 H, dt, $J = 9.2$ Hz, CHCHCH_2), 2.90 (1 H, q, $J = 9.2$ Hz, isoprop), 5.59 (1 H, dt, $J = 10.2$ Hz, CHCHCH_2), 6.56 (1 H, d, $J = 10.2$ Hz, CHCHCH_2), and 7.16 (4 H, ABq, Ar-H); δ_{C} 17.58 (CH_2CN), 23.93 (isopropyl), 24.51 (CHCHCH_2), 33.84 (CHMe_2), 124.93 (CN), 134.04 and 148.00 (Ar-C), 128.39 (Ar-C and 1-C and 2-C); m/z 199.1361 [M^+ (87%)]. $\text{C}_{14}\text{H}_{17}\text{N}$ requires 199.1361], 159 (32), 117 (100), and 91 (12).

86. *cis*-5-(4-Isopropylphenyl)pent-4-enylamine (134)

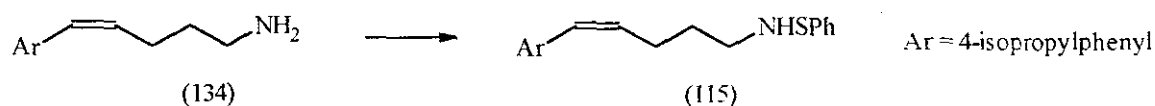
cis-1-(4-Isopropylphenyl)-4-cyanobut-1-ene (6.0 g, 30 mmol) was reacted with lithium aluminium hydride (2 equiv) using the same procedure as experiment 50. Work-up of the reaction mixture after stirring for 2 h at room temperature yielded the *cis*-5-(4-isopropylphenyl)pent-4-enylamine as a clear oil (5.8 g, 95%); ν_{max} 3367 and 3297 (NH_2), 3008 (aromatic CH), 1511 and 1460. (aromatic C=C), and 845 cm^{-1} (1,4-disubst. aromatic); δ_{H} 1.24 (6 H, d, $J = 7.1$ Hz, Me), 1.60 (2 H, q, $J = 9.2$ Hz, 2-H), 2.36 (2 H, t, $J = 9.0$ Hz, 3-H), 2.73 (2 H, t, $J = 8.2$ Hz, 1-H), 2.87 (1 H, m, CHMe_2), 5.59 (1 H, dt, $J = 10.2$ Hz, 4-H), 6.41 (1 H, d, $J = 10.2$ Hz, 5-H), and 7.23 (4 H, s, Ar-H); δ_{C} 23.97 (CH_3), 25.99 (2-C), 33.81 (CHMe_2), 34.04 (3-C), 41.84 (1-C), 141.34 (Ar-C), and 124.59-131.75 (Ar-C and 4-C and 5-C); m/z 204.175 [MH^+ (37%)]. $\text{C}_{14}\text{H}_{21}\text{N}$ requires 204.1752], 186 (34), 143 (100), 128 (26), and 56 (37).

87. *cis*-*N*-(But-3-enyl)-5-(4-isopropylphenyl)pent-4-enylamine (166)

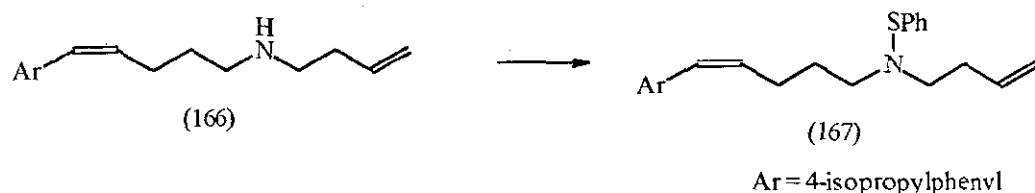
cis-5-(4-Isopropylphenyl)pent-4-enylamine (1.0 g, 4.93 mmol) was reacted with 4-bromobut-1-ene (665 mg, equimolar) using the same procedure as experiment 77. Work-up of the reaction mixture after refluxing for 17 h and subsequent purification on a dry alumina column using chloroform/methanol as eluent yielded the *cis*-*N*-(but-3-enyl)-5-(4-isopropylphenyl)pent-4-enylamine as a clear oil (1.0 g, 79%); ν_{\max} 3282 (NH), 3007 (aromatic CH), 1460 (aromatic C=C), and 845 cm^{-1} (1,4-disubst. aromatic); δ_{H} 1.25 (6 H, d, $J = 8.2$ Hz, Me), 1.62 (2 H, q, $J = 7.1$ Hz, 2-H), 2.19 (2 H, q, $J = 6.1$ Hz, 7-H), 2.33 (2 H, m, 3-H), 2.61 (4 H, m, 1-H and 6-H), 2.85 (1 H, q, $J = 8.2$ Hz, CHMe₂), 5.07 (2 H, t, $J = 10.2$ Hz, 9-H), 5.58 (1 H, dt, $J = 8.2$ Hz, 4-H), 5.77 (1 H, m, 8-H), 6.41 (1 H, d, $J = 11.2$ Hz, 5-H), and 7.17 (4 H, s, Ar-H); δ_{C} 23.97 (CH₃), 29.63 (2-C), 30.84 (7-C), 34.29 (3-C), 48.86 (1-C), 49.32 (6-C), 116.33 (9-C), 136.47 (8-C), 127.06-131.25 (Ar-C and 4-C and 5-C), and 135.37 and 147.65 (Ar-C); m/z 258.2222 [MH^+ (100%). C₁₈H₂₇N requires 258.2222], 246 (42), 102 (20), and 85 (13).

88. *N*-(Cyclohex-2-enyl)-5-(4-isopropylphenyl)pent-4-enylamine (154)

cis-5-(4-Isopropylphenyl)pent-4-enylamine (1.3 g, 6.21 mmol) was reacted with 3-bromocyclohexene (0.7 ml, 6.21 mmol) using the same procedure as experiment 77. Work up of the reaction mixture after refluxing for 18 h yielded the *N*-(cyclohex-2-enyl)-5-(4-isopropylphenyl)pent-4-enylamine as a clear oil (1.2 g, 68%) after purification on a dry alumina column using diethyl ether/ethyl acetate as eluent; ν_{\max} 3402 (NH), 3021 (aromatic CH), 1459 (aromatic CC), and 842 cm^{-1} (1,4-disubst. aromatic); δ_{H} 1.24 (6 H, d, $J = 9.2$ Hz, Me), 1.65 (6 H, m, 4'-H, 5'-H and 6'-H), 1.94 (2 H, m, 2-H), 2.33 (2 H, dt, $J = 8.1$ Hz, 3-H), 2.65 (2 H, t, $J = 8.2$ Hz, 1-H), 2.85 (1 H, q, $J = 9.2$ Hz, CHMe₂), 3.09 (1 H, m, 1'-H), 5.71 (3 H, m, 2'-H, 3'-H and 4-H), 6.40 (1 H, d, $J = 10.5$ Hz, 5-H), and 7.17 (4 H, m, Ar-H); δ_{C} 20.25 (5'-C), 23.96 (CH₃), 25.29 (6'-C), 26.40 (4'-C), 29.46 (2-C), 30.65 (3-C), 33.61 (CHMe₂), 46.37 (1-C), 52.98 (1'-C), 124.72-132.01 (Ar-C and 2'-C, 3'-C, 4-C and 5-C), and 135.12 and 147.13 (Ar-C); m/z 284.2378 [MH^+ (100%). C₂₀H₂₉N requires 284.2378], 284 (100%).

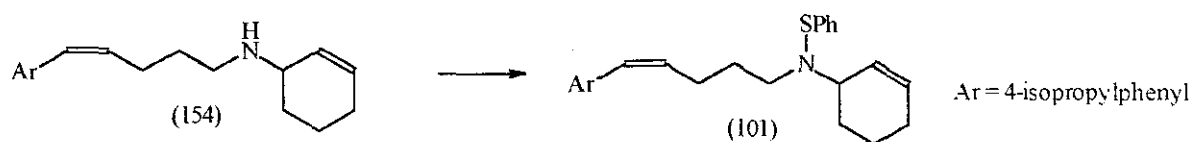
89. *cis*-*N*-(Benzenesulfonyl)-5-(4-isopropylphenyl)pent-4-enylamine (115)

cis-5-(Isopropylphenyl)pent-4-enylamine (2.0 g, 9.85 mmol) was reacted with *N*-(benzenesulfonyl)phthalimide (2.5 g, 9.85 mmol) using the same procedure as experiment 78. Work-up of the reaction mixture after 3 h reflux and subsequent purification on a dry alumina column using diethyl ether / light petroleum as eluent yielded the *cis*-*N*-(benzenesulfonyl)-5-(4-isopropylphenyl)pent-4-enylamine as a clear oil, (2.2 g, 72%); ν_{\max} 3344 (NH), 3007 (aromatic CH), 1583, 1477 and 1460 (aromatic C=C), 845 (1,4-disubst. aromatic), and 692 cm^{-1} (monosubst. aromatic); δ_{H} 1.26 (6 H, d, $J = 9.2$ Hz, Me), 1.72 (2 H, q, $J = 8.1$ Hz, 2-H), 2.37 (2 H, dt, $J = 9.1$ Hz, 3-H), 2.83 (1 H, m, CHMe_2), 2.95 (2 H, m, 1-H), 5.58 (1 H, dt, $J = 10.2$ Hz, 4-H), 6.41 (1 H, d, $J = 10.2$ Hz, 5-H), and 7.15 (9 H, m, Ar-H); δ_{C} 23.86 (CH_3), 25.88 (2-C), 30.38 (3-C), 33.71 (CHMe_2), 51.51 (1-C), and 125.05-130.85 (Ar-C and 4-C and 5-C); m/z 312.179 [MH^+ (36%)]. $\text{C}_{20}\text{H}_{25}\text{NS}$ requires 312.1786, 202 (100), 109 (25), and 70 (94).

90. *N*-(Benzenesulfonyl)-*N*-(but-3-enyl)-5-(4-isopropylphenyl)pent-4-enylamine (167)

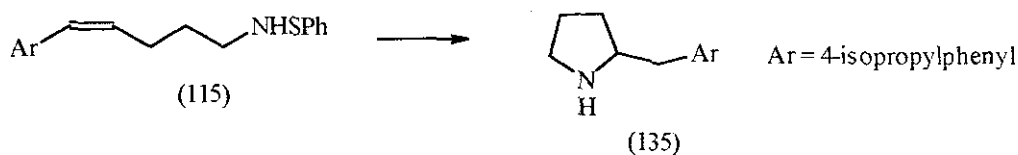
N-(But-3-enyl)-5-(4-isopropylphenyl)pent-4-enylamine (400 mg, 1.56 mmol) was reacted with benzenesulfonyl chloride (225 mg, 1.56 mmol) using the same procedure as experiment 56. Work-up of the reaction mixture after stirring at room temperature for 2 h and subsequent purification on a dry alumina column using diethyl ether / light petroleum as eluent yielded the *N*-(benzenesulfonyl)-*N*-(but-3-enyl)-5-(4-isopropylphenyl)pent-4-enylamine as a clear oil (532 mg, 93%); ν_{\max} 3004 (aromatic CH), 1581, 1477 and 1460 (aromatic C=C), 844 (1,4-disubst. aromatic), and 689 cm^{-1} (monosubst. aromatic); δ_{H} 1.18 (6 H, d, $J = 8.2$ Hz, Me), 1.50 (2 H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.77 (2 H, m, NCH_2CH_2), 2.17 (2 H, m, CH_2CHCH_2), 2.86 (1 H, q, $J = 8.3$ Hz, CHMe_2), 2.98 (4 H, m, NCH_2), 5.00 (2 H, d, $J = 13.2$ Hz, CHCH_2), 5.56 (1 H, m, CHCH), 5.60 (1 H, m, CHCH_2), 6.35 (1 H, d, $J = 11.2$ Hz, CHCH), 7.12-7.29 (4 H, m, Ar-H); δ_{C} 23.91 (CH_3), 26.05 (2-C), 28.72 (7-C), 32.96 (3-C), 33.75 (CHMe_2), 57.90 (1-C and 6-C), 115.96 (9-C), 131.57 (8-C), and 123.88-131.65 (Ar-C and 4-C and 5-C); m/z 366.2255 [MH^+ (32%)]. $\text{C}_{24}\text{H}_{31}\text{NS}$ requires 366.2255, 312 (100), 258 (29), 210 (56), 182 (22), 124 (32), and 109 (8).

91. *N*-(Benzenesulfonyl)-*N*-(cyclohex-2-enyl)-5-(4-isopropylphenyl)pent-4-enylamine (101)



N-(Cyclohex-2-enyl)-5-(4-isopropylphenyl)pent-4-enylamine (206 mg, 0.7 mmol) was reacted with benzenesulfonyl chloride (105 mg, 0.7 mmol) using the same procedure as experiment 56. Work-up of the reaction mixture after stirring at room temperature for 2.5 h and subsequent purification on a dry alumina column using diethyl ether / light petroleum as eluent yielded the *N*-(benzenesulfonyl)-*N*-(cyclohex-2-enyl)-5-(4-isopropylphenyl)pent-4-enylamine as a clear oil (250 mg, 88%); ν_{\max} 3005 (aromatic CH), 1581, 1477 and 1439 (aromatic C=C), 844 (1,4-disubst. aromatic), and 690 cm^{-1} (monosubst. aromatic); δ_{H} 1.26 (6 H, d, $J = 8.2$ Hz, Me), 1.51 (4 H, m, 2-H and 5'-H), 1.72 (2 H, m, 6'-H), 1.95 (2 H, m, 4'-H), 2.33 (2 H, dt, $J = 8.5$ Hz, 3-H), 2.89 (1 H, q, $J = 8.2$ Hz, CHMe_2), 3.00 (2 H, t, $J = 9.3$ Hz, 1-H), 3.69 (1 H, m, 1'-H), 5.54 (3 H, m, 2'-H, 3'-H and 4-H), 6.35 (1 H, d, $J = 10.2$ Hz, 5-H), and 7.27 (9 H, m, Ar-H); δ_{C} 18.64 (5'-C), 21.29 (CH_3), 23.97 (2-C), 24.96 (6'-C), 26.20 (4'-C), 28.89 (3-C), 33.81 (CHMe_2), 55.19 (1-C), 63.75 (1'-C), 122.47-132.01 (Ar-C and 2'-C, 3'-C, 4-C and 5-C), and 135.17 and 147.17 (Ar-C); m/z 392.2412 [MH^+ (100%)]. $\text{C}_{26}\text{H}_{33}\text{NS}$ requires 392.2412], 316 (26), 284 (97), 150 (15), and 110 (22).

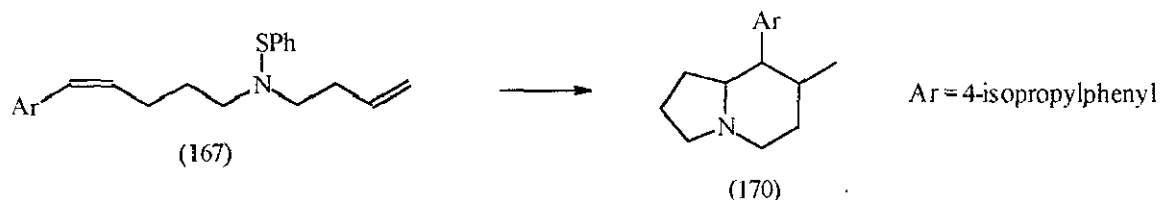
92. Reaction between *cis*-*N*-(Benzenesulfonyl)-5-(4-isopropylphenyl)pent-4-enylamine and Tri-*n*-butyltin Hydride



cis-*N*-(Benzenesulfonyl)-5-(4-isopropylphenyl)pent-4-enylamine (700 mg, 2.25 mmol) was reacted with tri-*n*-butyltin hydride (982 mg, 3.38 mmol) using the same procedure as experiment 59 except that benzene was used for the solvent in this case. Work-up of the reaction mixture after refluxing for 5 h yielded the crude product. Purification on an alumina column using chloroform/methanol as eluent yielded the pure 2-(4-isopropylbenzyl)pyrrolidine (135) as a clear oil (295 mg, 65%); ν_{\max} 3308 (NH), and 1514 and 1463 cm^{-1} (aromatic C=C); δ_{H} 1.27 (6 H, d, $J = 8.3$ Hz, Me), 1.76 (5 H, m, 3-H, 4-H and NH), 2.70 (2 H, d, $J = 9.2$ Hz, 5-H), 2.82 (2 H, m, CH_2Ar), 3.01 (1 H, m, CHMe_2), 3.20 (1 H, dt, $J = 8.7$ Hz, 2-H), 7.17 (4 H, s, Ar-H); δ_{C} 24.06 (CH_3), 24.86 (4-C), 31.29 (3-C), 33.69

(CHMe₂), 41.99 (CH₂Ar), 46.20 (5-C), 60.56 (2-C), 126.14 and 128.89 (Ar-C), and 137.53 and 146.52 (Ar-C); *m/z* 204.211 [MH⁺ (100%)]. C₁₄H₂₁N requires 204.1752], 70 (32).

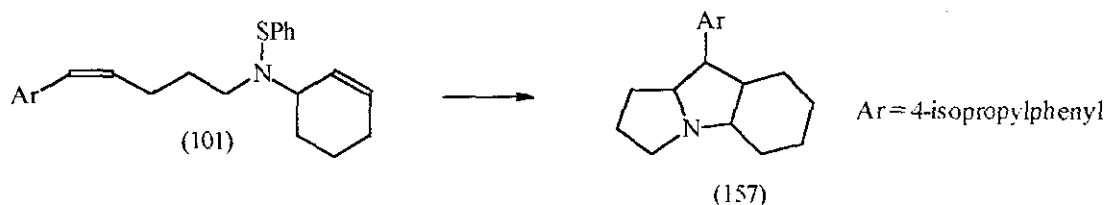
93. Reaction between *cis*-*N*-(Benzenesulfonyl)-*N*-(but-4-enyl)-5-(4-isopropylphenyl)pent-4-enylamine and Tri-*n*-butyltin Hydride



cis-*N*-(Benzenesulfonyl)-*N*-(but-4-enyl)-5-(4-isopropylphenyl)pent-4-enylamine (400 mg, 1.09 mmol) was reacted with tri-*n*-butyltin hydride (500 mg, 1.7 equiv) using the same procedure as experiment 59 except that benzene was used for the solvent in this case. Work-up of the reaction mixture after refluxing for 6 h yielded a mixture of *cis*-*N*-(but-4-enyl)-5-(4-isopropylphenyl)pent-4-enylamine and fully cyclised material (180mg, 64%). Purification on a dry alumina column using diethyl ether / light petroleum as eluent yielded fully cyclised material (170) as a clear oil (73 mg, 26%). The indolizidine was essentially one isomer which inverts very slowly, giving the appearance of two isomers being present; δ_{H} (400 MHz) (major 55%) 0.73 (3 H, d, *J* = 6.2 Hz, methyl), 1.20 (6 H, d, *J* = 6.0 Hz, (CH₃)₂), 1.33 (1 H, m, 1-H), 1.61 (1 H, m, 6-H), 1.66 (1 H, m, 2-H), 1.80 (1 H, m, 2-H), 1.86 (1 H, m, 1-H), 2.04 (1 H, m, 7-H), 2.08 (1 H, m, 6-H), 2.31 (1 H, dt, *J* = 8.0 Hz, 3-H), 2.39 (1 H, dt, *J* = 10.4 Hz, 5-H), 2.57 (1 H, m, 8a-H), 2.80 (1 H, dd, *J* = 6.2 Hz, 8-H), 2.87 (1 H, quin, *J* = 6.0 Hz, CH(CH₃)₂), 2.97 (1 H, ddd, 5-H), 3.19 (1 H, m, 3-H), 7.02 (2 H, m, Ar-H), and 7.12 (2 H, m, Ar-H); δ_{H} (minor 45%) 0.69 (3 H, d, *J* = 6.0 Hz, methyl), 1.20 (6 H, d, *J* = 6.0 Hz, (CH₃)₂CH), 1.27 (1 H, m, 8a-H), 1.42 (2 H, m, 1-H), 1.53 (1 H, m, 6-H), 1.57 (1 H, m, 2-H), 1.69 (1 H, m, 7-H), 1.78 (1 H, m, 2-H), 1.82 (1 H, m, 6-H), 2.06 (1 H, m, 8-H), 2.13 (1 H, m, 3-H), 2.17 (1 H, m, 5-H), 2.87 (1 H, quin, *J* = 6.0 Hz, CH(CH₃)₂), 3.14 (1 H, m, 3-H), 3.18 (1 H, m, 5-H), 7.04 (2 H, m, Ar-H), and 7.10 (2 H, m, Ar-H); δ_{C} (100 MHz) 19.39, 20.29, 20.61 (methyl), 23.85 (isoprop), 29.26 (6-C), 33.38 and 33.43 (2-C), 36.45 (1-C), 46.96 (7-C), 52.22 (isoprop), 54.02 and 54.19 (8-C), 55.53 (3-C), 60.26 (5-C), 69.53 (8a-C), and 126.00-128.11 (Ar-C); *m/z* 257.2144 [M⁺ (39%)]. C₁₈H₂₇N requires 257.2144], 218 (32), 97 (100), 84 (82), and 69(40).

An earlier experiment using triphenyltin hydride instead of tributyltin hydride with exactly the same experimental conditions gave upon work-up a 75% yield of the uncyclised amine, with no cyclised material being detected.

94. Reaction between *cis*-*N*-(Benzenesulfonyl)-*N*-(cyclohex-2-enyl)-5-(4-isopropylphenyl)pent-4-enylamine and Tri-*n*-butyltin Hydride



cis-*N*-(Benzenesulfonyl)-*N*-(cyclohex-2-enyl)-5-(4-isopropylphenyl)pent-4-enylamine (260 mg, 0.7 mmol) was reacted with tri-*n*-butyltin hydride (300 mg, 1.5 equiv) using the same procedure as experiment 59 except that benzene was used for the solvent in this case. Work of the reaction mixture after refluxing for 6 h in benzene yielded the fully cyclised material (157) as a clear oil (26 mg, 14%), with a small amount of uncyclised material being detected (2 mg, 1%). No monocyclised material was observed; δ_{H} (400 MHz) 1.20-1.25 (6 H, dt, $J = 6.0$ Hz, isoprop), 1.41 (4 H, m, 9-H, 10-H), 1.61 (4 H, m, 6-H, 8-H), 1.88 (2 H, m, 11-H), 1.95 (2 H, m, 7-H), 2.70 (1 H, m, 2-H), 2.78 (1 H, m, isoprop), 2.88 (2 H, m, 5-H), 3.06 (1 H, m, 1-H), 3.25 (1 H, q, $J = 5.0$ Hz, 3-H), 3.64 (1 H, q, $J = 6.0$ Hz, 7a-H), and 7.12-7.26 (5 H, m, Ar-H); δ_{C} (100 MHz) 21.00 (10-C), 23.79 (isoprop), 24.08 (9-C), 24.26 (8-C), 27.00 (6-C), 28.62 (11-C), 31.99 (7-C), 33.59 (2-C), 45.78 (isoprop), 58.21 (5-C), 50.59 (1-C), 59.98 (3-C), 73.37 (7a-C), and 125.80-129.72 (Ar-C); m/z 283.2303 [M^+ (76%)]. $C_{20}H_{29}N$ requires 283.2300, 240 (100), 84 (63), and 49 (70).

95. *N*-Butyl-3-phenylprop-2-enylamine (121)



Butylamine (20 ml, excess) was added in one portion to a stirred solution of cinnamyl bromide (5.0 g, 25 mmol) in dry diethyl ether (50 ml). The resulting suspension was stirred at room temperature for 90 min, when TLC indicated complete lack of cinnamyl bromide. The precipitate was filtered off (butylamine hydrobromide) and washed with diethyl ether. The ether washings were combined and evaporated to dryness to yield the *N*-butyl-3-phenylprop-2-enylamine as a clear oil, (3.3 g, 69%); ν_{max} 3309 (NH), 3026 (aromatic CH), 1496 (aromatic C=C), and 692 cm^{-1} (monosubst. aromatic); δ_{H} 0.94 (3 H, t, $J = 8.4$ Hz, Me), 1.33 (2 H, m, CH_2CH_3), 1.49 (2 H, tt, $J = 7.4$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_3$), 2.64 (2 H, t, $J = 8.4$ Hz, NCH_2CH_2), 3.41 (2 H, d $J = 8.2$ Hz, 1-H), 6.29 (1 H, dt, $J = 11.3$ Hz, 2-H), 6.41 (1 H, d, $J = 11.3$ Hz, 3-H), and 7.25 (5 H, m, Ar-H); δ_{C} 14.04 (Me), 20.50 (CH_2CH_3), 32.25 ($\text{CH}_2\text{CH}_2\text{CH}_3$), 49.19 (NCH_2CH_2), 51.96 (1-C), 128.19 (Ar-C and 2-C and 3-C), and 137.14 (Ar-C); m/z 190.1596 [MH^+ (49%)]. $C_{13}H_{19}N$ requires 190.1596, 74 (100).

96. *N*-(Benzenesulphenyl)-*N*-butyl-3-phenylprop-2-enylamine (102)



N-Butyl-3-phenylprop-2-enylamine (1.0 g, 5.29 mmol) was reacted with benzenesulphenyl chloride (0.76 ml, 5.29 mmol) using the same procedure as experiment 56. Work-up of the reaction mixture after stirring at room temperature for 2.5 h yielded the *N*-(benzenesulphenyl)-*N*-butyl-3-phenylprop-2-enylamine as a clear oil (1.3 g, 83%) after purification on a dry alumina column using diethyl ether/light petroleum as eluent; ν_{max} 3026 (aromatic CH), 1582 and 1476 (aromatic C=C), and 691 cm^{-1} (monosubst. aromatic); δ_{H} 0.89 (3 H, t, $J = 9.1$ Hz, Me), 1.17 (2 H, m, CH_2CH_3), 1.33 (2 H, tt, $J = 9.1$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_3$), 2.94 (2 H, t, $J = 8.5$ Hz, NCH_2CH_2), 3.76 (2 H, d, $J = 7.1$ Hz, 1-H), 6.29 (1 H, dt, $J = 15.3$ Hz, 2-H), 6.46 (1 H, d, $J = 15.3$ Hz, 3- H_6), and 7.30 (10 H, m, Ar-H); δ_{C} 13.99 (Me), 20.14 (CH_2CH_3), 30.53 ($\text{CH}_2\text{CH}_2\text{CH}_3$), 56.33 (NCH_2CH_2), 61.42 (1-C), and 127.40-133.61 (Ar-C and 2-C and 3-C); m/z 298.1629 [MH^+ (100%)]. $\text{C}_{19}\text{H}_{23}\text{NS}$ requires 298.1629, 190 (98), 117 (42), and 109 (6).

97. Reaction between *N*-(Benzenesulphenyl)-*N*-butyl-3-phenylprop-2-enylamine and Tri-*n*-butyltin Hydride



N-(Benzenesulphenyl)-*N*-butyl-3-phenylprop-2-enylamine (500 mg, 1.68 mmol) was reacted with tri-*n*-butyltin hydride (0.7 ml, 1.5 equiv) using the same procedure as experiment 59, except that benzene was used for the solvent in this case. Work-up of the reaction mixture after refluxing for 6 h yielded pure *N*-butyl-3-phenylprop-2-enylamine as a clear oil (169 mg, 53%), with no expected cyclised material being formed. The IR and NMR spectra for this compound were identical to those of an authentic sample of *N*-butyl-3-phenylprop-2-enylamine.

Disulfenamides

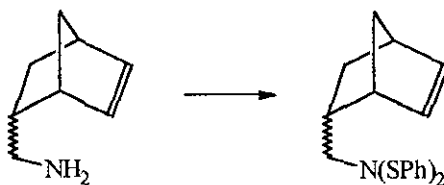
Attempted Synthesis of disulfenamides using *N*-(benzenesulfonyl)phthalimide

98. *exo*-*N,N*-di(Benzenesulfonyl)bicyclo[2.2.1]hept-2-ylamine



exo-Bicyclo[2.2.1]hept-2-ylamine (0.5 g, 45 mmol) in toluene (50 ml), and *N*-(benzenesulfonyl)phthalimide (2.3 g, 90 mmol) were reacted together using the same procedure as experiment 74. Unfortunately, only the monosulfenamide (173) was generated, with no sign of the disulfenamide being present. Therefore, this experiment was discontinued.

99. *N,N*-di(Benzenesulfonyl)-(bicyclo[2.2.1]hept-5-en-2-yl)-methylamine

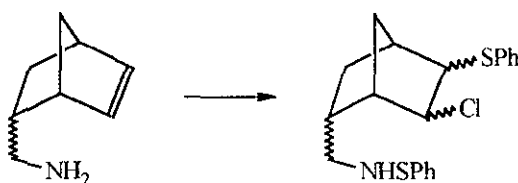


2-Aminobicyclo[2.2.1]hept-5-ene (0.5 g, 41 mmol) in toluene (50 ml), and *N*-(benzenesulfonyl)phthalimide (2.1 g, 81 mmol, 2 equiv.) were reacted by the same procedure as experiment 74. Unfortunately, only the monosulfenamide was generated, with no sign of the disulfenamide being present.

It appears that *N*-(benzenesulfonyl)phthalimide is not active enough to place another -SPh moiety on the monosulfenamide. Therefore, this approach was discontinued.

Synthesis of disulfenamides using benzenesulfonyl chloride

100. *N,N*-di(Benzenesulfonyl)-(bicyclo[2.2.1]hept-5-en-2-yl)-methylamine



exo-2-Aminomethylbicyclo[2.2.1]hept-5-ene (0.5 g, 41 mmol), triethylamine (20 ml) and benzenesulfonyl chloride (1.2 g, 85 mmol, 2.1 equiv.) were reacted together by the same procedure as experiment 56. Unfortunately, it was discovered upon analysis that the

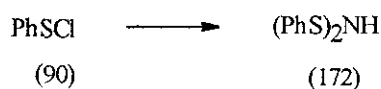
benzenesulfonyl chloride was reacting with the double bond to yield an inseparable mixture of compounds. No disulfenamide product was detected in this mixture, and so this experiment was discontinued.

101. *exo*-*N,N*-di(Benzenesulfonyl)bicyclo[2.2.1]hept-2-ylamine



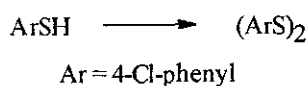
exo-Bicyclo[2.2.1]hept-2-ylamine (0.5 g, 45 mmol), triethylamine (20 ml) and benzenesulfonyl chloride (1.6 g, 110 mmol, 2.5 equiv.) in dry diethyl ether (40 ml) were reacted by the same procedure as experiment 56 to yield the crude disulfenamide after stirring for 14 h. Purification by column chromatography on alumina gave the disulfenamide as a clear oil (500 mg, 34%); ν_{\max} 3056 (aromatic CH), 1580 and 1474 (aromatic C=C), and 738 cm^{-1} (monosubst. aromatic); δ_{H} 1.04 (4 H, m, 5-H & 6-H), 1.41 (3 H, m, 3-H & 7-H), 2.24 (2 H, s, 1-H & 4-H), 2.65 (1 H, s, 7-H), 2.98 (1 H, m, 2-H), and 7.33 (10 H, m, Ar-H); δ_{C} 26.92 (5-C), 28.25 (6-C), 35.34 (7-C), 36.72 (4-C), 39.58 (3-C), 42.15 (1-C), 74.36 (2-C), and 124.45-129.82 (Ar-C); m/z 327.112 [M^+ (5%)]. $\text{C}_{19}\text{H}_{21}\text{NS}_2$ requires 327.1115, 218 (49), and 109 (100). TLC [light petroleum / alumina] showed the disulfenamide as the only product.

102. *N,N*-di(Benzenesulfonyl)amine (172)



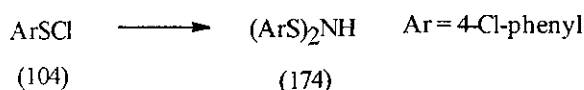
A solution of benzenesulfonyl chloride (5.0 g, 35 mmol) in dry diethyl ether (50 ml) was added dropwise to a stirred solution of diethyl ether (200 ml) saturated with dried ammonia gas at -50°C . An intense violet colour was initially observed, which changed on stirring at room temperature for 60 min to a pale yellow solution. The precipitate (ammonium chloride) was filtered off and the solvent evaporated to dryness to leave crude red crystals. Recrystallisation from diethyl ether gave the *N,N*-di(benzenesulfonyl)amine as colourless crystals (1.5 g, 18%); δ_{H} 4.62 (1 H, s, NH), and 7.21-7.34 (10 H, m, aromatic); δ_{C} 124.47-128.95 (aromatic); m/z 233.0333 [M^+ (100%)]. $\text{C}_{12}\text{H}_{11}\text{NS}_2$ requires 233.0333.

103. *N,N*-di-(*p*-Chlorophenyl)disulfide



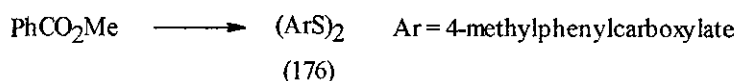
p-Chlorobenzenethiol (50 g, 0.35 mol) was added in one portion to a stirred solution of sodium hydroxide (14.1 g, 0.35 mol) in water (350 ml). A solution of iodine (88 g, 0.213 mol) and potassium iodide (57.7 g, 0.35 mol) in water (200 ml) was added to the first solution until the purple colouring persisted in the reaction mixture. The resulting precipitate was filtered off and recrystallised from ethanol to yield the *N,N*-di-(*p*-chlorophenyl)disulfide as colourless crystals (55 g, 89%); m.p. 71.9-72.3°C; lit¹⁰⁵ 75°C).

104. *N,N*-di(*p*-Chlorobenzenesulfonyl)amine (174)

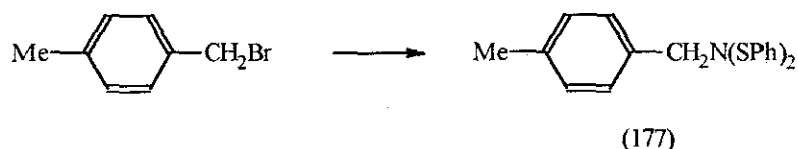


p-Chlorobenzenesulfonyl chloride (20.0 g, 0.14 mol) was reacted with ammonia using the same procedure as experiment 102. Work-up and purification in the usual manner gave the *N,N*-di(*p*-chlorobenzenesulfonyl)amine as colourless crystals (29%); δ_{H} 2.06 (1 H, s, NH), and 7.22-7.35 (8 H, m, Ar-H); δ_{C} 126.12, 129.07, and 132.37 (Ar-C).

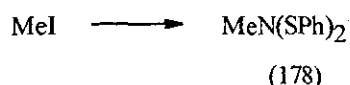
105. Attempted Synthesis of di(4-Methylphenylcarboxylate)disulfide (176)



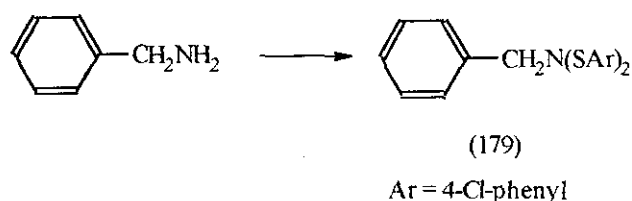
Sodium sulfide (86 g, 1.1 mol equiv) and powdered sulfur (10.3 g, 1.1 mol equiv) were dissolved in boiling water (88 ml). A solution of sodium hydroxide (12.1 g) in water (30 ml) was added to this solution and it was cooled to 0°C using an ice/salt bath. Meanwhile, a solution of 4-methylcarboxyphenyl (50 g, 0.3 mol) and concentrated hydrochloric acid (60.5 ml) in water (151 ml) was made up and cooled to 6°C. The sodium nitrite was slowly added to the acid solution so that the temperature did not rise above 6°C. The subsequent mixture was allowed to warm up to room temperature to aid the evolution of nitrogen gas. Concentrated hydrochloric acid (55 ml) was added and the subsequent precipitate was filtered off and washed with water (3 x 50 ml). Unfortunately, none of the required product was observed and so the experiment was discontinued.

106. *N,N*-di(Benzenesulfonyl)-4-methylbenzylamine (177)

A solution of *N,N*-di(benzenesulfonyl)amine (250 mg, 1.07 mmol) in dry tetrahydrofuran (30 ml) was placed in a flask under nitrogen and cooled to -78°C . To this was added dropwise a solution of *n*-butyllithium (0.7 ml, 1.05 equiv) in hexane. The anion was maintained at -78°C for 10 min when a solution of 4-methylbenzyl bromide (0.198 g, equimolar) in tetrahydrofuran (10 ml) was added dropwise. The reaction was allowed to warm up to 0°C and maintained at this temperature for 20 min. A saturated solution of ammonium chloride (20 ml) was added to quench the reaction and the organic layer separated. The aqueous layer was extracted with diethyl ether (3 x 50 ml). The organic washings were combined, dried (MgSO_4) and evaporated to dryness to yield the *N,N*-di(benzenesulfonyl)-4-methylbenzylamine as a brown crystalline solid (332 mg, 92%); m.p. $117\text{--}119^{\circ}\text{C}$ recrystallised from light petroleum); ν_{max} 1582 and 1440 (aromatic $\text{C}=\text{C}$), and 817cm^{-1} (1,4-disubst. aromatic); δ_{H} 2.34 (3 H, s, Me), 4.62 (2 H, s, CH_2N), and 7.24 (14 H, m, Ar-H); δ_{C} 21.19 (Me), 33.71 (CH_2N), and 124.43–129.47 (Ar-C).

107. *N,N*-di(Benzenesulfonyl)methylamine (178)

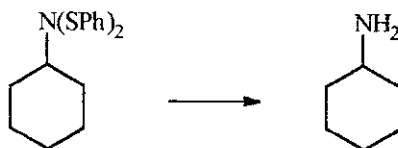
Methyl iodide (30 mg, 0.2 mmol) and *N,N*-di(benzenesulfonyl)amine (50 mg, 0.2 mmol) were reacted together using the same procedure as experiment 106. Reaction and work-up in the usual manner yielded the *N,N*-di(benzenesulfonyl)methylamine as a clear liquid (25 mg, 48%); δ_{H} 3.38 (3 H, s, Me), and 7.20–7.34 (10 H, m, Ar-H); δ_{C} 53.74 (Me), and 124.45–129.09 (Ar-C).

108. *N,N*-di(*p*-Chlorobenzenesulfonyl)benzylamine (179)

Benzyl bromide (70 mg, 0.4 mmol) was reacted with *N,N*-di(*p*-chlorobenzenesulfonyl)-amine (100 mg, 0.4 mmol) using the same procedure as experiment

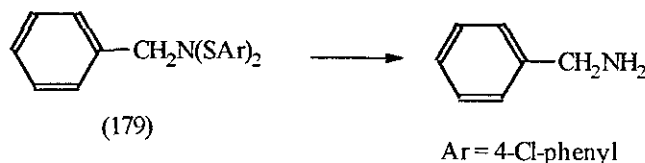
106. Reaction and work-up in the usual manner yielded the *N,N*-di(*p*-chlorobenzenesulfonyl)benzylamine as a clear oil (31 mg, 23%); δ_{H} 4.49 (2 H, s, CH_2N), and 7.21 (13 H, m, Ar-H).

109. Reaction between *N,N*-di(Benzenesulfonyl)cyclohexylamine and Tri-*n*-butyltin Hydride

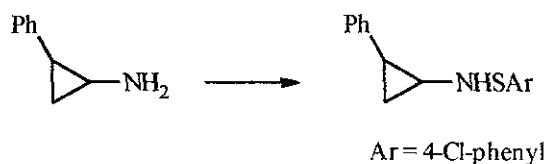


N,N-di(Benzenesulfonyl)cyclohexylamine (300 mg, 10 mmol) and tributyltin hydride (512 mg, 24 mmol, 2.5 equiv.) in cyclohexane (100 ml) were reacted together using the same procedure as experiment 36 to form the fully reduced amine, after refluxing for 2 h. The amine was extracted into DCM (100 ml) and the solvent distilled off to leave the amine as a clear liquid (58 mg, 62%); ν_{max} 3350 (amine NH); δ_{H} 1.53 (m, cyclohexyl CH_2 's and NH_2 and CHN). The IR and NMR spectra and TLC were all identical with authentic cyclohexylamine.

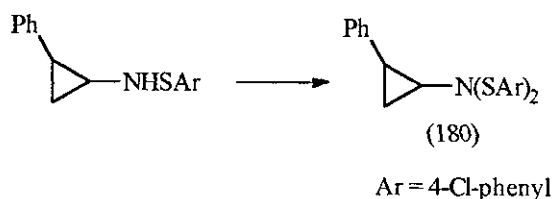
110. Reaction between *N,N*-di(*p*-Chlorobenzenesulfonyl)benzylamine and Tri-*n*-Butyltin Hydride



N,N-di(*p*-Chlorobenzenesulfonyl)methylbenzylamine (20 mg, 6.2×10^{-5} mol) and tributyltin hydride (37 mg, 2.7 equiv) in tetrahydrofuran (7 ml) were reacted together using the same procedure as experiment 36. Work-up and purification in the usual manner yielded benzylamine as a clear liquid (1 mg, 17%). The spectra for this compound were identical with authentic benzylamine.

111. *N*-(*p*-Chlorobenzenesulfenyl)-2-phenylcyclopropylamine

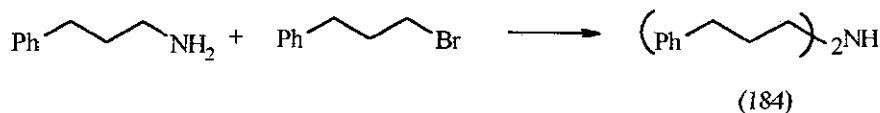
A solution of *p*-chlorobenzenesulfonyl chloride (2.6 g, 15 mmol) in dry diethyl ether (5 ml) was added dropwise to a stirred solution of 2-phenylcyclopropylamine-hydrochloride salt (2.5 g, 15 mmol) and triethylamine (10 ml) in dry diethyl ether (100 ml) at room temperature. The resulting solution was stirred at room temperature for a further 2 h when the white precipitate of triethylamine hydrochloride was filtered off and washed with diethyl ether (2 x 20 ml). The ether washings were combined and evaporated to dryness. Purification of the crude material on a dry alumina column using diethyl ether / light petroleum as eluent yielded the pure *N*-(*p*-chlorobenzenesulfenyl)-2-phenylcyclopropylamine as a clear oil (1.9 g, 46%); δ_{H} 1.22 (1 H, q, $J = 9.2$ Hz, 3-H), 1.43 (1 H, m, 3-H), 2.33 (1 H, m, 2-H), 3.16 (1 H, m, 1-H), and 7.16-7.31 (9 H, m, Ar-H); δ_{C} 20.21 (3-C), 29.47 (2-C), 54.83 (1-C), and 126.17, 128.08, 128.33 and 129.15 (Ar-C); m/z 275.0535 [M^+ (31%). $\text{C}_{15}\text{H}_{14}\text{ClNS}$ requires 275.0535], 218 (98), 204 (100), 132 (69), and 77 (62).

112. *N,N*-di-(*p*-Chlorobenzenesulfenyl)-2-phenylcyclopropylamine (180)

A solution of *p*-chlorobenzenesulfonyl chloride (650 mg, 3.63 mmol) in dry diethyl ether (5 ml) was added dropwise to a stirred solution of *N*-(*p*-chlorobenzenesulfenyl)-2-phenylcyclopropylamine (1.0 g, 3.63 mmol) and triethylamine (10 ml) in dry diethyl ether (100 ml) at room temperature. The resulting solution was stirred at room temperature for a further 2 h when the white precipitate of triethylamine hydrochloride was filtered off and washed with diethyl ether (2 x 20 ml). The ether washings were combined and evaporated to dryness. Purification of the crude material on a dry alumina column using diethyl ether / light petroleum as eluent yielded the pure *N,N*-di-(*p*-chlorobenzenesulfenyl)-2-phenylcyclopropylamine as a pale yellow oil (1.1 g, 73%); ν_{max} 1507 (aromatic C=C), 813 (1,4-disubst. aromatic), and 697 cm^{-1} (monosubst. aromatic); δ_{H} 1.21 (1 H, m, 3-H), 1.43 (1 H, m, 3-H), 2.33 (1 H, m, 2-H), 3.16 (1 H, m, 1-H), and 7.20-7.42 (13 H, m, Ar-H); δ_{C} 20.17 (3-C), 29.45 (2-C), 54.80 (1-C), and 126.15, 128.09, 129.24 and 129.27 (Ar-C); m/z

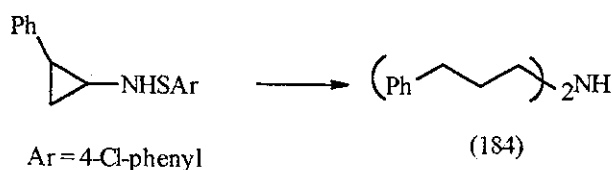
418.0258 [MH^+ (22%). $\text{C}_{21}\text{H}_{17}\text{Cl}_2\text{NS}_2$ requires 418.0258], 274 (82), 233 (41), and 132 (100).

113. *N,N*-di(3-Phenylpropyl)amine (184)



3-Phenylpropyl bromide (1.2 g, 6.17 mmol), 3-phenylpropylamine (1.0 g, 7.40 mmol), triethylamine (10 ml) and dry ethyl acetate (50 ml) were placed in a flask and heated to reflux for 5 h. The white precipitate of triethylamine hydrobromide was filtered off and washed with ethyl acetate (2 x 20 ml). The organic washings were combined and evaporated to dryness. Crystals of the suspected product formed from the residue oil whilst standing at room temperature for 24 h. These crystals were filtered off, washed with light petroleum (2 x 20 ml) and dried to leave the pure *N,N*-di(3-phenylpropyl)amine as light brown crystals (341 mg, 22%); ν_{max} 3415 (amine NH), 3024 (aromatic CH), 1582 (aromatic C=C), and 698 cm^{-1} (monosubst. aromatic); δ_{H} 2.21 (4 H, q, $J = 8.2$ Hz, 2-H), 2.65 (4 H, t, $J = 7.5$ Hz, 3-H), 2.91 (4 H, t, $J = 7.5$ Hz, 1-H), and 7.13-7.29 (10 H, m, Ar-H); δ_{C} 27.07 (2-C), 32.70 (3-C), 47.36 (1-C), and 126.44, 128.36, 128.64 and 139.65 (Ar-C); m/z 253.1830 [M^+ (12%). $\text{C}_{18}\text{H}_{23}\text{N}$ requires 253.1830], 148 (51), 91 (100), and 65 (32).

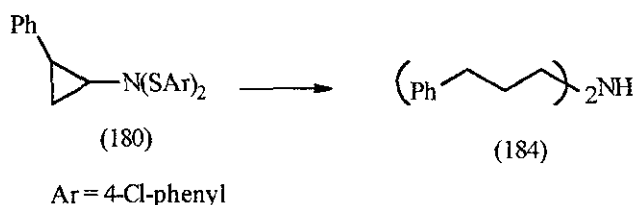
114. Reaction between *N*-(*p*-Chlorobenzenesulfonyl)-2-phenylcyclopropylamine and Tri-*n*-Butyltin Hydride



N-(*p*-Chlorobenzenesulfonyl)-2-phenylcyclopropylamine (100 mg, 0.4 mmol), tri-*n*-butyltin hydride (0.2 ml, 0.7 mmol), AIBN (catalytic amount) and dry toluene (100 ml) were all placed in a flask and heated to reflux for 2 h. The solution was allowed to cool to room temperature and sodium borohydride (14 mg, 0.4 mmol) was added in one portion. The reaction was stirred at room temperature for a further hour when the solvent was evaporated to dryness. The residue was taken up into diethyl ether (50 ml) and extracted with 2M hydrochloric acid solution (5 x 20 ml). The acid washings were combined and neutralised with saturated sodium carbonate solution, and made alkaline with sodium hydroxide pellets. The aqueous fraction was extracted with diethyl ether (3 x 50 ml). The ether extracts were combined, washed with water (70 ml), dried (MgSO_4) and evaporated to dryness. Purification of the crude material on a dry alumina column using dichloromethane /

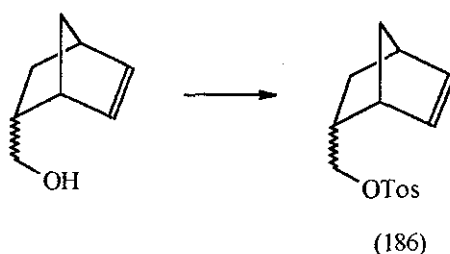
methanol as eluent yielded *N,N*-di(3-phenylpropyl)amine as a clear oil (**82**) (11 mg, 12%). All of the spectral data for this compound, including GC analysis, were identical with those for a sample of *N,N*-di(3-phenylpropyl)amine prepared in a separate manner.

115. Reaction between *N,N*-di(*p*-Chlorobenzenesulfenyl)-2-phenylcyclopropylamine and Tri-*n*-Butyltin Hydride



N,N-di(*p*-Chlorobenzenesulfenyl)-2-phenylcyclopropylamine (300 mg, 0.7 mmol) and tri-*n*-butyltin hydride (0.6 ml, 3 equiv) were reacted together using the same procedure as experiment 114. Work-up and purification in the usual manner yielded the *N,N*-di(3-phenylpropyl)amine as a clear oil (37 mg, 20%). The reaction was repeated using lithium aluminium hydride in place of sodium borohydride, though in all cases the product obtained was *N,N*-di(3-phenylpropyl)amine. The reaction was also repeated whereby the initially formed imine was not reduced *in situ*, but hydrolysed by the work-up procedure. However, reduction of the crude material after work-up with lithium aluminium hydride did not produce any recognisable product, particularly not the expected 3-phenylpropanol. This experiment was discontinued.

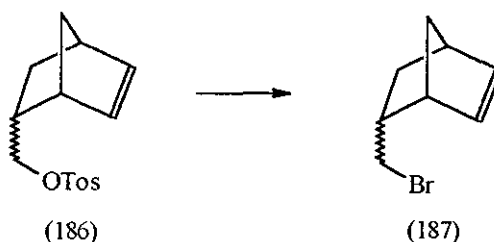
116. (Bicyclo[2.2.1]hept-5-en-2-yl)methyltosylate (186)



A solution of tosyl chloride (14.9 g, 0.066 mol) in triethylamine (40 ml) was placed in a flask and stirred at room temperature for 30 min under nitrogen. A solution of (bicyclo[2.2.1]hept-5-en-2-yl)methanol (2.5 g, 0.02 mol) was added dropwise and the resulting solution stirred for a further 17 h at room temperature. The solution was poured onto crushed ice (75 g) and extracted with dichloromethane (3 x 50 ml). The organic extracts were combined, washed with 2M hydrochloric acid solution (20 ml), saturated sodium bicarbonate solution (20 ml) and water (50 ml), dried (MgSO₄) and evaporated to dryness to yield the (bicyclo[2.2.1]hept-5-en-2-yl)methyltosylate as a clear oil (2.9 g, 52%);

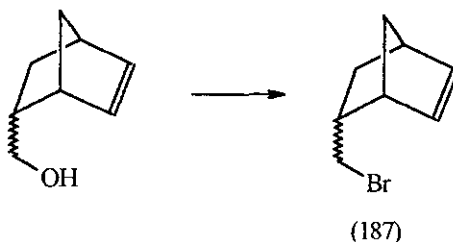
ν_{\max} 3064 (olefinic CH), 1595 and 1490 (aromatic C=C), and 813 cm^{-1} (1,4-disubst. aromatic); δ_{H} 0.44 (1 H, dt, $J = 8.2$ Hz, 3-H), 1.12 (1 H, d, $J = 8.2$ Hz, 3-H), 1.23 (1 H, m, 2-H), 1.57 (1 H, s, 7-H), 1.76 (1 H, m, 7-H), 2.45 (3 H, s, Me), 2.78 (1 H, s, 4-H), 2.88 (1 H, s, 1-H), 3.56 and 3.79 (2 H, ABX, 8-H), 5.67 (1 H, m, 5-H), 6.08 (1 H, m, 6-H), and 7.36-7.81 (4 H, dd, Ar-H).

117. (Bicyclo[2.2.1]hept-5-en-2-yl)methylbromide (187)



Lithium bromide (1.8 g, 3 equiv) was added in one portion to a stirred solution of (bicyclo[2.2.1]hept-5-en-2-yl)methyltosylate (2.0 g, 7.19×10^{-3} mol) in dry tetrahydrofuran (50 ml). The resulting solution was refluxed for 72 h and diluted with water (50 ml). The product was extracted with diethyl ether (3 x 50 ml). The organic extracts were combined, dried (MgSO_4) and evaporated to dryness to yield the (bicyclo[2.2.1]hept-5-en-2-yl)methylbromide as a clear oil (800 mg, 60%); ν_{\max} 3064 cm^{-1} (olefinic CH); δ_{H} 0.62 (1 H, dt, $J = 7.9$ Hz, 3-H), 1.28 (1 H, m, 3-H, $J = 7.9$ Hz), 1.49 (1 H, dt, $J = 8.3$ Hz, 2-H), 1.93 (1 H, m, 7-H), 2.50 (1 H, m, 7-H), 2.79 (1 H, s, 4-H), 3.00 (1 H, s, 1-H), 3.08 (1 H, d, $J = 8.2$ Hz, 8-H), 3.21 (1 H, m, 8-H), 6.00 (1 H, m, 6-H), and 6.20 (1 H, m, 5-H); δ_{C} 30.32 (2-C), 32.79 (3-C), 38.29 (7-C), 43.12 (4-C), 45.49 (1-C), and 49.68 (8-C).

118. (Bicyclo[2.2.1]hept-5-en-2-yl)methylbromide (187)

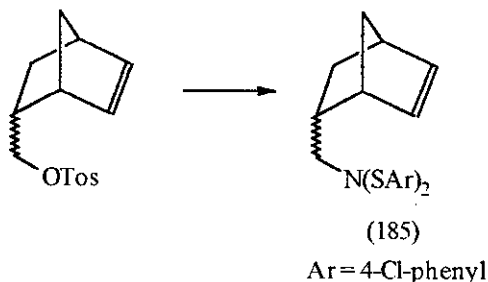


N-Bromosuccinimide (7.16 g, 0.04 mol) was slowly added to a stirred solution of (bicyclo[2.2.1]hept-5-en-2-yl)methanol (5.0 g, 0.04 mol) and triphenylphosphine (10.6 g, 0.04 mol) in DMF (20 ml) at room temperature. The reaction was warmed to 50°C for 30 min, and allowed to cool to room temperature for a further hour. Water (20 ml) was added and the mixture was extracted with diethyl ether (3 x 50 ml). The ether extracts were combined and washed with saturated sodium carbonate solution (20 ml), saturated sodium chloride solution (20 ml) and water (20 ml), before being dried (MgSO_4) and evaporated to

dryness to yield the crude bromide as a brown oil. Purification on a dry silica column using diethyl ether / light petroleum as eluent yielded the pure (bicyclo[2.2.1]hept-5-en-2-yl)bromide as a clear oil (2.8 g, 37%).

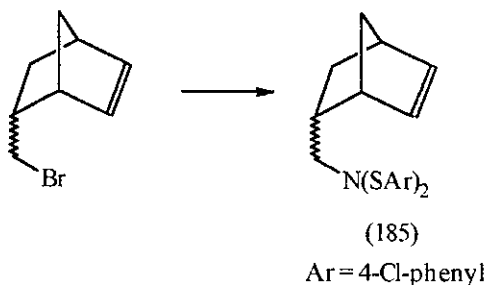
The experimental data for this compound was the same as the values quoted for the previous method for forming this molecule.

119. Attempted Synthesis of *N,N*-di(Benzenesulfonyl)-(bicyclo[2.2.1]hept-5-en-2-yl)methylamine (185)



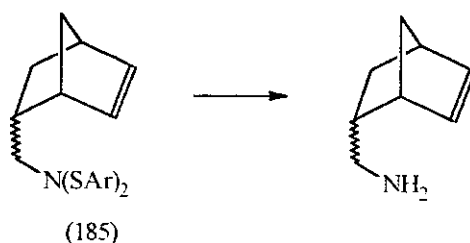
(Bicyclo[2.2.1]hept-5-en-2-yl)methyltosylate (119 mg, 0.4 mmol) was reacted with *N,N*-di(benzenesulfonyl)amine (100 mg, 0.4 mmol) using the same procedure as experiment 106. However, upon work-up, no evidence of expected product was observed. It appears that the tosylate is not active enough to react with the anion, and the bromide should instead be used.

120. *N,N*-di(*p*-Chlorobenzenesulfonyl)-(bicyclo[2.2.1]hept-5-en-2-yl)methylamine (185)



(Bicyclo[2.2.1]hept-5-en-2-yl)methylbromide (200 mg, 1 mmol) was reacted with *N,N*-di(*p*-chlorobenzenesulfonyl)amine (354 mg, 1.1 equiv) using the same procedure as experiment 106. Reaction and work-up in the usual manner yielded the *N,N*-di(*p*-chlorobenzenesulfonyl)-(bicyclo[2.2.1]hept-5-en-2-yl)methylamine as colourless crystals (164 mg, 34%); δ_{H} 0.61 (1 H, dt, $J = 8.2$ Hz, 3-H), 1.25 (1 H, m, 3-H), 1.48 (1 H, m, 2-H), 1.86 (1 H, m, 7-H), 2.59 (1 H, m, 7-H), 2.88 (1 H, s, 4-H), 2.99 (1 H, s, 1-H), 3.74 (2 H, t, $J = 8.2$ Hz, 8-H), 5.98 (1 H, m, 5-H), 6.20 (1 H, m, 6-H), and 7.25-7.38 (8 H, m, Ar-H); δ_{C} 32.66 (3-C), 38.18 (7-C), 41.97 (2-C), 42.99 (4-C), 45.37 (1-C), 67.85 (8-C), and 126.17-138.82 (Ar-C and 5-C and 6-C).

121. Reaction between *N,N*-di(*p*-Chlorobenzenesulfonyl)-(bicyclo[2.2.1]hept-5-en-2-yl)methylamine and Tri-*n*-Butyltin Hydride



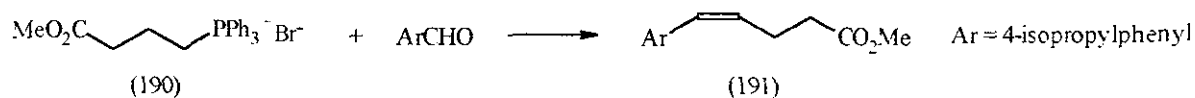
N,N-di(*p*-Chlorobenzenesulfonyl)-(bicyclo[2.2.1]hept-5-en-2-yl)methylamine (160 mg, 0.4 mmol) and tri-*n*-butyltin hydride (0.3 ml, 3 equiv.) were reacted together using the same procedure as experiment 59. Unfortunately, none of the expected cyclised product was recovered upon work-up. This experiment was discontinued.

122. 4-(Methoxycarbonyl)prop-1-yl-triphenylphosphonium bromide (190)



Methyl 4-bromobutyrate (25.0 g, 0.138 mol) and triphenylphosphine (36.2 g, 0.138 mol) were dissolved in dry toluene (200 ml) and heated to reflux for 60 h. The reaction was allowed to cool and the white precipitate of the phosphonium salt filtered off and washed with toluene (100 ml). The solid was dried to yield pure 4-(methoxycarbonyl)prop-1-yl-triphenylphosphonium bromide as a white solid (55.0 g, 90%). This experiment was repeated with a yield of 61%; δ_{H} 1.94 (2 H, m, 3-H), 2.90 (2 H, t, $J = 5.1$ Hz, 2-H), 3.66 (3 H, s, Me), 3.98 (2 H, m, 4-H), and 7.70-7.89 (15 H, m, Ar-H); δ_{C} 18.07 (3-C), 21.31 and 22.13 (2-C), 32.94 and 33.22 (4-C), 51.74 (Me), 117.38, 118.75, 130.62, 133.82, and 135.12 (Ar-C), and 173.47 (1-C).

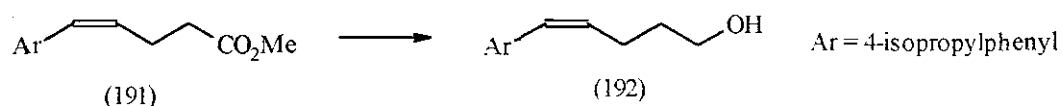
123. Methyl 5-(4-isopropylphenyl)pent-4-eneoate (191)



4-(Methoxycarbonyl)prop-1-yl-triphenylphosphonium bromide (50.0 g, 0.11 mol) was added in several portions to a suspension of cleaned sodium hydride (4.5 g, 0.11 mol) in dry tetrahydrofuran (200 ml) at room temperature. To this was added a solution of 4-isopropylbenzaldehyde (6.7 g, 45 mmol) in dry tetrahydrofuran (10 ml) dropwise over 15 min. The resulting suspension was stirred at room temperature for a further 18 h. The

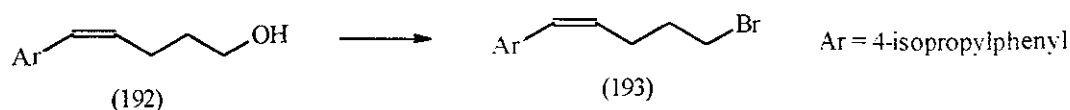
precipitate thus formed was filtered off and washed with diethyl ether (2 x 20 ml). The organic extracts were combined and evaporated to dryness. Purification of the crude material on a dry silica column using diethyl ether / light petroleum as eluent yielded the pure methyl 5-(4-isopropylphenyl)pent-4-eneoate as a clear oil (8.3 g, 79%). This experiment was repeated with a yield of 46%; ν_{\max} 1741 (ester carbonyl), 1437 (aromatic C=C), and 846 cm^{-1} (1,4-disubst. aromatic); δ_{H} 1.24 (6 H, d, $J = 9.1\text{ Hz}$, isoprop), 2.40 (2 H, q, $J = 8.5\text{ Hz}$, 3-H), 2.64 (2 H, q, $J = 8.2\text{ Hz}$, 2-H), 2.91 (1 H, q, $J = 9.1\text{ Hz}$, isoprop), 3.68 (3 H, s, Me), 5.57 (1 H, dt, $J = 11.3\text{ Hz}$, 4-H), 6.42 (1 H, d, $J = 11.3\text{ Hz}$, 5-H), and 7.22 (4 H, s, Ar-H); δ_{C} 23.89 (isoprop), 24.06 (3-C), 33.76 (Me), 34.17 (2-C), 51.54 (isoprop), 125.97 (4-C), 129.49 (5-C), 128.64, 129.97, 134.64 and 147.41 (Ar-C), and 174.53 (1-C).

124. 5-(4-Isopropylphenyl)pent-4-en-1-ol (192)



A solution of methyl 5-(4-isopropylphenyl)pent-4-eneoate (7.5 g, 32 mmol) in dry diethyl ether (10 ml) was carefully added dropwise over 30 min to a stirred suspension of lithium aluminium hydride (2.45 g, 64 mmol) in dry diethyl ether (100 ml) at room temperature. The reaction was allowed to stir at room temperature for a further hour when it was cooled to 0°C and 2M sodium hydroxide solution (7 ml) added to generate the insoluble lithium salts. The insoluble salts were filtered off and washed with diethyl ether (3 x 30 ml). The organic washings were combined and evaporated to dryness to yield the pure 5-(4-isopropylphenyl)pent-4-en-1-ol as a clear oil (5.4 g, 83%). This experiment was repeated to give a yield of 72%; ν_{\max} 3360 (alcohol OH), 1438 (aromatic C=C), and 844 cm^{-1} (1,4-disubst. aromatic); δ_{H} 1.24 (6 H, d, $J = 8.2\text{ Hz}$, isoprop), 1.75 (2 H, q, $J = 9.1\text{ Hz}$, 2-H), 2.43 (2 H, dq, $J = 8.2\text{ Hz}$, 3-H), 2.91 (1 H, q, $J = 8.2\text{ Hz}$, isoprop), 3.65 (2 H, t, $J = 7.3\text{ Hz}$, 1-H), 5.65 (1 H, dt, $J = 11.3\text{ Hz}$, 4-H), 6.42 (1 H, d, $J = 11.3\text{ Hz}$, 5-H), and 7.22 (4 H, m, Ar-H); δ_{C} 23.90 (isoprop), 24.89 (2-C), 32.81 (3-C), 33.75 (isoprop), 62.34 (1-C), 128.67 (4-C), 131.30 (5-C), and 126.19, 129.14, 134.98 and 147.46 (Ar-C).

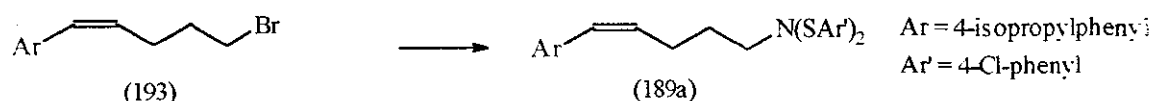
125. 1-Bromo-5-(4-isopropylphenyl)pent-4-ene (193)



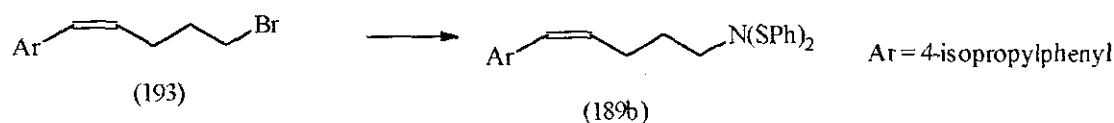
N-Bromosuccinimide (872 mg, 4.9 mmol) was carefully added in several portions to a stirred solution of 5-(4-isopropylphenyl)pent-4-en-1-ol (500 mg, 2.45 mmol) and triphenylphosphine (1.28 g, 4.9 mmol) in distilled dimethylformamide (5 ml) at room

temperature. The reaction was warmed up to 50°C for 30 min, and allowed to cool to room temperature over a further hour. Water (20 ml) was added and the product was extracted into diethyl ether (3 x 50 ml). The ether extracts were combined, washed with saturated sodium carbonate solution (20 ml), saturated sodium chloride solution (20 ml) and water (20 ml), dried (MgSO₄) and evaporated to dryness. Purification of the brown residue on a dry silica column using diethyl ether / light petroleum as eluent yielded the pure 1-bromo-5-(4-isopropylphenyl)pent-4-ene as a pale yellow oil (107 mg, 73%). This experiment was repeated to give yields of 54% and 24%; ν_{\max} 3009 (aromatic CH), 1513 (aromatic C=C), and 840 cm⁻¹ (1,4-disubst. aromatic); δ_{H} 1.28 (6 H, d, J = 8.2 Hz, isoprop), 2.01 (2 H, q, J = 7.5 Hz, 2-H), 2.48 (2 H, q, J = 7.5 Hz, 3-H), 2.91 (1 H, q, J = 8.2 Hz, isoprop), 3.44 (2 H, t, J = 7.5 Hz, 1-H), 5.59 (1 H, dt, J = 10.8 Hz, 4-H), 6.48 (1 H, d, J = 10.8 Hz, 5-H), and 7.22 (4 H, s, Ar-H); δ_{C} 23.92 (isoprop), 27.29 (2-C), 29.66 (3-C), 31.89 (1-C), 33.78 (isoprop), 126.22 (4-C), 129.77 (5-C), and 126.52, 128.48, 133.83 and 147.51 (Ar-C); m/z 266.0670 [M^+ (12%). C₁₄H₁₉Br requires 266.0670], 131 (31), 117 (100), 91 (28), and 49 (25).

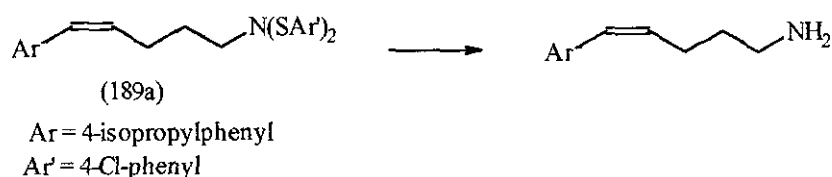
126. *N,N*-di(*p*-Chlorobenzenesulfonyl)-5-(4-isopropylphenyl)pent-4-enylamine (189a)



N,N-di(*p*-chlorobenzenesulfonyl)amine (142 mg, 0.5 mmol) was added in one portion to a stirred suspension of cleaned sodium hydride (19 mg, 0.5 mmol) in dry tetrahydrofuran (20 ml) at 0°C. The resulting suspension was stirred at this temperature for 10 min when a solution of 1-bromo-5-(4-isopropylphenyl)pent-4-ene (105 mg, 0.4 mmol) in tetrahydrofuran (2 ml) was added dropwise. The solution was allowed to warm up to room temperature and stirred for 2 h. The resulting precipitate was filtered off and washed with diethyl ether (2 x 20 ml). The organic extracts were combined and evaporated to dryness. Purification of the residue on a dry alumina column using diethyl ether / light petroleum as eluent yielded the pure *N,N*-di(*p*-chlorobenzenesulfonyl)-5-(4-isopropylphenyl)pent-4-enylamine as a clear oil (98 mg, 27%); ν_{\max} 1474 (aromatic C=C), and 813 cm⁻¹ (1,4-disubst. aromatic); δ_{H} 1.23 (6 H, d, J = 8.2 Hz, isoprop), 1.79 (2 H, q, J = 7.4 Hz, 2-H), 2.30 (2 H, q, J = 7.4 Hz, 3-H), 2.90 (1 H, q, J = 8.2 Hz, isoprop), 3.38 (2 H, t, J = 7.5 Hz, 1-H), 5.52 (1 H, dt, J = 11.3 Hz, 4-H), 6.37 (1 H, d, J = 11.3 Hz, 5-H), and 7.13-7.31 (12 H, m, Ar-H); δ_{C} 22.66 (isoprop), 23.91 (2-C), 29.33 (3-C), 33.77 (isoprop), 65.82 (1-C), and 125.86-130.66 (Ar-C and 4-C and 5-C); m/z 488.1040 [MH^+ (15%). C₂₆H₂₇Cl₂NS₂ requires 488.1040], 346 (100), 202 (73), and 70 (43).

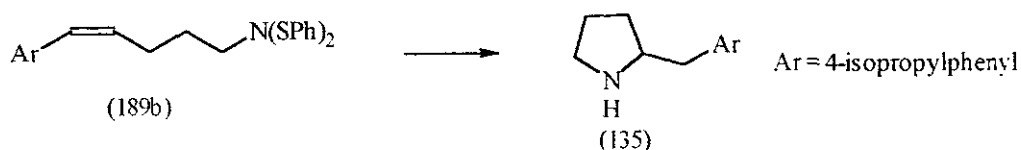
127. *N,N*-di(benzenesulfonyl)-5-(4-isopropylphenyl)pent-4-enylamine (189b)

1-Bromo-5-(4-isopropylphenyl)pent-4-ene (400 mg, 1.5 mmol) was reacted with *N,N*-di(benzenesulfonyl)amine (349 mg, 1.5 mmol) using the same procedure as experiment 141. Following work-up and purification, the pure *N,N*-di(benzenesulfonyl)-5-(4-isopropylphenyl)pent-4-enylamine was formed as a clear oil (389 mg, 62%); ν_{\max} 1468 (aromatic C=C), 840 (1,4-disubst. aromatic), and 693 cm^{-1} (monosubst. aromatic); δ_{H} 1.23 (6 H, d, $J = 8.2$ Hz, isoprop), 1.80 (2 H, q, $J = 7.5$ Hz, 2-H), 2.28 (2 H, q, $J = 7.5$ Hz, 3-H), 2.88 (1 H, m, isoprop), 3.46 (2 H, m, 1-H), 5.51 (1 H, dt, $J = 12.1$ Hz, 4-H), 6.32 (1 H, d, $J = 12.1$ Hz, 5-H), and 7.11-7.36 (14 H, m, Ar-H); δ_{C} 22.71 (isoprop), 23.97 (2-C), 29.49 (3-C), 33.82 (isoprop), 65.80 (1-C), and 125.18-131.05 (Ar-C and 4-C and 5-C); m/z 419.1741 [M^+ (5%)]. $\text{C}_{26}\text{H}_{29}\text{NS}_2$ requires 419.1741, 218 (55), 109 (100), 65 (38), and 43 (30).

128. Reaction between *N,N*-di(*p*-chlorobenzenesulfonyl)-5-(4-isopropylphenyl)pent-4-enylamine and Tri-*n*-butyltin Hydride

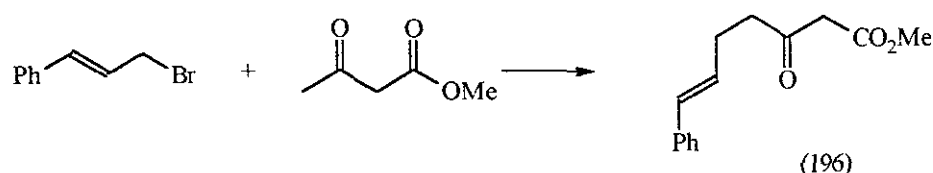
A solution of tri-*n*-butyltin hydride (0.15 ml, 3 equiv) and AIBN (catalytic amount) in dried toluene (30 ml) was added over 5 h to a refluxing solution of *N,N*-di(*p*-chlorobenzenesulfonyl)-5-(4-isopropylphenyl)pent-4-enylamine (90 mg, 0.2 mmol) in toluene (30 ml). The reaction was refluxed for a further hour when it was allowed to cool to room temperature and the solvent evaporated to dryness. The residue was taken up into diethyl ether (50 ml) and extracted with 2M hydrochloric acid solution (5 x 20 ml). The acid washings were combined and neutralised with saturated sodium carbonate solution, and made alkaline with sodium hydroxide pellets. The aqueous fraction was extracted with diethyl ether (3 x 50 ml). The ether extracts were combined, washed with water (70 ml), dried (MgSO_4) and evaporated to dryness. Upon analysis of the residue, no sign of any recognisable product could be detected. The experiment was discontinued.

129. Reaction between *N,N*-di(benzenesulphenyl)-5-(4-isopropylphenyl)pent-4-enylamine and Tri-*n*-butyltin Hydride



N,N-di(Benzenesulphenyl)-5-(4-isopropylphenyl)pent-4-enylamine (350 mg, 0.8 mmol) and tri-*n*-butyltin hydride (0.7 ml, 2.5 mmol) were reacted together using the same procedure as experiment 143. Work-up and purification in the usual manner gave a mixture of the cyclised and uncyclised products in the ratio of 9:1. 2-(4-Isopropylbenzyl)pyrrolidine (135) was formed as a clear oil (34 mg, 23%); δ_{H} 1.23 (6 H, d, $J = 8.2$ Hz, CHMe_2), 1.74–1.80 (4 H, m, 3-H and 4-H), 2.71 (2 H, d, $J = 8.7$ Hz, ArCH_2), 2.82 (2 H, m, 5-H), 3.03 (1 H, m, CHMe_2), 3.18 (1 H, m, 2-H), and 7.15 (4 H, s, Ar-H); δ_{C} 24.06 (CHMe_2), 24.77 (4-C), 31.29 (3-C), 33.70 (CHMe_2), 41.76 (ArCH_2), 46.06 (5-C), 60.55 (2-C), and 125.89, 126.54 and 129.38 (Ar-C); m/z 203.1680 [M^+ (5%), $\text{C}_{14}\text{H}_{21}\text{N}$ requires 203.1674], 70 (100), and 43 (9).

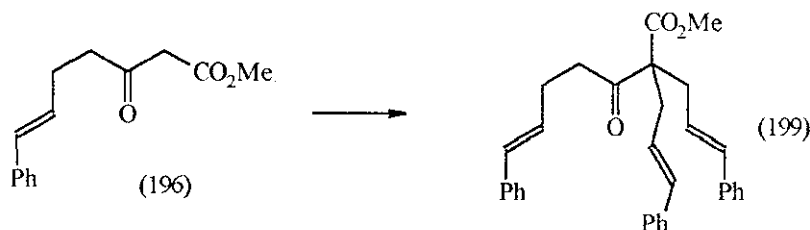
130. Methyl 2-oxo-6-phenylhex-5-enoate (196)



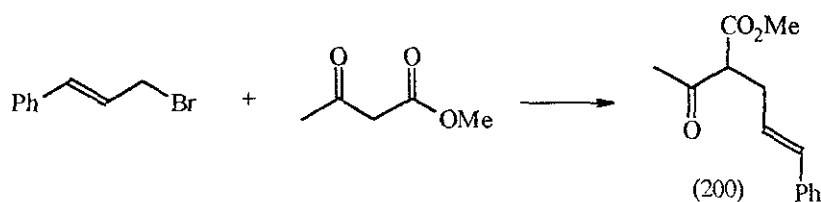
Sodium hydride (1.5 g, 60% dispersion in mineral oils) was placed in a flask flushed with nitrogen and washed clean with petrol (2 x 20 ml). The petrol washings were decanted off and replaced with dry tetrahydrofuran (100 ml). The suspension was cooled to 0°C for 10 min when methyl acetoacetate (5.0 ml, 38 mmol) was added dropwise. The mixture was stirred for a further 10 min at 0°C before a solution of *n*-butyllithium (24 ml, 1.6M solution in hexanes) was added dropwise. Finally, a solution of cinnamyl bromide (15.2 g, 2 equiv) in dry tetrahydrofuran (20 ml) was added dropwise to this stirred solution at 0°C. The mixture was allowed to warm up to room temperature and was stirred at this temperature for 30 min. The precipitate (inorganic salts) was filtered off and washed with diethyl ether (2 x 30 ml). The ether washings were combined and evaporated to dryness. Unfortunately, upon analysis of the crude material, the product of this reaction was found to be methyl 2-oxo-6-phenylhex-5-enoate (8.0 g) and not the expected 1,9-diphenyl-4-methylcarboxy-5-oxo-nona-1,8-diene (195); ν_{max} 3057 (olefinic CH), 3030 (aromatic CH), 1749 (ester carbonyl), 1716 (ketone carbonyl), 1496 (aromatic C=C), and 696 cm^{-1} (monosubst. aromatic); δ_{H} 2.52 (2 H, q, $J = 7.1$ Hz, 4-H), 2.71 (2 H, t, $J = 7.1$ Hz, 3-H), 3.47 (2 H, s, 1-H), 3.72 (3 H, s, Me).

6.19 (1 H, dt, 5-H), 6.42 (1 H, d, $J = 11.3$ Hz, 6-H), and 7.27 (5 H, m, Ar-H); δ_C 26.78 (4-C), 42.53 (3-C), 49.12 (1-C), 52.38 (Me), 126.03 (5-C), 131.08 (6-C), 127.42-137.28 (Ar-C), 167.54 (ester carbonyl), and 201.79 (4-C).

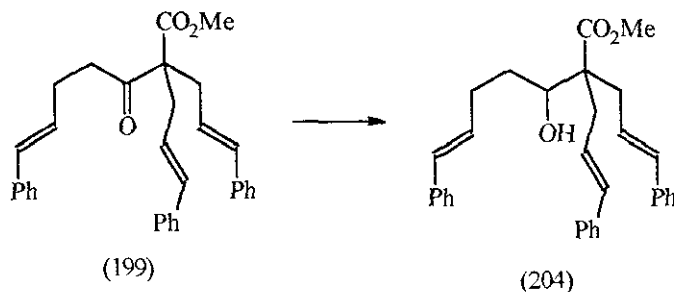
131. Attempted Synthesis of 1,9-Diphenyl-4-methoxycarbonyl-5-oxo-nona-1,8-diene (195)



Sodium hydride (473 mg, 60% dispersion in mineral oils, 1.3 equiv) was placed in a flask flushed with nitrogen and washed clean with petrol (2 x 20 ml). The petrol washings were decanted off and replaced with dry tetrahydrofuran (100 ml). Methyl 2-oxo-6-phenylhex-5-enoate (196) (2.0 g, 9.09 mmol) in dry tetrahydrofuran (10 ml) was added dropwise at room temperature, followed by a solution of cinnamyl bromide (1.8 g, 9.09 mmol) in tetrahydrofuran (20 ml). The solution was heated to reflux and maintained at this temperature for 17h. Saturated ammonium chloride (50 ml) was added and the product extracted with diethyl ether (3 x 50 ml). The ether washings were combined, washed with water (50 ml), dried (MgSO_4) and evaporated to dryness. Unfortunately, on purification using a dry silica column with diethyl ether as eluent, the product obtained was found to be 1,9-diphenyl-4-methoxycarbonyl-5-oxo-4-(3-phenylprop-2-enyl)nona-1,8-diene (199) (1.0 g, 32%) as a clear oil, and not the expected 1,9-diphenyl-4-methoxycarbonyl-5-oxo-nona-1,8-diene (195); ν_{max} 1742 (ester carbonyl), 1713 (ketone carbonyl), 1495 (aromatic C=C), and 693 cm^{-1} (monosubst. aromatic); δ_H 2.46 (2 H, dt, $J = 7.7$ Hz, 7-H), 2.67 (2 H, t, $J = 7.7$ Hz, 6-H), 2.83 (4 H, d, $J = 8.4$ Hz, 10-H and 3-H), 3.72 (3 H, s, Me), 5.97 (2 H, dt, $J = 17.1$ Hz, 2-H and 11-H), 6.14 (1 H, dt, $J = 17.1$ Hz, 8-H), 6.35 (1 H, d, $J = 17.1$ Hz, 9-H), 6.45 (2 H, d, $J = 17.1$ Hz, 1-H and 12-H), and 7.22-7.31 (15 H, m, Ar-H); δ_C 27.07 (7-C), 35.90 (6-C), 39.33 (10-C and 3-C), 52.49 (Me), 63.83 (4-C), 123.66, 127.50 and 128.52 (1-C, 2-C, 8-C, 9-C, 11-C and 12-C), 126.23-136.94 (Ar-C), 172.05 (ester carbonyl), and 205.48 (5-C).

132. 1-Phenyl-4-methoxycarbonyl-5-oxo-1-hexene (200)


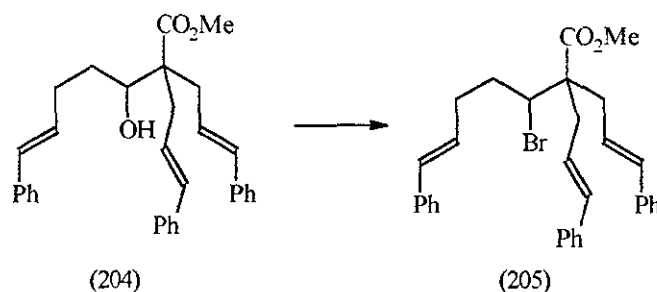
Sodium hydride (4.5 g, 1.3 equiv) was washed free of the mineral oil with light petroleum (2 x 20 ml) and suspended in dry tetrahydrofuran (70 ml). The suspension was cooled to -10°C and the methyl acetoacetate (12.9 g, 1.3 equiv) added dropwise over 10 min. Effervescence occurred and a yellow suspension was formed. The suspension was stirred at 0°C for 10 min when the cinnamyl bromide (16.9 g, 0.086 mol) in dry tetrahydrofuran (50 ml) was added over a period of 3 h. During this time, the reaction was allowed to warm up to room temperature. When addition was complete, the reaction was allowed to stir for a further 30 min, before the precipitated sodium bromide was filtered off. The precipitate was washed with dry diethyl ether (3 x 50 ml). The ether washings were combined and evaporated to dryness. Purification of the crude material on a dry silica column using diethyl ether / light petroleum as eluent yielded the pure 1-phenyl-4-methoxycarbonyl-5-oxo-1-hexene as a pale yellow oil (18.2 g, 91%); ν_{max} 1745 (ester carbonyl), 1717 (ketone carbonyl), 1436 (aromatic C=C), and 695 cm^{-1} (monosubst. aromatic); δ_{H} 2.21 (3 H, s, Me), 2.72 (2 H, t, $J = 8.2\text{ Hz}$, 3-H), 3.59 (1 H, t, $J = 8.2\text{ Hz}$, 4-H), 3.69 (3 H, s, OMe), 6.09 (1 H, dt, 2-H), 6.43 (1 H, d, $J = 15.3\text{ Hz}$, 1-H), and 7.24 (5 H, m, Ar-H); δ_{C} 29.24 (6-C), 31.51 (3-C), 52.38 (OMe), 59.25 (4-C), 125.67 (2-C), 137.72 (1-H), 125.99-136.98 (Ar-C), 169.62 (ester carbonyl), and 205.42 (5-C).

133. 1,9-diphenyl-5-hydroxy-4-methoxycarbonyl-4-(3-phenylprop-2-enyl)nona-1,8-diene (204)


1,9-Diphenyl-4-methoxycarbonyl-5-oxo-4-(3-phenylprop-2-enyl)nona-1,8-diene (199) (1.0 g, 2.87 mmol) was dissolved in dry methanol (20 ml) and stirred at room temperature. Sodium borohydride (437 mg, 3 equiv) in water (3 ml) was added dropwise and the resulting suspension stirred at room temperature for 1 h. The reaction was poured onto water (50 ml)

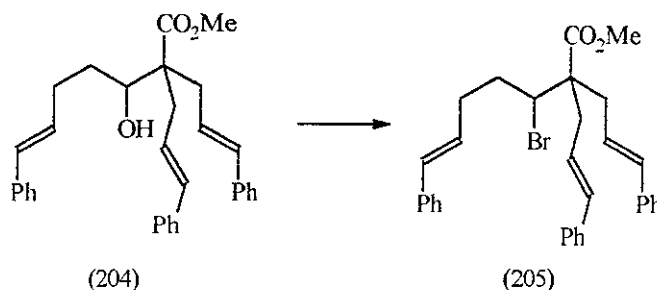
and conc. hydrochloric acid solution (5 ml) and extracted into diethyl ether (3 x 50 ml). The ether extracts were combined, dried (MgSO_4) and evaporated to dryness to give the crude alcohol. Purification of the crude material on a dry silica column using diethyl ether / light petroleum as eluent yielded the pure 1,9-diphenyl-5-hydroxy-4-methoxycarbonyl-4-(3-phenylprop-2-enyl)nona-1,8-diene as a clear oil (700 mg, 70%); ν_{max} 3730 (alcohol OH), 1725 (ester carbonyl), and 693 cm^{-1} (monosubst. aromatic); δ_{H} 2.35 (2 H, dt, 6-H), 2.53 (2 H, dt, 7-H), 2.66 (4 H, d, $J = 6.5\text{ Hz}$, 3-H and 10-H), 3.73 (3 H, s, OMe), 3.85 (1 H, t, $J = 7.7\text{ Hz}$, 5-H), 6.22 (3 H, dt, 2-H, 8-H and 11-H), 6.48 (3 H, d, $J = 14.4\text{ Hz}$, 1-H, 9-H and 12-H), and 7.21-7.28 (15 H, m, Ar-H); δ_{C} 29.74 (6-C), 31.77 (7-C), 35.84 (3-C), 36.99 (10-C), 51.89 (OMe), 54.99 (4-C), 73.80 (5-C), 125.19 (2-C, 8-C and 11-C), 133.46 (1-C, 9-C and 12-C), 125.23-131.78 (Ar-C), and 175.99 (ester carbonyl).

134. Attempted Synthesis of 5-Bromo-1,9-diphenyl-4-methoxycarbonyl-4-(3-phenylprop-2-enyl)nona-1,8-diene (205)



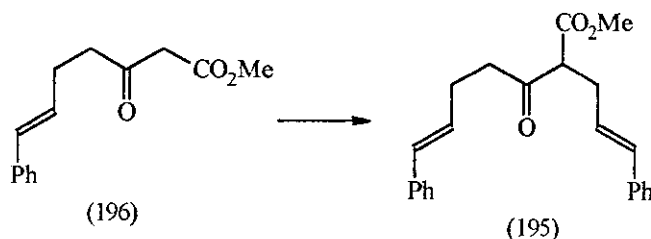
A solution of triphenylphosphine (394 mmol, 1.5 mmol) in dry tetrahydrofuran (3 ml) was added to a stirred solution of *N*-bromosuccinimide (267 mg, 1.5 mmol) in dry tetrahydrofuran (10 ml). A solution of 1,9-diphenyl-5-hydroxy-4-methoxycarbonyl-4-(3-phenylprop-2-enyl)nona-1,8-diene (700 mg, 1.5 mmol) in dry tetrahydrofuran (4 ml) was added to the white precipitate and the resulting suspension stirred at room temperature for 24 h. The remaining precipitate was filtered off and washed with tetrahydrofuran (2 x 20 ml). The organic washings were combined and evaporated to dryness to give a solid residue. The residue was taken up into diethyl ether (50 ml) and water (100 ml) and extracted into diethyl ether (3 x 50 ml). The ether extracts were combined, washed with water (50 ml), dried (MgSO_4) and evaporated to dryness. Purification of the crude material on a dry silica column using diethyl ether / light petroleum as eluent showed the main product to be 1,9-diphenyl-5-hydroxy-4-methoxycarbonyl-4-(3-phenylprop-2-enyl)nona-1,8-diene with no sign of expected bromide. This experiment was discontinued.

135. Attempted Synthesis of 5-Bromo-1,9-diphenyl-4-methoxycarbonyl-4-(3-phenylprop-2-enyl)nona-1,8-diene (205)



One drop of 48% aqueous hydrobromic acid was carefully added to a cooled solution (10°C) of phosphorus tribromide (65 mg, 2.4 mmol) in dry diethyl ether (10 ml). A solution of 1,9-diphenyl-5-hydroxy-4-methoxycarbonyl-4-(3-phenylprop-2-enyl)nona-1,8-diene (225 mg, 4.8 mmol) in dry diethyl ether (10 ml) was added dropwise to this cooled solution, and the resulting solution stirred at 10°C for 1 h, and room temperature for 72 h. The reaction flask was submerged in an ice-salt mixture for 30 min. The organic residue was decanted off and evaporated to dryness. Upon analysis, no expected 5-bromo-1,9-diphenyl-4-methoxycarbonyl-4-(3-phenylprop-2-enyl)nona-1,8-diene was detected. This experiment was discontinued.

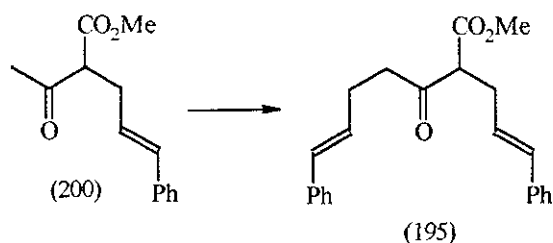
136. 1,9-Diphenyl-4-methoxycarbonyl-5-oxo-nona-1,8-diene (195)



Methyl 2-oxo-6-phenylhex-5-enoate (196) (5.0 g, 21 mmol) in dry tetrahydrofuran (10 ml) was added to a stirred suspension of cleaned sodium hydride (840 mg, 21 mmol) in tetrahydrofuran (100 ml). Cinnamyl bromide (4.3 g, 21 mmol) in tetrahydrofuran (25 ml) was added over 4.5 h to a refluxing solution of the monoanion. The solution was allowed to reflux for a further 12 h after addition was complete. Saturated ammonium chloride solution (50 ml) was added and the product extracted into diethyl ether (3 x 50 ml). The ether extracts were combined, washed with water (70 ml), dried (MgSO₄) and evaporated to dryness. Purification of the crude material on a dry silica column using diethyl ether / light petroleum as eluent gave the pure 1,9-diphenyl-4-methoxycarbonyl-5-oxo-nona-1,8-diene as a clear oil (7.0 g, 96%); ν_{\max} 3027 (aromatic CH), 1742 (ester carbonyl), 1715 (ketone carbonyl), 1495 (aromatic C=C), and 693 cm⁻¹ (monosubst. aromatic); δ_{H} 2.43 (2 H, q, J =

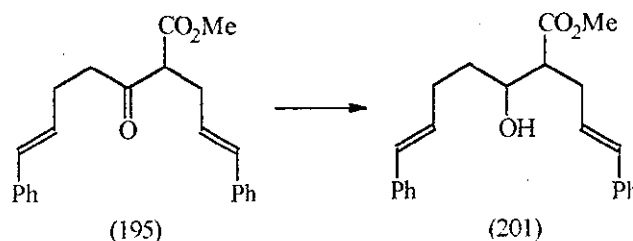
5.1 Hz, 6-H), 2.57 (2 H, t, $J = 5.1$ Hz, 7-H), 2.75 (2 H, m, 3-H), 3.53 (1 H, m, 4-H), 3.62 (3 H, s, OMe), 6.09 (2 H, dt, 2-H and 8-H), 6.39 (2 H, d, $J = 12.3$ Hz, 1-H and 9-H), and 7.14-7.28 (10 H, m, Ar-H); δ_C 26.77 (6-C), 31.58 (7-C), 41.89 (3-C), 52.39 (OMe), 58.71 (4-C), 125.65-134.98 (Ar-C and 1-C, 2-C, 8-C and 9-C), 169.78 (5-C), and 203.48 (ester carbonyl).

137. 1,9-Diphenyl-4-methoxycarbonyl-5-oxo-nona-1,8-diene (195)



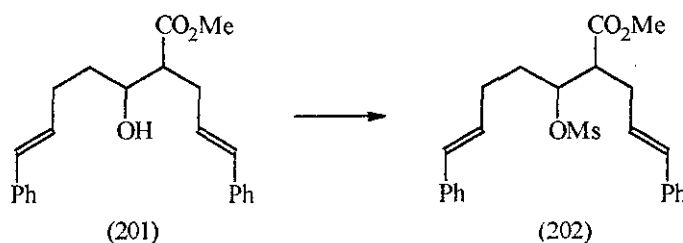
1-Phenyl-4-methoxycarbonyl-5-oxo-1-hexene (200) (2.0 g, 8.62 mmol) was added dropwise to a stirred suspension of cleaned sodium hydride (350 mg, 8.62 mmol) in dry tetrahydrofuran (50 ml). The resulting suspension was cooled to 0°C before *n*-butyllithium (5.4 ml, 8.62 mmol) was added dropwise to generate the dianion. Cinnamyl bromide (1.4 g, 7.18 mmol) in dry tetrahydrofuran (20 ml) was added to the cooled solution over 3.5 h, allowing the temperature to rise upon addition to room temperature. When addition was complete, the reaction was allowed to stir at room temperature for a further 17 h. Saturated ammonium carbonate solution (40 ml) was added and the product extracted into diethyl ether (3 x 50 ml). The organic extracts were combined, washed with saturated sodium chloride solution (3 x 25 ml), dried (MgSO₄) and evaporated to dryness. Purification of the crude material on a dry silica column using diethyl ether / light petroleum as eluent gave the pure 1,9-diphenyl-4-methoxycarbonylnon-2,8-diene-5-one as a clear oil (1.4 g, 56%); ν_{\max} 3027 (aromatic CH), 1742 (ester carbonyl), 1715 (ketone carbonyl), 1495 (aromatic C=C), and 693 cm⁻¹ (monosubst. aromatic); δ_H 2.43 (2 H, q, $J = 5.1$ Hz, 6-H), 2.57 (2 H, t, $J = 5.1$ Hz, 7-H), 2.75 (2 H, m, 3-H), 3.53 (1 H, m, 4-H), 3.62 (3 H, s, OMe), 6.09 (2 H, dt, 2-H and 8-H), 6.39 (2 H, d, $J = 11.9$ Hz, 1-H and 9-H), and 7.14-7.28 (10 H, m, Ar-H); δ_C 26.77 (6-C), 31.58 (7-C), 41.89 (3-C), 52.39 (OMe), 58.71 (4-C), 125.65-134.98 (Ar-C and 1-C, 2-C, 8-C and 9-C), 169.78 (5-C), and 203.48 (ester carbonyl).

138. 1,9-Diphenyl-5-hydroxy-4-methoxycarbonyl-nona-1,8-diene (201)



Sodium borohydride (470 mg, 5 equiv) in water (3 ml) was added to a stirred solution of 1,9-diphenyl-4-methoxycarbonyl-5-oxo-nona-1,8-diene (1.4 g, 4.02 mmol) in methanol (50 ml). The reaction was stirred at room temperature for 1 h, when it was poured onto a mixture of ice/water (30 ml) and concentrated hydrochloric acid solution (2 ml) and extracted into diethyl ether (3 x 50 ml). The ether extracts were combined, dried (MgSO_4) and evaporated to dryness to give the crude alcohol. Purification of the crude material on a dry silica column using diethyl ether / light petroleum as eluent yielded the pure 1,9-diphenyl-5-hydroxy-4-methoxycarbonyl-nona-1,8-diene as a pale yellow oil (1.0 g, 71%); ν_{max} 3433 (OH), 3026 (aromatic CH), 1736 (ester carbonyl), 1495 (aromatic C=C), and 693 cm^{-1} (monosubst. aromatic); δ_{H} 1.66 (2 H, m, 6-H), 2.29 (2 H, m, 7-H), 2.49 (2 H, m, 3-H), 3.64 (3 H, s, OMe), 3.67 (1 H, m, 4-H), 4.04 (1 H, m, 5-H), 6.14 (2 H, m, 2-H and 8-H), 6.40 (2 H, m, 1-H and 9-H), and 7.17-7.27 (10 H, m, Ar-H); δ_{C} 29.36 (6-C), 35.19 (7-C), 50.98 (OMe), 63.46 (3-C), 71.15 (4-C), 74.97 (5-C), and 125.98-132.49 (Ar-C and 1-C, 2-C, 8-C and 9-C).

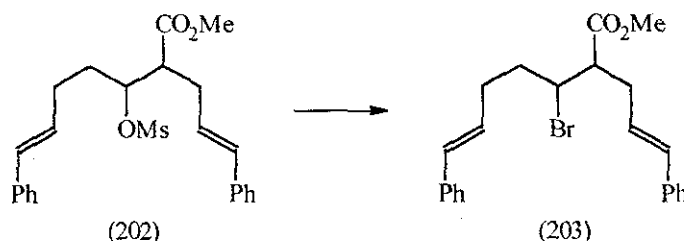
139. 1,9-Diphenyl-4-methoxycarbonyl-5-mesylnona-1,8-diene (202)



A solution of freshly distilled methylsulfonyl chloride (0.98 ml, 8.57 mmol) in dichloromethane (5 ml) was added dropwise at 0°C to a stirred solution of 1,9-diphenyl-5-hydroxy-4-methoxycarbonyl-nona-1,8-diene (1.0 g, 2.86 mmol) in dichloromethane (50 ml) and triethylamine (10 ml). The resulting solution was allowed to warm up to room temperature over 2 h, and maintained at this temperature for a further 18 h. Water (50 ml) was added and the product extracted into diethyl ether (3 x 50 ml). The ether extracts were combined, dried (MgSO_4) and evaporated to dryness to give the 1,9-diphenyl-4-

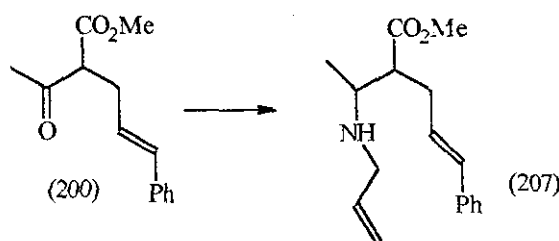
methoxycarbonyl-5-mesylnona-1,8-diene as a clear oil (530 mg, 43%) after purification in the usual manner. No spectra were available for this compound.

140. 5-Bromo-1,9-diphenyl-4-methoxycarbonyl-nona-1,8-diene (203)



Lithium bromide (140 mg, 3 equiv) was added in one portion to a stirred solution of 1,9-diphenyl-5-hydroxy-4-methoxycarbonyl-nona-1,8-diene (230 mg, 0.5 mmol) in tetrahydrofuran (100 ml) at room temperature. The resulting suspension was heated to reflux and maintained at this temperature for 72 h. Water (50 ml) was added and the product extracted into diethyl ether (3 x 50 ml). The ether extracts were combined, washed with water (50 ml), dried (MgSO_4) and evaporated to dryness. Upon analysis, none of the expected 5-bromo-1,9-diphenyl-4-methoxycarbonyl-nona-1,8-diene was detected. This experiment was discontinued.

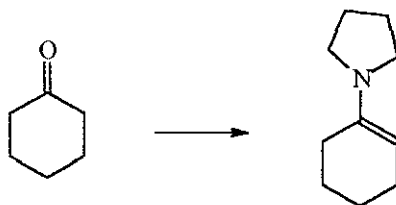
141. Attempted Synthesis of *N*-Allyl-3-methoxycarbonyl-6-phenylhex-5-ene-2-ylamine (207)



1-Phenyl-4-methoxycarbonyl-5-oxo-1-hexene (800 mg, 3.45 mmol) and allylamine (984 mg, 5 equiv) in dichloromethane (100 ml) were placed over activated molecular sieves (6.0 g) and stirred at room temperature for 24 h. The molecular sieves were filtered off, washed with dichloromethane (20 ml), and the dichloromethane extracts combined and evaporated to dryness to give the imine as a clear oil (456 mg, 46%); The imine (206) (456 mg, 1.58 mmol) was dissolved in methanol (20 ml) and stirred at room temperature. Sodium borohydride (301 mg, 5 equiv) was added and the resulting suspension stirred at room temperature for 1 h. The reaction was poured onto ice/water (100 ml) and extracted into diethyl ether (3 x 50 ml). The ether extracts were combined, dried (MgSO_4) and evaporated to dryness to give a clear oil. However, analysis of this oil indicated that it was not the

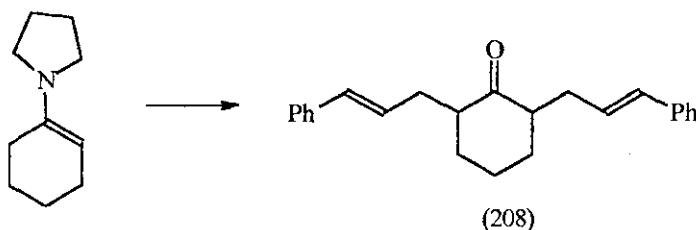
expected *N*-allyl-3-methoxycarbonyl-6-phenylhex-5-ene-2-ylamine. This experiment was discontinued.

142. Pyrrolidine Enamine of Cyclohexanone



Cyclohexanone (50.0 g, 0.51 mol), pyrrolidine (36.0 g, 0.51 mol), *p*-toluenesulfonic acid (catalytic amount) and toluene (200 ml) were all placed in a flask and stirred under reflux using a Deane-Stark water separator. The solution was allowed to cool to room temperature and was evaporated to dryness. The enamine was formed as an orange liquid (56.0 g, 73%); ν_{\max} 1642 cm^{-1} (enamine C=C), δ_{H} 1.49 (2 H, q, $J = 7.1$ Hz, 5-H), 1.65 (2 H, t, $J = 7.1$ Hz, 4-H), 1.77 (4 H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 2.05 (2 H, s, 3-H), 2.14 (2 H, s, 6-H), 2.94 (4 H, t, $J = 6.1$ Hz, CH_2N), and 4.24 (1 H, s, 2-H); δ_{C} 23.34 (5-C), 23.69 (4-C), 24.65 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 27.84 (6-C and 3-C), 47.70 (CH_2N), and 93.84 (2-C).

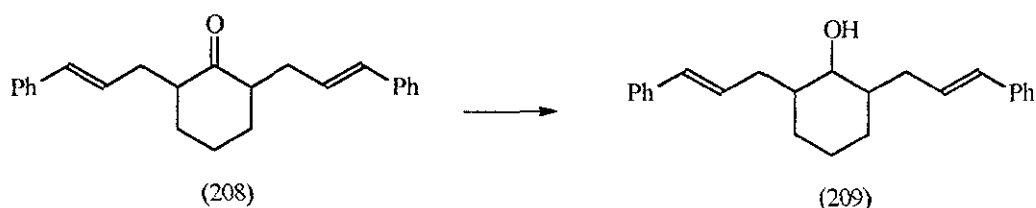
143. 2,6-di(3-Phenylprop-2-enyl)cyclohexanone (208)



The pyrrolidine enamine (3.6 g, 24 mmol) was added dropwise to a stirred solution of cinnamyl bromide (11.8 g, 2.5 equiv) and *N*-ethyldicyclohexylamine (5.0 g, 24 mmol) in dry chloroform (50 ml). The solution was refluxed for 5 h when 2M hydrochloric acid solution was added (50 ml). The solution was reheated to reflux and maintained at this temperature for a further 2 h. The reaction was allowed to cool to room temperature and the solvent evaporated to dryness. The resulting brown oil was extracted into dichloromethane (3 x 70 ml). The organic extracts were combined, washed with 2M hydrochloric acid solution (2 x 20 ml), dried (MgSO_4), and evaporated to dryness. Purification of the crude product on a dry silica column using light petroleum/diethyl ether as eluent yielded the pure 2,6-di(3-phenylprop-2-enyl)cyclohexanone as colourless crystals (230 mg, 3%), [m.p. 104°C]; ν_{\max} 3026 (aromatic CH), 1707 (ketone carbonyl), 1495 (aromatic C=C), and 693 cm^{-1} (monosubst. aromatic); δ_{H} 1.36 (2 H, qd, 4-H), 1.69 (2 H, m, 3-H and 5-H), 2.11 (2 H, q, $J =$

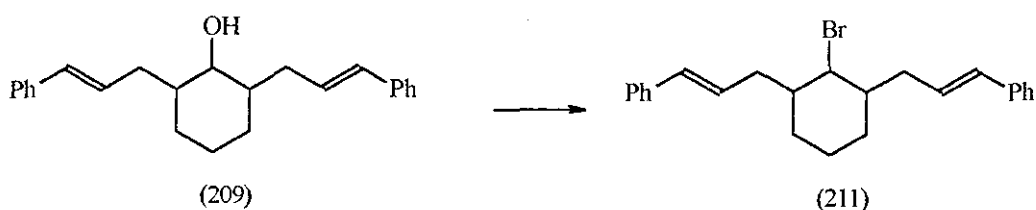
9.2 Hz, 3-H and 5-H), 2.26 (2 H, m, CH_2CHCH), 2.44 (2 H, s, CH_2CHCH), 2.69 (2 H, dt, 2-H and 6-H), 6.18 (2 H, dt, CHCHPh), 6.36 (2 H, d, $J = 13.3$ Hz, CHCHPh), and 7.15-7.35 (10 H, m, Ar-H); δ_{C} 25.43 (4-C), 32.96 (3-C and 5-C), 34.90 (CH_2CHCH), 51.16 (2-C and 6-C), 126.97 (CHCHPh), 131.57 (CHCHPh), and 125.99, 128.58 and 137.59 (Ar-C); m/z 330.1984 [M^+ (23%)]. $\text{C}_{24}\text{H}_{26}\text{O}$ requires 330.1983], 117 (81), 91 (100), and 49(22).

144. 2,6-di(3-Phenylprop-2-enyl)cyclohexanol (209)



Sodium borohydride (23 mg, 0.6 mmol) was added in one portion to a stirred solution of 2,6-di(3-phenylprop-2-enyl)cyclohexanone (200 mg, 0.6 mmol) and cerium chloride (227 mg, 0.6 mmol) in methanol (30 ml). The reaction was stirred at room temperature for 2 h when water (30 ml) was added and the product was extracted into diethyl ether (3 x 50 ml). The organic extracts were combined, dried (MgSO_4), and evaporated to dryness to leave the pure 2,6-di(3-phenylprop-2-enyl)cyclohexanol as colourless crystals (200 mg, 100%). The reaction was repeated to give a yield of 68%, and repeated in the absence of cerium chloride to give a yield of 56%. In all cases, the experimental data were identical; ν_{max} 3423 (alcohol OH), 1495 (aromatic $\text{C}=\text{C}$), and 693 cm^{-1} (monosubst. aromatic); δ_{H} 1.22 (2 H, m, 4-H), 1.54 (4 H, m, 3-H and 5-H), 1.73 (2 H, m, CH_2CHCH), 2.13 (2 H, m, CH_2CHCH), 2.33 (2 H, q, $J = 8.2$ Hz, 2-H and 6-H), 3.80 (1 H, s, 1-H), 6.15 (2 H, dt, CHCHPh), 6.37 (2 H, d, $J = 14.3$ Hz, CHCHPh), and 7.17-7.34 (10 H, m, Ar-H); δ_{C} 25.75 (4-C), 25.94 (3-C and 5-C), 36.89 (CH_2CHCH), 42.97 (2-C and 6-C), 71.37 (1-C), 126.90 (CHCHPh), 129.97 (CHCHPh), and 125.97, 128.48, 131.38 and 137.67 (Ar-C); m/z 332.2140 [M^+ (19%)]. $\text{C}_{24}\text{H}_{28}\text{O}$ requires 332.2140], 314 (14), 216 (37), 198 (100), and 193 (23).

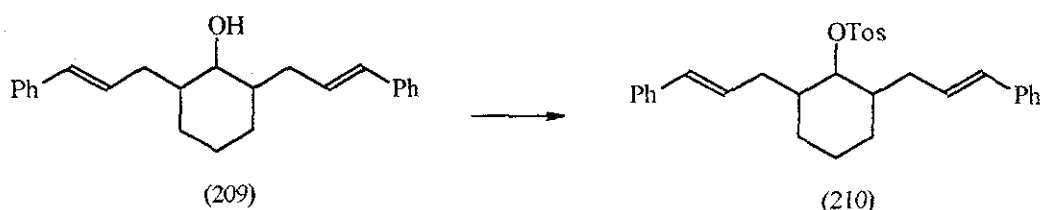
145. Attempted Synthesis of 2,6-di(3-Phenylprop-2-enyl)cyclohexyl bromide (211)



A solution of 2,6-di(3-phenylprop-2-enyl)cyclohexanol (100 mg, 0.3 mmol) in dry tetrahydrofuran (1 ml) was added dropwise to a stirred suspension of triphenylphosphine (79 mg, 0.3 mmol) and *N*-bromosuccinamide (54 mg, 0.3 mmol) in tetrahydrofuran (5 ml). The

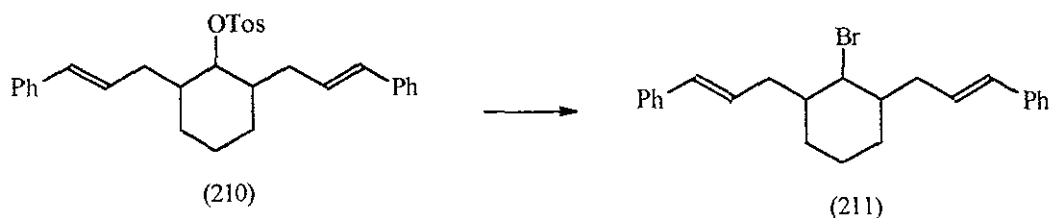
reaction was stirred at room temperature for 2 h when water (20 ml) was added and the product extracted into diethyl ether (3 x 50 ml). The organic extracts were combined, dried (MgSO_4), and evaporated to dryness to leave a brown residue (191 mg, >100%). Analysis showed that none of the expected 2,6-di(3-phenylprop-2-enyl)cyclohexylbromide was present. The experiment was discontinued.

146. 2,6-di(3-Phenylprop-2-enyl)-1-tosylcyclohexane (210)



p-Toluenesulfonyl chloride (1.15 g, 6.0 mmol) was added over 5 min to a stirred solution of 2,6-di(3-phenylprop-2-enyl)cyclohexanol (1.0 g, 3.0 mmol) in pyridine (10 ml). The resulting solution was stirred at room temperature for 3 h and water (30 ml) was added. Diethyl ether (3 x 50 ml) was used to extract the product; the ether extracts were combined, dried (MgSO_4) and evaporated to dryness to leave the 2,6-di(3-phenylprop-2-enyl)-1-tosylcyclohexane as an oil (500 mg, 34%). No further purification was performed. This experiment was repeated to give a yield of 87%; ν_{max} 3026 (aromatic CH), 1598 (aromatic C=C), and 694 cm^{-1} (monosubst. aromatic); δ_{H} 1.15 (2 H, m, 4-H), 1.32 (4 H, m, 3-H and 5-H), 1.51 (2 H, m, CH_2CHCH), 2.19 (2 H, m, CH_2CHCH), 2.29 (2 H, m, 2-H and 6-H), 2.46 (3 H, s, Me), 3.23 (1 H, q, $J = 8.2$ Hz, 1-H), 6.22 (2 H, dt, CHCHPh), 6.45 (2 H, d, $J = 13.3$ Hz, CHCHPh), and 7.17-7.41 (14 H, m, Ar-H); δ_{C} 22.05 (Me), 25.78 (4-C), 36.91 (3-C and 5-C), 42.01 (CH_2CHCH), 42.99 (2-C and 6-C), 71.39 (1-C), and 125.98-131.21 (Ar-C and CHCHPh).

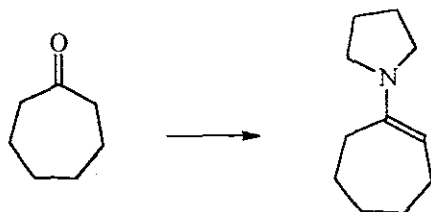
147. Attempted Synthesis of 1-Bromo-2,6-di(3-phenylprop-2-enyl)-cyclohexane (211)



A solution of 2,6-di(3-phenylprop-2-enyl)-1-tosylcyclohexane (600 mg, 1.23 mmol) in dry tetrahydrofuran (2 ml) was added dropwise to a stirred solution of lithium bromide (214 mg, 2.5 mmol) in tetrahydrofuran (10 ml). The resulting solution was heated to reflux and maintained at this temperature for 24 h. Water (20 ml) was added and the product extracted into diethyl ether (3 x 50 ml). The organic extracts were combined, dried (MgSO_4), and

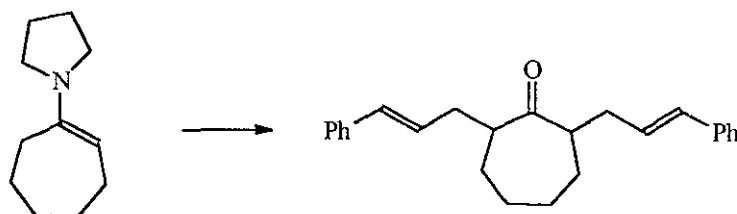
evaporated to dryness. Analysis of the crude mixture showed no evidence of expected 1-bromo-2,6-di(3-phenylprop-2-enyl)-cyclohexane. This experiment was discontinued.

148. Pyrrolidene Enamine of Cycloheptanone



Cycloheptanone (50.0 g, 0.45 mol), pyrrolidine (32.0 g, 0.45 mol) and *p*-toluenesulfonic acid (catalytic amount) in dry toluene (200 ml) were all placed in a flask and heated to reflux with a Deane-Starke water separator. After refluxing for 2 h, the reaction was allowed to cool to room temperature and the solvent was evaporated to dryness to leave the enamine as a pale yellow liquid (47.0 g, 64%). No further purification was performed; δ_{H} 1.49 (4 H, m, 5-H and 6-H), 1.52 (2 H, m, 4-H), 1.82 (4 H, m, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 2.09 (2 H, s, 3-H), 2.37 (2 H, m, 7-H), 3.13 (4 H, s, NCH_2), and 4.49 (1 H, s, 2-H); δ_{C} 24.62 ($\text{NCH}_2\text{CH}_2\text{CH}_2$), 26.24 (6-C), 26.97 (5-C), 32.81 (4-C), 41.32 (3-C), 43.90 (7-C), 48.52 (NCH_2), 74.02 (1-C), 99.16 (2-C).

149. Attempted Synthesis of 2,6-di(3-Phenylprop-2-enyl)cycloheptanone



The pyrrolidine enamine (7.8 g, 48 mmol) was added dropwise to a stirred solution of cinnamyl bromide (23.5 g, 0.12 mol) and *N*-ethyldicyclohexylamine (10.0 g, 48 mmol) in dry chloroform (100 ml). The solution was refluxed for 32 h when 2M hydrochloric acid solution was added (50 ml). The solution was reheated to reflux and maintained at this temperature for a further 2 h. The reaction was allowed to cool to room temperature and the solvent evaporated to dryness. The resulting brown oil was extracted into dichloromethane (3 x 70 ml). The organic extracts were combined, washed with 2M hydrochloric acid solution (2 x 20 ml), dried (MgSO_4), and evaporated to dryness. Purification of the crude product on a dry silica column using light petroleum/diethyl ether as eluent yielded no sign of the expected 2,6-di(3-phenylprop-2-enyl)cycloheptanone. This experiment was discontinued.

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