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Synthesis of nitrogen heterocycles *via* amidyl radical cyclisations

by

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Submitted for the degree of Doctor of Philosophy

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University of Warwick
March 1998

For Mum, with love

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Acknowledgements

I would like to thank my supervisor Dr Andrew Clark for all his help, ideas and masses of encouragement.

I would also like to thank Dr Jeremy Hastings and Dr Adam Clarke for the many NMR experiments they performed for me (special thanks to Adam for being such a star at the end and for brightening up the NMR room), Mr Inder Katyal and the EPSRC Mass Spectrometry Service for recording the mass spectra, Mr Paul Moore for the microanalyses and the EPSRC for their funding of my research.

Massive thanks go to all my lab colleagues, past and present for making C421 such a good place to work. So, thanks to Tim B and Jane for teaching me everything, Ismail (Mr Perfect) for leading the way, Andy S for making me laugh, Stuart (hellooooooo) for silly days and chips, Karen (my gassing partner) for sharing the ups and downs and helping me to finally get out of there, John for making columns more interesting, Robert for his great discussions and Awh, Yasair and Nicola who made up the happy team! Thanks to 'next door's lot' too, especially Annie for being the liveliest person I know and for keeping everyone going. Thanks also go to my house mates, Suzanne and Julie for putting up with me for two years and keeping it from getting too scary!

I would particularly like to thank Anthony for being there from start to finish and for looking after me during the thesis writing and my family for their encouragement throughout.

Declaration

The work described in this thesis is the original work of the author, except where acknowledgement has been made to results and ideas previously published. The work was carried out in the Department of Chemistry, University of Warwick between October 1st 1994 and October 1st 1997 and has not been previously submitted for a degree at any institution.

Abstract

Intramolecular radical additions to alkenes have become increasingly popular in synthetic organic chemistry as a means for constructing cyclic arrays. The majority of work has focused upon the reactions of carbon-centred radicals but nitrogen radical cyclisations can provide an effective route to forming a variety of *N*-heterocycles. Cyclisation of nucleophilic aminyl radicals can be problematic due to their potential reversibility so the more electrophilic amidyl radicals were used for this investigation.

O-Benzoyl hydroxamic acid derivatives proved to be suitable precursors for forming the desired amidyl radicals and all cyclisations were performed using these precursors. A stereoselectivity study was performed on 5-*exo* amidyl radical cyclisations. Hence, a range of methyl and phenyl 3-substituted *N*-alkyl-*N*-benzoyloxypent-4-enamides were prepared and cyclised by reaction with tributyltin hydride. A small preference for *trans* 5-*exo* cyclisation was observed (diastereomeric excesses ranging from 10-48%) with the 3-phenyl substituted precursors showing greater selectivity than the 3-methyl substituted precursors. The *N*-alkyl group was found to have little effect on the reaction. Systems capable of undergoing 5-*exo*, 5-*exo* tandem amidyl radical cyclisations were also studied. The presence of a methyl group at the 5-position of the second forming ring resulted in a change of regiochemistry with 5-*exo*, 6-*endo* cyclisation actually becoming the dominant pathway.

A range of *N*-alkyl-*N*-benzoyl-4-phenylbut-3-enamides were synthesised and cyclised in a 4-*exo* fashion to form β-lactams. Also produced in these reactions were 2-benzoyl substituted amides formed from rearrangement of the starting material. These rearrangement reactions were studied in more detail and were found to proceed smoothly when promoted by base. Use of stronger bases led to shorter reaction times. The rearrangements were also conducted thermally (with no added base) in excellent yields.

Abbreviations

AIBN	Azoisobutyronitrile
ap	Apparent
Ar	Aryl
Bn	Benzyl
br	Broad
Bu	Butyl
t-Bu	Tertiary butyl
Bz	Benzoyl
cat.	Catalytic
CI	Chemical ionisation
COSY	Correlated spectroscopy
d	Doublet
DBU	Diazabicycloundecene
DCC	Dicyclohexylcarbodiimide
dd	Doublet of doublets
ddd	Doublet of doublets of doublets
d.e.	Diastereomeric excess
DEPT	Direct enhancement by polarisation transfer
DMAP	Dimethylaminopyridine
dq	Doublet of quartets
dt	Doublet of triplets
EI	Electron impact

Et	Ethyl
EtOAc	Ethyl acetate
EPR	Electron paramagnetic resonance
g	Grams
HOMO	Highest occupied molecular orbital
Hz	Hertz
i	*ipso*
i-Pr	Isopropyl
IR	Infra red
J	Coupling constant
LUMO	Lowest unoccupied molecular orbital
m	*meta*
m	Multiplet
Me	Methyl
mg	Milligrams
ml	Millilitres
mmol	Millimoles
mol	Mole
mp	Melting point
MS	Mass spectrum
Ms	Mesyl
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
o	*ortho*

p	*para*
pet. ether	Petroleum ether
PFMC	Perfluoromethylcyclohexane
Ph	Phenyl
ppm	Parts per million
Pr	Propyl
PTOC	Pyridine-2-thioneoxycarbonyl
q	Quartet
qn	Quintet
R	Alkyl
RT	Room temperature
s	Singlet
SOMO	Singly occupied molecular orbital
sp	Septet
sx	Sextet
t	Triplet
td	Triplet of doublets
TEA	Triethylamine
Tf	Triflate (Trifluoromethane sulfonate)
tlc	Thin layer chromatography
TMS	Trimethylsilyl
TMSCN	Trimethylsilylcyanide
Ts	*p*-Toluenesulfonyl
tt	Triplet of triplets

w/w	Weight for weight

Chapter 1

Introduction

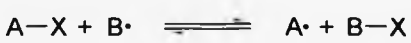
1.1 Introduction to radical chemistry

Radicals are species that contain at least one unpaired electron. In contrast to organic anions or cations they react easily with themselves in bond forming reactions. In the liquid phase most of these reactions occur at diffusion controlled rates.[1] Radical-radical reactions can be slowed down only if the radicals are stabilised by electronic effects or shielded by steric effects.

The lifetime of a radical depends not only on its inherent stability but also on the conditions under which it is generated. The terms persistent and stable are usually used to describe the nature of a radical. A stable radical is inherently stable; a persistent radical has a relatively long lifetime under the conditions under which it is generated, though it may not be very stable.[2] Thus, persistence is a kinetic property that is more often related to sterically hindered recombination than to electronic stabilisation.

The two main reactions undergone by free radicals are atom (or group) abstraction, and addition to multiple bonds. Atom abstraction is an S_H2 substitution reaction where a radical abstracts an atom or group from an organic molecule to produce a new radical where the atom or group was attached (Equation 1.1). The most commonly abstracted groups are univalent atoms such as halogens or hydrogen. With

addition to multiple bonds (Equation 1.2), a radical adds to an unsaturated functional group.



Equation 1.1

Equation 1.2

Radical reactions are becoming increasingly popular in synthetic organic chemistry. They can generally be conducted under mild, neutral conditions thereby avoiding many of the undesired side reactions that are often associated with ionic reagents. Radical reactions are also often tolerant of steric crowding, particularly on the radical centre and if heat-sensitive compounds are involved the application of heat can often be avoided by using photolysis to generate the required radicals. Radicals are free from the complications of anion kinetics such as ion-pairing, aggregation and large solvent effects. Although they should be conducted under an inert atmosphere, as they react with triplet oxygen, radical reactions do not need to be carried out under strictly anhydrous conditions. Carbon-centred radicals often show great chemoselectivities, regioselectivities and stereoselectivities upon addition to carbon-carbon multiple bonds. Carbon-centred radicals can only attack functional groups if the bimolecular rate constant k exceeds 10^2 $mol^{-1}s^{-1}$. Thus, due to the endothermic

nature of homolysis of strong O-H or N-H bonds, these functionalities require no protection prior to a radical reaction.

1.2 Carbon radicals

Carbon radicals are by far the most common type of radicals employed in synthesis and as such, an introduction into their chemistry is necessary here. However, as the research contained within this thesis involves only nitrogen-centred radicals a comprehensive treatment of carbon radicals will not be given.

Carbon-carbon bond formation is one of the most important synthetic steps in the construction of organic molecules and this is being increasingly achieved by the addition of carbon-centred radicals to carbon-carbon multiple bonds. The increase in synthetic applications of radical reactions has in part been due to the large number of mechanistic studies that have been conducted. The effects of substituents located on both the radical and the multiple bond on the rate and regioselectivity of the addition have been established.[3-5]

Carbon-centred radicals can either adopt a planar (sp^2 bonding) or pyramidal (sp^3 bonding) structure.[2,6] Conjugating substituents favour the planar structure while alkyl and heteroatom substituents can cause pyramidalisation.[7]

1.2.1 Electronic nature of carbon radicals

The addition of carbon-centred radicals to carbon-carbon multiple bonds is generally energetically favourable since a C-C σ-bond is formed at the expense of a C-C π-bond.[8] The exothermicity of these reactions means that they can be generally regarded as having early transition states and can therefore be analysed using Frontier Molecular Orbital (FMO) theory. The singly occupied orbital (SOMO) of the radical interacts with the lowest unoccupied orbital (LUMO) and/or the highest occupied orbital (HOMO) of the C-C multiple bond (Figure 1.1)[1]

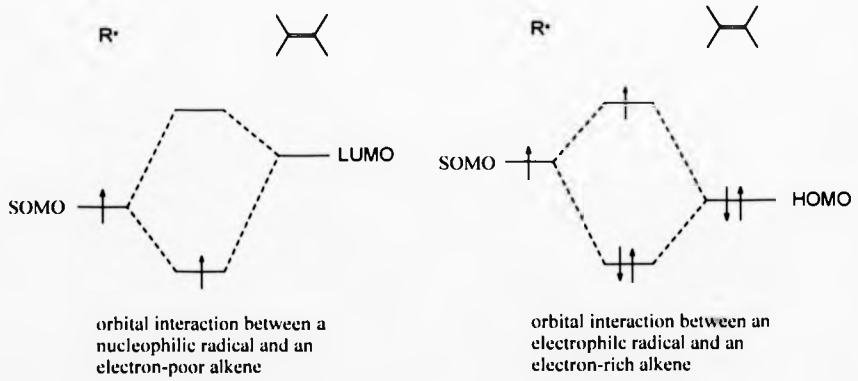


Figure 1.1 - Orbital interactions between radicals and alkenes

All carbon centred radicals can be classified as nucleophilic, electrophilic or ambiphilic depending upon the substituents attached to the carbon radical. The nature of the radical will determine the types of addition reactions that it can undergo. Simple alkyl radicals can be considered nucleophilic and react preferentially with

electron poor alkenes in high yields (Figure 1.1).[1] Electron withdrawing substituents at the alkene lower the LUMO and increase the rate of the reaction. Therefore, cyclohexyl radicals react 8500 times faster with acrolein than with 1-hexene.[7]

Carbon-centred radicals that contain two electron-withdrawing groups, such as esters or nitriles have SOMO energies so low that the SOMO-HOMO interaction dominates (Figure 1.1). These are electrophilic radicals and consequently electron donating substituents at the alkene increases the rate of addition. With some carbon radicals, the rates of reaction are increased by both electron donating or electron withdrawing substituents on the alkene. These have SOMO energies intermediate between that of nucleophilic and electrophilic radicals and are termed ambiphilic.

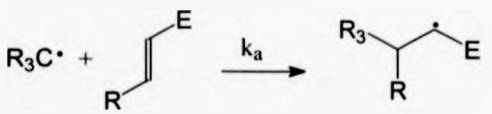
1.3 Intermolecular addition to multiple bonds

The addition of a carbon-centred radical to an alkene or alkyne is one of the mildest general techniques to extend a carbon chain. Radical addition reactions are reversible in principle and sometimes in practice. However, the addition of an unstabilized carbon-centred radical to a C-C double bond is not reversible at normal reaction temperatures because of its exothermicity. If the π-bond is strong, the forming σ-bond weak or the starting radical significantly more stable than the adduct radical though, the addition can become reversible.

The most commonly used method for radical addition reactions is the tin hydride method. Generally, nucleophilic radicals, generated from alkyl iodides, bromides or

related precursors are reacted with electron deficient alkenes. A complementary reaction is that of conjugate addition of an organometallic reagent to an electron deficient alkene. In many cases the standard organometallic route is the best due to consistently high yields and a greater tolerance of β-substituents on the acceptor. The radical method becomes advantageous when adding secondary, tertiary and hetero-atom substituted radicals or when either the halide or the alkene contains functionality sensitive to organometallic methods.

Generally, intermolecular additions of nucleophilic radicals to unactivated alkenes are too slow to be synthetically useful. Alkyl substituents at the radical centre give a small increase in the rate of addition (by raising the SOMO energy), hence tertiary radicals are more reactive than secondary radicals which are more reactive than primary radicals. However, additions can be accelerated by a factor of 10^3 or 10^4 by the introduction of an electron-withdrawing substituent on the β-position of the alkene (Equation 1.3).[8]



E = COR, CO_2R, Ph *etc.*

Equation 1.3

The magnitude of k_a is of great importance when planning chain reactions. Giese has summarised how substituents at C-1, C-2 and the radical centre affect this rate in terms of polar and steric effects.[5]

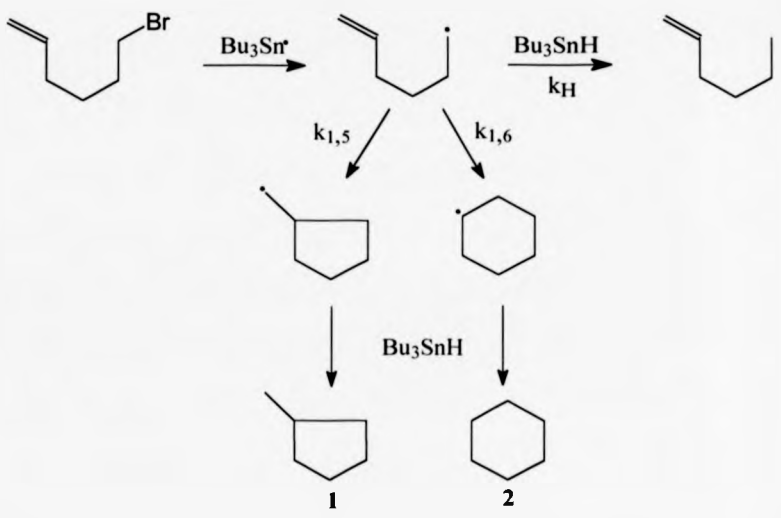
Alkynes have a higher LUMO and lower HOMO than alkenes. Hence, both nucleophilic and electrophilic radicals react faster with alkenes than with alkynes.[5] This is in contrast to nucleophiles with non-bonding electron pairs which attack triple bonds faster than double bonds.

1.4 Intramolecular addition to multiple bonds

If a free radical is generated in an unsaturated chain then it is possible for the radical to be trapped by a cyclisation reaction before H-atom abstraction takes place. Radical cyclisation reactions are normally easier to carry out than intermolecular radical additions and they can be a mild and convenient route into a variety of cyclic products.

1.4.1 Hex-5-enyl radical cyclisation reactions

The most widely studied carbon-centred radical cyclisation is that of the hex-5-enyl radical (Scheme 1.1).[4] There are two possible cyclised products, cyclohexane, **2** and methylcyclopentane, **1**.



Scheme 1.1

On thermochemical grounds the more stable cyclohexyl radical is expected to give cyclohexane as the major product. However, at 25°C the hex-5-enyl radical cyclises to give both the 5-*exo-trig* product and the 6-*endo trig* product in a ratio of 98:2 showing the reaction to be under kinetic control.[9] This is also in accordance with Baldwin's rules[10] which state that 3 to 7-*exo*-trig cyclisations are favoured. It is suggested that this is due to the necessity for maximum overlap in the transition state between the semi-occupied 2p orbital and the vacant π* orbital.[11] This arrangement can be much more easily accommodated in the transition complex for 1,5-ring closure than for 1,6. The transition state model devised by Beckwith[12,13] and developed further by Houk and Spellmeyer[14] contains three important low energy transition states: the 5-*exo* chair, **3**, the 5-*exo* boat, **4**, and the 6-*endo* chair, **5** (Figure 1.2). The lowest energy transition state is the 5-*exo* chair. This stereoelectronic

rationale first proposed by Beckwith, is generally regarded as the single most important factor that favours 5-*exo* over 6-*endo* cyclisation.[9]

3 **4** **5**

0 kcal mol^{-1} +1 kcal mol^{-1} +3 kcal mol^{-1}

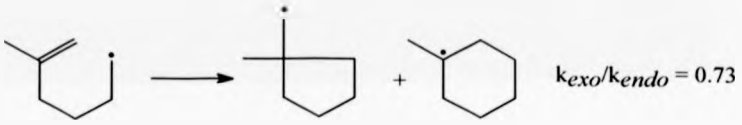
Figure 1.2 - Transition state models for hex-5-enyl radical cyclisations

Note that the unimolecular ring closure of the hex-5-enyl radical competes with bimolecular H-atom transfer from Bu_3SnH and so the yields of cyclic products decrease with increasing tin hydride concentration. However, at any given temperature the ratio of 5- and 6-membered ring cyclic products is a constant and reflects the respective rate constants for ring closure.

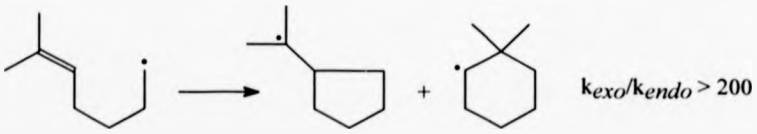
1.4.1.1 Substituent effects

There has been much research into the effects of substituents located on either the radical centre, the carbon chain or the multiple bond on the rate and regioselectivity of the reaction. Beckwith[4,11] found that the introduction of an alkyl group at the 5-position of the hex-5-enyl radical has a large effect on the regioselectivity of ring closure with 6-*endo* cyclisation now predominating (Scheme 1.2). They report the value of $k_{1,5}/k_{1,6}$ at 80^{0}C for the 5-methylhex-5-enyl radical to be 0.73. Examination

of the individual rate constants shows the change is due partly to a small increase in the rate of 1,6-ring closure but mainly due to a large decrease in the rate of the 1,5-reaction. Conversely, terminal alkene substituents increase the rate of 1,5-*exo*-cyclisation while decreasing the rate of 1,6-*endo*-cyclisation (Scheme 1.3). These effects are probably due to steric reasons and are a consequence of the fact that "substituents on an olefinic double bond disfavour addition at the substituted position."[15]

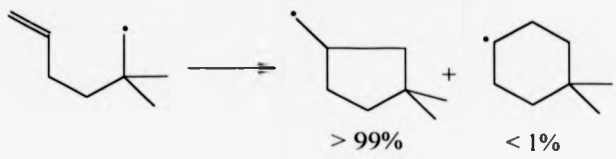


Scheme 1.2



Scheme 1.3

Beckwith also found that the 2,2-dimethylhex-5-enyl radical cyclised more rapidly and with higher regioselectivity than the parent 5-hexenyl radical,[11] (Scheme 1.4). In fact none of the 6-membered ring product was obtained at all.



Scheme 1.4

The rate enhancement (the rate constant *k* for ring closure of the 2,2-dimethylhex-5-enyl radical is almost ten times larger than that for the unsubstituted analogue) is attributable to the Thorpe-Ingold or '*gem*-dialkyl' effect.[16,17] The explanation put forward by Allinger and Zalkow[16] is that the two methyl substituents cause extra *gauche* interactions in the ground state which are partly relieved when the cyclic transition state is attained. In effect, the energy of the ground state has been raised relative to the transition state.

Mono-substituents at the C-2, C-3 and C-4 positions also enhance the rate of 1,5-ring closure but to a lesser extent. The trisubstituted 2,2,5-trimethylhex-5-enyl radical, gives similar quantities of five-and six-membered cyclic products. The '*gem*-dialkyl' substituents have enhanced both rates but 1,5 closure to a greater extent.

Substitutions of oxygen or nitrogen for C-3 are powerfully accelerating because they provide better orbital overlap in the 5-*exo* transition state.[9]

1.4.1.2 Stereoselectivity

The stereoselectivity of substituted hex-5-enyl radicals has been studied by Beckwith and experimental results usually follow the guidelines he put forward.[18] The Beckwith model (Figure 1.3)[9] represents the lowest energy transition state as a chair-like transition state for 5-*exo* cyclisation. Major products are predicted by placing a chain substituent in an equatorial-like orientation (Figure 3). Thus, 3-substituted hexenyl radicals give *cis* products, and 2- and 4-substituted radicals give *trans* products predominantly.

Figure 1.3 - The Beckwith model for stereoselectivity of hex-5-enyl radical cyclisations

Beckwith also proposed that since the difference in energy between the two conformers of a cyclic transition state will reflect the conformational preference of the substituent, the stereoselectivity of the ring closure should be most pronounced when the substituent is bulky.

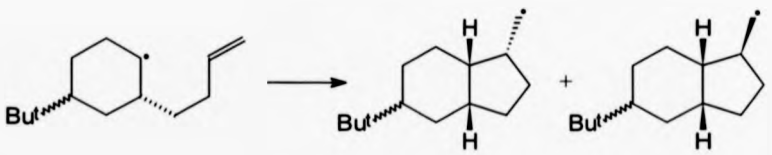
The sp^2 hybridized C-1 substituted radicals tend to give *cis* stereochemistry with small alkyl substituents but there is speculation as to the reason for this preference.

With bulky substituents however, steric factors take over and the trans product predominates.

Houk and Spellmeyer[14] advanced these proposals and proposed that the minor diastereomeric product may arise not only from the 5-*exo* chair with an axial substituent but also from the 5-*exo* boat.

1.4.2 Fused rings and tandem cyclisations

Trans-fused bicyclic products of medium sized rings (*e.g.* 5,5; 5,6; 6,6) have a high strain energy (the orbital overlap to form a *trans* ring is extremely poor) so cyclisations onto a ring will generally give *cis*-fused products.[4,9]. This effect is not so pronounced for larger ring conformations. Scheme 1.5 shows an example where the stereochemistry of the methyl group is apparently controlled by the *t*-butyl group.[9]

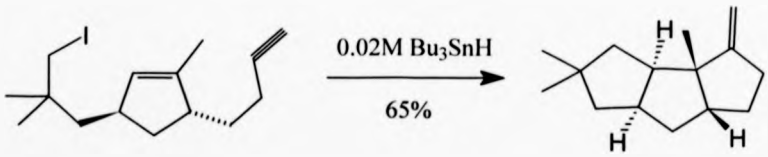


α-*t*-Bu	86	:	14
β-*t*-Bu	27	:	73

Scheme 1.5

The *t*-butyl group locks the conformation of the cyclohexane ring and also the conformation of the forming ring because the forming ring must be *cis*-fused. In each case the major diastereoisomer results from a chair-like transition state of the forming ring but, because the other possible chair is extremely high in energy it is likely that the minor products result from a boat-like transition state.

Tandem cyclisations are a convenient and popular route into polycyclic systems (e.g. Equation 1.4).[9] These transformations often enable complex structural frameworks to be produced from relatively simple radical precursors. The rules governing regioselectivity and stereoselectivity of normal radical cyclisations apply to tandem processes also.



Equation 1.4

1.4.3 Cyclisations to form different ring sizes

In general three- and four- membered ring radical cyclisation reactions are not synthetically useful because they are reversible.[1] When stabilised, larger rings can be formed more readily but 6-*exo* cyclisation of the hept-6-enyl radical is still more than one order of magnitude slower than 5-*exo* cyclisation of the hex-5-enyl radical. 6-*Exo*

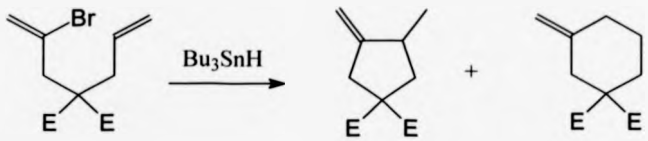
cyclisation is still favoured over 7-*endo* but the increased chain length now permits the formation of greater amounts of the *endo* product than in the hexenyl case.[3] As the size of the forming ring increases, the rate of ring closure begins to decrease for entropic reasons and so does the preference for *exo* cyclisation.

Another factor to consider with heptenyl radical cyclisations is that 1,5-allylic hydrogen transfer is another unimolecular reaction that competes with cyclisation. This intramolecular H-transfer is always thermodynamically favourable but is strongly disfavoured kinetically in both smaller rings (for stereoelectronic reasons) and larger rings (for entropic reasons).

1.4.4 Aryl and vinyl radical cyclisations

Vinyl[19] and aryl radicals[20] generated using the tin hydride method are extremely reactive and often provide excellent yields of cyclic products that contain useful functionality for subsequent transformations. However, because of the strength of sp^2 bonds to carbon, the only generally useful precursors of vinyl and aryl radicals in the standard tin hydride approach are bromides and iodides (Scheme 1.6). Note also that most vinyl radicals invert rapidly, and therefore the stereochemistry of the radical precursor is not important.[9] The regiochemical outcome of cyclisations of vinyl, aryl and acyl radicals often differ from those of alkyl radicals because the initially formed cyclic radicals can be interconverted via a ring expansion reaction that does not entail reversal of the original cyclisation.[9] This mechanism for the vinyl radical

rearrangement is shown in Scheme 1.7. With aryl radicals this rearrangement is usually called the neophyl rearrangement.



0.02M	75%	25%
1.7M	100%	0%

Scheme 1.6

Scheme 1.7

1.5 Methods for performing radical reactions

There are a variety of methods by which radical reactions can be conducted of which the tin hydride method is the most commonly used. As this is the only method which has been used in the research contained in this thesis it will be dealt with in the most detail. The other methods will be looked at only briefly. The selection of method is important as it will determine the fate of the intermediate radicals formed. Identical

radicals generated by different methods may have different lifetimes and, hence, provide different products.[3]

1.5.1 Chain reactions

1.5.1.1 General principles of chain reactions

The maintenance of a low concentration of radicals over the course of a reaction is generally desirable as free radicals are extremely reactive species that will react with themselves at rates approaching the diffusion controlled limit. Chain reactions are ideally suited to limit this side reaction as the radicals are generated in low concentrations throughout the reaction.

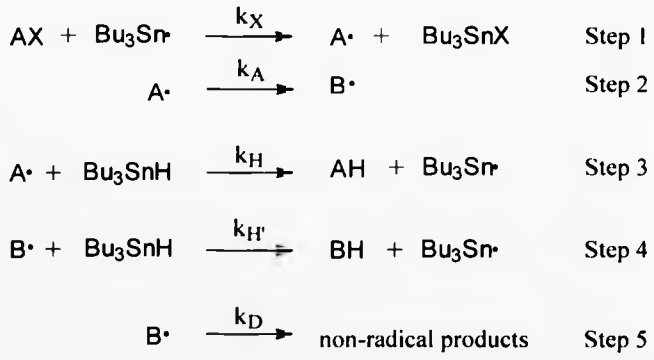
Chain reactions comprise of initiation, propagation and termination steps. Initiation steps generate radicals from non-radicals, while terminations steps generate nonradicals by removing radicals (*e.g.* dimerisation, disproportionation). All of the desired transformations in a chain occur in the propagation steps, which involve inter- or intra-molecular reactions of radicals with non-radicals.[8]

To be useful in the synthesis of carbon-carbon bonds, a given chain reaction must generate radicals site-selectively, and these radicals must have sufficient lifetime to react. This lifetime must be strictly controlled by the nature of the chain transfer step.[3] Radicals with too long a lifetime may undergo chain-termination steps.

Initiation can be accomplished by photochemical or redox reactions, but is most often accomplished by homolytic bond cleavage of a chemical initiator (promoted by heat or light) to give two radicals. The amount of initiator that is required depends on the efficiency of the chain (chain length) and on the temperature.

1.5.1.2 Tin hydride method

The tin hydride method generates radicals by abstraction of an atom or group from a pro-radical by the tri-*n*-butyltin radical and removes radicals by hydrogen transfer from Bu_3SnH.[8] (Scheme 1.8[3])



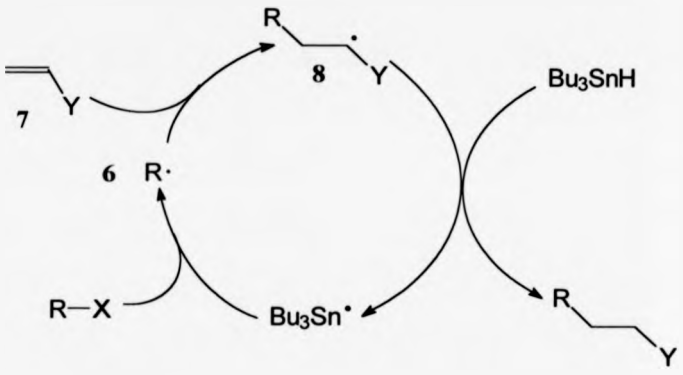
Scheme 1.8

The initial radical can react via a series of inter- or intramolecular reactions (step 2) to form a new radical. Steps 3 and 4 are the chain transfer steps and the rates of these reactions and the concentration of tin hydride controls the lifetimes of the radicals A• and B•. At high tin hydride concentrations only very rapid reactions can compete

against hydrogen abstraction and the reduction product will dominate. By lowering the tin hydride concentration the radicals have longer lifetimes and slower reactions can occur. If the dilution factor becomes too high however, the rate of step 4 could slow sufficiently to cause the chain to collapse.

Syringe pump techniques for addition of the tin hydride are often used to maintain a steady, low concentration of this reagent. Other techniques include the use of polymer-bound tin hydrides[21-26] and the generation of trialkyltin hydride *in situ* by the reaction of a catalytic amount of a tin halide with a standard hydride reducing agent ($NaBH_4$ or $NaCNBH_3$).[27-29]

The selectivity requirements for a successful reaction can be seen to greater effect in the intermolecular addition of radicals to alkenes (Scheme 1.9). Radical **6** must react with alkene **7** and adduct radical **8** must abstract a hydrogen atom from Bu_3SnH. If radicals **6** and **8** have the same selectivity then either polymerisation of alkenes or reduction of alkyl halides will occur. Both radicals are likely to have very similar rates of hydrogen abstraction so the selectivity difference must come in the addition to alkenes. Alkyl radicals react very well with electron deficient alkenes. The resulting adduct radical is much less nucleophilic and so will react much less rapidly with the original alkene, thus limiting polymerisation steps. For the tributyltin radical the competition between alkene addition and halogen abstraction from the alkyl halide is synthetically important.

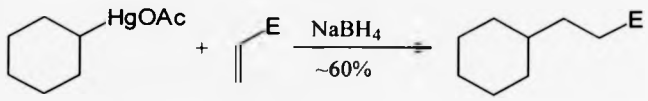


Scheme 1.9

Alkyl halides are not the only radical precursors that can be used in the tin hydride method. Beckwith and Pigou[30] devised a scale of reactivity of various substrates towards reduction by trialkyltin hydride. They found that the order of reactivity towards S_H2 attack by tributyltin radical is I > Br > PhSe > secondary and tertiary xanthate esters > tertiary nitro > Cl > *p*-CNC_6H_4S > PhS > *p*-MeC_6H_4S > MeS. For the least reactive alkyl chlorides and alkyl phenyl sulfides the rate of abstraction may not be sufficient to propagate a chain even with a rapid intermediate cyclisation. Iodides are often the precursors of choice because trialkyltin radicals abstract iodine from alkyl iodides at rates approaching the diffusion controlled limit. Substituents that stabilize radicals also facilitate atom transfer and less reactive precursors can be used. Hence, $XCH_2CO_2Et > RCH_2OCH_2X > RCO_2CH_2X > RCH_2X$.[30]

1.5.1.3 Other hydrides

Giese also introduced the use of mercury hydrides to conduct radical chain reactions.[31] The mercury hydride reagent is prepared *in situ* and the overall reaction is presented in Equation 1.5.[3]



E = -CN, -CO_2R, -COR etc.

Equation 1.5

Alkyl mercury salts (typically halides or acetates) are reduced with hydrogen donors, such as $NaBH_4$, to give alkylmercury hydrides. (Note that these hydrides have never been isolated but various stereochemical, polarographic and kinetic studies have provided evidence for their existence).[1] No thermal or photochemical initiation is necessary because the mercury hydrides start the chain by spontaneous decomposition.

The advantages of the mercury method over the tin method are the mild reaction conditions (room temperature, dichloromethane as solvent, no need to work under N_2), short reaction times (of the order of minutes) and unproblematic separation of mercury in the work-up.[31] The intermediate radicals compete for addition to an alkene and hydrogen abstraction from the mercury hydride. However, the Hg-H bond is weaker than the corresponding Sn-H bond and therefore mercury hydrides are

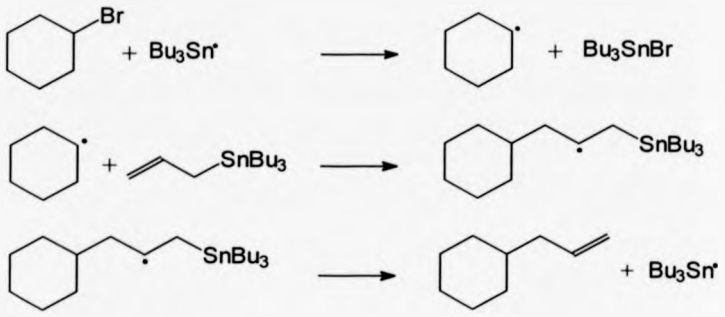
better hydrogen donors (by about one order of magnitude).[32] Thus, the mercury method can only be employed in syntheses involving reactive alkenes.

For less reactive alkenes, poorer hydrogen donors such as germanium hydride[33] or tris(trimethyl)silylsilane have been used. The Si-H bond is much stronger than the Ge-H or Sn-H bond, and hydrogen donation from simple alkyl silanes is too slow to maintain chains.[34] Tris(trimethylsilyl)silane (TTMSS) has a relatively weak Si-H bond and this enables it to take part in radical chain reactions as a hydrogen donor.[35,36] The reactions are still quite slow as a nucleophilic alkyl radical is extracting an electron rich hydrogen atom from silicon. Roberts improved this system by introducing thiols as polarity reversal catalysts.[37] The thiol donates a hydrogen atom to the alkyl radical and the resulting electrophilic thiyl radical can then propagate the chain by abstracting a hydrogen atom from the silane (triethylsilane can now be used).

1.5.1.4 The fragmentation reaction

In this method, the chain transfer agent is generated by a fragmentation rather than by hydrogen atom abstraction as in the tin hydride method. Instead of obtaining reduced products, substitution products are formed as an alkene is regenerated in the fragmentation step. The process makes use of the fact that relatively weak bonds such as C-Br, C-SnR and C-SR can fragment if they are located β to a radical. Allyl and vinyl stannanes have become the most popular reagents for this method.[38] Thus, an initiation event yields a carbon radical from the organic substrate. Addition to the

allylstannane, followed by β-scission of the trialkylstannyl radical gives the product and propagates the chain. An example from the work of Keck is shown in Scheme 1.10.

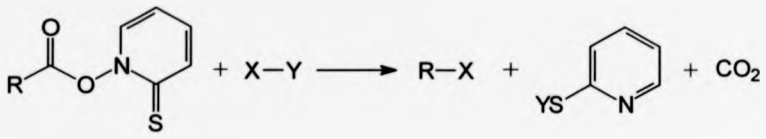


Scheme 1. 10

Although in this case the chain transfer agent is the same as in the tin hydride method there is an obvious advantage in that tin hydride is not required in the reaction. Hence, the lifetimes of intermediate radicals are not limited by the rate of hydrogen abstraction. This means that low concentrations are not required and a wide range of radical precursors can be used.

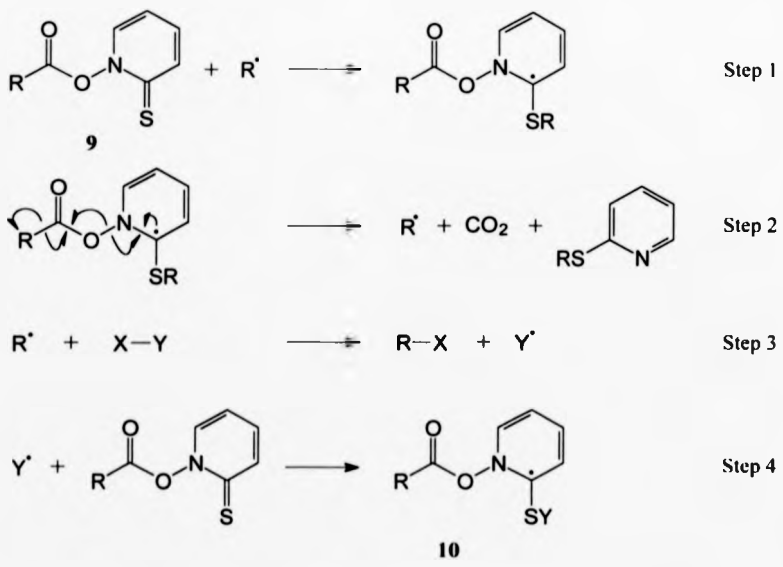
1.5.1.5 The thiohydroxamate method (Barton method)

Another non-reductive method developed by Barton involves the use of thiohydroxamate esters.[39-41] Reduction products can be obtained if desired but generally product radicals are trapped by addition to the thiohydroxamate and a thiopyridyl group results. The overall sequence is shown in Equation 1.6.



Equation 1.6

Mechanistic studies by Barton provided evidence for the reaction scheme shown in Scheme 1.11.[3] Initial decomposition of the thiohydroxamate ester **9** produces the alkyl radical R•. The alkyl radical R• must abstract an atom or group (X) from X-Y (step 3) at a rate more rapid than direct addition to the starting hydroxamate **9** (step 1). The resulting radical Y• must add to the precursor to produce **10** which then fragments to transfer the chain.

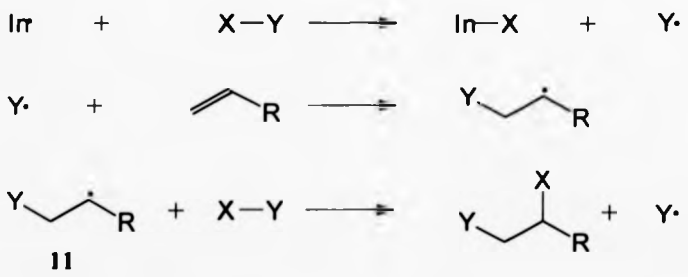


Scheme 1. 11

Whereas in the tin hydride method the lifetime of an intermediate radical is limited by the rate of hydrogen atom abstraction from the tin hydride, in the basic thiohydroxamate method, the lifetime of a radical is limited by the rate of addition to the starting thiohydroxamate.

1.5.1.6 The atom transfer method

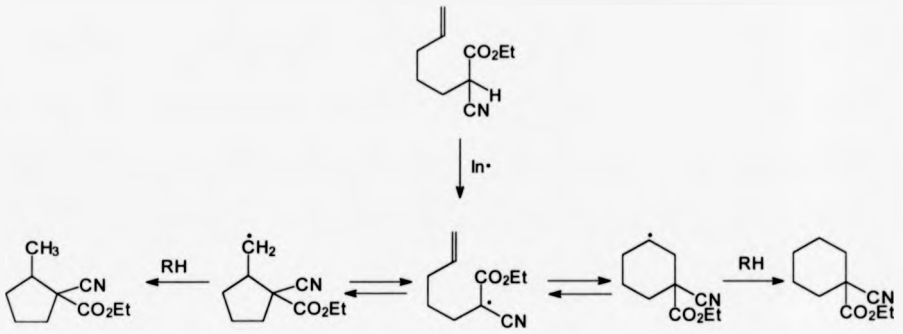
Developed by Kharasch the addition of a reagent X-Y across a carbon-carbon double (or triple) bond is an important reaction for organic free radicals.[42] A general mechanism for this addition reaction is outlined in Scheme 1.12.[3] For the atom transfer step to be favourable the generated radical (Y•) should be more stable than the adduct radical **11**.



Scheme 1. 12

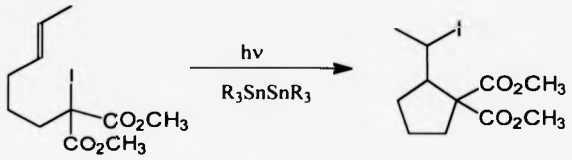
Both hydrogen and halogen atom transfer addition and cyclisation reactions are possible. Julia has studied hydrogen atom transfer cyclisations[43,44] and an example is

shown in Scheme 1.13.[45] The advantage of this method is that the thermodynamic product is formed.

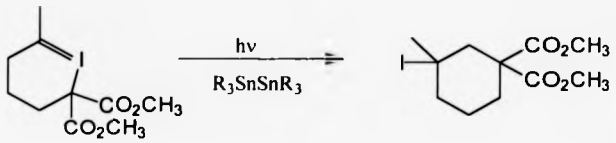


Scheme 1.13

Halogen atom transfer reactions are much more common. The method often allows initial and intermediate radicals to have long lifetimes with respect to chain transfer with final radicals having very short lifetimes prior to chain transfer. This situation cannot occur in the tin hydride method as all radicals have similar lifetimes with respect to chain transfer. "In fact, carbon-iodine bonds are such good iodine atom donors that rapid atom transfer can be expected to occur whenever an exothermic cyclisation or addition results in the formation of a less stabilised adduct radical then the initial radical."[3]



Equation 1.7



Equation 1.8

Halogen atom transfer radical cyclisations can also be carried out using transition metal complexes.[46]

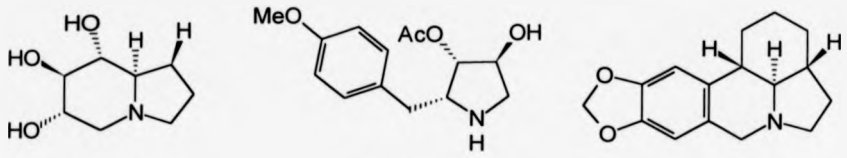
1.5.2 Other methods

Other methods for generating radicals which are less common include organocobalt group transfer,[47-49] and manganese(III) oxidation.[50,51]

1.6 Nitrogen radicals

1.6.1 Introduction

Progress in the use of nitrogen radicals in organic synthesis has been slower than with carbon radicals which is surprising in view of the many natural products containing nitrogen heterocyclic rings. (Figure 1.4)



Castonospermine Anisomycin Lycorane skeleton

Figure 1.4 - Nitrogen heterocyclic natural products

The electronic nature of nitrogen-centred radicals can be controlled by the reaction conditions and the radical precursor employed and is crucial to the mode of the reaction.[52] The electronic effects control the ability of the radical to undergo efficient intramolecular cyclisation or intermolecular addition reactions.

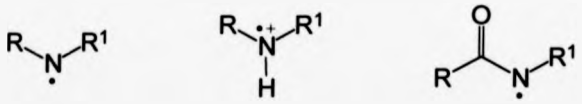
The main types of nitrogen-centred radicals are;

-Neutral aminyl radicals (amino radicals) - nucleophilic

-Aminium cation radicals (protonated aminyl radicals) - electrophilic

-Metal complexed aminyl radicals - electrophilic

-Amidyl radicals - electrophilic



aminyl aminium cation amidyl

Figure 1.5 - Examples of types of nitrogen-centred radicals

There are other examples including carbamyl, iminyl and urethanyl radicals which will be discussed briefly later.

1.6.2 Aminyl radicals

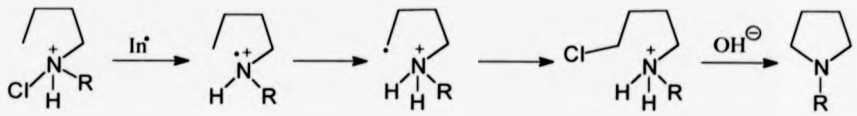
The types of reactions favoured by aminyl radicals can depend upon the extent to which the electron pair on the nitrogen is associated with electron-withdrawing or donating groups or with a proton or other acid (including transition metal ions). Neutral dialkylaminyl radicals are prone to dimerization and disproportionation leading to hydrazines, imines and amines.[53] In the presence of alkenes they show a strong tendency to abstract hydrogen in preference to addition reactions.[54] There is some evidence for the addition of dialkylamino radicals to aromatic rings, but not in the presence of non-aromatically bonded atoms.[55]

The nucleophilic nature of aminyl radicals has been verified with several rate studies.[56] The rate of cyclisation of radicals onto weakly nucleophilic alkenes at 50^0C is in the order: alkoxyl >> carbinyl > aminyl radicals.

1.6.3 Aminium cation radicals

Homolytic decomposition of *N*-chlorodialkylamines in acidic media leads to generation of protonated aminyl radicals, which behave very differently from neutral species.[55] The positive charge eliminates the tendency to dimerize or disproportionate, and the protonated aminyl radicals will now add efficiently to many

types of unsaturated hydrocarbons and arenes in preference to abstracting allylic or benzylic hydrogen atoms. Aminium cation radicals will also rearrange readily *via* internal hydrogen atom abstraction in the Hofmann-Löffler-Freytag (HLF) reaction (Scheme 1.14).[57] Note that although this rearrangement is faster than intermolecular additions it does not compete with 5-*exo* cyclisation.



Scheme 1.14

1.6.4 Aminyl radicals complexed to metal ions

The decomposition of *N*-chloroamines catalyzed by reducing metal salts in neutral solution generates aminyl radicals complexed to metal ions.[55] As in the case of protonation, complexation is presumed to take place via the lone pair of electrons of the aminyl radicals thereby increasing their electrophilic character. Complexed aminyl radicals tend to be intermediate in reactivity between that of neutral and protonated species. Like neutral aminyl radicals they do not undergo Hofmann-Löffler-Freytag reactions or selective intermolecular abstractions but, like protonated species, complexed aminyl radicals do not dimerize or disproportionate. They add efficiently to dienes, acetylenes, and alkenes. The mild experimental conditions required for generation of complexed aminyl radicals can prevent undesired reactions

which is of particular interest for sensitive systems which could be decomposed by strong acids.[55] Note though that non-catalytic amounts of metal salts must be used.[58]

1.6.5 Methods of formation of aminyl and aminium cation radicals

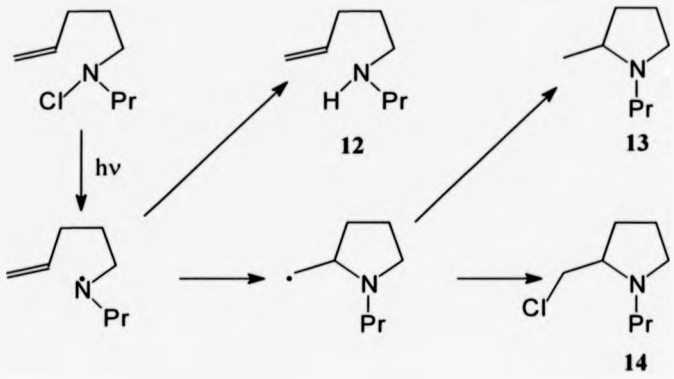
Aminyl radicals can be generated by photolysis or thermolysis of a tetrazene.[53] However, radicals produced in this manner do not undergo efficient radical chain reactions because high concentrations of radicals are obtained and good propagation steps are not usually available. Newcomb has shown that lithium dialkylamides can be used to generate aminyl radicals.[59] Chow and Perry[60] generated aminium radicals from photolysis of a nitrosamine.

1.6.5.1 *N*-Haloamines

The most widely used method for generating aminyl radicals involves *N*-chloramines and a number of publications have stressed the value of these homolytic reactions in synthetic organic chemistry.[55,58] Photolysis or thermolysis of *N*-chloramines in non-solvating media can give aminyl radicals and chlorine atoms. In the presence of reducing metal salts, a redox process generates an aminyl radical complexed to the metal salt, and a chloride ion.[55]

N-Chloroamines provide good precursors for generating aminyl radicals whereas chloroalkanes are poor radical precursors because the N-Cl bond is weaker than the C-Cl bond. If the aminyl radicals thus formed contain a suitably positioned double

bond in the carbon chain then cyclisation can occur. Stella[55] found that photolysis of *N*-chloro-*N*-propyl-4-pentenylamine in neutral solvents gave cyclisation products (Scheme 1.15).



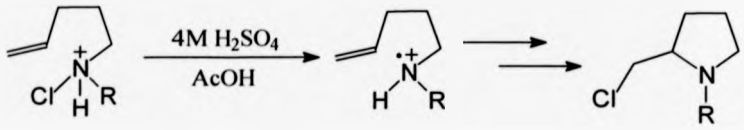
SH = non-protonating slovent which can act as a H-donor

Scheme 1.15

In aqueous acetic acid where *N*-chloroamines exist as free bases, 2-chloromethylpyrrolidine **14**, (70%) was the only product. The reactions of the acyclic and cyclic radicals depends only on the ability of the solvent (SH) to act as an H donor, the stronger this ability the higher the amount of reduced, **12,** and cyclic reduced, **13,** products formed and the less chlorinated cyclised product, **14**. Note that only the product from 5-*exo* cyclisation was formed.

The electrophilic nature of protonated aminyl radicals means that they undergo cyclisation reactions more readily than neutral aminyl radicals. Stella repeated the above reaction in acidic media (4M H_2SO_4 in AcOH) to form the protonated aminyl

radical. (Equation 1.9) Heat, UV light or metal ions all catalyzed the homolytic cyclisation with the best yields being obtained with the last two methods (e.g. $FeSO_4$ 25°C, 66% yield). Again, exclusive formation of the 5-membered ring suggests that the intramolecular cyclisation is kinetically controlled. Stella also notes that the product resulting from rearrangement of a protonated aminyl radical by a Hofmann-Löffler-Freytag reaction is not formed when intramolecular 1,5-addition to the double bond is possible.[55]



Equation 1.9

To compare metal-complexed aminyl radicals in this system the reaction was repeated generating the aminyl radicals in the presence of a variety of metal ions.[55] The best results were found using a solvent consisting of 50% aqueous acetic acid (which dissolves the metal salts and the *N*-chloramines) and titanium trichloride as the reducing agent (81% yield). Copper (I) and iron (II) salts are also suitable reducing agents; but in order to avoid reducing the aminyl radicals to amines they should be used in the presence of twice as much copper (II) or iron (III) salts.

1.6.5.1.1 Cyclisations to form different ring sizes

Stella found that aminyl radicals generated in both neutral and acidic media from *N*-chloro-*N*-propyl-3-butenylamine did not undergo cyclisation. Larger rings, however could be formed from *N*-chloro-*N*-propyl-5-hexenylamine. In neutral conditions low yields of both the six- (6%) and seven-membered rings (6%) were formed along with the reduced *N*-chloroamine (20%). Protonating media gave the six-membered product (2-chloromethylpiperidine) in 50% yield. Best results were obtained however using titanium trichloride in a non-protonating medium where 2-chloromethylpiperidine was produced in 72% yield. These conditions also allowed cyclisation of *N*-chloro-3-butenylamine to give 3-chloropyrrolidine in 13% yield.

1.6.5.2 Aminyl radicals from sulfenamides

Bowman has developed a procedure for generating aminyl radicals from sulfenamides. The sulfenamide precursors undergo S_H2 abstraction of the phenylsulfenyl group to generate the desired aminyl radicals. (Equation 1.10).[56] Beckwith and Tsanakatsidis have reported a similar procedure.[61]

Equation 1.10

Alkylsulfides are poor precursors due to a relatively strong C-S bond whereas alkylselenides with the weaker C-Se bond are often used in radical generation.[1,3,30] Sulfenamides and selenamides, have much weaker N-S or N-Se bonds and can therefore provide good precursors to aminyl radicals. The sulfenamide precursors were synthesized by reaction between amines and either phenylsulfenyl chloride or (phenylsulfenyl)phthalimide.[56]

In comparison with the work by Stella, the attempts by Bowman's group to cyclise *N*-butylpent-4-en-1-aminyl radicals using this method gave only low yields of cyclised products, even in the presence of low concentrations of tributylstannane in refluxing cyclohexane. This result, however, is in agreement with various reports in the literature of either a slow rate of cyclisation[62,63] of this and similar aminyl radicals or a reversible cyclisation.[64,65] There has also been speculation that the positive results observed by Stella could be due to the presence of protonated aminyl radicals formed due to hydrochloride produced in the reaction mixture.[66]

Maeda and Ingold[62] performed EPR experiments to study dialkylaminyl radicals. Interestingly they used an alternative method for generating the radicals involving direct hydrogen atom abstraction from the amine in cyclopropane by photochemically produced *t*-butoxy radicals. They confirmed abstraction of the amino hydrogen by generating the same radicals from photolysis of the corresponding tetrazenes. Despite observing *N*-propylpent-4-enylaminyl radicals in the EPR spectra, at no temperature was there any sign of the primary alkyl radical which would have resulted from

cyclisation. They concluded that the rate of intramolecular addition is immeasurably slow.

Experiments by Newcomb showed the cyclisation to be reversible[64] and indeed, that the rate of cyclisation is approximately equal to the rate of ring opening at room temperature. Newcomb claims that the results of cyclic products seen in their own work cannot be explained by such a slow cyclisation and that the cyclisation is much more rapid than Maeda and Ingold suggest but that the reversibility resulted in no EPR signal being seen for the cyclic radical.

However, in contrast to Newcomb's findings Maxwell reports results showing the cyclisation of the *N*-butyl-*N*-pent-4-enylaminyl radical to be slow and irreversible.[63] They also found that even low levels of bis(tributyltin)oxide had a large accelerating influence on the cyclisation. They argue that the bis(tributyltin)oxide could be complexing as a Lewis acid to produce a less nucleophilic nitrogen radical and thus facilitating cyclisation (as with protonated and metal complexed aminyls). Newcomb disputes these claims[65] and believes that the poor cyclisation results observed by Maxwell and co-workers were probably due to the highly reactive PhSeH being formed *in situ* by Bu_3SnH reduction of small amounts of impurities present. PhSeH is about 4500 times more reactive than Bu_3SnH towards aminyl radicals so reduction would be rapid.

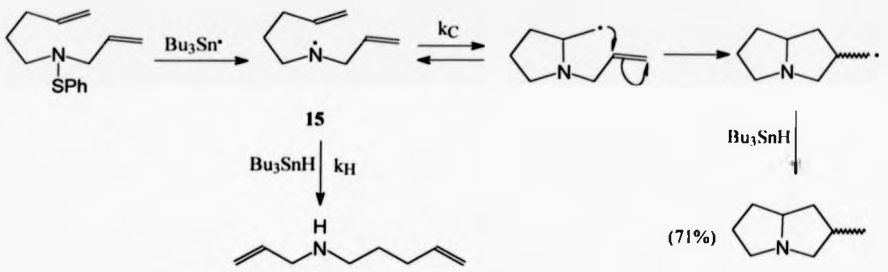
Bowman and co-workers looked at three alternatives to overcome the unfavourable cyclisation of aminyl radicals;

1) the use of aminyl radicals which cyclise rapidly,

2) aminyls which cyclise to yield stable benzylic radicals,

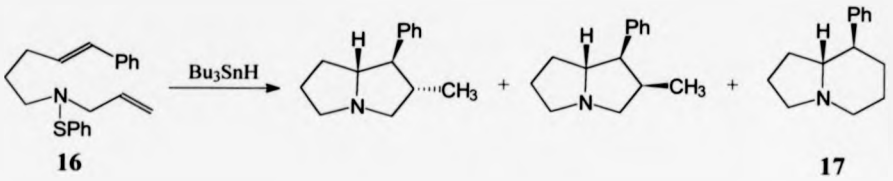
3) trapping the cyclised radicals in tandem reactions.

Hence, tandem cyclisations of aminyl radicals generated from sulfenamide precursors have been used for the synthesis of pyrrolizidines and other polycyclic nitrogen heterocycles.[67] Scheme 1.16 shows the simplest example, cyclisation of *N*-allylpent-4-enylaminyl radicals.



Scheme 1.16

The main competition was between trapping of the aminyl radical **15** by Bu_3SnH (reduction) and intramolecular addition of the aminyl radical. No monocyclisation products were detected. When *N*-allyl-*N*-(phenylsulfenyl)-5-phenylpent-4-enylamine, **16,** was used as the radical precursor no uncyclised material was seen. Ring opening of the first cyclisation is now slowed due to benzylic stabilisation of the cyclic carbon radical, so that no uncyclised amine is seen. Now, however the second cyclisation can become reversible and some of the thermodynamic product, **17** (6-membered ring indolizidine) can form. (Equation 1.11)

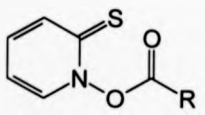


16 **17**

Equation 1.11

1.6.5.3 *N*-Hydroxypyridine-2-thione carbamates

Another important method for generating aminyl and aminium cation radicals has been developed by Newcomb utilising *N*-hydroxypyridine-2-thione carbamates, **19** as radical precursors.



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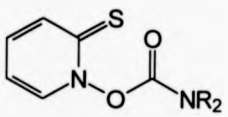
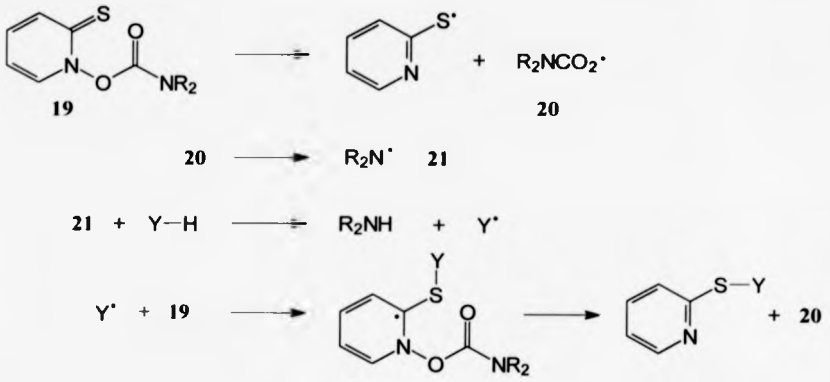


19

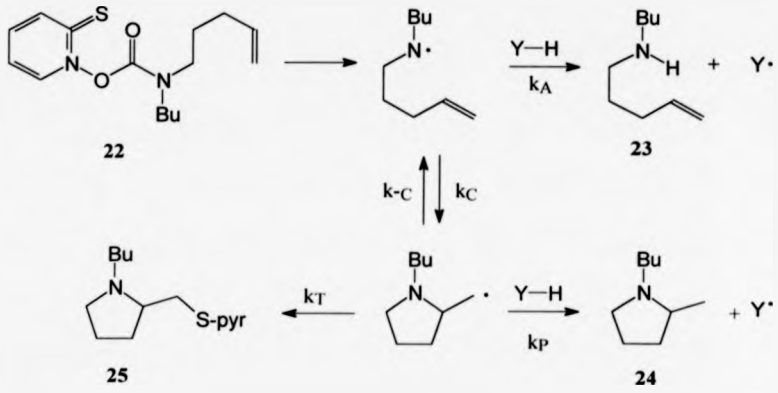
These compounds are related to Barton's *N*-hydroxypyridine-2-thione esters, **18** (Section 1.5.1.5). The acronym PTOC (**p**yridine-2-thione**o**xy**c**arbonyl) is often employed and will be used here. The PTOC carbamates, **19,** react in a radical chain sequence similar to that for reactions of PTOC esters, **18** (Scheme 1.17).[64] Photolytic initiation results in homolytic cleavage of the weak N-O bond. The carbamoyloxy radical **20,** thus formed decarboxylates rapidly to give the aminyl radical **21**. In the presence of a good hydrogen atom donor the aminyl radical can be reduced to an amine and the resulting radical Y adds to the PTOC carbamate precursor. Fragmentation followed by decarboxylation will propagate the chain.



Scheme 1.17

Alternatively, the aminyl radical can undergo further inter- or intramolecular reactions to produce an alkyl radical which can either be reduced by the H-donor or add to the PTOC carbamate giving a functionalised product.

Newcomb and co-workers initially studied the simple *N*-butylpent-5-enaminyl system, **22,** so the results could be compared with the work of others (Scheme 1.18).[68]



Scheme 1.18

With *t*-BuSH as the H-atom donor only **23** was formed as the aminyl radical was trapped before cyclisation occurred. With the less reactive H-atom donors, Bu_3SnH and Ph_3SiH, mixtures of acyclic, **23** and cyclic, **24,** products were obtained. The yields of cyclic products were still low however (17%, Bu_3SnH; 30% Ph_3SiH). This is in accord with the reversible nature of the cyclisation shown by Newcomb's experiments (see Section 1.6.5.2). However, by performing the reaction in the presence of weak organic acids, aminium cation radicals were formed which cyclised much more readily. In the presence of t-BuSH and CF_3CO_2H, pyrrolidine **24** was formed in 78% yield. Performing the reaction in the absence of a hydrogen atom donor gave the functionalised thiopyridyl-substituted pyrrolidine **25** in 84% yield.

Formation of the reduction product can be eliminated by taking advantage of the fact that aminyl and aminium cation radicals do not react with the PTOC carbamate precursors like the cyclic alkyl radicals. So, performing the reactions in the absence

of a hydrogen donor leads to increased yields of 'self-trapped' products with no acyclic amines.

Newcomb and co-workers have extended the use of aminium cation radicals to form pyrrolidines and other bicyclic systems.[69] Stereoselectivity studies have been done and also functionalization of the cyclic carbon radical by adding trapping agents to compete with addition to the PTOC carbamate precursors.[70]

1.7 Amidyl radicals

1.7.1 Introduction

Amidyl radicals can be thought to be intermediate in reactivity between the nucleophilic neutral aminyl radical and the electrophilic aminium cation radical due to the electron withdrawing ability of the carbonyl group. They have the advantage therefore, of increased electrophilicity without the need to generate them in acidic media. The ability to work in neutral conditions is important when there are other acid-sensitive groups in the compound.

E.S.R. studies have shown[71] that the amide radical is best described with location of the radical centred on N in a 2p orbital and intramolecular H-abstraction seems to take place preferentially with transfer of H to N rather than O.

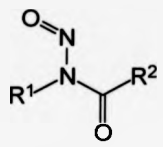
Saturated amidyl radicals can react by γ-hydrogen abstraction in a process similar to the Hofmann-Löffler-Freytag reaction of aminium cation radicals, and unsaturated systems undergo 4-*exo*, 5-*exo* and 6-*exo* cyclisations.[72]

1.7.2 Methods used to generate amidyl radicals

1.7.2.1 *N*-Halo and *N*-nitrosoamides

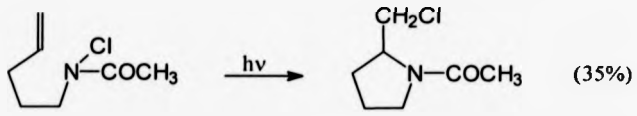
Originally amidyl radicals were generated by UV photolysis of *N*-chloroamides and *N*-nitrosoamides. In molecules with a suitably situated double bond the radicals were found to undergo efficient 5-*exo* cyclisation in neutral media to form substituted 2-pyrrolidinones and substituted pyrrolidine amides.

Chow and Lee[73] generated *N*-nitrosamides by nitrosation of *N*-alkenylamides with excess sodium nitrite in a mixture of acetic acid and acetic anhydride. *N*-nitrosamides, **26,** are characterised by their yellow to orange colour and are thermally stable only at or below room temperature. Their thermal stability is very much dependent on the structure of the parent amine (R^1) and on the acyl group (R^2). In general, the nitrosamides derived from primary, secondary and tertiary *N*-alkylamines show increasing instability whereas those derived from aromatic amines show a wide range of stability depending on the substituent group.

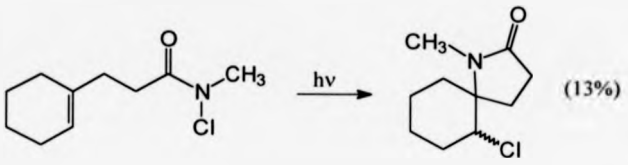


26

N-Haloamides are relatively strong oxidising agents that are not always easily prepared and handled, especially in the context of complex or fragile molecules. Their high reactivity makes it difficult sometimes to dissociate their ionic from their radical chemistry.[74] However, there has been some interesting work published in this area. Kuehne and Horne[71] synthesised *N*-chloroamides by the chlorination of alkenic *N*-monoalkylamide lithium derivatives with *N*-chlorosuccinimide. Photolysis led to bridged and unbridged *C*-chloro-*N*-alkylpyrrolidines and *C*-chloro-γ-lactams. Cyclisations onto both the alkyl (Equation 1.12) and acyl side chains (Equation 1.13) were observed. The strong preference for 5-*exo* cyclisation is seen in Equation 1.13 where none of the perhydroquinoline was detected.



Equation 1.12

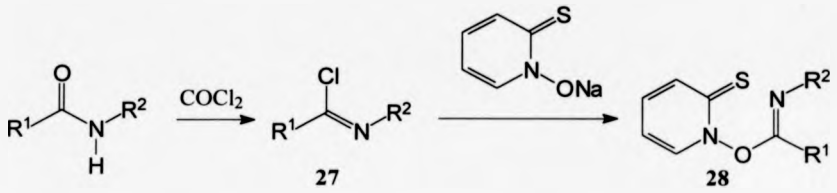


Equation 1.13

A further limitation in the reaction of *N*-halo and *N*-nitrosamides are that only products of halogen atom transfer or nitroso group transfer are obtained after a radical addition step. Also, competing 1,5 H-atom abstraction is promoted by the presence of halogen radicals formed on initiation, although this side reaction can be quenched by the presence of cuprous ions that scavenge the halogen radicals.[52]

1.7.2.2 *N*-Hydroxypyridine-2-thione-imidate esters

The Barton PTOC method for generating alkyl radical precursors[39-41] which, as described earlier (Section 1.6.5.3) was expanded by Newcomb to produce aminyl and aminium cation radicals also allows access to amidyl radicals through imidate ester derivatives,[72] **28**. The precursors can be easily prepared from secondary amides *via* stable imidoyl chlorides, **27** (Scheme 1.19).

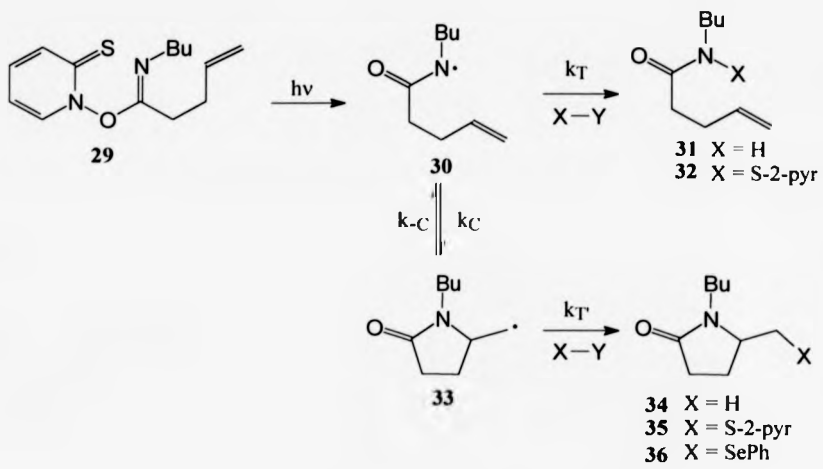


Scheme 1.19

The yellow imidate esters formed are found to be less stable than the related PTOC carbamates and PTOC esters. They are hydrolysed readily and the shelf life of the oils in the dark at room temperature is limited to a few days (although crystalline samples are more stable).

Esker and Newcomb have shown that amidyl radicals are formed directly by the action of light on the radical precursors. This is in contrast to Barton's PTOC esters which give acyloxyl radicals which then decarboxylate. The initiation step works due to the weakness of the N-O bond, but Newcomb found that in all the reactions studied the amidyl radicals reacted exclusively at nitrogen showing virtually instantaneous reorganisation to a nitrogen-centred amidyl radical.[72,75]

Newcomb and Esker generated *N*-butylpent-4-enylamidyl radicals, **30,** to study the cyclisation reaction (Scheme 1.20)



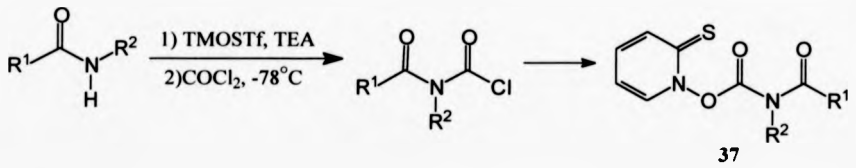
Scheme 1.20

In the absence of any radical trapping agent, radical **30** cyclised to cyclic radical **33** which subsequently reacted with precursor **29** to give the 2-pyridylthiosubstituted product **35** (72%) and another amidyl radical to propagate the chain. In the presence of radical trapping agents *t*-BuSH and PhSeSePh however, no 'self-trapped' product was observed and instead lactams **34** (95%) and **36** (76%) were formed by trapping of the cyclic radical by H-atom and SePh group transfer respectively. Even with high concentrations of *t*-BuSH (up to 0.7M) there was no evidence of trapping of the amidyl radical to give the amide **31**. With Bu_3SnH however, the amide was formed in competition to the lactam. This was expected as the more nucleophilic tin was found to react with electrophilic aminium cation radicals more rapidly than the thiol.[64] The 'self-trapping' reaction of the amidyl radical **30** by the PTOC imidate ester (to form **32**) also competes with the cyclisation although only to a minor extent. This is in contrast to the aminyl and aminium cation radicals which do not undergo addition to

their PTOC carbamate precursors. However, as intermolecular addition of amidyl radicals to alkenes is likely to be significantly slower than intramolecular cyclisation, self-trapping of the amidyl radical is expected to predominate in intermolecular addition reactions.

1.7.2.3 *N*-Acyl-*N*-alkyl PTOC carbamates

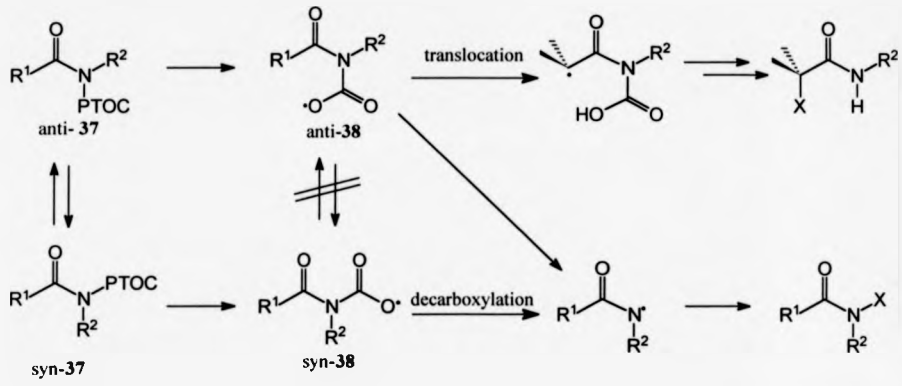
Newcomb has extended this methodology still further to show that amidyl radicals can also be generated from *N*-acyl-*N*-alkyl PTOC carbamates,[76] prepared as shown in Scheme 1.21.



37

Scheme 1.21

Visible light irradiation of precursor **37** or radical addition to the thione initially forms an *N*-acylcarbamoyloxy radical, **38,** analogous to the carbomoyloxy radical generated from *N*,*N*-dialkyl PTOC carbamates. The latter decarboxylate rapidly to generate an aminyl radical (the carbamoyloxy radical's lifetime is, in fact, too short for its detection). The decarboxylation of *N*-acylcarbamoyloxy radicals is, however, slower than 1,5 hydrogen atom abstraction of a suitably reactive α-hydrogen atom[76] (Scheme 1.22). Hence, amidyl or α-amide radicals are formed depending on whether decarboxylation or translocation occurs.



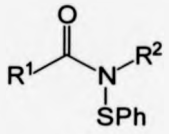
Scheme 1.22

Decarboxylation to generate amidyl radicals was found to be the dominant pathway when a bidentate Lewis acid, $MgBr_2$ was present. It appears that the Lewis acid was complexed by the carbonyl groups of the carbamoyloxy radical thus giving a syn conformation from which translocation was not possible.

The precursors are more stable than the PTOC imidate esters but are still generally prepared immediately before use.

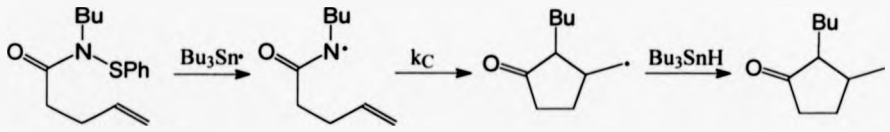
1.7.2.4 Amidyl radicals from *N*-(phenylsulfenyl)amides

Esker and Newcomb[77] have shown that *N*-(phenylsulfenyl)amides, **39,** can be prepared from secondary amides and that they are efficient precursors for Bu_3SnH mediated amidyl radical reactions.



39

Note that the -SPh functional group can be carried through a sequence of synthetic transformations. This stands in contrast to the halogen precursors which are generally introduced just prior to the radical reaction and may often be unstable (due to rapid solvolysis, for example). To test the efficiency of the radical precursors, *N*-butylpent-4-enylamidyl radicals, **31** were again generated and cyclised in a 5-*exo* manner (Scheme 1.23). Simple tandem cyclisations were also achieved (Scheme 1.24), **40** gave 7-methyl-2-pyrrolizidinone **41** in 95% isolated yield as a 3:1 mixture of diastereoisomers.



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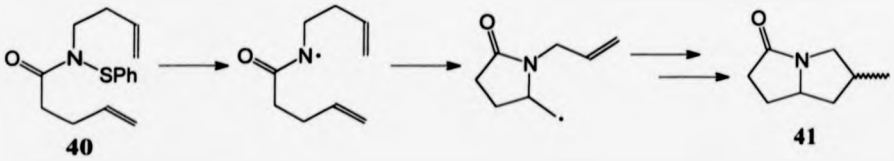
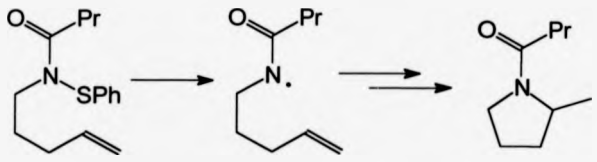
Scheme 1.23



40 **41**

Scheme 1.24

In order to compare the efficiency of cyclisation of the amidyl radicals onto the acyl and alkyl side chains kinetic studies were performed on radical **31** (Scheme 1.23) and the corresponding radical **42** (Scheme 1.25).



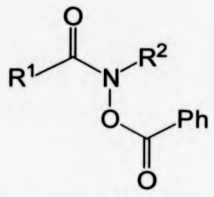
42

Scheme 1.25

Assuming that the rate constants for tin hydride trapping of both secondary amidyl radicals **31** and **42** are approximately equal they found that cyclisation onto the acyl side chain was about four times faster than the corresponding 5-*exo* cyclisation onto the alkyl side chain.

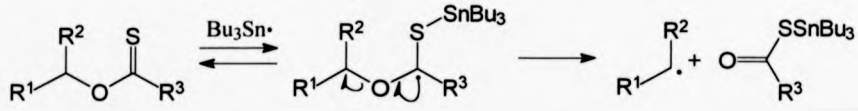
1.7.2.5 *O*-Benzoyl hydroxamic acid derivatives

Zard[74] has recently shown that amidyl radicals can be formed by the cleavage of *O*-benzoyl hydroxamic acid derivatives, **43**.



43

The cleavage of ordinary esters with tributylstannane was described some time ago by Khoo and Lee[78] but it has limited applicability as a method of radical deoxygenation. The Barton-McCombie reaction[79] where the carbonyl oxygen is replaced by a sulphur atom works much better (Scheme 1.26).

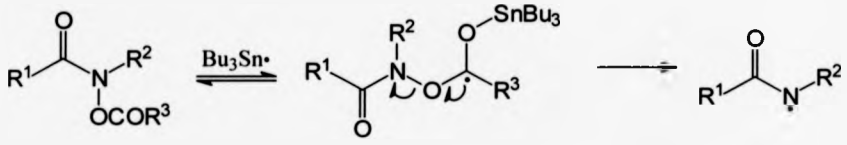


Scheme 1.26

The driving force of the reaction is the energy gained by the transition from a C=S to a C=O double bond. Trialkyltin radicals are particularly suitable for this reaction because the Sn-S bond is very stable and trialkyltin hydrides are exceptionally good H-donors. Ordinary esters do not react as readily due to the much lower reactivity of a carbonyl group towards tin radicals as compared with a thiocarbonyl group. This causes the equilibrium to shift to the left resulting in a lower concentration of the intermediate adduct radical and a slower fragmentation rate and hence shorter chain

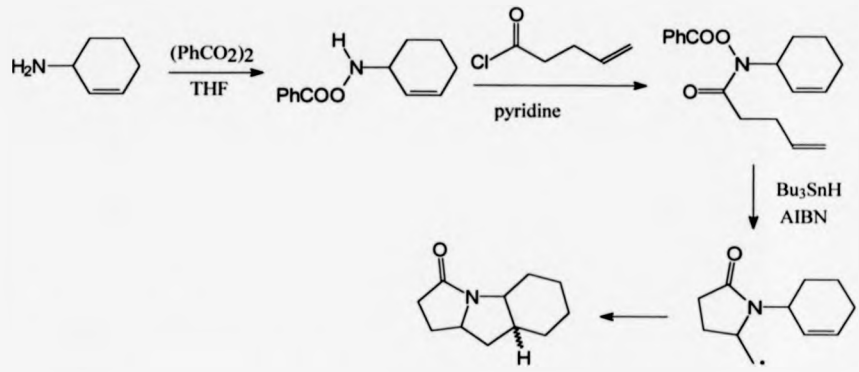
length. For the reaction to be practical the final radical must be stabilised (e.g. by resonance).

With hydroxamic acid derivatives however, the weakness of the N-O bond should strongly favour the fragmentation step which would compensate for an inefficient initial addition of stannyl radicals onto the carbonyl group (Scheme 1.27).



Scheme 1.27

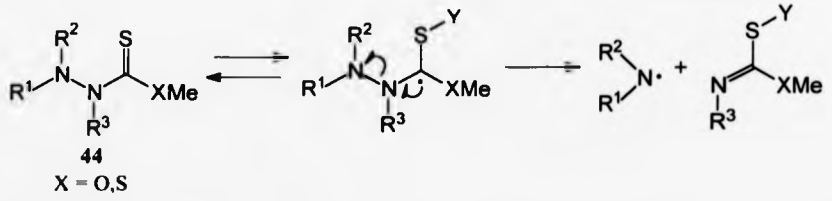
The precursors were prepared either by reaction of an alkenoyl chloride with a hydroxylamine followed by benzoylation, or oxidation of an allylic amine with dibenzoyl peroxide followed by reaction with a suitable acid chloride.[80] In both cases efficient cyclisations were observed with slow addition of tributyltin hydride and AIBN and an example of the latter is shown in Scheme 1.28.



Scheme 1.28

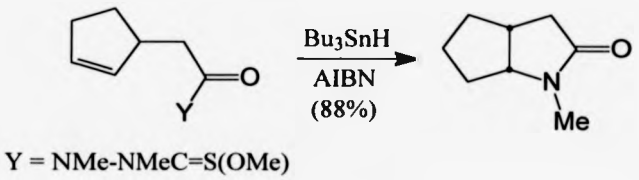
1.7.2.6 Thiocarbazone derivatives

Using a related methodology, Zard developed a new route into amidyl radicals utilising thiocarbazone derivatives, **44**. In this case the process relies on the weakness of a nitrogen-nitrogen bond while exploiting the high affinity of thiocarbonyl groups to tin. Again, fragmentation produces the desired nitrogen-centred radicals (Scheme 1.29)[81]



Scheme 1.29

Amidyl radical precursors were prepared by reacting the hydrazide **43** (R^1=H, R^2 = R^3 = Me, X=O) with the appropriate acid chloride. An example of a cyclisation reaction is shown in Scheme 1.30.

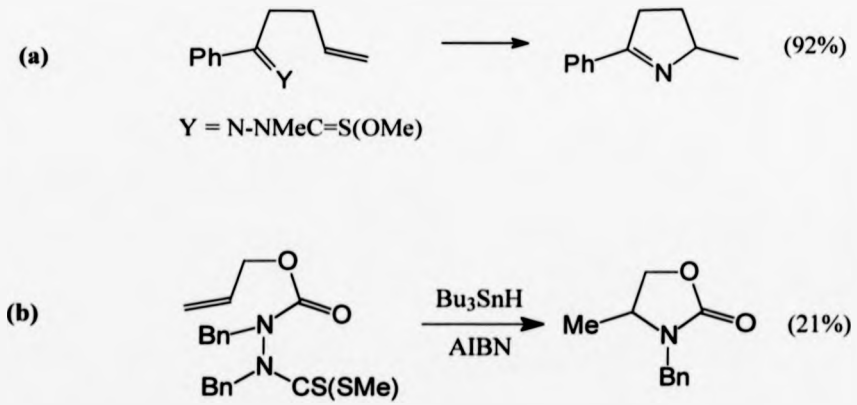


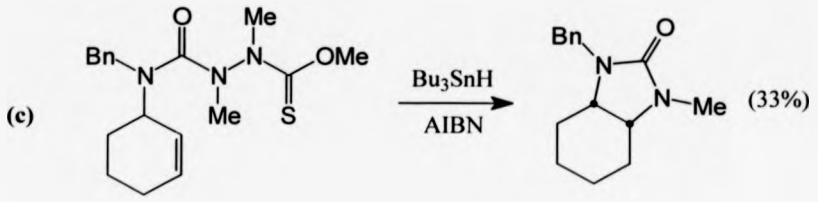
Y = NMe-NMeC=S(OMe)

Scheme 1.30

1.7.3 Other nitrogen radicals

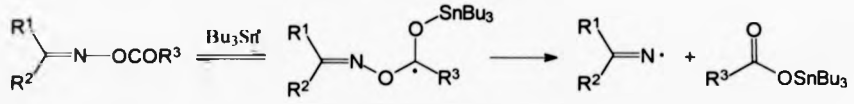
A modification of the thiocarbazone method (Section 1.7.2.6) allowed access to iminyl (a), carbamyl (b) and ureidyl radicals (c), (Scheme 1.31).





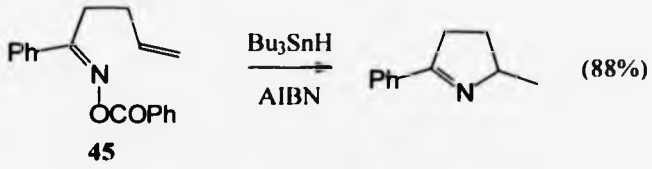
Scheme 1.31

Zard also showed that in the same way that hydroxamic acid derivatives can lead to amidyl radicals (Section 1.7.2.5), esters of oximes can give iminyl radicals.[80,82] Again, the weakness of the N-O bond favours the fragmentation step (Scheme 1.32).



Scheme 1.32

Oxime benzoates, **45** (found to be more reactive than the acetates), formed from the corresponding oximes gave excellent yields of cyclic products when treated with tributyltin hydride and AIBN (Scheme 1.33)



Scheme 1. 33

Zard also prepared and cyclised carbamyl radicals from *O*-benzoyl-*N*-hydroxyurethanes using this method.[80]

Chapter 2

Investigations into generating amidyl radicals

2.1 Introduction

In order to assess the suitability of amidyl radical cyclisations for the synthesis of nitrogen heterocyclic natural products we decided to investigate these types of cyclisation in some detail. In particular, it was felt that research into the stereochemical outcome of these cyclisations was important so that the factors which affected stereochemistry could be determined and controlled.

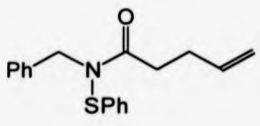
As mentioned earlier (Section 1.7.2) a number of methods have been developed to conduct amidyl radical cyclisations. However, both *N*-haloamides and *N*-nitrosamides are difficult to prepare and handle and give only products resulting from atom transfer, while Newcomb's PTOC imidate esters are relatively unstable and use of the PTOC carbamates leads to competition between the required decarboxylation and radical translocation pathways.

At the start of this research two new methods for the generation of amidyl radicals had recently been published; Newcomb's *N*-(phenylsulfenyl)amides and Zard's *O*-benzoyl hydroxamic acid derivatives. We chose to investigate both these methods further to determine their ease of use and generality.

2.2 *N*-(Phenylthio)amides

Esker and Newcomb[77] found that simple *N*-(phenylsulfenyl)amides could be prepared in excellent yield by reaction of a secondary amide with phenylsulfenyl chloride and triethylamine. However, with alkenylamides where electrophilic attack of the double bond by PhSCl is possible, the amide was first deprotonated with NaH. The resulting amide anion was then allowed to react with PhSCl at -78°C. Note that PhSSPh could not be used as the electrophile as at the higher temperatures that were required for electrophilic attack, α-(phenylsulfenyl)amides were produced, apparently from reactions of amide enolates.

We chose to investigate the preparation and reactions of the compound **46**. This target was chosen, because after cyclisation to give **47**, deprotection would furnish the pyrrolidinone **48**. The ability to facilitate such transformations would be useful if the heterocycle was to be used in further synthesis. Preparation and cyclisation was expected to be successful following the success of Newcomb's work with **49** as a radical precursor.



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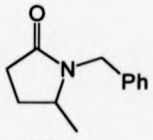

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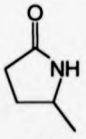

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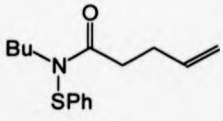

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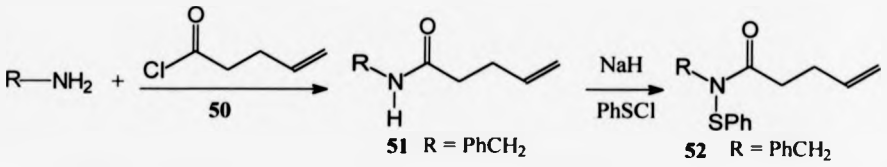
2.2.1 Preparation of precursors

We adopted two main approaches to forming the desired amidyl radical precursors (Method 1, Scheme 2.1 and Method 2, Scheme 2.3).

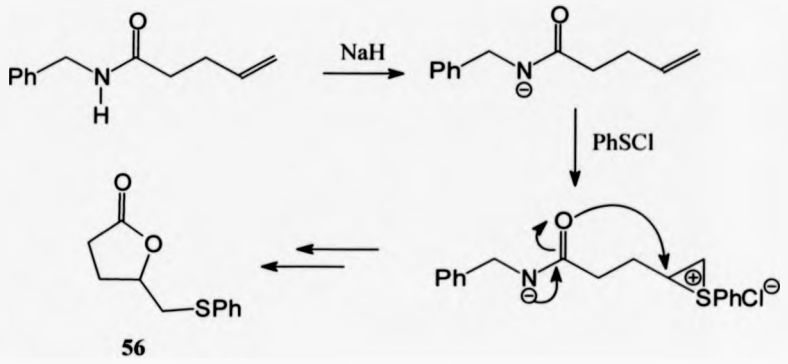
2.2.1.1 Method 1



Scheme 2.1

Initial studies followed the experimental details given by Newcomb.[77] Although the amide **51** could be formed easily (81%), addition of PhSCl to the anion of **51** proved unsuccessful. Various unidentified by-products (probably arising from electrophilic addition of SPh to the alkene) were formed. The reaction conditions were varied in many ways and finally, positive results were obtained. Hence, reaction of amide with NaH (1.1 eq.) at reflux for 5 hours followed by addition of PhSCl (1.0 eq.) at -78°C and stirring at this temperature for one hour gave the desired product **52** in a disappointing 29% yield (unreacted starting material also observed). However, another experiment [using NaH (1.5 eq.) and PhSCl (1.1 eq.) with all other conditions the same] gave **52** as the major product (26% isolated yield) but there was also a by-product formed with a similar Rf. Due to the by-product not being obtained

pure it was not fully analysed but ^{1}H-NMR of the mixture suggests that it could be the known cyclised product **56** formed by episulphonium ion mediated cyclisation. (Scheme 2.2).†



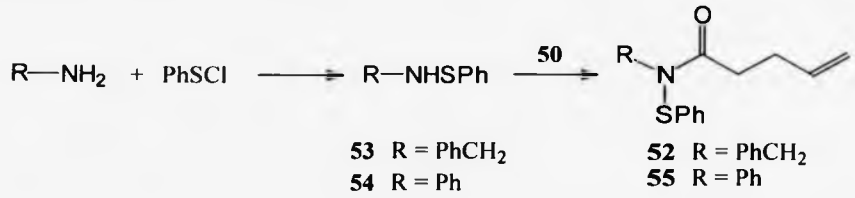
56

Scheme 2.2

In light of these disappointing results we repeated Newcomb's reported results using *n*-butyl as the R group on nitrogen. In contrast to Newcomb's findings our reactions produced none of the desired cyclisation precursor. Due to this failure we investigated an alternative route to the synthesis of the desired N-SPh compounds.

† Spectral details for **56**; ^{1}H NMR (250 MHz) δ_H 1.9-2.1 (1H, m, CH_2), 2.3-2.5 (1H, m, CH_2), 2.5-2.6 (2H, m, CH_2CO), 3.03 (1H, dd, J 13.9,7.7 Hz, CH_2S), 3.35 (1H, dd, J 13.9, 4.9 Hz, CH_2S), 4.58-4.67 (1H, m, CHO), 7.2-7.45 (5H, m, Ar).

2.2.1.2 Method 2

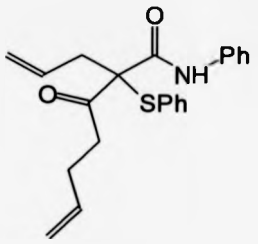


53 R = $PhCH_2$
54 R = Ph

52 R = $PhCH_2$
55 R = Ph

Scheme 2.3

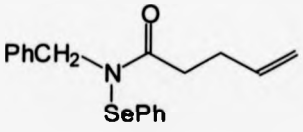
N-Benzylphenylsulfenamide, **53,** was prepared by reaction of benzylamine with PhSCl for 20 minutes in ether at room temperature under nitrogen. However, all attempts to react this sulfenamide with the acid chloride, **50,** to form **52** [e.g. refluxing with NaH for 5 hours before addition of **50**; stirring with Et_3N (2 eq.), adding **50** and heating to 50°C] proved unsuccessful. Likewise, the known *N*-phenylphenylsulfenamide, **54** (prepared using a procedure from Miura and Kinoshita[83]) failed to react with the acid chloride to form **55**. When phenylsulfenamide **54,** was reacted with 4-pentenoic acid in THF with three equivalents of DCC as a coupling agent no reaction occurred. However, when **54** was reacted with the acid chloride **50**, in dichloromethane with triethylamine and DMAP (as a catalyst) the main compound formed was assigned by NMR studies and mass spectroscopy to be **57** (7.2.6). At present it is unclear as to how this compound is formed.



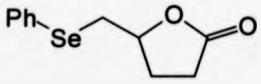
57

The failure of these reactions may be due to the reduced nucleophilicity of the nitrogen in the sulfenamides as compared to a simple amine due to the electron-withdrawing properties of the sulfur group.

Due to the poor results obtained with both Methods 1 and 2, attention was turned to preparing the N-SePh analogue. The N-Se bond is weaker than the N-S bond and so N-SePh precursors are expected to be much more reactive than the corresponding N-SPh compounds. Accordingly, an attempt to prepare **58** utilising Method 1 (Scheme 2.1) was made. Again however, the episelenium ion mediated cyclisation appeared to be the major pathway as only **59** was isolated (22%) from the reaction mixture.



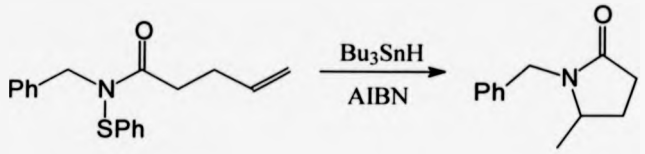
58



59

2.2.2 Cyclisation attempts

With adequate amounts of the precursor **52** in hand some attempts at generating an amidyl radical using tributyltin hydride and performing the 5-*exo* cyclisation were made (Scheme 2.4).



52

Scheme 2.4

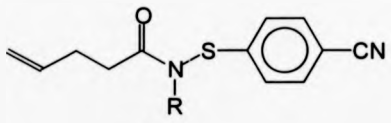
In the first attempt, **52**, (in degassed toluene under nitrogen), was reacted with a solution of Bu_3SnH (1.2 eq.) and AIBN (0.5 eq.), which was added in aliquots at 15 minute intervals over a two hour period at 65°C. No reaction was observed even when the temperature was allowed to rise up to reflux and with further additions of tin hydride and AIBN. It was thought that the lack of reaction may have been due to the N-S bond being stronger than first expected and so the experiment was repeated at a higher temperature in refluxing degassed xylene (140°C) but this was also unsuccessful.

There are a number of possible explanations for the lack of reactivity of the compound **52**. As mentioned previously, the phenylsulfenyl group is not readily abstracted by the trialkyltin radical and is usually only used in the formation of

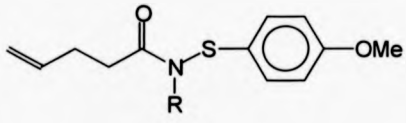
stabilised radicals. It may be that the stabilisation offered by the carbonyl group is not sufficient to make the N-SPh bond easily broken. Another problem may be that the chain length of the radical reaction is short and the chain was breaking down.[30]

2.2.3 Future work

Beckwith and Pigou[30] have found that the addition of a para activating group on the benzene ring of the -SPh group increased the reactivity of -SPh carbon radical precursors to attack by tributyltin radicals. Further studies could be done on **60** and **61** as these compounds are expected to cyclise more readily.



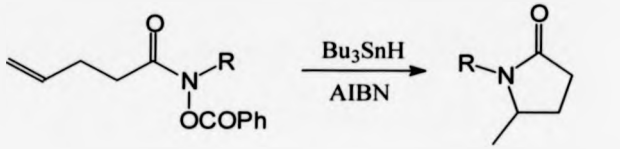
60



61

2.3 *O*-Benzoyl hydroxamic acid derivatives

Due to the obvious difficulties in preparing the desired sulfenamides we also undertook studies in assessing the application of the *O*-benzoyl hydroxamic acid method for generating amidyl radicals (Scheme 2.5).



62 R = ^{t}Bu
63 R = $PhCH_2$

64 R = $PhCH_2$

Scheme 2.5

2.3.1 Formation of precursors

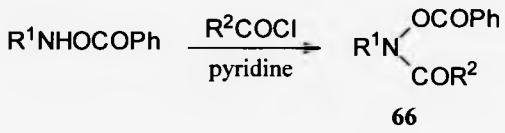
Alewood, Calder and Richardson[84] report a one-step synthesis of *O*-benzoyl-*N*-(*t*-butyl)hydroxylamine from dibenzoyl peroxide and *t*-butylamine involving nucleophilic displacement along the O-O linkage (Equation 2.1).

$$^tBuNH_2 + (PhCO_2)_2 \longrightarrow \underset{\mathbf{65}}{^tBuNHOCOPh} + PhCOOH$$

Equation 2.1

The above reaction requires an additional equivalent of alkylamine to trap the benzoic acid liberated. It is reported to be unsuitable for use with primary amines due to competitive formation of amide (RNHCOPh) produced by *in situ* transfer of the acyl moiety from **65** to the alkylamine. An adaptation of this method to include primary amines was reported by Grierson and Perkins[85] who precipitate the hydroxylamine derivative as the hydrochloride salt as it is formed. Yields of the hydrochloride salts were low however (*ca.* 10%). They then reacted the *O*-benzoyl-*N*-

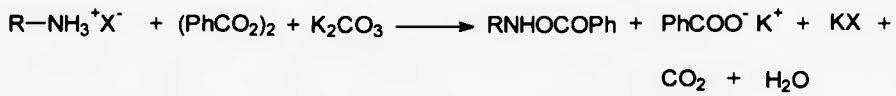
alkylhydroxylamine hydrochloride salts with an acid chloride and pyridine to give **66** (Scheme 2.6).



66

Scheme 2.6

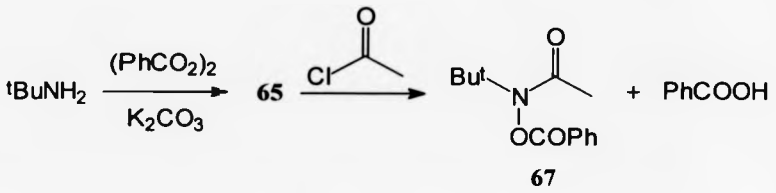
Biloski and Gamen[86] showed that the displacement reaction of secondary amines could be carried out in the presence of an appropriate auxiliary base which irreversibly removes the benzoic acid as it is formed and prevents the need for two equivalents of alkylamine, (examples they used were with Na_2HPO_4 or a cross-linked 4-vinyl pyridine copolymer). Later Psiorz and Zinner[87] reacted primary amines with dibenzoyl peroxide and used potassium carbonate as the auxiliary base and prepared *O*-benzoyl-*N*-(alkyl)hydroxylamines in good yields, (Equation 2.2).



Equation 2.2

We followed this latter procedure to form **65** (Scheme 2.7). These compounds were expected to be quite unstable so half of the oil produced was reacted immediately

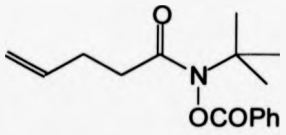
with acetyl chloride and pyridine while the other half was made into the hydrochloride salt for further analysis. Analysis showed the desired compound **67** to have been made and in good purity.



67

Scheme 2.7

Subsequently, the amidyl radical precursor **62** was prepared by a one-pot procedure from the starting *t*-butylamine in 32% yield after purification. A very similar procedure was reported by Milewska and Chimiak[88] where water is added along with the acid chloride.

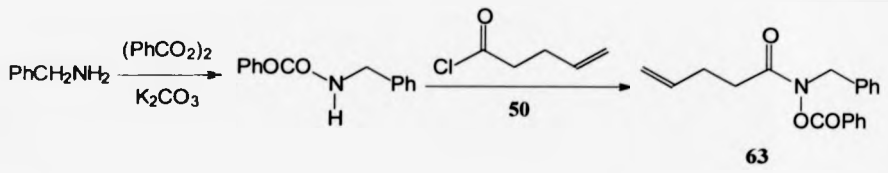


62

2.3.2 Cyclisation reactions

Unfortunately, attempts to cyclise **62** under the conditions reported by Zard for the generation of amidyl radicals failed. This could be due to the reactive centre being

too sterically hindered (bulky *t*-butyl group). In Zard's reported reaction less sterically demanding N-alkyl groups were utilised. To test this hypothesis we prepared the *N*-benzyl precursor **63** (28%) using the same procedure (Scheme 2.8).



63

Scheme 2.8

Heating the precursor **63** in degassed toluene with tributyltin hydride (1.1 eq.) and AIBN (0.1 eq.) (addition over 8 hours using a syringe pump) furnished the desired cyclised compound, **64**, the spectroscopic details of which matched those previously reported.

2.4 Conclusions

Two published methods for generating amidyl radicals have been investigated. Newcomb's *N*-phenylsulfenylamides proved difficult to prepare and an attempted cyclisation of *N*-benzyl-*N*-phenylsulfenylpent-4-enamide, **52**, failed. In contrast, Zard's *O*-benzoyl hydroxamic acid derivatives could be prepared in 'one-pot' reactions and *N*-benzoyl-*N*-benzylpent-4-enamide, **63**, furnished *N*-benzyl-5-methylpyrrolidin-2-one, **64** (not purified). Very recently, Phanstiel[89] has reported an improved synthesis of *O*-benzoyl protected hydroxamates utilising an aqueous

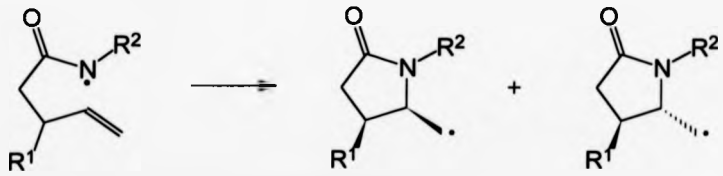
carbonate buffer/CH_2Cl_2 mixture. This greatly reduced the amount of amide by-product (RNHCOPh) and could prove to be a more convenient and high yielding method to produce the *O*-benzoyl hydroxamic acid derivatives used throughout this work.

Chapter 3

Investigations into the stereochemistry of 5-*exo* cyclisations of amidyl radicals

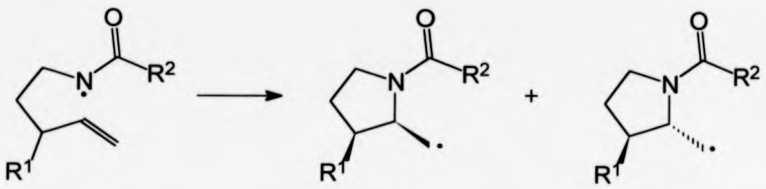
3.1 Introduction

In order for amidyl radical cyclisations to be synthetically useful in the formation of complex organic compounds information on the stereochemistry of these reactions is necessary. The rules governing the stereochemical outcome of 5-*exo* carbon radical cyclisations are well known[18] but the analogous nitrogen-centred radical cyclisations have been less well investigated. In particular, there is very little information on the stereochemistry of amidyl radical cyclisations. There are two possible cyclisation 'modes' for amidyl radicals, cyclisation onto the acyl side-chain (Scheme 3.1) and onto the alkyl side chain (Scheme 3.2).



cyclisation onto the acyl side chain

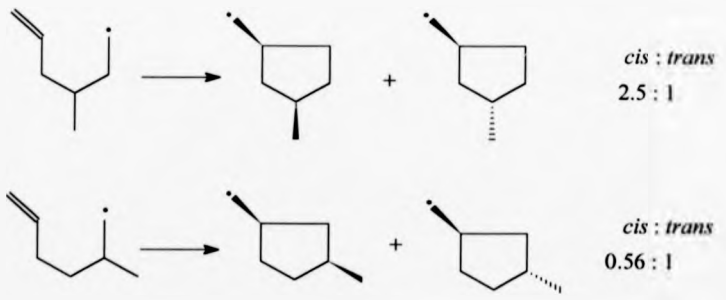
Scheme 3.1



cyclisation onto the alkyl side chain

Scheme 3.2

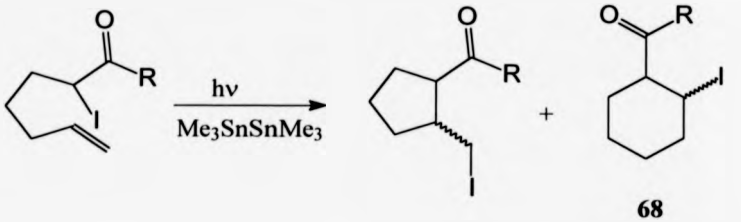
As mentioned earlier (Section 1.4.1.2), the stereochemical outcome of hex-5-enyl radical cyclisations can normally be predicted by application of the Beckwith model. Thus, 1- or 3-substituted hex-5-enyl radicals afford mainly *cis*-disubstituted products, whereas 2- or 4-substituted species give mainly *trans* products.[18] (Scheme 3.3)



Scheme 3.3

Carbon radicals with an α carbonyl group are more analogous to amidyl radicals than simple alkyl radicals and so are better suited to comparison. Curran and Chang[90] first investigated unsaturated α-iodo ketones with the carbonyl group outside (*exo* to) the forming ring and found that the presence of the carbonyl group lead to greater

amounts of the 6-*endo* product being formed than with simple alkyl radicals. They found that the use of tributyltin hydride and AIBN resulted only in decomposition but by irradiating in the presence of 10 mol% hexamethylditin, cyclic products could be formed, (Scheme 3.4).

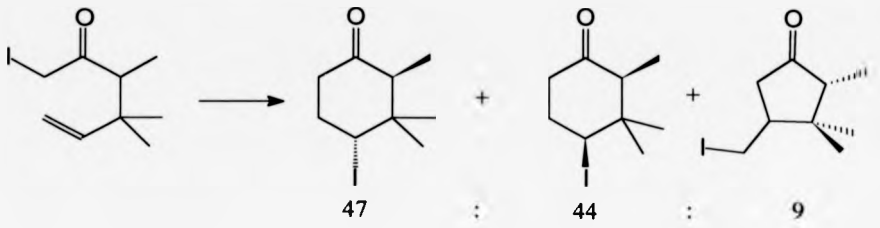


68

	cis : *trans*	**68** (*cis* : *trans*)
R = ^{t}Bu	20 : 54	26 (1 : 2.0)
R = Ph	21 : 54	25 (1 : 22)

Scheme 3.4

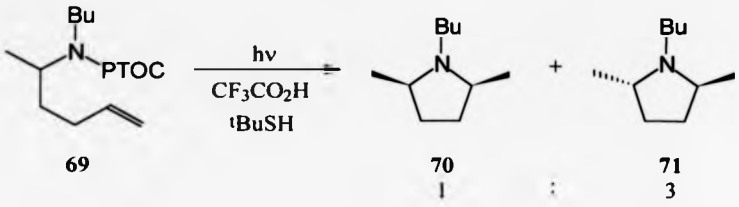
With the carbonyl group inside (*endo* to) the forming ring, 6-*endo* cyclisation actually became the dominant pathway, (Scheme 3.5) The cyclisations were performed as atom transfer reactions and the stereochemistry of the iodide trapped products was determined. Very little selectivity was observed in the 6-*endo* cyclisations but the minor 5-*exo* cyclisation gave a 3:1 ratio of unassigned stereoisomers.



Scheme 3.5

Clive and Cheshire report similar results and by using control experiments they demonstrated that the products from the cyclisations of *endo*-oriented ketones do form under kinetic control. Since most radical cyclisations proceed kinetically in an *exo* fashion to provide the smaller of the two rings, the ability of a carbonyl group inside the forming ring to promote *endo* cyclisation is synthetically important.

Investigations into the stereochemistry of aminyl and aminium cation radical cyclisations have been reported. Bowman looked at the stereoselectivity of tandem cyclisations of aminyl radicals derived from sulfenamides but these will be dealt with in the next chapter. Newcomb investigated the cyclisation of *N*-butyl-1-methylpent-4-enaminium cation radicals produced from the corresponding PTOC carbamates, (Scheme 3.6). (The aminyl analogue gave complex product mixtures).[69]



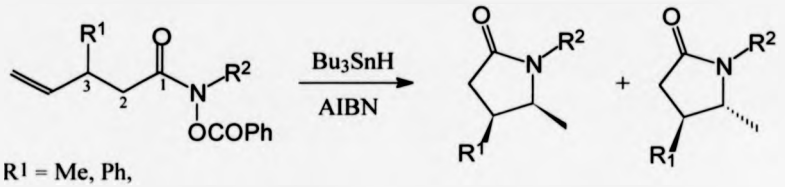
69 **70** : **71**
1 3

Scheme 3.6

Reaction of the PTOC carbamate precursor, **69,** in the presence of *t*-BuSH and CF_3CO_2H at 25°C gave pyrrolidines **70** and **71** in 72% yield by GC in a ratio of 1:3.[69] The *trans* stereoselectivity observed is predicted by the Beckwith[12] and Houk[14] transition state models.

3.2 Formation of precursors

Following the difficulties encountered in preparing and cyclising the *N*-phenylsulfenylamide precursors and the ease of preparation of the *O*-benzoyl hydroxamic acid derivatives, we chose the latter method to investigate the stereochemistry of 5-*exo* amidyl radical cyclisations. The work presented here involves only cyclisations onto the acyl side chain, the complementary reactions with the carbonyl group *exo* to the forming ring have been performed by another member of the group[91] and these results will be discussed briefly later.

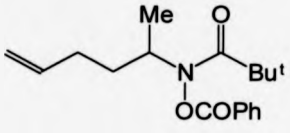


R^1 = Me, Ph,
R^2 = Me, *n*-Bu, CH_2Ph, $CH(CH_3)_2$

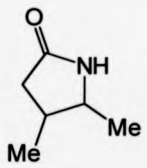
Scheme 3.7

The cyclisations of 3-substituted *N*-alkyl-*N*-benzoyloxypent-4-enamides were investigated with both methyl and phenyl substituents (R^1 = Me or Ph, providing a contrast in steric bulk of substituent) (Scheme 3.7). The corresponding 2-substituted compounds have been prepared and cyclised by another member of the group[92] and these results will also be compared later. A number of *N*-alkyl groups (R = methyl, benzyl, *n*-butyl and isopropyl) were chosen to investigate the influence of the nitrogen substituent upon the cyclisation. These substituents were chosen to provide a degree of steric variation. Ideally, the use of a range of primary, secondary and tertiary groups would provide this steric variety, however the lack of success when the *t*-butyl precursor, **62,** was used previously (Section 2.3.2) indicated that a tertiary group could not be used. The lack of reactivity of the *t*-butyl precursors was reinforced by other members of the group who observed no cyclisation on similar compounds, e.g. **74**.[91] Hence, the *N*-methyl group was chosen as a small, primary group, the *N*-*n*-butyl as a longer primary group, *N*-isopropyl as a secondary group and *N*-benzyl as a protecting group which could be easily removed. The use of this protecting group would be particularly useful if the stereochemistry of the cyclised products was difficult to determine by NMR because both *cis* and *trans* isomers of

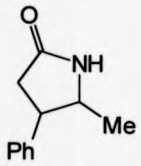
the de-benzylated versions, **75** and **76** have been reported previously in diastereomerically pure form.



74



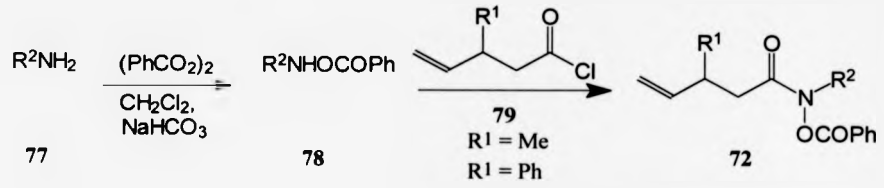
75



76

The precursors **72a-h** were prepared by one of two routes (Scheme 3.8). The first method (outlined earlier, section 2.3.1) was based on the procedures of Zinner[87] and Milewska[88] and involved a two-step, one-pot reaction starting from the corresponding alkylamine **77**. The second procedure utilised a two-step approach involving initial selective *N*-acylation of commercially available hydroxylamines **80** with acid chlorides **79**, followed by *O*-benzoylation of the resulting hydroxamic acids **81**. The yield shown for the precursors prepared by Method 2 is the combined yield for both steps.

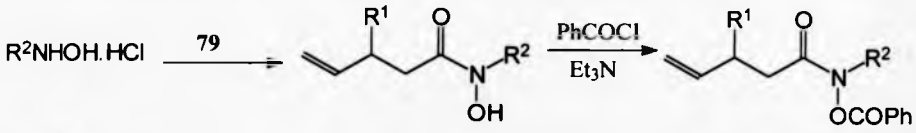
Method 1



77 78 72

72	R^1	R^2	Yield / %
72a	Me	*n*-Bu	53
72b	Me	$CH(CH_3)_2$	28
72e	Ph	*n*-Bu	50
72f	Ph	CH_2Ph	23

Method 2



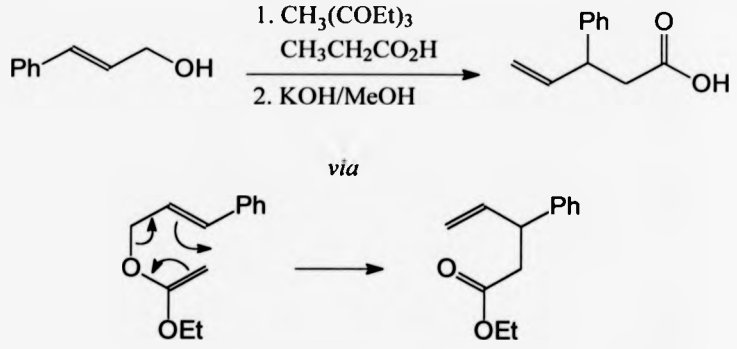
80 81 72

72	R^1	R^2	Yield / %
72c	Me	Me	27
72d	Me	CH_2Ph	50
72g	Ph	Me	75
72h	Ph	$CH(CH_3)_2$	81

Scheme 3.8

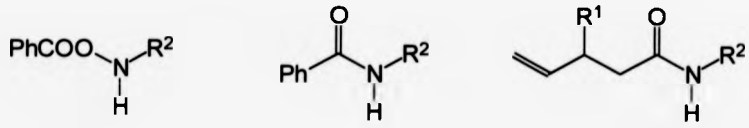
The substituted carboxylic acid chlorides (**79**, R^1 = Me, Ph) were prepared from the corresponding acids by refluxing with oxalyl chloride. The acids themselves could be easily prepared on a large scale by literature methods. Hence, reaction of crotyl and

cinnamyl alcohols with triethylorthoacetate furnished the methyl and the phenyl substituted pentenoic acids *via* an ortho-ester Claisen rearrangement (Scheme 3.9).[93]



Scheme 3.9

Although the first method (Method 1) was suitable for forming the *n*-butyl precursors [**72**a (R^1 = Me), 53%; **72**e (R^1 = Ph), 50%], lower yields were obtained for the *N*-benzyl [**72**f (R^1 = Ph), 23%] and *N*-isopropyl [**72**b (R^1 = Me), 28%] compounds. This was due in part to competitive formation of the amides **82** and **83** as by-products. The former is formed by transfer of the acyl moiety from the intermediate **78** to the starting amine[85] and **83** is due to competitive acylation of unreacted starting amine.



78 **82** **83**

To eliminate these by-products the two-step method (Method 2) was employed which generally gave much better yields of the desired precursors, **72,** and which required little purification. In each case the hydroxamic acid intermediates **81,** were used crude and without full characterisation. The *N*-Me, methyl substituted precursor **72c,** also gave low yields using this procedure due to the intermediate hydroxamic acid **81c,** being partially soluble in water and so lost at the work-up stage.

The intermediate hydroxamic acids, **81,** produced by this second method all gave broad signals in their NMR spectra, presumably due to the presence of rotamers. An example of the ^{1}H NMR spectrum of one of these intermediates is shown in Figure 3.1.

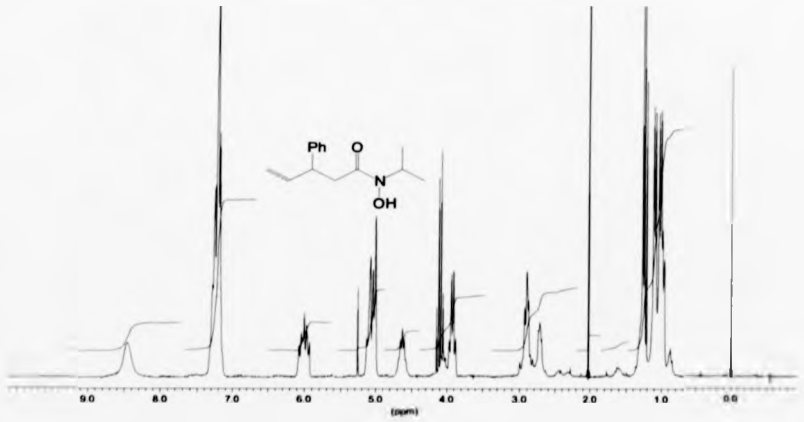


Figure 3.1- NMR Spectrum of *N*-hydroxy-*N*-isopropyl-3-phenylpent-4-enamide

There are two possible conformations for simple amides, (Figure 3.2). Conjugation between the nitrogen lone pair and the carbonyl leads to increased double bond character in the C-N bond and hence some degree of restricted rotation about this

bond at room temperature. This effect is observed in the NMR spectrum of *N,N*-dimethylformamide which shows two signals for the methyl groups at room temperature (Scheme 3.10). One methyl group is *cis* to the oxygen, the other is *trans*. At high temperature (~ 130^0C) only one signal is seen as rotation around the C-N bond becomes rapid on the NMR timescale.[94] For simple, secondary amides, generally only sharp resonances from conformation **84**, the most sterically favourable conformation, are observed in NMR spectra. The other conformation, **85**, is much higher in energy and so interconversion is very slow.

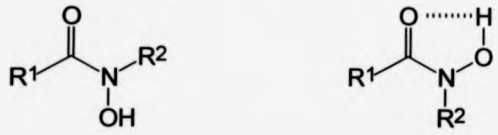
84 **85**

Figure 3.2 - Conformations of secondary amides

Scheme 3.10

For hydroxamic acids, there is now the possibility of hydrogen bonding in the less sterically favourable conformation, **87** (Figure 3.3). Consequently the energy difference between the two rotamers is much less and a mixture of both is usually observed. An interconversion which is slow on the NMR time scale results in broad resonances. Recording the NMR spectrum at low temperatures can 'freeze' the

rotation sufficiently for two resonances to be observed. Broad ^{1}H spectra were also observed for the hydroxamic acid intermediates to some of the 4-membered ring precursors (Chapter 5).



86 **87**

Figure 3.3 - Conformations of secondary hydroxamic acids

N-Benzoyloxy-*N*-isopropyl-3-phenylpent-4-enamide **72h,** also exhibited broad resonances in its ^{1}H NMR, particularly for the NCH proton (δ 4.8 ppm) suggesting a degree of restricted rotation in the final product also (Figure 3.4).

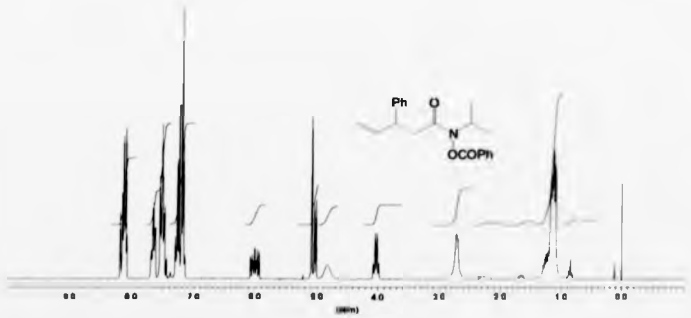


Figure 3.4 - NMR Spectrum of *N*-benzoyloxy-*N*-isopropyl-3-phenylpent-4-enamide

The ^{13}C NMR spectra of all the precursors showed broad signals for the NCO resonance and the carbon α to N in the N-R group. The carbonyl resonance is broad because of a long relaxation time. Once carbons are pushed into a higher energy state they return to the ground state by dissipating energy to protons. Carbonyls (or other tertiary carbons) generally relax more slowly as they are transferring their energy to β-protons or dispersing the energy by other mechanisms. In these compounds, the NCO carbonyl has only two β-protons and so relaxation is slow making the signal broad. Interestingly, for the OCOPh carbonyl, which has no β protons the signal is usually much sharper. This difference could again be due to the restricted rotation about the C-N bond, thereby making the NCO signal broader.

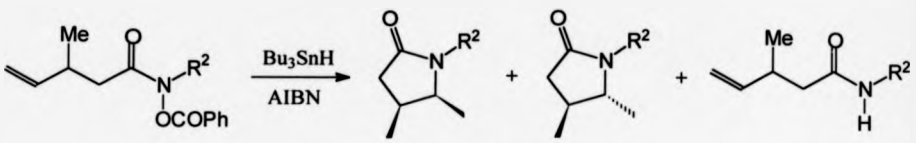
3.3 Cyclisation reactions

The cyclisations were conducted by slow addition (syringe pump over 8 hours) of a solution of tributyltin hydride (1.1 eq.) and AIBN (0.1 eq.) in toluene, to a refluxing solution of the precursor in toluene. In each reaction the initial concentration of precursor in toluene was 0.15 mmol/ml. The tin hydride and AIBN were added in an equivalent amount of toluene thereby doubling the initial volume. After refluxing for a further 12 hours, analysis by tlc showed the reactions to be not fully complete and in each case, an additional amount of tributyltin hydride (1.1 eq.) and AIBN (0.1 eq.) was added over another 8 hours. By maintaining the same concentration in each case direct comparisons can be made about the ratio of reduced and cyclised products formed and hence their relative rates for each N-R group combination.

After work-up, the majority of the tin residues were removed by partitioning the crude product mixtures between, firstly, acetonitrile and hexane and secondly, between acetonitrile and cyclohexane. Flash column chromatography was used to purify the mixtures further. Generally, the diastereoisomers formed could not be separated fully but in some cases a pure sample of the major isomer could be obtained after column chromatography.

3.3.1 Cyclisations of methyl substituted precursors

Table 3.1 shows the results of the cyclisations of the 3-Me substituted precursors. A combined yield for both diastereoisomers is reported because they could not be fully separated. The ratio of cyclised to reduced products was determined from the ^{1}H NMR spectra of the crude product (acetonitrile extracts) after partitioning to remove the excess tin residues. ^{1}H NMR spectra of the corresponding cyclohexane and hexane partitions were checked to ensure that no cyclised or reduced products had been taken up in these solvents. In all cases the hydrocarbon solvents were found to have removed only tin products from the mixture.



73 88

Compound number	R^2	Yield of **73**/%	Ratio of **73**:**88**	d.e./%
73a	*n*-Bu	55	a	10
73b	$CH(CH_3)_3$	42	7.4:1	11
73c	Me	47	17:1	17
73d	CH_2Ph	53	12:1	23

a negligible amount of reduced

Table 3.1 - Cyclisations of N-alkyl-3-methylpent-4-enamides

The results indicate that the nature of the R group has little effect on the yield or diastereoselectivity of the cyclised products, while the ratio of cyclised/reduced products is significantly altered. The yield is seen to decrease slightly with the bulky secondary R group **73b,** but this is a consequence of the poorer cyclised/reduced ratio. This could be due to the increased steric demand of the *N*-isopropyl substituent, resulting in a slower rate of cyclisation. The *N*-*n*-butyl group **73a,** gives the best cyclised to reduced ratio but the worst diastereoselectivity, while the *N*-benzyl group **73d,** gives a high cyclised to reduced ratio and shows the greatest diastereoselectivity. It should be noted that the diastereoselectivity is much poorer than for simple hex-5-enyl radical cyclisations and is not in fact great enough to be synthetically useful. This is probably due to the fact that the transition states for

cyclisation of the amidyl radicals is much flatter than for simple alkyl radicals. This will lead to poorer stereoselectivity due to a lower energy difference between the alternative transition states, (See Figure 3.6, later).

Comparison of the ^{1}H NMR spectra of each cyclised product showed that the major isomer was the same in each of the four cases studied. These isomers were assigned to be *trans* on the basis of nOe data and by comparison with data from authentic samples previously reported.

The nuclear Overhauser effect (nOe) is used as an aid to determine which protons (or groups of protons) in a molecule are in close proximity to each other. If two protons (H_a and H_b) are within 3.5 Angstroms of each other then irradiation of one can result in an enhancement of the signal for the other proton. This is because each proton contributes to the others spin-lattice relaxation process. Double irradiation of H_a stimulates absorption and emission processes for H_a and this stimulation is transferred through space to the relaxation mechanism of H_b. The increase in intensity of the H_b signal can be from 1-50% but the observable enhancement is usually less than 20%. The effect is normally viewed by obtaining nOe difference spectra. A conventional spectrum (no irradiation) is first recorded followed by one with irradiation of a specific proton or group of protons. Subtraction of the former from the latter gives the nOe difference spectrum with only the enhanced peaks remaining.[94,95]

An nOe experiment was performed on the major isomer of *N*-*n*-butyl-4,5-dimethylpyrrolidin-2-one, **73a**, the results of which are shown in Figure 3.5. Irradiating at the 5-Me resonance for the major isomer resulted in a 2% enhancement of the 4-H resonance. Likewise, irradiating the 4-Me protons enhanced the signal for the 5-H proton by 2%. This suggests a *trans* stereochemistry. Irradiating at the 5-H resonance for the major isomer gave no enhancement of the 4-H signal which again is in accord with a *trans* stereochemistry.

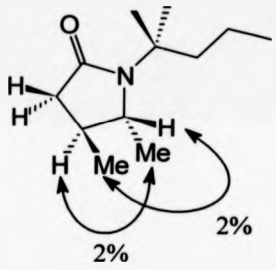
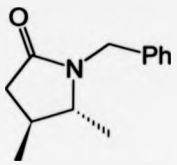


Figure 3.5 - nOe Data obtained for *N*-*n*-butyl-4,5-dimethylpyrrolidin-2-one

Trans-*N*-benzyl-4,5-dimethylpyrrolidin-2-one (*trans*-**73d**) has been reported earlier by Takahota *et al.*[96] and a comparison of their published spectral details and the δ-values obtained for both the major and minor isomers produced in our experiment is given in Table 3.2. The data published on the *trans* isomer fits most closely with the major isomer in our work (particularly the position of the methyl resonances) and so the major isomer was assigned as being *trans*.



Published δ-values for *trans* isomer (270 MHz)	δ-values for major isomer (400 MHz)	δ-values for minor isomer (400 MHz)
1.03 (3H, d, J 7.0)	1.01 (3H, d, J 6.6, 4-Me)	0.97 (3H, d, J 7.0, 4-Me)
1.14 (3H, d, J 6.4)	1.12 (3H, d, J 6.3, 5-Me)	1.00 (3H, d, J 6.7, 5-Me)
1.65-2.21 (2H, m)	1.90 (1H, m, 4-H) 2.04 (1H, dd, J 16.8, 7.7, 3-H)	2.13 (1H, ddd, J 16.0, 8.6, 0.9, 3-H) 2.39 (1H, m, 4-H)
2.41-2.71 (1H, m)	2.63 (1H, ddd, J 16.8, 8.4, 1.1, 3-H)	2.49 (1H, dd, J 16.0, 7.9, 3-H)
2.81-3.21 (1H, m)	3.00 (1H, q, J 6.2, 5-H)	3.47 (1H, q, J 6.7, 5-H)
3.93-4.94 (2H, AB q, J 15.2)	3.95 (1H, d, J 14.7, CH_2Ph) 4.94 (1H, d, J 14.7, CH_2Ph)	3.91 (1H, d, J 14.5, CH_2Ph) 4.97 (1H, d, J 14.5, CH_2Ph)

Table 3.2 - A comparison of ^{1}H NMR spectral details obtained with published results (J values given are in Hertz).

The *trans* stereoselectivity matches that predicted by the Beckwith model. Out of the four possible 'chair-like' transition states [(a-d), Figure 3.6], those with the substituent in an equatorial position [(a, and c) predicted to be of lower energy by

Beckwith] lead to the *trans* cyclised products. The minor *cis* products may arise from boat-like transition states as well as chair transition states with axial substituents, (Figure 3.6). The boat-like transition states (e-h), are usually assumed to be much higher in energy than the chair transition states (a-d), but the energy difference may be much less here for two reasons. Firstly, the carbonyl group flattens the transition state (c.f. with hex-5-enyl radical cyclisations) leading to a lower energy difference between alternative transition states. Secondly, an *E* amidyl radical geometry (the preferred conformation for secondary amides) places the N-R group pointing towards the double bond in the chair transition states (a and b), but away from it in the corresponding boat transition states (e and f). Placing the carbon substituent in an equatorial position in the boat-like transition state (e) leads to a *cis* stereochemistry.

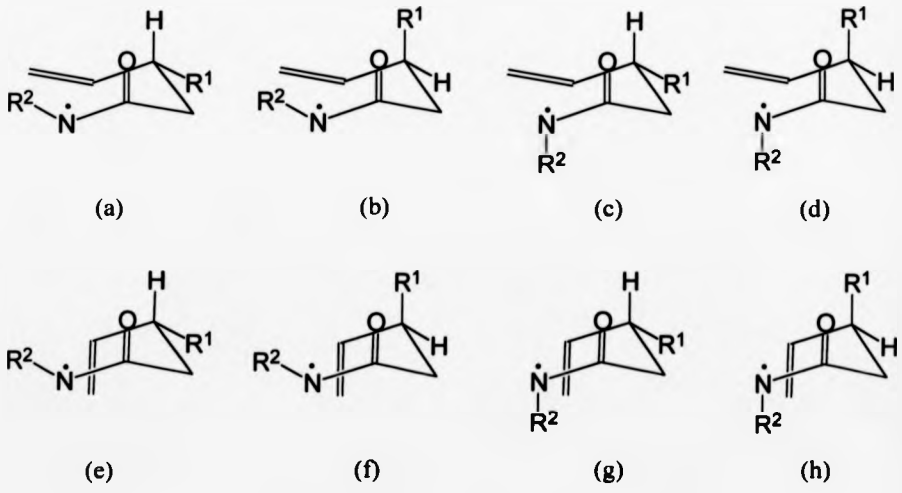
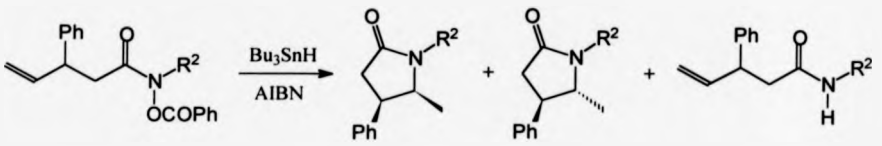


Figure 3.6 - Possible chair and boat transition states

3.3.2 Cyclisations of phenyl substituted precursors

Using the same cyclisation protocol as before we next turned our attention to the cyclisation of the phenyl substituted precursors, **73e-h**. As the reactions were run using the same concentrations as the previous methyl substituted precursors, results should be directly comparable (see Table 3.3).



73 **89**

Compound number	R^2	Yield of **73**/%	Ratio of **73**:**89**	d.e./%
73e	*n*-Bu	36 [a]	12:1	35
73f	CH_2Ph	17	2.3:1	37
73g	Me	22 [b]	3.5:1	43
73h	$CH(CH_3)_2$	46	3.5:1	45[c]

a 82% yield calculated from acetonitrile partition ^{1}H NMR.

b 14% yield isolated *trans* isomer.

c determined from isolated yield of **73**

Table 3.3- Cyclisations of N-alkyl-3-phenylpent-4-enamides

Table 3.3 shows the results of the cyclisations of the 3-phenyl substituted precursors. The amount of reduced product is greater than with the methyl substituted analogues

and hence the yields of cyclised products are lower. It may be that the phenyl group alters the conformation of the transition state such that the cyclisation is now slower and so under identical conditions less cyclisation will take place. The presence of the phenyl group could be making the 5-position more sterically hindered thereby slowing the rate of 5-*exo* cyclisation. With two phenyl groups present in the molecule, **73f,** the ratio of cyclised to reduced is particularly bad, with the secondary isopropyl group again giving a low ratio. The diastereoselectivity is however, much better than with the methyl substituted precursors **73a-d,** which is in accord with the larger R group having a greater preference to be in a pseudo-equatorial position. The N-*n*-butyl group again gives the best cyclised to reduced ratio with the worst diastereoselectivity.

Again, the major isomer was of the same sense for each cyclisation and identified as *trans*. Two further nOe NMR experiments were carried out to confirm the *trans* stereochemistry of the major isomer of **73g** (N-Me) and **73h** (N-*i*-Pr), (Figure 3.6). *N*-methyl-5-methyl-4-phenylpyrrolidin-2-one, **73g,** showed a 4% enhancement of the *ortho* phenyl protons with irradiation at 5-H (major isomer) and a 3% enhancement of the 4-H signal with irradiation at 5-Me (major isomer). Similar results were obtained by irradiating signals from the major isomer of *N*-isopropyl-5-methyl-4-phenylpyrrolidin-2-one, **73h** (Figure 3.7).

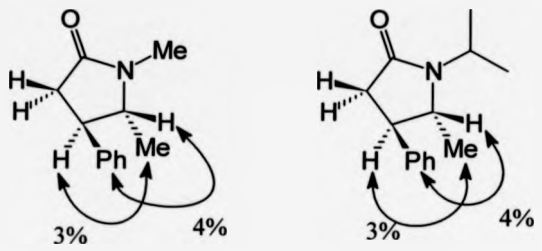
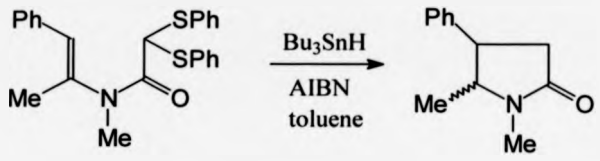


Figure 3. 7 - nOe Data obtained for *N*-methyl-5-methyl-4-phenylpyrrolidin-2-one and N-isopropyl-5-methyl-4-phenylpyrrolidin-2-one

Sato et al[97] prepared *N*-methyl-5-methyl-4-phenylpyrrolidin-2-one, **73g,** *via* a carbon radical cyclisation (Scheme 3.11). A mixture of *cis* and *trans* isomers were formed but they report the major isomer to be *cis*. A comparison of the spectral details published by Sato with those obtained in our research is given in Table 3.4. Comparison of the 5-Me, 5-H and 4-Me δ-values again shows our major isomer to be *trans*.



Scheme 3.11

Published δ-values for *cis* isomer (300MHz)	δ-values for major isomer (400Mhz)	δ-values for minor isomer (250MHz)
0.80 (3H, d, J 6.2, 5-Me)	1.24 (3H, d, J 6.3, 5-Me)	0.78 (3H, d, J 6.5, 5-Me)
2.66 (1H, ddd, J 16.6, 8.5, 0.7, 3-H)	2.53 (1H, ddd, J 16.8, 8.4, 0.7, 3-H)	2.64 (1H, ddd, J 15.9, 8.5, 0.6, 3-H)
2.77 (1H, dd, J 16.6, 9.0, 3-H)	2.81 (1H, dd, J 16.8, 8.8, 3-H)	2.76 (1H, ddd, J 15.9, 8.7, 0.6, 3-H)
2.86 (3H, s, N-Me)	2.84 (3H, s, N-Me)	2.85 (3H, s, N-Me)
3.70 (1H, ddd, J 9.0, 8.5, 7.5, 4-H)	2.95 (1H, m, 4-H)	3.63-3.73 (1H, m, 4-H)
3.87 (1H, dq, J 7.5, 6.6, 5-H)	3.53 (1H, ap qn, J 6.5, 5-H)	3.86 (1H, dq, J 7.5, 6.5, 5-H)
7.14-7.19 (2H, m, Ar) 7.21-7.37 (3H, m, Ar)	7.18-7.35 (5H, m, Ar)	7.14-7.37 (5H, m, Ar)

Table 3.4- A comparison of ^{1}H NMR spectral details obtained with published results (J values given are in Hertz)

3.4 Discussion and conclusions

A series of experiments have been performed in order to investigate the stereochemistry of amidyl radical cyclisations and the effect of the nitrogen substituent on the stereoselectivity. A preference for a *trans* stereochemistry was established although the diastereoselectivity was low with the nature of the *N*-alkyl group having little effect. The transition states for these amidyl radical cyclisations are likely to be much flatter than the hex-5-enyl analogues due to the carbonyl group and hence the diastereoselectivity is much lower (due to their being less energy difference between pseudo equatorial and axial positions). The low diastereselectivities may also be due to a lower energy difference between chair- and boat-like transition states. The increased diastereoselectivity for the phenyl substituents over the 3-methyl substituents is presumably a consequence of a greater energy difference between competing transition states. The *trans* stereoselectivity matches that predicted by the Beckwith model, assuming that a chair-like transition state with an equatorial carbon substituent is the lowest energy transition state. Molecular modelling work is necessary to provide more details on the nature of the transition states and explain the stereoselectivity.

A comparison of the results presented here with those obtained with 2-substituted precursors[92] is shown in Figure 3.8. A direct comparison cannot be made as different transition states are being dealt with, but as before, stereoselectivity is best with the 2-phenyl substituted compounds.

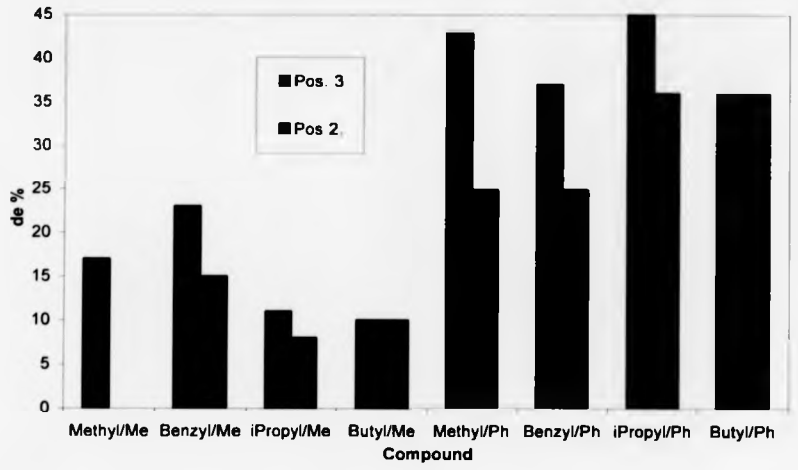
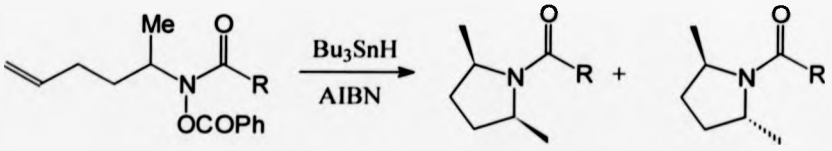


Figure 3.8 - Comparison of diastereoselectivities obtained with 2- and 3-substituted precursors

The research carried out with the carbonyl group *exo* to the forming ring[91] also showed a preference for the *trans* cyclised product and with a greater diastereoselectivity (Scheme 3.12) (R =Me, Bu; *trans*:*cis* 5:1).



Scheme 3.12

Interestingly, with R = OMe, no *cis* cyclised product was observed at all (15:1 ratio of *trans* cyclised product to reduction product). This result suggests that the electronic nature of the nitrogen may affect the stereoselectivity.

3.5 Future work

The reactions are currently performed in refluxing toluene, lower temperatures may improve the stereoselectivity of the reaction. In order to carry out a tin hydride mediated cyclisation at lower temperatures a triethylborane/oxygen mixture must be used to initiate the reaction (the reaction could then be performed at -78°C).[98] Molecular modelling could help to show whether the *trans* selectivity observed is expected and also which substituents would give the greatest stereoselectivity. By placing a hydroxy group as the alkyl chain substituent, Lewis acids could be used in the cyclisation reaction to form a bidentate chelate between the hydroxy group and the carbonyl (Figure 3.9). Locking the conformation in this way may lead to much greater diastereoselectivities. A range of Lewis acids could be tested in this way.

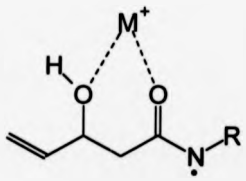


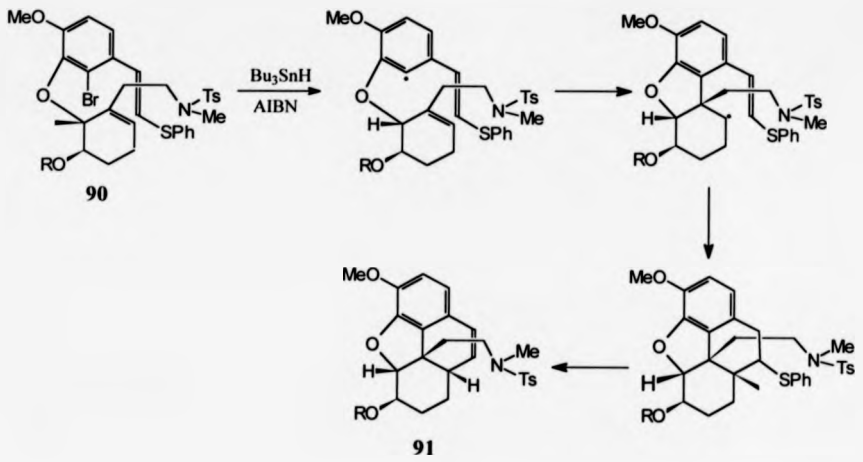
Figure 3.9 - Lewis acid complexation to 2-hydroxyamides

Chapter 4

Tandem amidyl radical cyclisations

4.1 Introduction

Tandem or sequential radical reactions enable complex frameworks to be formed from relatively simple precursors in one-pot reactions. In recent years, tandem radical cyclisations have been frequently used to synthesise polycyclic skeletons quickly and easily. Parker and Fokas[99] completed a formal total synthesis of morphine using a tandem radical cyclisation to form two of the 5 rings in the skeleton. (Scheme 4.1). Because of the preference for *cis* ring junctions the stereochemistry of two chiral centres were fixed by the tandem cyclisation. The second cyclisation occurs via a 6-*endo* closure rather than the more common 5-*exo* cyclisation due to the cyclised radical formed being in a stable benzylic position. On reaction with Bu_3SnH and AIBN **90** underwent tandem cyclisation followed by elimination of the S-phenyl radical to give **91** in 35% yield.



90 **91**

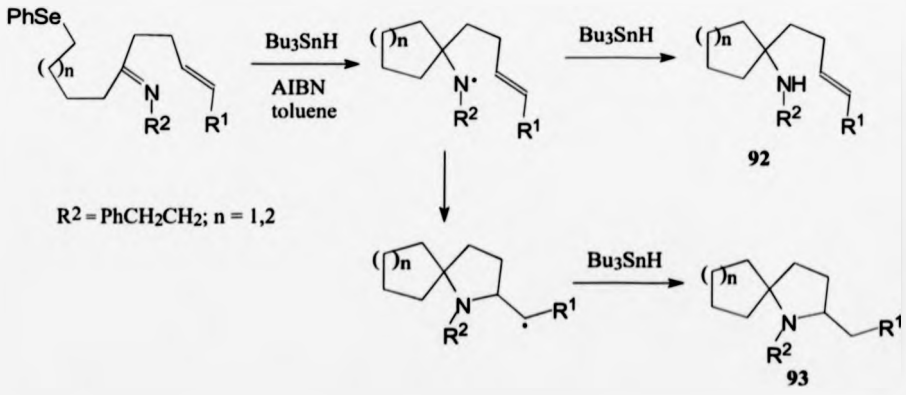
Scheme 4.1

Tandem reactions have the benefit of being 'atom efficient', which is particularly important when dealing with toxic, difficult to remove reagents like tributyltin hydride. Catalytic tin systems can provide a better solution to the tin problem.[27-29] In these catalytic cyclisation reactions the tin halide formed in the initiation step is reduced *in situ* by $NaBH_4$ thereby providing a constant source of tributyltin hydride at low concentration.

Radical reactions are naturally suited to sequencing as the product from one radical reaction is another radical and so tandem or cascade reactions are common in radical chemistry (particularly cyclisations). The important criteria are the nature and rate of the chain transfer step (as this will determine the lifetimes of the radicals in solution) and the differentiation between the intermediate radicals. It is necessary to selectively remove the final radical (by conversion to a stable product) but not the intermediate

ones. This differentiation is normally achieved by the structure of the radicals, intermediate radicals should have only one relatively rapid intramolecular option available while the final radical should have none. The slowest intramolecular reaction must still be more rapid than conversion of that radical to a non-radical product.

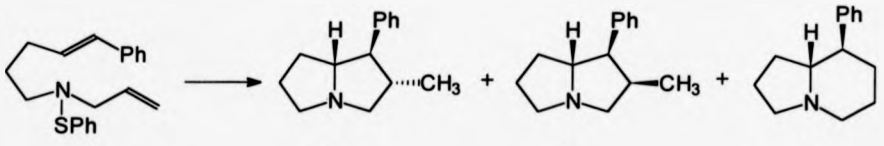
There have been various examples of tandem cyclisation reactions involving nitrogen-centred radicals. Bowman[100] produced bicyclic nitrogen heterocycles by tandem radical cyclisation of imines. Carbon radical cyclisation onto the carbon atom of imines generated intermediate aminyl radicals which could undergo a further cyclisation. Scheme 4.2 shows how this methodology was used in the synthesis of spirocyclic amines. With R^1=H, the monocyclic product **92** was the major product but with R^1=Ph, the intermediate aminyl radical cyclised efficiently to the spiroamine **93** (as expected due to the formation of the stable benzylic radical).



Scheme 4.2

The yield of tandem cyclised product was also improved by adding Lewis acids to the reaction mixture which complexed to the nitrogen thereby imparting electrophilic behaviour to the aminyl radicals.

Bowman also studied the tandem cyclisation of aminyl radicals generated from sulfenamide precursors.[67] The example shown in Scheme 4.3 shows the stereochemistry of the cyclisation. Cyclisation of *N*-allyl-*N*-(phenylsulfenyl)-5-phenylpent-4-enylamine, **16,** in a 5-*exo*, 5-*exo* fashion, gave the pyrrolizidines, **94**, **95** and a third minor diastereoisomer with unassigned stereochemistry) in 49% yield. The diastereoisomers were formed in the ratio 2.8:1.2:1 in THF. 5-*exo*, 6-*endo* cyclisation also occurred to give the indolizidine **17,** in 14% yield. Changing the solvent to benzene gave the same yield but a different ratio of pyrrolizidines (6.5:2.5:1) with less indolizidine (8%). No significance was noted on the stereochemistry.

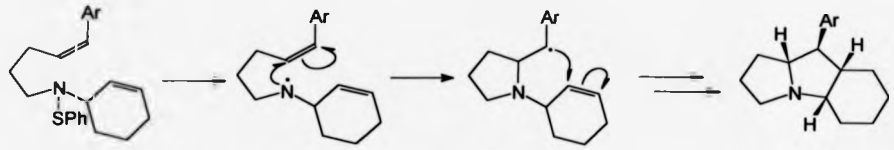


16 **94** **95** **17**

Scheme 4.3

Extending the reaction to the cyclohexyl analogue **96**, gave the tricyclic amine **98** (Scheme 4.4). The tricyclic product was formed as one diastereoisomer. The stereochemistry was not confirmed but molecular modelling indicated one favourable

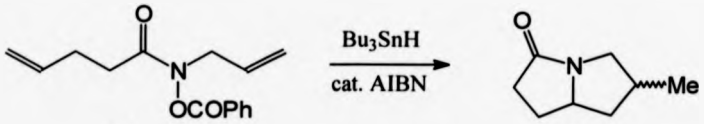
diastereoisomer as shown for **98**. The stereochemistry predicted was the same as the major product produced on cyclisation of **16**.



96 **98**

Scheme 4.4

Zard used his *O*-benzoyl hydroxamic acid derivatives to generate amidyl radicals capable of undergoing tandem cyclisations.[80] The simplest example is shown in Scheme 4.5. Zard reports that **99** afforded **100** as 2:1 mixture of epimers in 70% yield. The nature of the major isomer is not given.



99 **100**

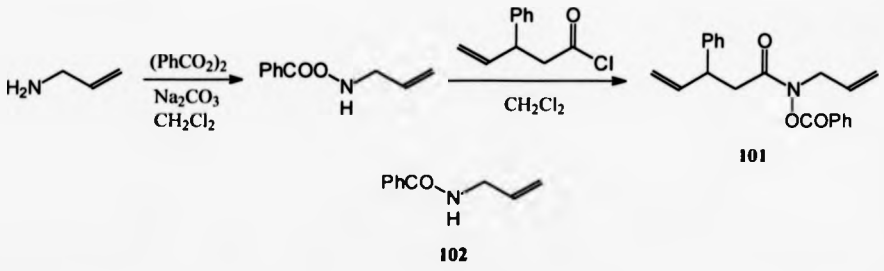
Scheme 4.5

We repeated this reaction as a starting point for further investigations into tandem amidyl radical cyclisations. Interestingly, although a lower yield of pure product was obtained (30%), the ratio of isomers was 10:1 (the isomers were inseparable and the ratio was determined by integration of the methyl resonances in the ^{1}H NMR). By comparison with data previously published on this compound[101] the major isomer

was determined to have the *cis* stereochemistry. The low yield was partly due to difficulties in removing the tin-containing by-products. Stirring with an 8% aqueous KF solution produced no change in the crude mixture and partitioning with acetonitrile/cyclohexane gave only limited success.

4.2 Results

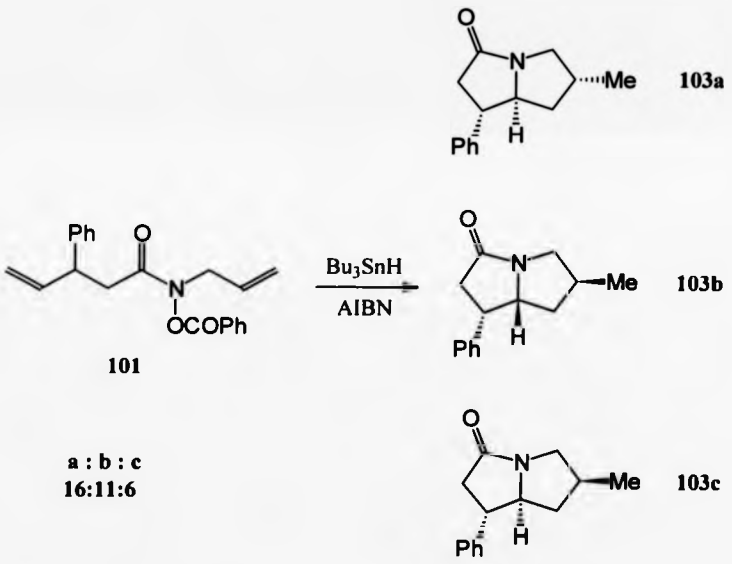
We wished to investigate the effect of substituents on both the regiochemistry and stereochemistry of these tandem amidyl radical cyclisations. Hence **101** was prepared in 27% yield from allylamine by the 'one-pot' method outlined in Scheme 4.6. The low yield was in part due to competitive formation of the amide by-product **102** in 36% yield.



Scheme 4.6

The cyclisation was conducted by addition of tributyltin hydride (1.2 eq., 1.43 mmol) and AIBN (0.1 eq.), in cyclohexane (3 ml) and toluene (3 ml), via a syringe pump over 6 hours, to a refluxing solution of **101**, (1 eq., 1.2 mmol) in degassed cyclohexane (6 ml). The conditions used were the same as those reported by Zard[80]

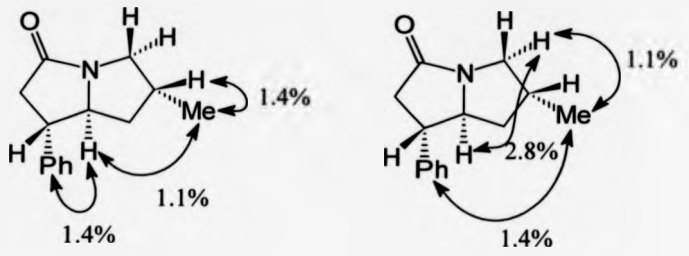
and gave a concentration of precursor at the start of the reaction as 0.2 mmol/ml. After refluxing for an additional 12 hours, another portion of Bu_3SnH (0.6 eq.) and AIBN was added in the same way. After two columns the desired tandem cyclised product was formed (17%) as a mixture of three of the four possible diastereoisomers (Scheme 4.7). None of the mono-cyclised product was detected. The isomers were assigned with the aid of NOE, COSY, ^1H-^{13}C correlations and decoupling NMR experiments.



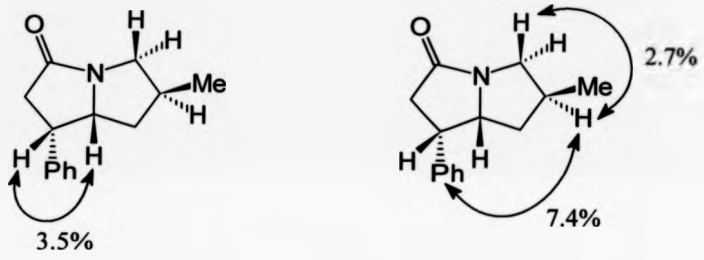
Scheme 4.7

The stereochemistry of the diastereoisomers was determined by NOE NMR experiments (Figure 4.1).

Isomer a



Isomer b



Isomer c

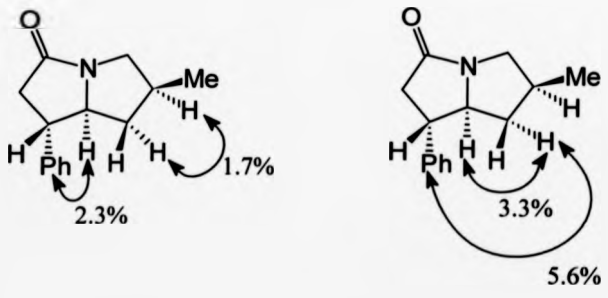


Figure 4.1 - nOe Information on 7-methyl-4-phenylpyrolizidin-2-one

Cyclisation of *N*-benzoyloxy-*N*-butyl-3-phenylpent-4-enamide, **72e,** gave *N*-butyl-5-methyl-4-phenylpyrrolidin-2-one, **73e,** as a mixture of isomers with a d.e. of 35%

(Section 3.3.2). The ratios of isomers produced in this reaction give a *trans*:*cis* ratio for the first cyclisation of 22:11 or a d.e. of 33% which is in good agreement with that observed in the related mono-cyclisation. The second cyclisation would be expected to be similar to a 2-substituted hexenyl radical cyclisation. The Beckwith model predicts the lowest energy transition state to be 'chair-like,' (Figure 4.2) and therefore predicts formation of the all *cis* isomer, **103a,** preferentially.

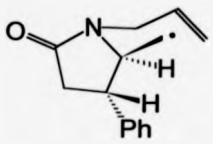
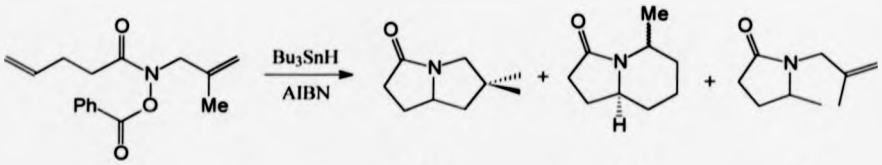


Figure 4.2 - Transition state model for cyclisation of *N*-benzoyloxy-*N*-butyl-3-phenylpent-4-enamide

In hex-5-enyl radical cyclisations the preference for 5-*exo* over 6-*endo* cyclisation is decreased by substitution at the 5-position. We were interested to see if replacing the *N*-allyl group with a *N*-(2-methyl)allyl substituent would result in competing 5-*exo*, 6-*endo* cyclisation taking place (Scheme 4.8).

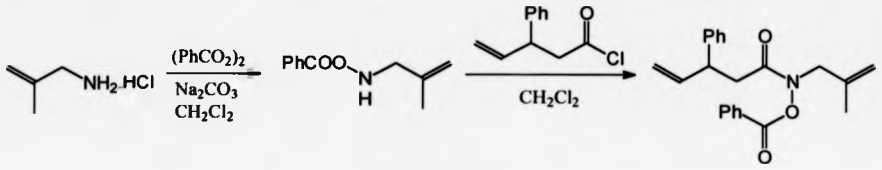


104 **105** **106** **107**

Scheme 4.8

The precursor **104** was prepared in 49% yield by an adaptation of the method outlined for **101** above (the hydrochloride salt of (2-methyl)allylamine was used with extra Na_2CO_3 to produce the free amine). The cyclisation was conducted under similar conditions to **101** [Bu_3SnH (1.1 eq.), initial precursor concentration 0.15 mmol/ml] and produced a mixture of 5-*exo*, 5-*exo*, **105** and 5-*exo*, 6-*endo*, **106,** tandem cyclised products (combined yield, 21%) along with a smaller amount of the mono-cyclised product **107** (5%). The tandem cyclised products (**105** and **106**) were inseparable but analysis by ^1H NMR showed the major product to be that resulting from 5-*exo*, 6-*endo* cyclisation, (in a ratio of 2:1 **106**:**105**) the stereochemistry of which could not be determined. The presence of a strong M-1 peak in the mass spectrum of the mixture also suggested the presence of the indolizidine product. It is likely that the increased amount of 6-*endo* cyclisation is due to a slower rate of 5-*exo* cyclisation (due to the steric hindrance presented by the methyl substituent), rather than an increased rate of 6-*endo* cyclisation. The two modes of cyclisation now compete effectively and a mixture of products is obtained. More kinetic data would be needed to confirm this.

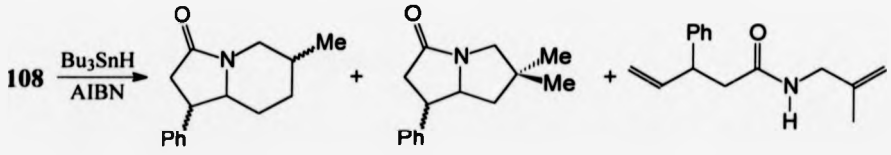
A fourth precursor, **108,** was also prepared containing both the 3-phenyl and (2-methylallyl) substituents previously studied (Scheme 4.9)



108

Scheme 4.9

Reaction with Bu_3SnH and AIBN under the same conditions as those described previously for **104** gave **109**, formed from 5-*exo*, 6-*endo* cyclisation as the major product (14%) after purification by flash column chromatography, (Scheme 4.10). There are four possible diastereoisomers of this compound and ^1H and ^{13}C NMR analysis indicates that only one isomer has been selectively produced. At present the stereochemistry of this diastereoisomer has not been determined. In addition a mixture containing products resulting from both 5-*exo*, 5-*exo*- **(110)** and 5-*exo*,-6-*endo*-cyclisation **(109, 4%)** was obtained. This mixture was never completely characterised. The reduced compound **111** was also formed (6%).



109 **110** **111**

Scheme 4.10

4.3 Conclusions and future work

O-Benzoyl hydroxamic acid derivatives have proven to be an appropriate precursor for tandem amidyl radical cyclisations. *N*-Allyl-*N*-benzoyloxy-3-phenylpent-4-enamide was found to cyclise with moderate diastereoselectivity and the selectivity shown was as expected based on the results from mono-cyclisations and predictions from the Beckwith model. A methyl substituent in the 5-position of the second forming ring was found to promote 6-*endo* cyclisation, with the major product being formed by this pathway in both cases studied

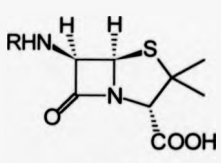
In future work, the effect of other substituents and substitution in different positions (*e.g.* terminal alkene positions on both side chains) could be investigated.

Chapter 5

β-Lactam synthesis *via* 4-*exo* amidyl radical cyclisations

5.1 Introduction

For many years medicinal chemists have utilised the important biological activity of β-lactams. High levels of anti-microbial activity are found in, for example, the penicillin,[102] **112** and cephalosporin,[103] **113** families and thienamycin,[104] **114**. The increasing resistance of bacteria to many antibiotics means there is a constant need for new variants of biologically active β-lactams and new methods to facilitate their synthesis.



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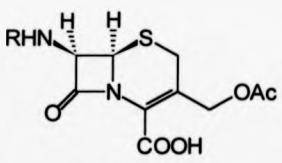

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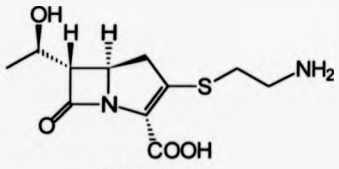
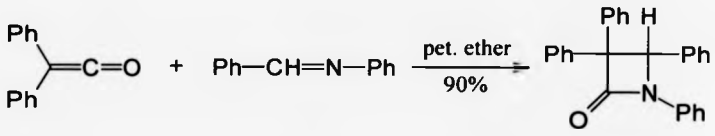


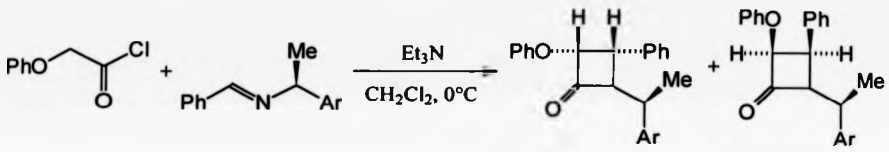
114

We wished to determine whether the amidyl radical methodology used successfully in the formation of pyrrolidinone and pyrrolizidinone skeletons could be adapted to the synthesis of 4-membered rings. There are various known synthetic strategies for forming azetidinone ring systems. These include DCC dehydration of a suitable amino acid precursor,[105] reaction of acid chlorides with imines[106] and reaction of zinc enolates or enol ethers with imines.[107,108] The first azetidinone was obtained by Staudinger from the reaction of diphenylketene with benzylideneaniline (Scheme

5.1). Asymmetric syntheses have been developed using this method, for example, Hashimoto[109] found that 1-(2,6-dichlorophenyl)ethylamine acted as an efficient chiral auxiliary (Scheme 5.2).



Scheme 5.1

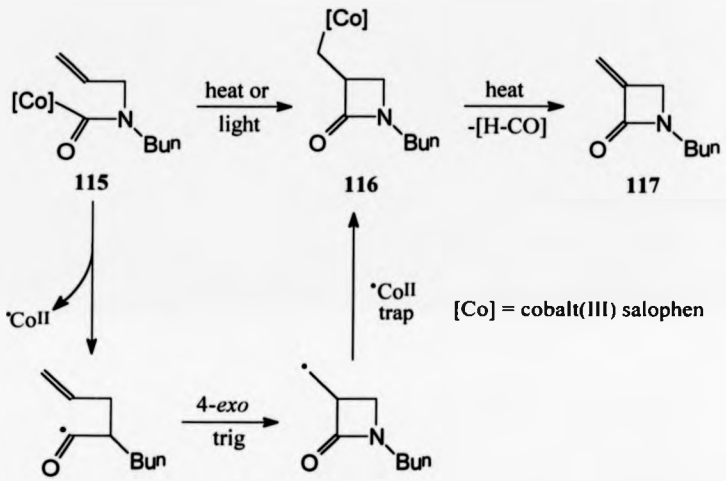


Scheme 5.2

Radical cyclisations have received much less attention as a method for forming β-lactams. This is possibly because 4-*exo* cyclisations are generally considered to be a reversible process due to the high strain of the 4-membered ring system. Kaplan observed the fragmentation of the cyclobutylmethyl radical to the corresponding pent-4-enyl radical.[110] (Scheme 5.3)

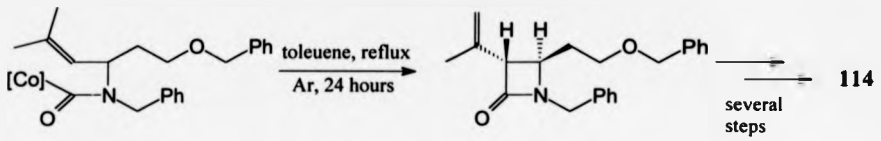
Scheme 5.3

However, successful 4-*exo* radical cyclisations to form azetidinone rings have been achieved by various groups. Pattenden pioneered the work in this area utilising carbamoyl radicals generated from carbamoylcobalt(III) salophen complexes under either thermal or photolytic conditions[104,111-113] (Scheme 5.4).



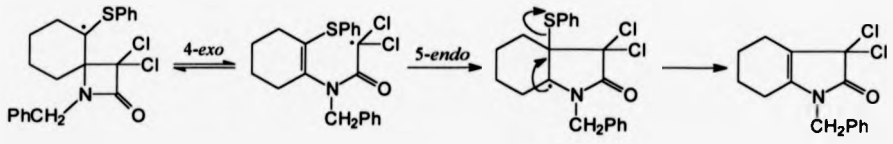
Scheme 5.4

4-*Exo-trig* radical cyclisation of the carbamoyl radical followed by trapping of the product radical with Co^{II} leads to the cobalt salophenmethyl substituted β-lactam **116**. Heating in boiling toluene leads to dehydrocobaltation and formation of **117**. In fact, **117** can be formed directly from **115** under thermolytic conditions. This methodology was extended and used in the formal synthesis of (±) thienamycin,[104,113] (Scheme 5.5).



Scheme 5.5

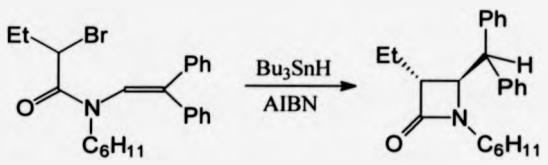
Ishibashi found that the competition between 4-*exo* and 5-*endo* cyclisation in his radical cyclisations of *N*-vinylic α-halo amides was greatly affected by temperature.[114] At low temperatures the reaction was kinetically controlled and the 4-*exo* product predominated where a steric repulsion was avoided. At higher temperatures, ring opening of the β-lactam occurred and allowed the 5-*endo* product to form. Elimination of the -SPh group meant that this process was essentially irreversible (Scheme 5.6).



Scheme 5.6

Similar cyclisations were performed by Zard[115] utilising nickel powder and acetic acid to conduct the radical reaction. Reduction is much slower than with tin hydride systems and so trapping agents (*e.g.* diphenyldiselenide) were used to trap the cyclised radicals.

Belletire performed 4-*exo* radical cyclisations to form β-lactams using tributyltin hydride (Scheme 5.7).[116] The cyclisations were successful because the cyclic radical was stabilised by two phenyl rings.

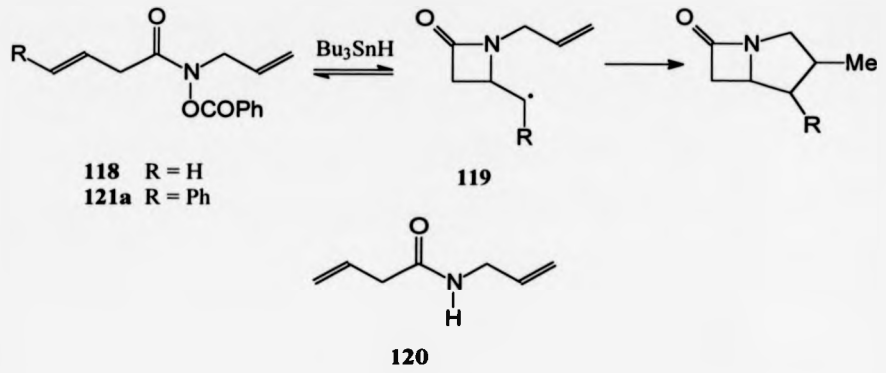


Scheme 5.7

5.2 Results and discussion

5.2.1 Initial investigations

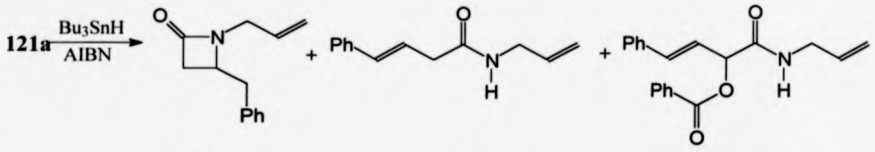
Due to the potential reversibility of 4-*exo* radical cyclisations, the first system we employed, **118,** involved a radical set up to undergo a 4,5-tandem radical cyclisation (Scheme 5.8). By trapping the intermediate cyclic radical **119,** in a second, irreversible cyclisation we hoped to reduce the amount of reduction to acyclic product **120.** This was one of the methods used by Bowman to overcome the reversible nature of aminyl radical cyclisations (Section 1.6.5.2). Thus **118** was prepared from allylamine, benzoyl peroxide and vinylacetyl chloride by the one-pot method previously described and treated with tributyltin hydride and AIBN (syringe pump, 8 hours) in refluxing toluene (under the conditions reported by Zard and mentioned previously).



Scheme 5.8

However, only the reduced acyclic product, **120** was detected suggesting that the rate of ring opening and reduction of the amidyl radical was faster than the second cyclisation. Adding a phenyl substituent to the 4-position of the pentenoyl chain would allow the intermediate cyclic radical to be stabilised by being in a benzylic position (**119,** R = Ph). We hoped that this would lead to formation of the desired 4,5-tandem cyclised product as the rate of ring opening would now be slowed. However, upon reaction of **121a** with Bu_3SnH and AIBN in the same manner as before, a mixture of products were detected in the crude NMR (Scheme 5.9). We were unable to completely remove all of the tin contaminants from the product bands by column chromatography. Consequently an attempt was made to remove some of these tin compounds prior to purification by silica gel flash column chromatography. Hence, the crude mixture was adsorbed onto silica gel (10% w/w) before continuous extraction with pentane. This was partially successful but did not remove all of the tin by-products. After columning, the three compounds **122a**, **123a** and **124a** were

obtained in a roughly 1:1:1 ratio although none of the compounds were obtained completely free of tin residues.



122a **123a** **124a**

Scheme 5.9

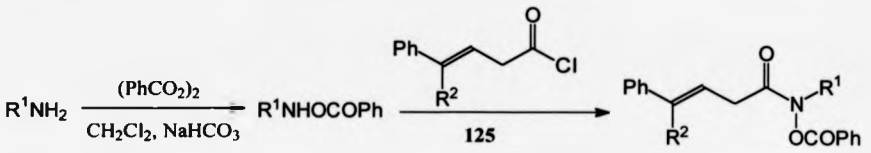
Despite the purification problems we were pleased to discover that the phenyl stabilising group had enabled the formation of a β-lactam product without the need for a second 'trapping' cyclisation. In fact, the lack of tandem cyclised product in both these reactions implies that the second cyclisation proposed is an unfavourable one. This was also proposed by D. Kelly *et al*[117] who prepared the same cyclic radical **119** (R = Ph) directly by action of Bu_3SnH on the corresponding halide and found no evidence of the bicyclic product.

The reduced acyclic product, **123a** was to be expected but the rearranged 2-benzoyloxy amide, **124a** was another surprise. The formation of this rearranged compound was investigated further and the results will be presented in the next Chapter.

5.2.2 Preparation of other cyclisation precursors

Having established that β-lactam synthesis was possible without the necessity of designing in a second irreversible cyclisation we decided to change the *N*-allyl group for a number of other R groups to determine how this might affect the reaction. The alkyl groups *N*-methyl, **121f,** *N*-*n*-butyl, **121b**, *N*-benzyl, **121c** and *N*-*t*-butyl, **121d,** were chosen to provide a variety of steric bulk at nitrogen. As before the benzyl group should be easily removed and offers the possibility of further functionalization at nitrogen. A precursor with two phenyl groups attached to the terminal alkene carbon atom, **121e,** was also prepared. It was thought that this would confer greater stability on the cyclic radical leading to an increased yield of cyclic product. The desired acid chloride, **125e,** was prepared by standard chemistry[118] in three steps from benzophenone. The precursors were prepared by the two routes previously discussed in Chapter 3 (Section 3.2), (Scheme 5.10 and 5.11)

Method 1



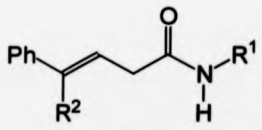
121

121	R^1	R^2	Yield / %
121a	$CH_2CH{=}CH_2$	H	19
121b	*n*-Bu	H	54
121c	CH_2Ph	H	22
121d	*t*-Bu	H	0[a]
121e	*n*-Bu	Ph	52

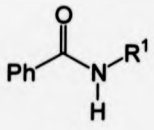
a the main product isolated was the rearranged compound **124d** (R^1 = ^{t}Bu)

Scheme 5.10

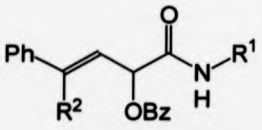
As before, Method 1 led to varying amounts of the amides **123** and **127**, but in addition the rearranged compounds **124** were detected. The formation of these three by-products resulted in the low to moderate yields obtained by this method. In fact, it proved impossible to prepare the *t*-butyl precursor **121d** as the rearrangement to give **124d** (19%) occurred under the reaction conditions.



123

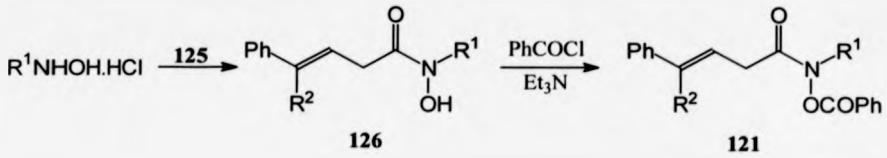


127



124

Method 2

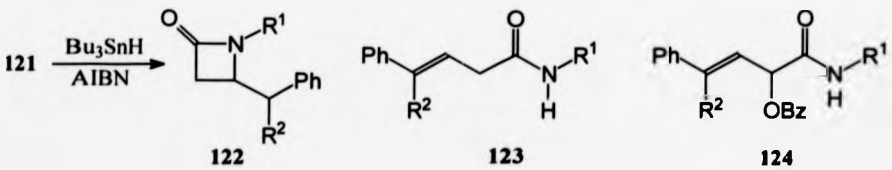


121	R^1	R^2	Yield / %
121c	CH_2Ph	H	90
121f	Me	H	51

Scheme 5.11

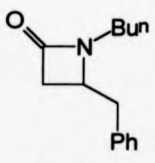
Precursor formation *via* Method 2 proved successful but again the hydroxamic acid intermediates (**126 c** and **f**) gave very broad signals in the ^{1}H NMR (see also section 3.2). Unfortunately attempts to perform variable temperature NMR experiments to sharpen the spectra resulted in decomposition of the samples. The *N*-benzyl precursor **121c**, could be prepared in much more acceptable yield *via* this strategy (90%) than *via* Method 1 (22%).

5.2.3 Cyclisation reactions

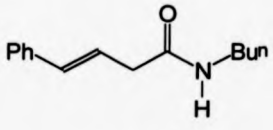


Scheme 5.12

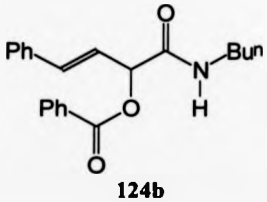
With the four precursors, **121b,c,e,f,** in hand their cyclisation reactions were attempted. Cyclisation conditions varied slightly between reactions and so will be described for each case. The *N*-*n*-butyl precursor, **121b,** was treated with Bu_3SnH and AIBN using the original conditions reported by Zard. [That is, Bu_3SnH (1.2 eq., 1 ml) and AIBN (0.1 eq.) in degassed toluene (7.5 ml) and cyclohexane (7.5 ml) added by a syringe pump over 6 hours to a solution of **121b** in degassed cyclohexane (15 ml)]. These conditions resulted in an initial precursor concentration of 0.2 mmol/ml at the start of the reaction and 0.1 mmol/ml after addition of the tin hydride. The crude NMR showed three products to be present [**122b**:**123b**:**124b** 3:3:4], but although they could all be separated after column chromatography none could be fully removed from the tin contaminants.



122b



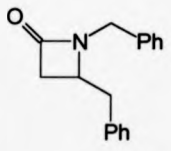
123b



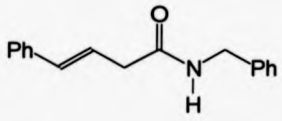
124b

Similar results were obtained with the *N*-benzyl precursor **121c**. When reacted under identical conditions as above the crude NMR showed a roughly 1:1:1 mixture of **122c**:**123c**:**124c** products. Flash column chromatography again separated the different products from each other but left all three with tin contaminants. This reaction was repeated under more dilute conditions with a precursor concentration of 0.1 mmol/ml at the start and 0.07 mmol/ml after addition of the tin hydride. Analysis by tlc (after 12 hours) showed very little reaction to have taken place so a further

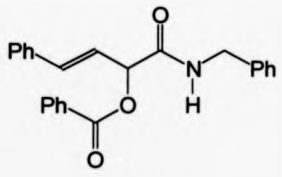
addition of Bu_3SnH (1.2 eq.) and AIBN (0.1 eq.) was made (over 6 hours with lowering of the precursor concentration to 0.06 mmol/ml). The crude ^1H NMR showed a roughly 3:1 ratio of cyclised, **122c** to reduced product, **123c,** with only trace amounts of the rearrangement product **124c**. A soxhlet extraction of the crude mixture using hexane allowed for removal of some tin contaminants. Partitioning this crude mixture between acetonitrile and cyclohexane removed virtually all of the remaining tin by-products into the cyclohexane layer (along with, unfortunately, a small amount of cyclised product). Column chromatography was now more successful and gave 13% isolated cyclised product, **122c** along with 23% of a 1:1 mixture of cyclised and reduced products (**122c**:**123c**). A small amount (1.5%) of the rearranged product **124c** was also isolated.



122c



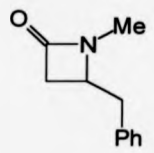
123c



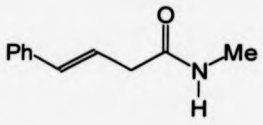
124c

The *N*-methyl precursor, **121f** was reacted at an initial concentration of 0.15 mmol/ml (decreasing to 0.06 mmol/ml on addition of Bu_3SnH) under otherwise identical conditions to the previous two examples. ^1H NMR analysis of the crude reaction mixture showed a 4:1.1:2.6:1 ratio of starting material **121f** : cyclised **122f** : reduced **123f** : rearranged **124f** compounds. Purification was carried out by partitioning the crude reaction mixture between firstly acetonitrile/hexane and then acetonitrile/cyclohexane. This removed most of the tin contaminants and the need for

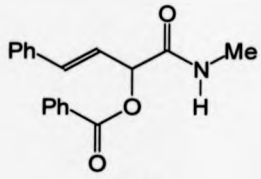
a soxhlet extraction. Note that partitioning initially with acetonitrile/hexane was unsuccessful as the layers were too miscible. Column chromatography then resulted in 6% starting material, 15% rearranged compound, **124f**, 40% reduced compound, **123f** and 14% cyclised product, **122f**.



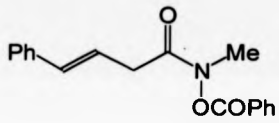
122f



123f

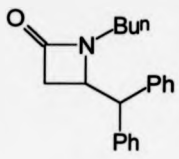


124f

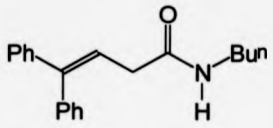


121f

Finally, the diphenyl precursor, **121e** was reacted under the same conditions as **121f** above (i.e. 0.15 mmol/ml initial precursor concentration). After the first addition of Bu_3SnH, analysis by tlc showed the presence of starting material so a further 0.6 eq. of Bu_3SnH and 0.1 eq. AIBN was added in the appropriate amount of solvent over a further 8 hours as before. Purification was again achieved by partitioning the crude mixture followed by column chromatography. Analysis of the ^1H NMR prior to the column showed a 2:1 ratio of cyclised, **122e** to reduced, **123e** product with no evidence of any rearranged compound. The cyclised product, **122e** was obtained, cleanly in 27% yield.

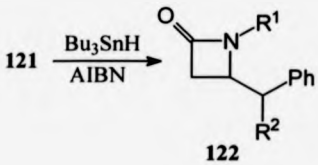


122e

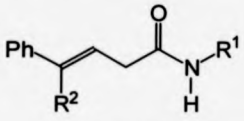


123e

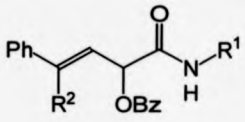
A summary of the results presented above is given in Table 5.1



122



123



124

Precursor	R^1	R^2	Isolated yield of **122**	Ratio **122**:**123**:**124**
121a	$CH_2CH{=}CH_2$	H	a	1:1:1
121b	*n*-Bu	H	b	3:3:4
121c	CH_2Ph	H	13%	3:1:trace
121f	Me	H	14%	1.1:2.6:1.7
121e	*n*-Bu	Ph	27%	2:1:0

a inseparable mixture

b inseparable from tin by-products

Table 5.1- Results of cyclisation reactions to form β-lactam rings.

The best ratio of cyclised product to reduced and rearranged compounds was achieved with the benzyl precursor **121c** (which was performed at the lowest

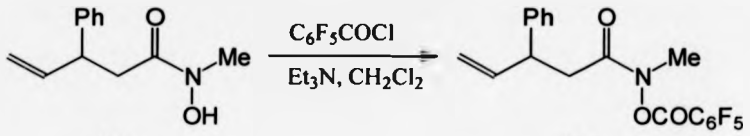
concentration). In contrast the methyl precursor, **121f** gave the worst ratio with large amounts of reduced and rearranged compounds being formed and an incomplete reaction. The best yield of β-lactam was achieved with the biphenyl precursor, **121e** which furnished no rearranged compound at all.

In summary, these reactions have shown that 4-*exo* cyclisation occurs with a variety of *N*-alkyl groups. The yields of cyclised products are low due partly to competing reactions resulting in a mixture of products. One of these competing reactions results in the formation of interesting rearranged compounds, **124**, which have been further investigated (see next chapter). The presence of two phenyl groups on the terminal end of the double bond, **121e,** resulted in a higher yield of cyclised product, presumably due to the increase in stability of the cyclised radical **119**.

5.2.4 Purification problems and solutions

The major problem associated with these reactions was the removal of tin contaminants from the product mixtures at the end of the reactions. As outlined above, the best results were obtained with a partitioning of the crude product mixture between acetonitrile, hexane and cyclohexane with the hydrocarbon solvents removing most of the tin contaminants. Other tin purification methods were also attempted during the course of this work. Curran describes a tin removal procedure involving diazabicycloundecene (DBU) used in the purification of atom transfer cyclisations of α-iodo esters.[90] The procedure involves addition of DBU to a diethyl ether solution of the product mixture followed by titration with an ethereal iodine

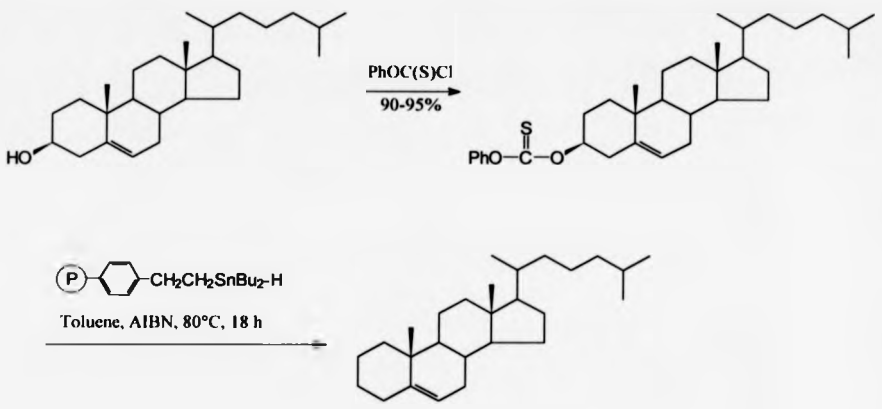
solution. They formulated that molecular iodine converts both hexaalkylditins and trialkyltin hydrides into trialkyltin iodides. The DBU hydrolyses the tin halides to tin hydroxides which are removed by a short column. This procedure was unsuccessful with our experiments. This is presumably because the main by-products involved in this work, tin benzoates, cannot be converted into tin halides in this way. Curran also reports use of a fluorinated tin reagent [tris(2-perflourohexyl)ethyl)tin hydride] which can be removed from the product mixture by simple phase separation techniques.[119] Adamantyl bromide was reduced with this reagent in (trifluoromethyl)toluene [which acted as a mixed, (part hydrocarbon, part fluorocarbon) solvent]. Evaporation of the solvent followed by phase separation between perfluoromethylcyclohexane (PFMC) and dichloromethane separated the tin products from adamantane. We encountered difficulties in the three step preparation to form the fluorinated tin hydride and therefore did not attempt to use this method in our cyclisations. However instead we looked at the use of a fluorinated precursor. A precursor for the 5-membered ring cyclisations presented in Chapter 3 was used. Hence **128** was prepared simply from the methyl hydroxamic acid, **81g** and perfluorobenzoyl chloride in 91% yield (Scheme 5.13). After treatment with Bu_3SnH and AIBN the crude ^1H NMR showed evidence of cyclised product but partitioning between PFMC/dichloromethane and PFMC/acetonitrile showed little removal of the tin by-products. As no improvement was seen this procedure was not developed further. A critical amount of fluorine substitution is necessary for organic fluoro compounds to be partitioned into fluorinated solvents and the lack of success here is presumably due to the relatively low amount of fluorination in the resulting tin perfluorobenzoate.



81g **128**

Scheme 5.13

Catalytic use of tin hydride has proved very successful with radical cyclisations involving halide precursors where the tin halides produced are reduced *in situ* by $NaBH_4$.[27-29] However, all attempts to reduce tributyltin benzoates failed and so this system was not compatible with the *O*-benzoyl hydroxamic acid derivatives used here. There have been various reports in the literature on using polymer- or carrier-supported tin reagents.[23-26] The idea is to bind the tin reagent in a very stable position to an insoluble porous polymer which can be separated after the reaction simply by filtration. These supported reagents have been used for both reductions and cyclisations of organic halides and in most cases show good regenerative ability of the active tin hydride by reduction with diisobutylaluminium hydride. Neumann also reported use of his polystyrene-supported, regenerable tin hydride in performing dehydroxylation of secondary alcohols and deamination of secondary or tertiary amines.[25,120] The dehydroxylation reactions are carried out as Barton-type deoxygenations which makes the leaving group similar to that used in this work (Scheme 5.14). Use of a polymer-supported tin hydride could prove to be a useful method to overcome our tin purification system but there was insufficient time to investigate the technique during the course of this work.



Scheme 5.14

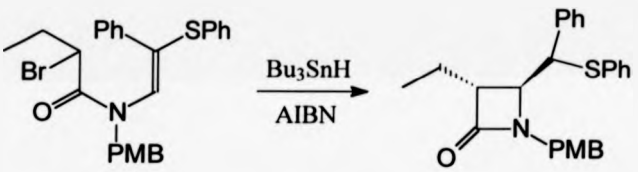
5.3 Conclusions and future work

The low yields obtained in the 4-*exo* amidyl radical cyclisations and the great purification problems encountered suggest that this is not yet a viable route for forming azetidinones. The reactions are important however in showing that amidyl radicals can undergo 4-*exo-trig* radical cyclisations to form β-lactams. By altering the way in which the radical is generated or the conditions under which the reaction is conducted a more successful, general method for this transformation may be found.

Use of the diphenyl precursor, **121e** gave the best results and so further experiments involving biphenyl precursors with different *N*-alkyl groups would hopefully improve the yields of all the cyclisations. The cyclisations could also be attempted with chiral N-R groups and with substituents attached to the chain in the 2-position. This might allow further functionality to be introduced for the synthesis of more complex

molecules. Varying the concentration at which the reactions are conducted would also be important in optimising the ratio of cyclised to reduced and rearranged compounds.

Ishibashi[121] recently performed carbon-centred 4-*exo* radical cyclisations to form β-lactams and used phenylsulfenyl substituents to stabilise the cyclic radicals produced. Thus, **129** was cyclised (by reaction with Bu_3SnH and AIBN) to the β-lactam **130** in 56% yield as a mixture of two diastereoisomers (Scheme 5.15).



129 **130**

PMB = *p*-methoxybenzyl

Scheme 5.15

Performing the reaction in the absence of the phenylsulfenyl group at the terminus of the *N*-vinylic bond resulted in only low yields of β-lactam formation along with the reduction product and the 5-*endo* cyclised product. Clearly the phenyl group alone was insufficient to stabilise the radical intermediate. With this in mind adapting our procedure to involve precursors with one or two phenylsulfenyl substituents at the terminal end of the double bond may well result in improved yields of cyclised products. It is likely also to have an effect on the ease of formation of the corresponding rearrangement products found in these reactions.

Chapter 6

Rearrangements of *O*-benzoyl hydroxamic acid derivatives

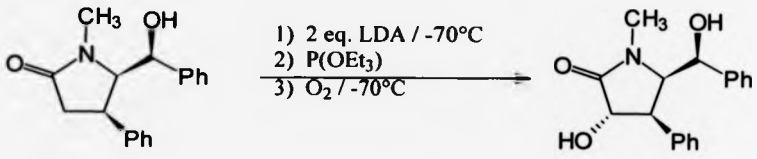
6.1 Introduction

The surprising formation of α-benzoyloxy substituted amides, **124,** as a by-product in the cyclisations of *N*-alkyl-*N*-benzoyloxy-4-phenylbut-3-enamides, **121** (Chapter 5) led us to investigate their formation in more detail. The rearranged compounds represent suitable protected versions of 2-hydroxyamides. 2-Hydroxy carbonyl compounds are widely distributed in nature and are often used as building blocks in organic synthesis.[122] In particular, 2-hydroxyamides have been found to be useful intermediates for the preparation of oxindoles[123] and oxazolidinediones,[124] and so new methods for their synthesis are of great interest.

6.1.1 Current methods for the preparation of 2-hydroxyamides

There are relatively few methods for the conversion of amides to 2-hydroxyamides. Classically, syntheses involved oxidation of tertiary amides. Wasserman,[125] reacted lithium enolates of *N,N*-dialkylamides with molecular oxygen to give α-hydroperoxide intermediates which were cleanly reduced to α-hydroxy derivatives. Hartwig and Born,[126] used a variant of this reaction to complete their synthesis of Clausenamide, **131** (Scheme 6.1). Clausenamide had been isolated as the active ingredient in the leaves of *Clausena lansium*, a plant used as a liver protecting agent in Chinese folk medicine. Triethyl phosphite was added to the reaction mixture to

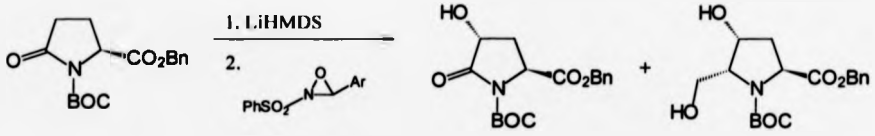
reduce the peroxide anion *in situ* (otherwise the strongly nucleophilic peroxide anion was found to attack the amide carbonyl group resulting in the ring opened amino acid as product).



131

Scheme 6.1

Davis and co-workers used sulfonyloxaziridines as oxidants to prepare optically active acyclic, tertiary α-hydroxy amides.[122,127] This reaction was developed as a key step in the synthesis of a number of natural products. An example is shown in Scheme 6.2, where an α-hydroxyamide was an intermediate in the synthesis of a glycopeptide isolated from *Pseudomonas acidophila*, **132**.

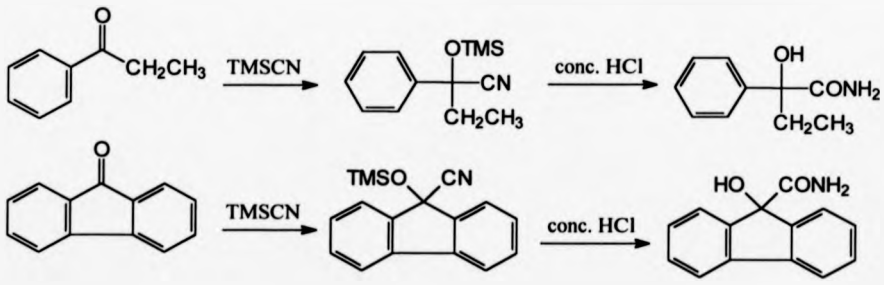


132

Scheme 6.2

These oxidative methods all produce tertiary α-hydroxyamides and are not applicable to the α-hydroxylation of primary and secondary amides as the enolates are not

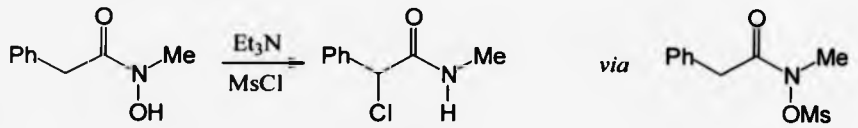
readily accessible. Seebach[128] described the titanium tetrachloride catalysed reaction between methyl isocyanide and aldehydes or ketones to give good yields of *N*-methyl-2-hydroxyamides after hydrolysis. This modification of the Passerini reaction was suitable with a wide range of aldehydes and ketones. Unsubstituted α-hydroxyamides can be prepared by the equilibrium addition of HCN to aldehydes and ketones to form the cyanohydrin which is then hydrolysed in concentrated acid to give the primary α-hydroxyamide.[129] This method is inefficient for conjugated aromatic ketones due to an unfavourable equilibrium. Grunewald[130] has modified this reaction employing trimethylsilyl cyanide (TMSCN) instead of HCN and reports good yields of primary α-hydroxyamides from conjugated aryl ketones (Scheme 6.3).



Scheme 6.3

Hoffman has published a series of papers on the rearrangement of *N*-(sulfonyloxy)amides to 2-substituted amides.[131-137] These rearrangements are conceptually similar to our own although it is likely that they are occurring *via* quite different mechanisms. Hoffman and co-workers were attempting to prepare O-sulfonylated *N*-alkyl hydroxamic acids by treatment of the corresponding hydroxamic

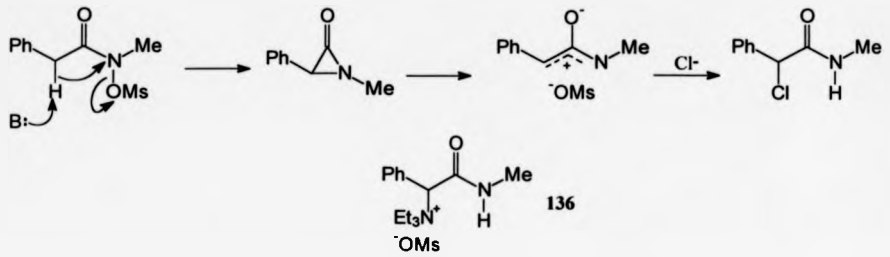
acid with triethylamine (2.25 eq.) and methanesulfonyl chloride (1.1 eq.) in dichloromethane. Instead, treatment of *N*-methylphenylacetohydroxamic acid, **133,** under these conditions produced 2-chloro-*N*-methylphenylacetamide, **134** in 72% isolated yield (Scheme 6.4).



133 **134** **135**

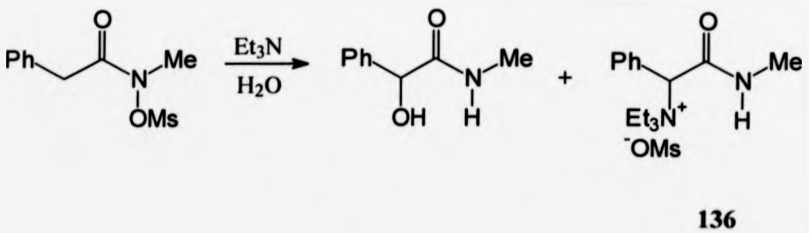
Scheme 6.4

It was determined that **133** is initially sulfonylated on oxygen to give the desired *O*-sulfonylated hydroxamic acid **135** and that excess triethylamine and the triethylammonium hydrochloride by-product caused the rearrangement to **134**. After many further experimental observations[132,133] they concluded that the mechanism was as follows; initial formation of an α-lactam by a Favorski-like, concerted 1,3-elimination, followed by ring opening to the ion-pair and capture at the 2-position by the chloride nucleophile (Scheme 6.5).



Scheme 6.5

In the absence of chloride ion, ion-pair capture by triethylamine gives the salt **136**. It was found that other nucleophiles could also capture the ion-pair efficiently and hence, 2-bromoamides and 2-hydroxyamides were prepared. Formation of 2-hydroxyamides required slow addition (6-12 hours) of triethylamine in acetonitrile to an aqueous acetonitrile solution of the precursor. Slow addition is required because the rate of ion-pair trapping by triethylamine is competitive with the rate of ion-pair trapping by water and mixed products result if all the base is added at the start (Scheme 6.6).



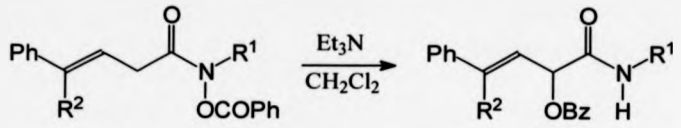
Scheme 6.6

A conjugating substituent is required to acidify the α-proton but a variety of conjugating groups, *N*-alkyl groups and sulfonyloxy leaving groups were employed with good success leading to a range of 2-substituted amides.

6.2 Optimisation of rearrangement of *O*-benzoyl hydroxamic acid derivatives

6.2.1 Reactions with triethylamine

In light of the problems associated with most of the methods described for the synthesis of 2-hydroxyamides we decided to investigate whether it was possible to optimise the yields of the rearranged α-benzoyloxyamides prepared from the corresponding *O*-benzoyl hydroxamic acid derivatives. Prompted by the work of Hoffman our initial investigations involved a study of the base induced rearrangement of the *O*-benzoyl hydroxamic acid derivatives, **121b,c,e** and **f,** prepared earlier as cyclisation precursors to β-lactams (Scheme 6.7). A description of the preparation of the precursors has already been given in Chapter 5 (Section 5.2.2).



121 **124**

b) R^1 = *n*-Bu, R^2 = H

c) R^1 = CH_2Ph, R^2 = H

e) R^1 = *n*-Bu, R^2 = Ph

f) R^1 = Me, R^2 = H

Scheme 6.7

Initial experiments involved addition of 1 equivalent of triethylamine to a dichloromethane solution of the precursor, **121** at room temperature and monitoring the reaction by tlc until complete removal of the starting material was noted. An aqueous work-up involving washing with dilute HCl to remove the base furnished the rearranged products **124**. Under these conditions **121b** (R^1=*n*-Bu) gave a 28% yield of rearranged compound **124b** while **121f** (R^1=Me), produced the rearranged product **124f** in 53% yield, (the reactions taking 40 hours and 24 hours respectively). Raising the temperature to reflux (40^0C) gave **124b** in 63% yield, and **124f** in 56% yield, in both cases reaction times being reduced to 4 hours. As the higher temperature obviously improved the reaction the benzyl precursor **121c** (R^1=CH_2Ph) was reacted at reflux also. This reaction did not occur as readily however and gave only 28% yield of **124c** in 24 hours. Having established that the use of triethylamine as base facilitated the rearrangement we wished to ascertain whether the reaction could occur with catalytic quantities of base or whether one equivalent was required. Hence, both the *N*-*n*-butyl, **121b** and *N*-benzyl, **121c** precursors were reacted with

only 25 mol% triethylamine in refluxing dichloromethane. The *N*-*n*-butyl precursor gave only 22% yield in 24 hours whereas the *N*-benzyl precursor gave a 41% yield after 4 days, indicating the reaction to be catalytic in base. We next investigated the reaction of the *N*-*n*-butyl precursor, **121e** under these conditions (25% Et_3N, CH_2Cl_2, reflux) and found that it proceeded in quantitative yield to the rearranged α-hydroxyamide, **124e** in 12 hours. A summary of these results is given in Table 6.1

Precursor	R^1	R^2	Equivalents of base	Temperature	Time	Yield of **124**/ %
121b	*n*-Bu	H	1	R.T.	40 hrs	28
121b	*n*-Bu	H	1	40^0C	4 hrs	63
121b	*n*-Bu	H	0.25	40^0C	24 hrs	22
121f	Me	H	1	R.T.	24 hrs	53
121f	Me	H	1	40^0C	4 hrs	56
121c	CH_2Ph	H	1	40^0C	24 hrs	28
121c	CH_2Ph	H	0.25	40^0C	4 days	41
121e	*n*-Bu	Ph	0.25	40^0C	12 hrs	> 95

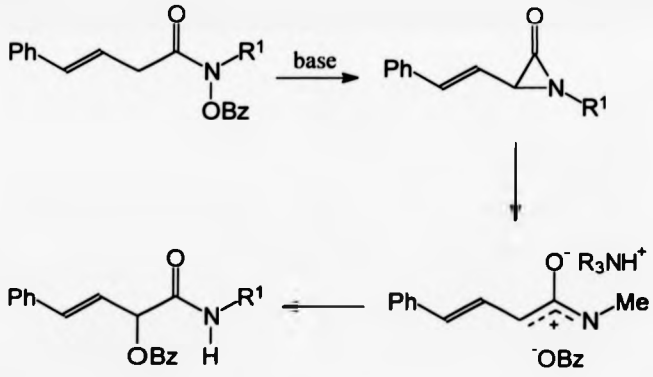
Table 6.1- Results from reaction of hydroxamic acid derivatives with triethylamine in dichloromethane

These reactions showed that the *O*-benzoyl hydroxamic acid derivatives studied undergo rearrangement to 2-benzoyloxy substituted pent-4-enamides on reaction with the tertiary base, triethylamine. Increased yields and shorter reaction times were

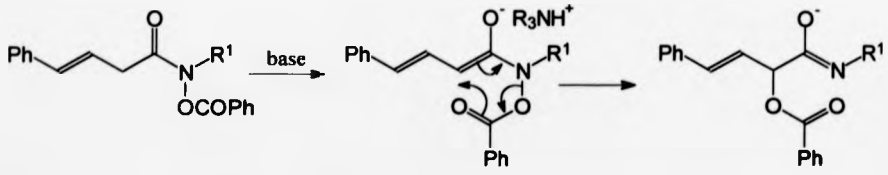
observed at higher temperatures (40°C) and a catalytic amount of base could be used, although this resulted in slower reactions.

Two possible mechanisms for the base mediated rearrangement are proposed in Scheme 6.8. Mechanism 1 involves an ion-pair trapping similar to that proposed by Hoffman for the reaction of *N*-mesyloxyamides with base while Mechanism 2 is a [3,3] sigmatropic rearrangement of the enol or enolate form of the *O*-benzoyl hydroxamic acid derivative.

Mechanism 1



Mechanism 2

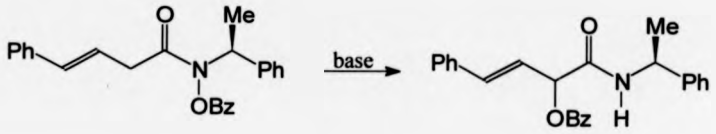


Scheme 6.8

6.2.2 Asymmetric reactions

In addition to the four precursors (**121b,c,e,f**) already prepared for use in the previously reported amidyl radical cyclisation reactions (Chapter 5), an optically active compound, (R)-*N*-α-methylbenzyl-*N*-benzoyloxy-4-phenylbut-3-enamide **121g** (R^1 = CH(Me)Ph, R^2 = H) was synthesised (30%, Method 1, Section 5.2.2). Reaction of **121g** with 1 equivalent of triethylamine at room temperature gave 45% of the rearranged compound **124g,** in 3 hours and with a d.e. of 32%.

In both of the two possible mechanisms illustrated above (Scheme 6.8) the base derived counterion (Et_3NH^+) is likely to be intimately involved with the reactive intermediate during the key O-C bond forming step. Thus, we investigated whether the use of chiral bases could improve upon the diastereoselectivity of the process. Reactions were carried out on **121g** with both quinine and quinidine acting as bases instead of triethylamine. Both reactions were carried out in refluxing dichloromethane and both gave 13% yield of the rearranged product **124g** in 5 hours and 24 hours respectively. Quinine gave **124g** with only 2% d.e. while quinidine gave only a 24% d.e. (less than that achieved for a non-chiral base). This clearly indicated that a chiral base could influence the key C-O bond forming step and suggested that the use of an appropriate chiral base might induce greater stereoselectivity. With this in mind we investigated the reaction of **121g** with 1 eq. of (+) Trögers base (as both the (+) and (-) forms of the base are commercially available) but unfortunately no product was observed. A summary of these results is given in Table 6.2.



121g **124g**

Base	Eq. of base	Temperature	Time	Yield /%	d.e. / %
Et_3N	1	R.T.	3 hrs	45	32
quinine	1	40^0C	5 hrs	13	2
quinidine	1	40^0C	24 hrs	13	24

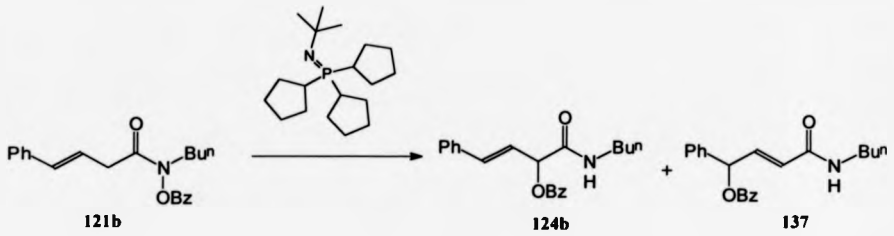
Table 6.2- Rearrangement reactions of *N*-α-methylbenzyl-*N*-benzoyloxy-4-phenylbut-3-enamide in dichloromethane

6.2.3 Rearrangements with different bases

In order to investigate the reaction further the effect of different organic bases on the reaction was assessed. The *N*-*n*-butyl precursor, **121b** was reacted with the bulky base *N,N*-diisopropylethylamine (1.3 eq.) in dichloromethane. After refluxing for 12 hours, followed by washing the crude product with dilute acid and purifying by column chromatography, **124a** was obtained in 48% yield. This was a lower yield than when triethylamine was used as base under similar conditions.

In an attempt to speed the reaction up and hence conduct it at a lower temperature a much stronger base was used. After noting (above) that a bulky base did not hinder

the reaction greatly the phosphazene base [P_1-*t*-butyl-tris(tetramethylene)] was used and was found to accelerate the reaction remarkably, tlc analysis indicating the reaction to be complete in a matter of minutes. Interestingly though, upon work-up, a mixture of rearranged products **124b** and **137** were isolated (Scheme 6.9).



Scheme 6.9

Presumably the base is sufficiently strong to promote the isomerisation of **124b** to **137** possibly *via* a [3,3]-sigmatropic rearrangement, or *via* deprotonation of **124b** followed by isomerisation. Performing the reaction at 0°C lead to slightly increased yields of both isomers while the use of a catalytic amount of the phosphazene base resulted in a much longer reaction time and only 22% yield of **124b** with none of the other isomer detected. The results of these reactions are presented in Table 6.3. All experiments were performed on the *N*-*n*-butyl precursor **121b** in dichloromethane. The yields given are after washing the crude mixture with dilute HCl to remove the base and flash column chromatography on silica gel to separate the isomers.

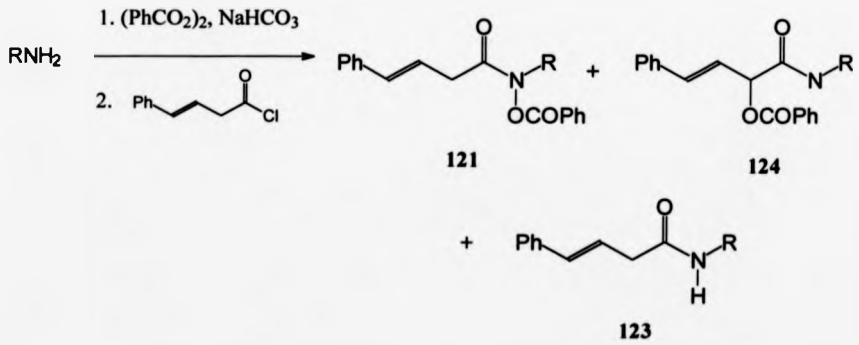
Eq. of base	Temperature	Time	Yield of (**124b**) /%	Yield of (**137**) / %
1	R.T.	5 mins	15	12
1	0^0C	10 mins	19	16
0.10	R.T.	24 hours	22[a]	-

a 18% of starting material was also recovered.

Table 6.3- Rearrangement reactions using a phosphazene base

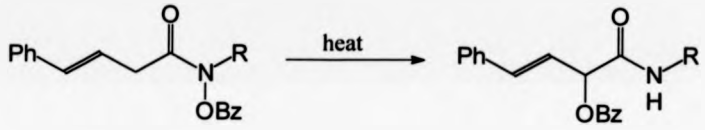
6.2.4 Thermally induced rearrangements

As the rearrangement reactions are obviously facilitated by base it can now be explained why, in some cases, the formation of rearranged products was observed during the preparation of the radical cyclisation precursors **121** (Scheme 6.10, see also Section 5.22). Preparation of these precursors using Method 1 involved sodium carbonate as an auxiliary base.



Scheme 6.10

However, no base was present in the radical cyclisation reactions themselves where the rearranged compounds were also formed. This led us to investigate whether the rearrangement could also occur thermally without the need of base (Scheme 6.11). The radical cyclisations were performed in refluxing toluene so we simply heated a number of the precursors in refluxing toluene. Heating the *N*-methyl precursor **121f** at 110^0C in toluene resulted in a very slow isomerisation (10% conversion after 24 hours). Increasing the temperature to 140^0C resulted in the reaction proceeding smoothly and cleanly in much less time (**124f**, 95% in 15 hours).



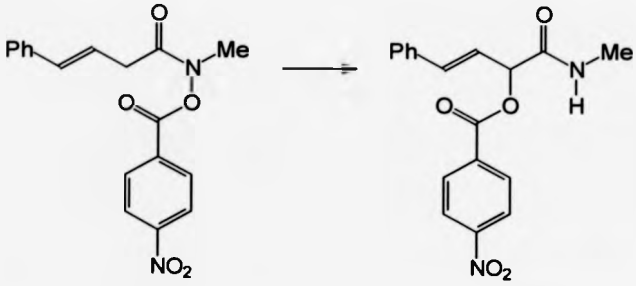
121b R = *n*-Bu
121c R = CH_2Ph
121f R = Me

124b R = *n*-Bu
124c R = CH_2Ph
124f R = Me

Scheme 6.11

Repeating this reaction with the *N*-*n*-butyl precursor **121b** gave complete conversion in 3 days and with the *N*-benzyl precursor **121c**, 80% yield in 4 days. From these results it can be seen that although the reactions took much longer than the base catalysed reactions they were much cleaner and gave excellent yields of rearranged compounds. In other work[138] it has been found that performing the reactions with triethylamine (1 eq.) in refluxing toluene resulted in much reduced reaction times (**121f** gave 85% yield in 45 minutes). It was also demonstrated that the rearrangement occurred much faster with a *para*-nitrobenzoyl migrating group (reaction of **138** with

1 eq. of Et_3N in toluene at 110^0C gave **139** in 58% yield in 10 minutes, Scheme 6.12).



138 **139**

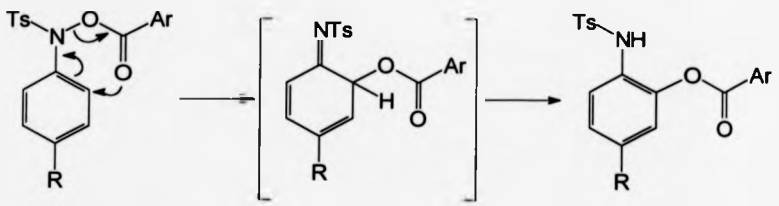
Scheme 6.12

6.3 Possible mechanisms

As mentioned earlier in Section 6.2.1, it is possible that the mechanism for this rearrangement is the same as that proposed by Hoffman (i.e. *via* an ion-pair intermediate) but it may also be a novel 3,3-sigmatropic rearrangement proceeding *via* the enol or enolate form of the precursors, (Scheme 6.8). Both processes can in theory be catalysed by a base capable of reversible H^+ transfer under the reaction conditions.

Related [3,3] sigmatropic rearrangements of different hydroxamic acid derivatives have been reported previously. Oae[139] reports the thermal conversion of *O*-(*p*-

substituted benzoyl)-*N*-(*p*-toluenesulfonyl)-*N*-arylhydroxylamines, **140**, to *o*-acyloxy-*p*-toluenesulfonanilides, **141** (Scheme 6.13).

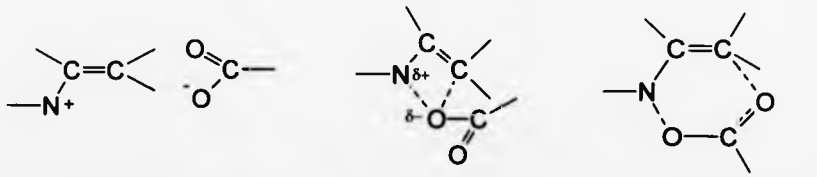


140 **141**

R = CH_3, H, Cl;
Ts = *p*- $CH_3C_6H_4SO_2$

Scheme 6.13

Oae divides reactions which involve concurrent *N*-O bond cleavage and O-C bond formation into three classes, *i.e.* (a) scrambling process, (b) sliding process and (c) cyclic process, involving the transition states shown schematically in Figure 6.1



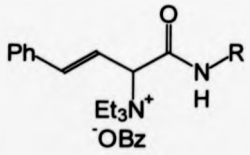
a) scrambling process b) sliding process c) cyclic process

Figure 6.1 - Possible transition states for [3,3] sigmatropic rearrangements

On the basis of ^{18}O tracer and kinetic experiments, Oae concludes that the process shown above (Scheme 6.13) proceeds *via* an intramolecular concerted process. The

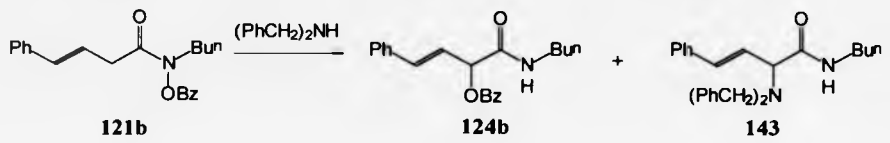
cyclic mechanism is rationalised by the strong electron-withdrawing nature of the sulfonyl group attached to the N atom and the poor leaving ability of the benzoyloxy leaving group.

Hoffman and co-workers performed a range of experiments to prove that their rearrangements proceeded *via* an ion-pair intermediate and that the rate determining step was a concerted proton removal by base and α-lactam formation. Hoffman found that triethylamine competitively trapped the ion-pair to give **136** (see Scheme 6.6) when only weak nucleophiles were present. In order to gain insight into the mechanism of our rearrangement we checked for the formation of the corresponding triethylammonium salt in our reactions, (selected reaction mixtures were evaporated directly without aqueous work-up) but no evidence of the triethylamine trapped product **142**, was detected.



142

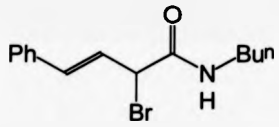
In addition, an experiment was performed with dibenzylamine in place of triethylamine. Reaction of the *N*-*n*-butyl precursor **121b** (CH_2Cl_2, 40^0C, 24 hours) with dibenzylamine gave no evidence of competitive trapping by the amine to give **143** (Scheme 6.14). On working up the reaction, **124b** was obtained as before in 80% yield.



121b **124b** **143**

Scheme 6.14

The reaction was also performed in the presence of lithium bromide to test for competitive trapping by bromide to give the 2-bromoamide **144**. However, under the same conditions as those used by Hoffman only the 2-benzoyloxy compound, **124b** was isolated.



144

These results indicate that it is unlikely that the Hoffman mechanism is operating in our reactions and it is more likely that a concerted [3,3] sigmatropic process is occurring.

6.4 Conclusions and future work

The thermal and base catalysed rearrangements of *O*-benzoyl hydroxamic acid derivatives, **121b,c,e-g**, shown here provide a convenient route to the formation of benzoyl ester protected α-hydroxyamides, **124b,c,e-g**. The use of chiral auxiliaries **121g** produced only modest diastereoselectivities and if used in conjunction with

chiral bases these selectivities could be moderated. This suggests that it may be possible to develop an asymmetric version of the reactions using catalytic chiral bases. The use of strong organic bases had a large accelerating influence on the reaction but better yields were obtained with the slower, thermally induced rearrangements. The use of catalytic amounts of base showed that the reaction is not stoichiometric with respect to base

Experimental observations so far indicate a mechanism involving a [3,3]-sigmatropic rearrangement but more needs to be done to prove this. ^{18}O labelling experiments would be useful in determining if the reaction is concerted or involves an ion-pair intermediate as could cross-over experiments. The [3,3]-sigmatropic rearrangement is initiated by formation of the enolate so reagents could be added which stabilise the enolate and their effect on the reaction determined.

Chapter 7

Experimental

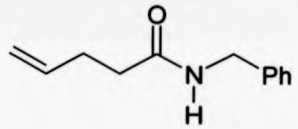
7.1 General experimental

Melting points were recorded on a Stuart Scientific SMP1 melting point apparatus and are uncorrected. Accurate masses were performed either on a Kratos MS80 spectrometer at the University of Warwick or by the EPSRC Mass Spectroscopy Service at Swansea University. Only molecular ions (M+ or MH+) and major peaks are reported and the intensities of these peaks are quoted as percentages of the base peak. Microanalyses were recorded at the University of Warwick on a Leeman Labs Inc. CE440 Elemental Analyser. Infra-red spectra were recorded in a solution cell, as Nujol mulls or neat, as stated in the text on a Perkin-Elmer 1720X Fourier transform spectrometer, with only selected absorbances (ν_{max}) being reported. ^{1}H NMR spectra were recorded at either 250 MHz or 400 MHz on a Bruker ACF250 or Bruker ACP 400 instrument respectively. Chemical shifts (δ) are quoted in parts per million (ppm) and referenced to the appropriate solvent peak. Coupling constants are quoted in Hertz. ^{13}C NMR spectra were recorded at 62.9 MHz on a Bruker ACF250 or 100.6 MHz on a Bruker ACP 400 instrument. Chemical shifts are quoted in ppm and referenced to the appropriate solvent peak. Chemicals used in the experimental were obtained from Sigma-Aldrich, Lancaster or Avocado at the highest grade available. All solvents were purchased from Fisons Scientific Equipment at SLR grade and purified, when needed, by literature methods.[140] Anhydrous dichloromethane was obtained by distilling from calcium hydride over nitrogen and dry toluene was

obtained by distilling from sodium under nitrogen. Flash column chromatography was carried out on silica gel (Merck Kieselgel $60F_{254}$, 230=400 mesh). Tlc was carried out using aluminium backed plates precoated with silica (0.2mm, $60F_{254}$). The tlc plates were developed using one or more of the following agents: UV fluorescence (254 nm), phosphomolybdic acid or potassium permanganate solution.

7.2 Experimental for Chapter 2

7.2.1 *N*-Benzylpent-4-enamide, 51[141]

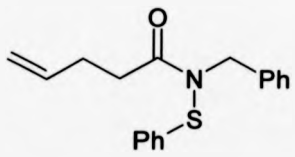


Pent-4-enoyl chloride was prepared by addition of oxalyl chloride (8.0 ml) dropwise to pent-4-enoic acid (4.0 ml) and refluxing the solution for 3 hours. Distillation (25°C, atmospheric pressure) gave pent-4-enoyl chloride as colourless oil which was used immediately or stored at -7°C. The pent-4-enoyl chloride (0.6 ml, 5.03 mmol, 1.1 eq.) was added dropwise to a stirring solution of benzylamine (0.5 ml, 4.57 mmol, 1 eq.) in diethyl ether. A white precipitate formed immediately and the reaction was left stirring at room temperature for 3 hours. Water was added to dissolve the precipitate and the ether layer extracted. The organic extracts were washed with 10% HCl, $NaHCO_3$ and water, dried over anhydrous magnesium sulphate and concentrated on a rotary evaporator. *N*-Benzylpent-4-enamide was

obtained in 81% yield (1.5 g) as a colourless oil. (Found C 75.93, H 7.93, N 7.25. $C_{12}H_{15}NO$ requires C 76.16, H 7.99, N 7.40).

Rf (1:1 pet.ether:EtOAc): 0.42 ν_{max} (neat)/cm^{-1} 3376, 1717, 1652; δ_H(250 MHz; $CDCl_3$) 2.28-2.48 (4H, m, CH_2CH_2), 4.45 (2H, d, J=5.5, CH_2Ph), 5.01 (1H, dq, J=10.2, 1.3, CH=CH_2), 5.07 (1H, dq, J=17.1, 1.6, CH=CH_2), 5.71 (1H, br s, NH), 5.83 (1H, ddt, J=17.1, 10.2, 6.3, CH=CH_2), 7.24-7.38 (5H, m, Ph); δ_C(250 MHz; $CDCl_3$) 29.56 (CH_2CH_2CO), 35.45 (CH_2CO), 43.24 (CH_2Ph), 115.33 (CH=CH_2), 127.16, 127.51, 128.43 (3 x Ar), 136.99 (CH=CH_2), 138.40 (Ph C_1), 172.50 (CO); *m/z* (EI) 189 (M^+, 36%), 106 (55), 91 (100).

7.2.2 *N*-Benzyl-*N*-phenylthiopent-4-enamide, 52

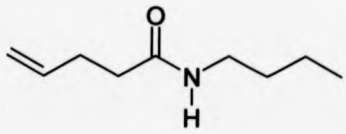


Sodium hydride (60% dispersion in oil, 0.06 g, 1.45 mmol) was stirred in pet. ether (5 ml) for 5 minutes. The pet. ether was decanted off and this procedure repeated twice more to remove all traces of oil. Dry tetrahydrofuran (25 ml) was added, followed by amide **51** (0.25 g, 1.32 mmol). The reaction was refluxed for 5 hours and then left stirring at room temperature overnight. The reaction was cooled to -78^{0}C before PhSCl[142] (0.15 ml, 1.0 eq.) was added and the reaction stirred at this temperature for one hour. The reaction was poured into water (10 ml) and extracted

into diethylether (3 x 20 ml). The organic layers were combined, dried over anhydrous magnesium sulphate and evaporated under vacuum. Purification by flash column chromatography, eluting with 15:1 pet. ether/EtOAc gave 0.114 g (29%) of *N*-benzyl-*N*-phenylsulfenylpent-4-enamide as a colourless oil. (Found M^+ 297.1180. $C_{18}H_{19}NOS$ requires 297.1189).

ν_{max} (neat)/cm^{-1} 3064, 3031, 1674, 1640, 1439 916, 738; δ_H(250 MHz; $CDCl_3$) 2.36-2.45 (2H, m, CH_2CH), 2.86 (2H, t, J=7.5, CH_2CH_2), 4.82 (2H, s, PhCH_2), 4.93-5.08 (2H, m, CH=CH_2), 5.82 (1H, ddt, J=17.0, 10.3, 6.6, CH=CH_2), 7.06 (2H, d, J=8.1, SPh), 7.19-7.37 (8H, m, Ph, SPh); δ_C(250 MHz; $CDCl_3$) 29.41 (*C*H_2CH_2CO), 32.38 (*C*H_2CO), 54.04 (PhCH_2), 115.36 (CH=*C*H_2), 122.78, 126.43, 127.58, 128.34, 128.70, 129.34 (6 x Ar), 137.07 (*C*H=CH_2), 137.32, 137.44 (Ar C_1), 177.76 (CO); *m/z* (CI; NH_3) 298 (M^+, 19%), 190 (100), 91 (29).

7.2.3 *N*-Butylpent-4-enamide[143]

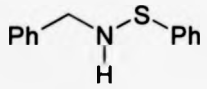


Pent-4-enoyl chloride (0.50 ml, 5.5 mmol) (prepared as described previously, 7.21) was added dropwise to a stirring solution of butylamine (1.10 ml, 11 mmol.) in diethyl ether. A white precipitate formed immediately and the reaction was left stirring at room temperature for 3 hours. Water was added to dissolve the precipitate

and the ether layer extracted. The organic extracts were washed with water, dried over anhydrous magnesium sulphate and concentrated on a rotary evaporator. *N*-butylpent-4-enamide was obtained in 76% yield (0.65 g) as a yellow oil. Spectral details matched those published.

δ_H(250 MHz; $CDCl_3$) 0.72 (3H, t, J=7.2, CH_3), 1.08-1.36 (4H, m, $CH_2CH_2CH_3$), 2.07-2.23 (4H, m, CH_2CH_2CO), 3.03, (2H, q, J=6.5, $NHCH_2$), 4.79, (1H, d, J=10.4, $CH=CH_2$), 4.86 (1H, d, J=17.0, $CH=CH_2$), 5.63 (1H, ddt, J=17.0, 10.4, 6.2, $CH=CH_2$), 6.92 (1H, br s, NH); δ_C(250 MHz; $CDCl_3$) 13.95 (CH_3), 20.32 ($NHCH_2$), 30.07 and 31.55 ($CH_2CH_2CH_3$), 35.86 (CH_2CH_2CO), 39.47 (CH_2CO), 115.41 ($CH=CH_2$), 137.38 ($CH=CH_2$), 173.10 (CO); *m/z* (EI) 155 (M^+, 50%), 113 (50), 100 (58), 55(96), 44 (100).

7.2.4 *N*-Benzylbenzenesulfenamide, 53

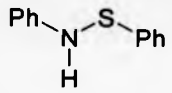


Phenylsulfenyl chloride[142] (0.63 ml, 4.58 mmol) was added dropwise to a stirring solution of benzylamine (1.00 ml, 9.15 mmol) in dry diethyl ether (125 ml) under nitrogen. After stirring for 20 minutes water was added to dissolve the precipitate and the ether layer extracted. The organic extracts were washed with water, dried over anhydrous magnesium sulphate and concentrated on a rotary evaporator to give 0.86 g of *N*-benzylphenylsulfenamide as an orange-brown oil (93% from PhSCl). The

product was found to decompose on silica gel and so was used without further purification. (Found MH^+ 216.0843. $C_{13}H_{13}NS$ requires 216.0848).

Rf (30:1 pet. ether:EtOAc): 0.45; ν_{max} (neat)/cm^{-1} 3300 (NH), 3508, 1581, 1477; δ_H(250 MHz; $CDCl_3$) 4.59 (2H, s, CH_2), 7.19-7.75 (10H, m, Ph); δ_C(250 MHz; $CDCl_3$) 69.57 (CH_2) 125.85, 126.80, 127.91, 128.29, 128.90, 129.42, 137.68, 139.42, (8 x Ar), *m/z* (EI) 215 (M^+, 24%), 136 (20), 109 (70), 77 (26).

7.2.5 N-Phenylbenzenesulfenamide, 54[144]



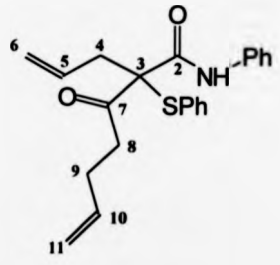
A solution of phenylsulfenyl chloride[142] (0.77 g, 5.5 mmol) in dry diethyl ether (5 ml) was added dropwise to a stirring solution of phenylamine (1.00 ml, 11 mmol) in dry diethyl ether at -20°-30°C under nitrogen. The reaction mixture was stirred at this temperature for 30 minutes before warming to room temperature. A thick, dark cream precipitate (phenylamine hydrochloride) formed and was filtered off. The solvent was evaporated to give 0.84 g of crude *N*-phenylphenylsulfenamide (38%) as a red-brown solid.

ν_{max} (neat)/cm^{-1} 3357, 2922, 1709, 1600, 1463, 1377; δ_H(250 MHz; $CDCl_3$) 5.18 (1H, br s, NH), 6.70-7.35 (10H, m, Ph); δ_C(250 MHz; $CDCl_3$) 115.35, 121.29,

123.14, 126.25, 129.73, 130.11, 142.38, 147.54; *m/z* (EI) 201 (M^+, 64%), 109 (32), 92 (100), 65 (93).

7.2.6 Reaction of *N*-phenylbenzenesulfenamide with pent-4-enoyl chloride, triethylamine and DMAP

Pent-4-enoyl chloride (0.12 ml, 0.99 mmol) was added dropwise to a stirring solution of *N*-phenylphenylsulfenamide **54** (0.20 g, 0.99 mmol), triethylamine (0.28 ml, 1.98 mmol) and DMAP (0.03 g, 0.2 mmol) in dichloromethane (15 ml) and the mixture refluxed for 12 hours. Diethyl ether was added to the orange-black solution to form the triethylamine hydrochloride precipitate which was removed by filtration. The filtrate was concentrated and purified by flash column chromatography. The product isolated was tentatively assigned as **57** on the basis of limited spectral details.



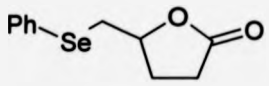
57

δ_H(400 MHz; $CDCl_3$) 2.37 (2H, ddt, J = 7.3, 1.5, 9-H), 2.67 (1H, ddt, J=15.3, 6.8, 0.9, 4-H), 2.74 (1H, dt, J=18.0, 7.6, 8-H), 3.00 (1H, dt, J=18.0, 7.3, 8-H), 3.14 (1H, ddt, J=15.3, 6.8, 1.0, 4-H), 4.98 (1H, dq, J=10.0, 1.8, 11-H), 5.07 (1H, dq, J=18.0, 1.8, 11-H), 5.15 (2H, m, 5-H, 10-H), 7.06-7.58 (10H, m, Ar); δ_C(400 MHz; $CDCl_3$)

27.8 (9-C), 37.0 (4-C), 37.6 (8-C), 115.6 (11-C), 119.3 (6-C), 120.1, 124.9, 129.5, 128.9, 129.2, 130.8, 133.3, 136.0 (Ar), 133.9 and 136.6 (5-C and 10-C), 165.8 (2 C), 204.0 (7-C); *m/z* (EI, FAB) 366 (80%), 283 (36), 136 (26), 93 (46), 55 (100).

7.2.7 Reaction of *N*-benzylpent-4-enamide, 51, with phenylselenyl chloride[142]

Sodium hydride (0.025 g, 60% dispersion in oil, 0.63 mmol), was washed with pet. ether to remove the oil (as described earlier). *N*-Benzylpent-4-enamide, **51** (0.10 g, 0.53 mmol) was added with tetrahydrofuran (20 ml) and the solution refluxed under nitrogen overnight. The reaction mixture was cooled to -78°C and light excluded before phenylselenyl chloride (0.10 g, 0.53 mmol) was added. The reaction was stirred at this temperature for one hour and then poured into water to quench the reaction. The product was extracted into diethyl ether and washed with H_2O. The organic extracts were dried over anhydrous magnesium sulphate and concentrated on a rotary evaporator. Purification by flash column chromatography on silica gel, eluting with 5:1 pet. ether:EtOAc gave only one product which was assigned as 4-(phenylseleno)methylbutan-4-olide (0.03 g, 22%, yellow oil). (Found M^+ 256.0003, $C_{11}H_{12}O_2{}^{80}Se$ requires 256.0003).



59

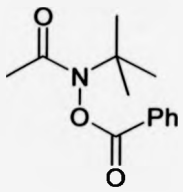
ν_{max} (neat)/cm^{-1} 2928, 1772, 1576, 1154; δ_H(250 MHz; $CDCl_3$) 1.85-2.03 (1H, m), 2.32-2.65 (3H, m), 2.99 (1H, dd, J=12.8, 7.9, $PhSeCH_2$), 3.28 (1H, dd, J=12.8, 4.9, $PhSeCH_2$), 4.58-4.69 (1H, m, CHO), 7.25-7.28 (3H, m, Ph), 7.51-7.55 (2H, m, Ph); δ_C(250 MHz; $CDCl_3$) 28.04, 29.16, 32.28, 79.95, 128.08, 129.17, 129.74, 133.63, 176.98; *m/z* (EI) 256 (M^+ for ^{80}Se, 66%), 171 (33), 91 (60), 85 (93), 55 (100), 43 (47).

7.2.8 Preparation of *N*-benzoyloxy-*t*-butylamine hydrochloride salt (^{t}BuNHOCOPh.HCl)[145]

t-Butylamine (1.05 ml, 10 mmol), dibenzoyl peroxide (2.40 g, 10 mmol, freshly recrystallised from chloroform/methanol 5:1) and potassium carbonate (2.40 g) were stirred together under nitrogen in chloroform (50 ml) at 60°C (reflux) for 24 hours. A white precipitate formed which was filtered off and the filtrate concentrated under reduced pressure to give a yellow oil (2.39 g crude). The oil was dissolved in ether (80 ml) and hydrogen chloride gas bubbled through half the resulting solution to yield 0.38 g (33% yield from starting amine) of the hydrochloride salt of *O*-benzoyl-*N*-(*t*-butyl)hydroxylamine.

Rf (10:1 Pet.ether:EtOAc): 0.42; mp 150-153°C; ν_{max} (neat)/cm^{-1} 1763, 1215, 753; δ_H(250 MHz; $CDCl_3$) 1.64 (9H, s, ^{t}Bu), 7.46 (2H, t, J=7.9, *m*-Ph), 7.64-7.70 (1H, m, *p*-Ph), (2H, m, *o*-Ph); δ_C(250 MHz; $CDCl_3$) 24.68 ($C(CH_3)_3$), 63.09 ($C(CH_3)_3$), 125.71, 129.57, 130.88, 135.67 (4 x Ar), 163.40 (CO); *m/z* (CI; NH_3) 194 (MH^+ 7%), 105 (9), 74 (100), 58(30).

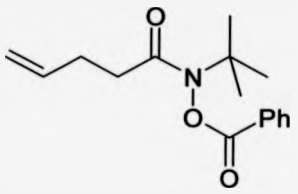
7.2.9 Reaction of *O*-benzoyl-*N*-(*t*-butyl)hydroxylamine with acetyl chloride - preparation of *N*-benzoyloxy-*N*-*t*-butyl-acetamide, 67[145]



The remaining *O*-benzoyl-*N*-(*t*-butyl)hydroxylamine, **65** formed in 7.28 (1.19 g, 6.2 mmol), was taken and immediately reacted with acetyl chloride (0.44 ml, 6.2 mmol) in diethyl ether (40 ml) and pyridine (0.5 ml, 6.2 mmol) added dropwise to the stirring solution. The reaction was refluxed overnight and a white precipitate formed. The precipitate was filtered off and the filtrate concentrated to give a colourless oil. Purification by flash column chromatography on silica gel (10:1 pet. ether:EtOAc) gave 0.28 g (24%) of *N*-benzoyloxy-*N*-*t*-butyl-acetamide, **67** as a colourless oil. Spectral details matched those published.

Rf (10:1 Pet.ether:EtOAc): 0.19; ν_{max} (neat)/cm^{-1} 2983, 1764, 1678, 1366, 1234, 1041,708; δ_H(250 MHz; $CDCl_3$) 1.43 (9H, s, ^tBu), 1.92 (3H, s, Me), 7.43-7.49 (2H, m, *m*-Ph), 7.61 (1H, tt, J=7.4, 1.5, *p*-Ph), 8.05 (2H, dd, J=8.4, 1.5, *o*-Ph); δ_C(250 MHz; $CDCl_3$) 22.71 and 27.33 ($C(CH_3)_3$), 62.35 ($C(CH_3)_3$), 126.57, 128.84, 129.81. 134.30 (4 x Ar), 165.29 (OCOPh), 171.83 (NCO); *m/z* (CI; NH_3) 236 (MH^+, 100%), 180 (19), 116 (40), 105 (60).

7.2.10 *N*-Benzoyloxy-*N*-*t*-butylpent-4-enamide, 62

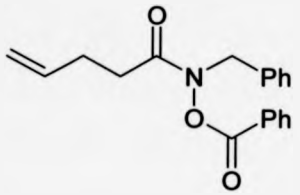


t-Butylamine (0.9 ml, 8.66 mmol), dibenzoyl peroxide (2.1 g, 8.69 mmol, freshly recrystallised from chloroform/methanol 5:1) and potassium carbonate were refluxed together in ether for 24 hours. The formed white precipitate was filtered off to give a clear yellow solution to which was added pyridine (0.7 ml, 8.66 mmol) followed by dropwise addition of pent-4-enoyl chloride (7.2.1). The reaction was refluxed overnight. The reaction mixture was washed with H_2O, 10% HCl and $NaHCO_3$ solution to remove the pyridine hydrochloride and any excess pentenoic acid. The combined organic phases were dried over anhydrous magnesium sulphate and evaporated under vacuum. Purification by flash column chromatography (10/1 pet.ether/EtOAc) gave 0.8 g (32%) of *N*-benzoyloxy-*N*-*t*-butylpent-4-enamide, **62** as a colourless oil. (Found M^+ 275.1525. $C_{16}H_{21}NO_3$ requires 275.1522).

Rf (10:1 Pet.ether:EtOAc): 0.39; ν_{max} (neat)/cm^{-1} 3073, 2982, 1761, 1678, 1237, 1041, 709; δ_H(250 MHz; $CDCl_3$) 1.49 (9H, s, *t*-Bu), 2.20-2.42 (4H, m, CH_2CH_2), 4.93 (1H, dq, J=10.2, 1.8, CH=CH_2), 4.99 (1H, dq, J=17.2, 1.8, CH=CH_2), 5.77 (1H, ddt, J=17.2, 10.2, 6.2 CH=CH_2), 7.48-7.56 (2H, m, *m*-Ph), 7.68 (1H, t, J=7.6, 1.3, *p*-Ph), 8.10 (2H, dd, J=8.4, 1.3, *o*-Ph); δ_C(250 MHz; $CDCl_3$) 27.36 (C(CH_3)$_3$), 28.03 (C$H_2$$CH_2$CO), 33.24 (C$H_2$CO), 62.57 (C(CH$_3$)$_3$), 114.99 (CH=C$H_2$), 126.61, 128.85,

129.84, 134.30, 137.16 (*C*H=CH_2), 165.40 (OCOPh), 173.7 (NCO); *m/z* (CI; NH_3) 276 (MH^+, 99%), 220 (27), 194 (32), 105(100).

7.2.11 *N*-Benzoyloxy-*N*-benzylpent-4-enamide, 63

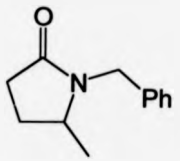


Dibenzoyl peroxide (3.20 g, 70% in H_2O, 9.2 mmol) in dichloromethane (10 ml) was added to a dichloromethane solution (20 ml) of benzylamine (1.0 ml, 9.2 mmol) and potassium carbonate (3.2 g). The reaction was stirred at room temperature for 2 hours before addition of pent-4-enoyl chloride (7.2.1) (1.0 ml, 10.1 mmol). The reaction was stirred for a further 1.5 hours before being quenched with water. The organic extracts were washed with water, dried over anhydrous magnesium sulphate and evaporated on a rotary evaporator. Purification by flash column chromatography (5:1. 3:1, pet. ether:EtOAc) gave 0.80 g (28%) of *N*-benzoyloxy-*N*-benzylpent-4-enamide as a colourless oil. (Found MH^+ 310.1445. $C_{19}H_{19}NO_3$ requires 310.1444).

ν_{max} (neat)/cm^{-1} 1764, 1674, 1452, 1265, 738; δ_H(250 MHz; $CDCl_3$) 2.43 (4H, br s, CH_2CH_2), 4.93-5.05 (4H, m, CH_2Ph, CH=CH_2), 5.75-5.94 (1H, m, C*H*=CH_2), 7.27-7.38 (5H, m, Ph), 7.42-7.55 (2H, m, *m*-Ph, OCOPh), 7.60-7.67 (1H, m, *p*-Ph, OCOPh), 7.96 (2H, dd, J=7.8, 1.5, *o*-Ph, OCOPh); δ_C(250 MHz; $CDCl_3$) 28.69

(CH_2), 32.00 (CH_2CO), 52.23 (NCH_2), 115.87 ($CH=CH_2$), 127.05, 128.31, 128.99, 129.29, 130.30, 134.89, 135.76 (7 x Ar), 137.32 ($CH=CH_2$), 164.74 (OCOPh), 173.06 (NCO); *m/z* (CI, NH_3) 310 (MH^+, 47%), 190 (92), 105 (100).

7.2.12 Cyclisation of *N*-benzoyloxy-*N*-benzylpent-4-enamide, 63 to form *N*-benzyl-5-methylpyrrolidin-2-one, 64[146]

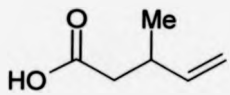


A solution of tributyltin hydride (0.32 ml, 1.07 mmol, 1.1 eq.) and AIBN (0.02 g, 0.1 eq.) in degassed toluene (6.5 ml) was added *via* a syringe pump over 8 hours to a refluxing solution of *N*-benzoyloxy-*N*-benzylpent-4-enamide (0.30 g, 0.97 mmol) in degassed toluene (6.5 ml). After refluxing for a further 12 hours the solvents were removed on a rotary evaporator. Analysis of the crude product by ^1H NMR indicated the presence of the desired cyclised product, *N*-benzyl-5-methylpyrrolidin-2-one, by comparison with published data.[146]

δ_H(250 MHz; $CDCl_3$) 1.56 (3H, CH_3), 1.5-2.2 (2H, m, 4-H), 2.3-2.5 (2H, m, 3-H), 3.48-3.56 (1H, m, 5-H), 3.98 (1H, d, J=15.1, CH_2Ph), 4.96 (1H, d, J=15.1, CH_2Ph), 7.20-7.36 (5H, m, Ph).

7.3 Experimental for Chapter 3

7.3.1 3-Methylpent-4-enoic acid[147]

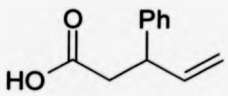


Crotyl alcohol (8.53 ml, 0.1 mol), triethylorthoacetate (46 μl, 0.25 mol) and hexanoic acid (85 μl, 6 mmol) were added to a dried flask which was set up for distillation. The solution was heated in an oil bath with distillation of ethanol. Additional portions of hexanoic acid were added after 3, 3.5 and 4.5 hours. After 6 hours, the solution was cooled and potassium hydroxide (0.1 mol) in water (3 ml) and methanol (75 ml) was added. The reaction mixture was heated at reflux for 1 hour under nitrogen. After cooling to room temperature the solution was washed 3 times with diethyl ether (ether washings discarded) and then acidified with concentrated hydrochloric acid before being extracted with diethyl ether. The organic extracts were dried over anhydrous magnesium sulphate and concentrated on a rotary evaporator to give 3-methylpent-4-enoic acid as a yellow oil (74%) which was used without further purification.[93] Spectral details matched those published.

δ_H(250 MHz; $CDCl_3$) 1.07 (3H, d, J=6.7, Me), 2.28 (1H, dd, J=15.1, 7.6, CH_2), 2.39 (1H, dd, J=15.1, 7.0, CH_2), 2.59-2.73 (1H, m, C*H*Me), 4.96 (1H, ap dt, J=10.4, 1.3, CH=CH_2), 5.03 (1H, ap dt, J=17.4, 1.3, CH=CH_2), 5.77 (1H, ddd, J=17.4, 10.4, 6.7, C*H*=CH_2), 11.6 (1H, s, -CO_2H); δ_C(250 MHz; $CDCl_3$) 19.79 (Me), 34.33 (CHMe),

41.31 (CH_2CO), 113.71 ($CH{=}CH_2$), 142.38 ($CH{=}CH_2$), 179.37 (CO); *m/z* (EI) 114 (M^+, 26%), 99 (36), 96 (43), 69 (84), 55 (94), 42 (100).

7.3.2 3-Phenylpent-4-enoic acid[93]

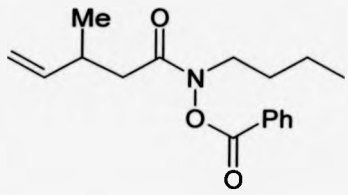


Method as for 3-methylpent-4-enoic acid above (7.3.1). Cinnamyl alcohol (0.22 mol), triethylorthoacetate (0.22 mol) and hexanoic acid ($4.5x10^{-5}$ mol) were heated together with distillation of ethanol. Following work-up, 3-phenylpent-4-enoic acid was obtained as a yellow oil (24% yield) which was used without further purification.[93] Spectral details matched those published.

δ_H(250 MHz; $CDCl_3$) 2.75 (1H, dd, J=15.6, 7.4, CH_2), 2.83 (1H, dd, J=15.6, 8.0, CH_2), 3.88 (1H, q, J=7.5, CHPh), 5.09 (1H, tt, J=17.4, 1.5, CH=CH_2), 5.10 (1H tt, J=10.1, 1.2, CH=CH_2), 5.99 (1H, ddd, J=17.4, 10.1, 7.0, C*H*=CH2), 7.21-7.37 (5H, m, Ph); δ_C(250 MHz; $CDCl_3$) 39.93 (CH_2CO), 45.11 (CHPh), 114.97 ($CH{=}CH_2$), 126.74, 128.59, 139.87, (3 x Ar), 142.06 ($CH{=}CH_2$), 178.26 (CO);

7.3.3 Preparation of N-benzoyloxypent-4-enamides - Method 1

7.3.3.1 *N*-Benzoyloxy-*N*-butyl-3-methylpent-4-enamide, 72a

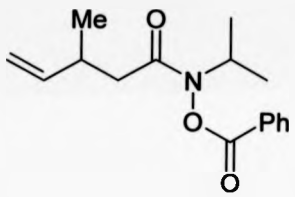


A slurry of $(PhCO_2)_2$ (2.63 g, 1 eq., 70% in H_2O) in dichloromethane (30 ml) was added to a solution of $NaHCO_3$ (2.60 g, 4.5 eq.) and *n*-butylamine (0.75 ml, 7.58 mmol, 1eq.) in dichloromethane (40 ml) at room temperature. The reaction was left stirring for 1.5 hours. 3-Methyl-pent-4-enoyl chloride (1.11 g, 1.1 eq.) (prepared by reaction of 3-methylpent-4-enoic acid with oxalyl chloride) was then added dropwise and the reaction left stirring for a further 2 hours. The reaction was quenched with water and the product extracted with dichloromethane and washed with water. The combined organic phases were dried over anhydrous magnesium sulphate and evaporated under vacuum. Purification by flash column chromatography (15:1, 10:1, 5:1, pet. ether:ethyl acetate) furnished the above compound as a yellow oil (1.17 g, 53%). (Found MH^+ 290.1759. $C_{18}H_{23}NO_3$ requires 290.1757).

ν_{max} (neat)/cm^{-1} 3075, 2960, 2873, 1766, 1680, 1600, 1453, 1408, 1242, 1015, 915, 710; δ_H(250 MHz; $CDCl_3$) 0.93 (3H, t, J=7.3, CH_3), 1.06 (3H, d, J=6.7, Me), 1.39 (2H, sx, J=7.3, C*H*$_2$CH$_3$), 1.63 (2H, qn, J=7.3, C*H*$_2$CH$_2$CH$_2$), 2.23 (1H, dd, J=15.5, 7.3, CH_2CO), 2.37 (1H, dd, J=15.5, 6.1 CH_2CO) 2.79, (1H, sp, J=6.7, CHMe), 3.82

(2H, t, J=7.3, NCH_2), 4.94 (1H, d, J=11.0, CH=CH_2), 5.00 (1H, , J=17.7, CH=CH_2), 5.79 (1H, m, CH=CH_2), 7.53 (2H, t, J=7.6 *m*-Ph), 7.68 (1H, t, J=7.2, *p*-Ph), 8.08-8.12 (2H, m, *o*-Ph); δ_C(250 MHz; $CDCl_3$) 13.99 (CH_2CH_3), 19.84 (Me), 20.18 and 29.44 ($CH_2CH_2CH_3$), 34.50 (*C*HMe), 39.28 (CH_2CO), 48.12 (NCH_2), 113.38 (CH=CH_2), 127.16, 129.24, 130.21, 134.76, (4 x Ar), 143.05 (*C*H=CH_2), 164.68 (O*C*OPh), 172.39 (NCO); *m/z* (CI; NH_3) 290 (MH^+, 57%), 194 (14), 170 (14), 105 (100).

7.3.3.2 *N*-Benzoyloxy-*N*-isopropyl-3-methylpent-4-enamide, 72b

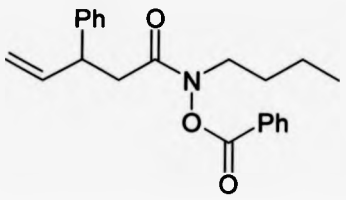


Prepared using the above procedure (7.3.3.1) with isopropylamine (0.75 ml, 11.7 mmol). Flash column chromatography (10:1, 5:1, pet.ether:ethyl acetate) gave the above product as a pale, yellow oil (0.90 g, 28%). (Found MH^+ 276.1603 $C_{16}H_{22}NO_3$ requires 276.1601).

ν_{max} (neat)/cm^{-1} 2979, 1767, 1681, 1238, 1007, 709; δ_H(400 MHz; $CDCl_3$) 1.01 (3H, d, J=7.0, CHMe), 1.07-1.29, (6H, m, CH(CH_3)$_2$), 2.11-2.39 (2H, br m, CH_2), 2.76 (1H, sp, J=6.8, CHMe), 4.83 (1H, br s, CH(CH_3)$_2$), 4.89 (1H, d, J=10.5, CH=CH_2), 4.96 (1H, d, J=17.4, CH=CH_2), 5.74 (1H, ddd, J=17.4, 10.2, 7, CH=CH_2), 7.50 (2H, t, J=7.7 *m*-Ph), 7.64 (1H, t, J=7.4, *p*-Ph), 8.08, (2H, dd, J=8.6, 1.2, *o*-Ph); δ_C(250

MHz; $CDCl_3$) 19.17 ($CH(CH_3)_3$), 19.37 (Me), 33.34 (*C*HMe), 39.22, (CH_2), 49.70 (*C*H(CH_3)$_2$), 112.8 (CH=*C*H_2), 126.6, 128.69, 129.73, 134.12 (4xAr), 142.59 (*C*H=CH_2), 164.78 (O*C*OPh), 172.12 (NCO); *m/z* (CI; NH_3) 276 (MH^+, 84%), 180 (47), 105 (100).

7.3.3.3 *N*-Benzoyloxy-*N*-butyl-3-phenylpent-4-enamide, 72e

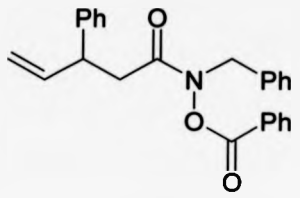


Prepared by the above procedure (7.3.3.1) using *n*-butylamine (0.75 ml, 7.58 mmol) and 3-phenyl pent-4-enoyl chloride (1.63 g, 8.35 mmol) (prepared itself from reaction of 3-phenylpent-4-enoic acid with oxalyl chloride). Flash column chromatography (10:1 pet.ether:EtOAc) gave the above product as a pale yellow oil (1.34 g, 50%). (Found MH^+ 352.1915. $C_{22}H_{25}NO_3$ requires 352.1914).

ν_{max} (neat)/cm^{-1} 2957, 1764, 1676, 1451, 1224, 700; δ_H(250 MHz; $CDCl_3$) 0.89 (3H, t, J=7.3, CH_3), 1.23-1.38 (2H, m, C*H*$_2$CH$_3$), 1.49-1.61 (2H, m, C*H*$_2$CH$_2$CH$_3$), 2.69 (1H, dd, J=15.5, 7.0, CH_2CO), 2.77 (1H, dd, J=15.5, 7.7, CH_2CO), 3.68-3.88 (2H, m, NCH_2), 4.02 (1H, ap q, J=7.1, CHPh), 5.02-5.11 (2H, m, CH=C*H*$_2$), 6.01 (1H, ddd, J=17.0, 10.4, 6.8, C*H*=CH2), 7.16-7.31 (5H, m, Ph), 7.53 (2H, t, J=7.7, *m*-Ph), 7.69 (1H, t, J=7.4, *p*-Ph), 8.06-8.11 (2H, m, *o*-Ph); δ_C(250 MHz; $CDCl_3$) 14.06 (CH_3),

20.14 and 29.40 ($CH_2CH_2CH_3$), 38.30 (CH_2CO) 45.34 (CHPh), 48.18 (NCH_2), 115.11 ($CH=CH_2$), 126.95, 128.12, 128.87, 129.37, 130.03, 130.30, 134.94, 140.87 (8 x Ar), 143.02 ($CH=CH_2$), 164.72 (OCOPh), 171.88 (NCO); *m/z* (CI, NH_3) 352 (MH^+, 36%), 232 (42), 117 (18), 105 (100).

7.3.3.4 *N*-Benzoyloxy-*N*-benzyl-3-phenylpent-4-enamide, 72f



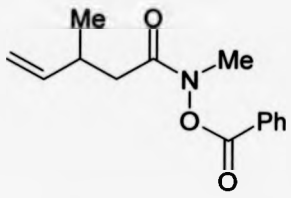
The above procedure (7.3.3.4) was repeated using benzylamine (0.75 ml, 6.87 mmol). Flash column chromatography (5:1 pet.ether:EtOAc) gave the above compound as a yellow oil (0.60 g, 23%). (Found MH^+ 386.1752. $C_{25}H_{24}NO_3$ requires 386.1757).

ν_{max} (neat)/cm^{-1} 1764, 1667, 1235, 698; δ_H(250 MHz; $CDCl_3$) 2.76 (2H, d, J=7.3, CH_2CO, 4.03 (1H, ap q, J=7.2, CHPh), 4.92-5.08 (4H, m, $CH=CH_2$ and CH_2Ph), 5.99 (1H, ddd, J=17.1, 10.4, 6.7, $CH=CH_2$), 7.15-7.32 (10H, m, Ph), 7.45 (2H, t, J=7.4, *m*-Ph, OCOPh,), 7.57-7.72 (1H, m, *p*-Ph OCOPh), 7.94 (2H, dd, J=8.6, 1.2, *o*-Ph, OCOPh); δ_C(250 MHz; $CDCl_3$) 38.28 (CH_2CO), 45.27 (CHPh), 52.04 (NCH_2), 115.33 ($CH=CH_2$), 127.03, 128.15, 128.24, 128.82, 128.87, 128.95, 128.97, 129.30, 130.40, 134.92, 135.55, 140.75, (12 x Ar), 143.02 ($CH=CH_2$) 164.73 (OCOPh),

171.95 (NCO); *m/z* (CI; NH_3) 386 (MH^+, 81%, 266 (55), 228 (30), 105 (100), 91 (32).

7.3.4 Preparation of N-benzoyloxypent-4-enamides - Method 2

7.3.4.1 *N*-Benzoyloxy-*N*-methyl-3-methylpent-4-enamide, 72c

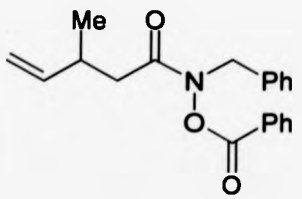


3-Methylpent-4-enoyl chloride (0.66 g, 5 mmol) in dichloromethane (40 ml) was added over 45-60 minutes to a 0°C solution of *N*-methylhydroxylamine hydrochloride (500 mg, 6 mmol) and triethylamine (1.53 ml, 11 mmol) in dichloromethane (50 ml). After addition was complete the reaction was warmed to room temperature and stirred for 1 hour. The reaction was quenched with water and the organic extracts washed with water, 10% HCl and brine, dried over anhydrous magnesium sulphate and concentrated on a rotary evaporator. *N*-Hydroxy-*N*-methyl-3-methylpent-4-enamide, **81c** was obtained as a yellow oil in 39% yield (0.28 g) and was used without further purification. Triethylamine (0.27 ml, 1.96 mmol) was added to a 0°C solution of *N*-hydroxy-*N*-methyl-3-methylpent-4-enamide **81c** (0.28 g, 1.96 mmol) in dichloromethane (10 ml). The reaction was stirred at this temperature for 10-12 minutes before dropwise addition of benzoyl chloride (0.25 ml, 2.15 mmol). The reaction was stirred for a further two hours at 0°C and two hours at room

temperature. The reaction mixture was washed with H_2O, 10% HCl and brine. Purification by flash column chromatography furnished *N*-benzoyloxy-*N*-methyl-3-methylpent-4-enamide [0.34 g, 69% (overall yield from *N*-methyl hydroxylamine hydrochloride - 27%) as a yellow oil. (Found MH^+ 248.1280. $C_{14}H_{18}NO_3$ requires 248.1287).

ν_{max} (neat)/cm^{-1} 2932, 1765, 1681, 1243, 1012, 709; δ_H(400 MHz; $CDCl_3$) 1.01 (3H, d, J=6.6, CH*Me*), 2.22 (1H, dd, J=15.4, 7.7, CH_2), 2.35 (1H, dd, J=15.4, 6.3, CH_2), 2.73 (IH, ap sp, J=6.8, C*H*Me), 4.89 (1H, d, J=10.0, CH=C*H*$_2$), 4.96 (1H, d, J=17.2, CH=C*H*$_2$), 5.74 (1H, ddd, J=17.2, 10.0, 7.0, C*H*=CH_2), 7.48 (2H, t, J=7.7, *m*-Ph), 7.64 (1H, t, J=7.5, *p*-Ph), 8.03-8.07 (2H, m, *o*-Ph); δ_C(400 MHz; $CDCl_3$) 19.43 (Me), 33.43 (*C*HMe), 35.45 (NMe), 38.71 (CH_2), 113.01 (CH=*C*H$_2$), 142.61 (*C*H=CH_2), 164.11 (OCOPh), 172.70 (NCO); *m/z* (CI; NH_3) 248 (MH^+, 37%), 128 (100), 105 (46).

7.3.4.2 *N*-Benzoyloxy-*N*-benzyl-3-methylpent-4-enamide, 72d

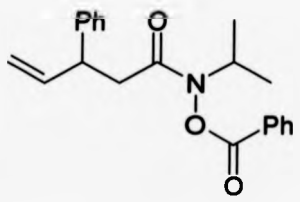


N-Benzyl-*N*-hydroxy-3-methylpent-4-enamide, **81d** [(0.58 g, 2.65 mmol), prepared as described above (7.3.4.1) in quantitative yield] was reacted with triethylamine

(0.38 ml, 2.74 mmol) and benzoyl chloride (0.35 ml, 3.00 mmol) using the procedure described above (7.3.4.1). Purification of the crude reaction mixture by flash column chromatography furnished *N*-benzoyloxy-*N*-benzyl-3-methylpent-4-enamide, **72d** in 50% yield (from *N*-benzyl hydroxylamine hydrochloride) as a yellow oil. (Found MH^+ 324.1598. $C_{20}H_{22}NO_3$ requires 324.1601).

ν_{max} (neat)/cm^{-1} 3066, 2962, 1764, 1679, 1452, 1231, 1009, 709; δ_H(250 MHz; $CDCl_3$) 1.05 (3H, d, J=7.0, Me), 2.27 (1H, dd, J=15.6, 7.6, CH_2CO), 2.41 (1H, dd, J=15.6, 6.6, CH_2CO), 2.81 (1H, ap sp, J=6.7, CHMe), 4.88-5.03 (2H, m, CH=CH_2), 5.77 (1H, ddd, J=17.1, 10.4, 6.7, C*H*=CH_2), 7.29-7.34 (5H, m, Ph), 7.45 (2H, t, J=7.8, *m*-Ph, OCOPh), 7.63 (1H, t, J=7.5, *p*-Ph, OCOPh), 7.97 (2H, d, J=7.7, *o*-Ph, OCOPh); δ_C(400 MHz; $CDCl_3$) 19.67 (Me), 33.66 (CHMe), 39.05 (CH_2CO), 51.66 (CH_2Ph), 113.27 (CH=CH_2), 142.75 (CH=CH_2), 164.37 (OCOPh), 172.30 (NCO); *m/z* (Cl; NH_3) 324 (MH^+, 75%), 228 (25), 204 (18), 105 (100).

7.3.4.3 *N*-Benzoyloxy-*N*-isopropyl-3-phenylpent-4-enamide, 72h

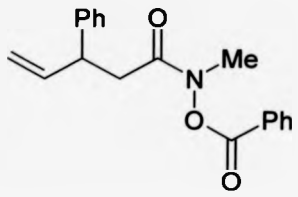


N-Hydroxy-*N*-isopropyl-3-phenylpent-4-enamide, **81h** [(0.50 g, 2.14 mmol), prepared as described above (7.3.4.1) in 80% yield] was reacted with triethylamine

(0.30 ml, 2.14 mmol) and benzoyl chloride (0.27 ml, 2.36 mmol) using the procedure described above (7.3.4.1). Washing of the crude reaction mixture with H_2O, 10% HCl and brine gave clean product and so purification by flash column chromatography was not necessary. *N*-Benzoyloxy-*N*-isopropyl-3-phenylpent-4-enamide, **72h**, was obtained as a yellow oil in 91% yield (0.66 g), (81% overall yield from *N*-isopropyl hydroxylamine hydrochloride). (Found M^+ 337.1677. $C_{21}H_{23}NO_3$ requires 337.1672).

ν_{max} (neat)/cm^{-1} 2980, 1766 (OCOPh), 1672 (NCO), 1238 (C-N), 703 (Ar); δ_H(250 MHz; $CDCl_3$) 1.11 (3H, d, J=6.4, $CH(CH_3)_2$), 1.16 (3H, d, J=6.4, $CH(CH_3)_2$), 2.72 (2H, br s, CH_2), 4.03 (1H, q, J=6.9, CHPh), 4.83 (1H, br s, $CH(CH_3)_2$), 5.06 (1H, dd, J=16.7, 1.2, $CH=CH_2$), 5.07 (1H, d, J=10.7, $CH=CH_2$), 6.00 (1H, ddd, J=16.7, 10.7, 6.7 $CH=CH_2$), 7.13-7.26 (5H, m, Ph), 7.47-7.54 (2H, m, *m*-Ph, OCOPh), 7.62-7.69 (1H, m, *p*-Ph, OCOPh), 8.05-8.17 (2H, m, *o*-PH, OCOPh); δ_C(250 MHz; $CDCl_3$) 19.69 ($CH(CH_3)_2$), 38.74 (CH_2CO), 45.30 (CHPh), 50.35 $CH(CH_3)_2$, 115.20 ($CH=CH_2$), 127.01, 128.16, 128.82, 128.92, 129.39, 130.44, 134.92, 140.81 (8 x Ar), 143.07 ($CH=CH_2$), 165.48 (OCOPh), 171.36 (NCO) *m/z* (CI; NH_3) 338 (MH^+, 12%), 278 (19), 180 (25), 105 (100).

7.3.4.4 *N*-Benzoyloxy-*N*-methyl-3-phenylpent-4-enamide, 72g

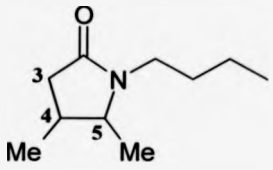


N-Hydroxy-*N*-isopropyl-3-phenylpent-4-enamide, **81g** [(0.50 g, 2.44 mmol), prepared as described above (7.3.4.1) in 83% yield] was reacted with triethylamine (0.34 ml, 2.44 mmol) and benzoyl chloride (0.31 ml, 2.68 mmol) using the procedure described above (7.3.4.1). Washing of the crude reaction mixture with H_2O, 10% HCl and brine gave clean product and so purification by flash column chromatography was not necessary. *N*-Benzoyloxy-*N*-methyl-3-phenylpent-4-enamide, **72g**, was obtained in 90% yield (0.68 g), (overall yield from *N*-methyl hydroxylamine hydrochloride - 75%). (Found MH^+ 310.1443. $C_{19}H_{19}NO_3$ requires 310.1444).

ν_{max} (neat)/cm^{-1} 1763, 1705, 1451, 1243, 1004, 701; δ_H(250 MHz; $CDCl_3$) 2.72 (1H, dd, J=15.9, 7.0, CH_2), 2.80 (1H, dd, J=15.9, 7.6, CH_2), 3.35 (3H, s, Me), 4.01 (1H, ap q, J=7.2, CHPh), 5.01-5.09 (2H, m, CH=CH_2), 6.00 (1H, ddd, J=16.9, 10.5, 6.6, C*H*=CH_2), 7.14-7.31 (5H, m, Ph), 7.44-7.53 (2H, m, *m*-Ph, OCOPh), 7.65 (1H, t, J=7.5, *p*-Ph, OCOPh), 8.04-8.17 (2H, m, *o*-Ph, OCOPh); δ_C(250 MHz; $CDCl_3$) 36.14 (Me), 38.25 (CH_2CO), 45.18 (CHPh), 115.34 (CH=CH_2), 127.04, 128.08, 128.85, 128.97, 129.40, 131.80, 135.01, 140.74 (8 x Ar), 164.60 (OCOPh), 171.60 (NCO); *m/z* (CI NH_3) 310 (MH^+, 11%), 190 (45), 122 (62), 105 (100), 77 (61).

7.3.5 Cyclisation reactions

7.3.5.1 *N*-Butyl-4,5-dimethylpyrrolidin-2-one, 73a

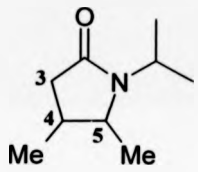


A solution of tributyltin hydride (0.89 ml, 3.0 mmol, 1.1eq.) and AIBN (0.05 g, 0.1eq.) in degassed toluene (18 ml) was added *via* a syringe pump over 8 hours to a refluxing solution of *N*-benzoyloxy-*N*-butyl-3-methylpent-4-enamide **72a** (0.80 g, 2.76 mmol) in degassed toluene (18 ml). The reaction was refluxed for a further 12 hours. Analysis by tlc showed the reaction not to be complete so a further addition of tributyltin hydride (0.45 ml, 1.5 mmol) and AIBN (0.05 g) in toluene (9 ml) was made over another 8 hours. The solvent was removed by rotary evaporation and the crude product mixture was purified by partitioning between acetonitrile/hexane followed by acetonitrile/cyclohexane. Further purification by flash column chromatography (2:1, 1:1, 1:2 hexane:Et_2O; Et_2O; 9:1 Et_2O:methanol) furnished 0.26 g of *N*-butyl-4,5-dimethylpyrrolidin-2-one as a mixture of diastereoisomers in 55% isolated yield. (Found MH^+ 170.1545. $C_{10}H_{19}NO$ requires 170.1541).

ν_{max} (neat)/cm^{-1} 2960, 1681; δ_H(400 MHz; $CDCl_3$) *trans* isomer: 0.88 (3H, t, J=7.2, CH_3), 1.06 (3H, dd, J=6.7, 0.7, 4-Me), 1.16 (3H, dd, J=6.2, 0.7, 5-Me), 1.22-1.53 (4H, m, $CH_2CH_2CH_3$), 1.86 (1H, m, 4-H), 1.95 (1H, dd, J=16.7, 7.9, 3-H), 2.5 (1H, dd, J=16.7, 8.1, 3-H), 2.78-2.88 (1H, m, NCH_2), 3.15 (1H, qn, J=6.2, 5-H), 3.5-3.7,

(1H, m, NCH_2); *cis* isomer: 0.88 (3H t, J=7.2 CH_3), 0.97 (3H, d, J=6.3, 4-Me), 1.02 (3H, dd, J=6.7, 0.7, 5-Me), 1.22-1.53 (4H, m, CH_2CH_2), 1.98-2.06 (1H, m, 3-H), 2.31-2.45 (2H, m, 4-H and 3-H), 2.78-2.88 (1H, m, NCH_2), 3.52-3.65 (2H, m, NCH_2 and 5-H); δ_C(400 MHz; $CDCl_3$) 13.61, 14.14, 15.04, 18.68, 19.02, 20.51, 29.81, 30.02, 31.38, 35.38, 38.51, 39.09, 40.04, 40.23, 56.70, 60.94, 174.46, 174.63; *m/z* (CI; NH_3) 170 (MH^+, 100%), 154 (44), 126 (88), 98 (42).

7.3.5.2 4,5-Dimethyl-*N*-isopropylpyrrolidin-2-one, 73b

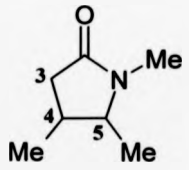


A solution of tributyltin hydride (0.89 ml, 3.0 mmol, 1.2 eq.) and AIBN (0.05 g, 0.1 eq.) in degassed toluene (17 ml) was added *via* a syringe pump over 8 hours to a refluxing solution of *N*-benzoyloxy-*N*-isopropyl-3-methylpent-4-enamide, **72b** (0.70 g, 2.54 mmol) in degassed toluene (17 ml). The reaction was refluxed for a further 12 hours. Analysis by tlc showed the reaction not to be complete so a further addition of tributyltin hydride (0.89 ml, 3.0 mmol) and AIBN (0.05 g) in toluene (17 ml) was made over another 8 hours. The solvent was removed by rotary evaporation and the crude product mixture was purified by partitioning between acetonitrile/hexane followed by acetonitrile/cyclohexane. Further purification by flash column chromatography (1.5:1, 1:1 hexane:Et_2O; Et_2O) furnished 0.16 g of 4,5-dimethyl-*N*-

isopropylpyrrolidin-2-one as a mixture of diastereoisomers in 42% isolated yield. (Found MH^+ 156.1384. $C_9H_{18}NO$ requires 156.1384).

ν_{max} (neat)/cm^{-1} 2970 (CH), 1681 (CO), 1416 (CH); δ_H(400 MHz; $CDCl_3$) *trans* isomer: 0.93 (3H, d, J=6.6, 4-Me), 1.09-1.11 (6H, m, $CH(CH_3)_2$), 1.13 (3H, d, J=6.3, 5-Me), 1.78 (1H, dd, J=17.7, 4.4, 3-H), 1.76-1.83 (1H, m, 4-H), 2.49 (1H, dd, J=17.7, 9.3, 3-H), 3.15 (1H, qd, J=6.3, 3.5, 5-H), 4.05 (1H, sp, J=7.0, $CH(CH_3)_2$); *cis* isomer: 0.89 (3H, d, J=7.0, 4-Me), 0.97 (3H, d, J=6.6, 5-Me), 1.09-1.11 (6H, m, $CH(CH_3)_2$), 1.97 (1H, dd, J=16.1, 11.2, 3-H), 2.19 (1H, dd, J=16.1, 8.0, 3-H), 2.23-2.35 (1H. m, 4-H), 3.58 (1H, qn, J=6.6, 5-H), 4.00 (1H, sp, J=7.0, $CH(CH_3)_2$); δ_C(400 MHz; $CDCl_3$) 14.45, 15.34, 19.32, 19.35, 19.54 (*trans*), 21.09, 21.41, 21.59, 32.06, 34.68 (*trans*), 38.01, 38.41 (*trans*), 43.52, 43.82 (*trans*), 55.36, 59.83 (*trans*), 173.53, 173.74; *m/z* (CI; NH_3) 156 (MH^+, 100%), 140, (19), 98 (7), 70 (6), 44 (7).

7.3.5.3 1,4,5-Trimethylpyrrolidin-2-one, 73c

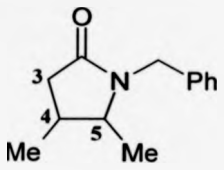


A solution of tributyltin hydride (0.39 ml, 1.33 mmol, 1.1 eq.) and AIBN (0.02 g, 0.1 eq.) in degassed toluene (8 ml) was added *via* a syringe pump over 8 hours to a refluxing solution of *N*-benzoyloxy-*N*-methyl-3-methylpent-4-enamide, **72c** (0.30 g, 1.21 mmol) in degassed toluene (8 ml). The reaction was refluxed for a further 12

hours. Analysis by tlc showed the reaction not to be complete so a further addition of tributyltin hydride (0.39 ml, 1.33 mmol) and AIBN (0.02 g) in toluene (8 ml) was made over another 8 hours. The solvent was removed by rotary evaporation and the crude product mixture was purified by partitioning between acetonitrile/hexane followed by acetonitrile/cyclohexane. Further purification by flash column chromatography (Et_2O) furnished 0.033 g (21%) of *trans*-1,4,5-trimethylpyrrolidin-2-one and 0.072 g (47%) of a mixture of *cis*- and *trans*-1,4,5-trimethylpyrrolidin-2-one. (Found M^+ 127.0999. $C_7H_{13}NO$ requires 127.0998).

ν_{max} (neat)/cm^{-1} 2968, 1667, 1427; δ_H(400 MHz; $CDCl_3$) *trans* isomer: 1.01 (3H, dd, J=6.7, 0.7, 4-Me), 1.12 (3H, dd, J=6.2, 0.7, 5-Me), 1.75-1.85 (1H, m, 4-H), 1.88 (1H, dd, J=16.5, 8.1 3-H), 2.46 (1H, dd, J=16.5, 8.0, 3-H), 2.67 (3H, d, J=0.7, NMe), 3.00 (1H, qn, J=6.2, 5-H); *cis* isomer: 0.91 (3H, d, J=7.0, 4-Me), 0.98 (3H, dd, J=6.7, 0.7, 5-Me), 1.94 (1H, dd, J=16.1, 8.4, 3-H), 2.24-2.41 (1H, m, 4-H), 2.37 (1H, dd, J=16.1, 7.2, 3-H), 2.69 (3H, d, J=0.7, NMe), 3.47 (1H, qn, J=6.7, 5-H); δ_C(250 MHz; $CDCl_3$) *trans* isomer: 18.67, 18.98, 27.60, 35.38, 39.04, 63.22, 174.35; *cis* isomer: 13.45, 15.01, 27.84, 31.80, 38.25, 59.14, 174.69; *m/z* (EI) 127 (MH^+, 49%), 112 (100), 55 (21).

7.3.5.4 *N*-Benzyl-4,5-dimethylpyrrolidin-2-one, 73d[96]

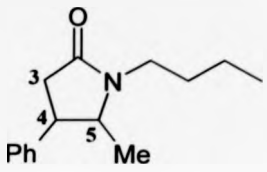


A solution of tributyltin hydride (0.25 ml, 0.85 mmol, 1.1 eq.) and AIBN (0.013 g, 0.1 eq.) in degassed toluene (5 ml) was added *via* a syringe pump over 8 hours to a refluxing solution of *N*-benzoyloxy-*N*-benzyl-3-methylpent-4-enamide, **72d** (0.250 g, 0.77 mmol) in degassed toluene (5 ml). The reaction was refluxed for a further 12 hours. Analysis by tlc showed the reaction not to be complete so a further addition of tributyltin hydride (0.25 ml, 0.85 mmol) and AIBN (0.013 g) in toluene (5 ml) was made over another 8 hours. The solvent was removed by rotary evaporation and the crude product mixture was purified by partitioning between acetonitrile/hexane followed by acetonitrile/cyclohexane. Further purification by flash column chromatography (2:1, 1:1, 1:2, pentane:Et_2O; Et_2O) furnished 0.083 g (53%) of *N*-benzyl-4,5-dimethylpyrrolidin-2-one. (Found M^+ 189.1155. $C_{12}H_{15}NO$ requires 189.1155).

ν_{max} (neat)/cm^{-1} 2959, 1682, 1454; δ_H(400 MHz; $CDCl_3$) *trans* isomer: 1.01 (1H, d, J=6.4, 4-Me), 1.12 (1H, d, J=6.2, 5-Me), 1.90 (1H, m, 4-H), 2.04 (1H, dd, J=16.8, 7.7, 3-H), 2.63 (1H, ddd, J=16.8, 8.4, 1.1, 3-H), 3.00 (1H, qn, J=6.2, 5-H), 3.95 (1H, d, J=14.7, CH_2Ph), 4.94 (1H, d, J=14.7, CH_2Ph), 7.18-7.31 (5H, m, Ph); *cis* isomer: 0.97 (1H, d, J=7.0, 4-Me), 1.00 (1H, d, J=6.7, 5-Me), 2.13 (1H, ddd, J=16.0, 8.6, 0.9,

3-H), 2.39 (1H, m, 4-H), 2.49 (1H, dd, J=16.0, 7.9, 3-H), 3.47 (1H, qn, J=6.7, 5-H), 3.91 (1H, d, J=14.6, CH_2Ph), 4.97 (1H, d, J=14.6, CH_2Ph), 7.18-7.31 (5H, m, Ph); δ_C(250 MHz; $CDCl_3$) 13.42, 15.05, 18.53, 18.82, 27.21, 28.22, 31.39, 35.36, 44.29, 44.38, 56.21, 60.47, 127.76, 128.24, 128.33, 128.97, 137.14, 137.32, 174.87; *m/z* (EI) 203 (MH^+, 38), 188 (25), 146 (28), 91 (100).

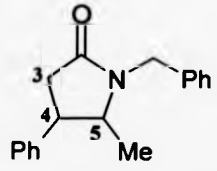
7.3.5.5 *N*-Butyl-5-methyl-4-phenylpyrrolidin-2-one, 73e



A solution of tributyltin hydride (0.27 ml, 0.94 mmol, 1.1 eq.) and AIBN (0.014 g, 0.1 eq.) in degassed toluene (6 ml) was added *via* a syringe pump over 8 hours to a refluxing solution of *N*-benzoyloxy-*N*-butyl-3-phenylpent-4-enamide, **72e** (0.300 g, 0.85 mmol) in degassed toluene (6 ml). The reaction was refluxed for a further 12 hours. Analysis by tlc showed the reaction not to be complete so a further addition of tributyltin hydride (0.27 ml, 0.94 mmol) and AIBN (0.014 g) in toluene (6 ml) was made over another 8 hours. The solvent was removed by rotary evaporation and the crude product mixture was purified by partitioning between acetonitrile/hexane followed by acetonitrile/cyclohexane. Further purification by flash column chromatography (7:1, 5:1, 3:1 pet.ether:EtOAc) furnished 0.042 g (21%) of *N*-butyl-5-methyl-4-phenylpyrrolidin-2-one. (Found M^+ 231.1624. $C_{15}H_{21}NO$ requires 231.1624).

ν_{max} (neat)/cm^{-1} 2961, 2872, 1680, 1454, 702; δ_H(250 MHz; $CDCl_3$) *trans* isomer: 0.90-0.95 (3H, m, CH_3), 1.23 (3H, d, J=6.3, 5-Me), 1.54-1.86 (4H, m, $CH_2CH_2CH_3$), 2.54 (1H, dd, J=17.0, 8.9, 3-H), 2.80 (1H, dd, J=17.0, 9.1, 3-H), 2.88-2.99 (3H, m, NCH_2 and 4-H), 3.59-3.68 (1H, m, 5-H), 7.14-7.34 (5H, m, Ph); *cis* isomer: 0.76 (3H, d, J=6.7, 5-Me), 0.90-0.95 (3H, m, CH_3), 1.54-1.86 (4H, m, $CH_2CH_2CH_3$), 2.63 (1H, dd, J=16.6, 8.4, 3-H), 2.75 (1H, dd, J=16.6, 9.3, 3-H), 3.59-3.68 (3H, m, NCH_2 and 4-H), 3.94 (1H, qn, J=6.7, 5-H), 7.14-7.34 (5H, m, Ph); δ_C(250 MHz; $CDCl_3$) 13.83 (CH_2CH_3), 14.64 (*trans* Me), 18.13 (*cis* Me), 18.57 and 20.25 (CH_2CH_3), 29.52 and 29.76 ($CH_2CH_2CH_3$), 35.17, 39.01, 39.95, 40.20, 42.43, 46.66, 57.09, 61.08, 127.08, 127.19, 127.32, 128.02, 128.54, 128.87, 138.80, 141.79 (8 x Ar), 173.40, 173.89 (2 x CO); *m/z* (EI) 231 (M^+, 58%), 216 (52), 188 (95), 104 (95), 43 (100).

7.3.5.6 *N*-Benzyl-5-methyl-4-phenylpyrrolidin-2-one, 73f

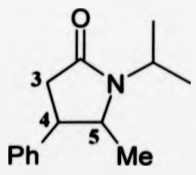


A solution of tributyltin hydride (0.36 ml, 1.25 mmol, 1.2 eq.) and AIBN (0.017 g, 0.1 eq.) in degassed toluene (9 ml) was added *via* a syringe pump over 8 hours to a refluxing solution of *N*-benzoyloxy-*N*-benzyl-3-phenylpent-4-enamide, **72f** (0.40 g, 1.04 mmol) in degassed toluene (9 ml). The reaction was refluxed for a further 12 hours. Analysis by tlc showed the reaction not to be complete so a further addition of

tributyltin hydride (0.36 ml, 1.25 mmol) and AIBN (0.017 g) in toluene (9 ml) was made over another 8 hours. The solvent was removed by rotary evaporation and the crude product mixture was purified by partitioning between acetonitrile/hexane followed by acetonitrile/cyclohexane. Further purification by flash column chromatography (2:1, 1:1 hexane:Et_2O; Et_2O; 95:5 Et_2O:methanol) furnished 0.046 g (17%) of *N*-benzyl-5-methyl-4-phenylpyrrolidin-2-one (Found M^+ 265.1469. $C_{18}H_{19}NO$ requires 265.1468).

ν_{max} (neat)/cm^{-1} 3030, 1682, 1417, 701; δ_H(250 MHz; $CDCl_3$) *trans* isomer: 1.18 (3H, d, J=6.3, 5-Me), 2.61 (1H, dd, J=16.9, 9.0, 3-H), 2.90 (1H, ddd, J=16.9, 9.0, 1.0, 3-H), 2.97-3.03 (1H, m, 4-H), 3.48 (1H, ap qn, J=6.3, 5-H), 4.06 (1H, d, J=14.9, CH_2Ph), 5.01 (1H, d, J=14.9, CH_2Ph); *cis* isomer: 0.74 (3H, d, J=6.9, 5-Me), 2.73 (1H, dd, J=16.5, 8.4, 3-H), 2.85 (1H, dd, J=16.5, 9.5, 3-H),3.62 (1H, m, 4-H), 3.78 (1H, ap qn, J=6.9, 5-H), 3.93 (1H, d, J=15.1, CH_2Ph), 5.08 (1H, d, J=15.1, CH_2Ph); δ_C(250 MHz; $CDCl_3$) *trans* isomer: 19.77, 22.05, 23.17, 39.16, 44.52, 46.74, 61.44, 127.24, 127.42, 128.93, 129.21, 61.44; *m/z* (EI) 265 (M^+ 66%), 134 (24), 104 (49), 91 (100), 49 (95).

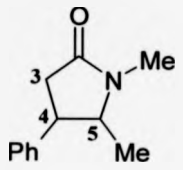
7.3.5.7 *N*-Isopropyl-5-methyl-4-phenylpyrrolidin-2-one, 73h



A solution of tributyltin hydride (0.52 ml, 1.78 mmol, 1.2 eq.) and AIBN (0.024 g, 0.1eq.) in degassed toluene (9 ml) was added *via* a syringe pump over 8 hours to a refluxing solution of *N*-benzoyloxy-*N*-isopropyl-3-phenylpent-4-enamide, **72h** (0.500 g, 1.48 mmol) in degassed toluene (10 ml). The reaction was refluxed for a further 12 hours. Analysis by tlc showed the reaction not to be complete so a further addition of tributyltin hydride (0.52 ml, 1.78 mmol) and AIBN (0.024 g) in toluene (9 ml) was made over another 8 hours. The solvent was removed by rotary evaporation and the crude product mixture was purified by partitioning between acetonitrile/hexane followed by acetonitrile/cyclohexane. Further purification by flash column chromatography (2:1, 1:1 pentane:Et_2O; Et_2O) furnished 0.076 g (24%) of *trans*-*N*-isopropyl-5-methyl-4-phenylpyrrolidin-2-one and 0.063 g (20%) of a mixture of *cis*- and *trans*-*N*-isopropyl-5-methyl-4-phenylpyrrolidin-2-one. (Found M^+ 217.1470. $C_{14}H_{19}NO$ requires 217.1468).

ν_{max} (neat)/cm^{-1} 2974, 1680, 1546; δ_H(250 MHz; $CDCl_3$) *trans* isomer: 1.21 (3H, d, J=6.7, $CH(CH_3)_2$), 1.25 (3H, d, J=6.9, $CH(CH_3)_2$), 1.31 (1H, d, J=6.3, 5-Me), 2.44 (1H, dd, J=16.5, 6.0, 3-H), 2.84 (1H, dd, J=16.5, 9.1, 3-H), 2.91-2.96 (1H, m, 4-H), 3.65 (1H, qn, J=6.3, 5-H), 4.19 (1H, sp, J=6.8, $CH(CH_3)_2$); *cis* isomer: 0.80 (3H, d, J=6.7, 5-Me), 1.23 (3H, d, J=7.4, $CH(CH_3)_2$), 1.27 (3H, d, J=7, $CH(CH_3)_2$), 2.50 (1H, dd, J=16.2, 8.1, 3-H), 2.82 (1H, dd, J=16.2, 12.0, 3-H), 3.60-3.68 (1H, m, 4-H), 3.97 (1H, qn, J=6.7, 5-H), 4.11-4.22 (1H, m, $CH(CH_3)_2$); δ_C(250 MHz; $CDCl_3$) *trans* isomer: 19.77, 22.05, 39.16, 44.52, 46.74, 61.44, 127.24, 127.42, 129.21, 143.44 (4 x Ar), 173.75 (CO) *m/z* (EI) 217 (M^+, 28%), 202 (100), 104 (57), 43 (44).

7.3.5.8 1,5-Dimethyl-4-phenylpyrrolidin-2-one, 73g[97]



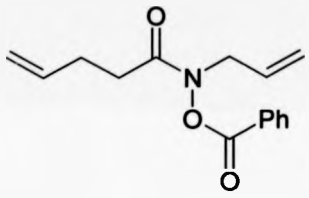
A solution of tributyltin hydride (0.31 ml, 1.07 mmol, 1.1 eq.) and AIBN (0.016 g, 0.1 eq.) in degassed toluene (6 ml) was added *via* a syringe pump over 8 hours to a refluxing solution of *N*-benzoyloxy-*N*-methyl-3-phenylpent-4-enamide, **72g** (0.300 g, 0.97 mmol) in degassed toluene (6.5 ml). The reaction was refluxed for a further 12 hours. Analysis by tlc showed the reaction not to be complete so a further addition of tributyltin hydride (0.31 ml, 1.07 mmol) and AIBN (0.016 g) in toluene (6 ml) was made over another 8 hours. The solvent was removed by rotary evaporation and the crude product mixture was purified by partitioning between acetonitrile/hexane followed by acetonitrile/cyclohexane. Further purification by flash column chromatography (2:1 Et_2O:pentane; Et_2O) furnished 0.020 g (11%) of *trans*-1,5-dimethyl-4-phenylpyrrolidin-2-one and 0.020 g (11%) of a mixture of *cis*- and *trans*-1,5-dimethyl-4-phenylpyrrolidin-2-one. (Found M^+ 189.1155. $C_{12}H_{15}NO$ requires 189.1155).

ν_{max} (neat)/cm^{-1} 2928, 1682, 1399, 700; δ_H(250 MHz; $CDCl_3$) *trans* isomer: 1.24 (3H, d, J=6.4, 5-Me), 2.53 (1H, ddd, J=16.8, 8.4, 0.7, 3-H), 2.81 (1H, dd, J=16.8, 8.8, 3-H), 2.84 (3H, s, N-Me), 2.95 (1H, m, 4-H), 3.53 (1H, qn, J=6.4, 5-H), 7.18-7.35 (5H, m, Ph); *cis* isomer (250 MHz): 0.78 (3H, d, J=6.5, 5-Me), 2.64 (1H, ddd,

J=15.9, 8.5, 0.6, 3-H), 2.76 (1H, ddd, J=15.9, 8.7, 0.6, 3-H), 2.85 (3H, s, N-Me), 3.63-3.73 (1H, m, 4-H), 3.86 (1H, dq, J=7.5, 6.5, 5-H), 7.14-7.37 (5H, m, Ph); δ_C(250 MHz; $CDCl_3$) *trans* isomer: 18.49, 27.36, 39.03, 46.86, 63.13, 127.07, 127.20, 128.73, 141.62, 173.59; *m/z* (EI) 189 (M^+, 55%), 174 (100), 117 (50), 104 (95).

7.4 Experimental for Chapter 4

7.4.1. *N*-Benzoyloxy-*N*-allylpent-4-enamide, 99[80]

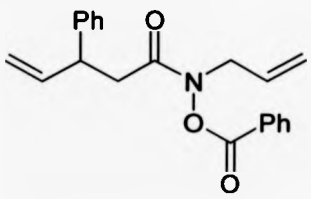


Dibenzoyl peroxide (1.73 g, 70% in H_2O, 5 mmol) in dichloromethane (20 ml) was added to a stirring solution of allylamine (0.37 ml, 5 mmol) and sodium carbonate (2.4 g, 22.5 mmol) in dichloromethane (10 ml). The reaction was left stirring at room temperature for 2 hours. Pent-4-enoyl chloride was prepared by heating at 50°C a mixture of pent-4-enoic acid (2 ml) and oxalyl chloride (2.5 ml) for 1 hour. Distillation gave pure pent-4-enoyl chloride, 0.5 ml (5.5 mmol) of which was added dropwise to the reaction mixture in dichloromethane (5 ml). After stirring at room temperature for 1.5 hours, water was added and the product extracted into dichloromethane. The organic extracts were washed with water, dried over anhydrous magnesium sulphate and concentrated on a rotary evaporator. Purification by flash

column chromatography (5:1 pet.ether:EtOAc) gave 0.50 g (38%) of *N*-benzoyloxy-*N*-allylpent-4-enamide as a brown oil. Spectral details matched those published. (Found MH^+ 260.1287. $C_{15}H_{18}NO_3$ requires 260.1287).

ν_{max} (neat)/cm^{-1}; δ_H(250 MHz; $CDCl_3$) 2.39 (4H, m, CH_2CH_2), 4.40 (2H, d, J=6.4, NCH_2), 4.93 (1H, d, J=11.3, CH=CH_2, *cis*), 4.99 (1H, d, J=17.4, CH=CH_2 *trans*), 5.17 (1H, d, J=9.4, CH=CH_2, *cis*), 5.22 (1H, d, J=16.6, CH=CH_2, *trans*), 5.68-5.93 (2H, m, CH=CH_2), 7.47 (2H, t, J=7.6, *m*-Ph), 7.63 (1H, t, J=7.3, *p*-Ph), 8.03 (2H, dd, J=7.3, 0.6, *o*-Ph); δ_C(250 MHz; $CDCl_3$); *m/z* (CI, NH_3) 260 (MH^+, 92%), 214 (55), 178 (49), 140 (84), 105(100).

7.4.2 *N*-Benzoyloxy-*N*-allyl-3-phenylpent-4-enamide, 101

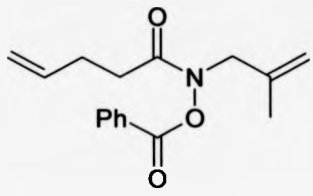


Oxalyl chloride (1.5 ml, 17.2 mmol) was added dropwise to an ice-cooled solution of 3-phenylpent-4-enoic acid [2.00 g, 12.4 mmol, prepared as described earlier (Section 7.3.2.3)] in dichloromethane (15 ml) containing a few drops of dimethylformamide. After stirring in ice for 10 minutes and then at room temperature for 1 hour solvents and excess reagents were removed on a rotary evaporator to give 3-phenylpent-4-enoyl chloride (1.79 g, 9.20 mmol) which was used immediately. Dibenzoyl peroxide

(2.31 g, 70% in H_2O, 6.66 mmol) in dichloromethane (20 ml) was added to a stirring solution of allylamine (0.50 ml, 6.66 mmol) and sodium carbonate (3.2 g, 31 mmol) in dichloromethane (30 ml). The reaction was left stirring at room temperature for 2 hours. 3-Phenylpent-4-enoyl chloride (1.79 g, 9.20 mmol) was added dropwise to the reaction mixture in dichloromethane (10 ml). After stirring at room temperature for 1.5 hours, water was added and the product extracted into dichloromethane. The organic extracts were washed with water, dried over anhydrous magnesium sulphate and concentrated on a rotary evaporator. Purification by flash column chromatography (10:1 pet.ether:EtOAc) furnished 0.60 g, (27%) of *N*-benzoyloxy-*N*-allyl-3-phenylpent-4-enamide as a yellow oil. (*N*-allylbenzamide was also formed in 36% yield). (Found MH^+ 336.1595. $C_{21}H_{22}NO_3$ requires 336.1601).

ν_{max} (neat)/cm^{-1}; 1764, 1677, 1452, 1234, 1016, 701; δ_H(250 MHz; $CDCl_3$) 2.68-2.85 (2H, m, CH_2CO), 4.02 (1H, ap q, J=7.2, CHPh), 4.40 (2H, dd, J=6.2, 0.9, NCH_2), 5.03-5.21 (4H, m, CH=CH_2), 5.80 (1H, ddt, J=16.9, 10.5, 6.2, NCH_2CH=CH_2), 6.01 (1H, ddd, J=17.2, 10.5, 6.7, CH=CH_2), 7.17-7.33 (5H, m Ph), 7.51 (2H, t, J=7.6, *m*-Ph, OCOPh), 7.63-7.71 (1H, m, *p*-Ph, OCOPh), 8.04-8.08 (2H, m, *o*-Ph, OCOPh); δ_C(400 MHz; $CDCl_3$) 37.99 (CH_2CO), 44.75 (CHPh), 50.98 (NCH_2), 114.96 (CH=CH_2), 119.24 (CH(Ph)CH=CH_2), 126.65, 127.75, 128.50, 128.58, 128.93, 130.07, 131.33, 134.50 (8xAr), 140.35 (CH=CH_2), 142.75 (CHPhC=), 164.30, 173.88; *m/z* (CI; NH_3) 336 (MH^+, 39, 282 (20), 215 (11), 178 (29), 105(100).

7.4.3 *N*-Benzoyloxy-*N*-(2-methylallyl)pent-4-enamide, 104

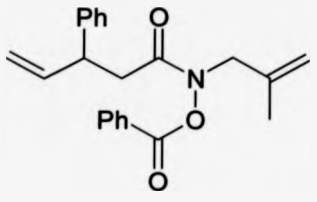


Dibenzoyl peroxide (6.84 g, 70% in H_2O, 19.8 mmol) in dichloromethane (40 ml) was added to a stirring solution of 2-(methylallyl)amine hydrochloride (2.13 g, 19.8 mmol) and sodium carbonate (12.6 g, 0.118 mol) in dichloromethane (50 ml). The reaction was stirred at room temperature for 2 hours. Pent-4-enoyl chloride (2.35 g, 19.8 mmol, see 7.4.1) in dichloromethane (20 ml) was added dropwise and the reaction left stirring at room temperature for a further 1.5 hours. The crude reaction product was washed with water, saturated $NaHCO_3$ solution and 5% NaOH solution to remove all traces of acid chloride. Purification by flash column chromatography (15:1 pet. ether:EtOAc) gave 2.64 g (49%) of *N*-benzoyloxy-*N*-(2-methylallyl)pent-4-enamide as a pale yellow oil. (Found MH^+ 274.1446. $C_{16}H_{20}NO_3$ requires 274.1444).

ν_{max} (neat)/cm^{-1} 1763, 1678, 1452, 1240, 707; δ_H(250 MHz; $CDCl_3$) 1.78 (3H, s, Me), 2.41 (4H, br s, CH_2CH_2), 4.37 (2H, br s, CH_2), 4.88-5.05 (4H, m, $C=CH_2$), 5.72-5.88 (1H, m, $CH=CH_2$), 7.48 (2H, t, J=7.6, *m*-Ph), 7.64 (1H, tt, J=7.6, 1.3, *p*-Ph), 8.02 (2H, dd, J=8.5, 1.3, *o*-Ph); δ_C(400 MHz; $CDCl_3$) 19.89 (Me), 28.19 (CH_2CH_2CO), 31.43 (CH_2CO), 53.62 (NCH_2), 114.57 ($C(Me)=CH_2$), 115.31 ($CH=CH_2$), 126.64, 128.75, 129.84, 134.29, (4xAr), 136.84 ($CH=CH_2$), 139.27

(*C*(Me)=CH_2), 158.41 (NCO), 164.25 (OCOPh); *m/z* (CI, NH_3), 274 (MH^+, 68%), 192 (11), 154 (43), 105 (100).

7.4.4 *N*-Benzoyloxy-*N*-(2-methylallyl)-3-phenylpent-4-enamide, 108

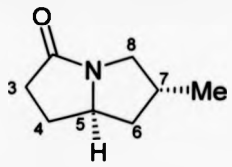


Dibenzoyl peroxide (3.91 g, 70% in H_2O, 11.3 mmol) in dichloromethane (30 ml) was added to a stirring solution of 2-(methylallyl)amine hydrochloride (1.21 g, 11.3 mmol) and sodium carbonate (7.19 g, 0.068 mol) in dichloromethane (40 ml). The reaction was stirred at room temperature for 2 hours. 3-Phenylpent-4-enoyl chloride (2.64 g, 13.5 mmol, see 7.4.2) in dichloromethane (20 ml) was added dropwise and the reaction left stirring at room temperature for a further 1.5 hours. The crude reaction product was washed with water and saturated $NaHCO_3$ solution. Purification by flash column chromatography (10:1, 5:1; pet. ether:EtOAc) gave 0.74 g (14%) of *N*-benzoyloxy-*N*-(2-methylallyl)-3-phenylpent-4-enamide as cream crystals. (Found M$^+$ 349.1674. $C_{22}H_{23}NO_3$ requires 349.1679).

ν_{max} (neat)/cm^{-1} 3078, 2974, 1775, 1681, 1451, 1240, 1014, 703; δ_H(250 MHz; $CDCl_3$) 1.70 (3H, s, Me), 2.76 (2H, m, CH_2CO), 4.02 (1H, ap q, J=7.1, CHPh), 4.27-4.41 (2H, m, NCH_2), 4.82 (2H, d, J=12.5, C(Me)=CH_2), 5.06 (1H, d, J=17.0,

CH=CH_2), 5.08 (1H, d, J=10.0, CH=CH_2), 6.00 (1H, ddd, J=17.0, 10.0, 6.6, C*H*=CH2), 7.13-7.31 (5H, m, Ph); δ_C(250 MHz; $CDCl_3$) 19.89 (Me), 37.78 (*C*H_2CO), 44.79 (*C*HPh), 53.65 (NCH_2), 114.67, 114.88 (2 x C=*C*H_2), 126.62, 126.70, 127.73, 128.54, 128.90, 130.02, 134.48, 139.33 (8x Ar), 140.39, 142.68 (2x *C*=CH_2), 164.33 (OCOPh), 171.67 (NCO); *m/z* (CI; NH_3), 350 (MH^+, 95%), 230 (43), 192 (60), 105 (100).

7.4.5 Cyclisation of *N*-benzoyloxy-*N*-allylpent-4-enamide, 99 - preparation of 7-methylpyrrolizidin-2-one, 100[80]

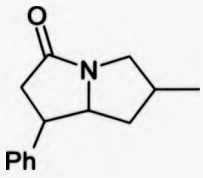


A solution of tributyltin hydride (0.52 ml, 1.92 mmol, 1eq.) in degassed cyclohexane (10 ml) was added *via* a syringe pump over 8 hours to a refluxing solution of *N*-allyl-*N*-benzoyloxypent-4-enamide, **99** (0.500 g, 1.92 mmol, 1eq.) in degassed cyclohexane (300 ml). Small amounts of AIBN were added manually every 15-30 minutes throughout the reaction. After stirring at room temperature overnight tlc analysis showed the reaction not to be complete so a further 1eq. (0.52 ml) of tributyltin hydride was added in the same manner as before (with regular additions of AIBN). The solvent was removed on a rotary evaporator and the crude product purified by flash column chromatography (1:1 Et_2O:pentane; Et_2O; 1:1

Et_2O:methanol). 7-Methylpyrrolizidin-2-one, **100** was obtained in 30% yield (0.040 g) as mixture of diastereoisomers (10:1 *cis*:*trans*). Spectral details matched those published. (Found M^+ 139.0994. $C_8H_{13}NO$ requires 139.0998).

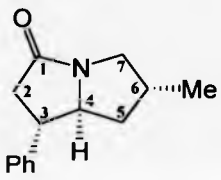
ν_{max} (neat)/cm^{-1} 2925, 1667, 1453; δ_H(250 MHz; $CDCl_3$) 1.01 (3H, d, J=7.0, Me), 1.49-1.66 (3H, m, 6-H (x 2), 4-H), 2.20-2.41 (3H, m, 4-H, 3-H, 7-H), 2.49 (1H, ddd, J=11.6, 5.4, 1.3, 8-H *endo*), 2.56-2.66 (1H, m, 3-H), 3.74 (1H, dd, J=11.6, 7.3, 8-H *exo*), 3.96 (1H, ap qn, J=7.4, 5-H); δ_C(250 MHz; $CDCl_3$) 19.4 (Me), 28.0 (C-6), 34.3 (C-7), 34.7 (C-4), 39.4 (C-8), 48.8 (C-3), 59.9 (C-5), 175.1 (CO); *m/z* (EI) 139 (M^+, 35%), 122 (66), 105 (100), 97 (57), 77(33).

7.4.6 Cyclisation of *N*-benzoyloxy-*N*-allyl-3-phenylpent-4-enamide, 101 - preparation of 7-methyl-4-phenylpyrolizidin-2-one, 103

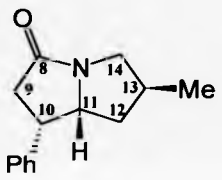


A solution of tributyltin hydride (0.38 ml, 1.43 mmol) and AIBN (0.020 g, 0.1eq.) in degassed cyclohexane (3 ml) and toluene (3 ml) was added *via* a syringe pump over 6 hours to a refluxing solution of *N*-benzoyloxy-*N*-allyl-3-phenylpent-4-enamide, **101** (0.400 g, 1.20 mmol) in degassed cyclohexane (6 ml). After stirring the reaction for a further 12 hours tlc analysis showed the reaction not to be complete so a further

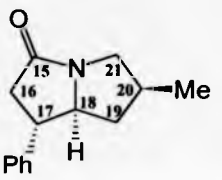
addition of tributyltin hydride (0.38 ml) and AIBN (0.020 g) was added in the same manner as before. The solvent was removed by rotary evaporation and the crude product was purified by flash column chromatography (1st column, 20:1, 10:1. 2:1 pet.ether:EtOAc; 2nd column 20:1, 1:1 pentane:Et_2O, Et_2O; 95:5 Et_2O:methanol). 7-Methyl-4-phenylpyrolizidin-2-one was obtained as a mixture of the three diastereoisomers shown below in 17% yield (0.044 g, pale yellow oil). (Found MH^+ 216.1385. $C_{14}H_{17}NO$ requires 216.1389).



103a



103b



103c

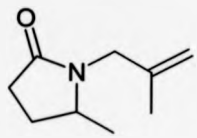
ν_{max} (neat)/cm^{-1} 2960, 2359, 1680, 1452; δ_H(250 MHz; $CDCl_3$); δ_H (400 MHz; $CDCl_3$) **103a** 1.05 (3H, d, J=6.6, Me), 1.66-1.73 (1H, m, 5-H), 1.78-1.84 (1H, m, 5-H), 2.44 (1H. ap o, J=6.7, 6-H), 2.56-2.62 (1H, m, 7-H), 2.73 (1H, dd, J=16.0, 8.2, 2-H), 2.91 (1H, dd, J=16.0, 11.8, 2-H), 3.21 (1H, ap dt, J=11.8, 8.0, 3-H), 3.86 (1H, dd, J=11.6, 7.4, 7-H), 4.04 (1H, ap q, J=7.6, 4-H), 7.05-7.35 (m, Ph); **103b** 0.92 (3H, d, J=7.0, Me), 1.18-1.23 (2H, m, 12-H), 1.94 (1H, ap sx, J=6.9, 13-H), 2.50-2.54 (1H, m, 14-H), 2.56-2.62 (1H, m, 9-H), 3.11-3.17 (1H, m, 9-H), 3.63 (1H, ap t, J=7.5, 10-H), 3.76 (1H, dd, J=11.6, 7.4, 14-H), 4.38 (1H, q, J=7.4, 11-H), 7.05-7.35 (m, Ph); **103c** 1.11 (3H, d, J=6.7, Me), 1.25-1.36 (1H, m, 19-H), 2.19 (1H, ap qn, J=5.8, 19-H), 2.50-2.54 (1H, m, 20-H), 2.56-2.62 (1H, m, 16-H), 2.79 (1H, dd, J=16.1, 8.4, 16-H), 3.06-3.11 (1H, m, 21-H), 3.28-3.34 (2H, m, 21-H, 17-H), 3.93-3.99 (1H, m, 18-

H), 7.05-7.35 (m, Ph); δ_C (400 MHz; $CDCl_3$) 18.40 (Me c), 18.93 (Me b), 19.04 (Me a), 33.70 (12-C), 34.10 (13-C), 34.43 (6-C), 36.43 (20-C), 38.42 (5-C), 40.42 (19-C), 41.12 (9-C), 42.17 92-C), 42.56 (10-C), 42.59 (16-C), 48.23 (21-C), 48.89 (17-C), 48.95 (14-C), 49.24 (3-C), 49.29 (7-C), 64.21 (11-C), 66.78 (4-C), 68.99 (18-C), 126.79, 126.90, 126.92, 127.55, 128.38, 128.60, 128.62, 140.09, 140.26, 140.34 (10 x Ar), 172.68 (15-C), 173.65 (1-C), 174.52 (8-C); *m/z* (EI) 216 (M, 40%), 105 (100), 99 (39), 84 (73), 49 (88).

7.4.7 Cyclisation of *N*-benzoyloxy-*N*-(2-methylallyl)pent-4-enamide, 104

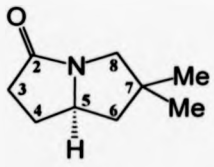
A solution of tributyltin hydride (0.54 ml, 1.85 mmol) and AIBN (0.028 g, 0.1eq.) in degassed toluene (10 ml) was added *via* a syringe pump over 8 hours to a refluxing solution of *N*-benzoyloxy-*N*-(2-methylallyl)pent-4-enamide, **104** (0.460 g, 1.68 mmol) in degassed toluene (11 ml). After stirring the reaction for a further 12 hours tlc analysis showed the reaction not to be complete so a further addition of tributyltin hydride (0.54 ml) and AIBN (0.028 g) was added in the same manner as before. The solvent was removed by rotary evaporation and the crude product was purified by partitioning between firstly, acetonitrile/hexane and secondly, acetonitrile/cyclohexane. The hydrocarbon solvents removed most of the tin contaminants. Flash column chromatography (2:1 hexane:Et_2O, Et_2O) furnished 0.013 g (5%) of tin-contaminated *N*-(2-methylallyl)-5-methylpyrrolidin-2-one (the product from mono-cyclisation) and 0.053 g (21%) of a 2:1 mixture of 8-methylindolizidin-2-one : 7,7-dimethylpyrrolizidin-2-one, the products resulting from 5-*exo*, 6-*endo* and 5-*exo*, 5-*exo* cyclisation respectively.

N-(2-Methylallyl)-5-methylpyrrolidin-2-one, **107**[101]

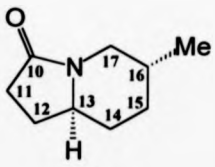


Discernible data is as follows; ν_{max} (neat)/cm^{-1} 2923, 1658, 1462; δ_H(250 MHz; $CDCl_3$) 2.46-2.11 (4H, m, 3-H, 4-H), 3.43 (1H, d, J=15.7, NCH_2), 3.68-3.56 (1H, m, 5-H), 4.23 (1H, d, J=15.7, NCH_2), 4.79-4.87 (2H, m, C(Me)=CH_2).

Data acquired on mixture of 8-methylindolizidin-2-one, **106**[101] and 7,7-dimethylpyrrolizidin-2-one, **105**[101,148]



105



106

(Found M^+ 153.1151. $C_9H_{15}NO$ requires 153.1155).

ν_{max} (neat)/cm^{-1} 2930, 1681, 1422, 1268; δ_H(400 MHz; $CDCl_3$) **105** 1.10 (3H, s, Me), 1.07 (3H, s, Me), 1.08 (3H, s, Me), 1.21-1.27 (1H, m, 6-H), 1.65-1.72 (1H, m, 4-H), 1.77 (1H, dd, J=6.2, 12.1, 6-H), 2.23 (1H, m, 4-H), 2.34-2.41 (1H, m, 3-H), 2.61-2.71 (1H, m, 3-H), 2.78 (1H, d, J=11.1, 8-H), 3.26 (1H, d, J=11.1, 8-H), 4.03-4.08 (1H, m,

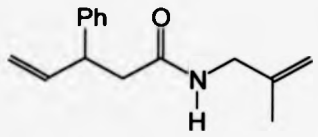
5-H); **106** 0.87 (3H, d, J=6.4, Me), 1.05-1.18 (2H, m, 14-H, 15-H), 1.40-1.49 (1H, m, 16-H), 1.49-1.58 (1H, m, 12-H), 1.73-1.79 (1H, m, 15-H), 1.82-1.86 (1H, m, 14-H), 2.11-2.22 (2H, m, 12-H, 17-H), 2.31-2.36 (2H, m, 11-H), 3.31-3.37 (1H, m, 13-H), 4.00-4.05 (1H, m, 17-H); δ_C(400 MHz; $CDCl_3$) 18.98 (CH_3), 24.95 (CH_2), 28.00 (CH_3), 28.29 (CH_2), 28.38 (CH_3), 30.52 (CH), 30.64 (CH_2), 32.57 (CH_2), 33.46 (CH_2), 34.98 (CH_2), 42.17 (C), 46.96 (CH_2), 47.17 (CH_2), 54.82 (CH_2), 56.86 (CH), 61.11 (CH), 175.05, 173.38 (2 x CO); *m/z* (EI) 153 (M^+ 84%), 152 (86), 138 (73), 110 (76), 97 (100), 69 (78), 55 (89).

7.4.8 Cyclisation of *N*-benzoyloxy-*N*-(2-methylallyl)-3-phenylpent-4-enamide, 108

A solution of tributyltin hydride (0.23 ml, 0.79 mmol) and AIBN (12 mg, 0.1eq.) in degassed toluene (5 ml) was added *via* a syringe pump over 8 hours to a refluxing solution of *N*-benzoyloxy-*N*-(2-methylallyl)pent-4-enamide, **108** (250 mg, 0.72 mmol) in degassed toluene (4.5 ml). After stirring the reaction for a further 12 hours tlc analysis showed the reaction not to be complete so a further addition of tributyltin hydride (0.23 ml) and AIBN (12 mg) was added in the same manner as before. The solvent was removed by rotary evaporation and the crude product was purified by partitioning between firstly, acetonitrile/hexane and secondly, acetonitrile/cyclohexane. The hydrocarbon solvents removed most of the tin contaminants. Flash column chromatography (2:1, 1:1 pentane:Et_2O; Et_2O) furnished 9 mg (6%) of *N*-(2-methylallyl)-3-phenylpent-4-enamide, 23 mg (14%) of a single compound which has been tentatively assigned as 4-phenyl-8-methylindolizidin-2-

one (stereochemistry not determined) and 7 mg (4%) of a mixture of 4-phenyl-7,7-dimethylpyrrolizidin-2-one and 4-phenyl-8-methylindolizidin-2-one (which was never fully characterised).

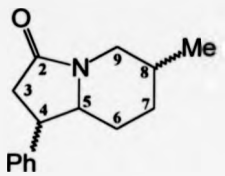
N-(2-methylallyl)-3-phenylpent-4-enamide, **111**



(Found M^+ 229.1468. $C_{15}H_{19}NO$ requires 229.1468).

Discernible data as follows: δ_H(250 MHz; $CDCl_3$) 1.57 (3H, s, Me), 2.54 (1H, dd, J=14.1, 8.0, CH_2CO), 2.64 (1H, dd, J=14.1, 7.1, CH_2CO), 3.65-3.76 (2H, m, $NHCH_2$), 3.87-3.95 (1H, m, CHPh), 4.55-4.58 (1H, m, $C=CH_2$), 4.71 (1H, sp, J=1.5, $C=CH_2$), 5.08 (1H, dq, J=16.3, 1.5, $CH=CH_2$), 5.09 (1H, dq, J=10.8, 1.5, $CH=CH_2$), 5.95-6.08 (1H, m, $CH=CH_2$), 7.3-7.7 (5H, m, Ph); *m/z* (EI) 229 (M^+, 36%), 132 (32), 117 (76), 71 (100), 55 (54), 43 (42).

4-Phenyl-8-methylindolizidin-2-one, **109**



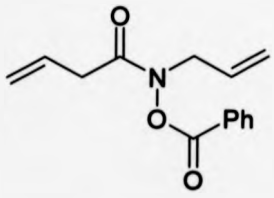
109

Discernible data as follows: δ_H(400 MHz; $CDCl_3$) 0.92 (3H, d, J=6.7, Me), 0.98-1.08 (1H, m, 7-H), 1.21-1.30 (1H, m, 6-H), 1.46-1.57 (1H, m, 8-H), 1.76-1.84 (1H, m, 7-H), 1.94 (1H, ap dq, J=13.1, 3.4, 6-H), 2.25 (1H, m, 9-H), 2.58 (1H, ddd, J=17.1, 9.7, 1.7, 3-H), 2.80 (1H, dd, J=17.1, 9.4, 3-H), 3.03 (1H, td, J=9.5, 7.4, 4-H), 3.30 (1H, ddd, J=11.2, 7.4, 3.4, 5-H), 4.13 (1H, ddd, J=13.1, 4.7, 2.1, 9-H); δ_C(400 MHz; $CDCl_3$) 18.8 (Me), 30.3 (8-C), 32.0, 32.2 (6-C,7-C), 39.3 (3-C), 45.8 (4-C), 47.0 (9-C), 64.0 (5-C), 127.0, 127.2, 128.7 (3 x Ar);

7.5 Experimental for Chapter 5

7.5.1 Preparation of *O*-benzoyl hydroxamic acid derivatives- Method 1

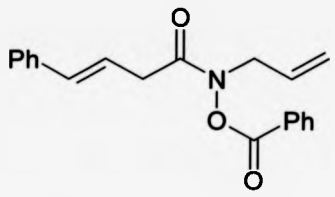
7.5.1.1 *N*-Allyl-*N*-benzoyloxyprop-3-enamide, 118



Dibenzoyl peroxide (4.70 g, 13.4 mmol) in dichloromethane (15 ml) was added dropwise to a stirring solution of allylamine (1.0 ml, 13.4 mmol) and sodium carbonate (6.4 g) in dichloromethane (15 ml). The reaction was stirred at room temperature for 2 hours. But-3-enoyl chloride was prepared by addition of oxalyl chloride (2.5 ml) to but-3-enoic acid (2 ml). The resulting solution was heated at 40°C for one hour and then distilled to give pure but-3-enoyl chloride (1.56 g). This but-3-enoyl chloride (14.9 mmol, 1.1 eq.) was added dropwise to the reaction mixture in dichloromethane (15 ml). The reaction mixture was stirred at room temperature for a further 1.5 hours. Water was added and the product extracted into dichloromethane, washed with water, dried over anhydrous magnesium sulphate and concentrated on a rotary evaporator. Purification by flash column chromatography (5:1 pet.ether:EtOAc) furnished 0.74 g (25%) of *N*-allyl-*N*-benzoyloxyprop-3-enamide as a yellow oil, along with 0.99 g (51%) of $PhCONHCH_2CH{=}CH_2$ (Found MH^+ 246.1130. $C_{14}H_{15}NO_3$ requires 246.1131); (Found C 65.05, H 6.13, N 5.16. $C_{14}H_{15}NO_3$ requires C 68.56, H 6.16, N 5.71).

Rf (5:1 pet.ether:ethyl acetate) 0.39; ν_{max} (neat)/cm^{-1} 2924, 1765, 1680, 1234,1013, 708; δ_H(250 MHz; $CDCl_3$) 3.14 (2H, dt, J=6.8, 1.4 CH_2CO), 4.43 (2H, dt, J=6.3, 1.2, NCH_2), 5.0-5.30 (4H, m, $CH{=}CH_2$), 5.81-6.02 (2H, m, $CH{=}CH_2$), 7.48-7.54 (2H, m, *m*-Ph), 7.67 (1H, t, J=7.3, *p*-Ph), 8.07 (2H, dd, J=8.4, 1.5, *o*-Ph); δ_C(250 MHz; $CDCl_3$) 37.61 (CH_2CO), 51.05 (NCH_2), 118.73 and 119.32 ($CH{=}CH_2$), 126.61, 128.79, 129.85, 131.09 (4 x Ar), 134.38 ($CH{=}CH_2$), 164.27 (OCOPh), 171.0 (NCO); *m/z* (CI, NH_3) 246 (MH^+, 92%), 178 (45), 126 (68), 105 (100).

7.5.1.2 *N*-Allyl-*N*-benzoyloxy-4-phenylbut-3-enamide, 121a



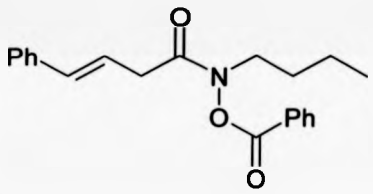
Trans-styrylacetylchloride was prepared by dropwise addition of oxalyl chloride (2 eq.) to a stirring solution of *trans*-styrylacetic acid (1 eq.) in dichloromethane. The reaction was stirred at room temperature for one hour before solvent and excess reagents were removed by rotary evaporation to give *trans*-styrylacetyl chloride as a yellow solid which was used immediately or stored in the freezer. The procedure outlined above (7.5.1.1) was used with allylamine (0.34 ml, 4.53 mmol) and *trans*-styrylacetyl chloride (0.90 g, 8.92 mmol) to prepare *N*-allyl-*N*-benzoyloxy-4-phenylbut-3-enamide in 19% yield (0.28 g) as a brown oil after purification by flash column chromatography (5:1, 2:1 pet.ether:EtOAc). (Found MH^+ 322.1444. $C_{20}H_{19}NO_3$ requires 322.1443).

ν_{max} (neat)/cm^{-1} 1763 (CO), 1672 (CO amide), 1242, 1010; δ_H(250 MHz; $CDCl_3$) 3.31 (2H, d, J=6.0, CH_2CO), 4.47 (2H, d, J=6.4, NCH_2), 5.23 (1H, dd, J=10.0, 1.4, CH=CH_2), 5.28 (1H, dd, J=16.8, 1.4, CH=CH_2), 5.91 (1H, ddt, J=16.8, 10.0, 6.4, C*H*=CH_2), 6.30 (1H, dt, J=16.1, 6.0, C*H*=CHPh), 6.41 (1H, d, J=16.1, CH=C*H*Ph), 7.17-7.31 (5H, m, Ph), 7.51 (2H, t, J=7.6, *m*-Ph, OCOPh), 7.68 (1H, tt, J=7.6, *p*-Ph, OCOPh), 8.07 (2H, dd, J=8.4, 1.5, *o*-Ph, OCOPh). δ_C(250 MHz; $CDCl_3$) 37.11 (CH_2CO), 53.39 (NCH_2), 119.39 (CH=CH_2), 121.42 (*C*H=CHPh), 126.16, 127.40,

128.70, 128.81, 129.90, 131.11 (6 x Ar), 133.61 (CH=*C*HPh), 134.41 (*p*-Ph, OCOPh), 136.69 (*i*-Ph, PhCH=), 165.16 (OCOPh), 171.03 (NCO); *m/z* (CI, NH_3) 322 (MH^+, 87%), 202 (86), 105 (100), 58 (82).

Also isolated in this reaction were *N*-allylbenzamide,[149] **127a** (orange oil, 0.23 g, 31%) and *N*-allyl-4-phenylbut-3-enamide, **123a** (yellow oil, 0.41 g, 45%, for data see 7.5.2.2).

7.5.1.3 *N*-Benzoyloxy-*N*-butyl-4-phenylbut-3-enamide, 121b

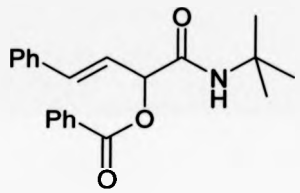


Procedure as above for 7.5.1.2 using *n*-butylamine (0.69 ml, 6.92 mmol). *N*-Benzoyloxy-*N*-butyl-4-phenylbut-3-enamide obtained in 54% yield (1.22 g) as a yellow oil (25% of $PhCONH^nBu$, **127b** also formed). (Found MH^+ 338.1756. $C_{21}H_{23}NO_3$ requires 338.1752).

ν_{max} (neat)/cm^{-1} 3060, 2958, 1764, 1674, 1600, 1451; δ_H(250 MHz; $CDCl_3$) 0.92 (3H, t, J=7.3, CH_2CH_3), 1.39 (2H, sx, J=7.4, CH_2CH_3), 1.65 (2H, qn, J=7.4, $CH_2CH_2CH_3$), 3.27 (2H, d, J=5.2, CH_2CO), 3.85 (2H, t, J=7.3, NCH_2), 6.24-6.47 (2H, m, CH=CH), 7.12-7.22 (5H, m, Ph), 7.48 (2H, t, J=7.7, *m*-Ph, OCOPh), 7.64

(1H, t, J=7.6, *p*-Ph, OCOPh), 8.09 (2H, d, J=7.7, *o*-Ph, OCOPh); δ_C(250 MHz; $CDCl_3$) 13.68 (CH_3), 19.85 and 28.99 ($CH_2CH_2CH_3$), 37.11 (CH_2CO), 47.97 (NCH_2), 121.68 (*C*H=CHPh), 126.16, 126.7, 127.35, 128.35, 128.85, 129.92 (6 x Ar), 133.42 (CH=*C*HPh), 136.76 (*i*-Ph, PhCH=), 164.35 (OCOPh), 171.14 (NCO), 164.35 (OCOPh). 171.14 (NCO); *m/z* (EI) 338 (M^+, 0.5%), 217 (12), 118 (100), 105 (99), 57 (97).

7.5.1.4 *N-t*-Butyl-2-benzoyloxy-4-phenylbut-3-enamide, 124d

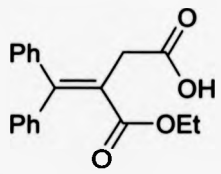


An adaptation of the procedure used above for 7.5.1.2 was used in an attempt to prepare *N*-benzoyloxy-*N-t*-butyl-4-phenylbut-3-enamide. Dibenzoyl peroxide (0.93 g, 70% in H_2O, 2.67 mmol), sodium carbonate (1.3 g) and *t*-butylamine (0.28 ml, 2.67 mmol) were stirred at reflux in chloroform for 24 hours. The solution was cooled and *trans*-styrylacetylchloride (0.72 g, 4.0 mmol, 1.5 eq.) was added dropwise and the reaction stirred at room temperature for 2 hours under nitrogen. None of the desired product was produced but on purification of the crude reaction mixture by flash column chromatography (7:1, 5:1, 2:1 pet. ether:EtOAc), *N-t*-butyl-2-benzoyloxy-4-phenylbut-3-enamide was obtained in 19% yield (0.17 g) as cream crystals. (Found

MH^+ 338.1756. $C_{21}H_{23}NO_3$ requires 338.1757); (Found C 71.20, H 8.07, N 7.12. $C_{21}H_{23}NO_3$ requires C 74.76, H 6.87, N 4.15).

mp = 116-118 °C; ν_{max} (neat)/cm^{-1} 3320 (NH), 2924, 1722 (CO), 1662 (CO), 1454, 1107; δ_H(250 MHz; $CDCl_3$) 1.30 (3H, s, CH_3), 1.38 (3H, s, CH_3), 1.47 (3H, s, CH_3), 5.90 (1H, dd, J=6.6, 1.2, CHCO), 6.41 (1H, dd, J=16.0, 6.6, C*H*=CHPh), 6.80 (1H, dd, J=16.0, 1.2, CH=C*H*Ph), 7.21-7.75 (8H, m, Ph), 8.09-8.14 (2H, m, *o*-Ph, OCOPh); δ_C(250 MHz; $CDCl_3$) 29.44, 28.77, 28.61 (C(CH_3)$_3$), 51.51 (*C*(CH_3)$_3$), 74.94 (*C*H(OCOPh), 126.61, 126.74, 128.26, 128.37, 128.49, 128.57, 129.65, 133.55, 134.49, 135.61, 164.84 (OCOPh), 167.16 (NCO); *m/z* (CI, NH_3) 338 (MH^+ 4%), 233 (57), 216 (100), 105 (85).

7.5.1.5 2-Benzhydrylidene succinic acid 1-ethyl ester[150]

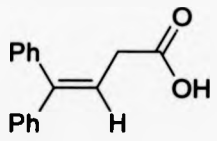


Benzophenone (9.11 g, 0.05 mol) and diethyl succinate (13.05 g, 0.075 mol) were added to a cooled solution of potassium (2.15 g, 0.055 mol) in dry *t*-butanol (45 ml). The reaction mixture was refluxed gently for 30 minutes before being cooled and acidified with dilute HCl. The *t*-butanol was removed on a vacuum line, water added to the residue and the product extracted with diethyl ether. The ethereal extracts were washed several times with 2% NaOH solution. Acidification of the solution gave

yellow crystals of 2-benzhydrylidene succinic acid 1-ethyl ester in 28% yield (4.40 g). Spectral details matched those published.

mp = 125-127 °C (lit.,[150] 126-127 °C); δ_H(250 MHz; $CDCl_3$) 0.87 (3H, t, J=7.1, CH_3), 3.54 (2H, s, CH_2), 3.97 (2H, q, J=7.1, CH_2CH_3), 7.11-7.40 (10H, m, Ph); δ_C(250 MHz; $CDCl_3$) 13.29 (CH_2CH_3), 37.86 (CH_2CO_2H), 60.76 (CH_2CH_3), 124.23 (=CCH_2), 127.83, 128.19, 128.33, 128.41, 128.55, 128.94, 140.34, 141.92 (8 x Ar), 152.53 (Ph(Ph)C=), 169.29 (CO_2Et), 177.26 (CO_2H);

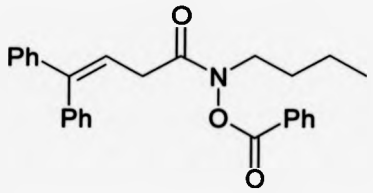
7.5.1.6 4,4-Diphenyl-but-3-enoic acid[151]



A solution of 2-benzhydrylidene succinic acid 1-ethyl ester (7.5.1.4, 2 g, 6.44 mmol) in acetic acid (30 ml) with 48% HBr (20 ml) and H_2O (10 ml) was heated under reflux for 5 hours (until no more gas was evolved). The solvent mixture was removed under reduced pressure, H_2O added and the residue extracted with diethyl ether. The ether layer was washed once with 5% sodium bicarbonate solution and then extracted with 5% K_2CO_3 solution (x3). Acidification of the aqueous solution gave 4,4-diphenyl-but-3-enoic acid as brown crystals in 72% yield (1.11g). Spectral details matched those published.

mp = 112-114 °C (lit.,[151] 114.5-115.5 °C); δ_H(250 MHz; $CDCl_3$) 3.22 (2H, d, J=7.4, CH_2), 6.24 (t, J=7.4, C=CH), 7.17-7.42 (10H, m, Ph);

7.5.1.7 *N*-Benzoyloxy-*N*-*n*-butyl-4,4-diphenylbut-3-enamide, 121e



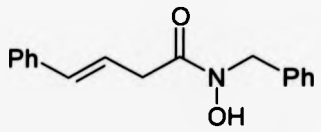
Method 1 used. 4,4-Diphenylbut-3-enoyl chloride was prepared by addition of oxalyl chloride (0.55 ml, 6.29 mmol) to a solution of 4,4-diphenyl-but-3-enoic acid (7.5.1.6, 0.660 g, 2.77 mmol) in dichloromethane (5 ml). After refluxing the solution for one hour the solvent and excess reagents were removed by rotary evaporation and the acid chloride product used crude in the next step of the reaction. A solution of dibenzoyl peroxide (0.643 g, 70% in H_2O, 1.86 mmol) in dichloromethane (10 ml) was added dropwise to a solution of sodium carbonate (0.64 g) and *n*-butylamine (0.18 ml, 1.86 mmol) in dichloromethane (15 ml). The reaction was stirred at room temperature for 2 hours. 4,4-Diphenylbut-3-enoyl chloride (0.715 g, 2.79 mmol) was added dropwise and the reaction mixture stirred at room temperature for a further 2 hours. The resulting solution was washed with water, dried over anhydrous magnesium sulphate and concentrated on a rotary evaporator. Purification by flash column chromatography (10:1, 7:1, 5:1 pet.ether:EtOAc) gave *N*-benzoyloxy-*N*-

butyl-4,4-diphenylbut-3-enamide in 55% yield (0.426 g) as a yellow oil. (Found MH^+ 414.2067. $C_{27}H_{27}NO_3$ requires 414.2070).

ν_{max} (neat)/cm^{-1} 2932, 1765, 1674, 1494, 1242, 761); δ_H(250 MHz; $CDCl_3$) 0.93 (3H, t, J=7.3, CH_3), 1.38 (2H, sx, J=7.3, C$H_2$$CH_3$), 1.63 (2H, qn, J=7.3, C$H_2$$CH_2CH_3$), 3.24 (2H, d, J=7.0, CH_2CO), 3.85 (2H, br s, NCH_2), 6.30 (1H, t, J=7.0, CH=C), 7.01-7.34 (10H, m, Ph), 7.42-7.50 (2H, m, *m*-Ph, OCOPh), 7.64 (1H, tt, J=7.4, 1.4, *p*-Ph, OCOPh), 7.96 (2H, br d, J=7.0, *o*-Ph, OCOPh); δ_C(250 MHz; $CDCl_3$) 13.59 (CH_3), 19.75 and 28.95 ($CH_2CH_2CH_3$), 33.98 (CH_2CO), 47.8 (NCH_2), 120.54 (*C*H=C), 127.09, 127.20, 127.38, 127.95, 128.04, 128.67, 129.62, 129.85, 134.16, 139.07, 141.83 (11 x Ar), 144.48 (CH=*C*(Ph)2), 164.3 (OCOPh), 170.2 (NCO); *m/z* (CI, NH_3), 414 (MH^+, 14%), 386 (26), 294 (67), 266 (39), 194 (38), 105 (100).

7.5.2 Preparation of *O*-benzoyl hydroxamic acid derivatives - Method 2

7.5.2.1 *N*-Benzyl-*N*-hydroxy-4-phenylbut-3-enamide, 126c

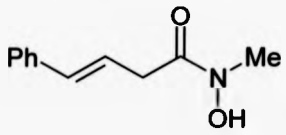


A solution of *trans*-styrylacetyl chloride (prepared as for 7.5.1.2) (1.89 g, 10.4 mmol) in dichloromethane (75 ml) was added over 45-60 minutes to a stirring solution of *N*-benzylhydroxylamine hydrochloride (2.00 g, 12.5 mmol) and triethylamine (3.20 ml, 23 mmol) in dichloromethane (100 ml) at 0°C. The reaction mixture was warmed to room temperature and stirred for one hour. The solution was washed with dilute HCl

and brine, dried over anhydrous magnesium sulphate. Removal of the solvent on a rotary evaporator gave *N*-benzyl-*N*-hydroxy-4-phenylbut-3-enamide as white crystals in 95% yield (2.55 g). (Found MH^+ 268.1338. $C_{17}H_{17}NO_2$ requires 268.1338); (Found C 76.23, H 6.41, N 5.30. $C_{17}H_{17}NO_2$ requires C 76.38, H 6.41, N 5.24).

mp = 106-108 °C; ν_{max} (Nujol)/cm^{-1} 3130 (OH), 2922, 1607 (CO), 1492; δ_H(250 MHz; $CDCl_3$) 3.27-3.49 (2H, br m, CH_2CO), 4.85 (2H, br s, CH_2Ph), 6.16-6.50 (2H, br m, CH=CH), 7.17-7.37 (5H, br m, Ph); *m/z* (EI) 267 (M^+, 12%), 251 (11), 144 (56), 117 (100), 91 (91).

7.5.2.2 *N*-Hydroxy-*N*-methyl-4-phenylbut-3-enamide, 126f[134]

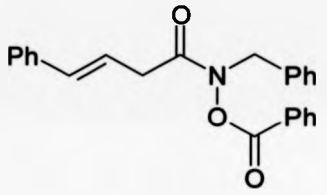


A solution of *trans*-styrylacetyl chloride (prepared as for 7.5.1.2) (1.80 g, 10.0 mmol) in dichloromethane (75 ml) was added over 45-60 minutes to a stirring solution of *N*-methylhydroxylamine hydrochloride (1.00 g, 12.0 mmol) and triethylamine (3.06 ml, 22.0 mmol) in dichloromethane (100 ml) at 0°C. The reaction mixture was warmed to room temperature and stirred for one hour. The solution was washed with dilute HCl and brine, dried over anhydrous magnesium sulphate. Removal of the solvent on a rotary evaporator gave *N*-methyl-*N*-hydroxy-4-phenylbut-3-enamide as orange crystals in 95% yield (1.81 g). Spectral details matched those published. (Found MH^+

192.1029. $C_{11}H_{13}NO_2$ requires 192.1023); (Found C 68.80, H 6.82, N 7.49. $C_{11}H_{13}NO_2$ requires C 69.09, H 6.85, N 7.33).

ν_{max} (neat)/cm^{-1} 3125, 1612, 967, 738; δ_H(250 MHz; $CDCl_3$) 3.29 (3H, s, Me), 3.29-3.48 (2H, m, CH_2), 6.19-6.51 (2H, m, CH=CH), 7.30-7.40 (5H, m, Ph); *m/z* (EI) 191 (M^+, 25%), 175 (10), 145 (25), 117 (100), 107 (55), 91 (46).

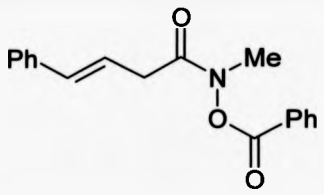
7.5.2.3 *N*-Benzoyloxy-*N*-benzyl-4-phenylbut-3-enamide, 121c



Triethylamine (1.10 ml, 7.89 mmol) was added to a solution of *N*-hydroxy-*N*-benzyl-4-phenylbut-3-enamide, **126c** (7.5.2.1, 2.11 g, 7.89 mmol) in dichloromethane at 0°C. The reaction mixture was stirred at 0°C for 10-12 minutes before dropwise addition of benzoyl chloride (1.00 ml, 8.68 mmol). The reaction mixture was stirred at 0°C for 2 hours and then at room temperature for 2 hours. The crude solution was washed with dilute HCl and brine and dried over anhydrous magnesium sulphate. Evaporation of the solvent gave 95% of *N*-benzoyloxy-*N*-benzyl-4-phenylbut-3-enamide as a yellow oil (giving an overall yield from *N*-benzylhydroxylamine hydrochloride of 90%). (Found MH^+ 372.1602. $C_{24}H_{21}NO_3$ requires 372.1601).

Rf (7:1, pet.ether:EtOAc) 0.3; ν_{max} (neat)/cm^{-1} 3031, 1766, 1682, 1453, 1225, 1018; δ_H(250 MHz; $CDCl_3$) 3.36 (2H, d, J=5.2, CH_2CO), 5.08 (2H, s, CH_2Ph), 6.30-6.46 (2H, m, CH=CH), 7.21-7.52 (10H, m, Ph), 7.40 (2H, t, J=7.6, *m*-Ph, OCOPh), 7.61-7.69 (1H, m, *p*-Ph, OCOPh), 7.99-8.03 (2H, m, *o*-Ph, OCOPh); δ_C(250 MHz; $CDCl_3$) 37.08 (CH_2CO), 51.72 (NCH_2), 121.82 (*C*H=CHPh), 126.19, 126.54, 127.41, 127.93, 128.38, 128.59, 128.82, 129.71, 129.90 (9 x Ar), 133.64 (CH=*C*HPh), 134.45, 135.03, 136.71 (3 x Ar), 164.77 (OCOPh), 171.33 (NCO); *m/z* (CI, NH_3), 372 (MH^+, 61%), 266 (14), 250 (71), 105 (100), 91 (37).

7.5.2.4 *N*-Benzoyloxy-*N*-methyl-4-phenylbut-3-enamide, 121f



Triethylamine (0.73 ml, 5.24 mmol) was added to a solution of *N*-hydroxy-*N*-methyl-4-phenylbut-3-enamide, **126f** (7.5.2.2, 0.99 g, 5.18 mmol) in dichloromethane at 0°C. The reaction mixture was stirred for 10-12 minutes before dropwise addition of benzoyl chloride (0.67 ml, 5.75 mmol). The reaction mixture was stirred at 0°C for 2 hours and then at room temperature for 2 hours. The crude solution was washed with dilute HCl and brine and dried over anhydrous magnesium sulphate. Evaporation of the solvent gave 54% of *N*-benzoyloxy-*N*-methyl-4-phenylbut-3-enamide as an

orange oil (giving an overall yield from *N*-methylhydroxylamine hydrochloride of 51%). (Found MH^+ 296.1287. $C_{18}H_{18}NO_3$ requires 296.1287).

ν_{max} (neat)/cm^{-1} 1763, 1710, 1248; δ_H(250 MHz; $CDCl_3$) 3.30 (2H, d, J=6.0, CH_2), 3.44 (3H, s, Me), 6.29 (1H, dt, J=16.1, 6.0, C*H*=CHPh), 6.40 (1H, d, J=16.0, CH=C*H*Ph), 7.15-7.34 (5H, m, Ph), 7.51 (2H, t, J=6.8, *m*-Ph, OCOPh), 7.61-7.70 (1H, m, *p*-Ph, OCOPh), 8.09 (2H, dd, J=8.4, 1.5, *o*-Ph, OCOPh); δ_C(250 MHz; $CDCl_3$) 35.75 (Me), 36.99 (*C*H_2CO), 121.49 (*C*H=CHPh), 126.17, 126.59, 127.41, 128.38, 128.86, 129.93 (6 x Ar), 133.26 (CH=*C*HPh), 134.51 (*p*-Ph, OCOPh), 136.69 (*i*-Ph, PhCH=), 164.19 (OCOPh), 171.06 (NCO); *m/z* (CI, NH_3) 296 (MH^+, 21%), 176 (100), 105 (27).

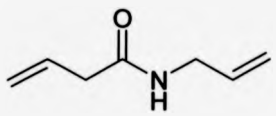
7.5.3 Cyclisation reactions

7.5.3.1 Attempted cyclisation of *N*-allyl-*N*-benzoyloxybut-3-enamide, 118

A solution of tributyltin hydride (0.71 ml, 2.45 mmol) and AIBN (0.033 g, 0.1 eq.) in degassed toluene (5 ml) and cyclohexane (5 ml) was added *via* a syringe pump over 8 hours to a refluxing solution of *N*-allyl-*N*-benzoyloxybut-3-enamide, **118** in degassed cyclohexane (10 ml). After stirring the solution for a further 12 hours, tlc analysis showed the reaction not to be complete so a further addition of Bu_3SnH (0.35 ml) and AIBN (0.016 g) in toluene (2.5 ml) and cyclohexane (2.5 ml) was made over 4 hours. Solvents were removed on a rotary evaporator. No cyclised product was observed in the crude NMR. A soxhlet extraction of the resulting residue was performed by adsorbing crude product mixture (1.52 g) onto silica gel and extracting with pentane

for 24 hours. The pentane solution removed 0.20 g of tin by-products. Further purification by flash column chromatography (1:1, 3:4, 1:2 pentane:Et_2O) furnished the reduced product *N*-allylbut-3-enamide in 24% yield.[152]

N-allylbut-3-enamide, **120**[152]



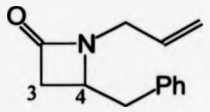
δ_H(250 MHz; $CDCl_3$) 3.01 (2H, d, J=7.0, CH_2CO), 3.84-3.94 (2H, m, NCH_2), 5.09-5.25 (4H, m, CH=CH_2), 5.66 (1H, br s, NH), 5.74-6.01 (2H, m, CH=CH_2); δ_C(250 MHz; $CDCl_3$) 41.98, 42.35, (NCH_2 and CH_2CO), 116.81, 120.41 (2 x CH=CH_2), 131.66, 134.41 (2 x CH=CH_2), 171 (CO).

7.5.3.2 Cyclisation of *N*-allyl-*N*-benzoyloxy-4-phenylbut-3-enamide, 121a

A solution of tributyltin hydride (0.27 ml, 0.93 mmol, 1.2 eq.) and AIBN (0.010 g, 0.1 eq.) in degassed toluene (1.5 ml) and cyclohexane (1.5 ml) was added *via* a syringe pump over 8 hours to a refluxing solution of *N*-allyl-*N*-benzoyloxy-4-phenylbut-3-enamide (0.250 g, 0.78 mmol) in degassed cyclohexane (3 ml). After refluxing for a further 12 hours tlc analysis showed the reaction not to be complete so a further addition of Bu_3SnH (0.14 ml) and AIBN (0.005 g) in toluene (1.5 ml) was made over 4 hours. Solvents were removed on a rotary evaporator and the crude product partially purified by soxhlet extraction with pentane (0.274 g tin benzoate

removed). Further purification by flash column chromatography (1:1, 1:2 pentane:Et_2O; Et_2O; 1:1 Et_2O:methanol) separated the three main products; *N*-Allyl-4-benzyl-2-azetidinone (0.021 g, 13%), *N*-allyl-4-phenylbut-3-enamide (0.026 g, 17%) and *N*-allyl-2-benzoyloxy-4-phenylbut-3-enamide (0.037 g, 15%) but none of these products were obtained completely pure.

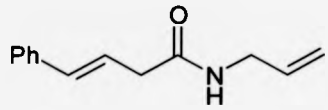
N-Allyl-4-benzyl-2-azetidinone **122a**



(Found MH^+ 202.1232. $C_{13}H_{15}NO$ requires 202.1233).

ν_{max} (neat)/cm^{-1} 2925, 1731 (CO), 1403 (alkene), 700 (Ph); δ_H(250 MHz; $CDCl_3$) 2.66 (1H, dd, J=14.6, 1.9, 3-H), 2.76 (1H, dd, J=13.7, 7.9, CH_2Ph), 2.98 (1H, dd, J=14.6, 4.9, 3-H), 3.06 (1H, dd, J=13.7, 5.8, CH_2Ph), 3.48-3.56 (1H, m, NCH_2), 3.79-3.87 (1H, m, 4-H), 4.02 (1H, ddt, J=15.5, 5.2, 1.5, NCH_2), 5.01-5.16 (2H, m, $CH=CH_2$), 5.62-5.77 (1H, m, $CH=CH_2$), 7.15-7.24 (5H, m, Ph); δ_C(400 MHz; $CDCl_3$) 39.88 (3-C), 42.43 (CH_2Ph), 43.61 (NCH_2), 52.23 (4-C), 118.51 ($CH=CH_2$), 126.90, 128.44, 128.75, 128.90, 130.17, 131.96, 133.48 (6 x Ar and $CH=CH_2$); *m/z* (EI) 201 (M^+, 21%), 110 (100), 91 (52), 68 (58).

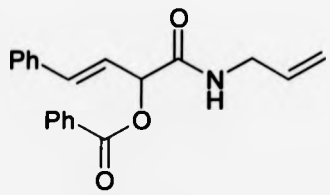
N-Allyl-4-phenylbut-3-enamide, **123a**



(Found M^+ 201.1150. $C_{13}H_{15}NO$ requires 201.1155); (Found C 75.85, H 7.25, N 6.60. $C_{13}H_{15}NO$ requires C 77.58, H 7.51, N 6.96).

ν_{max} (neat)/cm^{-1} 3243, 2923, 1633, 1462, 1376, 964; δ_H(250 MHz; $CDCl_3$) 3.16 (2H, dd, J=7.2, 1.1, CH_2CO), 3.85 (2H, ap tt, J=5.5, 1.5, NCH_2), 5.12 (1H, dq, J=10.2, 1.5, CH=CH_2), 5.17 (1H, dq, J=17.1, 1.5, CH=CH_2), 5.81 (1H, ddt, J=17.1,10.2, 5.5, C*H*=CH_2), 6.29 (1H, dt, J=15.9, 7.2, C*H*=CHPh), 6.44 (1H br s, NH), 6.50 (1H, d, J=15.9, CH=C*H*Ph), 7.22-7.33 (5H, m, Ph); δ_C(250 MHz; $CDCl_3$) 41.08, 42.43 (NCH_2 and *C*H_2CO), 116.74 (CH=*C*H_2), 122.88 (*C*H=CHPh), 126.69, 128.14, 129.01, 134.47, 134.80, 137.01, 171.31 (CO); *m/z* (EI) 201 (M^+, 13%), 122 (91), 105 (100), 77 (99), 51 (93).

N-Allyl-2-benzoyloxy-4-phenylbut-3-enamide, **124a**



(Found C 74.61, H 6.00, N 4.47. $C_{20}H_{19}NO_3$ requires C 74.75, H 5.96, N 4.4%).

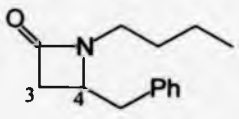
Rf (2:1 pet.ether:EtOAc) 0.41; mp 135-135.5 °C; ν_{max} (neat)/cm^{-1} 3000, 1713, 1675, 1500, 1248, 1075; δ_H(250 MHz; $CDCl_3$) 3.95 (2H, ap t, J=5.5, CH_2), 5.14 (1H, ap dq, J=10.7, 1.5, CH=CH_2), 5.20 (1H, ap dq, J=17.5, 1.5, CH=CH_2), 5.84 (1H, ddt, J=17.5, 10.7, 5.5, C*H*=CH_2), 6.05 (1H, dd, J=6.7, 1.2, CHCO), 6.36 (1H, br s, NH), 6.44 (1H, dd, J=16.0, 6.7, C*H*=CHPh), 6.85 (1H, d, J=16.0, CH=C*H*Ph), 7.22-7.50 (7H, m, Ph), 7.59-7.63 (1H, m, *p*-Ph, OCOPh), 8.11-8.15 (2H, m, *o*-Ph, OCOPh); δ_C(250 MHz; $CDCl_3$) 41.66 (NCH_2), 74.75 (*C*HOCOPh), 116.5 (CH=*C*H_2), 122.39 *C*H=CHPh), 126.77, 128.35, 128.52, 128.37, 129.09, 129.76, 133.50, 133.63, 134.71, 135.52, 164.94 (OCOPH), 168.06 (NCO); *m/z* (CI, NH_3) 322 (MH^+, 43%), 202 (100), 118 (22), 105(50).

7.5.3.3 Cyclisation of *N*-benzoyloxy-*N*-butyl-4-phenylbut-3-enamide, 121b

A solution of tributyltin hydride (1.04 ml, 3.56 mmol, 1.2 eq.) and AIBN (0.050 g, 0.1 eq.) in degassed toluene (7.5 ml) and cyclohexane (7.5 ml) was added *via* a syringe pump over 8 hours to a refluxing solution of *N*-benzoyloxy-*N*-butyl-4-phenylbut-3-enamide, **121b** (1.00 g, 2.96 mmol) in degassed cyclohexane (15 ml). After refluxing for a further 6 hours the solvents were removed on a rotary evaporator. ^{1}H NMR analysis (400 MHz) of the crude product mixture showed three products *N*-butyl-4-benzyl-2-azetidinone, *N*-butyl-4-phenylbut-3-enamide and *N*-butyl-2-benzoyloxy-4-phenylbut-3-enamide to have been formed in a ratio of 3:3:4. Purification by flash column chromatography (2:1, 1:1, 1:2 pentane:Et_2O; Et_2O; 1:1

Et_2O:methanol) separated the three main products but none of these products could be obtained completely free of tin by-products.

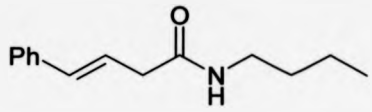
N-Butyl-4-benzyl-2-azetidinone, **122b**



(Found MH^+ 218.1545. $C_{14}H_{19}NO$ requires 218.1546).

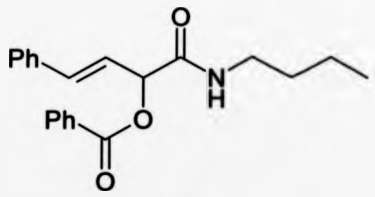
ν_{max} (neat)/cm^{-1} 2929, 1730, 1643, 1454, 716; δ_H(400 MHz; $CDCl_3$) 0.83-0.92 (3H, m, CH_3), 1.16-1.44 (2H, m, CH_2CH_3), 1.60-1.68 (2H, m, $CH_2CH_2CH_3$), 2.59 (1H, dd, J=14.6, 2.3, 3-H), 2.75 (1H, dd, J=13.8, 8.0, CH_2Ph), 2.86-2.94 (1H, m, NCH_2), 2.92 (1H, dd, J=14.6, 4.8, 3-H), 3.03 (1H, dd, J=13.8, 5.7, CH_2Ph), 3.33 (1H dt, J=14.1, 7.6, NCH_2), 3.79 (1H, ap dtd, J=8.0, 5.3, 2.3, 4-H), 7.12-7.30 (5H, m, Ph); δ_C(400 MHz; $CDCl_3$) 13.38 (CH_3), 19.90 and 26.69 ($CH_2CH_2CH_3$), 39.51 (3-C), 40.27 (NCH_2), 41.73 (CH_2Ph), 52.03 (4-C), 126.58, 127.92, 128.45, 128.53, 129.77, 132.31, 136.80, 166.93 (CO); *m/z* (EI) 217 (M^+, 24%), 175 (18), 126 (100), 105 (59), 84 (71).

N-Butyl-4-phenylbut-3-enamide, **123b**



Discernible data for this compound is as follows; δ_H(250 MHz; $CDCl_3$) 0.86-0.94 (3H, m, CH_3), 1.15-1.50 (4H, m, $CH_2CH_2CH_3$), 3.14 (2H, dd, J=7.3, 1.2, CH_2CO), 3.20-3.28 (2H, m, NCH_2), 6.27 (1H, dt, J=15.8, 7.3, C*H*=CHPh), 6.52 (1H, d, J=15.8, CH=C*H*Ph); δ_C(250 MHz; $CDCl_3$) 13.96 (CH_3), 20.43 and 30.25 ($CH_2CH_2CH_3$), 39.89 (CH_2CO), 42.28 (NCH_2), 123.03-137.37 (Ar), 171.65 (CO).

N-Butyl-2-benzoyloxy-4-phenylbut-3-enamide, **124b**



(Found M^+ 337.1672. $C_{21}H_{23}NO_3$ requires 337.1679).

ν_{max} (neat)/cm^{-1} 2959, 1723, 1665, 1261, 700; δ_H(250 MHz; $CDCl_3$) 0.90 (3H, t, J=7.2, CH_3), 1.25-1.57 (4H, m, $CH_2CH_2CH_3$), 3.31 (2H, td, J=7.1, 6.0, NCH_2), 6.00 (1H, dd, J=6.7, 1.2, C*H*(OCOPh)), 6.20 (1H, br s, NH), 6.41 (1H, dd, J=15.9, 6.7, C*H*=CHPh), 6.81 (1H, dd, J=15.9, 1.2, CH=C*H*Ph), 7.26-7.66 (8H, m, Ph), 8.12 (2H,

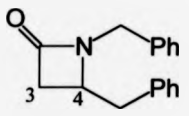
dd, J=8.4, 1.4, *o*-Ph, OCOPh); δ_C(250 MHz; $CDCl_3$) 14.09 (CH_3), 20.38 and 31.94 ($CH_2CH_2CH_3$), 39.65 (NCH_2), 75.23 (*C*HOCOPh), 123.04 (*C*H=CHPh), 127.24, 128.78, 128.99, 129.06, 129.66, 130.21, 134.07, 135.03, 136.07 165.38 (OCOPh), 168.49 (NCO); *m/z* (EI) 337 (M^+, 3%), 238 (50), 115 (36), 105 (100).

7.5 3.4 Cyclisation of *N*-benzoyloxy-*N*-benzyl-4-phenylbut-3-enamide, 121c

A solution of tributyltin hydride (0.94 ml, 3.23 mmol, 1.2 eq.) and AIBN (0.044 g, 0.1 eq.) in degassed toluene (5 ml) and cyclohexane (5 ml) was added *via* a syringe pump over 6 hours to a refluxing solution of *N*-benzoyloxy-*N*-benzyl-4-phenylbut-3-enamide (1.000 g, 2.69 mmol) in degassed cyclohexane (27 ml) under nitrogen. After refluxing for a further 12 hours tlc analysis showed very little reaction to have occurred. Half of the solvent was removed by evaporation under a stream of nitrogen and a further addition of Bu_3SnH (0.94 ml) and AIBN (0.044 g) in toluene/cyclohexane (10 ml) was made over a further 6 hours. The reaction mixture was refluxed for 12 hours before the solvents were removed on a rotary evaporator. ^1H NMR analysis (250 MHz) of the crude product mixture showed a 3:1 ratio of cyclised (*N*-benzyl-4-benzyl-2-azetidinone) to reduced (*N*-butyl-4-phenylbut-3-enamide) products with very little evidence of any rearranged (*N*-benzyl-2-benzoyloxy-4-phenylbut-3-enamide) product. Purification was achieved by soxhlet extraction with hexane, partitioning between acetonitrile:hexane and acetonitrile:cyclohexane. The combined acetonitrile portions were purified further by flash column chromatography (2:1, 1:1 hexane:EtOAc) to give 0.085 g (13%) of *N*-benzyl-4-benzyl-2-azetidinone along with 0.152 g (23%) of a 1:1 mixture of *N*-

benzyl-4-benzyl-2-azetidinone:*N*-butyl-4-phenylbut-3-enamide and 0.015g (1.5%) of *N*-Benzyl-2-benzoyloxy-4-phenylbut-3-enamide.

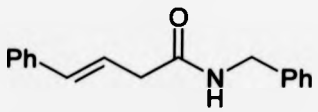
N-Benzyl-4-benzyl-2-azetidinone, **122c**



(Found M^+ 251.1309. $C_{17}H_{17}NO$ requires 251.1311).

yellow oil; ν_{max} (neat)/cm^{-1} 2923, 1731, 1454, 698; δ_H(250 MHz; $CDCl_3$) 2.64 (1H, dd, J=14.7, 2.5, 3-H), 2.71 (1H, dd, J=13.7, 7.6, CHC*H*$_2$Ph), 2.92 (1H, dd, J=13.7, 5.8, CHC*H*$_2$Ph), 2.93 (1H, dd, J=14.7, 4.9, 3-H), 3.64-3.72 (1H, m, 4-H), 3.95 (1H, d, J=14.8, NC*H*$_2$Ph), 4.60 (1H, d, J=14.8, NC*H*$_2$Ph); δ_C(250 MHz; $CDCl_3$) 39.76 (3-C), 42.39 (CH_2Ph), 44.88 (NCH_2Ph), 51.81 (4-C), 126.77, 127.02, 127.39, 127.60, 127.78, 128.18, 128.44, 128.65, 128.80, 135.81, 136.99, 166.99, 167.38; *m/z* (EI) 251 (M^+, 6%), 211 (27), 160 (62), 105 (78), 91 (100), 77 (60).

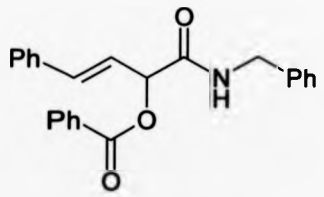
N-Benzyl-4-phenylbut-3-enamide, **123c**



(Found MH^+ 252.1388. $C_{17}H_{18}NO$ requires 252.1389).

ν_{max} (neat)/cm^{-1} 3200, 1632, 1538, 1450; δ_H(250 MHz; $CDCl_3$) 3.17 (2H, dd, J=7.0, 1.2, CH_2CO), 4.42 (2H, d, J=5.8, C*H*$_2$Ph), 6.30 (1H, dt, J=15.7, 7.0, C*H*=CHPh), 6.50 (1H, d, J=15.7, CH=C*H*Ph), 6.5 (1H, br s NH), 7.21-7.35 (10H, m, Ph); δ_C(250 MHz; $CDCl_3$) 40.60 (CH_2CO), 45.57 (NCH_2), 122.26 (*C*H=CHPh), 126.24, 127.41, 127.68, 128.54, 128.62, 134.45 (6 x Ar), 136.51 (CH=*C*HPh), 138.07 (Ar), 170.94 (NCO); *m/z* (EI) 251 (M^+, 11%), 160 (10), 117 (76), 91 (100), 77 (20).

N-Benzyl-2-benzoyloxy-4-phenylbut-3-enamide, **124c**



(Found M^+ 371.1529. $C_{24}H_{21}NO_3$ requires 371.1522).

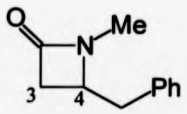
ν_{max} (Nujol)/cm^{-1} 1711, 1655, 1561; δ_H(250 MHz; $CDCl_3$) 4.50 (1H, dd, J=14.9, 5.8, C*H*$_2$Ph), 4.57 (1H, dd, J=14.9, 5.8, C*H*$_2$Ph), 6.07 (1H, dd, J=6.7, 1.3, C*H*(OCOPh)), 6.45 (1H, dd, J=15.9, 6.7, C*H*=CHPh), 6.45 (1H, br s, NH), 6.84 (1H, dd, J=15.9, 1.3, CH=C*H*Ph), 7.23-7.65 (13H, m, Ph), 8.10 (2H, dd, J=8.3, 1.2, *o*-Ph, OCOPh); δ_C(250 MHz; $CDCl_3$) 43.28 (NCH_2), 74.76 (*C*H(OCOPh), 122.28 (*C*H=CHPh), 126.76, 127.53, 128.36, 128.51, 128.53, 128.67, 129.04, 129.74, 133.59, 134.83,

135.50, 136.41, 137.56, 164.94 (OCOPh), 168.13 (NCO); *m/z* (EI) 371 (M^+, 2%), 238 (34), 105 9100), 91 (64), 77 (57).

7.5.3.5 Cyclisation of *N*-benzoyloxy-*N*-methyl-4-phenylbut-3-enamide, 121f

A solution of tributyltin hydride (0.36 ml, 1.22 mmol, 1.2 eq.) and AIBN (0.017 g, 0.1 eq.) in degassed toluene (3 ml) and cyclohexane (3 ml) was added *via* a syringe pump over 7 hours to a refluxing solution of *N*-benzoyloxy-*N*-methyl-4-phenylbut-3-enamide (0.300 g, 2.96 mmol) in degassed cyclohexane (7 ml). After refluxing for a further 6 hours the solvents were removed on a rotary evaporator. Purification was achieved by partitioning between acetonitrile/hexane and acetonitrile/cyclohexane followed by flash column chromatography (1:1, 2:1 Et_2O:hexane; Et_2O; 95:5 Et_2O:methanol).

N-Methyl-4-benzyl-2-azetidinone, **122f**[97]

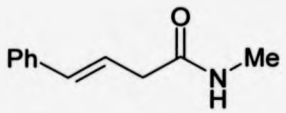


Obtained as a yellow oil in 14% (0.025 g) yield. (Found MH^+ 176.1070. $C_{11}H_{13}NO$ requires 176.1076).

ν_{max} (neat)/cm^{-1} 2923, 1731, 1453, 1097, 701; δ_H(250 MHz; $CDCl_3$) 2.64 (1H, ddd, J=14.6, 2.1, 0.9, 3-H), 2.73 (3H, s, NMe), 2.80 (1H, dd, J=13.9, 7.6, C*H*$_2$Ph), 2.97

(1H, ddd, J=14.6, 4.9, 0.6, 3-H), 3.05 (1H, dd, J=13.9, 5.8, C*H*$_2$Ph), 3.71-3-79 (1H, m, 4-H), 7.15-7.80 (5H, m, Ph); δ_C(250 MHz; $CDCl_3$) 27.10, 39.21, 42.38, 53.56, 125.74, 128.64, 129.61 136.84, 167.15; *m/z* (EI) 175 (M^+, 4%), 117 (18), 91 (25), 84 (63), 42 (100).

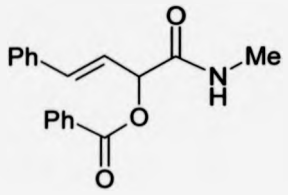
N-Methyl-4-phenylbut-3-enamide, **123f**



Obtained as an orange oil in 40% yield (0.070 g). (Found M^+ 175.0996. $C_{11}H_{13}NO$ requires 175.0998).

ν_{max} (neat)/cm^{-1} 3275, 1650; δ_H(250 MHz; $CDCl_3$) 2.81 (3H, d, J=4.9, NMe), 3.15 (2H, dd, J=7.3, 0.9, CH_2), 6.28 (1H, dt, J=15.9, 7.3, C*H*=CHPh), 6.53 (1H, dd, J=15.9, 1.2, (CH=C*H*Ph), 7.13-7.36 (5H, m, Ph); δ_C(250 MHz; $CDCl_3$) 26.87 (NMe), 41.04 (*C*H_2CO), 122.70 (*C*H=CHPh), 126.67, 128.21, 129.02, 135.16, 136.89, 171.96 (CO); *m/z* (EI) 175 (M^+, 55%), 117 (100), 91 (54), 58 (67).

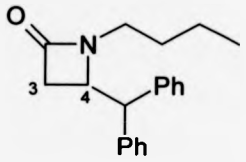
N-Methyl-2-benzoyloxy-4-phenylbut-3-enamide, **124f**



Obtained as an orange oil in 15% yield (0.044 g). (Found M^+ 295.1208. $C_{18}H_{17}NO_3$ requires 295.1209).

ν_{max} (neat)/cm^{-1} 3311, 1722, 1668, 1264, 1109, 712; δ_H(250 MHz; $CDCl_3$) 2.89 (3H, d, J=5.0, Me), 6.04 (1H, dd, J=6.7, 1.2, C*H*(OCOPh)), 6.29 (1H, br s, NH), 6.42 (1H, dd, J=16.0, 6.7, C*H*=CHPh), 6.82 (1H, dd, J=16.0, 1.2, CH=C*H*Ph), 7.26-7.66 (8H, m, Ph), 8.12 (2H, dd, J=7.7, 1.5, *o*-Ph, OCOPh); δ_C(250 MHz; $CDCl_3$) 26.18 (NMe), 74.63 (CHCO), 122.40 (*C*H=CHPh), 126.74, 128.30, 128.50, 128.54, 129.74, 129.96, 133.30, 133.60, 134.61, 164.85 (OCOPh), 168.79 (NCO); *m/z* (EI) 295 (M^+, 6%), 238 (19), 115 (53), 105 (100), 91 (41), 77 (79).

7.5.3.6 Cyclisation of *N*-benzoyloxy-*N*-butyl-4,4-diphenylbut-3-enamide - Preparation of *N*-butyl-4-(Dibenzyl)methyl-2-azetidinone, 122e



A solution of tributyltin hydride (85 μl, 0.24 mmol, 1.2 eq.) and AIBN (4 mg, 0.1 eq.) in degassed toluene (2 ml) was added *via* a syringe pump over 8 hours to a refluxing solution of *N*-benzoyloxy-*N*-butyl-4,4-diphenylbut-3-enamide, **121e** (100 mg, 0.24 mmol) in degassed cyclohexane (2 ml). After refluxing for a further 12 hours tlc analysis showed the reaction not to be complete so a further addition of Bu_3SnH (43 μl) and AIBN (4 mg) in toluene (1 ml) was made over 4 hours. Solvents were removed on a rotary evaporator and the crude product partially purified by partitioning between acetonitrile/hexane and acetonitrile/cyclohexane. The combined acetonitrile portions were purified further by flash column chromatography (1:1, 2:1 Et_2O:hexane; Et_2O; 95:5 Et_2O:methanol) to afford 19 mg of *N*-butyl-4,4-(dibenzyl)methyl-2-azetidinone as a yellow oil in 27% yield. (Found MH^+ 294.1856. $C_{20}H_{24}NO$ requires 294.1859).

ν_{max} (neat)/cm^{-1} 2956, 1746, 1666, 1451, 704; δ_H(250 MHz; $CDCl_3$) 0.72 (3H, t, J=7.2, CH_3), 0.85-1.54 (4H, m, $CH_2CH_2CH_3$), 2.31-2.42 (1H, m, NCH_2), 2.57 (1H, ddd, J=14.7, 2.4, 0.9, 3-H), 3.03 (1H, dd, J=14.7, 4.9, 3-H), 3.15 (1H, dt, J=14.0, 7.6, NCH_2), 3.96 (1H, d, J=9.8, $CH(Ph)_2$), 4.40 (1H, ddd, J=9.8, 4.9, 2.4, 4-H), 7.16-7.39

(10H, m, Ph); δ_C(250 MHz; $CDCl_3$) 13.34, 15.12, 19.82, 29.44, 41.02, 42.22, 54.45, 56.41, 65.72 ($CH(Ph)_2$), 126.84, 127.12, 127.38, 127.86, 128.69, 128.76 (6 x Ar), 141.19, 142.06 (2 x C_1 Ar), 167.33 (CO); *m/z* (CI, NH_3) 294 (MH^+, 100%), 252 (74), 212 (62), 126 (32), 91 (32).

7.6 Experimental for Chapter 6

7.6.1 Reaction of *N*-benzoyloxy-*N*-*n*-butyl-4-phenylbut-3-enamide, 121b with base

121b **124b**

7.6.1.1 Triethylamine (21 µl, 0.15 mmol) was added dropwise to a solution of **121b** (50 mg, 0.15 mmol) in dichloromethane (2.5 ml). The reaction mixture was stirred for 40 hours at room temperature after which time tlc analysis indicated the reaction to be complete. Water was added and the product extracted into dichloromethane and washed with water and 10% HCl. The combined organic phases were dried over anhydrous magnesium sulphate and concentrated on a rotary evaporator. Purification by flash column chromatography (10:1 pet. ether:EtOAc gave 14 mg, (28%) of **124b** as a yellow solid. (for data see 7.5.2.3).

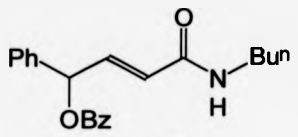
7.6.1.2 Triethylamine (41.3 μl, 0.30 mmol) was added dropwise to a solution of **121b** (100 mg, 0.30 mmol) in dichloromethane (5 ml). The reaction mixture was refluxed (40°C) for 4 hours after which time tlc analysis indicated the reaction to be complete. Work up as for 7.6.1.1 gave 63 mg, (63%) of pure **124b.**

7.6.1.3 Triethylamine (10 μl, 0.075 mmol, 0.25 eq.) was added dropwise to a solution of **121b** (100 mg, 0.30 mmol) in dichloromethane (2.5 ml). The reaction mixture was refluxed (40°C) for 24 hours. Removal of the solvent by rotary evaporation followed by recrystallization from diethyl ether gave 22 mg (22%) of **124b** as a yellow solid.

7.6.1.4 *N,N*-Diisopropylethylamine (31 μl, 0.18 mmol) was added dropwise to a solution of **121b** (40 mg, 0.12 mmol) in dichloromethane (5 ml). The reaction mixture was stirred at room temperature for 24 hours and as tlc analysis indicated no reaction to have occurred was refluxed (40°C) for a further 4 hours. Work up as for 7.6.1.1 followed by purification by flash column chromatography (5:1 pet. ether:EtOAc) gave 19 mg, (48%) of pure **124b**.

7.6.1.5 The phosphazene base P_1-*t*-butyltris(tetramethylene), (91 μl, 0.30 mmol) was added dropwise to a stirring solution of **121b** (100 mg, 0.30 mmol) in dry dichloromethane (10 ml) at room temperature and under an atmosphere of nitrogen. An immediate colour change from colourless to yellow, to orange to red was noted and after 5 minutes tlc analysis indicated the reaction to be complete. Work up as for 7.6.1.1 followed by purification by flash column chromatography (3:1 pet.

ether:EtOAc) gave 15 mg, (15%) of pure **124b** along with 12 mg (12%) of the isomer **137.**



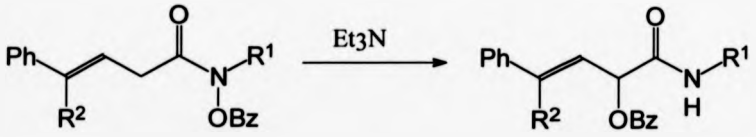
137

δ_H (400 MHz) 0.89 (3H, t, J=7.3, CH_3), 1.33 (2H, sx, J=7.3, CH_2CH_3), 1.48 (2H, qn, J=7.3, $CH_2CH_2CH_3$), 3.29 (2H, q, J=6.8, NCH_2), 6.03 (1H, d, J=15.2, C*H*Ph), 6.62 (1H, d, J=5.3, C*H*CO), 7.03 (1H, dd, J=15.2, 5.3, C*H*=CHCO), 7.23-7.61 (8H, m, Ph), 8.08 (2H, d, J=7.4, OCOPh); δ_c (400 MHz) 13.75 (CH_3), 20.09 and 31.62 ($CH_2CH_2CH_3$), 39.47 (NCH_2), 74.98 (*C*HOCOPh), 124.59, 127.39, 128.51, 128.70, 128.84, 129.80, 133.34, 137.70, 140.60, 164.83 (NCO), 165.33 (OCOPh);

7.6.1.6 The phosphazene base P_1-*t*-butyltris(tetramethylene), (91 µl, 0.30 mmol) was added dropwise to a stirring solution of **121b** (100 mg, 0.30 mmol) in dry dichloromethane (10 ml) at 0°C and under an atmosphere of nitrogen. An immediate colour change from colourless to yellow, to orange to red was noted and after 10 minutes tlc analysis indicated the reaction to be complete. Work up as for 7.6.1.1 followed by purification by flash column chromatography (5:1 pet. ether:EtOAc) gave 19 mg, (19%) of pure **124b** along with 16 mg (16%) of the isomer **137.**

7.6.1.7 The phosphazene base P_1-*t*-butyltris(tetramethylene), (9.1 µl, 0.03 mmol, 0.1 eq.) was added dropwise to a stirring solution of **121b** (100 mg, 0.30 mmol) in dry dichloromethane (10 ml) at room temperature and under an atmosphere of nitrogen. An immediate colour change from colourless to yellow was noted with a slower change to orange. After stirring at room temperature for 24 hours the reaction was worked up as for 7.6.1.1. Purification by flash column chromatography (5:1 pet. ether:EtOAc) gave 22 mg, (22%) of pure **124b** along with 18 mg of the recovered starting material.

7.6.2 Reaction of other *N*-alkyl-*N*-benzoyloxy-4-phenylbut-3-enamides with triethylamine



121c $R^1 = CH_2Ph$, $R^2 = H$
121e $R^1 = n$-Bu, $R^2 = Ph$
121f $R^1 = Me$, $R^2 = H$

124c $R^1 = CH_2Ph$, $R^2 = H$
124e $R^1 = n$-Bu, $R^2 = Ph$
124f $R^1 = Me$, $R^2 = H$

7.6.2.1 Triethylamine (29 µl, 0.21 mmol), was added dropwise to a stirring solution of *N*-benzoyloxy-*N*-methyl-4-phenylbut-3-enamide, **121f** (62 mg, 0.21 mmol), in dichloromethane (5 ml) at room temperature. The reaction was left stirring at this temperature for 24 hours after which time tlc analysis indicated the reaction to be complete. Work-up as for 7.6.1.1 furnished 33 mg (53%) of *N*-methyl-2-benzoyloxy-4-phenylbut-3-enamide, **124f** as an orange oil. Data as for 7.5.3.4.

7.6.2.2 Triethylamine (26 μl, 0.19 mmol), was added dropwise to a stirring solution of *N*-benzoyloxy-*N*-methyl-4-phenylbut-3-enamide, **121f** (55 mg, 0.19 mmol), in dichloromethane (5 ml) at room temperature. The reaction mixture was refluxed (40°C) for 4 hours after which time tlc analysis indicated the reaction to be complete. Work-up as for 7.6.1.1 furnished 31 mg (56%) of *N*-methyl-2-benzoyloxy-4-phenylbut-3-enamide, **124f** as an orange oil. Data as for 7.5.3.5.

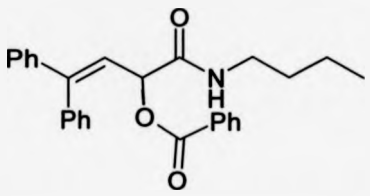
7.6.2.3 Triethylamine (26 μl, 0.19 mmol), was added dropwise to a stirring solution of *N*-benzoyloxy-*N*-benzyl-4-phenylbut-3-enamide, **121c** (50 mg, 0.19 mmol), in dichloromethane (2.5 ml) at room temperature. The reaction mixture was refluxed (40°C) for 24 hours. Solvent and excess triethylamine were removed on the rotary evaporator and purification by flash column chromatography (5:1 pet. ether:EtOAc) furnished 14 mg (28%) of *N*-benzyl-2-benzoyloxy-4-phenylbut-3-enamide, **124c**. Data as for 7.5.3.4.

7.6.2.4 Triethylamine (13 μl, 0.094 mmol), was added dropwise to a stirring solution of *N*-benzoyloxy-*N*-benzyl-4-phenylbut-3-enamide, **121c** (100 mg, 0.37 mmol), in dichloromethane (2.5 ml) at room temperature. The reaction mixture was refluxed (40°C) for 4 days. Solvent and excess triethylamine were removed on the rotary evaporator. The crude product was recrystallised in ether to furnish 41 mg (41%) of *N*-benzyl-2-benzoyloxy-4-phenylbut-3-enamide, **124c**. Data as for 7.5.3.4.

7.6.2.5 Triethylamine (4.6 μl, 0.033 mmol), was added dropwise to a stirring solution of *N*-benzoyloxy-*N*-benzyl-4,4-diphenylbut-3-enamide, **121e** (55 mg, 0.13

mmol), in dichloromethane (3 ml) at room temperature. The reaction mixture was refluxed (40°C) for12 hours. Solvent and excess triethylamine were removed on the rotary evaporator to furnish 55 mg (>95%) of *N*-benzyl-2-benzoyloxy-4,4-diphenylbut-3-enamide, **124c**.

N-Butyl-2-benzoyloxy-4,4-diphenylbut-3-enamide, **124e**

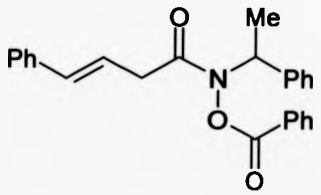


Obtainable data as follows: ν_{max} (neat)/cm^{-1} 3334, 2930, 1723, 1666, 1264, 1094, 701; δ_H(250 MHz; $CDCl_3$) 0.90 (3H, t, J=7.2, CH_3), 1.24-1.54 (4H, m, $CH_2CH_2CH_3$), 3.23-3.32 (2H, m, NCH_2), 5.81 (1H, d, J=9.7, CHCO), 6.30 (1H, d, J=9.7, CH=C), 7.23-7.64 (13H, m, Ph); δ_C(250 MHz; $CDCl_3$) 13.64 (CH_3), 19.90 and 31.42 ($CH_2CH_2CH_3$), 39.18 (NCH_2), 72.89 (*C*HCO), 121.18 (*C*H=C), 127.66, 128.05, 128.14, 128.21, 128.41, 129.30, 129.69, 129.77, 133.39, 138.26, 140.85 (11 x Ar), 148.66 (CH=*C*(Ph)$_2$), 165.07 (OCOPh), 168.32 (NCO);

7.6.3 *N*-Benzoyloxy-*N*-(α-methylbenzyl)-4-phenylbut-3-enamide, 121g

Dibenzoyl peroxide (2.00 g, 70% in H_2O, 5.82 mmol) in dichloromethane (10 ml) was added dropwise to a stirring solution of α-methylbenzylamine (0.75 ml, 5.82

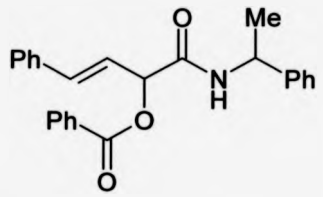
mmol) and potassium carbonate (2 g) in dichloromethane (10 ml). The reaction was stirred at room temperature for 1.5 hours. *Trans*-styrylacetyl chloride (1.05 g, 5.82 mmol, prepared as described earlier for 7.5.1.2) in dichloromethane (10 ml) was added dropwise to the reaction mixture and the resulting solution stirred at room temperature for a further 1.5 hours. Water was added and the product extracted into dichloromethane, washed with water, dried over anhydrous magnesium sulphate and concentrated on a rotary evaporator. Purification by flash column chromatography (5:1 pet. ether:EtOAc) furnished the desired *N*-benzoyloxy-*N*-(α-methylbenzyl)-4-phenylbut-3-enamide (0.67 g, 30%) as a yellow oil. (Found MH^+ 386.1755. $C_{25}H_{23}NO_3$ requires 386.1757).



Rf 0.26 (5:1 pet.ether:EtOAc); ν_{max} (neat)/cm^{-1} 3061, 1766, 1674, 1451, 1237, 1015, 699; δ_H(400 MHz; $CDCl_3$) 1.64 (3H, d, J=7.1, Me), 3.24 (2H, d, J=6.3, CH_2), 5.91 (1H, q, J=7.0, CH), 6.27 (1H, dt, J=16.0, 6.3, C*H*=CHPh), 6.36 (1H, d, J=16.0, CH=C*H*Ph), 7.17-7.49 (12H, m, Ph), 7.63 (1H, t, J=7.5, *p*-Ph, OCOPh), 7.98 (2H, dd, J=7.8, 1.3, *o*-Ph, OCOPh); δ_C(250 MHz; $CDCl_3$) 16.91 (br) (Me), 37.25 (CH_2CO), 56.61 (br) (*C*HMe), 121.42 (*C*H=CHPh), 126.11, 126.47, 127.27, 127.78, 128.29, 128.75, 129.84, 130.52 (8 x Ar), 133.38 (CH=*C*HPh), 134.26, 136.72,

139.22 (3 x Ar), 164.40 (OCOPh), 171.66 (NCO); *m/z* (CI, NH_3) 386 (MH^+, 52%), 266 (32), 196 (27), 120 (83), 105 (100), 78 (34).

7.6.4 *N*-(α-Methylbenzyl)-2-benzoyloxy-4-phenylbut-3-enamide, 124g



7.6.4.1 Triethylamine (36 μl, 0.26 mmol) was added dropwise to a stirring solution of *N*-benzoyloxy-*N*-(α-methylbenzyl)-4-phenylbut-3-enamide, **121g** (100 mg, 0.26 mmol) in dichloromethane (10ml) at room temperature. After stirring at room temperature for 3 hours tlc analysis indicated the reaction to be complete. Work-up as for 7.6.1.1 furnished 45 mg (45%) of *N*-(α-Methylbenzyl)-2-benzoyloxy-4-phenylbut-3-enamide as a yellow oil.

7.6.4.2 Quinine (84 mg, 0.26 mmol, 1 eq.) was added dropwise to a stirring solution of *N*-benzoyloxy-*N*-(α-methylbenzyl)-4-phenylbut-3-enamide (100 mg, 0.26 mmol) in dichloromethane (10ml) at room temperature. The reaction was refluxed (40°C) for 5 hours. Work-up as for 7.6.1.1 followed by flash column chromatography (5:1 pet. ether:EtOAc) furnished 13 mg (13%) of *N*-(α-methylbenzyl)-2-benzoyloxy-4-phenylbut-3-enamide as a yellow oil.

7.6.4.3 As above (7.6.4.2) replacing quinine with quinidine (84 mg, 0.26 mmol) and refluxing the reaction for 24 hours. *N*-(α-Methylbenzyl)-2-benzoyloxy-4-phenylbut-3-enamide obtained in 13% yield (13 mg). (Found MH^+ 386.1756. $C_{25}H_{23}NO_3$ requires 386.1757).

ν_{max} (neat)/cm^{-1} 3300, 2925, 1721, 1664, 1274, 1110, 698; δ_H(250 MHz; $CDCl_3$) Isomer a 1.51 (3H, d, J=7.0, Me), 5.13-5.25 [1H, m, CH(Me)], 6.04 [1H, dd, J=6.7, 1.3, C*H*(OCOPh)], 6.41 (1H, dd, J=15.9, 6.7, C*H*=CHPh), 6.79 (1H, dd, J=15.9, 1.3, CH=C*H*Ph), 7.26-7.67 (13H, m, Ph), 8.10 (2H, d, J=8.4, *o*-Ph, OCOPh); Isomer b 1.55 (3H, d, J=7.0, Me), 5.13-5.25 [1H, m, CH(Me)], 6.00 [1H, dd, J=6.7, 1.3, CH(OCOPh)], 6.43 (1H, dd, J=15.9, 6.2, C*H*=CHPh), 6.82 (1H, dd, J=15.9, 1.2 (CH=C*H*Ph); δ_C(400 MHz; $CDCl_3$) 21.75 (Me), 48.83 (CHMe), 74.83 (CHCO), 122.44 (CH=CHPh), 126.05, 126.11, 126.91, 128.49, 128.64, 128.69, 128.73, 128.76, 128.84, 129.84, 133.71, 133.74, 134.96; *m/z* 386 (MH^+, 8%), 281 (50), 264 (70), 238 951), 120 (55), 105 (100), 77 (47).

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