Silver-catalysed hydroamination: synthesis of functionalised pyrroles

by

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Declaration

The experimental work described in this thesis was carried out in the School of Chemistry, University of KwaZulu-Natal, Pietermaritzburg, under the supervision of Dr David Gravestock.

These studies represent original work by the author and have not otherwise been submitted in candidature for any other degree.

Signed: .....M.C. Dovey (Candidate)

Signed: .....Dr R. S. Robinson (Co-supervisor)

Signed: .....Dr M. R. Low (Head of Chemistry)

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Abbreviations

Ac	acetyl
AIBN	azobisisobutyronitrile
aq	aqueous
Ar	aryl
atm	atmosphere
9-BBN	9-borabicyclo[3.3.1]nonane
b.p.	boiling point
Bn	benzyl
Bu	butyl
cat	catalyst / catalytic
cm	centimetre
cod	1,5-cyclooctadiene
Cp	cyclopentadiene
cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]non-ene
DME	ethylene glycol dimethyl ether
DMF	dimethylformamide
e.e.	enantiomeric excess
EI	electron impact
eq	equivalent/s
Et	ethyl
EWG	electron-withdrawing group
GC	gas chromatography
GC-MS	gas chromatography-mass spectrometry
GLC	gas liquid chromatography
Hz	Hertz
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectrometry
IR	infrared
KHMDS	potassium hexamethyldisilazide

L	ligand
LAH	lithium aluminium hydride
LDA	lthium diisopropylamide
LHMDS	lithium hexamethyldisilazide
LUMO	lowest unoccupied molecular orbital
M	metal
m	metre
Me	methyl
mg	milligram
min	minute
mm	millimetre
MS	mass spectrometry
NBS	*N*-bromosuccinimde
NMR	nuclear magnetic resonance
Ph	phenyl
ppm	parts per million
psi	pounds per square inch
PTSA	para-toluenesulphonic acid
RAMP	(***R***)-1-amino-2-methoxymethyl-pyrrolidine
RT	room temperature
SAMP	(*S*)-1-amino-2-methoxymethyl-pyrrolidine
TBAF	tetrabutylammonium fluoride
THF	tetrahydrofuran
T.L.C.	thin layer chromatography
TMEDA	*N, N, N', N'*-tetramethylethylenediamine
Ts	tosyl

Summary

The aim of this project was a broad one, namely to develop general methods for the preparation of nitrogen-containing heterocycles. This topic also encompasses the preparation of precursors to heterocycles with the goal of obtaining compounds that can undergo various transformations to give different cyclic products (general synthetic precursors).

Workers in our group have previously reported the preparation of indolizinones from *N*-propargyl enaminones. Immediate goals were to elucidate the mechanism of this transformation, optimise its yields and explore its generality. Initial work revealed a possible reaction intermediate in the form of isomeric *N*-allenyl enaminones. These compounds can be easily prepared from *N*-propargyl enaminones using potassium *tert*-butoxide. Although parallels between the two reactions were noted, the presence of *N*-allenyls as reaction intermediates was not substantiated.

In spite of this, *N*-allenyl enaminones were considered to be potentially valuable compounds in their own right and their chemistry was briefly explored. It was shown that they undergo hydroboration smoothly yielding only one hydroboration product. This was observed using dynamic ^{11}B NMR spectroscopy. Subsequent oxidation gave interesting results and these are discussed further.

At this stage it was considered important to prepare piperidine and acyclic analogues of the *N*-allenyl enaminones already synthesised. Both preparations proved problematic and were ultimately abandoned. Although these attempts were not fruitful, a number of interesting observations were made *en route* and contribute to the discussion.

Whilst attempting to prepare acyclic analogues it was found that when a mixture of a secondary enaminone and propargyl bromide was treated with silver nitrate functionalised pyrroles were formed. This method of pyrrole formation, although low yielding (~25%), was both novel and intriguing.

As pyrroles are important heterocycles and common synthetic targets, further work was carried out to elucidate the mechanism in operation during this conversion. A thorough investigation led to a proposed mechanism involving silver-mediated hydroamination followed by an intramolecular nucleophilic substitution. This proposed mechanism is discussed further.

Carrying out the reaction over two steps was found to improve the procedure. Carbon-carbon bond formation prior to an intramolecular silver-catalysed hydroamination provides superior overall yields. Intramolecular hydroamination can be carried out at room temperature or using microwave irradiation. Employing microwave irradiation reduces reaction times from sixteen hours to sixty seconds without any decrease in yields.

This process was extended to bicyclic systems, namely *N*-bridgehead pyrroles. The preparation of the necessary cyclic precursors *via* a protection-deprotection strategy is described. *N*-Bridgehead pyrroles provide the framework for pyrrolizidine, indolizidine and lehmizidine alkaloids and general synthetic protocols toward the synthesis of such alkaloids is proposed.

Publications and conference proceedings

Robinson, R.S., Dovey, M.C. and Gravestock, D., *Euro. J. Org. Chem.*, **2004** (200400598).

Robinson, R.S., Dovey, M.C. and Gravestock, D., *Tetrahedron Lett.*, **2004**, 45, 6787-6789.

Gravestock, D. and Dovey, M.C., *Synthesis*, **2003**, 523-530. (see also Gravestock, D., Dovey, M.C., *Synthesis*, **2003**, 1470.)

Gravestock, D. and Dovey, M.C., *Acta Cryst*, **2002**, E*58*, o631-o633.

Silver-catalysed hydroamination: Synthesis of functionalised pyrroles, (poster presentation), 37th Convention of the South African Chemical Institute, CSIR convention centre, Pretoria, July 2004.

Silver-catalysed hydroamination: Synthesis of functionalised pyrroles, (oral presentation), SACI post-graduate research colloquium, University of KwaZulu-Natal, Pietermaritzburg, June 2004.

Preparation and reactions of vinylogous ynamides, (poster flash), Frank Warren conference, Rhodes University, Grahamstown, April 2003.

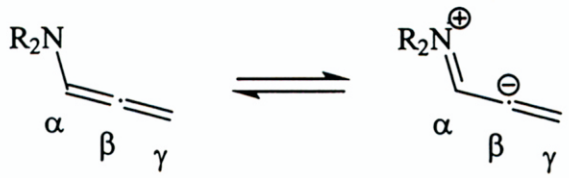
Preparation and reactions of vinylogous ynamides, (oral presentation), SACI post-graduate research colloquium, University of Natal, Durban, April 2003.

Mechanistic and computational studies on the synthesis of 2,3-dihydro-7(1H)-indolizinones, (poster presentation), 36th Convention of the South African Chemical Institute, University of Port Elizabeth, Port Elizabeth, August 2002. Received honourable mention.

Introduction

1 Allenamines and allenamides

Allenes have interested chemists for more than 100 years with the first examples reported in 1887.[1] They are interesting from an electronic, stereochemical and synthetic perspective and their overall chemistry has been reviewed several times.[2] Allenes substituted with a nitrogen atom (allenamines) are a useful subgroup of compounds that shows improved utility as synthetic precursors due to the ability of the nitrogen atom to donate its lone pair of electrons and, in doing so, introduce electronic bias upon the allenic unit (Scheme 1). This bias theoretically allows a high degree of regioselectivity in further transformations.



Scheme 1

Although allenamines were described by research groups during the 1960's,[3] a limited amount of work has emerged subsequent to these early reports. This has been attributed to the difficulties encountered in their synthesis and usage thereafter as they display susceptibility to hydrolysis, polymerisation and isomerisation.[4]

Interest in this field has been renewed in the past decade by the observation that allenamines substituted with an electron-withdrawing group, generally known as allenamides, show greater tolerance to hydrolysis etc. without a great loss of reactivity. This has led to a resurgence in the number of groups working towards methods of preparing these compounds and, particularly, investigating their chemical characteristics.

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[1] Favorsky, A.E., *J. Russ. Phys. Chem. Soc.*, **1887**, *19*, 414-eoa. (Cited in Ref. 2b).

[2] For comprehensive reviews: a) Pasto, D.J., *Tetrahedron*, **1984**, *40*, 2805-2827. b) Taylor, D.R., *Chem. Rev.*, **1967**, *67*, 317-359.

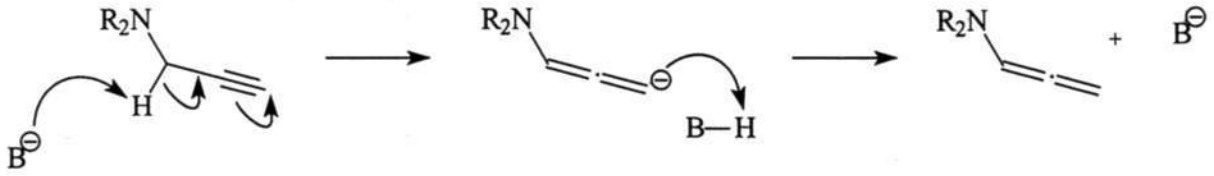
[3] Hubert, A.J., Viehe, H.G., *J. Chem. Soc. (C)*, **1968**, 228-230.

[4] Wei, L.-L., Xiong, H., Hsung, R.P., *Acc. Chem. Res.*, **2003**, *36*, 773-782.

Recent publications dedicated to this subject, most notably those of Hsung and co-workers,[4] have treated allenamines and allenamides as separate entities. It is not the intention of this discussion to follow this trend, nor is it to provide a broad overview of the subject, instead it is hoped it will serve to highlight the enormous potential this class of compounds show as general synthetic precursors. These compounds shall be referred to as *N*-allenyls for general discussion purposes, however, the terms 'allenamine' and 'allenamide' will be used when appropriate.

1.1 Preparation

The most commonly used method of *N*-allenyl preparation is base-catalysed isomerisation of the corresponding propargyl compounds (Scheme 2).



Scheme 2

A variety of conditions have been employed to effect this isomerisation although the most frequently used combination is *t*-BuOK in THF.[5] Other examples of bases used are *n*-BuLi,[6] KNH_2 / Al_2O_3,[3] NaH,[7] NaOEt,[8] KOH,[9] and in the extreme case of *N*-propargyl pyridinium salts, the isomerisation can be effected using weak bases such as K_2CO_3 or NEt_3.[10] The stoichiometry of these reactions is dependent on the base. A disadvantage of

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[5] For general examples see a) Wei, L.-L., Mulder, J.A., Xiong, H., Zificsak, C.A., Douglas, C.J., Hsung, R.P., *Tetrahedron*, **2001**, *57*, 459-466. b) Noguchi, M., Okada, H., Watanabe, M., Okuda, K., Nakamura, O., *Tetrahedron*, **1996**, *52*, 6581-6590. c) Broggini, G., Zecchi, G., *J. Chem. Soc., Perkin Trans. 1*, **1991**, 1843-1846.

[6] Craig, J.C., Ekwuribe, N.N., *Tetrahedron Lett.*, **1980**, *21*, 2587-2590.

[7] Corbel, B., Paugam, J.-P., *Tetrahedron Lett.*, **1976**, *17*, 835-838.

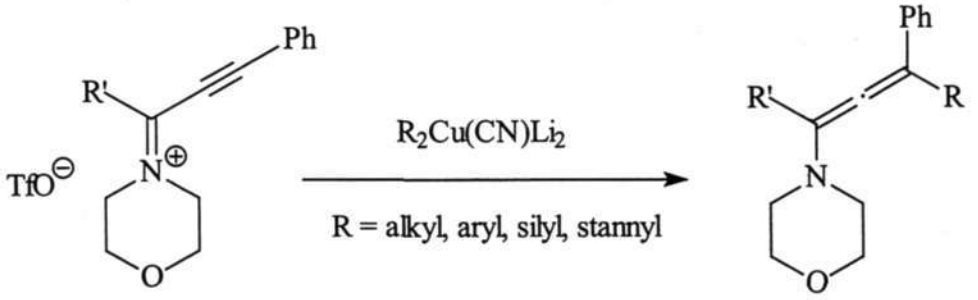
[8] Bogentoft, C., Ericsson, Ö., Stenberg, P., Danielsson, B., *Tetrahedron Lett.*, **1969**, *10*, 4745-4748.

[9] Broggini, G., Bruché, L., Zecchi, G., *J. Chem. Soc., Perkin Trans. 1*, **1990**, 533-539.

[10] Katritzky, A.R., Schwarz, O.A., Rubio, O., Markees, D.G., *Helv. Chim. Acta*, **1984**, 67, 939-946.

using this method of *N*-allenyl formation is the possibility of further isomerisation to 2-propynylamines (ynamines) if the original propargyl compound contains two α-protons. The ratio of these three compounds is dependent on the electronic character of the nitrogen atom, the duration of the reaction and the base-solvent system employed.[12a]

A number of slightly different approaches have also appeared in the literature. A reasonably elegant method is to prepare the *N*-propargyl compound and effect its isomerisation in one step.[11] *N*-allenyl compounds have also been prepared *via* dehydrohalogenation[12] and thermolysis.[13] A valuable method used to prepare highly functionalised *N*-allenyls is the conjugate addition of organocuprates to (2-propynylidene) morpholonium triflates (Scheme 3).[14]



Scheme 3

A number of other methods have appeared in the literature to date but have not found widespread use.[4]

1.2 Reactivity

Hsung and co-workers have established themselves as the leaders in the field of *N*-allenyl compounds, specifically allenamide chemistry. Their work, along with that of others, has

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[11] a) van Boxtel, L.J., Körbe, S, Noltemeyer, M., de Meijere, A., *Eur. J. Org. Chem.*, **2001**, 2283-2292. b) Galons, H., Bergerat, I., Combet-Farnoux, C., Miocque, M., Decodts, G., Bram, G., *J. Chem. Soc., Chem. Commun.*, **1985**, 1730-1731. c) Dickinson, W.B., Lang, P.C., *Tetrahedron Lett.*, **1967**, *8*, 3035-3040.

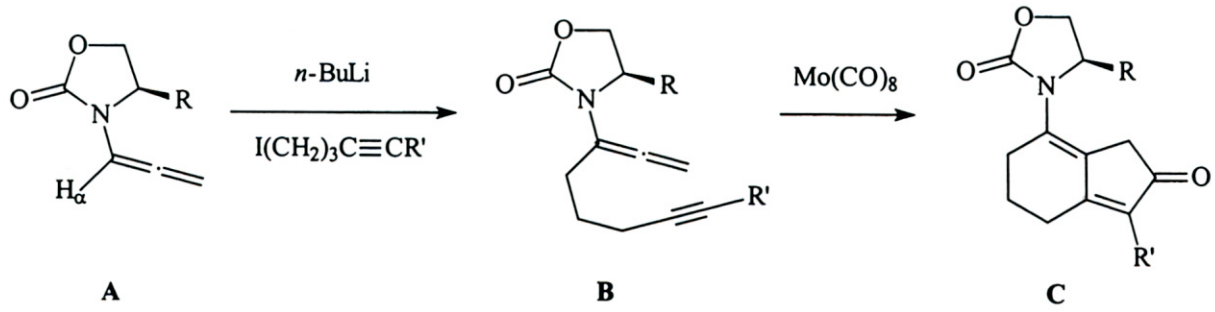
[12] a) Tarasova, O.A., Brandsma, L., Trofimov, B.A., *Synthesis*, **1993**, 571-572. b) Coy, D.H., Haszeldine, R.N., Newlands, M.J., Tipping, A.E., *J. Chem. Soc., Chem. Commun.*, **1970**, 456-457. c) Coy, D.H., Haszeldine, R.N., Newlands, M.J., Tipping, A.E., *J. Chem. Soc., Perkin Trans. 1*, **1973**, 1066-1071.

[13] Overman, L.E., Marlowe, C.K., Clizbe, L.A., *Tetrahedron Lett.*, **1979**, *20*, 599-600.

[14] a) Maas, G., Mayer, T., *Synthesis*, **1991**, 1209-1215. b) Mayer, T., Maas, G., *Synlett*, **1990**, 399-400. For similar see a) Cunico, R.F., Kuan, C.P., *J. Organomet. Chem.*, **1995**, *487*, 89-93.

been recently reviewed[4] and an identical coverage of this literature would not serve any purpose at this stage, however, a brief overview highlighting some key reactivity and transformations is important.

Hsung's group has shown that it is possible to selectively abstract the α-proton from the allenic unit using *n*-BuLi.[15] Blocking this site by treatment with an appropriate electrophile allows for subsequent abstraction of the γ-proton. This parallels earlier work using *N*-allenyl phosphoramides,[7] and shows it is possible to functionalise the allenic unit regioselectively once it has been formed. Hsung has demonstrated the synthetic usefulness of this by preparing α-substituted chiral allenamides (Scheme 4, **B**) and has used these substrates in intramolecular Pauson-Khand reactions.[15]



Scheme 4

Hsung has also shown that allenamides can undergo [4+2] cycloaddition reactions[16] and expanded on earlier work[17] by employing chiral allenamides to render these cycloadditions highly stereoselective (Scheme 5).[18]

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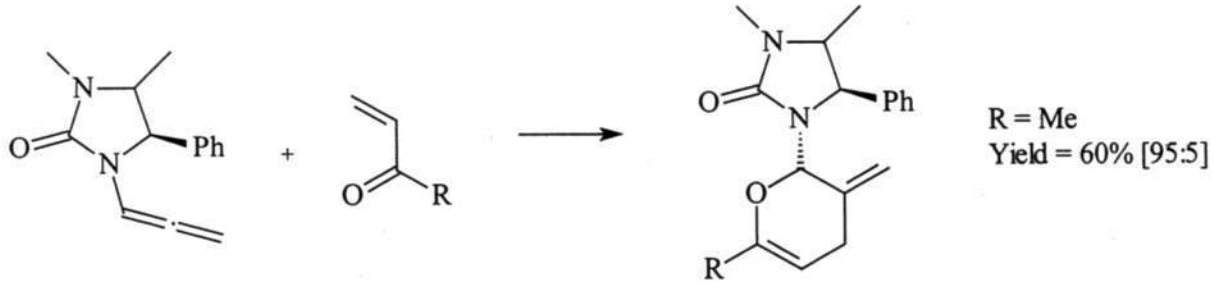
[15] Xiong, H., Hsung, R.P., Wei, L.-L., Berry, C.R., Mulder, J.A., Stockwell, B., *Org. Lett.*, **2000**, *2*, 2869-2871.

[16] Wei, L.-L., Xiong, H., Douglas, C.J., Hsung, R.P., *Tetrahedron Lett.*, **1999**, *40*, 6903-6907.

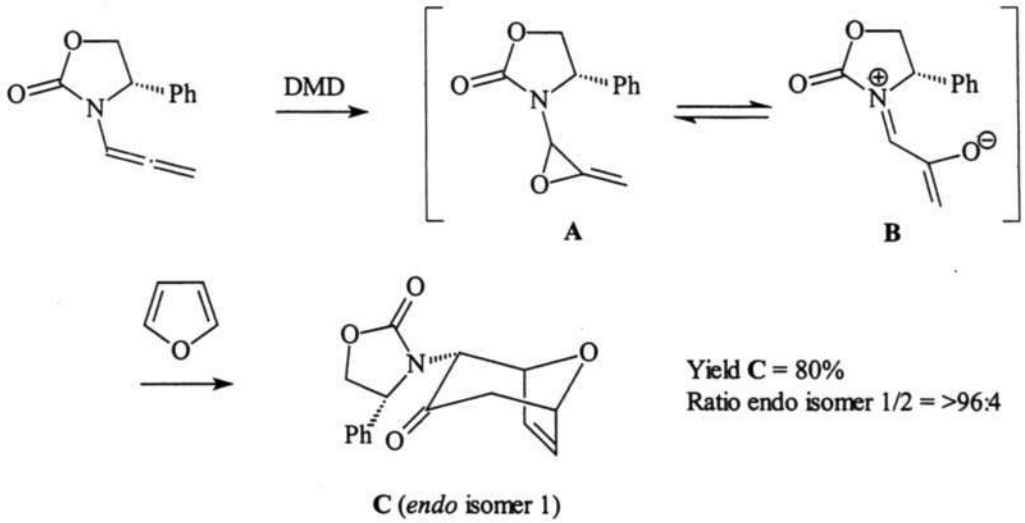
[17] Klop, W., Klusener, P.A.A., Brandsma, L., *Recl. J. Royal Neth. Chem. Soc.*, **1984**, *103*, 85-86.

[18] Wei, L.-L., Hsung, R.P., Xiong, H., Mulder, J.A., Nkansah, N.T., *Org. Lett.*, **1999**, *1*, 2145-2148.



Scheme 5

One further note-worthy section of Hsung's work is the epoxidation of chiral allenamides.[19] The products of these reactions, nitrogen-substituted oxyallyl cations (Scheme 6, **B**), can undergo [4+3] cycloadditions to afford cycloadducts in a highly stereoselective manner. Diastereoselectivity is also excellent if the reactions are carried out at low temperature in the presence of $ZnCl_2$.[19]



C (*endo* isomer 1)

Scheme 6

In addition to the excellent work carried out by Hsung's group, a number of other elegant transformations of *N*-allenyls have appeared in the literature.

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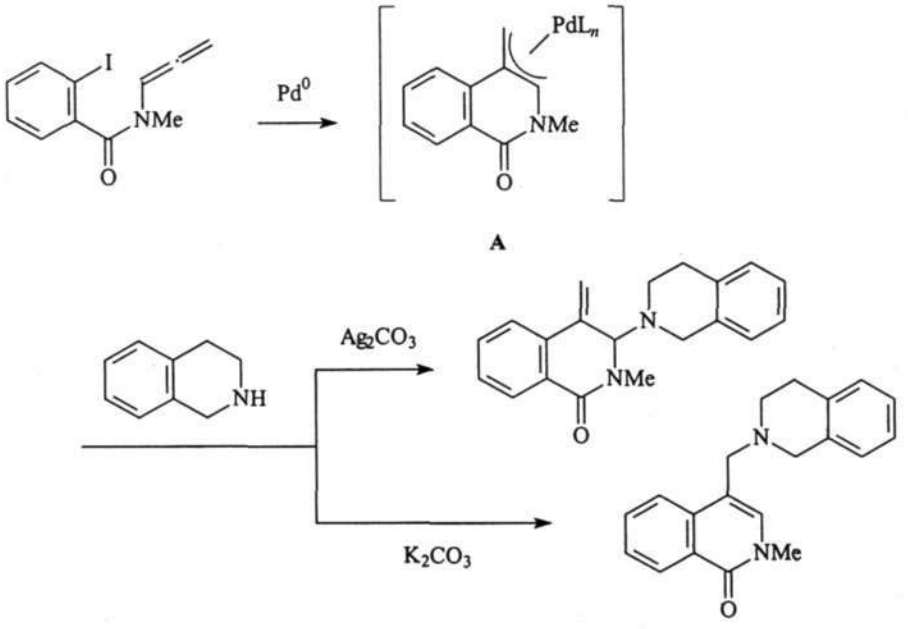
[19] Xiong, H., Hsung, R.P., Berry, C.R., Rameshkumar, C., *J. Am. Chem. Soc.*, **2001**, *123*, 7174-7175.

Grigg has reported a succession of publications involving palladium-catalysed cyclisations of allenamides onto aryl iodides.[20] An example is the $Pd(OAc)_2$-catalysed cyclisation which generates a π-allyl intermediate (Scheme 7, **A**). This intermediate is then trapped by a secondary amine to afford one of two products. The preference of one product over the other is dependent on the identity of the inorganic base present.[20]



Scheme 7

Broggini and Zecchi have described 1,3-dipolar cycloadditions with *N*-allenyl compounds.[5c, 9] These compounds have two potential sites for this type of reaction as well as two orientations. Thus, a wide product distribution is expected. Unusually, *N*-allenyl anilines show a high degree of regioselectivity, exclusively affording adducts containing an exocyclic double bond (Scheme 8, **A**). These adducts can undergo a second cycloaddition to provide spiro bisadducts (Scheme 8, **B**).[5c] This regioselectivity is unique to *N*-allenyl anilines.[9]

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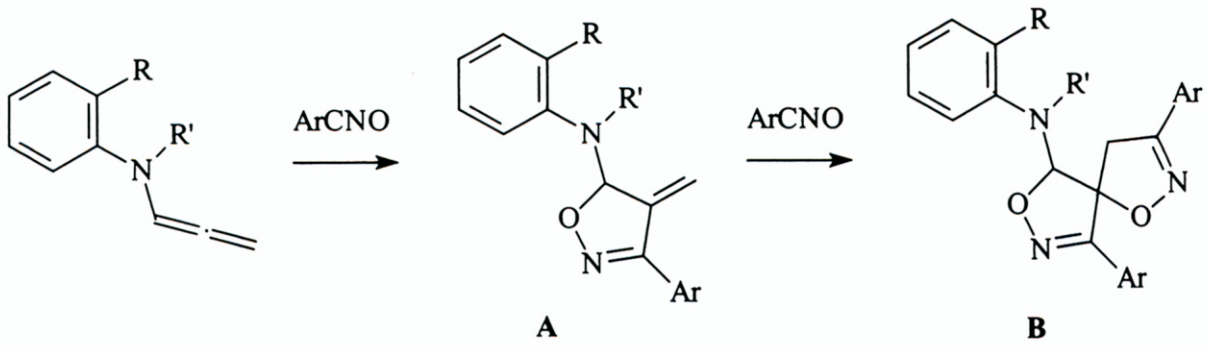
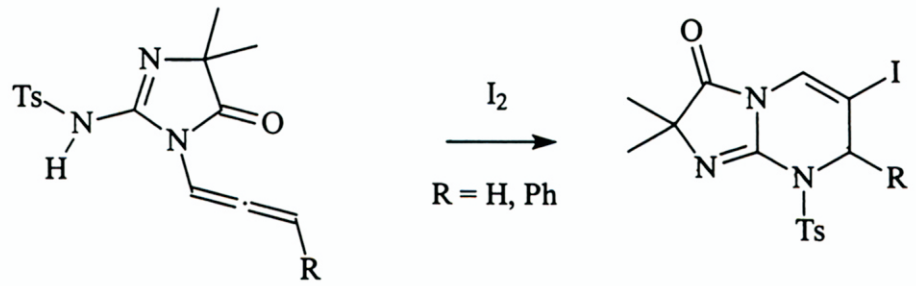
[20] Grigg, R., Sridharan, V., Xu, L.-H., *J. Chem. Soc., Chem. Commun.*, **1995**, 1903-1904 and subsequent papers.



A **B**

Scheme 8

It has been shown that molecular iodine can promote nucleophilic attack at the terminal carbon of allenamides (Scheme 9).[21] This appears to be a valuable reaction as it proceeds *via* attack of a weak nucleophile, forming highly functionalised compounds with further synthetic handles to be exploited.



Scheme 9

In contrast to procedures described thus far, *N*-allenyls also undergo simple nucleophilic addition reactions.[22] (Dimethylamino)allene (Scheme 10, **A**) has been shown to react smoothly with alcohols, thiols and aliphatic secondary amines without the need for a catalyst.[22a]

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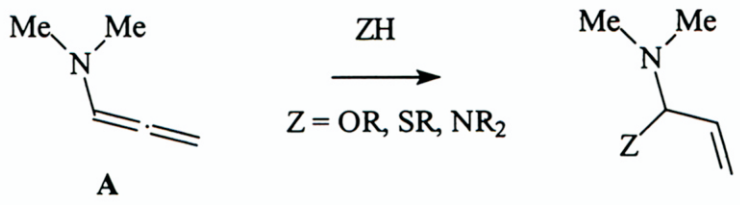
[21] Noguchi, M., Okada, H., Watanabe, M., Okuda, K., Nakamura, O., *Tetrahedron*, **1996**, *52*, 6581-6590.

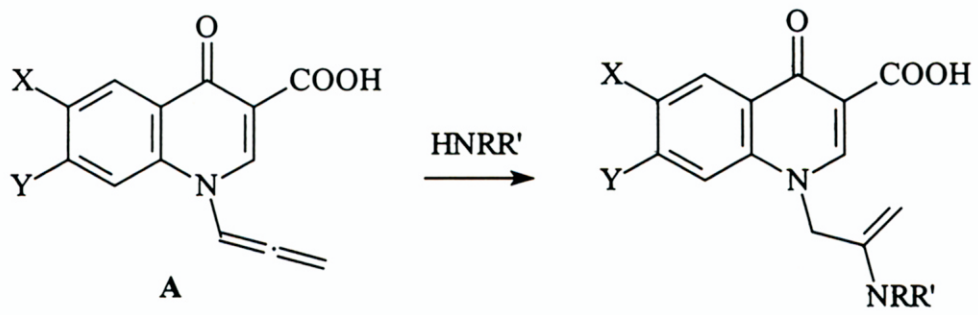
[22] a) Klop, W., Klusener, P.A.A., Brandsma, L., *Recl. Trav. Chim.*, **1984**, *103*, 27-29. b) Radl, S., Kovarova, L., *Collect. Czech. Chem. Commun.*, **1991**, *56*, 2413-2419.



A

Scheme 10

It is interesting to note that these nucleophiles attack the α-carbon of the allenic unit whereas similar amine nucleophiles have been reported to attack the β-carbon of *N*-allenyl quinolones (Scheme 11, **A**).[22b]



A

Scheme 11

2 Hydroamination

Hydroamination is, typically, the addition of an amine N-H across a C-C multiple bond although other nitrogen nucleophiles have been employed.[23] This definition is not restricted to non-activated multiple bonds though it is generally accepted that reactions where the multiple bond is activated by a neighbouring group, such as the Michael reaction, do not fall into this category. The hydroamination reaction is a highly desirable process as it is a fundamental method of preparing nitrogen-containing compounds.[23] Compounds containing a nitrogen functionality are important bulk chemicals (imines, enamines and highly substituted amines) and comprise a vast portion of pharmaceutical products.[23] In addition, hydroamination is an atom economical process, producing no by-products.[24] This is important considering current global trends regarding environmentally friendly chemistry and waste minimisation. For the purposes of this introduction the term 'hydroamination' shall refer to the addition of an amine N-H across a *non-activated* multiple bond and is applicable to both inter- and intramolecular reactions.

2.1 Mechanistic considerations

Chemically speaking, hydroamination is an illogical process as both amines and unsaturated C-C bonds are inherently nucleophilic, however, looking at the reaction more closely we can see that, at least from a thermodynamic standpoint, the reaction appears to be a feasible one (Table 1).[25]

---

[23] Müller, T.E., Beller, M., *Chem. Rev.*, **1998**, *98*, 675-703.

[24] Trost, B.M., *Angew. Chem. Int. Ed.*, **1995**, *34*, 259-281.

[25] Taube, R., In *Applied Homogenous Catalysis with Organometallic Compounds*, Cornils, B., Herrman, W.A., Eds., Wiley-VCH, Weinheim, 2000, 507-520.

Table 1: Thermodynamic data for the hydroamination of ethylene[26]

Reaction	$\Delta_R G°$ (kJ/mol)	$\Delta_R H°$ (kJ/mol)	$\Delta_R S°$ (J/mol.K)
$NH_3 + C_2H_4 \rightleftharpoons EtNH_2$	-14.7	-52.7	-127.3
$EtNH_2 + C_2H_4 \rightleftharpoons Et_2NH$	-33.4	-78.7	-152.2
$Et_2NH + C_2H_4 \rightleftharpoons Et_3N$	-30.0	-79.5	-166.3

Nevertheless, the HOMO-LUMO overlap needed in order for a [2+2] cycloaddition to occur is symmetry forbidden and, as a result of this unfavourable interaction, the activation barrier to be overcome is high.[25] Furthermore, performing these reactions at high temperature is not practical as the highly negative reaction entropy dictates that high temperatures tend to favour reactants rather than products.

With this in mind, the reaction needs some form of activation in order to proceed in the desired fashion. There are two principal ways of achieving activation and these consist of interaction of either the amine N-H or the C-C multiple bond with a metal centre.[23] The details of these interactions are, in reality, extremely complex and will be covered in appropriate depth in the paragraphs that follow.

2.1.1 Alkali metals

Activation of an amine N-H by alkali metals essentially involves the formation of the corresponding amide which is a far more nucleophilic species. In most instances the amide is employed in a catalytic quantity and a rational mechanism is shown below (Scheme 12).[23] Although this ionic mechanism is commonly accepted, a radical mechanism has also been suggested.[27]

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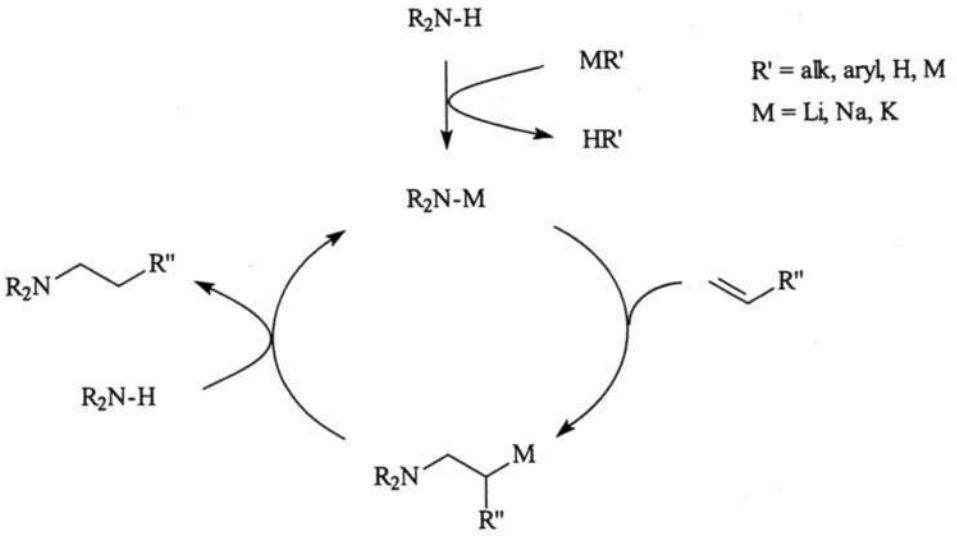
[26] Steinborn, D., Taube, R., *Z. Chem.*, **1986**, *26*, 349-359.

[27] Razdan, R.K., *J. Chem. Soc., Chem. Commun.*, **1969**, 770-771.



Scheme 12

The amides are usually prepared *in situ* from the appropriate alkyl alkali metal with alkyl lithium reagents being the most commonly used.[28] Nevertheless, the amides have also been prepared from metal hydrides[29] and *tert*-butoxides,[30] other amides,[26, 31] and the metals themselves.[32] These reagents have been employed catalytically or as full stoichiometric equivalents. In the case of other amides, the reaction will only proceed if the pK_a of the amide is greater than that of the amine that is to be converted.[26, 31]

Although the catalytic cycle shown above (Scheme 12) is a useful representation of the hydroamination in question, the reality is that the reaction is more complex than it appears.[23] It has been shown that the alkali metal counter-ion of the amide plays an important role in the reaction, although it has not been determined what this exact role

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[28] a) Narita, T., Imai, N., Tsuruta, T., *Bull. Chem. Soc. Jpn.*, **1973**, *46*, 1242-1246. b) Imai, N., Narita, T., Tsuruta, T., *Tetrahedron Lett.*, **1971**, *12*, 3517-3520. c) Beller, M., Breindl, C., *Tetrahedron*, **1998**, *54*, 6359-6368. d) Seijas, J.A., Vázquez-Tato, M.P., Entenza, C., Martínez, M.M., Ónega, M.G., Veiga, S., *Tetrahedron Lett.*, **1998**, *39*, 5073-5076. e) García, A., Domínguez, D., *Tetrahedron Lett.*, **2001**, *42*, 5219-5221. f) Hartung, C.G., Breindl, C., Tillack, A., Beller, M., *Tetrahedron*, **2000**, *56*, 5157-5162. g) Ates, A., Quinet, C., *Eur. J. Org. Chem.*, *2003*, 1623-1626.

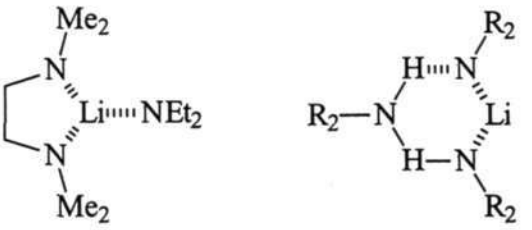
[29] Howk, B.W., Little, E.L., Scott, S.L., Whitman, G.M., *J. Am. Chem. Soc.*, **1954**, *76*, 1899-1902.

[30] a) Seijas, J.A., Vázquez-Tato, M.P., Martínez, M.M., *Synlett*, **2001**, 875-877. b) Beller, M., Breindl, C., Riermeier, T.H., Eichberger, M., Trauthwein, H., *Angew. Chem. Int. Ed.*, **1998**, *37*, 3389-3391.

[31] Closson, R.D., Napolitano, J.P., Ecke, G.G., Kolka, A.J., *J. Org. Chem.*, **1957**, *22*, 646-649.

[32] Wollensak, J., Closson, R.D., *Org. Syntheses*, **1963**, *43*, 45-48.

is.[31b] This importance has been demonstrated by the observation that reactions employing lithium amides are inhibited by addition of lithium-complexing crown ethers. In contrast, the reaction rate is increased by the addition of tetramethylethylenediamine (TMEDA). As a result of these observations, a complex has been proposed as the active catalyst species (Figure 1, **A**).[31b]



A **B**

Figure 1

A similar complex has been proposed as the active species for the reaction of lithium diethylamide and 1,3-butadiene (Figure 1, **B**).[28a] As further evidence of these complexes as the actual active catalyst species, it has been reported that in the reaction of lithium diethylamide and styrene, the reaction does not proceed unless at least a two fold excess of diethylamine is present in addition to the lithium amide.[33]

The importance of the metal counter-ion is highlighted by the reaction of lithium, sodium and potassium diethylamide with ethylene. The reaction proceeds up to a hundred times faster with the latter two metals, although the rate drops off after the reaction has attained 25% conversion.[34] This enhanced reactivity has been attributed to the greater separation of the metal amide ion-pair for the less electronegative metals.[23] Although separation of the ion-pair initially results in a greater reaction rate, it also leads to side-reactions and decomposition of the active species.[23]

Alkali metal mediated hydroamination has seen something of a resurgence in the years subsequent to Müller and Beller's review on the subject.[23] In particular, the intermolecular

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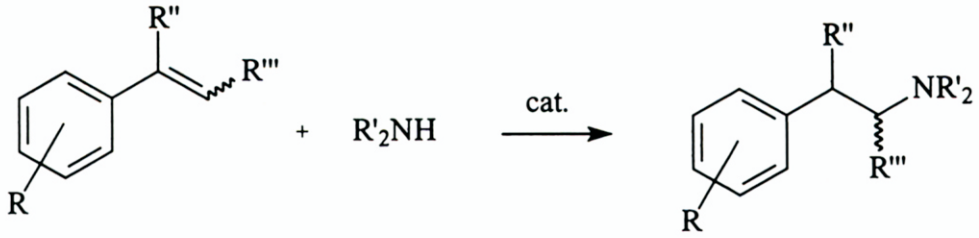
[33] Narita, T., Yamaguchi, T., Tsuruta, T., *Bull. Chem. Soc. Jpn.*, **1973**, *46*, 3825-3828.

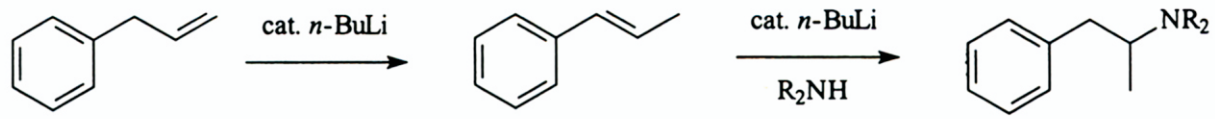
[34] Pez, G.P., Galle, J.E., *Pure Appl. Chem.*, **1985**, *57*, 1917-1926.

addition of simple amines to styrenes has become an important and versatile method of preparing the pharmacologically important β-phenylethylamine motif (Scheme 13).[35]



Scheme 13

Beller and co-workers have shown this transformation is possible with a variety of catalysts (*t*-BuOK, *n*-BuLi) and substituents on the aromatic ring, the olefin and the amine.[28c, 30b] An impressive extension of this work is the preparation of amphetamines *via* a base-catalysed domino-isomerisation-hydroamination reaction (Scheme 14).[28f] The reaction proceeds *via* a fast isomerisation of allylbenzene to β-methylstyrene followed by hydroamination. This is an attractive method of amphetamine preparation as allylbenzene is a far cheaper starting material than β-methylstyrene.[28f]



Scheme 14

A styrene containing an α-keto group has been shown to readily undergo this type of hydroamination (Scheme 15).[36] It would be interesting to investigate the extent to which the neighbouring group influences this particular reaction.

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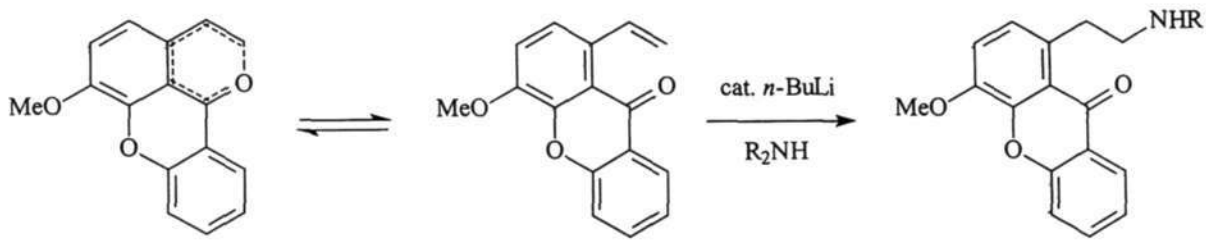
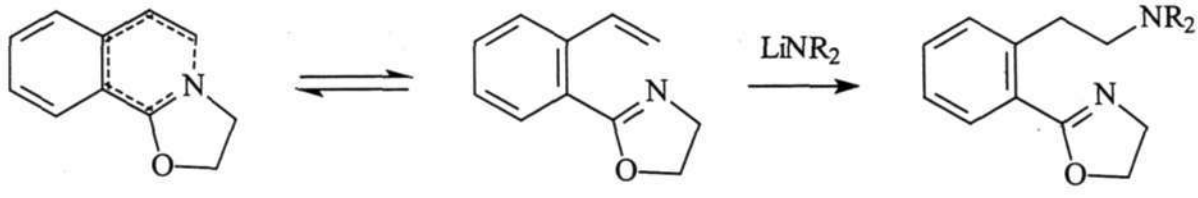
[35] *The Merck Index*, Budvari, S. Ed., Merck&Co., Inc.:Whitehouse Station, NJ, 12th Ed.,1996, ppTher1-28.

[36] Garcia, A., Domínguez, D., *Tetrahedron Lett.*, **2001**, *42*, 5219-5221.



Scheme 15

It appears as if a similar affect may be in operation in the addition of amines to styrenes containing a neighbouring oxazoline group (Scheme 16).[28d, 30a] Yields for this reaction are markedly higher when the oxazoline is present compared to when it is not.



Scheme 16

Alkali metal mediated hydroaminations have also found application in intramolecular cyclisations.[28g, 37] Most noteworthy is the lithium diisopropylamide (LDA) mediated hydroamination employed by Trost and Tang as the final step in the enantioselective synthesis of (-) codeine and (-) morphine.[37] This reaction is, remarkably, promoted by visible light.

2.1.2 Group IV metals, lanthanides and actinides

These three sets of metals catalyse hydroamination in, effectively, the same manner.[23] That is by formation of the active species *via* nucleophilic amine substitution at the metal centre. The active species themselves are, however, slightly different (Figure 2). Metal amides originate from lanthanides as the catalytically active species whereas metal imido species originate from group IV metals and actinides.[23] Nevertheless, hydroamination catalysts

[37] Trost, B.M., Tang, W., *J. Am. Chem. Soc.*, **2002**, *124*, 14542-14543.

based on metals from these groups will be discussed under one heading. An examination of the recent literature shows that the majority of hydroamination catalysts developed in the past 4-5 years are based on metals belonging to one of these groups, in particular those based on lanthanides and titanium.[38]

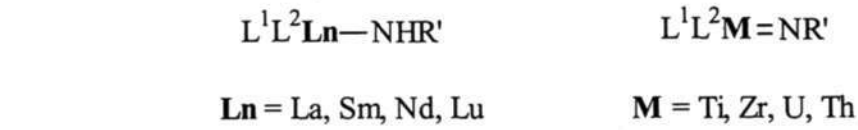
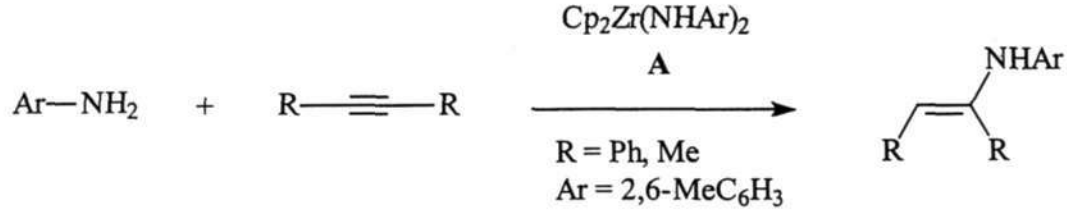


Figure 2

Zirconium complexes were first employed as hydroamination catalysts in 1992 when Bergman *et al.* discovered that a zirconocene bis(amide) (Scheme 17, **A**) catalyses the intermolecular addition of 2,6-dimethylaniline to alkynes and allenes.[39]



Scheme 17

A detailed kinetic study was carried out to investigate the mechanism of this addition and, consequently, an imidozirconium species has been proposed as the active catalytic species.[39] The proposed catalytic cycle is shown below (Scheme 18). It involves the initial rate-determining α-elimination of amine from the bisamide complex to form the active imido intermediate.[39] The expelled amine and incoming alkyne then compete for the intermediate species, forming the original bisamide complex or an azazirconacyclobutene. The azazirconacyclobutene is produced *via* a [2+2] cycloaddition reaction. Protonation of this species by a further amine molecule affords an enaminic amide complex that regenerates the active catalytic species upon α-elimination of the enamine.[39]

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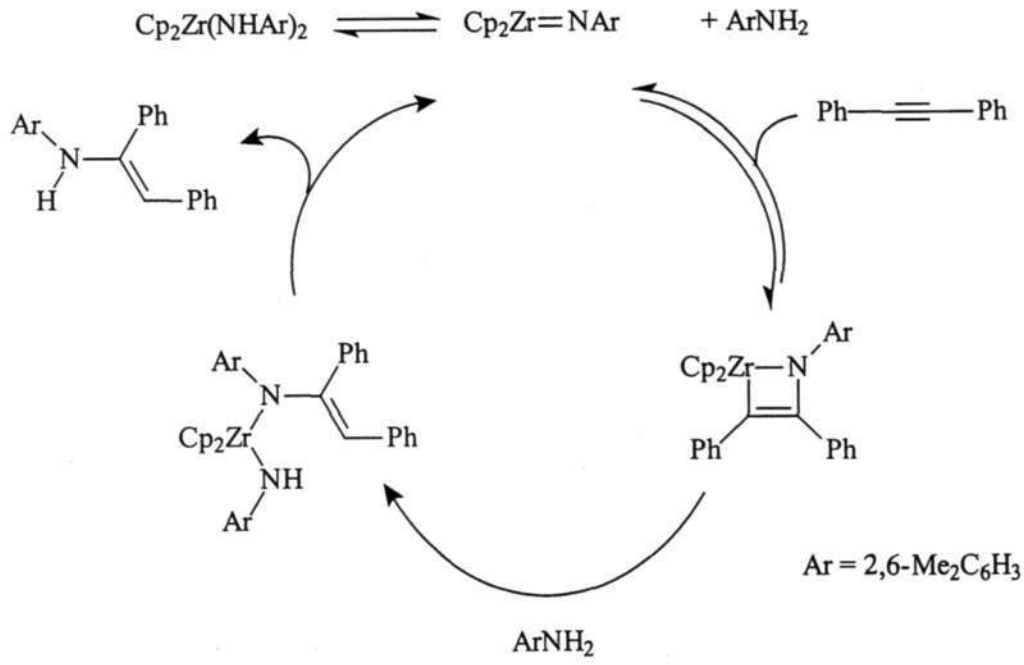
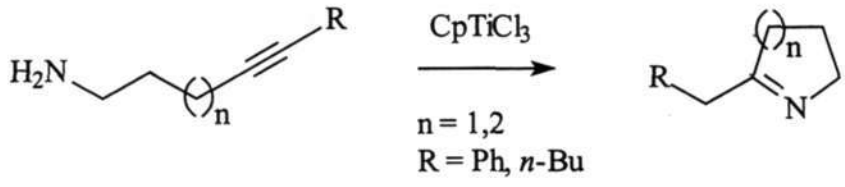
[38] a) Pohlki, F., Doye, S., *Chem. Soc. Rev.*, **2003**, *32*, 104-114. b) Bytschkov, I., Doye, S., *Eur. J. Org. Chem.*, **2003**, 935-946.

[39] Walsh, P.J., Baranger, A.M., Bergman, R.G., *J. Am. Chem. Soc.*, **1992**, *114*, 1708-1719.



Scheme 18

At about the same time that Bergman *et al.* reported the use of zirconium based hydroamination catalysts; Livingston *et al.* reported the intramolecular hydroamination of γ- and δ-aminoalkynes using $CpTiCl_3$ (Scheme 19).[40]



Scheme 19

This methodology has subsequently been used in the total synthesis of the indolizidine alkaloid (±) monomorine (Scheme 20, **B**).[41]

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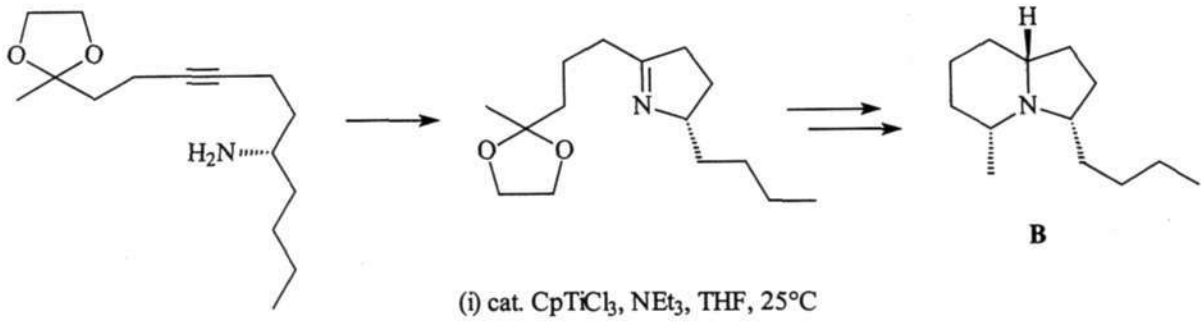
[40] McGrane, P.L., Jensen, M., Livingstone, T., *J. Am. Chem. Soc.*, **1992**, *114*, 5459-5460.

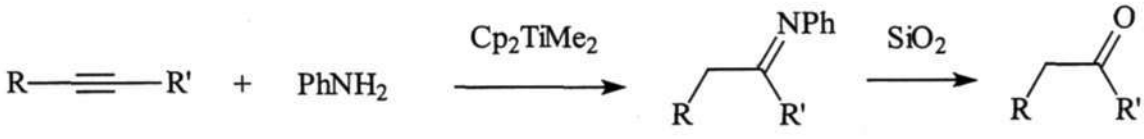
[41] McGrane, Livingstone, T., *J. Org. Chem.*, **1992**, *57*, 1323-1324.



(i) cat. $CpTiCl_3$, NEt_3, THF, 25°C

Scheme 20

Although the complexes discussed above are effective hydroamination catalysts, zirconium and titanium complexes found limited application between these early reports and 1999 when Doye *et al.*. reported that the readily available complex dimethyltitanocene (Cp_2TiMe_2), catalyses the hydroamination of alkynes (Scheme 21).[42] This was an important breakthrough in the field as this titanium complex was found to be a general catalyst precursor capable of effecting the *intermolecular* addition of primary aryl and alkyl amines to symmetrically and unsymmetrically substituted internal and terminal alkynes. In addition, the complex is readily available, inexpensive and has a low toxicity.[42]



R = alkyl, aryl
R' = H, alkyl, aryl

Scheme 21

Kinetic analysis led Doye and co-workers to propose the following mechanism for this intermolecular hydroamination (Scheme 22).[43] Initial nucleophilic substitution at the metal centre affords the catalytically active imidotitanium species with loss of two moles of methane. The remainder of the catalytic cycle is identical to that of the zirconium-catalysed

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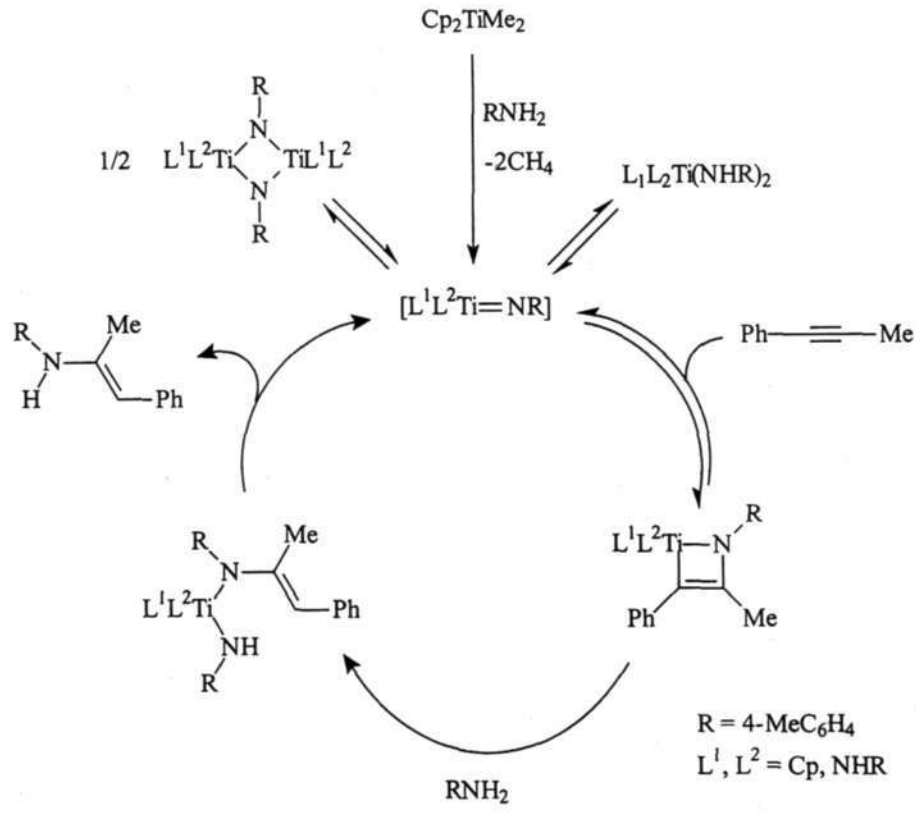
[42] Haak, E., Bytschkov, I., Doye, S., *Angew. Chem. Int. Ed.*, **1999**, *38*, 3389-3391.

[43] Pohlki, F, Doye, S., *Angew. Chem. Int. Ed.*, **2001**, *40*, 2305-2308.

hydroamination discussed above (Scheme 18) bar the reversible equilibrium between the imidotitanium complex and its dimer. This equilibrium accounts for the non-linear relationship between the catalyst concentration and the reaction rate.[43]



Scheme 22

Since these initial reports, the use of titanium complexes as hydroamination catalysts has become far more prevalent.[38] The range of catalysts used for this purpose varies from simple complexes such as $TiCl_4$[44] and $Ti(NMe_2)_4$[45] to intricate pyrrolyl,[46] silylalkynyl[47] and tetrakisamido[48] complexes (Figure 3).

---

[44] Ackerman, L., *Organometallics*, **2003**, *22*, 4367-4368.

[45] Shi, Y., Ciszewski, J.T., Odom, A.L., *Organometallics*, **2001**, *20*, 3967-3969.

[46] a) Cao, C., Ciszewski, J.T., Odom, A.L., *Organometallics*, **2001**, *20*, 5011-5013. b) Shi, Y., Hall, C., Ciszewski, J.T., Cao, C., Odom, A.L., *Chem. Commun.*, **2003**, 586-587.

[47] Garcia Castro, I., Tillack, A., Hartung, C.G., Beller, M., *Tetrahedron Lett.*, **2003**, *44*, 3217-3221.

[48] a) Ackerman, L., Bergman, R.G., *Org. Lett.*, **2002**, *4*, 1475-1478. b) Ackerman, L., Bergman, R.G., Loy, R.N., *J. Am. Chem. Soc.*, **2003**, *125*, 11956-11963.

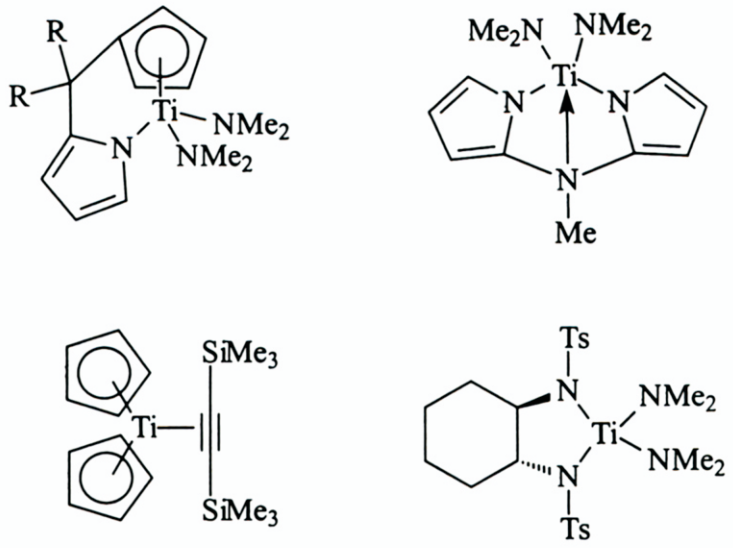


Figure 3

Actinide complexes have also been used as hydroamination catalysts, although to a far lesser extent.[49] Their mechanism of operation is analogous to that of zirconium complexes.[49]

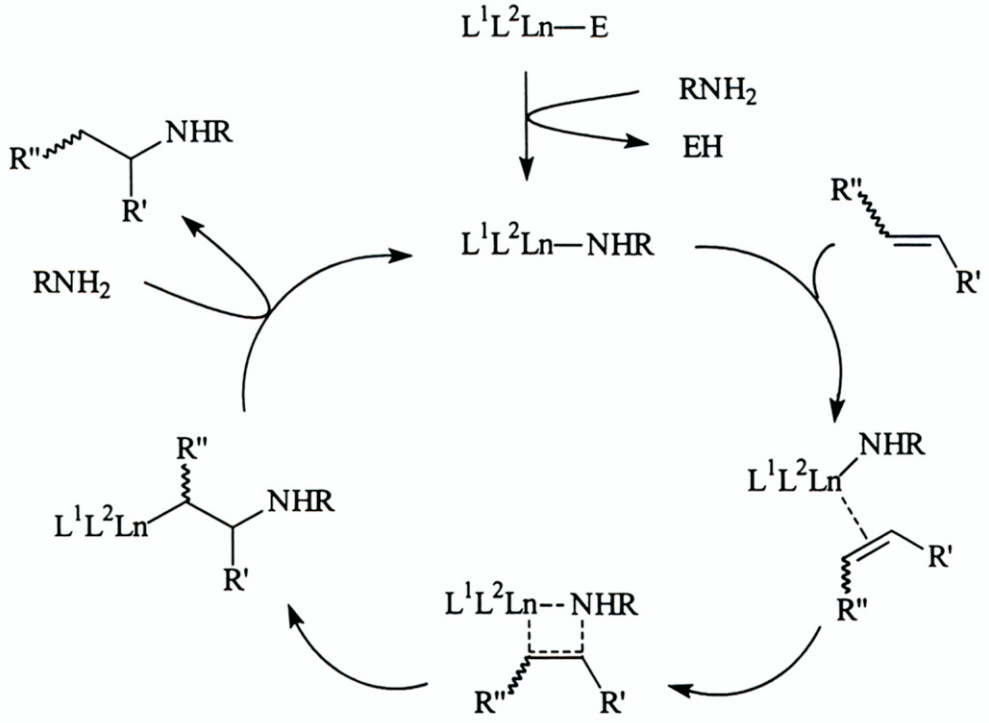
Lanthanide complexes, on the other hand, have found widespread use since their action was first reported in 1992 by Marks *et al.*[50] Lanthanides are exceptionally versatile hydroamination catalysts in terms of substrates, being able to tolerate primary and secondary aryl and alkyl amines and effect their addition to alkenes, alkynes and allenes.[23] However, in spite of their versatility, lanthanide complexes require rigorously anhydrous and anaerobic conditions.[38a] The active catalytic species in these hydroaminations is a lanthanide amide which is formed upon nucleophilic amine substitution at the metal centre.[51] The catalytic cycle (Scheme 23) proceeds by alkene insertion into the Ln-N bond to afford an alkyl lanthanide complex. Protonation of the complex by a second amine molecule releases the alkylated amine product and regenerates the active catalytic lanthanide amide.[51]

---

[49] a) Haskel, A., Straub, T., Eisen, M.S., *Organometallics*, **1996**, *15*, 3773-3775. b) Straub, T., Haskel, A., Gueta Neyroud, T., Kapon, M., Botoshansky, M., Eisen, M.S., *Organometallics*, **2001**, *20*, 5017-5035. c) Stubbert, B.D., Stern, C.L., Marks, T.J., *Organometallics*, **2003**, *22*, 4836-4838.

[50] Gagné, M.R., Stern, C.L., Marks, T.J., *J. Am. Chem. Soc.*, **1992**, *114*, 275-294.

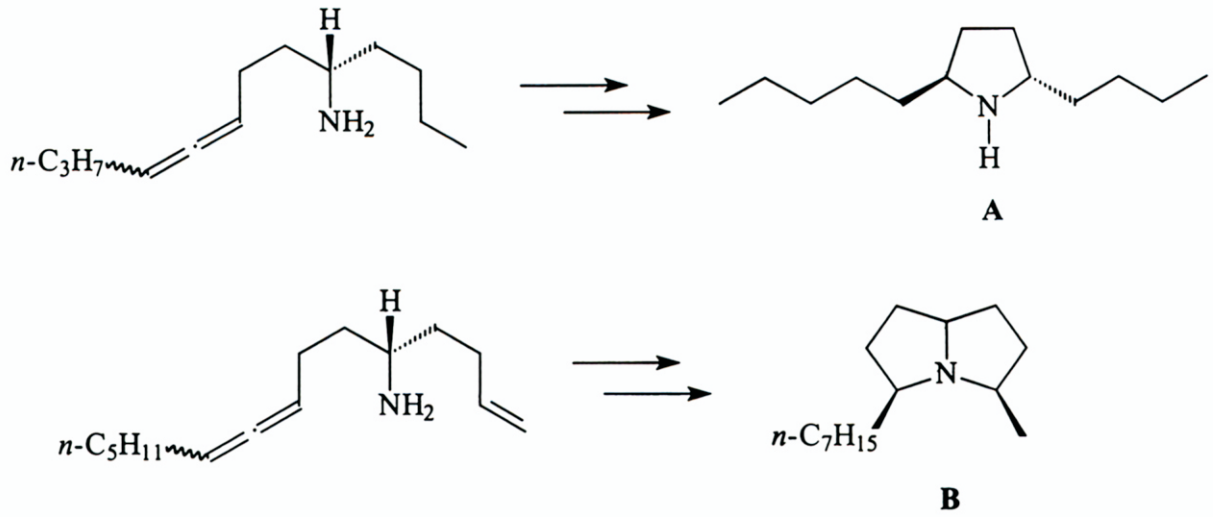
[51] Li, Y., Marks, T.J., *Organometallics*, **1996**, *15*, 3770-3772.



Scheme 23

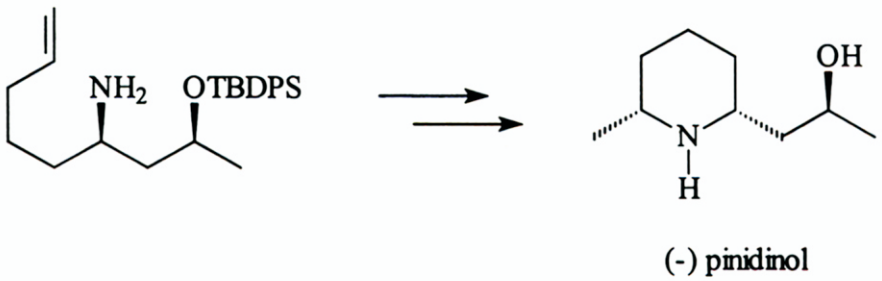
Lanthanide complexes are able to effect hydroaminations in a stereoselective manner.[23] As an example, Marks *et al.* have reported the stereoselective total synthesis of the ant alkaloids 197B (Scheme 24, **A**) and (+) xenovenine (Scheme 24, **B**) from aminoallene precursors.[52]

[52] Arredondo, V.M., Tian, S., McDonald, F.E., Marks, T.J., *J. Am. Chem. Soc.*, **1999**, *121*, 3633-3639.



Scheme 24

Marks *et al.* have attributed the observed diastereoselectivity to the chiral centre bearing the amine group and claim it is not influenced by the stereochemistry of the allene.[53] A further example of lanthanide complexes effecting hydroamination in a diastereoselective manner is the synthesis of (+), (±) and (-) pinidinol (Scheme 25).[54]



Scheme 25

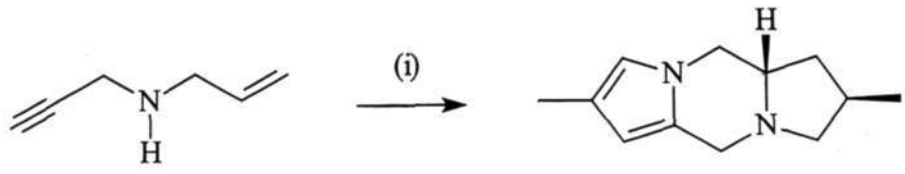
As a final, most impressive, example of hydroaminations catalysed by lanthanide complexes, Marks and Li have reported the formation of a tricyclic structure (Scheme 26, **A**) from allylpropargylamine in one step in 93% yield.[55]

---

[53] Arredondo, V.M., McDonald, F.E., Marks, T.J., *J. Am. Chem. Soc.*, **1998**, *120*, 4871-4872.

[54] Molander, G.A., Dowdy, E.D., Pack, S.K., *J. Org. Chem.*, **2001**, *66*, 4344-4347.

[55] Li, Y., Marks, T.J., *J. Am. Chem. Soc.*, **1998**, *120*, 1757-1771.



(i) 20% $Cp'_2SmCH(SiMe_3)_2$, C_6D_6, 60°C

Scheme 26

2.1.3 Late transition metals (Oxidative addition)

The possibility of performing hydroamination *via* an oxidative addition - reductive elimination sequence, in a "classical catalysis" manner, is an attractive prospect. A viable mechanism would entail the formation of a metal hydrido-amido complex $[ML_nH(NR_2)]$ by oxidative addition of the amine to an appropriate unsaturated metal centre.[25] Insertion of an alkene/alkyne into the M-N bond would afford a 2-aminoalkyl complex which, in turn, would provide the alkylamine product and regenerate the active metal catalyst upon reductive elimination. In practice, however, the factors influencing this form of hydroamination are far more complex than this brief explanation and are covered in some detail by Müller and Beller.[23] In spite of this, reports of hydroamination *via* this pathway have been reported, although the reactions in question are highly substrate specific. For example Uchimaru has reported the addition of *N*-methylaniline to alkynes catalysed by $Ru_3(CO)_{12}$ (Scheme 27).[56] The addition of aniline to norbornene has also been reported.[57]

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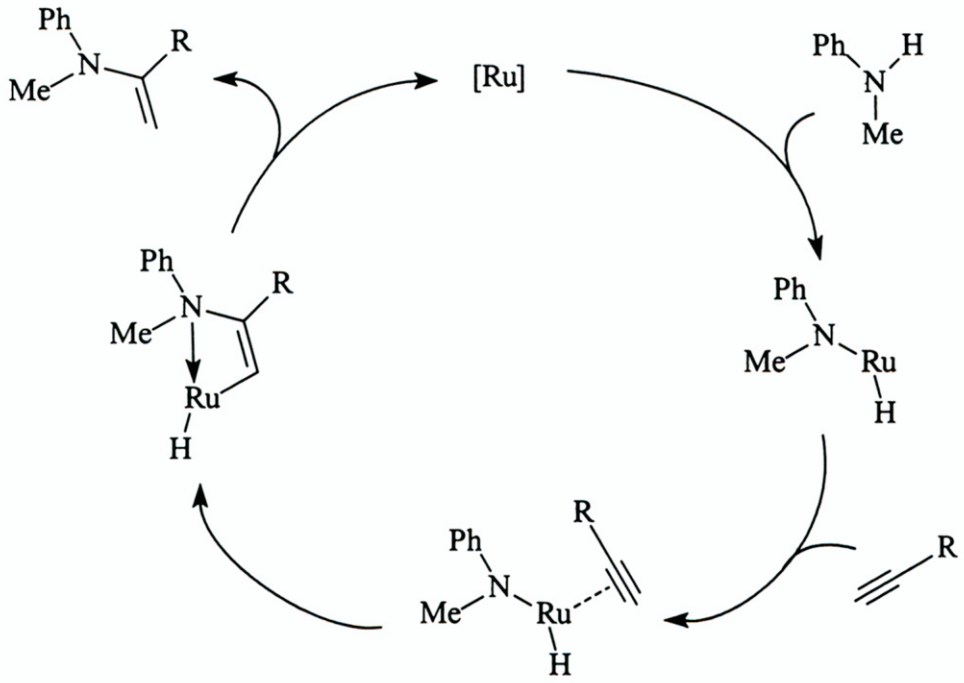
[56] Uchimaru, Y., *Chem. Commun.*, **1999**, 1133-1134.

[57] Casalnuovo, A.L., Calabrese, J.C., Milstein, D., *J. Am. Chem. Soc.*, **1988**, *110*, 6738-6744.



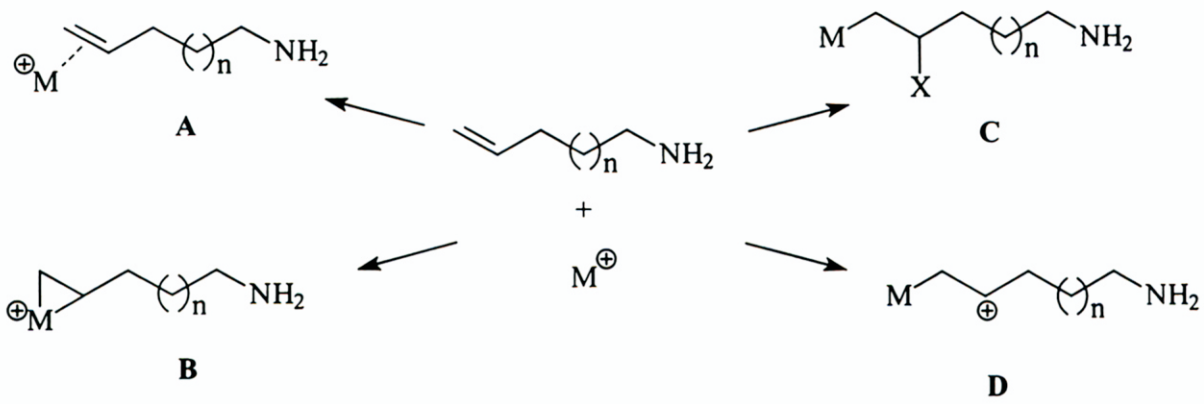
Scheme 27

2.1.4 Late transition metals (π-coordination)

All forms of the hydroamination reaction that have been covered thus far have involved activation of the amine N-H in some form. The final type of hydroamination that will be covered in this section, is the addition of amine nucleophiles to C-C multiple bonds that have been activated by π-coordination to an electrophilic metal centre. This is a general explanation as reaction of a C-C π system with an electrophile can lead to several different intermediates susceptible to nucleophilic attack.[58] These intermediates have been labelled as either π-complexes (Scheme 28, **A**), 'onium' ions (Scheme 28, **B**), addition products (Scheme 28, **C**) or carbocations (Scheme 28, **D**). There is also the possibility of interconversion between the different intermediates. The mechanism in operation for specific reactions depends on the substrate, reaction conditions and, not least, the electrophile, however, most hydroaminations in this category are believed to involve π-complexes or 'onium' ions.[58]

---

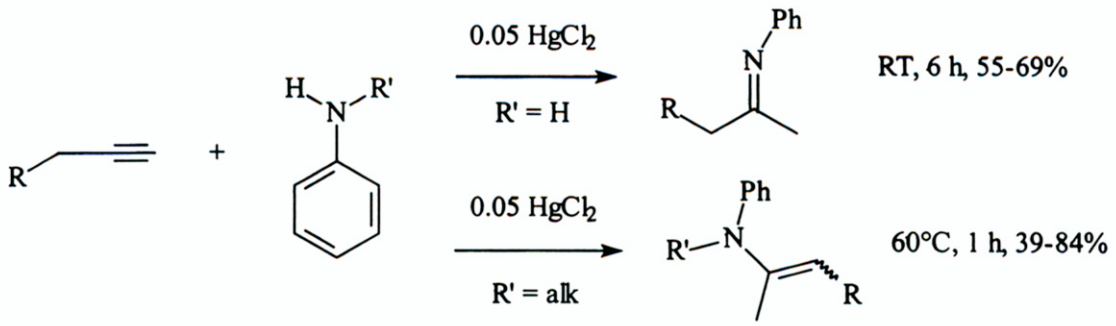
[58] Harding, K.E., Tiner, T.H., Electrophilic Heteroatom Cyclizations, In *Comprehensive Organic Synthesis*, Trost, B.M., Fleming, I., Eds.,Pergamon Press, Oxford, 1991, Vol. 4, pp. 363-421.



Scheme 28

The fate of these intermediates is controlled by electronic, stereoelectronic and steric effects, with additional conformational and entropic effects introduced for intramolecular additions.[58] However, generally speaking *exo* ring closure is preferred over *endo* for intramolecular additions to alkenes and vice versa for alkynes;[59] and Markovnikov addition predominates in intermolecular additions.[38a]

Mercury and its compounds have been used as hydroamination catalysts for over 20 years.[38a] Barluenga *et al.* reported the addition of aromatic amines to terminal alkynes in the presence of a catalytic amount of $HgCl_2$ (Scheme 29).[60] Imines are produced from aniline whereas enamines, as a mixture of *E* and *Z* isomers, are produced when *N*-substituted anilines are employed.[60]



Scheme 29

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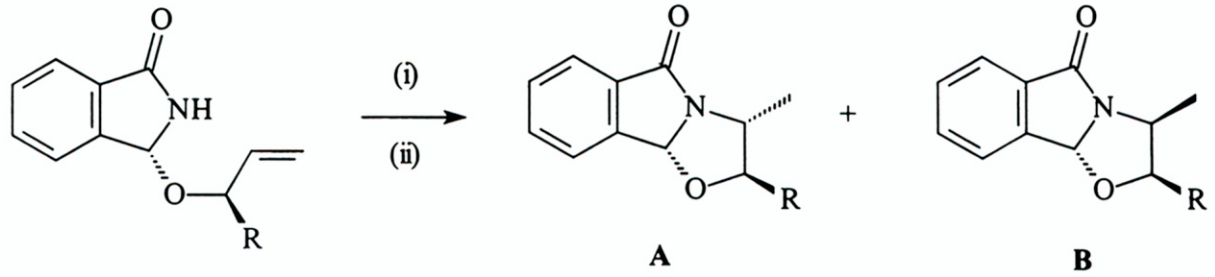
[59] Baldwin, J.E., *J. Chem. Soc., Chem. Commun.*, **1976**, 734-736.

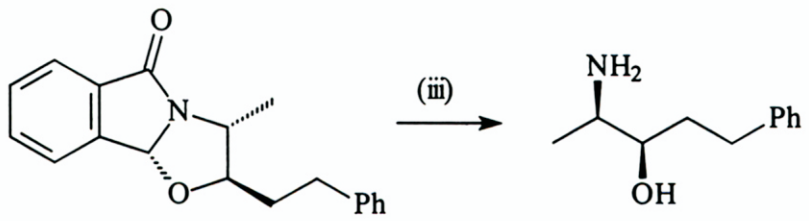
[60] Barluenga, J., Aznar, F., Liz, R., Rodes, R., *J. Chem. Soc., Perkin Trans 1*, **1980**, 2732-2737.

As an extension of work on the stereoselectivity in intramolecular amidomercuration by Harding and Marman,[61] Takacs and co-workers reported the use of a removable auxiliary to prepare β-hydroxy amines stereoselectively.[62] The hydroamination in question (R = CH_2CH_2Ph) proceeds smoothly to afford the *endo*, *trans* isomer (Scheme 30, **A**) in 75% yield. Less than 0.5% of the *exo*, *cis* isomer was formed in the reaction.[62] Treatment of the 1,3-oxazolidine product with hydrazine hydrate led to the β-hydroxy amine in 85% yield.



A **B**

(i) 1.5 $Hg(OAc)_2$, 2.2 $NaHCO_3$, CH_3CN, 25°C, 10 min (ii) 4 $LiBH_4$, THF, -78°C



(iii) 4 $NH_2NH_2.H_2O$, TsOH, EtOH, Δ

Scheme 30

Palladium, when compared to other late transition metals, has found widespread use as a hydroamination catalyst.[23] Hegedus and McKearin reported the cyclisation of *N*-tosyl amino alkenes using a Pd(II) catalyst (Scheme 31).[63] The *N*-tosyl products were then reduced and photolytically deprotected to yield the saturated heterocycle. The stereochemistry of the products was not specified.

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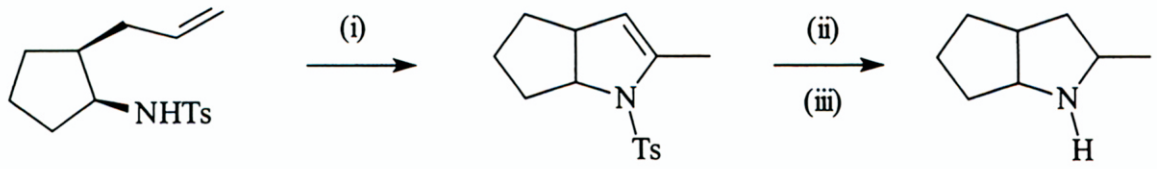
[61] Harding, K.E., Marman, T.H., *J. Org. Chem.*, **1984**, *49*, 2838-2840.

[62] Takacs, J.M., Helle, M.A., Yang, L., *Tetrahedron Lett.*, **1989**, *30*, 1777-1780.

[63] Hegedus, L.S., McKearin, J.M., *J. Am. Chem. Soc.*, **1982**, *104*, 2444-2451.

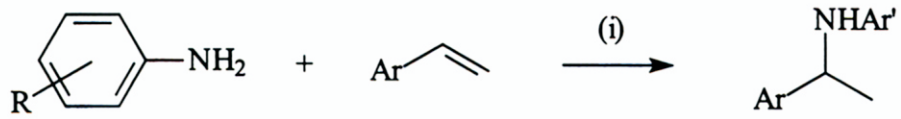


85%

(i) 1-10% $PdCl_2$ $[CH_3CN]_2$, Na_2CO_3, THF, Δ (ii) H_2, Pd/C/HOAc/EtOH (iii) *hν*, MeOH

Scheme 31

Intermolecular additions have also been accomplished using palladium catalysts, as demonstrated by Hartwig and Kawatsura (Scheme 32).[64]



R = H (83%), MeO (93%), CF_3 (64%)

(i) 2% $Pd(PPh_3)_4$, 20% TfOH, 100°C, 12h

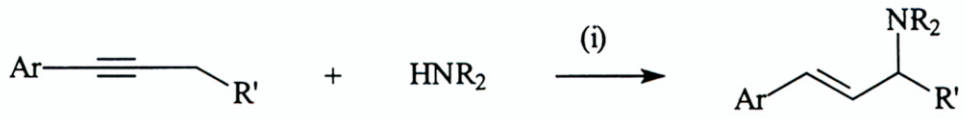
Scheme 32

Yamamoto *et al.* have reported the preparation of allylic amines *via* the intermolecular hydroamination of alkynes by a palladium/benzoic acid catalyst system (Scheme 33).[65] This procedure has been successfully extended to encompass intramolecular hydroamination, and yields for these conversions are typically greater than 80%.[65]

---

[64] Kawatsura, M., Hartwig, J.F., *J. Am. Chem. Soc.*, **2000**, *122*, 9546-9547.

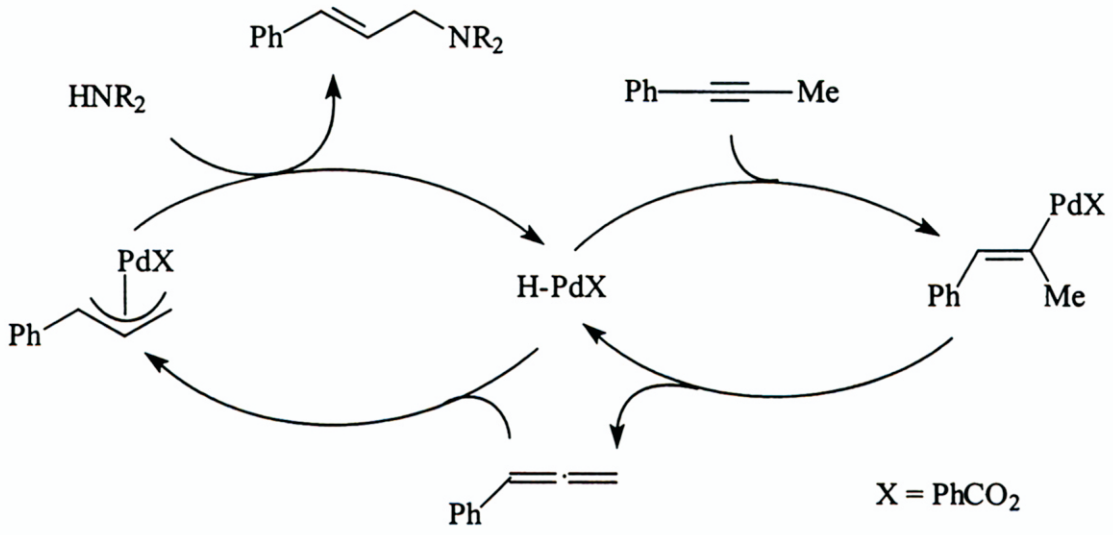
[65] a) Lutete, L.M., Kadota, I., Shibuya, A., Yamamoto, *Heterocycles*, **2002**, *58*, 347-357. Y.,b) Kadota, I., Shibuya, A., Lutete, L.M., Yamamoto, Y., *J. Org. Chem.*, **1999**, *64*, 4570-4571.



(i) 5% $Pd(PPh_3)_4$, 10% $PhCO_2H$, dioxane, 100°C

Scheme 33

The proposed catalytic cycle involves initial formation of a hydrido palladium species generated from Pd(0) and benzoic acid.[65] This complex performs a hydropalladation of the alkyne to afford a vinylpalladium species. This species undergoes β-elimination to produce an allene. Hydropalladation of the allene, in similar fashion to that already reported,[66] produces a π-allylpalladium species which reacts with the incoming amine to afford the product allylic amine and regenerate the active catalytic species.[65]



Scheme 34

Beller *et al.* have shown that rhodium complexes can also be used as hydroamination catalysts.[67] They have shown that $[Rh(cod)_2]BF_4$ (cod = 1,5-cyclooctadiene) with three tricyclohexylphosphine ligands effectively catalyses the intermolecular addition of aromatic amines to terminal alkynes (Scheme 35). In addition, they have shown that the

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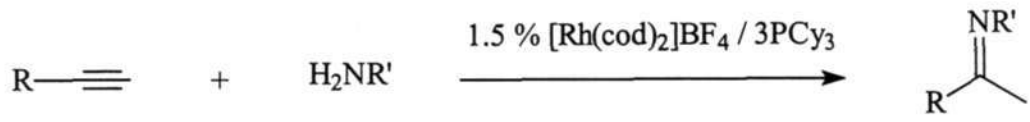
[66] Al-Masum, M., Meguro, M., Yamamoto, Y., *Tetrahedron Lett.*, **1997**, *38*, 6071-6074.

[67] Hartung, C.G., Tillack, A., Trauthwein, H., Beller, M., *J. Org. Chem.*, **2001**, *66*, 6339-6343.

product imines can be treated with organolithium compounds to afford functionalised secondary amines.[67]



Scheme 35

The above section is not a review of all relevant literature but rather serves to highlight important aspects of the field. The extent to which each sub-section has been discussed is intended to parallel its importance to the overall subject matter.

2.2 Silver-catalysed hydroamination

Silver complexes and salts have received far less attention as hydroamination catalysts in comparison to other late transition metals. Nevertheless, these compounds have been employed to effect the intramolecular addition of amines to allenes and alkynes.[23, 58]

Claesson *et al.* first reported the use of a silver salt as a hydroamination catalyst when they observed that allenic amines (Scheme 36, **A**) 'decompose' to pyrrolines (Scheme 36, **B**) when subjected to purification by GLC.[68] They rationalised that this cyclisation may be metal-catalysed as the allenic amines in question are thermally stable under normal distillation conditions. They confirmed this theory by demonstrating that the allenic amines could be cyclised to the corresponding pyrrolines in the presence of a catalytic amount of $AgBF_4$.[68]

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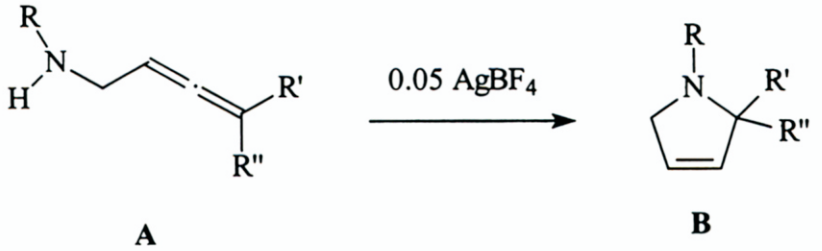
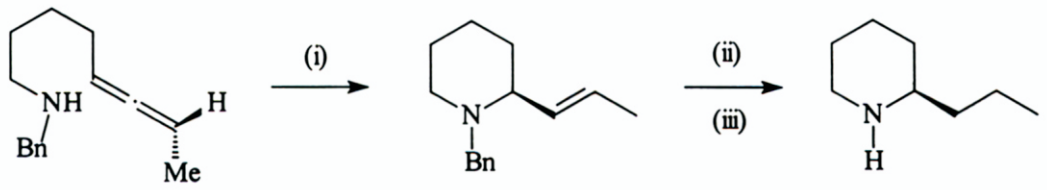
[68] Claesson, A., Sahlberg, C., Luthman, K., *Acta Chem. Scand., Ser. B.*, **1979**, *33*, 309-310.



A **B**

Scheme 36

Several procedures employing this methodology have appeared in the literature subsequent to this initial report. Most notably those carried out by Gallagher and Lathbury. They first reported the stereoselective synthesis of (***R***)-(-)-coniine (Scheme 37) using a silver-catalysed hydroamination of a chiral allenic amine as the key synthetic step.[69]



(*R*)-(-)-coniine

(i) $AgBF_4$, CH_2Cl_2, 20°C (ii) *p*-$MeC_6H_4SO_2NHNH_2$, NaOAc, THF-H_2O, 70°C
(iii) $PdCl_2$, H_2, EtOH, 20°C

Scheme 37

A small amount of racemisation does occur during the cyclisation step and the synthetic coniine produced is a mixture of (*R*) and (*S*) isomers (8:1). This enantiomeric excess has been attributed to the presence of a chiral silver cyclopropane (Figure 4) rather than an achiral allylic species.[69]

[69] Lathbury, D., Gallagher, T., *J. Chem. Soc., Chem. Commun.*, **1986**, 114-115.

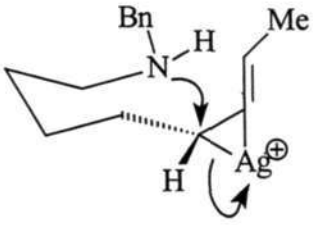
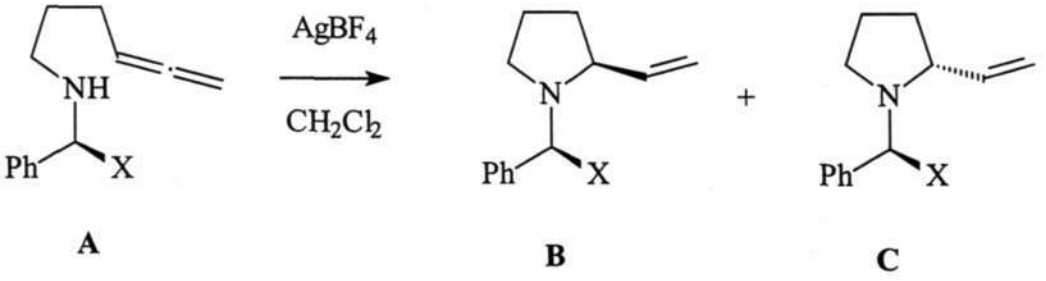


Figure 4

As an extension to this study it has been shown that the silver-catalysed addition to unsubstituted allenes can be carried out diastereoselectivity by employing amines bearing a chiral substituent (Scheme 38).[70] This diastereoselectively has been attributed to the silver being preferentially delivered to the face of the allene that allows chelation between the silver and the 'X' substituent. The cyclisation is completed by amine nucleophilic attack of the chiral silver cyclopropane intermediate.[70]



A **B** **C**

X = CONHMe, **B**:**C** = 9.3:1
X = CH_2NHMe, **B**:**C** = 9:1

Scheme 38

Similar methodologies have been used to prepare (±) anatoxin-a (Figure 5, **A**),[71] (±) pinidine (Figure 5, **B**)[72] and a 3,5-disubstituted pyrrolizidine alkaloid (Figure 5, **C**).[73]

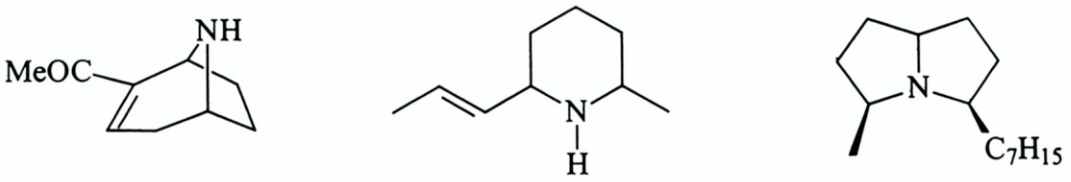
---

[70] a) Fox, D.N.A., Gallagher, T., *Tetrahedron*, **1990**, *46*, 4697-4710. b) Fox, D.N.A., Lathbury, D., Mahon, M.F., Molloy, K.C., Gallagher, T., *J. Chem. Soc., Chem. Commun.*, **1989**, 1073-1075.

[71] Vernon, P., Gallagher, T., *J. Chem. Soc., Chem. Commun.*, **1987**, 245-246.

[72] Arseniyadis, S., Sartoretti, J., *Tetrahedron Lett.*, **1985**, *26*, 729-732.

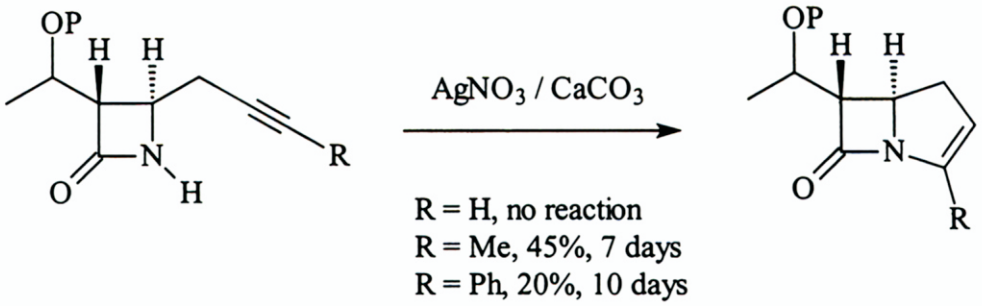
[73] Lathbury, D., Gallagher, T., *J. Chem. Soc., Chem. Commun.*, **1986**, 1017-1018.



A **B** **C**

Figure 5

Alkynes have found limited application in silver-catalysed hydroaminations. Liebeskind and Prasad have reported the preparation of Δ^2-carbapenems *via* the silver-catalysed cyclisation of 4-(2-propynyl)-azetidinones although yields and reaction times are not favourable (Scheme 39).[74]



R = H, no reaction
R = Me, 45%, 7 days
R = Ph, 20%, 10 days

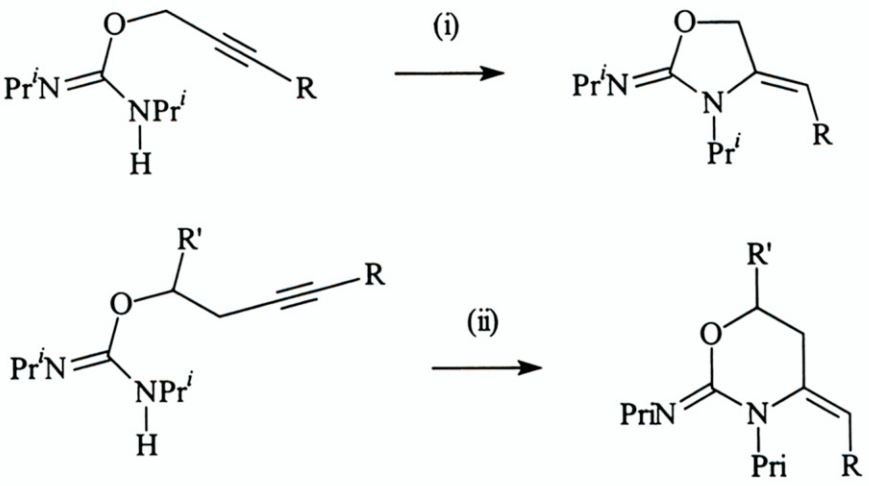
Scheme 39

Accounts of silver-mediated reactions involving alkynes show this reaction to be unpromising, however, Clegg *et al.* have shown that α- and β-acetylenic isoureas (Scheme 40) can be converted to oxazolidines and oxazines respectively, *via* silver-catalysed hydroamination.[75] These reactions are reported to proceed in high yield, although these yields are not specified, and selectively produce the *Z*-isomer in each case.

---

[74] Prasad, J.S., Liebeskind, L.S., *Tetrahedorn Lett.*, **1988**, *29*, 4253-4256.

[75] Clegg, W., Collingwood, S.P., Golding, B.T., Hodgson, S.M., *J. Chem. Soc., Chem. Commun.*, **1988**, 1175-1176.



(i) 2-5% AgOTf, RT, 10 min (ii) 25-30% AgOTf, 80°C

Scheme 40

There has been a resurgence in the field of transition metal-catalysed hydroamination since the late 1990's.[23] Silver and its compounds, however, have not followed the same trend and few reports have made mention of silver compounds as effective hydroamination catalysts.[76]

[76] a) Müller, T.E., Grosche, M., Herdtweck, E., Pleier, A.-K., Walter, E., Yan, Y.-K., *Organometallics*, **2000**, *19*, 170-183. b) Müller, T.E., Pleier, A.-K., *J. Chem. Soc., Dalton Trans.*, **1999**, 583-587. c) Müller, T.E., *Tetrahedron Lett.*, **1998**, *39*, 5961-5962.

3 Pyrroles in natural product synthesis

Pyrroles are amongst the most recognisable structures in organic chemistry; this being due to the enormous amount of research focused on their synthesis and reactivity,[77] as well as their abundance in nature either as monopyrrolic compounds[78] or cyclic tetrapyrroles (porphyrins, chlorins etc.).[79] In terms of natural product synthesis, pyrrolic compounds are attractive targets for total synthesis as well as important intermediates in other reaction sequences.

3.1 Monopyrrolic natural products

Natural products containing a pyrrole ring are too abundant to mention all but a few examples. This area of natural products chemistry has been recently reviewed[78] and this short discussion serves to briefly illustrate the enormous variation of these compounds isolated from natural sources.

The myrmicarins (examples shown as Figure 6) have been isolated from the African ant *Myrmicaria opaciventris*.[80] The myrmicarins contain three families of alkaloids represented by a 'monomeric' type including 15 carbon atoms and 'dimers' and 'trimers' containing 30 and 45 carbon atoms respectively.

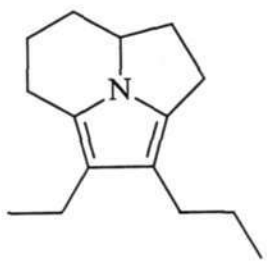
---

[77] a) Gilchrist, T.L., *Heterocyclic Chemistry*, Addison Wesley Longman Ltd., UK, 1997, 3rd Edition, pp. 193-207. b) Jones R.A., Pyrroles and their Benzo Derivatives: (ii) Reactivity, In *Comprehensive Heterocyclic Chemistry*, Katritsky, A.R. and Rees, C.W., Eds., Pergamon Press, New York, 1984, Vol. 4, pp. 201-312. c) Sundberg, R.J., Pyrroles and their Benzo Derivatives: (i) Synthesis and Applications, *ibid*, pp. 313-376.

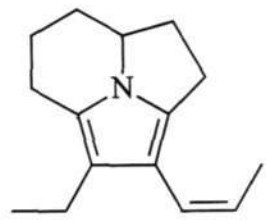
[78] Gossauer, A., Monopyrrolic Natural Compounds Including Tetramic Acid Derivatives, In *Progress in the Chemistry of Organic Natural Products*, Herz, W., Falk, H. and Kirby, G.W. Eds., Springer-Verlag, Vienna, 2003, Vol. 86, pp. 2-188.

[79] Montforts, F.-P. and Glasenapp-Breiling, M., Naturally Occurring Cyclic Tetrapyrroles, In *Progress in the Chemistry of Organic Natural Products*, Herz, W., Falk, H. and Kirby, G.W. Eds., Springer-Verlag, Vienna, 2002, Vol. 85, pp. 1-55.

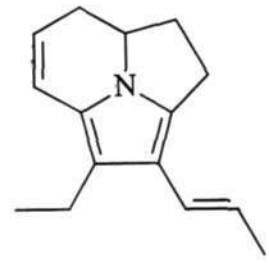
[80] Schröder, F., Franke, S., Francke, W., *Tetrahedron*, **1996**, *52*, 13539-13546.



Myrmicarin **217**



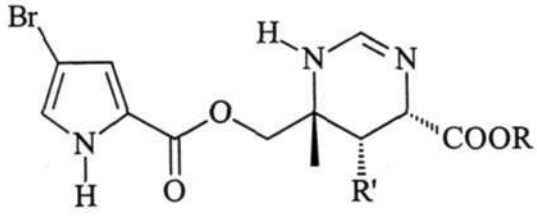
Myrmicarin **215A**



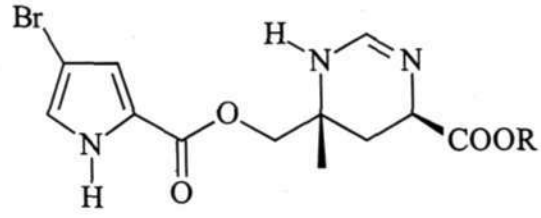
Myrmicarin **213B**

Figure 6

Manzacidins A-C (Figure 7) have been isolated from the marine sponge *Hymeniacidon* sp. and are the first examples of bromopyrroles containing a tetrahydropyrimidine ring.[81]



Manzacidin A, R = R' = H
Manzacidin B, R = OH, R = H



Manzacidin C

Figure 7

N-Bridgehead pyrrole derivatives are also commonly found in nature; for example, the acyl pyrrole shown below (Figure 8) was isolated from the roots of the South African *Senecio stapeliaeformis*.[82] Compounds belonging to this class have also been found in animal tissue and are thought to be responsible for the hepatotoxicity of pyrrolizidine alkaloids in animals.[83]

---

[81] Kobayashi, J., Kanda, F., Ishibashi, M., Shigemori, H., *J. Org. Chem.*, **1991**, *56*, 4574-4576.

[82] Bohlmann, F., Zdero, C., Jakupovic, J., Grenz, M., Castro, V., King, R.M., Robinson, H., Vincent, L.P.D., *Phytochemistry*, **1986**, *25*, 1151-1159.

[83] Mattocks, A.R., *Nature*, **1968**, *217*, 723-728.

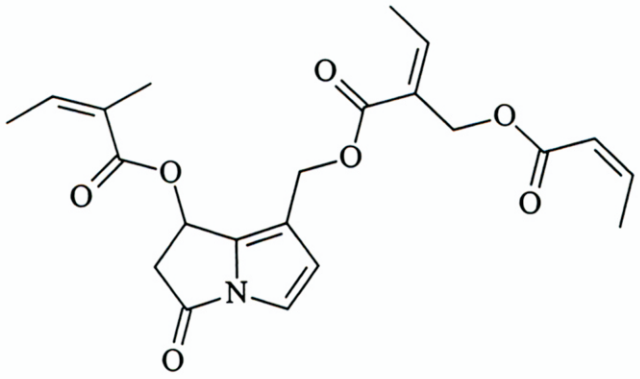


Figure 8

Pyrrolic compounds such as netropsin (Figure 9), an oligopeptide isolated from *Streptomyces netropsis*, have also been isolated from bacteria and exhibit antibiotic properties.[84] Although its structure was not determined by its discoverers, subsequent reports suggested a structure which has been confirmed by total synthesis.[85]

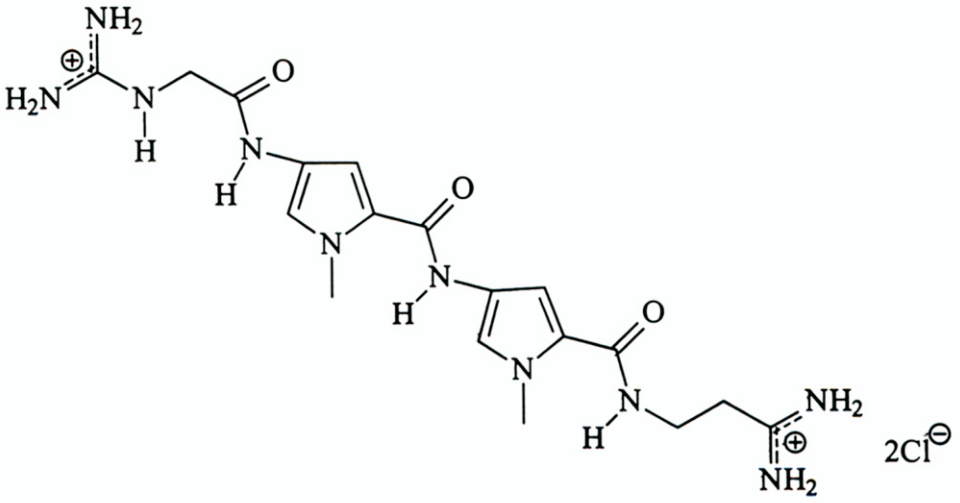
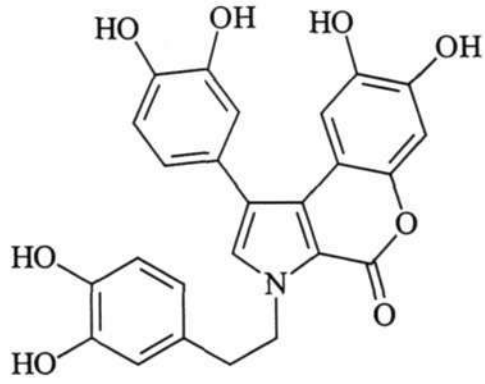


Figure 9

[84] Finlay, A.C., Hochstein, F.A., Sobin, B.A., Murphy, F.X., *J. Am. Chem. Soc.*, **1951**, *73*, 341-342.

[85] Lown, J.W., Krowicki, K., *J. Org. Chem.*, **1985**, *50*, 3774-3779.

As a final example, ningalins A-D (Figure 10) are a group of aromatic alkaloids that have been the focus of a number of total syntheses[86] since their isolation from an Australian ascidian of the genus *Didemnum*.[87]



Ningalin B

Figure 10

3.2 Pyrroles as synthetic precursors

Synthetic protocols employing pyrroles as building blocks are extensive in the literature,[88] however, one common strategy that is worthy of emphasis, is the preparation of alkaloids *via* the hydrogenation of pyrroles.

Jefford has employed this approach extensively for the preparation of indolizidines.[89] The total synthesis of (±) ipalbidine has been accomplished by the decomposition of a pyrrolyl diazo ketone (Scheme 41, **A**), followed by catalytic hydrogenation of the *N*-bridgehead pyrrole intermediate (Scheme 41, **B**) as the key synthetic steps.[90] Further transformation of

---

[86] For examples see a) Iwao, M., Takeuchi, T., Fujikawa, N., Fukuda, T., Ishibashi, F., *Tetrahedron Lett.*, **2003**, *44*, 4443-4446. b) Gupton, J.T., Clough, S.C., Miller, R.B., Lukens, J.R., Henry, C.A., Kanters, R.P.F., Sikorski, J.A., *Tetrahedron*, **2003**, *59*, 207-215. c) Bullington, J.L., Wolff, R.R., Jackson, P.F., *J. Org. Chem.*, **2002**, *67*, 9439-9442.

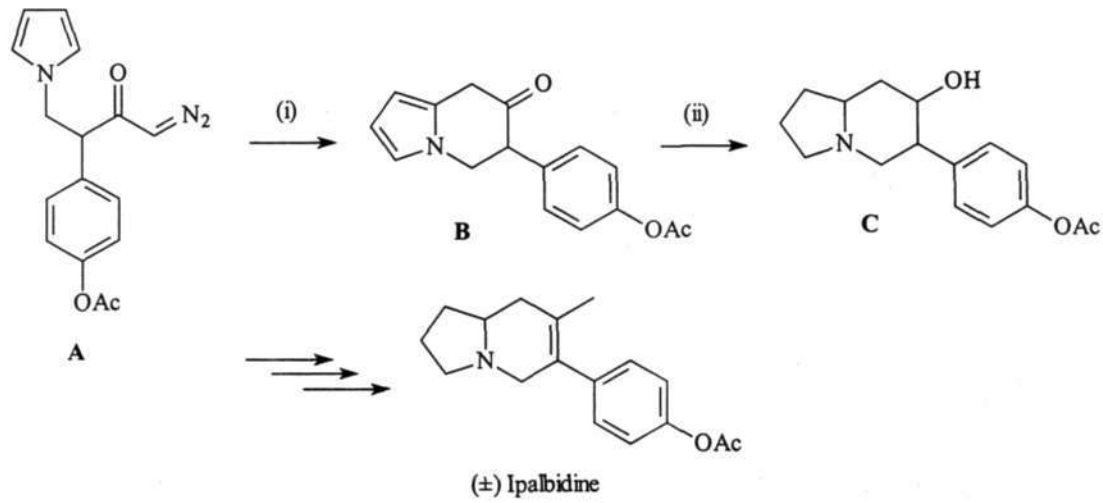
[87] Kang, H., Fenical, W., *J. Org. Chem.*, **1997**, *62*, 3254-3262.

[88] For recent examples see a) Hungerford, N.L., Armitt, D.J., Banwell., M.G., *Synthesis*, **2003**, 1837-1843. b) Banwell, M.G., Smith, J.A., *J. Chem. Soc., Perkin Trans. 1*, **2002**, 2613-2618.

[89] Jefford, C.W., *Curr. Org. Chem.*, **2000**, *4*, 205-230.

[90] Jefford, C.W., Kubota, T., Zaslona, A, *Helv. Chim., Acta*, **1986**, *69*, 2048-2061.

the indolizidine product (Scheme 41, **C**) afforded (±) ipalbidine in 11% yield from the diazo ketone.[90]



(i) $Rh(OAc)_2$, CH_2Cl_2, RT, 90 min (ii) PtO_2, 60 psi, EtOH, AcOH, 50°C

Scheme 41

By employing chiral amino acid starting materials Jefford has been able to extend this methodology to the enantiospecific synthesis of several indolizidine alkaloids (Figure 11) including; indolizidines 167B,[91] 209D,[92] 209B,[93] (+)[91] and (-)[94] monomorine and piclavine A.[93]

---

[91] Jefford, C.W., Tang, Q., Zaslona, A., *J. Am. Chem. Soc.*, **1991**, *113*, 3513-3518.

[92] Jefford, C.W., Wang, J.B., *Tetrahedron Lett.*, **1993**, *34*, 3119-3122.

[93] Jefford, C.W., Sienkiewicz, K., Thornton, S.R., *Helv. Chim. Acta*, **1995**, *78*, 1511-1524.

[94] Jefford, C.W., Sienkiewicz, K., Thornton, S.R., *Tetrahedron Lett.*, **1994**, *35*, 4759-4762.

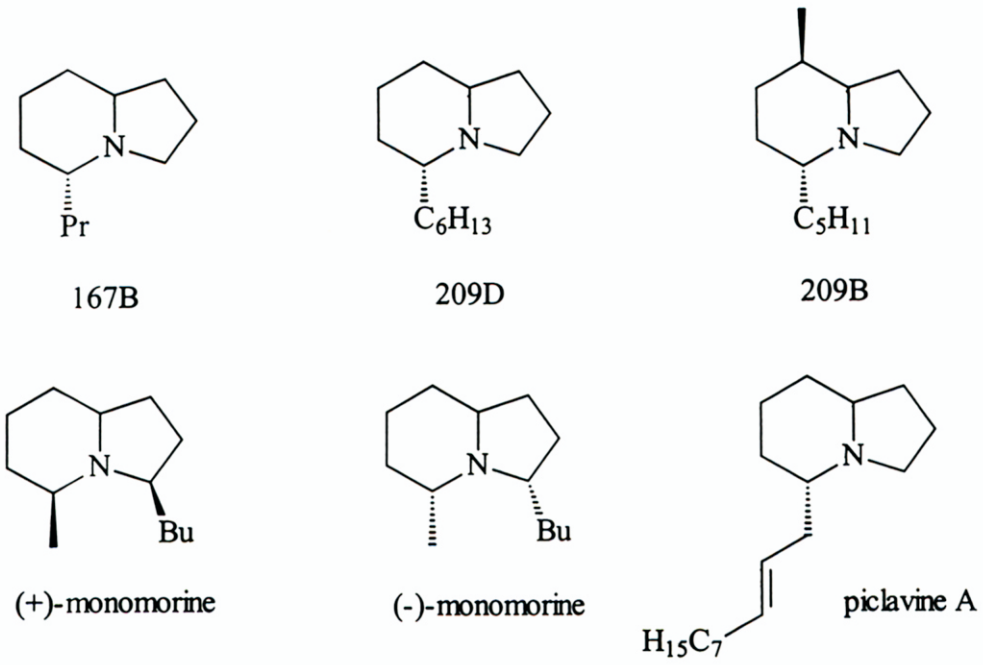
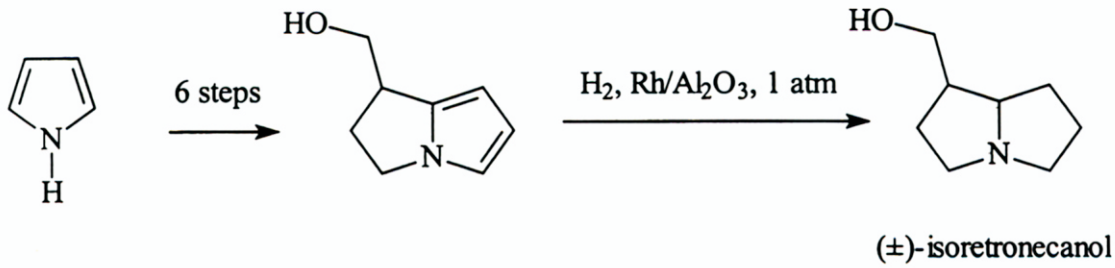


Figure 11

Hydrogenation of pyrrole analogues has also been used to prepare pyrrolizidine alkaloids. Greenhouse has reported the total synthesis of (±)-isoretronecanol from pyrrole (Scheme 42).[95]



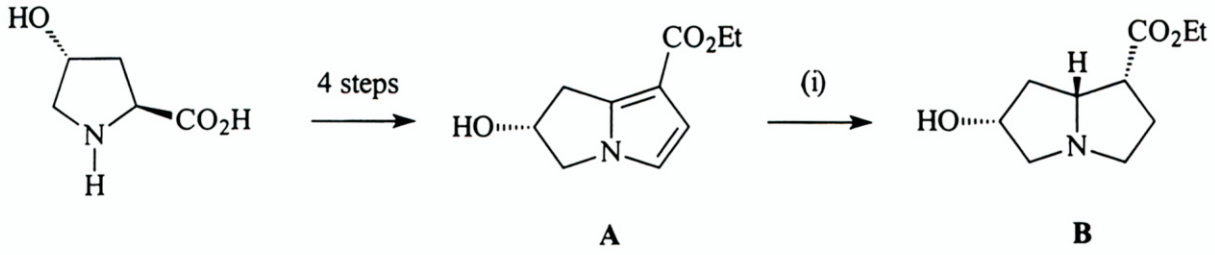
Scheme 42

In an effort to prepare optically active pyrrolizidine bases, Robins has described the preparation of a *N*-bridgehead pyrrole containing a remote chiral centre (Scheme 43, **A**) which affords one stereoisomer as the major product upon hydrogenation.[96] The *N*-bridgehead pyrrole is prepared from naturally occurring (2*S*, 4*R*) 4-hydroxyproline in 4

[95] Ortiz, C., Greenhouse, R., *Tetrahedron Lett.*, **1985**, *26*, 2831-2832.

[96] Robins, D.J., *J. Chem. Soc., Perkin Trans. 1*, **1981**, 909-913.

steps and the optically active pyrrolizidine (Scheme 43, **B**) can be converted to (+)-isoretronecanol, (+)-laburnine and (+)-supinidine using simple synthetic procedures. The corresponding (-)-enantiomers of these alkaloids can be prepared from the same starting materials.[96]



A **B**

(i) H_2, Pd/C, 21 atm, 2 days, RT, AcOH

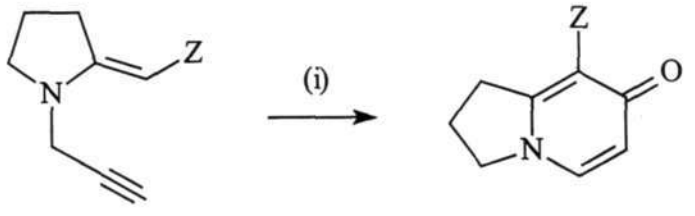
Scheme 43

Discussion

4 Preface

The aim of this project was a broad one, namely to develop general methods for the preparation of nitrogen containing heterocycles. This topic also encompasses the preparation of precursors to heterocycles with the goal of obtaining compounds that can undergo various transformations to give different cyclic products (general synthetic precursors).

Workers in our group had previously reported the novel synthesis of 2,3-dihydro-7(1*H*)-indolizinones from *N*-propargyl enaminones (Scheme 44).[97] This was an important breakthrough, as few methods are known for constructing this ring system.[98]



Z = CN (19%), CO_2Et (16%)
Z = COPh, NO_2 (No product observed)

(i) 9-BBN (1 eq), catecholborane (1 eq), $AgNO_3$/KOH (2 eq)

Scheme 44

The reaction was carried out with the intention of forming a bicyclic system *via* hydroboration of the C≡C and C=C using catecholborane and 9-borabicyclo[3.3.1]nonane (9-BBN) respectively, followed by coupling of the intermediate boranes using alkaline silver nitrate.[97] The indolizinone product isolated from the reaction was not anticipated and, therefore, the mechanism of its formation is interesting.

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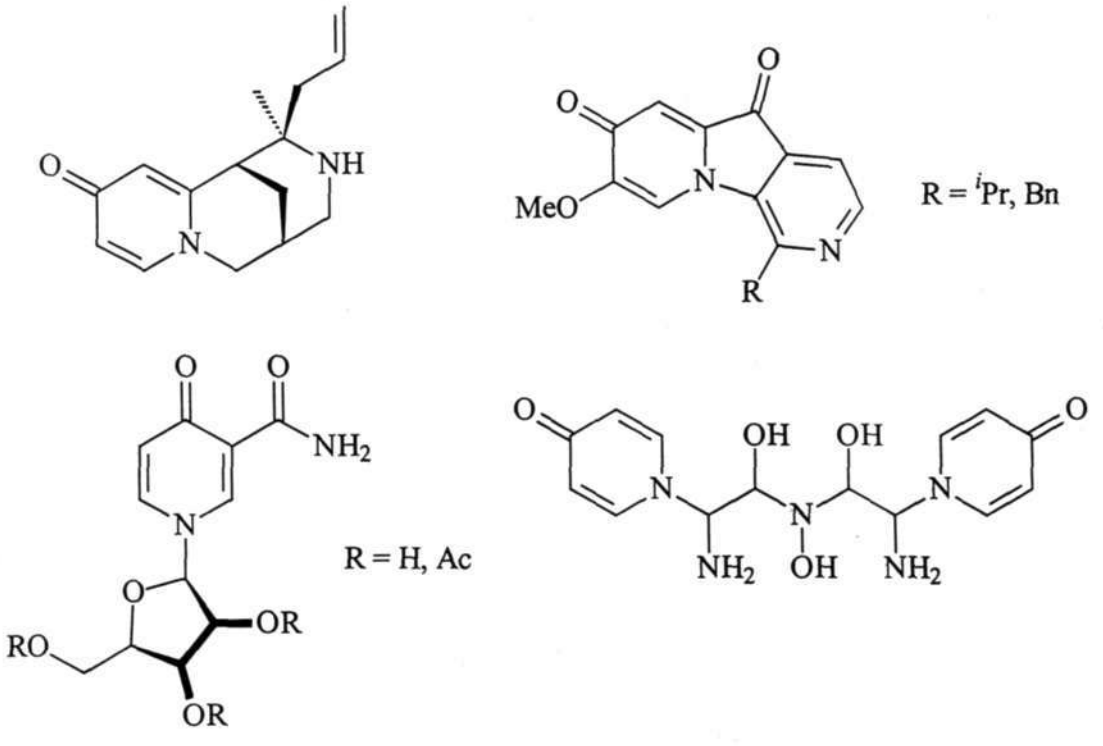
[97] Gravestock, D., Peirson, I.G., *Tetrahedron Lett.*, **2000**, *41*, 3497-3500.

[98] a) Fang, F.G., Prato, M., Kim, G., Danishefsky, S.J., *Tetrahedron Lett.*, **1989**, *30*, 3625-3628. b) Jiang, J.B., Urbanski, M.J., *Tetrahedron Lett.*, **1985**, *26*, 259-262.

The current project was undertaken with three immediate goals; these were to elucidate the mechanism in operation during this transformation, optimise its yields and to generalise the reaction with the specific goal of synthesizing natural products containing the dihydro-γ-pyridone ring system. Some examples of this family of natural products are shown below (Scheme 45).[99]



Scheme 45

Note: The term 'enaminone' should be restricted to compounds containing the β-acyl enamine functionality (Figure 12, **A**). However, throughout the following discussion the term shall be used as a general one to describe any enamine with an electron-withdrawing β-substituent (Figure 12, **B**). The terms 'vinylogous cyanamide' (Z = CN), 'vinylogous carbamate' (Z = CO_2R), 'vinylogous amide' (Z = COR) and 'vinylogous nitramine' (Z = NO_2) shall be used when describing individual compounds.

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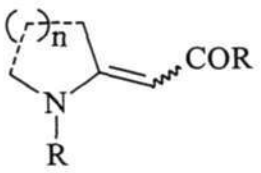
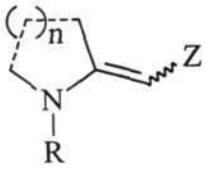
[99] a) Mohamed, M.H., Saito, K., Kadry, H.A., Khalifa, T.I., Ammar, H.A., Murakoshi, I., *Phytochemistry*, **1991**, *30*, 3111-3115. b) Yao, B., Prinsep, M.R., Nicholson, B.K., Gordon, D.P., *J. Nat. Prod.*, **2003**, *66*, 1074-1077. c) Bringmann, G., Ochse, M., Wolf, K., Kraus, J., Peters, K., Peters, E.-M., Herderich, M., Assi, L.A., Tayman, F.S.K., *Phytochemistry*, **1999**, *51*, 271-276. d) Ueda, M., Yamamura, S., *Tetrahedron*, **1999**, *55*, 10937-10948.



A



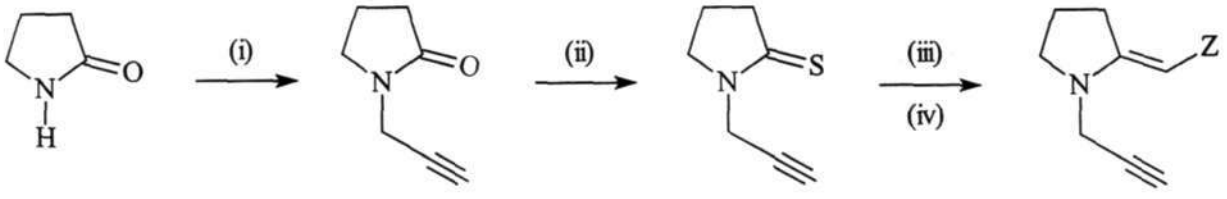
B

n = 1,2,3
Z = CN, CO_2R, COR, NO_2

Figure 12

5 Preparation of *N*-propargyl enaminones: pyrrolidine analogues

N-Propargyl enaminones were prepared according to the protocols outlined in a prior report.[97] *N*-Propargyl pyrrolidinone (Scheme 46, **A**) was prepared by treating a mixture of pyrrolidinone and propargyl bromide with sodium hydride.[100] Subsequent thionation using Brillon's procedure (P_4S_{10} / Na_2CO_3) afforded *N*-propargyl pyrrolidinethione (Scheme 46, **B**).[101] The thiolactam was converted to the appropriate enaminones (Scheme 46, **C**, Z = CN, CO_2Et, COPh) using the elegant Eschenmoser coupling reaction.[102] The vinylogous nitramine analogue (Scheme 47, **A**, Z = NO_2) was prepared from *N*-propargyl pyrrolidinethione according to the method reported by Gugelchuk *et al.* (Scheme 47).[103]



(i) $BrCH_2CCH$, NaH, THF, 0°C to RT, 91% (ii) P_4S_{10}, Na_2CO_3, THF, RT, 41%
(iii) ZCH_2Br, CH_3CN, RT (iv) NEt_3, PPh_3, CH_2Cl_2 (Z = CN, 48%, Z = CO_2Et, 38%, Z = COPh, 32%)

Scheme 46

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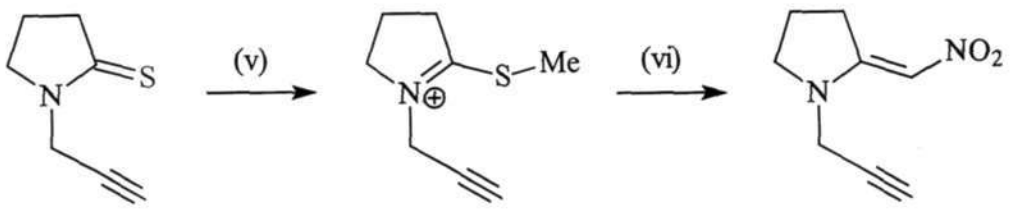
[100] Fones, W.S., *J. Org. Chem.*, **1949**, *14*, 1099-1102.

[101] Brillon, D., *Synth. Commun.*, **1990**, *20*, 3085-3095.

[102] Shiosaki, K., The Eschenmoser Coupling Reaction, In *Comprehensive Organic Synthesis*, Trost, B.M., Fleming, I., Eds., Pergamon Press, Oxford, 1991, Vol. 2, pp. 865-892.

[103] Gugelchuk, M.M., Hart, D.J., Tsai, Y.-M., *J. Org. Chem.*, **1981**, *46*, 3671-3675.



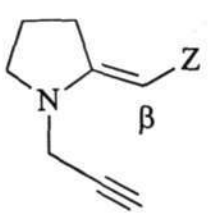
A

(iv) CH_3I, RT, $CHCl_3$ (vi) CH_3NO_2, K_2CO_3, RT, 10%

Scheme 47

The *N*-propargyl enaminones are easily isolated using silica gel chromatography but are relatively unstable thereafter and should be stored under nitrogen. This instability, attributed to the propargyl substituent, contrasts that of other *N*-substituted enaminones which can be stored and used almost indefinitely. The chemical shifts of the β-carbons and protons of enaminones are indicative of their electronic character, particularly their nucleophilicity. [104] The chemical shifts of the β-carbons and protons of *N*-propargyl enaminones (Table 2) are in keeping with typical values and this would seem to indicate that, in spite of their instability, the prepared enaminones should display reactivity characteristic of this class of compounds.

Table 2: Chemical shifts for β-carbons and protons of *N*-propargyl enaminones



Z	δ_C / *ppm*	δ_H / *ppm*
CN	56.2	3.75
CO_2Et	80.1	4.63
COPh	87.7	5.82
NO_2	110.6	6.77

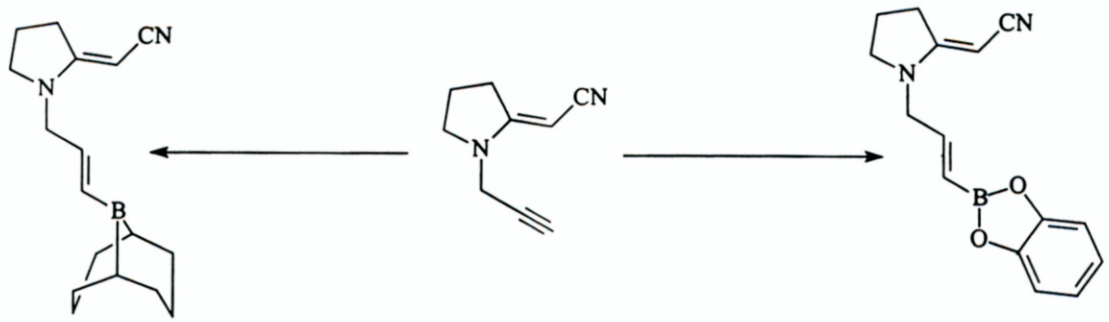
[104] Michael, J.P., de Koning, C.B., Gravestock, D., Hosken, G.D., Howard, A.S., Jungman, C.M., Krause, R.W.M., Parsons, A.S., Pelly, S.C., Stanbury, T.V., *Pure App. Chem.*, **1999**, *71*, 979-988.

6 Mechanistic investigation of indolizinone formation

The mechanism of indolizinone formation is intriguing. The formation of the new C-C bond is not unusual, as enaminones are known to participate in intramolecular nucleophilic reactions that afford cyclic products of this nature;[104] however, the change in oxidation state of the terminal carbon of the propargyl group is peculiar.

A closer inspection of the literature showed no occurrence of the hydroboration of enaminones and it is, therefore, believed that this portion of the molecule acts as a nucleophile and facilitates ring closure. With these observations in mind, a rough mechanistic model could involve; hydroboration of the C≡C by either 9-BBN or catecholborane, followed by alkaline silver nitrate oxidation of the borane intermediate to afford an electrophilic species. The presence of an electrophile would effect ring closure *via* the nucleophilic enaminone functionality. Any appropriate rearrangements would afford the final product.

Immediate goals were to investigate the role of the hydroborating agents; specifically, which of the two agents effect hydroboration and in what regiochemical fashion? Brown and co-workers have shown that 9-BBN and catecholborane hydroborate terminal aliphatic alkynes to give the corresponding *trans*-alkenylboranes, which are stable enough to be purified by conventional means.[105] Although the systems studied by Brown and co-workers are far simpler than those currently under consideration, it was assumed that these reactions would have the same stereochemical outcome (Scheme 48).



Scheme 48

[105] Smith, M.B., *Organic Synthesis*, McGraw-Hill Inc., New York, 1994, pp 506-566.

In a set of two control reactions we have shown that both 9-BBN and catecholborane react with, and consume, *N*-propargyl enaminones (Z = CN) efficiently at ambient temperature. These reactions were carried out overnight in THF. This result is remarkable as catecholborane does not typically react with alkynes at room temperature and hydroborations of this nature are normally carried out in refluxing THF.[106] Unfortunately, the hydroboration intermediates, assumed to be alkenylboranes (Scheme 48), could not be isolated in either reaction.

In order to gain further insight, the reaction of an *N*-propargyl enaminone (Z = CN) with 9-BBN was monitored by dynamic ^{11}B NMR spectroscopy (Figure 13). The enaminone was added to a solution of 9-BBN (0.5 M) in THF in a quartz NMR tube at 0°C. Quartz tubes are used due to the presence of borosilicates in Pyrex. It is evident from this experiment that the 9-BBN (27.0 ppm)[107] is consumed over the course of the reaction (complete after 3 hours) and gives rise to a single new borane species (57.6 ppm). The broad resonance at 55.7 ppm is attributed to an oxidation product derived from 9-BBN and its concentration does not appear to change over the course of the reaction.

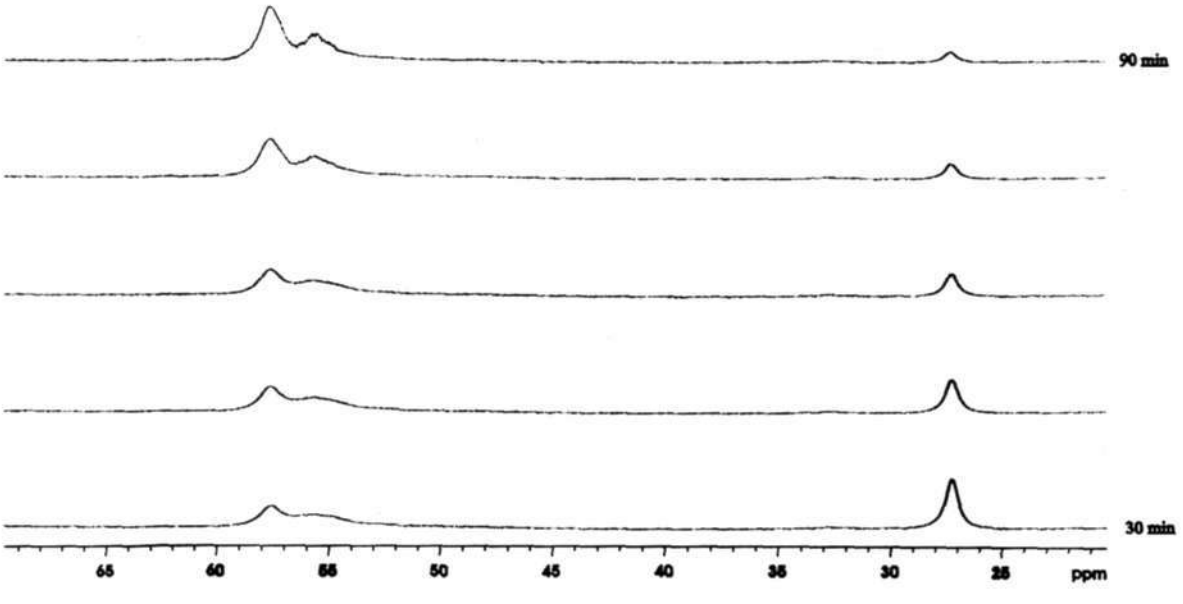


Figure 13

[106] a) Brown, H.C., Chandrasekharan, J., *J. Org. Chem.*, **1983**, *48*, 5080-5082. b) Brown, H.C., Gupta, S.K., *J. Am. Chem. Soc.*, **1972**, *94*, 4370-4371.

[107] Soderquist, J.A., Brown, H.C., *J. Org. Chem.*, **1980**, *45*, 3571-3578.

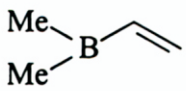
The chemical shift of the new borane species is not very informative. The boron atom of a trialkylborane resonates in a narrow range between 83-93 ppm.[108] Unsaturation β to the boron atom does not influence its chemical shift (Figure 14, **A-B**), however, an sp^2 or sp hybridised carbon atom α to the boron atom allows for π interaction between the nuclei and results in shielding of the ^{11}B nuclei (Figure 14, **C-D**).[109] This affect is additive. It is not clear how the introduction of a nitrogen atom to the system influences these values and, therefore, it is uncertain whether the observed chemical shift (57.6 ppm) of the new borane species can, unambiguously, be assigned to the alkenylborane species shown above.

87.4 ppm

A

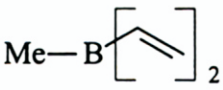
85.5 ppm

B



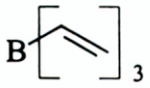
74.5 ppm

C



64.4 ppm

D



55.2 ppm

E

Figure 14

Attempts to identify the borane intermediates by other means were not successful. Oxidation using alkaline hydrogen peroxide (H_2O_2 / NaOH) did not afford any distinguishable products, as was the case for the milder oxidant, alkaline silver nitrate ($AgNO_3$ / KOH). Deuteriolysis using trifluoroacetic acid-d_1 afforded a similar result. A blank experiment was conducted in which the *N*-propargyl enaminone was subjected to mild oxidation conditions ($AgNO_3$ / KOH) and, again, the starting material was consumed without affording any conclusive results.

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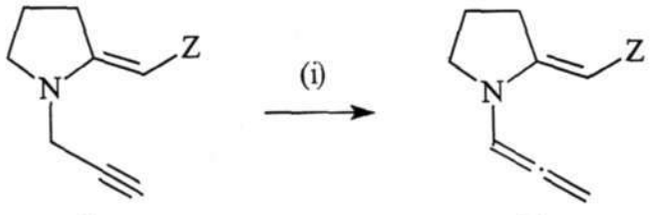
[108] Nöth, H., Wrackmeyer, B., *Nuclear magnetic resonance spectroscopy of boron compounds*, Springer-Verlag, Berlin, 1978, pp 19-20.

[109] San Diego State University web site, http://www.chemistry.sdsu.edu/research/BNMR

From the reactions carried out and the observations described above it is apparent that *N*-propargyl enaminones are exceptionally sensitive compounds and the complicated reaction conditions involved in the formation of indolizinones may belie a far simpler reaction mechanism. Attention was, therefore, shifted towards the possible function of the inorganic base (KOH) as the hydroborating agents and the oxidant appear to consume and, ultimately, destroy the molecule.

7 Preparation of *N*-allenyl enaminones: pyrrolidine analogues

The base-catalysed isomerisation of *N*-propargyl compounds to their *N*-allenyl counterparts is well known and this reaction is covered in further detail in a prior section (p2). In particular, the preparation and reactivity of electron-deficient variants of *N*-allenyls (allenamides) has become a major area of study over the past decade.[4] It was not immediately clear whether the highly reactive *N*-propargyl enaminones would undergo this isomerisation; nevertheless, the same four *N*-propargyl enaminones that were studied previously with regard to indolizinone formation (i.e. Z = CN, CO_2Et, COPh, NO_2) were treated with potassium *tert*-butoxide (1 eq) in an attempt to prepare their isomers. This experiment has given rise to interesting results (Scheme 49) that parallel those of the earlier study (Scheme 44, p40). The reaction proceeds cleanly, in good yield, for the vinylogous cyanamide (Z = CN, 66%) and carbamate (Z = CO_2Et, 96%) and yet no product is observed for the vinylogous amide (Z = COPh) and nitramine (Z = NO_2).



A **B**

Z = CN (66%), CO_2Et (96%)
Z = COPh, NO_2 (No product observed)

(i) *t*-BuOK, THF, RT, 30 min

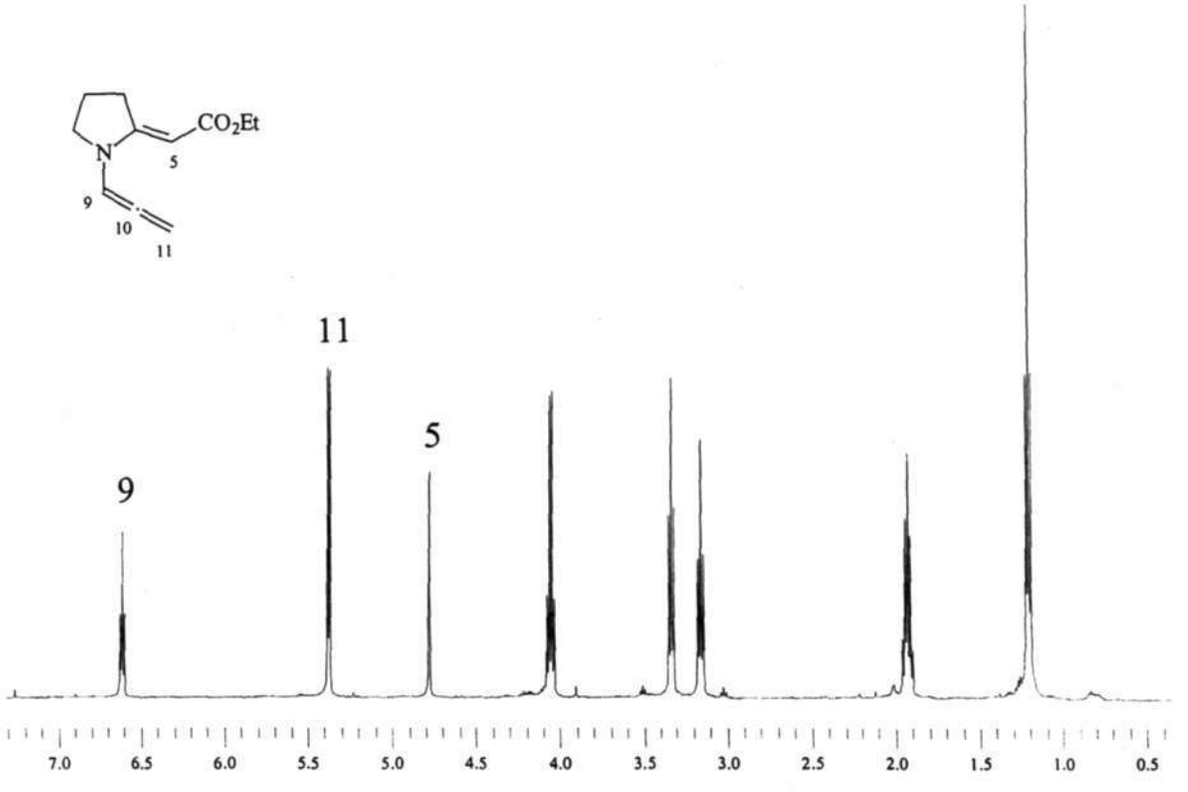
Scheme 49

The practical aspects of this reaction are straightforward. Potassium *tert*-butoxide (as a powder or a solution in *tert*-butanol) was added to a solution of the enaminone (Scheme 49, **A**) in THF at room temperature. The colour of the solution immediately changed from a pale yellow or brown to a brilliant red on addition of the base. Although these isomerisations are usually rapid (typically 5 minutes),[5c,9] the reactions of the *N*-propargyl enaminones were allowed to proceed for 30 minutes to ensure completion. The solvent was removed and the crude material was filtered (EtOAc) through a plug of basic alumina. This crude purification afforded *N*-allenyl enaminones (Scheme 49, **B**, Z = CN and CO_2Et) of

excellent purity and further chromatography was not required. The purity of these 'crude' compounds is evident from their NMR spectra (Spectrum 1 and Spectrum 2).

7.1 *N*-Allenyl enaminones as general synthetic precursors

In addition to the purity, the spectra themselves give some valuable insights into the character of the molecule and the discussion that follows is representative of both the vinylogous cyanamide and carbamate.



Spectrum 1

The signals corresponding to the protons of the ring and the ester group are typical, however, the remaining three signals deserve further mention. The β-proton (5) resonates at 4.77 ppm, which is comparable to the shift of the same proton of the original *N*-propargyl compound (4.63 ppm) (Table 2). This suggests that the electronic character of the enaminone functionality and, in particular its nucleophilicity, is not altered by isomerisation of the propargyl substituent. The protons of the *N*-allenyl substituent also display interesting characteristics; long-range coupling, usually shown by this functionality, is evident as the methine proton (9) α to nitrogen is split into a triplet (6.61

ppm, J = 6.4 Hz) and the terminal methylene protons (11) are split into a doublet (5.37 ppm, J = 6.3 Hz).

More significant, however, is the *chemical shift* of the methine proton (9). Just to recap (The following points have been covered in more depth in the 'Introduction', p1); the advantage of allenes containing a nitrogen substituent (allenamines) is the ability of the nitrogen atom to donate its lone pair to the allene, introducing electronic bias, and allowing for regioselective transformations. The advantage of electron-deficient allenamines (Figure 15, **A**) over their electron-rich counterparts (Figure 15, **C**) is that this donation is tempered, thus reducing the problems associated with these highly reactive species. It is clear, when comparing *N*-allenyl morpholine[9] and *N*-allenyl pyrrolidinone[5a] (Figure 15), that the chemical shift of the methine proton α to nitrogen is indicative of the extent of this donation. The chemical shift of the corresponding proton of *N*-allenyl enaminones is between these two extremes but suggests that *N*-allenyl enaminones would display the favourable characteristics of electron-deficient allenamines.

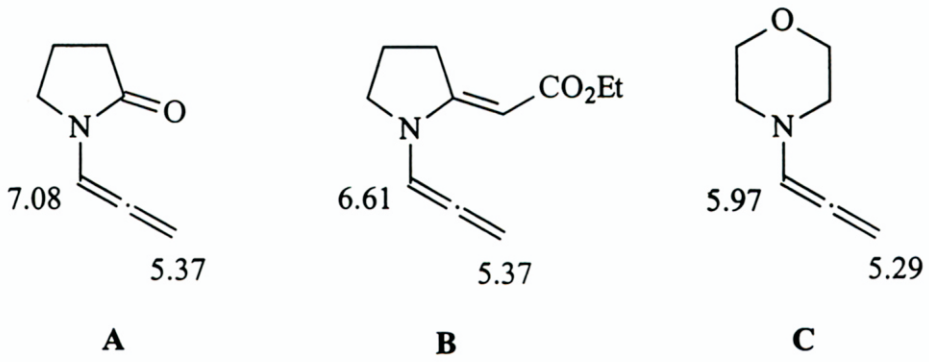
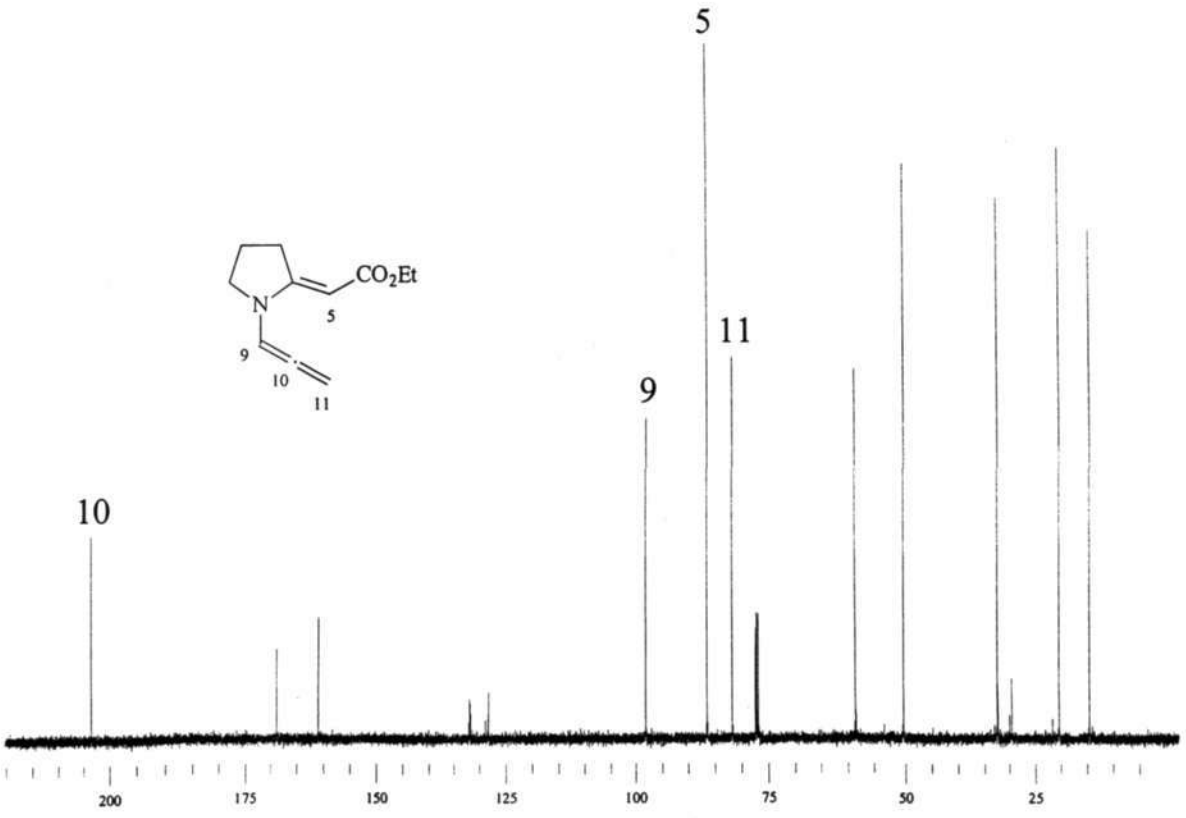


Figure 15

The ^{13}C NMR spectrum (Spectrum 2) shows the same trends as the ^{1}H spectrum above. The chemical shifts of the three carbons of the *N*-allenyl substituent (9 = 98.1 ppm, 10 = 203.5 ppm, 11 = 81.7 ppm) are comparable to those of *N*-allenyl pyrrolidinone (Figure 15, **A**) (9 = 95.6 ppm, 10 = 202.5 ppm, 11 = 86.5 ppm),[5a] and the shift of the β-carbon atom (5 = 86.5 ppm) is similar to the same carbon of the starting material (80.1 ppm) (Table 2).



Spectrum 2

From these observations we can draw some tentative conclusions regarding *N*-allenyl enaminones; their electronic character suggests that they would display the nucleophilic properties of typical enaminones, molecules that have been employed very successfully as part of a general strategy towards alkaloid synthesis by Michael and co-workers.[104] In addition, *N*-allenyl enaminones are predicted to display similar properties to those of electron-deficient allenamines, extremely versatile molecules (see p3-9) that are currently the subject of a large amount of research the world over. Considering the synthetic flexibility of these two functionalities, *N*-allenyl enaminones can be regarded as potentially valuable general synthetic precursors.

7.2 Differing behaviour of *N*-propargyl enaminones towards isomerisation

In spite of their potential as synthetic precursors, some fundamental questions regarding their preparation remain to be answered. Why does base-induced isomerisation afford the desired *N*-allenyl compounds cleanly, and in good yield, when Z = CN and CO_2Et yet there is no trace of the analogous products when Z = COPh or NO_2? Moreover, does this

observation, which parallels the earlier study, indicate that the isomerised form of *N*-propargyl enaminones may be present as an intermediate in the formation of indolizinones?

Without a substantial investigation, answers to the first question can be sceptical at best. Nevertheless, we can put forward some suggestions based on a survey of the literature and some chemical intuition. At the outset, it was expected that the yields of the *N*-allenyl enaminones would increase as the electron-withdrawing ability of the Z substituent became greater. This was assumed on the basis that the electron-withdrawing group (EWG) stabilises the intermediate anion and the final product. In reality this is not observed. As mentioned earlier, all four reactions carried out gave an immediate red colouration on addition of base. Although this was noted as nothing more than an innocuous observation, in retrospect it does suggest that the reaction proceeds in a similar manner in all four cases, at least initially.

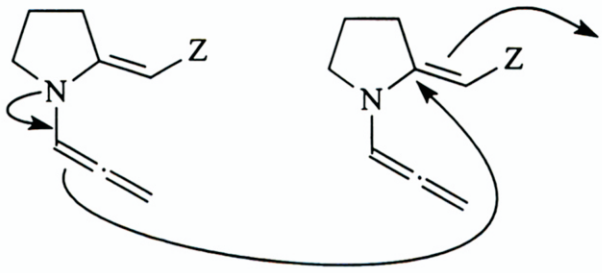
Changing the EWG on the enaminone has a number of implications, one of which is to alter the electrophilic character of the double bond. This character increases as the strength of the EWG increases so; for example, a vinylogous nitramine is more electrophilic than a vinylogous cyanamide. This trend has been established by Michael and co-workers through the reduction of the C=C double bond (Scheme 50).[104] Vinylogous nitramines are reduced with sodium borohydride whereas vinylogous amides are not and, this reduction requires the use of the more rigorous reducing agent lithium aluminium hydride (LAH). Vinylogous carbamates, on the other hand, are not reduced by LAH.

A **B**

(i) $NaBH_4$ (Z = NO_2)
(i) $LiAlH_4$ (Z = COMe)
(i) $LiAlH_4$ (Z = CO_2Et, no reaction)

Scheme 50

We propose that the desired *N*-allenyl enaminones are, indeed, formed in all four of the reactions carried out (i.e. Z = CN, CO_2Et, COPh and NO_2). Further, we propose that the enaminone C=C double bond of the vinylogous amide and nitramine (Z = COPh and NO_2) is sufficiently electrophilic that intermolecular conjugate addition reactions are possible *via* the nucleophilic *N*-allenyl substituent (Scheme 51). This would result in the formation of dimers, trimers and higher polymers.



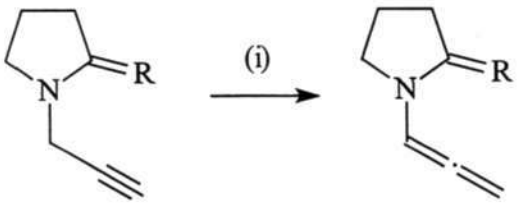
Z = COPh, NO_2

Scheme 51

A control experiment has shown that *N*-propargyl pyrrolidinone is efficiently converted to the corresponding *N*-allenyl using the experimental procedure and crude purification described above, however, *N*-propargyl pyrrolidinethione does not undergo the same isomerisation and there is no evidence of the desired *N*-allenyl compound (Scheme 52). This supports the proposal described above as thiolactams are more electrophilic than their lactam counterparts. To parallel the argument presented above, thiolactams can be reduced using relatively mild conditions (Raney nickel)[110] whereas lactams are reduced by much harsher means ($NaBH_4$ or $LiAlH_4$).[111]

[110] March, J., *Advanced Organic Chemistry*, Wiley-Interscience, New York, 4th Edition, pp 728-729.

[111] March, J., *Advanced Organic Chemistry*, Wiley-Interscience, New York, 4th Edition, pp 1212-1213.



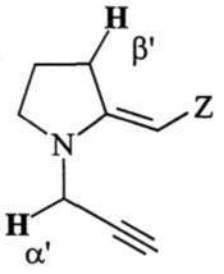
A **B**

R = O (77%)
R = S (no product observed)

(i) *t*-BuOK, THF, RT, 30 min

Scheme 52

There is one additional characteristic that may contribute to the observed reactivity of the *N*-propargyl enaminones. Although it is less likely to play a role it is still worthy of mention. That characteristic is the acidity of the β′ protons and, more importantly, their pK_a relative to the methylene protons of the propargyl group (α′ protons) (Figure 16). Although strong amide bases (pK_a ~35) are usually employed to abstract β′ protons in similar systems,[112] there is no evidence to suggest that a weaker base cannot remove these protons.



R = CN, CO_2Et, COPh, NO_2.

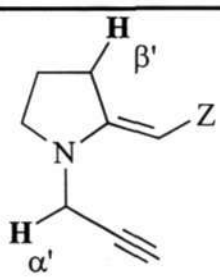
Figure 16

Using ^{1}H NMR chemical shifts as a rough indication of the acidity of the α′ and β′ protons (Table 3), it is possible to suggest that the β′ protons of the vinylogous amide and nitramine may be acidic enough to be abstracted by a base such as potassium *tert*-butoxide. This would further complicate an already complex system.

---

[112] a) Bartoli, G., Bosco, M., Cimarelli, C., Dalpozzo, R., Guerra, M., Palmieri, G., *J. Chem. Soc., Perkin Trans. 2*, **1992**, 649-655. b) Chen, Y.L., Mariano, P.S., Little, G.M., O'Brien, D., Huesmann, P.L., *J. Org. Chem.*, **1981**, *46*, 4643-4654.

Table 3: ^{1}H and ^{13}C NMR chemical shifts of N-propargyl enaminones



Z	$\delta_{H\text{-}\alpha'}$ / ppm	$\delta_{C\text{-}\alpha'}$ / ppm	$\delta_{H\text{-}\beta'}$ / ppm	$\delta_{C\text{-}\beta'}$ / ppm
CN	2.82	32.7	3.82	35.8
CO_2Et	3.14	32.3	3.91	35.6
COPh	3.37	33.5	4.05	35.8
NO_2	3.45	34.6	3.95	36.8

7.3 *N*-Allenyl enaminones as intermediates in indolizinone formation

Whether *N*-allenyl enaminones are intermediates in indolizinone formation is a difficult question to answer and, after some investigation, we cannot present any evidence to support this hypothesis other than the comparable results already mentioned above. Nevertheless, a number of interesting results have been noted during this investigation and these are presented below.

As observed with the *N*-propargyl analogues, 9-BBN and catecholborane consume the *N*-allenyl enaminones at room temperature, however, 9-BBN (40 min) is far more efficient than catecholborane (overnight) and further studies were restricted to the former hydroborating agent. Hydroboration of an *N*-allenyl enaminone (Z = CN) using 9-BBN was conducted (Scheme 53) and monitored using dynamic ^{11}B NMR (Figure 17). The *N*-allenyl enaminone was added to a solution of 9-BBN (0.5 M) in an identical manner to that described for its *N*-propargyl analogue. Two possible outcomes are envisaged for this reaction. Hydroboration of the C=C double bond α to nitrogen, a common and facile reaction of enamines,[113] or hydroboration of the terminal C=C double bond, a reaction typical of mono-substituted allenes.[114] The former would afford an alkenyl borane (Scheme 53, **A**) whilst the latter would afford an allyl borane (Scheme 53, **B**).

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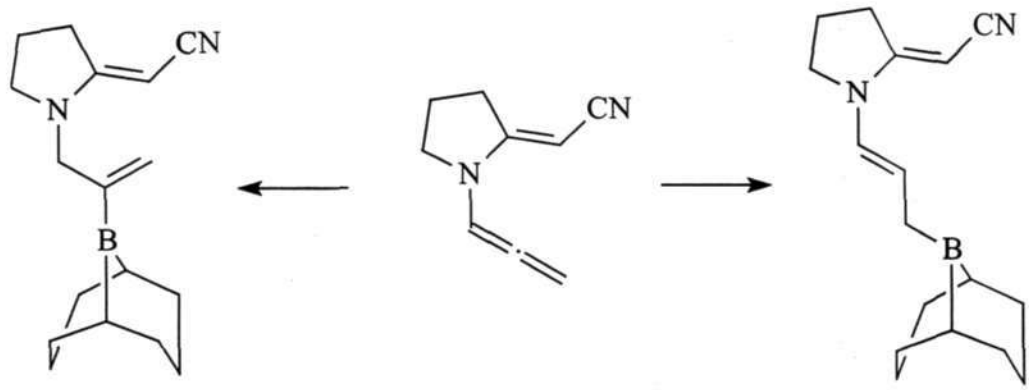
[113] a) Goralski, C.T., Hasha, D.L., Nicholson, L.W., Singaram, B., *Tetrahedron Lett.*, **1994**, *35*, 5165-5168. b) Singaram, B., Rangaishenvi, M.V., Brown, H.C., Goralski, C.T., Hasha, D.L., *J. Org. Chem.*, **1991**, *56*, 1543-1549.

[114] a) Wang, K.K., Liu, C., Gu, Y.G., Burnett, F.N., Sattsangi, P.D., *J. Org. Chem.*, **1991**, *56*, 1914-1922. b) Brown, H.C., Liotta, R., Kramer, G.W., *J. Am. Chem. Soc.*, **1979**, *101*, 2966-2970.



A **B**

Scheme 53

The spectra reveal that 9-BBN (27.0 ppm) is consumed after 40 minutes at room temperature and gives rise to a single hydroboration product (55.3 ppm). By the same argument applied to *N*-propargyl analogues (p46), the chemical shift of the resonance cannot be used to, unambiguously, assign the product as either of those described above; nevertheless, the reaction is clean and efficient.

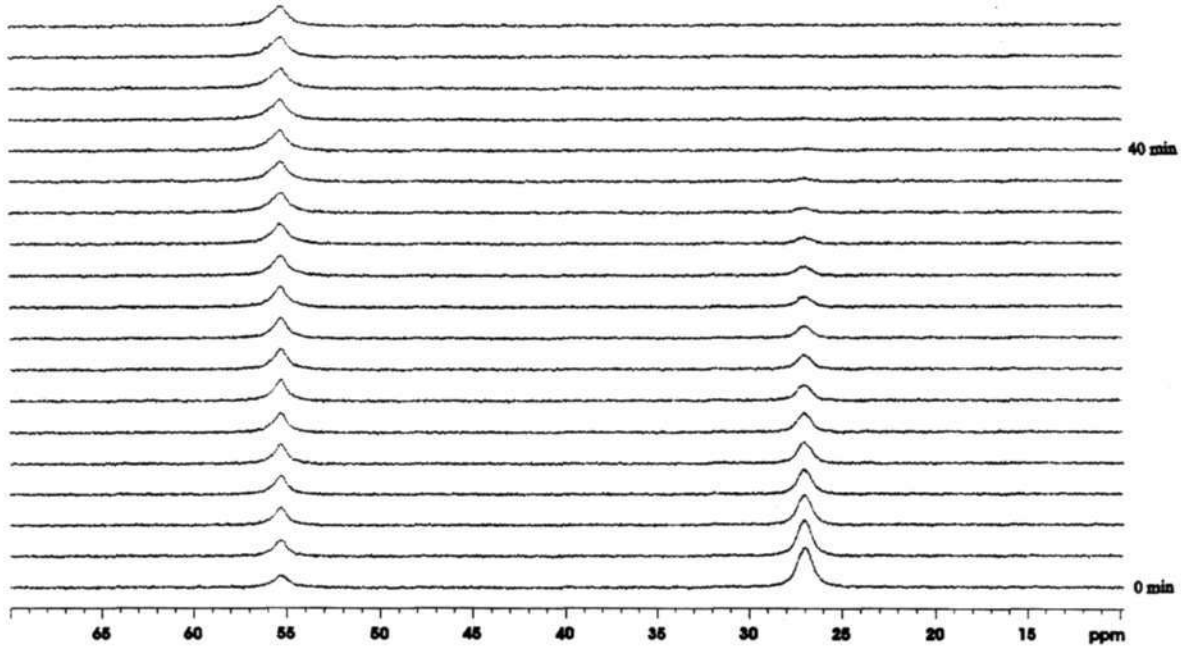
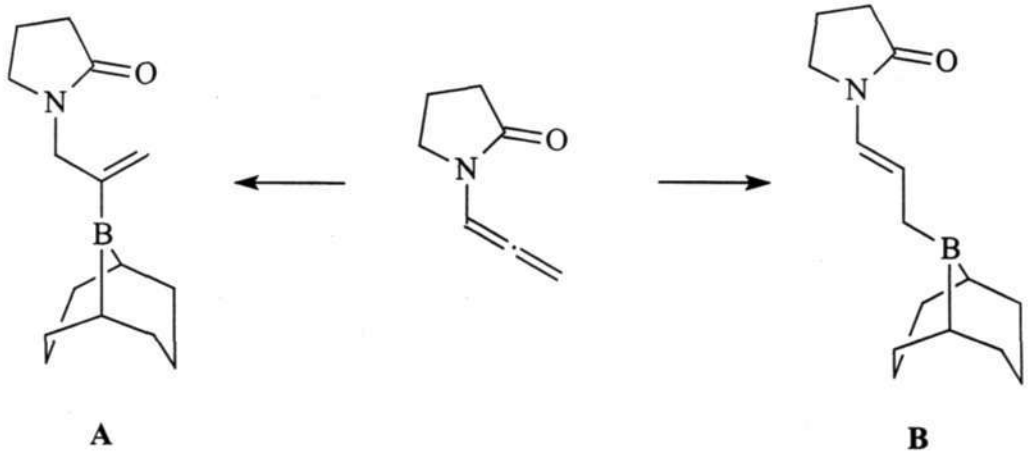


Figure 17

A control experiment was carried out to determine whether the observed resonance could be due to oxidation of the 9-BBN and not necessarily a hydroboration product. A solution

of 9-BBN in THF was monitored over a period of 60 minutes. The characteristic signal at ~55 ppm, attributed to an oxidation product, was present in a typical amount. During the course of the experiment no depletion of 9-BBN was noted nor was any increase in the oxidation product, therefore, it is evident that the signal at 55.3 ppm (Figure 17) is a hydroboration product and not due to oxidation. A further experiment was conducted to compare the reactivity of *N*-allenyl enaminones with other electron-deficient *N*-allenyls (Scheme 54). Hydroboration of the commonly employed allenamide, *N*-allenyl pyrrolidinone, showed the reaction to be far less selective than the enaminone variation, a fact that is apparent from the numerous signals observed after 9-BBN has been consumed (Figure 18).



A **B**

Scheme 54

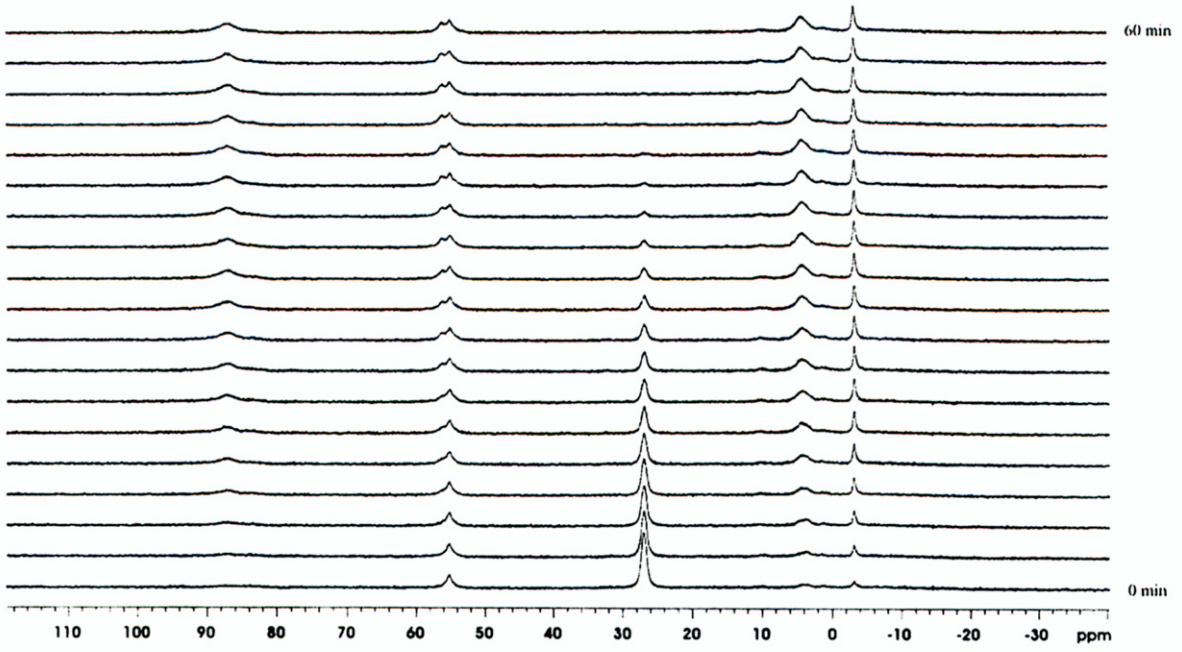


Figure 18

Although the hydroboration of *N*-allenyl enaminones is a promising procedure, isolation or identification of the borane intermediate was not possible. As noted previously with the *N*-propargyl analogue, oxidation by traditional means (H_2O_2/NaOH) and milder means ($AgNO_3$/KOH or $AgNO_{3(aq)}$) provided no identifiable products. Even treatment of the borane with the strongly complexing Lewis base pyridine, did not afford a stable product.[115]

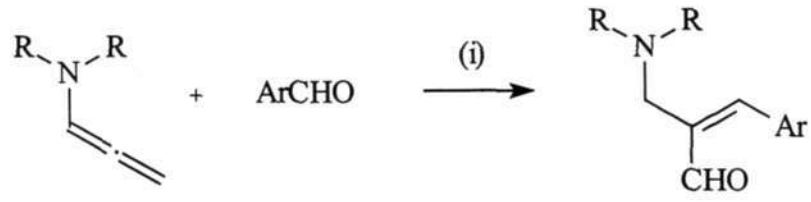
None of the observations described above lend support to the hypothesis that *N*-allenyl enaminones are intermediates in the formation of indolizinones and, as such, this theory was abandoned.

The general reactivity of *N*-allenyl enaminones was also briefly explored. Brandsma *et al.* have reported a remarkable reaction that affords vinyl aldehydes when a mixture of an allenamine and an aromatic aldehyde is treated with a catalytic amount of lithium bromide (Scheme 55).[116] This reaction is attractive in terms of *N*-allenyl enaminones because of the electrophilic nature of vinyl aldehydes and the possible ring closure that could be effected

[115] Kramer, G.W., Brown, H.C., *J. Organomet. Chem.*, **1977**, *132*, 9-27.

[116] Nijs, R., Verkruijsse, H.D., Harder, S., van der Kerk, A.C.H.T.M., Brandsma, L., *Synth. Commun.*, **1991**, *21*, 653-656.

via nucleophilic conjugate addition of the enaminone functionality. Unfortunately, only starting material was recovered when this reaction was carried out using an *N*-allenyl enaminone (Z = CO_2Et) as the allene substrate.



(i) LiBr (0.1), THF, -15°C, AcOH, 10°C

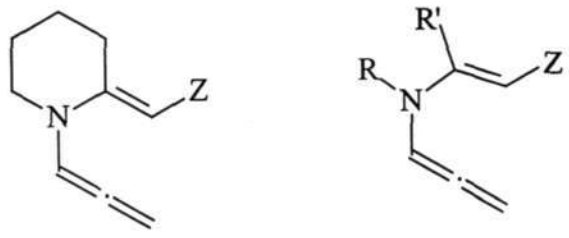
Scheme 55

A reaction that is also commonly employed to functionalise *N*-allenyls is the Diels-Alder reaction.[117] Treatment of an *N*-allenyl enaminone (Z = CO_2Et) with cyclopentadiene afforded no products, however, and starting material was, again, recovered. These unsuccessful results, in combination with mixed fortunes with regard to hydroboration studies, forced us to acknowledge the complex nature of these molecules and the difficulties associated with their handling. Consequently, extending the existing methodology (i.e. formation of *N*-allenyl enaminones) was considered of immediate importance.

[117] a) Bacci, J.P., Greenman, K.L., Van Vranken, D.L., *J. Org. Chem.*, **2003**, *68*, 4955-4958. b) Banert, K., Groth, S., Hückstädt, H., Lehmann, J., Schlott, J., Vrobel, K., *Synthesis*, **2002**, 1423-1433.

8 Preparation of *N*-propargyl enaminones: piperidine and acyclic analogues

The obvious extension of the existing methodology was to prepare piperidine (Figure 19, **A**) and acyclic analogues (Figure 19, **B**).



A **B**

Z = CN, CO_2Et, COPh, NO_2

Figure 19

The prerequisite for the formation of these compounds is the preparation of their *N*-propargyl analogues. Surprisingly, the synthetic route that is used to prepare pyrrolidine *N*-propargyl enaminones (p43) cannot be employed in either of these instances. Although δ-valerolactam is efficiently converted to the required *N*-propargyl compound (79%), subsequent thionation was not realised, even though a number of procedures have been employed to effect this transformation (Scheme 56). All these procedures are variations of phosphorus pentasulphide (P_4S_{10}) protocols since Lawesson's reagent was found to harm the C≡C triple bond. Procedures attempted include P_4S_{10} solubilised by sodium carbonate,[101] P_4S_{10} solubilised by triethylamine,[118] P_4S_{10} in dichloromethane[119] and P_4S_{10} in benzene.[120] In all cases only starting material was recovered and this synthetic sequence was ultimately abandoned.

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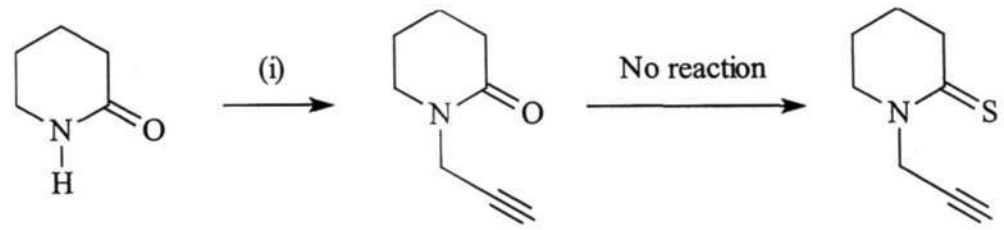
[118] Rao, C.S., Dave, M.P., Mody, P.N., Pandya, A.D., *Indian J. Chem., Sect. B*, **1976**, *14B*, 999-1000.

[119] Heyde, C., Zug, I., Hartmann, H., *Euro. J. Org. Chem.*, **2000**, 3273-3278.

[120] Michael, J.P., Hosken, G.D., Howard, A.S., *Tetrahedron*, **1988**, 44, 3025-3036.



A **B** **C**

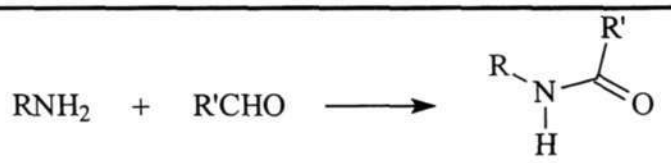
(i) $BrCH_2CCH$, NaH, THF, 0°C to RT, 79%

Scheme 56

Preparation of the acyclic *N*-propargyl analogues was equally unsuccessful. In order to determine the versatility of *N*-allenyl formation in terms of possible substituents, a range of sterically demanding amides were chosen for study. These amides were prepared from the appropriate aldehydes using an elegant free radical process that employs *N*-bromosuccinimide (NBS) and azobisisobutyronitrile (AIBN) to generate an acid bromide *in situ*, followed by treatment with an appropriate amine to afford the amide (Table 4).[121] NBS and AIBN are added to a solution of the aldehyde in carbon tetrachloride and heated under relux until the orange colouration disappears. This duration is different for each aldehyde but is typically about 15 minutes. The mixture is cooled to 0°C and the amine is added thereafter.[121]

[121] Markó, I.E., Mekhalfia, A., ***Tetrahedron Lett.***, **1990**, *31*, 7237-7240.

Table 4: Preparation of secondary amides



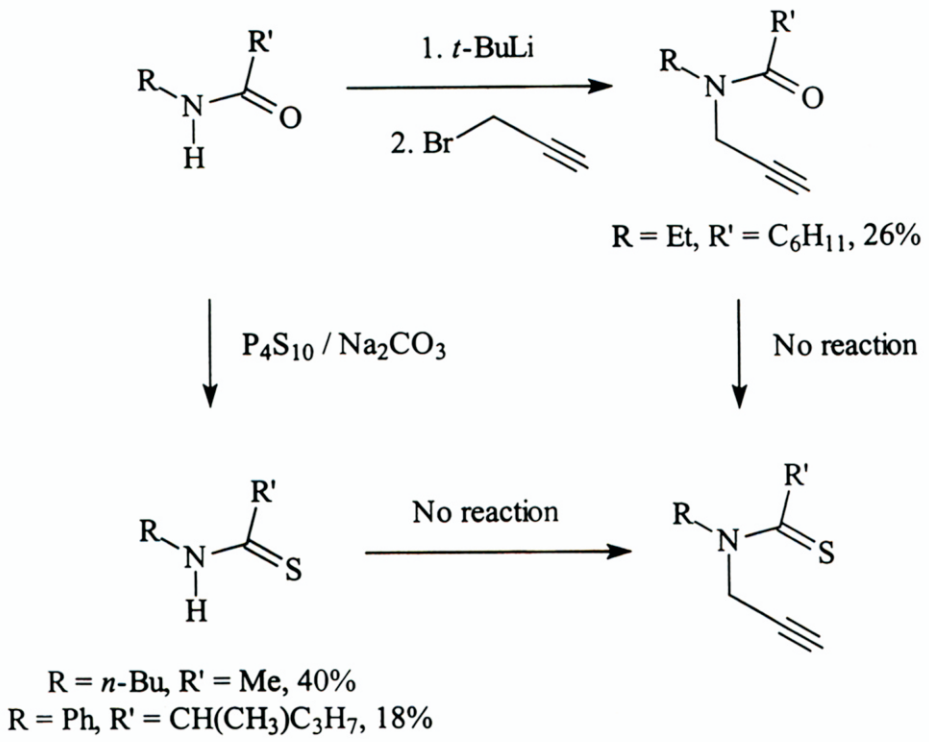
R	R'	Yield / %
t-Bu	C_6H_{11}	37
Et	C_6H_{11}	43
Et	C_6H_{13}	57
Ph	$CH(CH_3)C_3H_7$	19
n-Bu	Me	63*

* Prepared by acetylation of *n*-butylamine

Attempts to *N*-propargylate the amides using propargyl bromide and sodium hydride were unsuccessful, however, employing *tert*-butyllithium[122] as base gave the desired *N*-propargyl adducts albeit in low yield (Scheme 57) (R = Et, R′ = C_6H_{11}, 26%, R = Et, R′ = C_6H_{13}, 34%). These compounds are exceptionally unstable and only one of the two analogues (R = Et, R′ = C_6H_{11}) was fully characterised. Thionation of the *N*-propargyl amides, however, could not be achieved using any of the methods described and this route had to be abandoned.

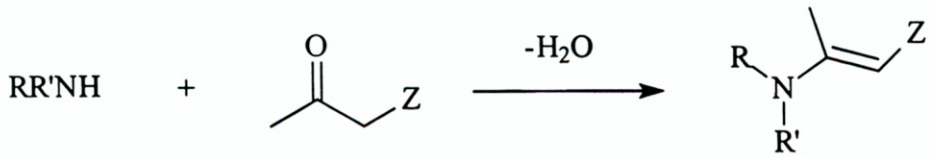
Thionation of the secondary amides, followed by *N*-propargylation is another possible route to the required *N*-propargyl thioamides (Scheme 57). Although thionation was accomplished without complication, subsequent *N*-propargylation proved impossible. No *N*-propargyl product was observed after treatment with *tert*-butyllithium and propargyl bromide but instead the *S*-propargyl analogue was observed by GC-MS. These compounds were extremely unstable and were not isolated. Consequently, this synthetic route to acyclic *N*-propargyl enaminones was abandoned all together.

[122] Beak, P., Lee, B., *J. Org. Chem.*, **1989**, *54*, 458-464.



Scheme 57

An alternate approach to the synthesis of the acyclic analogues is *via* the addition of an appropriate secondary amine to an active methylene compound with concomitant dehydration (Scheme 58).



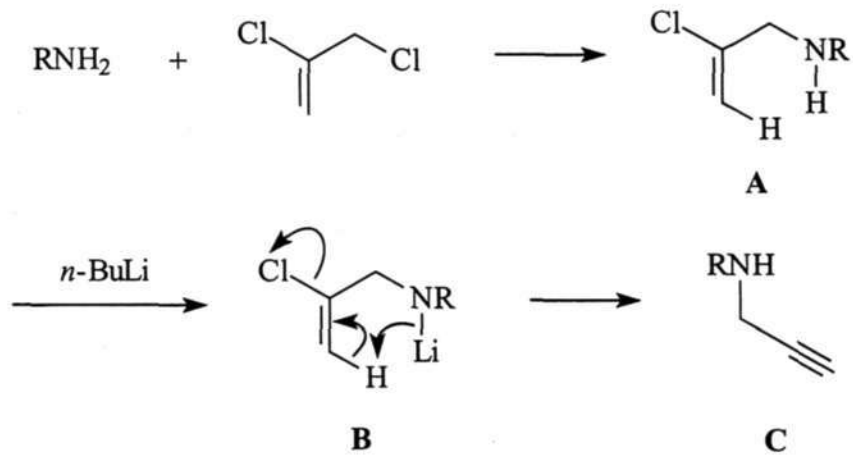
Z = CN, CO_2R', COR', NO_2

Scheme 58

The problem associated with this approach is that of preparation of the desired secondary propargyl amine. Preparation of secondary amines is a difficult synthetic operation in itself and a great deal of research has been devoted to this subject alone.[123] The additional problems due to incorporation of the reactive C≡C triple bond make this an even tougher

[123] Salvatore, R.N., Yoon, C.H., Jung, K.W., *Tetrahedron*, **2001**, *57*, 7785-7811.

task. One such method for preparing the required amines has been reported as a side reaction during a study of β-substituted organolithium compounds.[124] The preparation involves treatment of an *N*-alkyl 2-chloroallylamine (Scheme 59, **A**) with *n*-butyllithium at –80°C. The resultant lithioamide (Scheme 59, **B**) eliminates lithium chloride to afford the secondary *N*-alkyl propargylamine (Scheme 59, **C**). This route to *N*-propargyl enaminones was investigated through the preparation of *N*-methyl, *N*-isopropyl and *N*-butyl propargylamines. However, the results obtained were not satisfactory from a number of standpoints; only aliphatic substituents are tolerated, excluding aromatic groups from further study, and due to the cost of the reagents involved, only small amounts of the desired compounds were produced. This, coupled with their volatility and high reactivity, made handling and purification complicated. As a result, this strategy was abandoned in order to investigate a general cost-effective synthetic route.



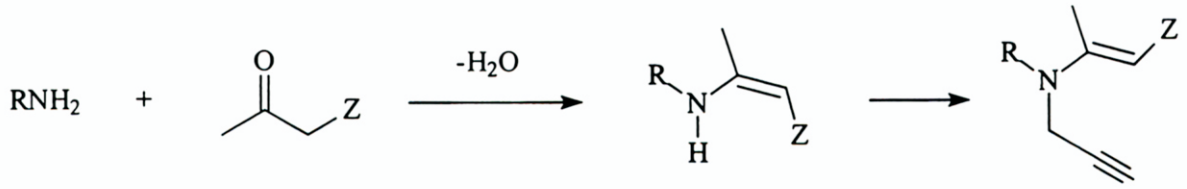
Scheme 59

[124] a) Barluenga, J., Canteli, R.-M., Flórez, J., *J. Org. Chem.*, **1996**, *61*, 3646-3649. b) Barluenga, J., Canteli, R.-M., Flórez, J., *J. Org. Chem.*, **1994**, *59*, 602-606. c) Barluenga, J, Foubelo, F., Fañanás, F.J., Yus, M., *J. Chem. Soc., Perkin Trans. 1*, **1989**, 553-557.

9 Preparation of functionalised pyrroles

9.1 Preparation of secondary enaminones

Another possible synthetic strategy, comparable to that described above, is *N*-propargylation of secondary enaminones (Scheme 60).



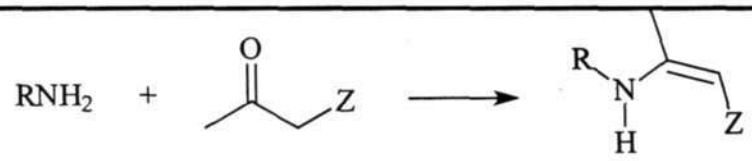
Z = CN, CO_2R', COR', NO_2

Scheme 60

Secondary enaminones can be rapidly prepared from the appropriate amine and β-dicarbonyl compounds using microwave irradiation (Table 5).[125] The experimental procedure is straightforward; the amine and β-dicarbonyl compound are mixed and poured onto a bed of silica gel (3 g of silica per 10 mmol of β-dicarbonyl compound) in a small beaker. The mixture is irradiated for 3 minutes, extracted and filtered to afford the enaminones without further purification. The original procedure calls for a catalytic amount of *p*-toluenesulfonic acid (PTSA) to be present, however, this was found to be unnecessary. Yields of all reactions are good bar those that incorporate the bulky *tert*-butylamine. The secondary enaminones are reported to possess a *Z*-configuration due to hydrogen bonding.[125] This has been confirmed by NOE experiments.

[125] Rechsteiner, B., Texier-Boullet, F., Hamelin, J., *Tetrahedron Lett.*, **1993**, *34*, 5071-5074.

Table 5: Preparation of secondary vinylogous amides and carbamates



R	Z	Yield / %	R	Z	Yield / %
Me	COMe	80	Me	CO_2Et	82
n-Bu	COMe	76	*n*-Bu	CO_2Et	70
C_6H_{11}	COMe	88	C_6H_{11}	CO_2Et	76
t-Bu	COMe	6	*t*-Bu	CO_2Et	0
Bn	COMe	95	Bn	CO_2Et	97
Ph	COMe	94	Ph	CO_2Et	70

9.2 Microwave-assisted synthesis

Note: At this point it is appropriate to elaborate on microwave-assisted synthesis, a practice that is becoming more and more prevalent in organic research.[126] In terms of the electromagnetic spectrum, microwaves are located at a frequency of 0.3-300 GHz (1 mm – 1 m). Most of these frequencies are used for telecommunications and, therefore, industrial and domestic applications employ microwaves with a frequency of 2.450 (± 0.050) GHz (12.2 cm).[126a] Although microwaves have been used to heat food for the past 50 years, their application in organic synthesis has only received interest since the mid-1980s.[126a] This increased interest has been attributed to the availability of commercial microwave ovens and improved safety aspects. The obvious advantage of microwave heating over traditional methods is the dramatic reduction in reaction times, however, the direct and uniform heating of the sample, leading to fewer by-products and reduced decomposition, is another major advantage that should not be overlooked.[126a] The theory of microwave dielectric heating is complex and an overview of this subject is not appropriate in the current context.

This technique has been employed wherever possible and many hours of reaction time have been saved in this fashion. Some applications have been successful, others less so,

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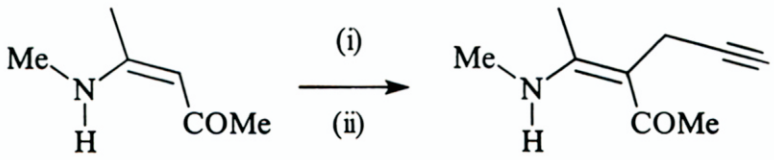
[126] a) Lidström, P., Tierney, J., Wathey, B., Westman, J., *Tetrahedron*, **2001**, *57*, 9225-9283. b) Caddick, S., *Tetrahedron*, **1995**, *51*, 10403-10432.

however, all are discussed in the relevant sections of the text. Although most have literature precedents, fine-tuning of the procedures has always been necessary due to the inconsistencies associated with domestic microwave ovens.

9.3 *C*-Propargylation and ambident nucleophilicity

Some remarkable results have been achieved during the attempts to *N*-propargylate secondary enaminones and these are presented below. *N*-Propargylation was firstly attempted *via* abstraction of the amino proton with sodium hydride, followed by nucleophilic addition to propargyl bromide. This sequence did not afford the desired product but rather the isomeric *C*-propargylated product (~50% yield by ^{1}H NMR) (Scheme 61). Similar results were obtained when using sodium hydride or *n*-butyllithium as base. These interesting compounds form the basis of a discussion in future parts of the text (p86) and their formation and properties will be examined therein.



(i) NaH, THF, 0°C (ii) $BrCH_2CCH$, RT

Scheme 61

The preference of *C*-propargylation over *N*-propargylation is not surprising, as enamines and related compounds are known to be ambident nucleophiles (Figure 20). [127] Ambident nucleophilicity is displayed by species for which different canonical forms can be drawn, with each form containing an atom with an unshared pair of electrons.[127]

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[127] March, J., *Advanced Organic Chemistry*, Wiley-Interscience, New York, 4th Edition, pp 365-368.

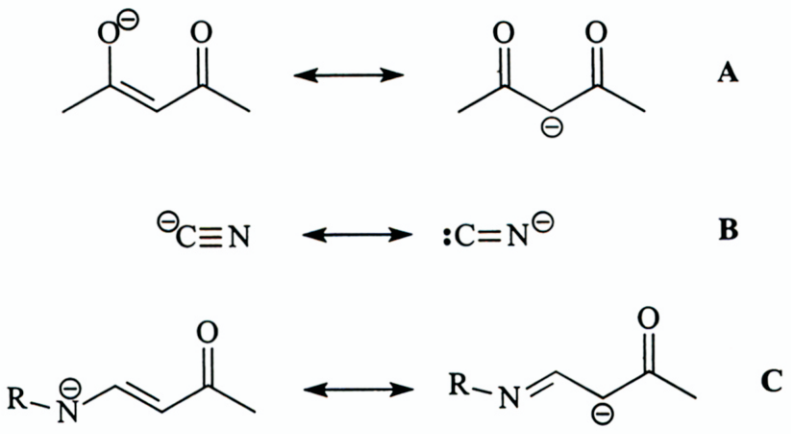

Figure 20

The observed regioselectivity of these reactions can be rationalised using the theory of hard and soft acids and bases (HSAB).[127] The theory states that hard acids prefer to react with hard bases and soft acids prefer to react with soft bases; furthermore, the harder an electrophile is, the more likely it is to react with the harder, more electronegative atom of an ambident nucleophile.[127] This principle has been explained in terms of the character of the transition state by Kornblum *et al.*; 'The greater the S_N1 character of the transition state the greater is the preference for covalency formation with the atom of higher electronegativity and, conversely, the greater the S_N2 contribution to the transition state the greater the preference for bond formation to the atom of lower electronegativity.'[128] This dual reactivity has been observed for the reaction of alkyl halides with silver cyanide (AgCN) and sodium cyanide (NaCN).[129] The reaction with AgCN produces isocyanides (Scheme 62, **A**) while the reaction with NaCN produces cyanides (Scheme 62, **B**).[129] The unexpected reactivity of AgCN has been attributed to interaction of the halide and the silver ion, increasing the lability of the halide and producing an 'S_N1-like' transition state. This results in attack by the more electronegative nitrogen atom and produces an isocyanide.[129]

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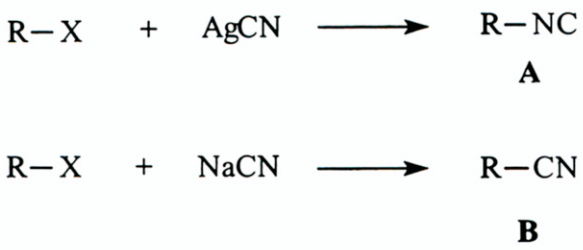
[128] Kornblum, N., Smiley, R.A., Blackwood, R.K., Iffland, D.C., *J. Am. Chem. Soc.*, **1955**, *77*, 6269-6280.

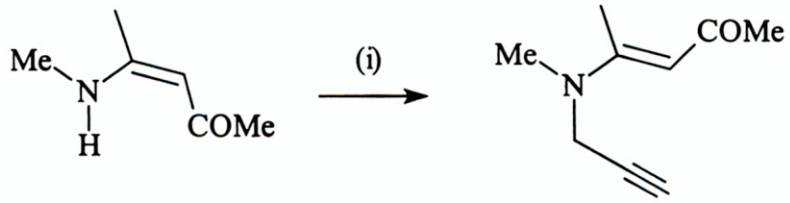
[129] Austad, T., Songstad, J., Stangeland, L.J., *Acta Chem. Scan.*, **1971**, *25*, 2327-2336.



Scheme 62

9.4 Preparation of pyrroles: originally identified as vinylogous ynamides

It was believed that the same bias introduced by the silver ion could be used to control the reactivity of secondary enaminones. Hence, a mixture of a secondary enaminone and propargyl bromide in acetonitrile was treated with a molar equivalent of silver nitrate in a second attempt to induce reaction *via* the more electronegative nitrogen atom (Scheme 63). The mixture was stirred overnight after which the organic layer was washed with sodium iodide solution to precipitate any residual silver(I). Acetonitrile was chosen as solvent due to its ability to solubilise silver nitrate.

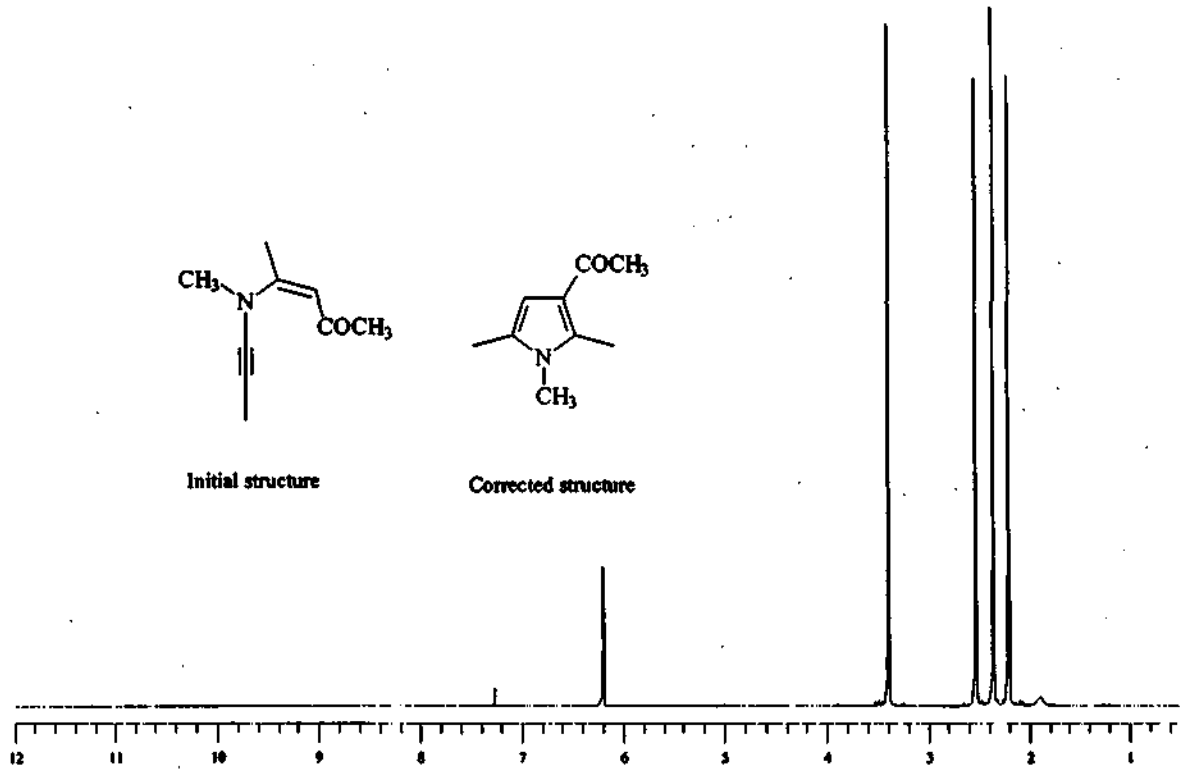


(i) $BrCH_2CCH$, $AgNO_3$, CH_3CN, RT

Scheme 63

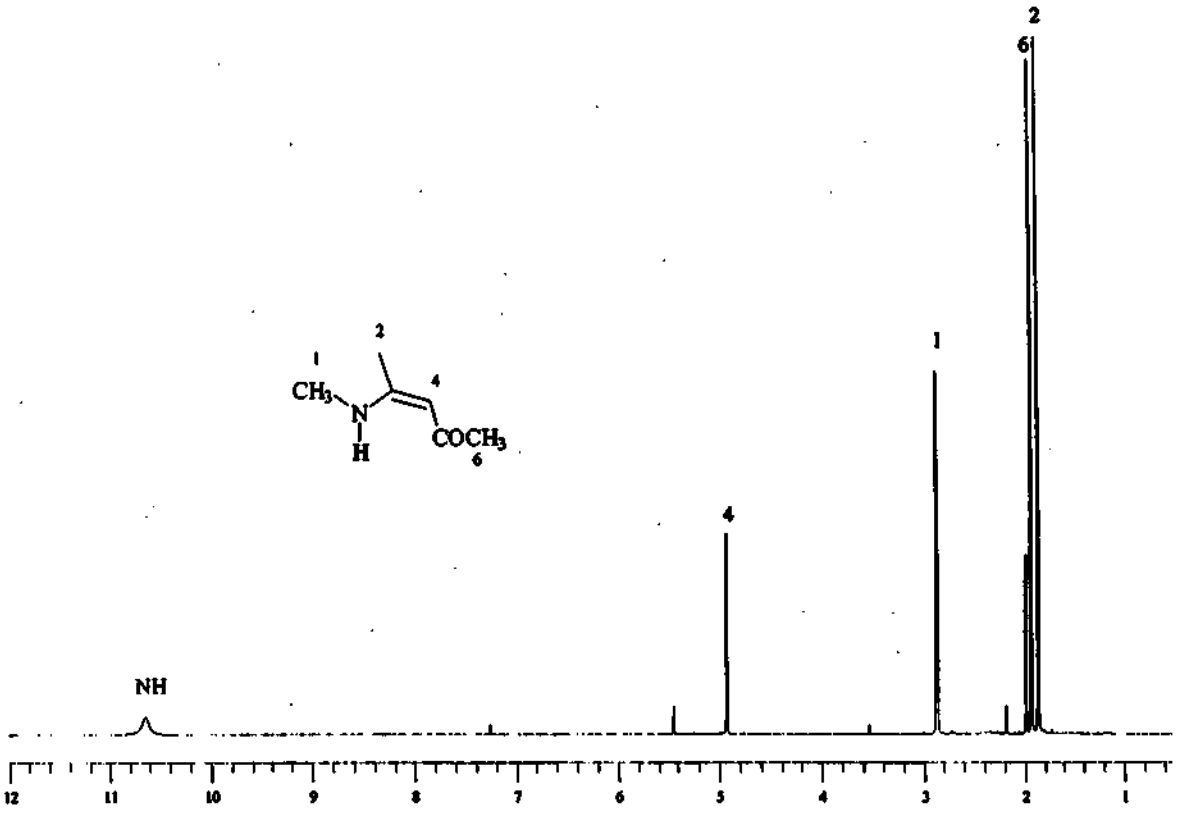
It was immediately apparent from T.L.C. analysis that a reaction had occurred and GC-MS analysis showed the crude product to be exceptionally clean with the major compound having a molar mass of 151, corresponding to the addition of three carbon atoms, and matching the molecular mass of the desired *N*-propargyl enaminone. However, chromatography afforded a clean product that was immediately identified by ^1H NMR as neither the desired *N*-propargyl compound nor the previously prepared *C*-propargyl compound (Spectrum 3). This was evident from the absence of the typical splitting pattern

(doublet and triplet $J \approx 2.5$ Hz) corresponding to the methylene and methine protons of the propargyl group.



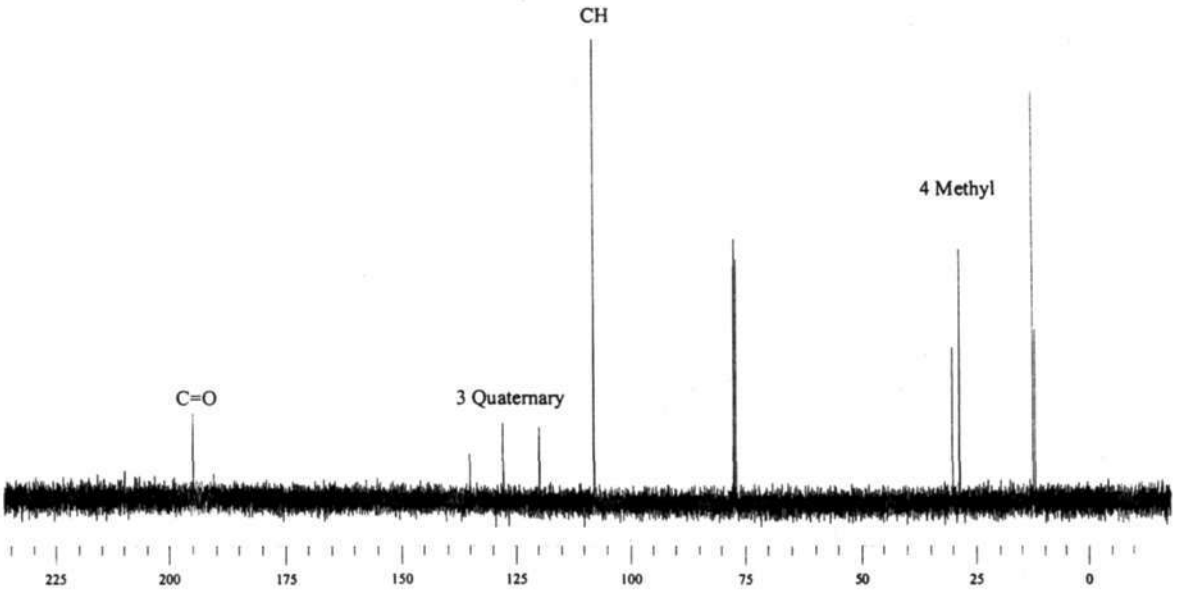
Spectrum 3

When comparing the ^{1}H NMR spectrum of the product (Spectrum 3) to that of the starting material (Spectrum 4), two features are immediately apparent; the disappearance of the amino proton (10.65 ppm) and the appearance of a fourth methyl signal. The absence of the amino proton is confirmed by the change in the splitting pattern of the *N*-methyl signal from a doublet to a singlet. The remaining signals, a methine singlet and three methyl signals, appear to be unchanged bar a slight shift downfield.



Spectrum 4

It was concluded that the enaminone functionality had not been altered during the reaction and the only modification to the molecule was further substitution on the nitrogen atom. This *N*-substituent must be comprised of three carbon atoms, a methyl group (mass = 15) and two quaternary carbon atoms (mass = 24), evident from the difference in mass of the product and starting material (151 – 113 + H = 39). These conclusions were reinforced by the presence of two new quaternary carbons in the ^{13}C NMR spectrum of the product (Spectrum 5).



Spectrum 5

Although this was, in hindsight, a hasty assignment, these conclusions led us to identify the product as a vinylogous ynamide (Scheme 64).[130] Ynamides and ynamines (N-C≡C-R) are an interesting class of compounds that show remarkable similarities to allenamines (p1) and have been the subject of a large amount of research.[131] Vinylogous ynamides show similar attributes to *N*-allenyl enaminones in terms of versatility and, therefore, a range of compounds was prepared with the intent of investigating their potential as general synthetic precursors.

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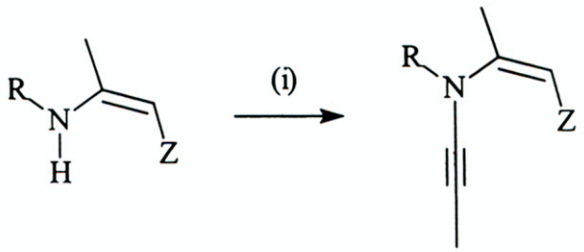
[130] Gravestock, D.; Dovey, M.C. *Synthesis* **2003**, 523-530.

[131] a) Zificsak, C.A., Mulder, J.A., Hsung, R.P., Rameshkumar, C., Wei, L.-L., *Tetrahedron*, **2001**, *57*, 7575-7606. b) Ficini, J., *Tetrahedron*, **1976**, *32*, 1449-1486. c) Viehe, H.G., *Angew. Chem. Int. Ed.*, **1967**, *6*, 767-778.



A

(i) $BrCH_2CCH$, $AgNO_3$, CH_3CN, RT

Z = COMe, CO_2Et
R = Me, Bu, Cy, Bn, Ph

Scheme 64

Some preliminary investigation into the behaviour of vinylogous ynamides showed their reactivity to be unpredictable and questions arose as to their electronic character. Fortunately, one of the compounds prepared is solid at room temperature and a suitable crystal was obtained for a single-crystal X-ray diffraction study. The structure determined in this fashion was a surprise and showed the prepared compound to be a pyrrole and not a vinylogous ynamide as originally thought (Figure 21).[132]

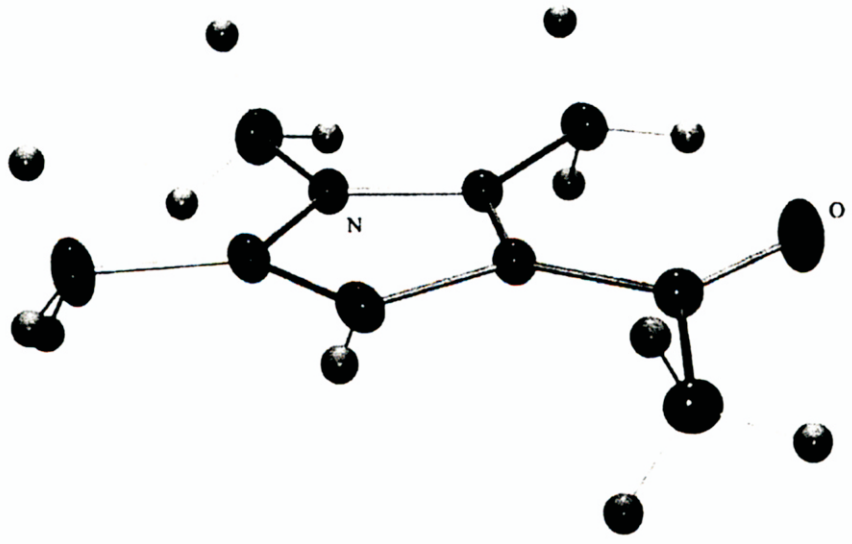
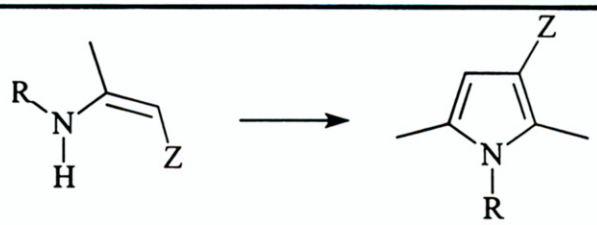


Figure 21

[132] Gravestock, D., Dovey, M.C., *Synthesis*, **2003**, 1470. (Correction)

The observations that had been made up to this point, and the anomalies that had arisen, could now be explained in a trivial manner. Although, spectral assignments were changed accordingly, experimental results are still applicable and are tabulated below (Table 6).

Table 6: Preparation of functionalised pyrroles



R	Z	Yield / %	R	Z	Yield / %
Me	COMe	32	Me	CO_2Et	21
n-Bu	COMe	24	*n*-Bu	CO_2Et	24
C_6H_{11}	COMe	25	C_6H_{11}	CO_2Et	24
Bn	COMe	21	Bn	CO_2Et	14*
Ph	COMe	7*	Ph	CO_2Et	trace

* Product present as an inseparable mixture of SM and product. Yield from ^1H NMR.

In spite of the misassignment discussed above, a novel route to functionalised pyrroles has been discovered and, although it is low yielding, the reaction must operate by an interesting mechanism when one takes into account the number of changes occurring at the molecular level. This is apparent from the fact that two new C-C bonds are formed in one-pot and more significantly because the substrates are not compatible for this type of reaction i.e. secondary enaminones have two nucleophilic sites whereas propargyl bromide has only one electrophilic site.

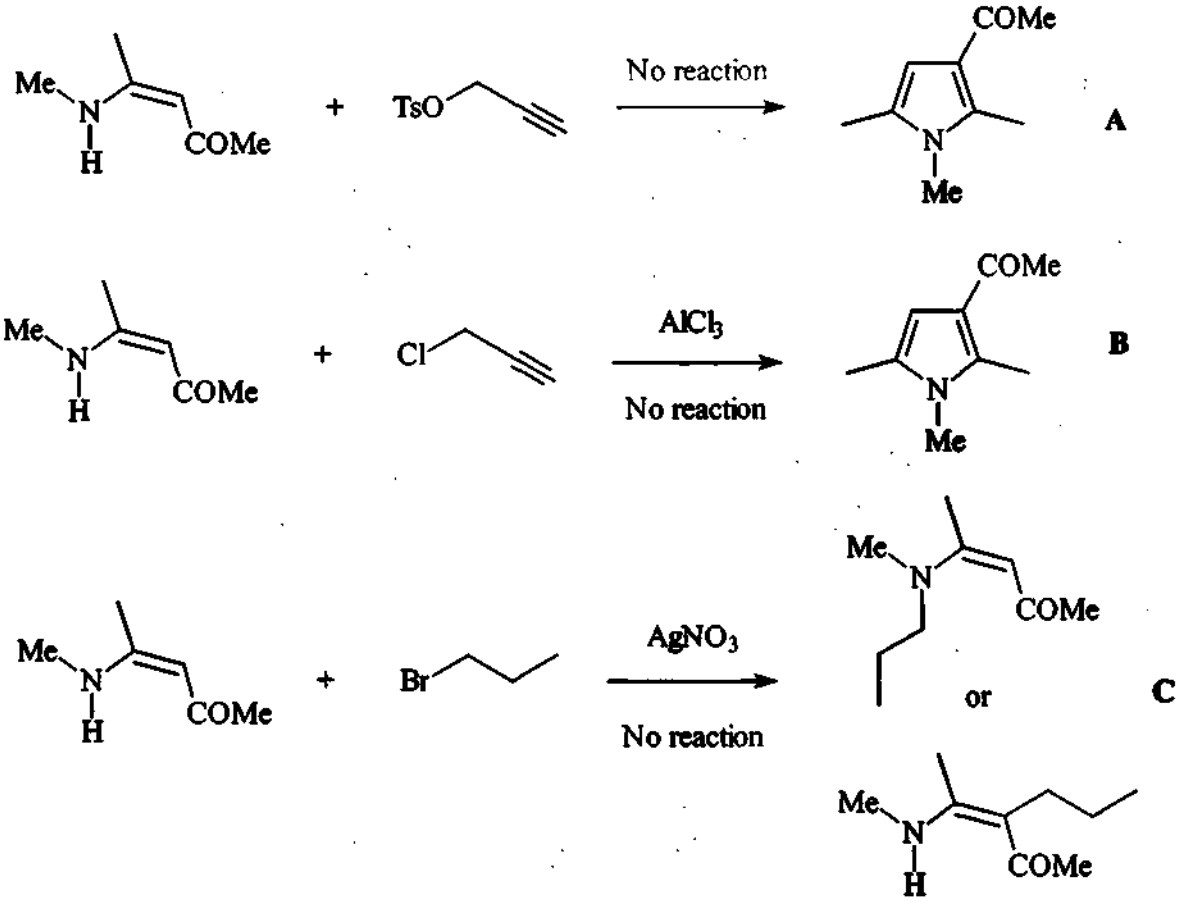
10 Mechanistic investigations of pyrrole formation

The fundamental question regarding this reaction's mechanism is that of the role of silver nitrate seeing that the presence of silver(I) is required for the outcome of the reaction. The intended role of the silver(I) was to interact with the bromide, creating a better leaving group, and making the carbon to which it is attached a harder electrophilic centre. The extent of this interaction and the degree of the carbon atom's cationic character is not apparent.

10.1 Interaction between silver(I) and bromide

When propargyl bromide is added to a solution of silver nitrate in acetonitrile, a yellow precipitate of silver bromide is observed. The same yellow precipitate is observed when *n*-propyl bromide is used as the bromide source. This suggests that silver(I) actually abstracts the bromide ion from alkyl bromides, producing a cationic spiecies whose lifetime would be dependent on a number of factors. Whether this cation formation is significant in the presence of a nucleophilic species is hard to predict.

Three simple reactions were carried out in order to determine whether the silver-hailde interaction is a determining factor in terms of pyrrole formation (Scheme 65).



Scheme 65

The addition of organometallic reagents to propargyl derivatives containing a good leaving group is a common method employed to prepare substituted allenes (Scheme 66).[133] In order to investigate the possibility that silver(I) forms a better leaving group through interaction with the bromide, a secondary enaminone was treated with propargyl tosylate (Scheme 65, **A**). No reaction was observed and this confirms that a good leaving group is not the only requirement for pyrrole formation.

X = good leaving group

Scheme 66

[133] a) Aidhen, I.S., Braslau, R., *Synth. Commun.*, **1994**, *24*, 789-797. b) Alexakis, A., Marek, I., Mangeney, P., Normant, J.F., *J. Am. Chem. Soc.*, **1990**, *112*, 8042-8047.

In the second reaction, a secondary enaminone was treated with propargyl chloride and aluminium trichloride ($AlCl_3$) using typical Friedel-Crafts conditions (Scheme 65, **B**). It was hoped that these conditions would simulate the production of an alkynyl cationic species. These cations have been studied extensively by Olah and co-workers using ^{13}C NMR spectroscopy who have shown that the positive charge is extensively delocalised, indicating a large contribution from the mesomeric allenyl form to the overall structure.[134] Again no reaction is observed with the secondary enaminone, indicating that a cationic species does not bring about a reaction and cannot be significant in pyrrole formation.

As additional confirmation, a third reaction was carried out in which a mixture of a secondary enaminone and *n*-propyl bromide was treated with silver nitrate. No reaction was observed, further indicating that secondary enaminones do not react with cationic species under the employed reaction conditions.

These results indicate that interaction between silver(I) and the bromide is not sufficient to bring about the reaction (or reactions) necessary for pyrrole formation. This is not surprising as any reaction brought about by this type of interaction would result in the formation of either an allenyl or propargyl species, both of which are nucleophilic and incapable of undergoing a reaction with the remaining nucleophilic component of the enaminone.

10.2 Interaction between silver(I) and C≡C triple bond

On the other hand, silver(I) is well known to form π-complexes with C≡C triple bonds.[135] In complexes of this nature there are two bonds between the metal and the multiple bond, a σ bond formed between the filled π orbital of the multiple bond and the empty 5*s* orbital of the silver ion, and a π bond between the filled 4*d* orbital of the silver ion and the empty π* orbital of the multiple bond.[136] This complexation shifts electron density away from the

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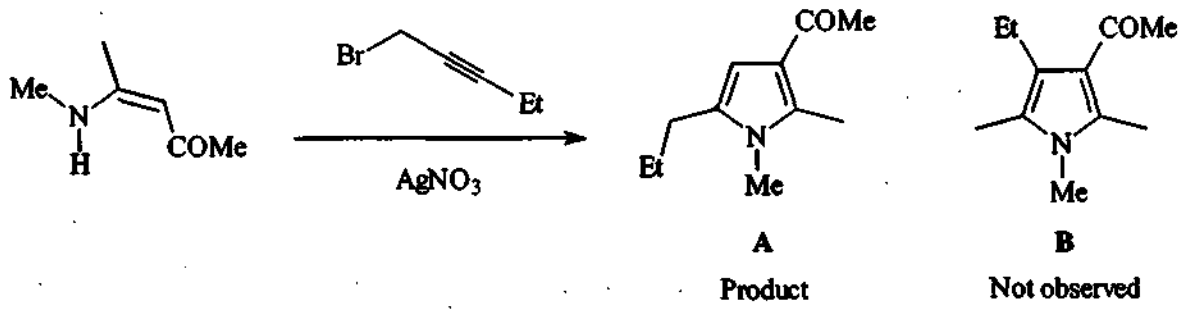
[134] Olah, G.A., Spear, R.J., Westerman, P.W., Denis, J.-M., *J. Am. Chem. Soc.*, 1974, 98, 5855-5859.

[135] a) Lewandos, G.S., Maki, J.W., Ginnebaugh, J.P., *Organometallics*, **1982**, *1*, 1700-1705. b) Lewandos, G.S., *Tetrahedron Lett.*, **1978**, *19*, 2279-2282.

[136] March, J., *Advanced Organic Chemistry*, Wiley-Interscience, New York, 4th Edition, pp 79-80.

C≡C triple bond, allowing attack at either of the carbon atoms by oxygen, sulphur, selenium, phosphorus and nitrogen nucleophiles.[137]

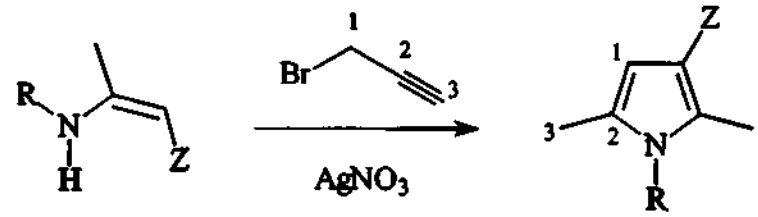
This π-coordination is a very plausible scenario in terms of pyrrole formation as it results in umpolung of the C≡C triple bond, generating an electrophilic centre. However, the question of which atom of the enaminone (N or C) attacks the C≡C triple bond was still unanswered. A simple experiment was carried out to answer this question and determine which of the original carbon atoms of propargyl bromide is incorporated into the ring and which is exocyclic (Scheme 67).



A Product **B** Not observed

Scheme 67

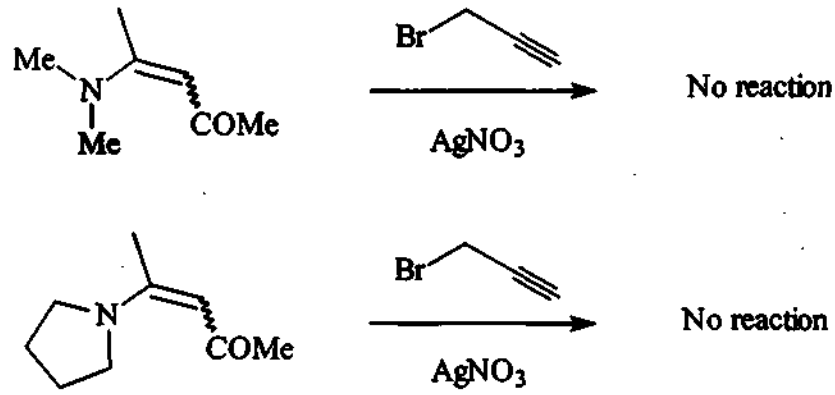
A secondary enaminone was treated with silver nitrate and 1-bromopent-2-yne using standard conditions and afforded an α-propyl substituted pyrrole (Scheme 67, **A**) (13%) as the single product. This indicates that the nitrogen atom of the original enaminone becomes bonded to the internal carbon of the C≡C triple bond and that the new C-C bond is formed between the β-carbon of the enaminone and the carbon of propargyl bromide that previously bore the bromide (Scheme 68).



Scheme 68

[137] Alonso, F., Beletskaya, I.P., Yus, M., *Chem Rev.*, **2004**, *104*, 3079-3159.

This evidence indicates that the amine nitrogen of the enaminone attacks the silver-coordinated C≡C triple bond of propargyl bromide, a reaction commonly known as hydroamination, and a very topical subject of current organic, organometallic and catalysis research. This subject has been covered in more detail in the 'Introduction' (p9). A second experiment, employing tertiary enaminones, was conducted in order to determine whether hydroamination is the initial reaction or is rather the ring-closing step (Scheme 69).

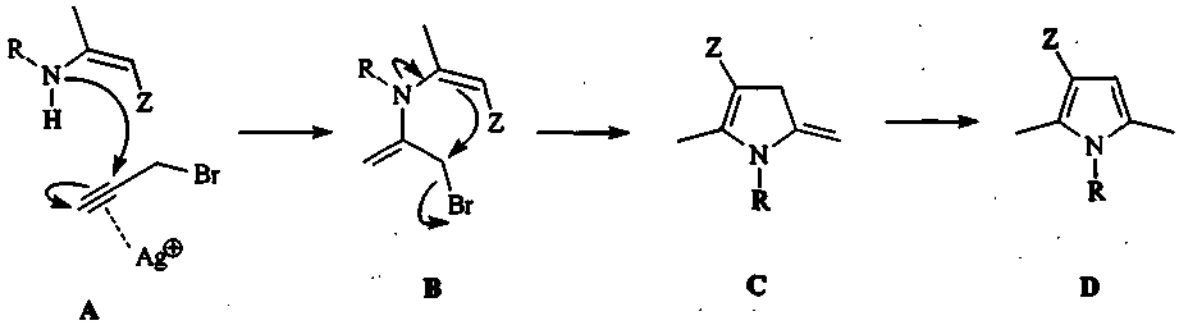


Scheme 69

Tertiary enaminones were treated with propargyl bromide and silver nitrate under normal reaction conditions, however, neither experiment showed any consumption of the tertiary enaminone. This indicates that hydroamination is the initial step of pyrrole formation and, in conjunction with other evidence described above, allows the following mechanism to be proposed (Scheme 70).

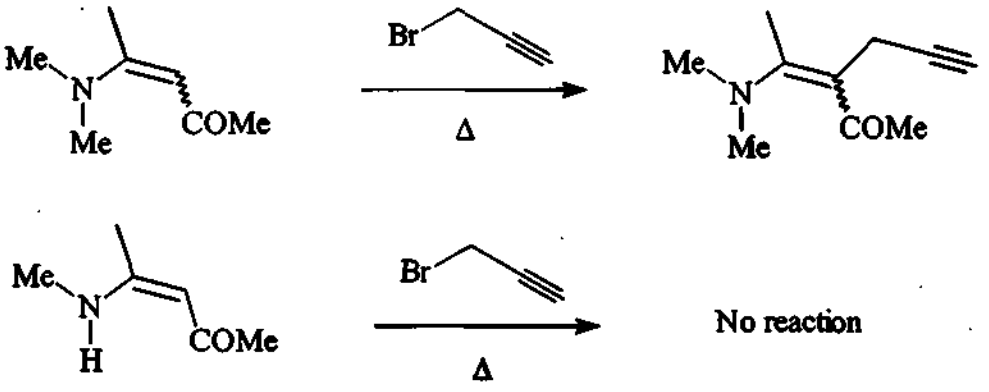
10.3 Mechanistic proposal

Coordination between the silver ion and the C≡C triple bond of propargyl bromide facilitates hydroamination (Scheme 70, **A**) and gives rise to a bromo methylvinylenamine (Scheme 70, **B**). The enamine, also a tertiary enaminone, undergoes an intramolecular cyclisation to afford an exocyclic enamine (Scheme 70, **C**). Rearrangement of the cyclic enamine *via* a 1,3-hydrogen shift affords the thermodynamically more stable pyrrole (Scheme 70, **D**).



Scheme 70

The question of how intramolecular cyclisation occurs is not certain. We have shown that tertiary enaminones are far more reactive than secondary analogues; this is evident from a set of experiments in which a tertiary and a secondary enaminone were treated with propargyl bromide and heated under reflux in acetonitrile (Scheme 71). The tertiary enaminone was converted, almost quantitatively, to the corresponding *C*-propargyl compound, however, no reaction was observed with the secondary enaminone, even after prolonged heating.



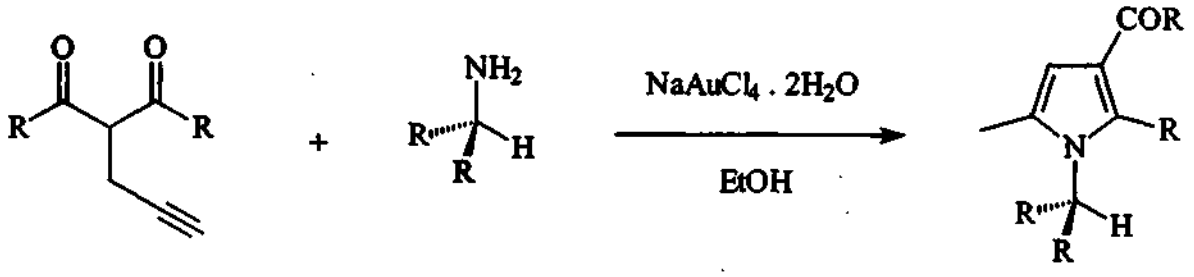
Scheme 71

It has been suggested that the tertiary enaminone formed after hydroamination (Scheme 70, **B**) is reactive enough to undergo an intramolecular S_N2 reaction without external heating. Although this scenario is plausible, it should be noted that no intermolecular S_N2 reaction is observed between tertiary enaminones and propargyl bromide at room temperature (Scheme 69). This contradiction could be challenged on entropic grounds. Another possibility is that silver(I) aids in the removal of the bromide as a leaving group and the driving force for the cyclisation is the formation of silver bromide. This proposition is also

contradicted by the intermolecular reactions described above (Scheme 69) but this could, again, be challenged on entropic grounds. The exact reason for the cyclisation is not apparent and could be a combination of the effects discussed above, nonetheless, the cyclisation is essential for pyrrole formation and the proposed mechanism is a viable one.

10.4 Optimisation of reaction conditions

Although this route to pyrroles is novel and interesting, it is low yielding and the reasons for this are not immediately obvious. It is believed that there are simply too many potential reaction pathways subsequent to hydroamination and formation of the bromo methylvinylenamine intermediate (Scheme 70, **B**). Therefore, the intramolecular cyclisation, or more specifically the new C-C bond formation, is the limiting step in the synthesis. This is underlined by a recent publication in which a similar method is employed to prepare homochiral pyrroles (Scheme 72).[138] In this method the equivalent C-C bond is formed in the first part of the synthesis by reaction of the appropriate β-dicarbonyl compound with propargyl bromide in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[138] This propargyl compound is then treated with an amine to produce a secondary enaminone, and cyclised *via* a gold-mediated hydroamination to afford functionalised pyrroles.[138] The overall yields for this procedure are excellent and highlight the importance of efficient C-C bond formation.



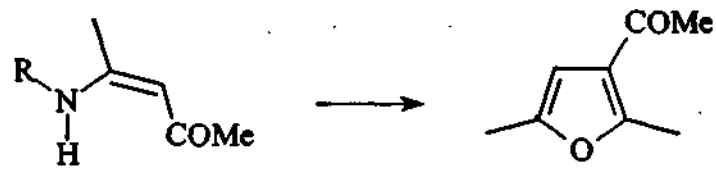
Scheme 72

In the silver-mediated preparation of pyrroles, strange observations are made during work-up; the crude products are normally very clean and further purification is not always necessary, therefore, the calculated yields would indicate a significant mass loss during the course of the reaction. The source of this mass loss has not been determined but suffice to

[138] Arcadi, A., Di Giuseppe, S., Marinelli, F., Rossi, E., *Tetrahedron: Asymmetry*, **2001**, *12*, 2715-2720.

say, it is most likely due to the formation of volatile amines. This has been concluded from comparisons between mass-recoveries for secondary enaminones with large *N*-substituents and those with small *N*-substituents. For example, in a typical experiment, a crude product from the reaction of 200 mg of an *N*-benzyl enaminone has a mass of 240-250 mg, whereas that from 200 mg of an *N*-methyl enaminone has a mass of 70-80 mg. The yields of pyrrole after purification are similar.

An interesting by-product has been isolated during these mechanistic studies and its structure lends support to the argument for the formation of volatile amines. A substituted furan has been isolated during the preparation of *N*-methyl and *N*-benzyl enaminone analogues (Scheme 73). Compounds of this type have been prepared in a similar manner to the homochiral pyrroles described above and the procedure differs only in terms of the starting material; in the case of furan preparation, β-dicarbonyl compounds are used instead of secondary enaminones. [139]



R = Me (8%), Bn (11%)

Scheme 73

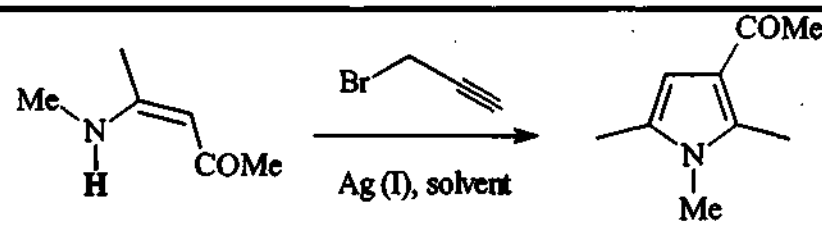
The isolation of furans during silver-mediated pyrrole formation should, therefore, be due to hydrolysis of the secondary enaminone, reforming the amine and the β-dicarbonyl compound from which it is derived. The β-dicarbonyl compound could then attack the C≡C triple bond and cyclise in a similar fashion to that proposed above. Hydrolysis was originally believed to be due to the presence of water in the solvent, acetonitrile, however, it has been shown that pyrrole formation proceeds cleanly in aqueous media (H_2O / MeOH). This suggests that an alternative mechanism of 'hydrolysis' is in operation. How this comes about is not certain and reference to this type of reaction has not been found in

[139] Arcadi, A., Cerichelli, G., Chiarini, M. Di Guiseppe, S., Marinelli, F., *Tetrahedron Lett.*, **2000**, *41*, 9195-9198.

the literature. Nevertheless, formation of a β-dicarbonyl compound from a secondary enaminone must result in formation of the amine from which it was derived and this could explain the significant mass loss observed for reactions involving enaminones with small *N*-alkyl substituents and could account for the low yields observed.

Routine optimisation studies were conducted in order to determine the experimental factors that influence the reaction. A number of silver salt-solvent combinations were employed while other parameters were kept constant; the results are tabulated below (Table 7).

Table 7: Silver salt-solvent dependencies.



Ag (I)	Solvent	Result
$AgNO_3$	CH_3CN	32% yield
$AgClO_4$	CH_3CN	23% yield
Ag_2CO_3	CH_3CN	Trace. Ag_2CO_3 sparingly soluble.
$AgClO_4$	THF	No reaction. $AgClO_4$ is soluble.
$AgNO_3$	THF	No reaction. $AgNO_3$ insoluble.
$AgNO_3$	$CHCl_3$	No reaction. $AgNO_3$ insoluble.
$AgNO_3$	DMF	30% yield
$AgNO_3$	CH_3OH / water (1:1)	18% yield. Reaction incomplete.

The results of the reactions carried out in acetonitrile show that the reaction is not dependent on the silver(I) counterion provided that the salt is soluble. Even the reaction employing silver carbonate, which is sparingly soluble in acetonitrile, affords the desired pyrrole, although in trace quantity. The presence of the pyrrole was determined from crude ^1H NMR and GC-MS spectra. On the other hand, the reaction is very dependent on the nature of the solvent. The reaction employing silver perchlorate in THF shows that although the salt is soluble, the solvent is not suitable and no reaction is observed. It is remarkable that the reaction even proceeds, although more slowly, in aqueous media. In conclusion, the reaction appears to require either protic or aprotic polar solvents and is

independent of the nature of the silver salt provided that it is soluble in the reaction medium. Ironically, the most efficient of the silver salt-solvent combinations employed was the original silver nitrate-acetonitrile combination.

Temperature studies have shown that the yields of the desired pyrrole were comparable for reactions conducted at 0°C or in refluxing acetonitrile. The yield obtained from the reaction carried out in refluxing DMF was also similar to the same reaction at room temperature, however, some decomposition products were noted.

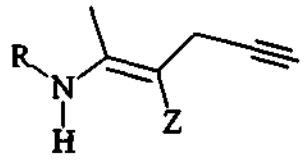
The addition of base to the reaction mixture gave strange results. No reaction was observed if one equivalent of an organic base was added; this was observed for triethylamine and 1,4-diazabicyclo[2.2.2]octane (DABCO), both non-nucleophilic bases. In contrast, the addition of an inorganic base (potassium carbonate) only slowed the reaction without affecting the overall yield. These observations may be due to a solubility issue but are more likely to be due to some interaction between the base and the enaminone that prevents hydroamination. This precludes the use of co-solvents such as tetramethylethylenediamine (TMEDA). Competitive attack of the C≡C triple bond is improbable. The addition of acid (trifluoroacetic acid) to the reaction medium did not affect the overall yield, although some decomposition products were noted.

Varying stoichiometric ratios also had little affect on the reaction provided that at least one molar equivalent of silver nitrate and propargyl bromide were present. Employing 0.2 molar equivalents of silver nitrate resulted in an incomplete reaction and indicates that the reaction is not catalytic. Employing excesses of the reagents provided no significant increase in yields. The use of propargyl chloride, unsurprisingly, gave rise to a slower reaction and a lower yield.

From these results, it is clear that the reaction is a complex and, perhaps, an inefficient one, however, silver-mediated hydroamination is an exciting prospect and further efforts were aimed at investigating this methodology.

11 Silver-catalysed pyrrole formation *via* intramolecular hydroamination

To re-emphasise, intramolecular cyclisation and more specifically the formation of the new C-C bond, is the limiting step in silver-mediated pyrrole formation. Therefore, an efficient means of forming this bond was sought in order to optimise the procedure. As a result, *C*-propargyl enaminones (Figure 22), compounds that were inadvertently prepared in an earlier study (p68), became immediate synthetic targets. The intention was to prepare these compounds and then to effect cyclisation *via* a silver-mediated intramolecular hydroamination.

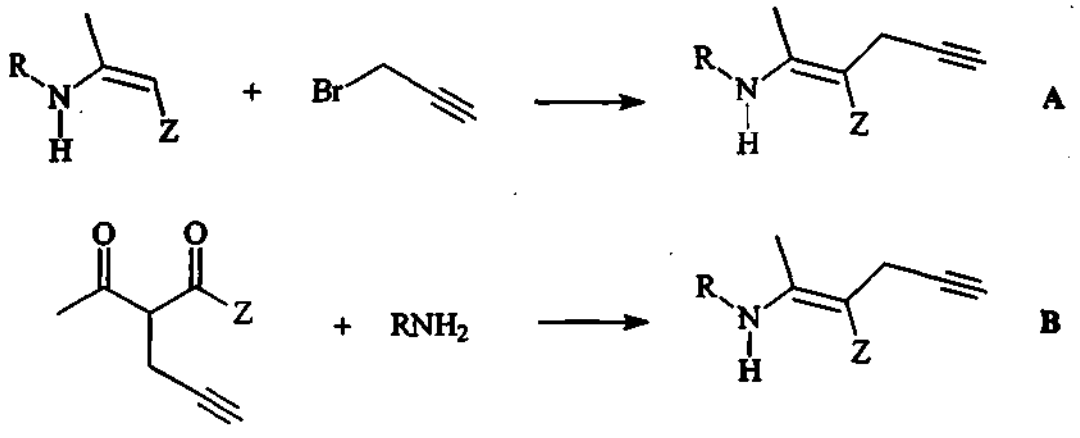


R = alkyl, aryl
Z = COMe, CO_2Et

Figure 22

11.1 Preparation of *C*-propargyl enaminones

Two possible synthetic strategies could be employed to prepare these compounds, *C*-propargylation of secondary enaminones (Scheme 74, **A**) or enaminone formation using an amine and a propargyl substituted β-dicarbonyl compound (Scheme 74, **B**).



Scheme 74

The latter strategy was seen as limiting as it cannot be used to prepare *N*-bridgehead pyrroles (Figure 23), compounds that were earmarked as important synthetic targets.

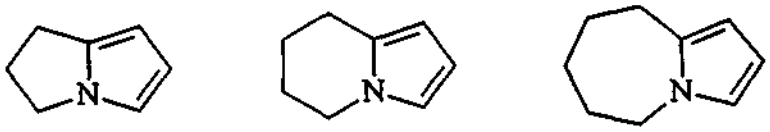
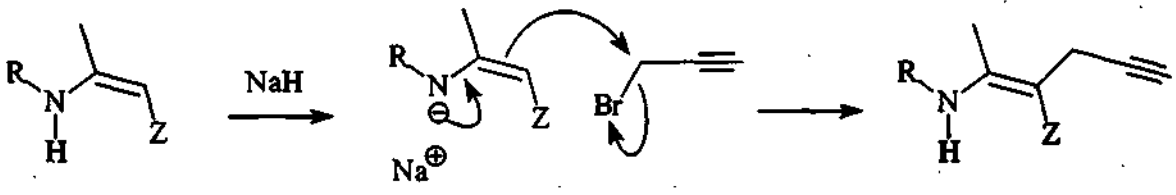


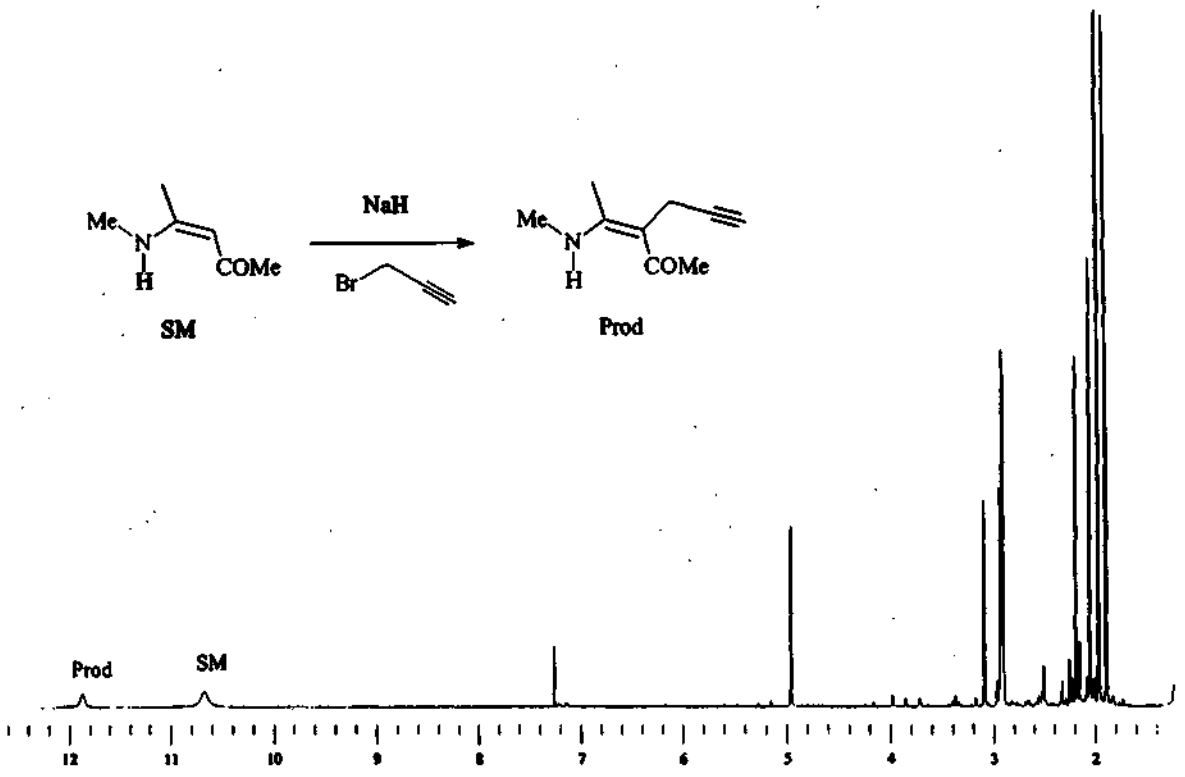
Figure 23

Therefore, efforts were concentrated on the first strategy, that of *C*-propargylation of secondary enaminones. This reaction had been accomplished during earlier work *via* abstraction of the amino proton using sodium hydride, followed by treatment with propargyl bromide (Scheme 75). The reaction is carried out overnight at room temperature in THF after addition of the base at 0°C.



Scheme 75

Although the desired compound can be prepared using this route, the reaction is not an efficient one and a large amount of unreacted starting material is observed in the crude reaction mixture (~50% by ^{1}H NMR) (Spectrum 6) and an isolated yield of only 46% was achieved.



Spectrum 6

Performing the reaction under reflux or using prolonged reaction times did not substantially increase the amount of product produced. Sodium hydride was replaced with *n*-butyllithium in the hope that the more electronegative counterion may alter the reactivity of the system. The reaction was carried out in an identical manner to that employing sodium hydride and it is evident from the GC trace of the crude reaction mixture (Figure 24) that a far greater proportion of starting material is consumed during this reaction than during the equivalent process involving a sodium counterion. Chromatography afforded a satisfactory 55% yield, a value that was, again, not improved by heating the reaction mixture or employing longer reaction times. It is also important to note that no products derived from nucleophilic addition of *n*-butyllithium are observed. The product itself was found to be very unstable once isolated and darkened within minutes of exposure to the atmosphere.

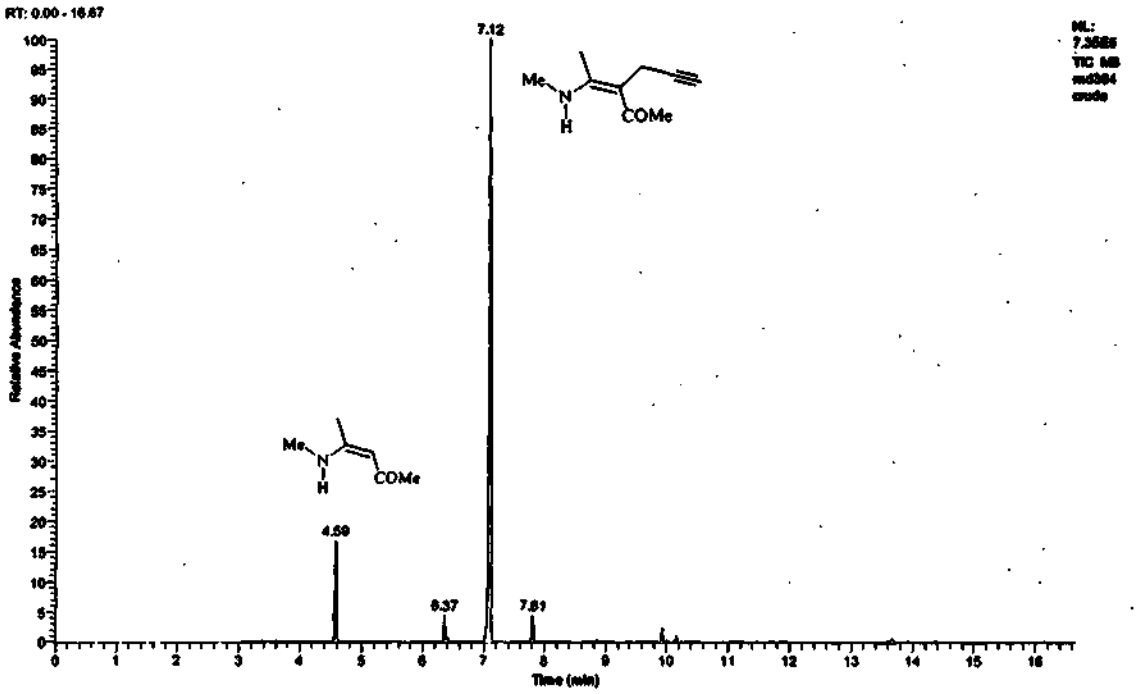
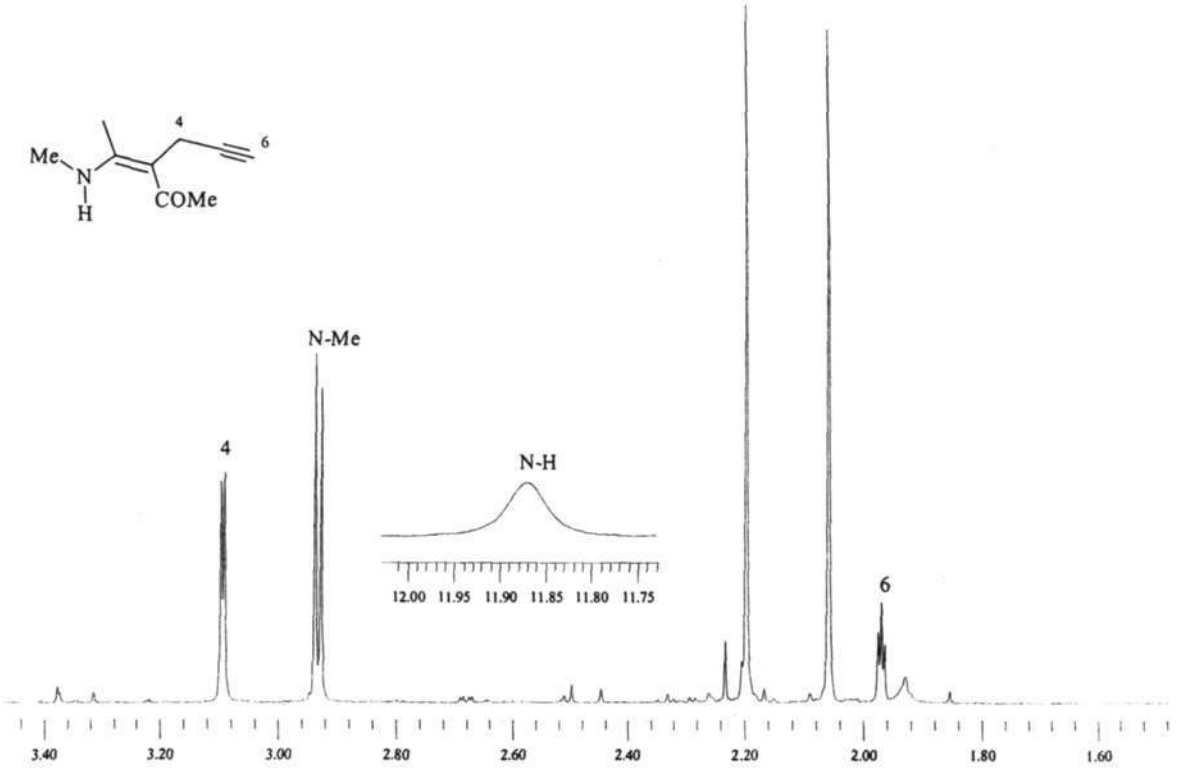


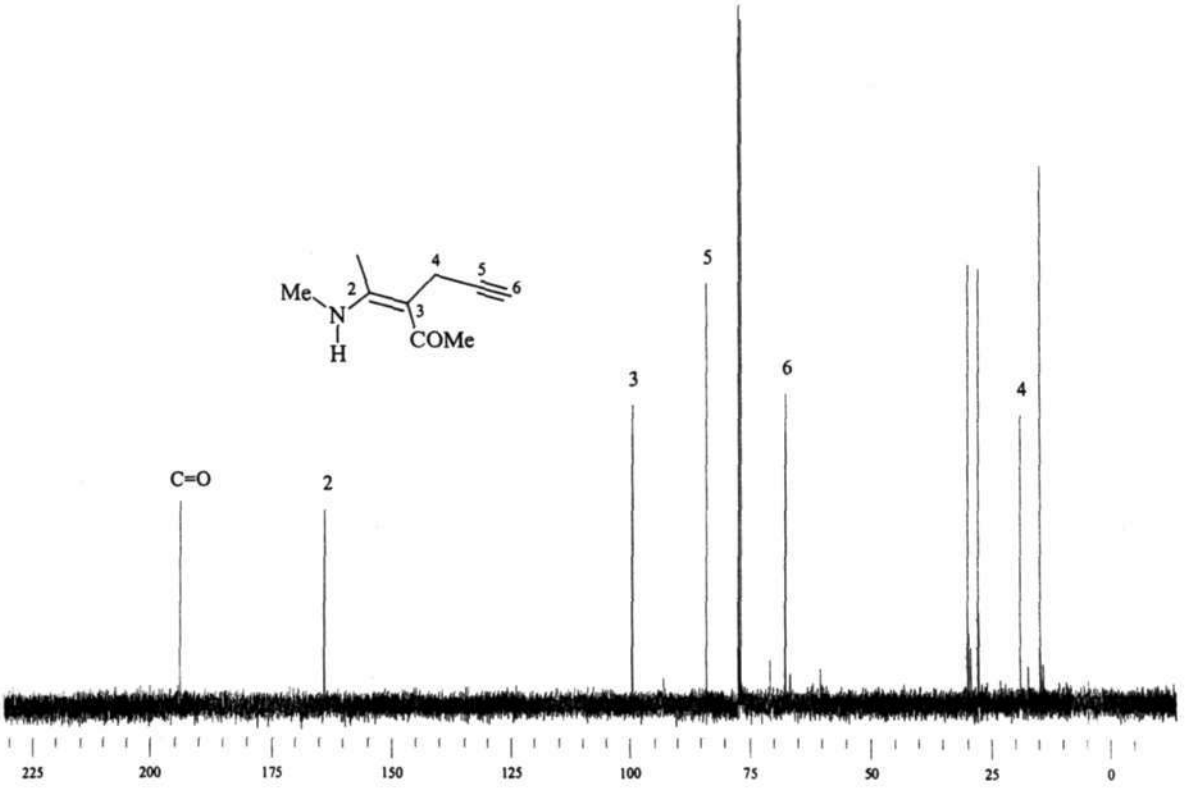
Figure 24

The NMR spectra of the clean *C*-propargyl compound are worthy of mention; the ^{1}H NMR spectrum (Spectrum 7) shows a signal corresponding to the amino proton at 11.87 ppm and resonates at this frequency due to hydrogen bonding to the oxygen of the carbonyl group. This indicates that the *Z*-configuration of the starting material is maintained in the product. The signals corresponding to the protons of the propargyl group, a doublet (3.09 ppm, J = 2.7 Hz) and a triplet (1.97 ppm, J = 2.6 Hz) are typical of this functionality.



Spectrum 7

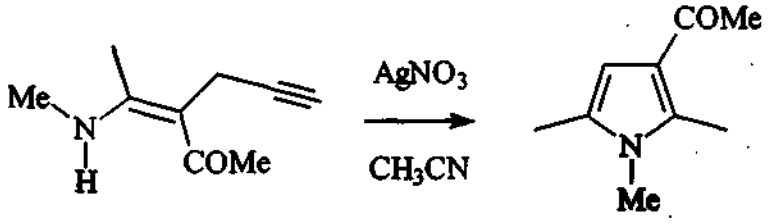
The ^{13}C NMR spectrum (Spectrum 8) displays expected chemical shifts and is shown below.



Spectrum 8

11.2 Silver-catalysed hydroamination

The question of whether *C*-propargyl enaminones could, indeed, be cyclised by a silver-mediated process remained to be answered. Therefore, a secondary *C*-propargyl enaminone was treated with a molar equivalent of silver nitrate in acetonitrile, expecting to isolate the desired pyrrole (Scheme 76). The reaction was allowed to proceed overnight at room temperature after which, the organic layer was washed with sodium iodide solution to precipitate any residual silver(I). An immediate colour change from a pale yellow to a dark silver/grey was observed on addition of the silver nitrate.



Scheme 76

Upon examination of the spectra of the crude material, it was evident that the *C*-propargyl enaminone had been efficiently converted to the corresponding pyrrole. In fact, no trace of starting material was observed and, in similar fashion to the one-pot procedure, the pyrrole is obtained very cleanly. Filtration through a plug of silica gel affords a spectroscopically pure product. In contrast to the one-pot procedure, however, no mass loss is observed and the yield for the intramolecular hydroamination is >90%. This result serves to emphasise the fact that the inefficiency of the one-pot procedure is not due to the initial hydroamination but rather the new C-C bond formation.

At this stage it was apparent that the reaction might be catalytic with respect to silver(I). In order to investigate this possibility, the same *C*-propargyl enaminone was treated with 0.2 molar equivalents of silver nitrate in acetonitrile. The reaction was monitored using ^{1}H NMR spectroscopy (Figure 25), which shows the methine signal (6.19 ppm) of the product pyrrole increase over the duration of the reaction while the amino signal (11.87 ppm) decreases accordingly. More significantly, however, is the fact that the reaction proceeds to completion, consuming the starting material after ~16 hours, indicating the reaction is catalytic with respect to silver(I). This is contrary to the one-pot reaction in which only a

small amount of starting material is consumed when using 0.2 molar equivalents of silver nitrate (10.4 Optimisation of reaction conditions, p82).

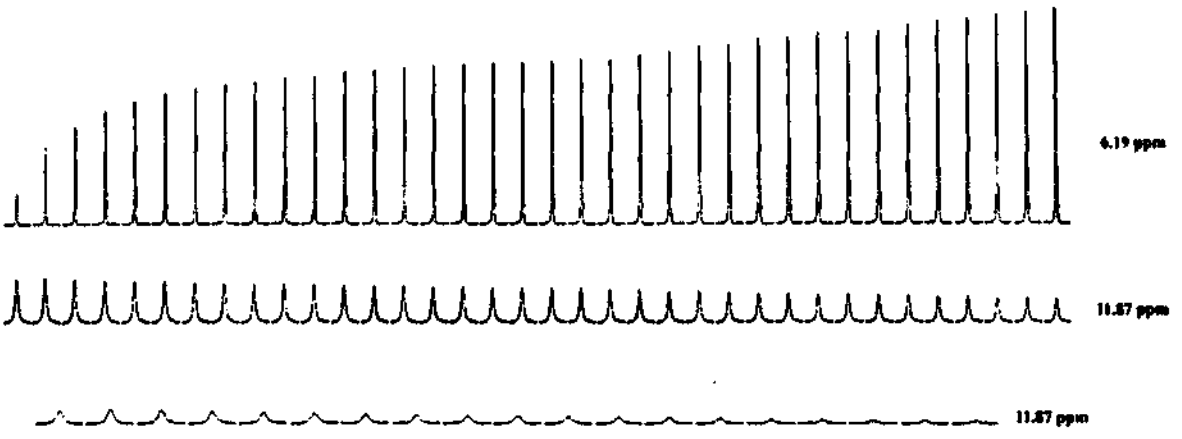
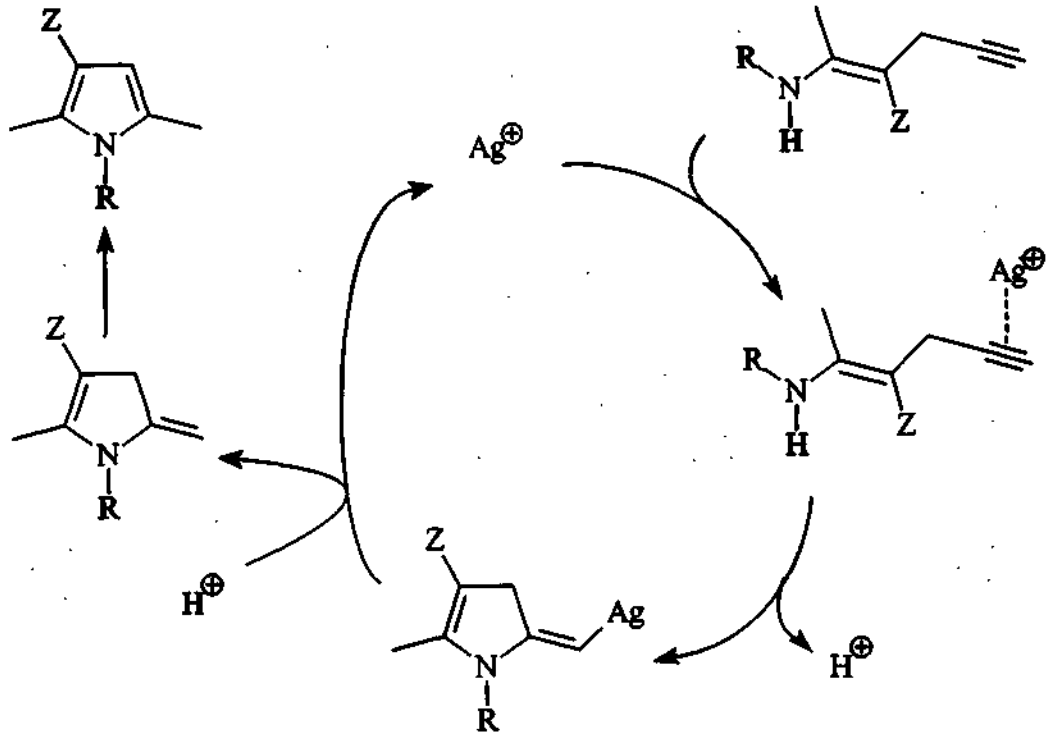


Figure 25

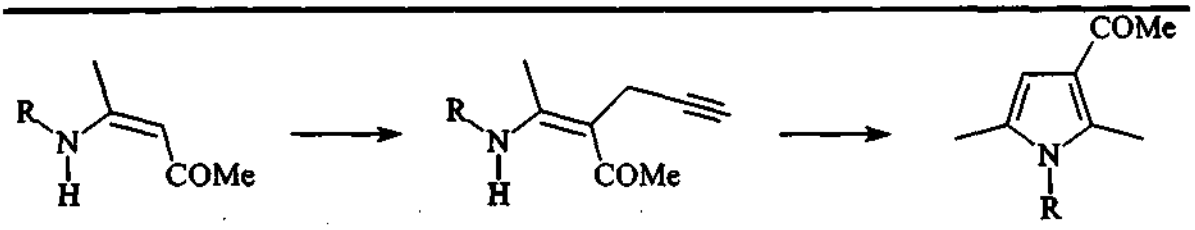
The mechanism of this conversion is believed to proceed *via* the catalytic cycle shown below (Scheme 77). Coordination between the silver ion and the C≡C triple bond facilitates hydroamination and affords a vinyl silver species. Protonation of this species yields an exocyclic enamine and regenerates silver(I) which allows the catalytic cycle to continue. Rearrangement of the enamine affords the final pyrrole product. The hydroamination itself cannot occur while the C-propargyl enaminone is in the stable *Z*-configuration; therefore, it is assumed that the small proportion of the compound that exists in the *E*-configuration is the species that actually undergoes hydroamination. Removal of the *E*-isomer from the equilibrium would then drive the reaction.



Scheme 77

Accordingly, a range of *C*-propargyl enaminones (only Z = COMe) were prepared by treating the appropriate secondary enaminones with *n*-butyllithium and propargyl bromide. Thereafter the *C*-propargyl compounds were subjected to silver-catalysed hydroamination to afford the corresponding pyrroles (Table 8). The results and discussion that follow are not applicable to vinylogous carbamates (Z = CO_2Et) and an explanation for this is given in a subsequent section (p96).

Table 8: Preparation of *C*-propargyl enaminones and pyrroles



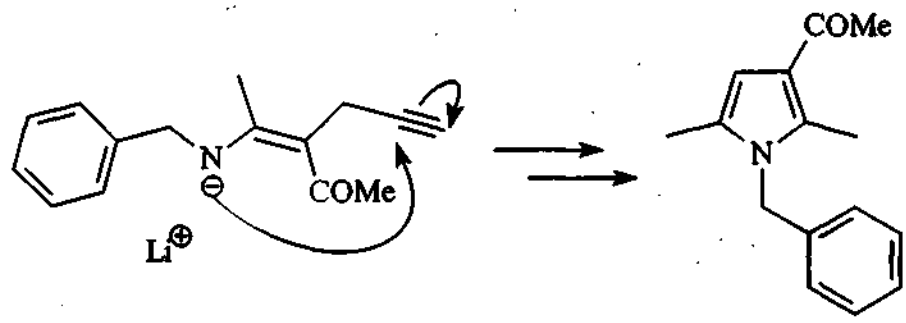
R	Base	Yield (*C*-prop) / %	Yield (pyrrole) / %
Me	*n*-BuLi	55	93
Me	NaH	46	93
n-Bu	*n*-BuLi	51	95
C_6H_{11}	*n*-BuLi	52	87
Ph	*n*-BuLi	21	75
Bn	*n*-BuLi	-	43*

* Pyrrole was obtained directly from secondary enaminone.

The *C*-propargyl compounds were isolated using standard silica gel chromatography and, although the observed yields are not excellent, they are acceptable. Attempts to improve this procedure are described in a later section. The yield of the aromatic analogue is substantially lower than the aliphatic analogues, an observation that is in line with with the stability of the lithium amide generated upon proton abstraction. The analogues containing larger *N*-alkyl substituents (R = *n*-Bu, C_6H_{11}) appeared to be slightly more stable than the *N*-methyl analogue as they only darkened on extensive exposure to the atmosphere. The aromatic analogue showed even greater stability. The size of *N*-alkyl substituents does not appear to influence the reaction.

The conversion of the *C*-propargyl compounds to the appropriate pyrroles proceeded efficiently in all instances. In each case 0.2 equivalents of silver nitrate was sufficient to ensure complete consumption of the starting material. Again, the size of the *N*-alkyl substituent does not appear to influence the hydroamination and excellent yields of the order of 90% were achieved for all three occasions. The yield of the aromatic analogue (75%) is, again, lower than the aliphatic examples however this is in line with typical trends concerning the nucleophilic character of aromatic amines.

The most remarkable observation is that the *N*-benzyl pyrrole analogue is obtained directly from the secondary enaminone without isolation, or detection, of the *C*-propargyl compound. This is believed to be due to an *n*-butyllithium-catalysed hydroamination (Scheme 78). This type of hydroamination has been covered in the 'Introduction' (p10).

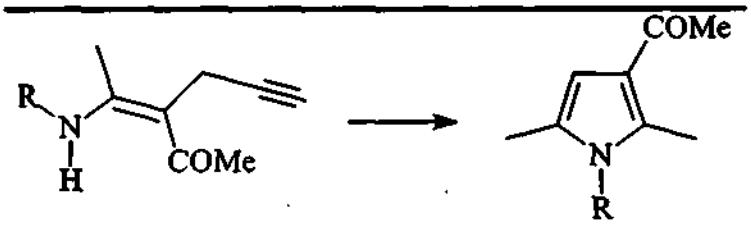


Scheme 78

There is no reason to suggest that the *N*-benzyl amide should be any more reactive than the other aliphatic analogues. The reason for this increased reactivity may lie in the formation of a small percentage of a benzyl anion due to the excess (1.1 eq) of *n*-butyllithium used in the reaction. This resonance-stabilised anion could be regarded as an electron-rich substituent and may increase the nucleophilic character of the amide and formation of the thermodynamically stable pyrrole could be the driving force for the reaction.

A further investigation was carried out to determine the affects of microwave irradiation on the silver-catalysed hydroamination (Table 9). Silver nitrate (0.2 equivalents) was added to a solution of the *C*-propargyl compound in acetonitrile in a thick-walled Pyrex test-tube. The test-tube was sealed and the mixture was irradiated for 60 seconds using the 'Low' power setting. The mixture was allowed to cool prior to the normal workup procedure. Again, filtration through a plug of silica gel afforded the spectroscopically pure pyrrole and the observed yields are comparable to those obtained at room temperature. In all cases the starting material was completely consumed and, therefore, this procedure represents a dramatic reduction in reaction time from ~16 hours to 60 seconds.

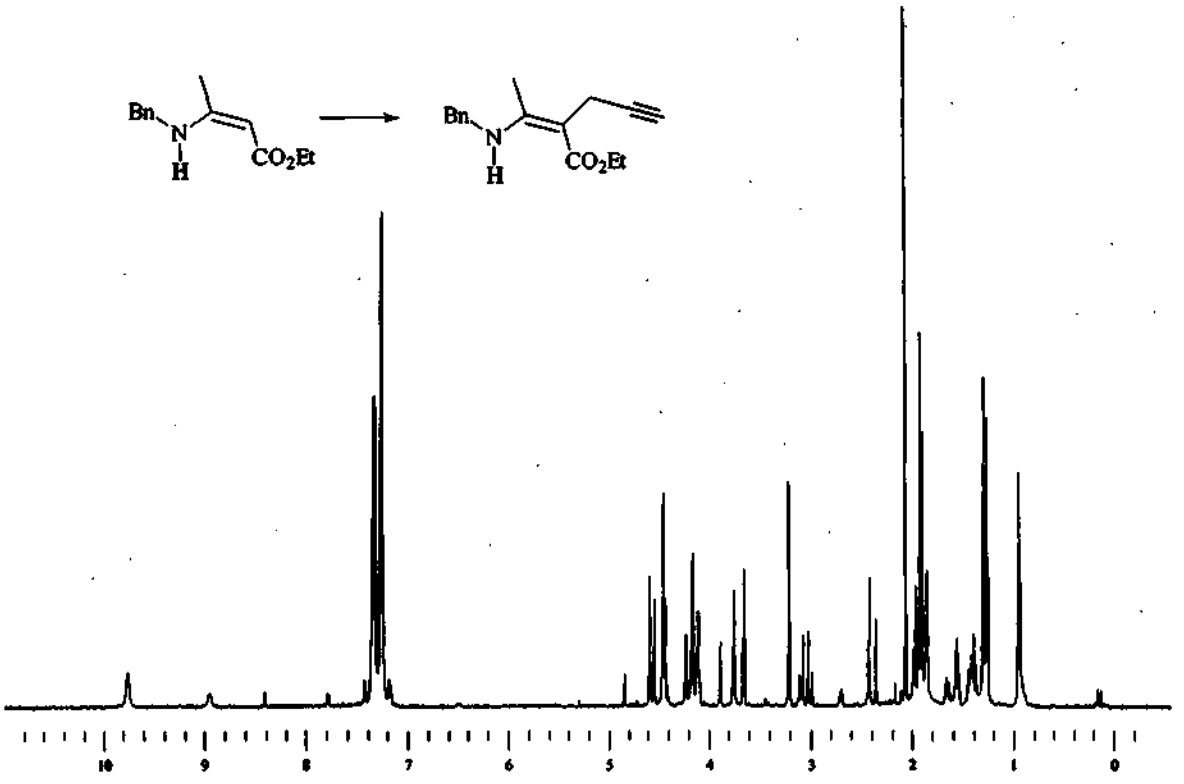
Table 9: Microwave-assisted hydroamination



R	Yield (pyrrole) / %
Me	93
n-Bu	91
C_6H_{11}	96
Ph	78

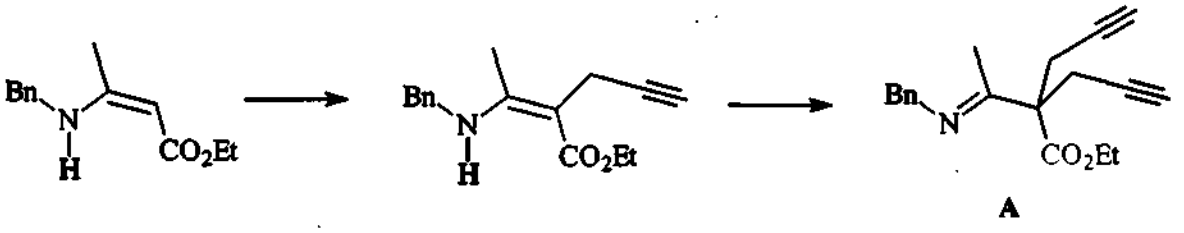
11.3 Limitations associated with vinylogous carbamates

It should be stressed that the methodology discussed above only applies to compounds derived from vinylogous amides (Z = COMe) and not from vinylogous carbamates (Z = CO_2Et). The same methodology has not been successfully applied to the carbamate analogues due to notable differences in the reactivity of the two precursors. *C*-Propargylation of vinylogous amides proceeds smoothly to the desired product, the only limitation of the reaction being that it never proceeds to completion. On the other hand, *C*-propargylation of vinylogous carbamates, using identical reaction conditions, affords a complex reaction mixture. The crude ^{1}H NMR spectrum for the reaction of the *N*-benzyl analogue is shown below and is typical (Spectrum 9). It should be noted that, unlike the equivalent vinylogous amide example, there is no evidence of pyrrole formation.



Spectrum 9

Some important characteristics of the reaction can be determined from the ^{1}H NMR spectrum of the crude material. Both starting material and the desired *C*-propargyl product are observed, evident from their amino protons at ~8.9 ppm and ~9.7 ppm respectively. This is in line with the reactions involving vinylogous amides. However, the remainder of the spectrum is complex, representing a number of products and only one, besides the starting material and product, has been identified. That compound (Scheme 79, **A**) is the result of a second addition of propargyl bromide to the *C*-propargyl product.

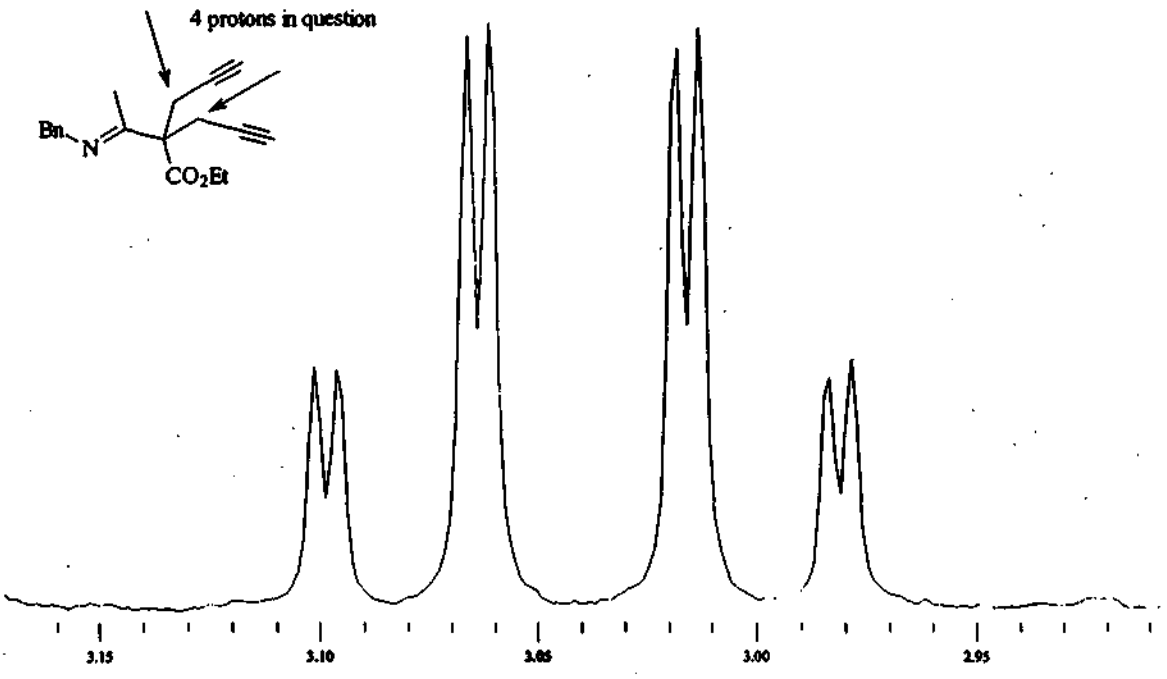


A

Scheme 79

Compounds containing this functionality are characterised by a pair of double doublets resonating at ~3 ppm (Spectrum 10). These signals, integrating to a total of four protons, represent the two pairs of methylene protons of the propargyl groups and the observed

splitting pattern is due to the protons being diastereotopic.[140] They are diastereotopic because the carbon to which they are attached is a pro-chiral centre.[140] This coupling results in the emergence of a pair of doublets (J = 17.5 Hz), which are split further due to long-range coupling with the terminal acetylenic proton (J = 2.8 Hz).



Spectrum 10

The formation of these bisadducts is believed to be due to the greater nucleophilicity of vinylogous carbamates compared to the equivalent vinylogous amides. This phenomenon has been discussed in an earlier section (p52). The amount of the bisadduct varies with each *N*-substituent but there appears to be no correlation between the character of the substituent and the amount of bisadduct observed. For example, very little of the bisadduct is observed for *N*-butyl and *N*-cyclohexyl analogues and yet appreciable amounts are noted for *N*-methyl and *N*-benzyl analogues. The reaction of the *N*-phenyl analogue gives rise to the bisadduct almost exclusively. A number of reaction parameters were altered in an attempt to prevent, or even hinder, the formation of these bisadducts. A variety of bases, LDA, lithium hexamethyldisilazide (LHMDS) and sodium hydride, a variety of solvents, THF and diethyl ether, and the aggregating agent TMEDA, were all employed to this end, without any success. Employing the methyl ester gave similar results.

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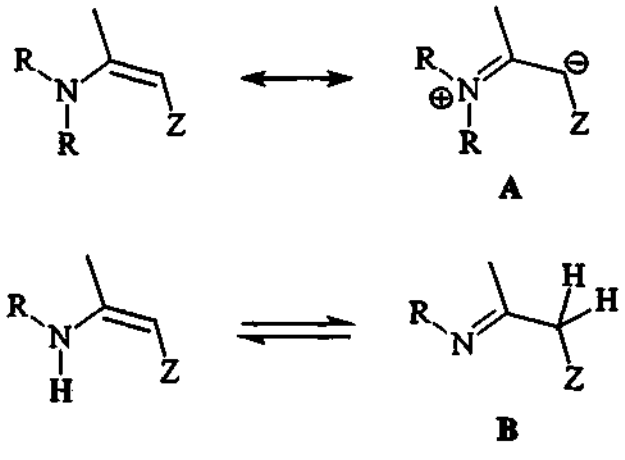
[140] Personal communication with Prof B.M. Trost (Stanford University, USA).

Coincidentally, both the *C*-propargyl compounds and bisadducts are exceptionally unstable and isolation of the individual products proved to be impossible. Therefore, the methodology described above, incorporating silver-catalysed hydroamination, could not be successfully extended to vinylogous carbamates.

11.4 Potential improvements to *C*-propargylation reaction

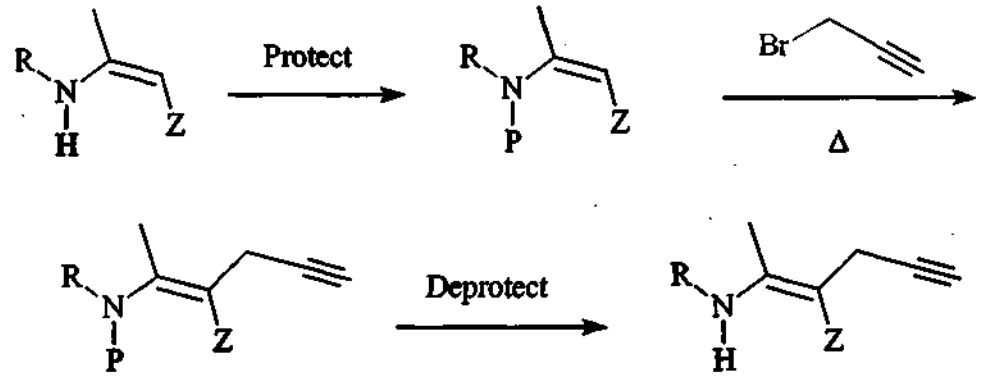
Although yields of the order of 50% are satisfactory, *C*-propargylation of secondary enaminones (Z = COMe) cannot be regarded as an efficient reaction. On the other hand, silver-catalysed hydroamination provides excellent yields and, therefore, any improvements to *C*-propargylation would improve the overall yields and, hence, the developed methodology.

Tertiary enaminones are known to undergo *C*-substitution in a facile manner,[104] a characteristic that can be attributed to the nucleophilic character of its β-carbon atom. The difference in reactivity between tertiary and secondary enaminones is evident when examining their canonical forms (Scheme 80). The iminium mesomer of the tertiary enaminone (Scheme 80, **A**) contains a highly nucleophilic carbanion, whereas the equivalent tautomer of the secondary enaminone contains a saturated β-carbon atom (Scheme 80, **B**).



Scheme 80

Therefore, a possible strategy for improving the *C*-propargylation of secondary enaminones would be to protect the amino group, effectively creating a tertiary enaminone, and to remove the protecting group subsequent to efficient *C*-propargylation (Scheme 81).



P = protecting group

Scheme 81

Although a sound strategy on paper, the appropriate protecting group has not been found. In theory, the amine may be protected before or after enaminone formation. Traditional amine protecting groups, carbamates and amides, are not suitable in either instance due to the fact that these groups deactivate the amine, making both enaminone formation and *C*-propargylation impossible. Protection of the amine prior to enaminone formation is greatly influenced by the size of the amine. This is evident from the observation that reactions between *t*-butylamine and β-dicarbonyl compounds produce very little enaminone product, if any at all (Table 5, p67). Therefore, enaminone formation would not be possible when employing a trimethylsilyl-protected amine. Protection of the enaminone subsequent to its formation is also not an easy procedure, as shown in earlier sections discussing the ambident nucleophilicity of enaminones (p68). So, although this strategy appears to be a viable alternative to base-induced *C*-propargylation, it could not be implemented.

12 Preparation of *N*-bridgehead pyrroles

N-Bridgehead pyrroles are important synthetic building blocks as they provide the framework for pyrrolizidine (Figure 26, **A**), indolizidine (Figure 26, **B**) and lehmizidine[141] (Figure 26, **C**) alkaloids. These compounds are common synthetic targets and have been prepared on numerous occasions.[142]

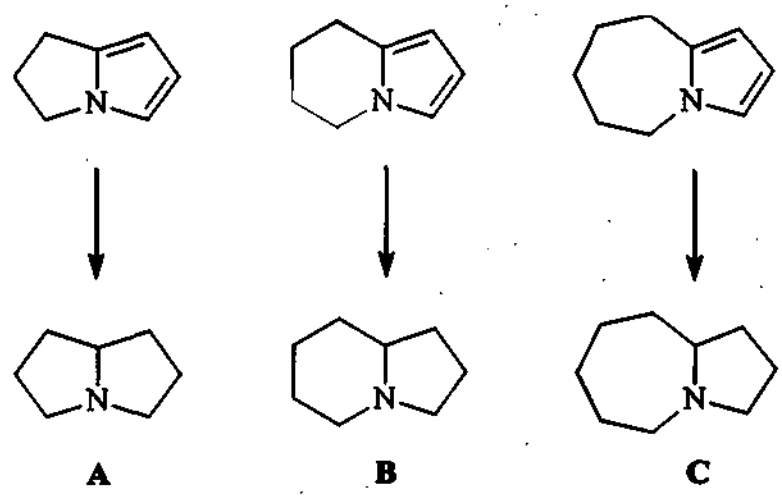


Figure 26

It was hoped that the same methodology that has been developed to prepare pyrroles could be used to prepare *N*-bridgehead pyrroles. *N*-Bridgehead pyrroles derived from vinylogous carbamates were specifically targeted, as it is possible to remove the ester group from the final product, affording the 'izidine' skeleton.[143]

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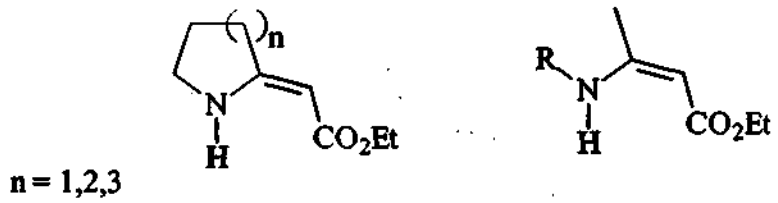
[141] The term lehmizidine has been proposed by Garraffo *et al* to describe the '5-7 izidines'. Garraffo, H.M., Jain, P., Spande, T.F., Daly, J.W., Jones, T.H., Smith, L.J., Zottig, V.E., *J. Nat. Prod.*, **2001**, *64*, 421-427.

[142] For examples see a) Calvo, L., González, A., Sañudo, M.C., *Synthesis*, **2002**, 2450-2456. b) Croce, P.D., La Rosa, C., *Heterocycles*, **2001**, *55*, 1843-1858. c) Barluenga, Tomás, M., Kouznetsov, V., Suárez-Sobrino, A., Rubio, E., *J. Org. Chem.*, **1996**, *61*, 2185-2190. d) Barluenga, Tomás, M., Kouznetsov, V., Suárez-Sobrino, A., Rubio, E., *J. Chem. Soc., Chem. Commun.*, **1992**, 1419-1420.

[143] a) Pizzorno, M.T., Albonico, S.M., *J. Org. Chem.*, **1977**, *42*, 909-910. b) Treibs, A., Dietl, A., *Liebigs Ann.*, **1958**, *619*, 80-95.

12.1 Preparation of cyclic secondary vinylogous carbamates

In order to access the *N*-bridgehead pyrroles in question, it was necessary to prepare cyclic secondary vinylogous carbamates (Figure 27, **A**) and, although their acyclic analogues (Figure 27, **B**) can be readily obtained in high yield (Table 5, p67), synthesis of the cyclic compounds can be problematic.



n = 1,2,3

A **B**

Figure 27

A number of methods exist for preparation of vinylogous carbamates; these include preparation from lactim ethers,[144] from azido dicarbonyl compounds,[145] from alkenyl substituted β-enamino esters[146] and by lithiation of ketimines.[147] However, the vast majority of procedures employ the Eschenmoser coupling reaction (also known as the Eschenmoser sulphide contraction) as the key synthetic step.[102]

A typical synthetic strategy (Scheme 82) would entail thionation of an appropriate lactam to afford the corresponding thiolactam, which would be treated, sequentially, with an activated alkyl halide ($BrCH_2CO_2Et$), a weak base (NEt_3) and a thiophile (PPh_3) to give the vinylogous carbamate at ambient temperature.

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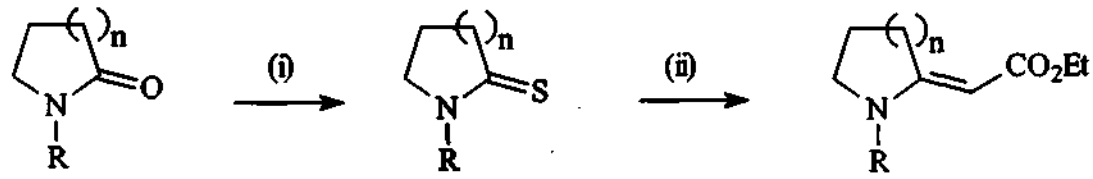
[144] Célérier, J.-P., Deloisy, E., Lhommet, G., Maitte, P., *J. Org. Chem.*, **1979**, *44*, 3089.

[145] Lambert, P.H., Vaultier, M., Carrié, R., *J. Org. Chem.*, **1985**, *50*, 5352-5356.

[146] Ferraz, H.M.C., de Oliveira, E.O., Payret-Arrua, M.E., Brandt, C.A., *J. Org. Chem.*, **1995**, *60*, 7357-7359.

[147] Bartoli, G., Cimarelli, C., Dalpozzo, R., Palmieri, G., *Tetrahedron*, **1995**, *51*, 8613-8622.

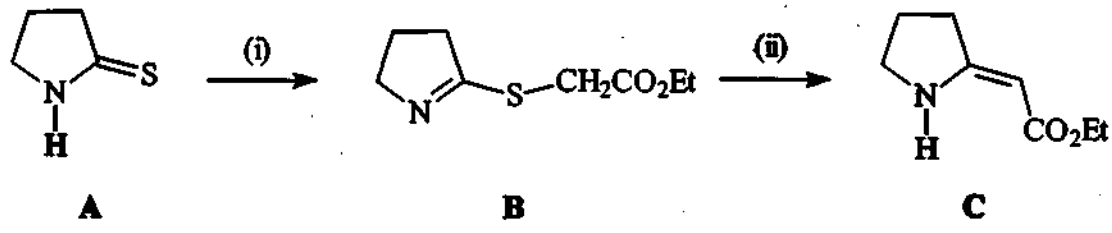


n = 1,2,3
R = alkyl, aryl

(i) Lawesson's reagent (ii) $BrCH_2CO_2Et$, NEt_3, PPh_3, MeCN

Scheme 82

However, if a secondary thiolactam (Scheme 84, **B**) is employed in the sulphide contraction, much harsher conditions are required.[102] Typical conditions for this form of the reaction are the use of potassium *tert*-butoxide, a large excess of thiophile (4 equivalents) and prolonged reaction times at high temperature (72 hours in refluxing xylene).[148] These conditions were employed to prepare a desired vinylogous carbamate (Scheme 83, **C**) and, although the intermediate thioimino ester (Scheme 83, **B**) was prepared in an excellent 96% yield, only a small amount of the desired carbamate was isolated thereafter. This was mainly due to difficulties associated with the large amount of phosphines.



A **B** **C**

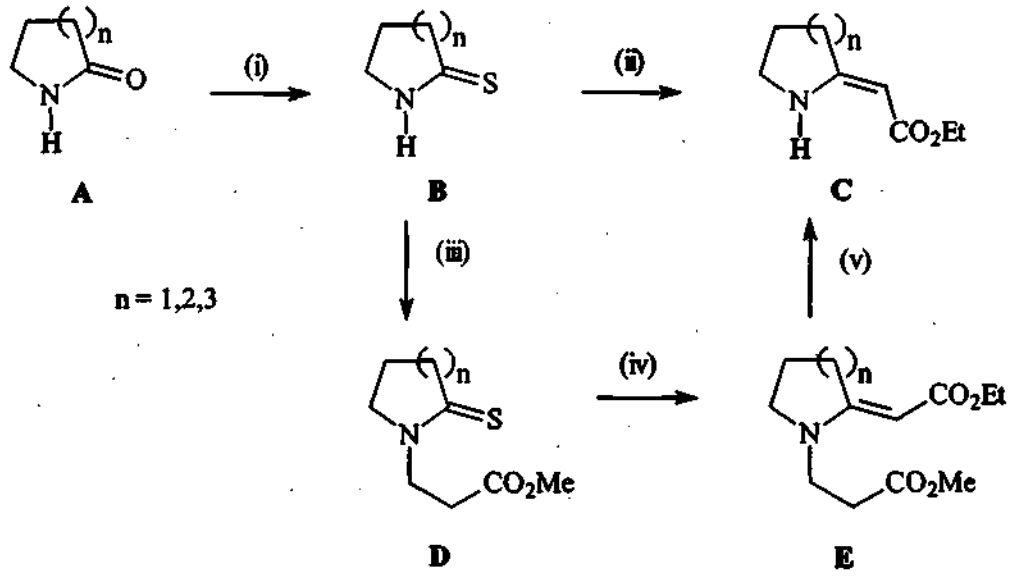
(i) $BrCH_2CO_2Et$, CH_2Cl_2, RT, 96% (ii) *t*-BuOK, PPh_3, xylene

Scheme 83

[148] Pinnick, H.W., Chang, Y.-H., *J. Org. Chem.* **1978**, *43*, 4662-4663.

12.2 Preparation of cyclic secondary vinylogous carbamates using a protection-deprotection strategy

Nevertheless, the Eschenmoser coupling reaction is an efficient procedure and it was considered important to investigate ways of simplifying the reaction conditions in order to prepare the desired secondary vinylogous carbamates (Scheme 84). Conjugate addition to acrylates has been widely employed as a method of functionalising the nitrogen atom of thiolactams.[149] It has also been shown that this addition can be reversed by the addition of a strong base.[150] Both of these reactions are reported to give high yields (>90%) and it was believed that this sequence of reactions could be employed to improve the overall vinylogous carbamate preparation.



(i) Lawesson's reagent, MW (ii) $BrCH_2CO_2Et$, *t*-BuOK, PPh_3, xylene (iii) CH_2=$CHCO_2Me$, NaOH, THF (iv) $BrCH_2CO_2Et$, NEt_3, PPh_3, MeCN (v) KHMDS, THF

Scheme 84

[149] a) Michael, J.P., Gravestock, D., *J. Chem. Soc., Perkin Trans. 1*, **2000**, 1919-1928. b) Michael, J.P., Jungmann, C.M., *Tetrahedron*, **1992**, *48*, 10211-10220. c) Howard, A.S., Gerrans, G.C., Michael, J.P., *J. Org. Chem.*, **1980**, *45*, 1713-1715.

[150] a) Michael, J.P., Parsons, A.S., *Tetrahedron*, **1996**, *52*, 2199-2216. b) Mkhize, Z., M.Sc. Dissertation, University of Natal (Pmb), 2002.

Lactams can be efficiently converted to the corresponding thiolactams (Scheme 84, **B**) using microwave irradiation and Lawesson's reagent.[151] In this application, the appropriate lactam and Lawesson's reagent were mixed in a small beaker, which was then placed in a bed of alumina contained in a larger beaker. The mixture was irradiated on a 'Low' setting until the mixture became homogeneous, typically 30 seconds. Any further irradiation resulted in charring of the mixture. The crude reaction mixture was cooled and dissolved in dichloromethane, prior to chromatography. The yields of thiolactam prepared in this fashion were excellent (~90%) (Table 10). The thiolactams were treated with methyl acrylate and a catalytic amount of sodium hydroxide to obtain the acrylate adducts in average to good yield (Scheme 84, **D**).[150a] Undried THF was found to be the best solvent for this purpose and the reactions were, typically, complete in two hours or less. In all instances the crude material obtained after an aqueous washing was sufficiently pure to be used in the subsequent step. The acrylate adducts, being tertiary thiolactams, can be converted to vinylogous carbamates using standard Eschenmoser coupling conditions.[102] Therefore, each of the adducts was treated, sequentially, with ethyl bromoacetate, triphenylphosphine and triethylamine to afford tertiary vinylogous carbamates (Scheme 84, **E**) after chromatography. Triphenylphosphine and triethylamine were added as a solution in dichloromethane.[152] The initial salt formation was carried out overnight in acetonitrile, prior to addition of the remaining reagents. The procedure is complete in less than 24 hours and affords good yields.

Table 10: Preparation of cyclic secondary vinylogous carbamates (Scheme 84)

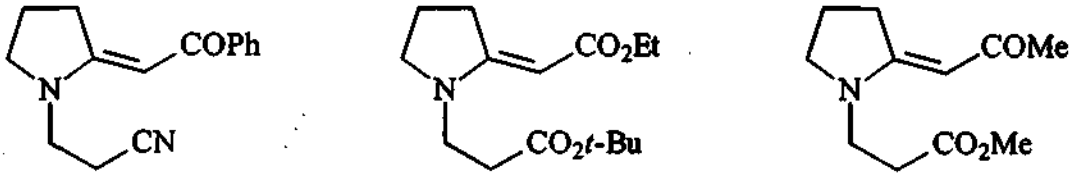
Entry	n	Yield / %	Entry	n	Yield / %
B1	1	97	**C1**	1	63*
B2	2	92	**C2**	2	86*
B3	3	89	**C3**	3	83*
D1	1	70	**E1**	1	83
D2	2	58	**E2**	2	84
D3	3	90	**E3**	3	23

*Yields of C from E

[151] Varma, R.S., Kumar, D., *Org. Lett.*, **1999**, *1*, 697-700.

[152] Peterson, J.S., Fels, G., Rapoport, H., *J. Am. Chem. Soc.*, **1984**, *106*, 4539-4547.

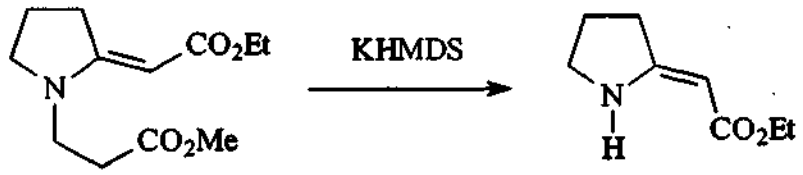
Michael and Parsons have shown that acrylonitrile can be successfully removed from a similar adduct (Figure 28, **A**) by treatment with excess potassium *tert*-butoxide.[150a] However, when employing this method to remove methyl acrylate from a vinylogous carbamate adduct (n = 1), the only product isolated was, rather surprisingly, a transesterification product (Figure 28, **B**). KHMDS has been used in our laboratories to remove methyl acrylate from another similar adduct (Figure 28, C).[150b] It was found that KHMDS can be employed to remove the same group from vinylogous carbamate adducts to afford the desired secondary compounds (Scheme 84, **C**). KHMDS was added to a solution of the vinylogous carbamate in THF and stirred at room temperature for 15 minutes. The reaction was quenched with water and filtered through a short plug of silica gel to afford spectroscopically pure secondary vinylogous carbamates in good yield (Table 10).



A **B** **C**

Figure 28

Although this reaction sequence affords the desired compounds from the original lactams in less than 48 hours, employing mild reagents and conditions, it is limited by the last, deprotection step, which does not provide reproducible results. Shown below (Figure 29) is the GC trace of the crude reaction mixture after removal of methyl acrylate from a vinylogous carbamate using two equivalents of KHMDS (Scheme 85). The observed peak corresponds to the desired compound and shows that the reaction has proceeded efficiently.



Scheme 85

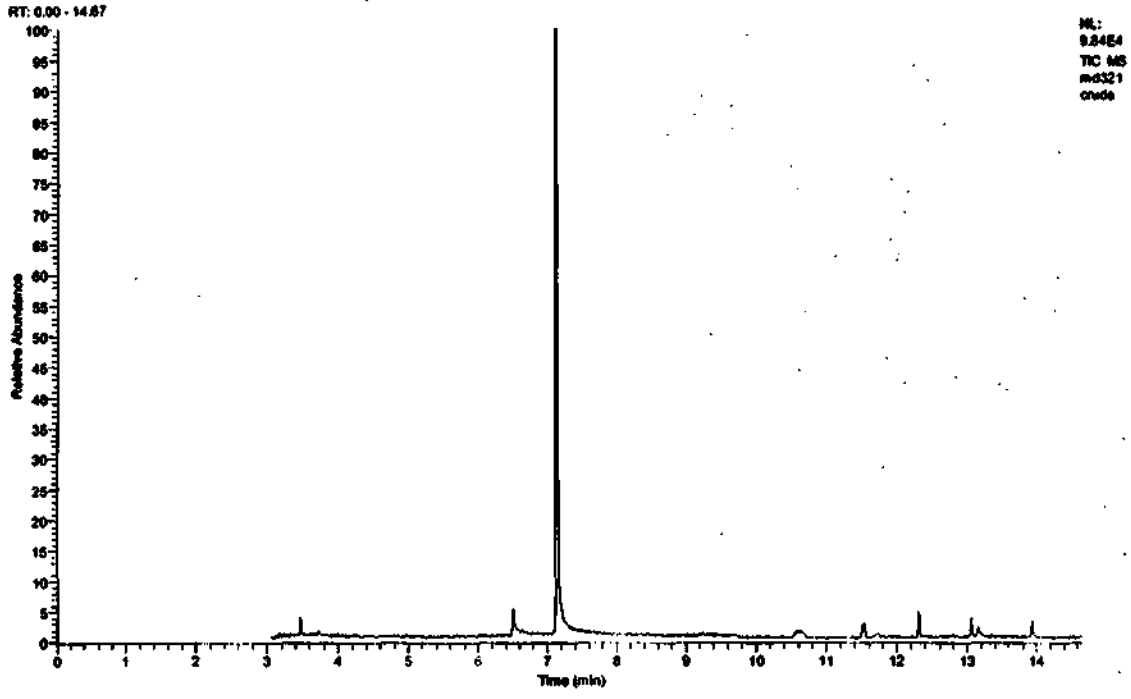


Figure 29

The GC trace shown below (Figure 30) is the same reaction carried out on another occasion. The two major peaks correspond to the correct product and to its methyl ester. This assignment has been confirmed by using NMR spectroscopy. The presence of the methyl ester cannot be explained and, although a mixture of the two esters would not influence further transformations, it does show that the reaction used to remove the acrylate group is not an effective one.

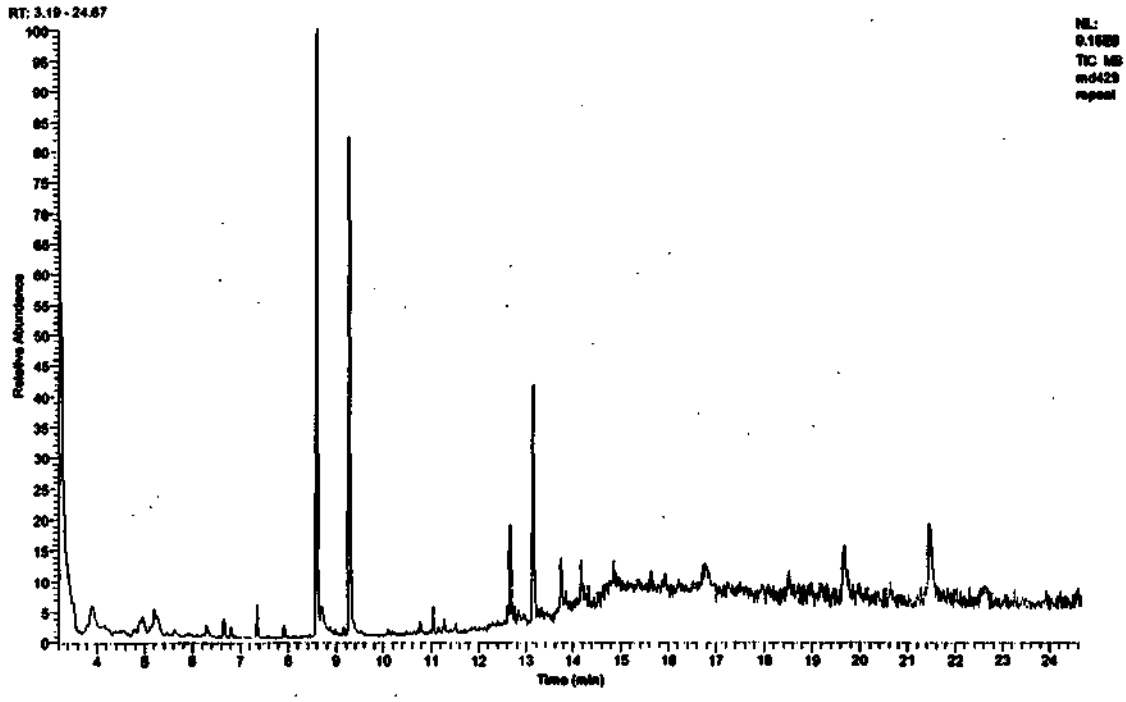
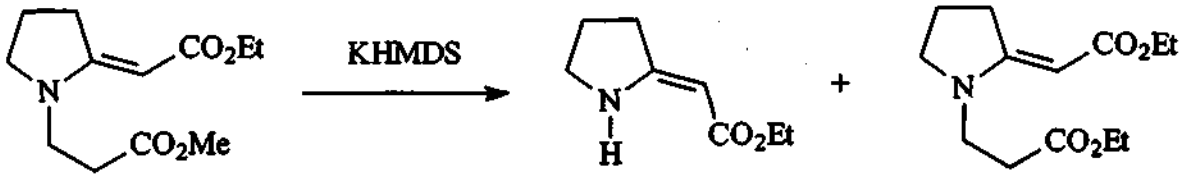


Figure 30

Employing 1.2 equivalents of base, an amount that efficiently removes the acrylate group from the larger ring systems (n = 2, 3), affords even stranger results (Figure 31). The GC trace shows the presence of the desired compound (~9.2 min) as well as an appreciable amount of starting material (~13.9 min). The other major peak alongside that of the starting material (~14.1 min) appears to correspond to its ethyl ester (Scheme 86). This assignment is based on the observed mass of the compound and its fragmentation pattern and has not been verified by other means. The presence of the ethyl ester is, once again, inexplicable.



Scheme 86

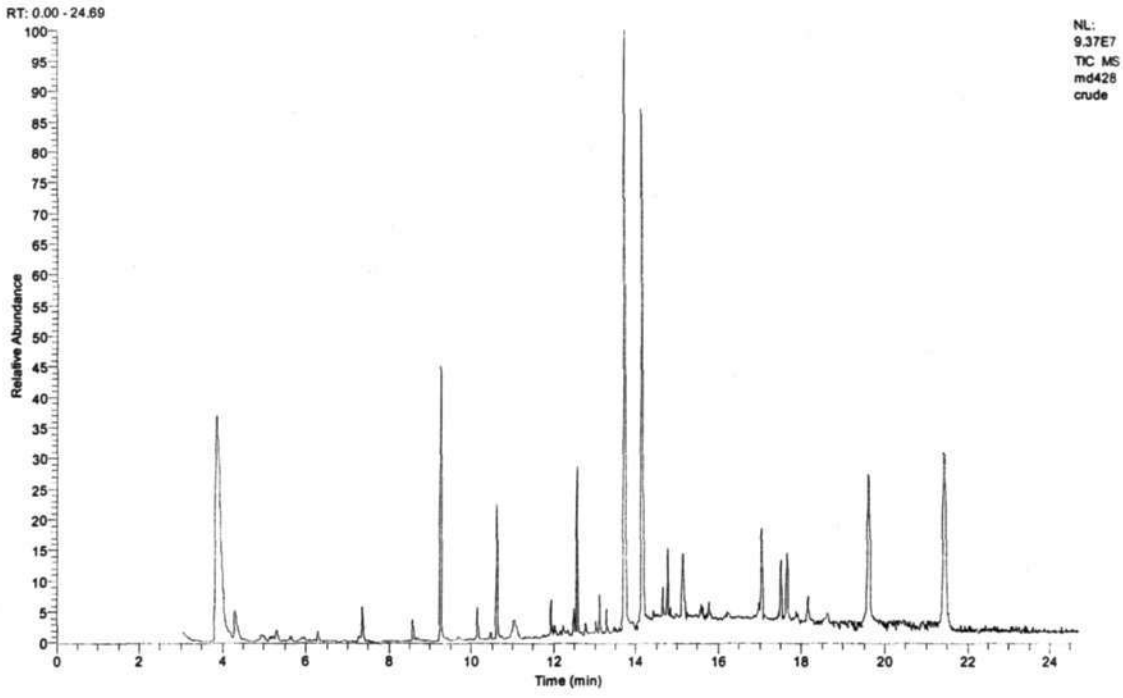
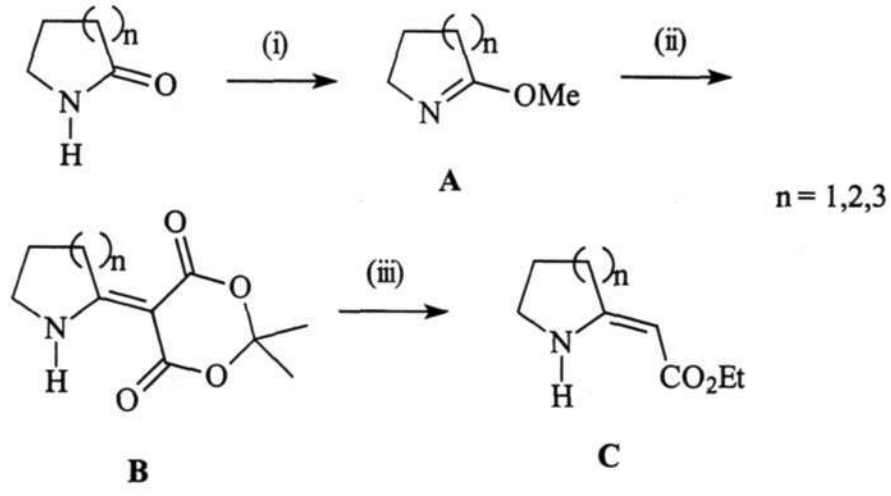


Figure 31

12.3 Preparation of cyclic secondary vinylogous carbamates from lactim ethers

Therefore, an alternative method was used to prepare the desired secondary vinylogous carbamates (Table 11). The method chosen was that of Célérier and co-workers (Scheme 87).[144]



(i) $(CH_3)_2SO_4$, 60°C (ii) Meldrum's acid, base, benzene, Δ (iii) NaOEt, EtOH, Δ

Scheme 87

The synthetic route involves preparation of lactim ethers (Scheme 87, **A**) by treating the appropriate lactam with dimethyl sulfate.[153] The reaction is carried out in a water bath at 60°C and the crude material is distilled to afford the desired compounds in fair yield.[153] The lactim ethers are, in turn, heated under reflux in a solution of Meldrum's acid and either triethylamine (n = 1, 2) or piperidinium acetate (n = 3) in benzene.[144] The cyclic diesters obtained in this fashion (Scheme 87, **B**) were purified by either recrystallisation (n = 1, 3) or chromatography (n = 2). Heating the cyclic diesters under reflux in a solution of sodium ethoxide in absolute ethanol affords the desired secondary vinylogous carbamates in adequate overall yield. Although this sequence is rather laborious, and the reactions are occasionally not high yielding, a sufficient quantity of the desired compounds was produced using this synthetic sequence.

Table 11: Preparation of cyclic secondary vinylogous carbamates (Scheme 87)

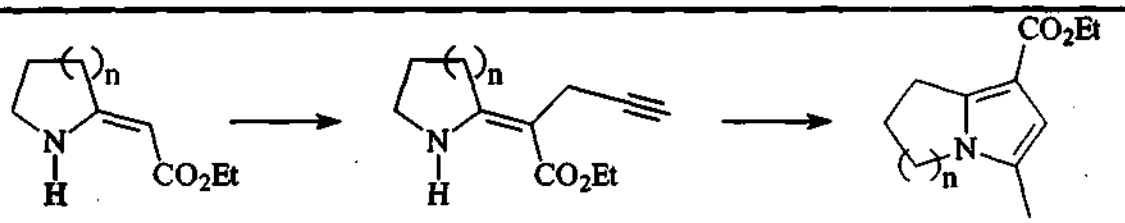
Entry	n	Yield / %	Entry	n	Yield / %	Entry	n	Yield / %
A1	1	52	B1	1	17	C1	1	60
A2	2	18	B2	2	38	C2	2	38
A3	3	61	B3	3	67	C3	3	19

12.4 Preparation of *N*-bridgehead pyrroles

It was hoped that the methodology developed to prepare pyrroles *via* *C*-propargylation of vinyologous amides prior to silver-catalysed hydroamination (p91) could be employed to prepare *N*-bridgehead pyrroles, however, the limitations associated with acyclic vinylogous carbamates (p96) were expected to be a problem. In spite of this, the methodology was applied to the prepared cyclic vinylogous carbamates and the results of this investigation are shown below (Table 12).

[153] Wick, A.E., Bartlett, P.A., Dolphin, D., *Helv. Chim. Acta*, **1971**, *54*, 513-522.

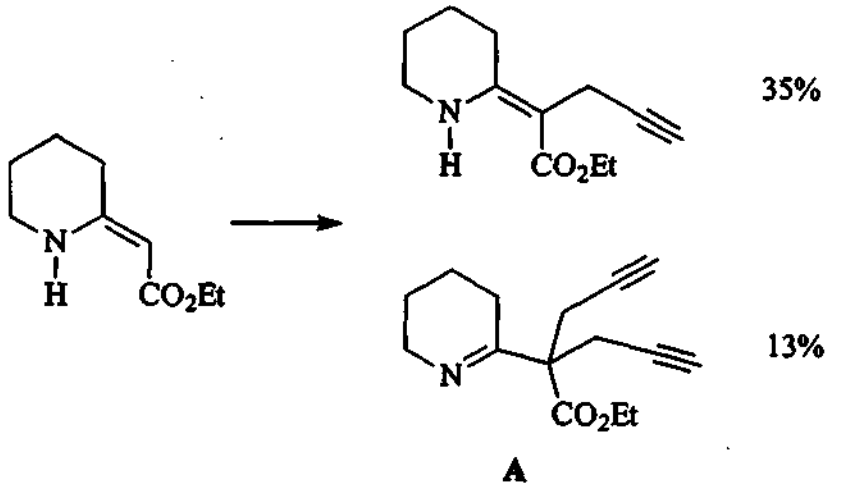
Table 12: Preparation of *N*-bridgehead pyrroles



n	Yield (*C*-prop) / %	Yield (pyrrole) / %
1	66	75
2	35*	75
3	24	71

* Also isolated bisadduct (13%).

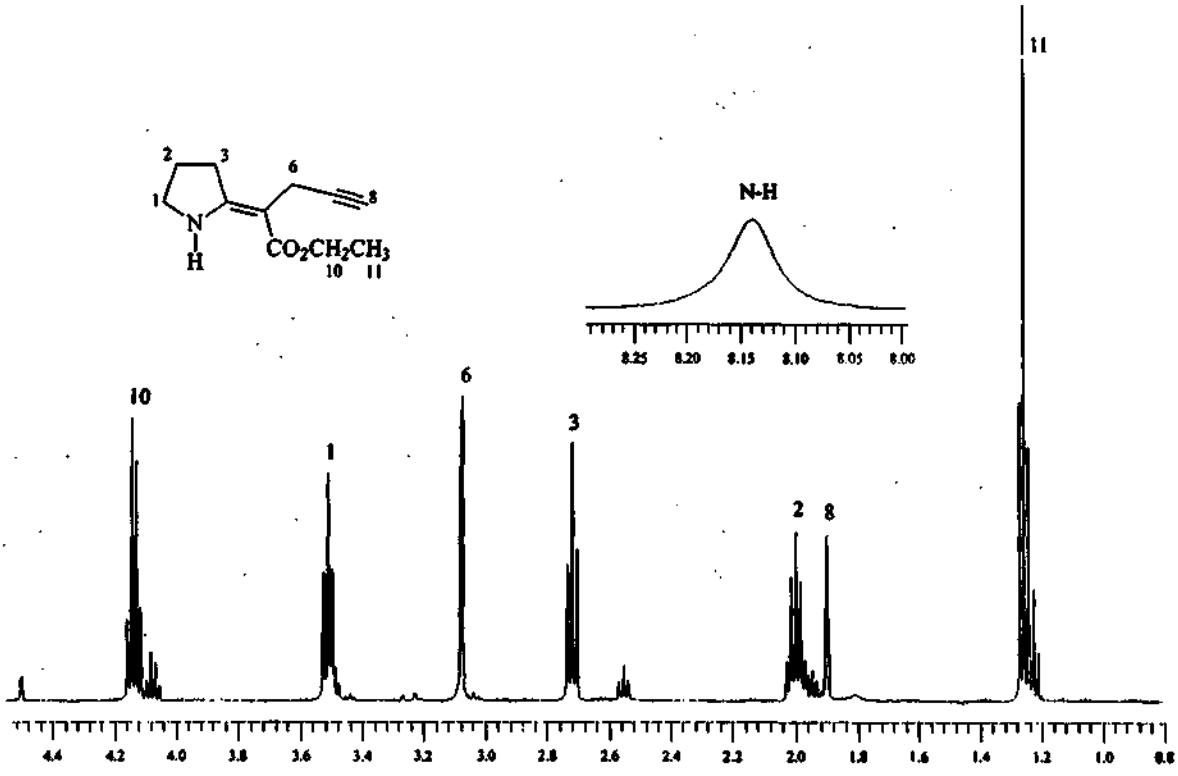
The table shows that *C*-propargylation of the cyclic carbamates was not as problematic as the corresponding reaction employing the acyclic analogues. The reactions, on the whole, were clean, and the formation of bisadduct was only observed for one of the examples (n = 2) (Scheme 88, A). In fact, the yield obtained for the smallest of the ring systems (n = 1) was the best yield obtained for any example, cyclic or acyclic, and emphasises just how important the structure of the substrate is to the outcome of the reaction. On the other hand, the largest of the ring systems (n = 3) gave a very poor yield. The *C*-propargyl compounds were purified using silica gel chromatography but were found to be unstable on exposure to the atmosphere and were thus used immediately after purification.



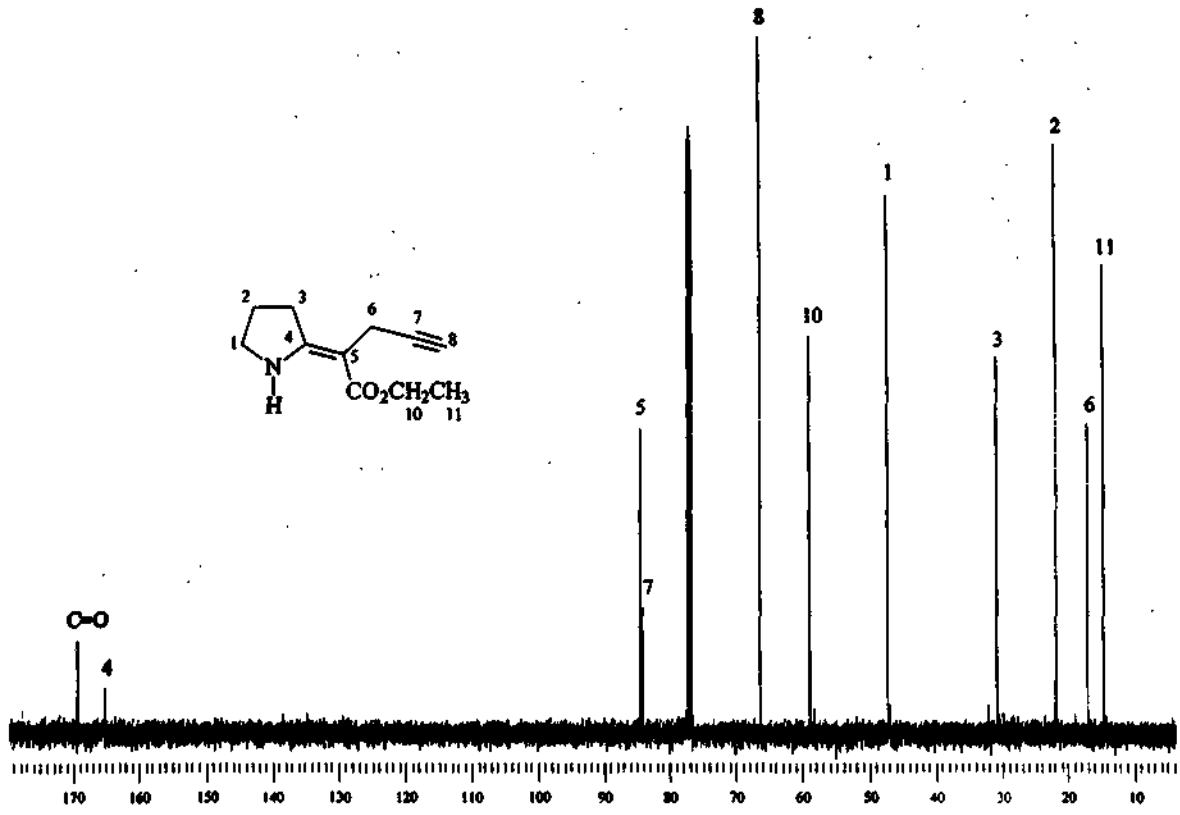
A

Scheme 88

The NMR spectra of one of the *C*-propargyl analogues (n = 1) are shown below (Spectrum 11 and Spectrum 12). The ^{1}H NMR spectrum shows a hydrogen bonded amino proton, which confirms the *Z*-configuration of the prepared compound. The remainder of the spectrum is typical, with signals corresponding to the protons of the ring and the ester group resonating at expected chemical shifts and the signals corresponding to the protons of the propargyl group are characteristic of this functionality. The ^{13}C NMR spectrum shows no unusual features and both spectra have been fully assigned.

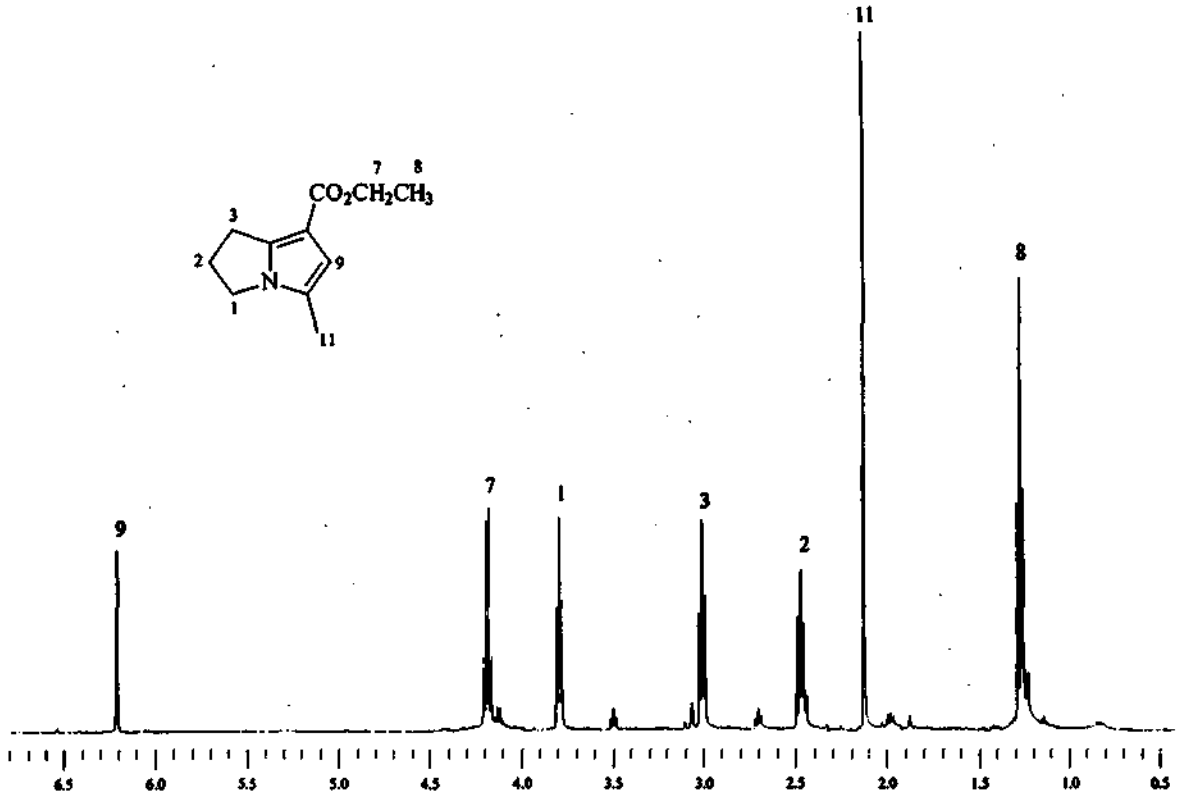


Spectrum 11

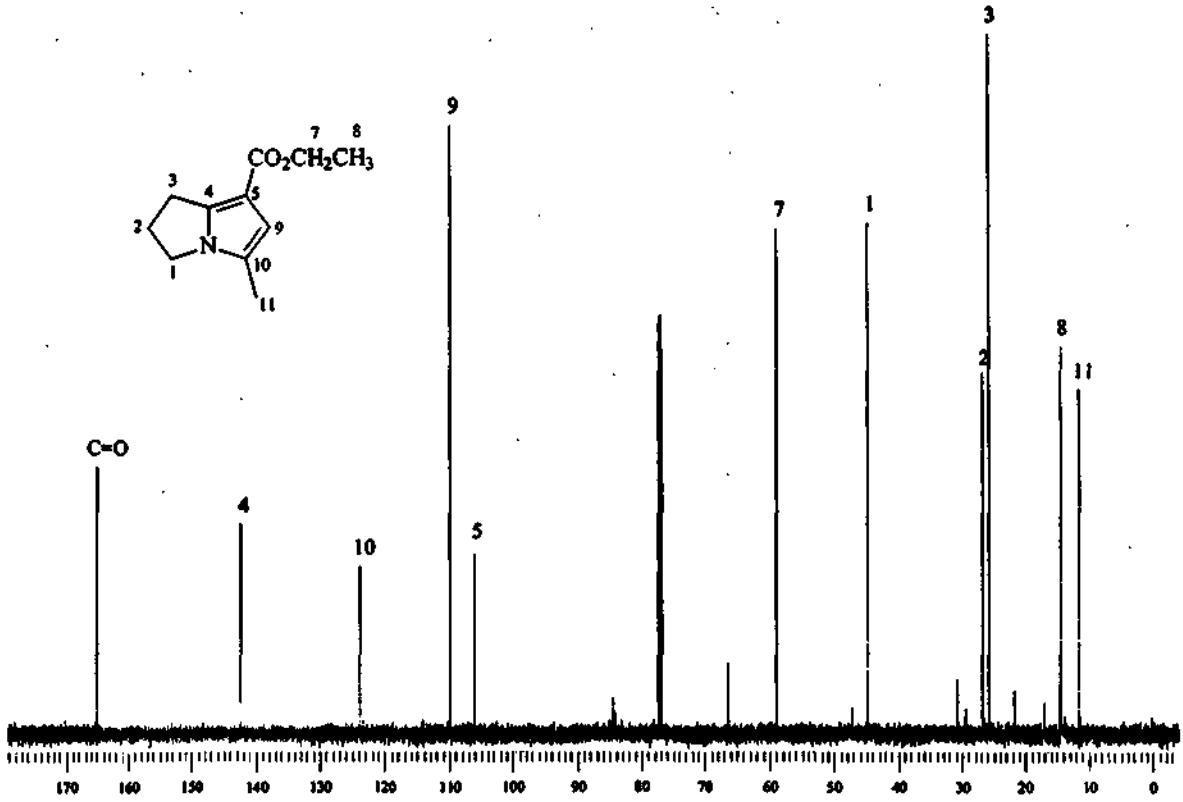


Spectrum 12

Conversion of the *C*-propargyl compounds to the corresponding *N*-bridgehead pyrroles proceeded efficiently, using microwave irradiation, to afford the desired compounds in good yield (Table 12). The observed yields are slightly lower than those obtained for the same reaction employing acyclic compounds (Table 8, p94) but the reaction can still be regarded as an efficient one. The NMR spectra of the smallest of the prepared *N*-bridgehead pyrroles are shown below (Spectrum 13 and Spectrum 14). Both the ^{1}H and ^{13}C NMR spectra are identical to those for the same compound prepared using a different method[142a] and full spectral assignments are displayed accordingly.



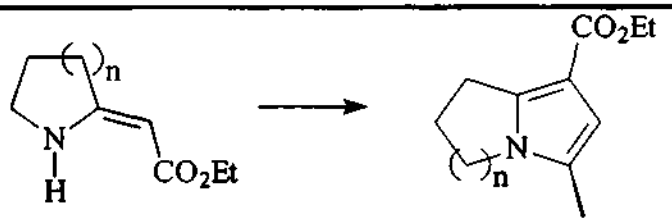
Spectrum 13



Spectrum 14

The original, one-pot, preparation of pyrroles was also employed to prepare *N*-bridgehead pyrroles directly from cyclic secondary vinylogous urethanes (Table 13). As expected, the yields of *N*-bridgehead pyrroles obtained in this fashion were very low and, in addition, the largest of the analogues (n = 3) could only be isolated as an inseparable mixture of starting material and product.

Table 13: Preparation of *N*-bridgehead pyrroles using one-pot method

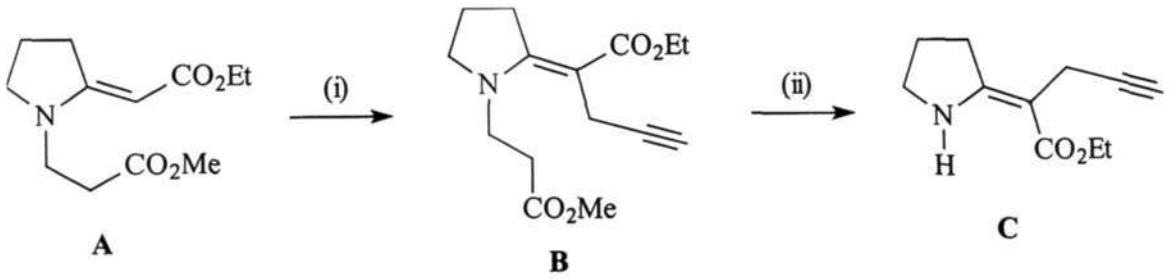


n	Yield / %
1	13
2	19
3	14*

* Isolated as an inseparable mixture of starting material and product.

12.5 Alternative preparation of cyclic *C*-propargyl vinylogous carbamates

An alternative preparation of cyclic *C*-propargyl vinylogous carbamates has also been investigated (Scheme 89). Heating the appropriate acrylate adduct and propargyl bromide in acetonitrile[149b] afforded the *C*-propargyl compound in high yield (>90%). This yield is approximate as the crude reaction mixture was deemed of sufficient purity (^{1}H NMR) to be used in the subsequent reaction. Removal of the acrylate protecting group using KHMDS did afford the correct secondary *C*-propargyl vinylogous carbamate, but in a low 15% yield. Analysis of the crude reaction mixture showed a complex mixture of compounds. This has been attributed to the additional acidic protons introduced by the propargyl group. The terminal acetylenic proton, at least, has a similar pK_a to the proton that is abstracted in order to effect removal of the acrylate group. The abstraction of the methylene protons of the propargyl group is also possible. Different reaction times (10 or 30 minutes) did not affect the yield of the final product.



A **B** **C**

(i) $BrCH_2CCH$, CH_3CN, Δ, >90% (ii) KHMDS, THF, RT, 15%

Scheme 89

13 Applications in total synthesis

Since the *C*-propargylation-silver-catalysed hydroamination strategy has been successfully extended to *N*-bridgehead pyrroles, the possibility of applying this methodology to the total synthesis of 'izidine' alkaloids was explored. General strategies for preparation of alkaloids are widespread in the literature and that of Michael and co-workers has been referred to on numerous occasions in this text.[104] It was hoped that the methodology developed here could be used as a general strategy towards 3,5-disubstituted pyrrolizidines, indolizidines and lehmizidines (Figure 32).[154] The following discussion refers to work that has been explored only briefly due to time constraints and mainly constitutes proposed future work.

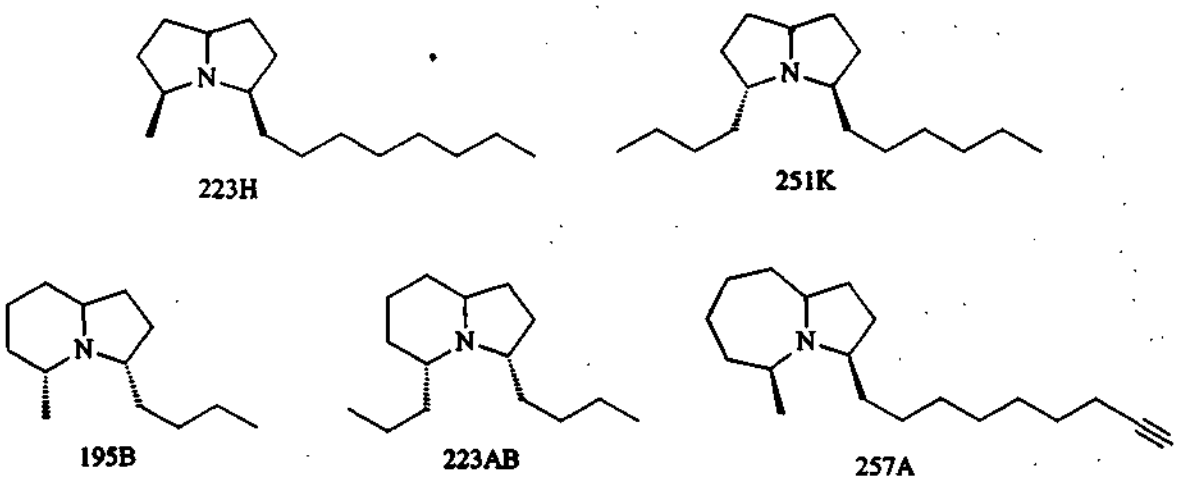


Figure 32

13.1 Overview of proposed general strategy

The brief discussion that follows is an overview of the strategy that was initially proposed to access the desired alkaloids and shall be elaborated upon in subsequent sections.

The starting point for each of the syntheses would be a chiral cyclic secondary vinylogous carbamate (Scheme 90, **A**). Treatment of the appropriate compound with 1-trimethylsilyl propargyl bromide[155] would afford the corresponding *C*-propargyl compound (Scheme

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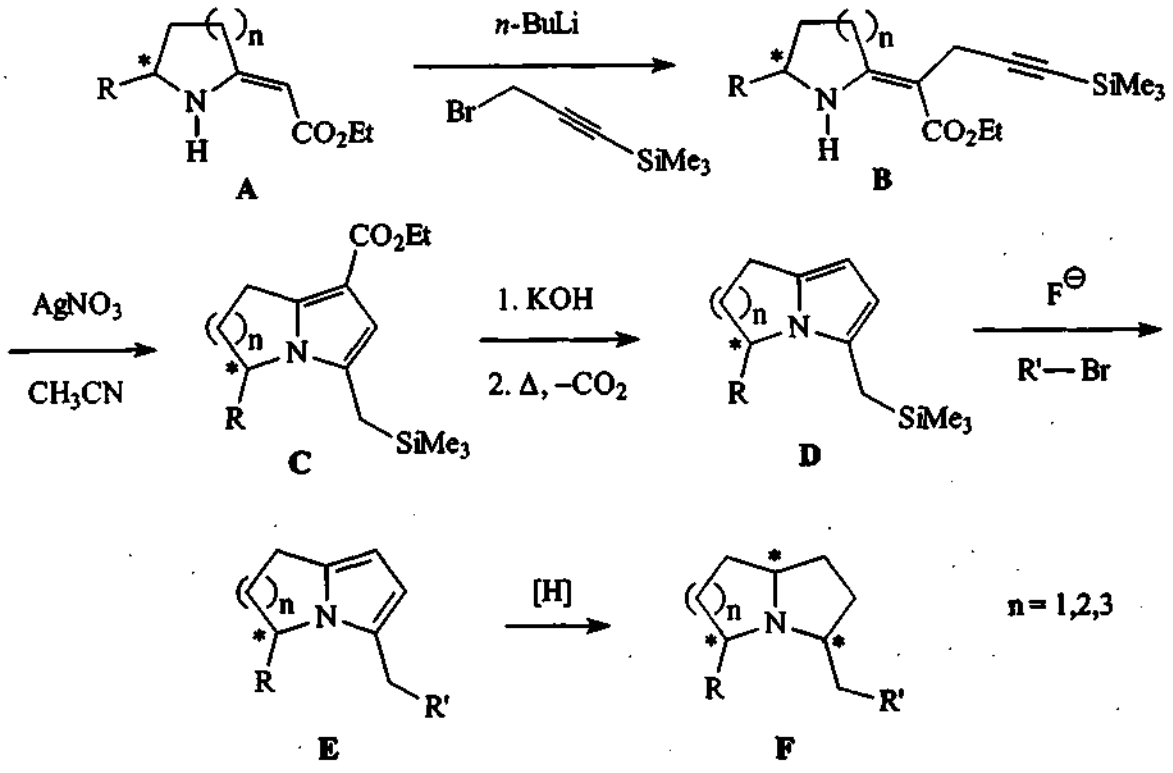
[154] a) Daly, J.W., *J. Med. Chem.*, **2003**, *46*, 445-452. b) Daly, J.W., *J. Nat. Prod.*, **1998**, *61*, 162-172.

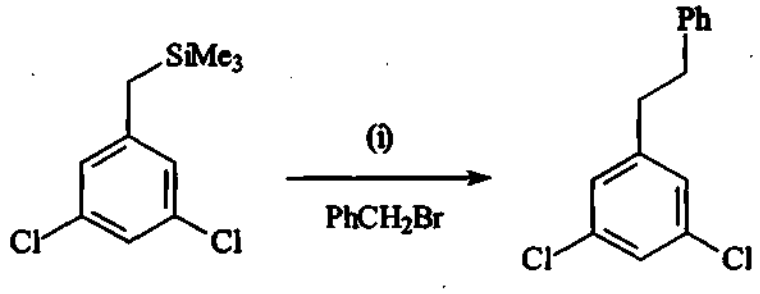
[155] Verkruijsse, H.D., Brandsma, L., *Synth. Commun.*, **1990**, *20*, 3375-3378.

90, **B**). Silver-catalysed hydroamination would provide the appropriate *N*-bridgehead pyrrole (Scheme 90, **C**) whose ester group could then be removed over two steps.[143] The step following deesterification is the most ambitious of the sequence and involves removal of the trimethylsilyl group with fluoride, affording a transient carbanion, that would be trapped with an alkyl halide affording the desired substituent at that position. This step is based on a related procedure in which benzyl trimethylsilanes are treated with different electrophiles in the presence of fluoride ions (Scheme 91).[156] The net result of this sequence is alkyl substitution at the carbon that previously bore the silicon atom.[156] Hydrogenation of the pyrrole intermediate (Scheme 90, **E**), a commonly employed step in alkaloid synthesis, would afford the desired 'izidine' alkaloid containing two new stereogenic centres as a result of the hydrogenation (Scheme 90, **F**) (Hydrogenation of pyrroles as a key step in alkaloid synthesis has been covered in more depth in the 'Introduction' p36). The stereochemical outcome of hydrogenation would be dependent upon a number of factors; the stereochemistry of the chiral centre introduced in the first step, the size of the substituent introduced in that step and also the catalyst and reaction conditions employed to effect hydrogenation.[89] A thorough investigation would be necessary to optimise this step.

[156] Ricci, A., Degl'innocenti, A., Fiorenza, M., Taddei, M., Spartera, M.A., Walton, D.R.M., *Tetrahedron Lett.*, **1982**, *23*, 577-578.



Scheme 90

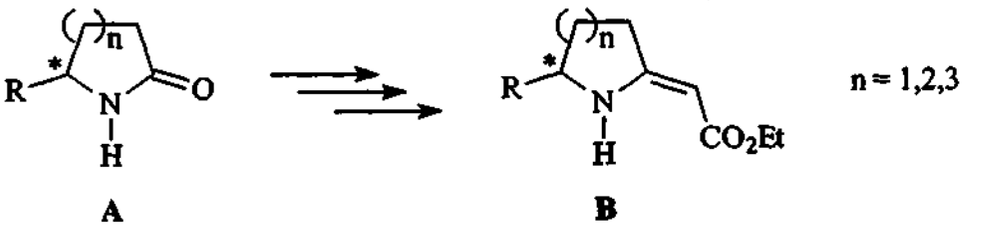


(i) KF / 18-crown-6 or silica-TBAF, THF, 20°C

Scheme 91

13.2 Preparation of enantiomerically pure starting materials

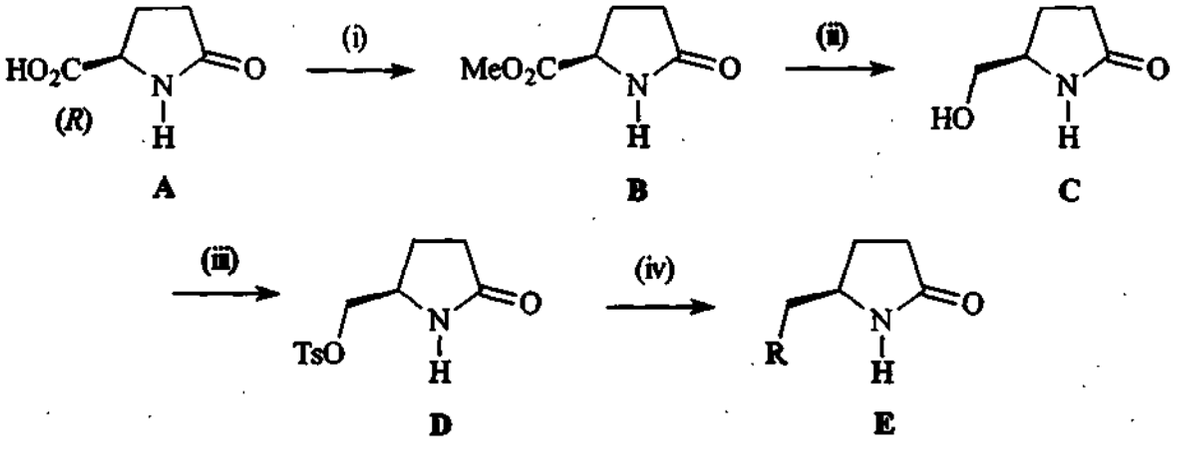
The success of this strategy would depend on the availability of chiral vinylogous carbamates (Figure 33, **B**), which would be prepared from corresponding chiral lactams (Figure 33, **A**).



A B

Figure 33

Enantiomerically pure 5-substituted pyrrolidinones (n = 1) can be prepared from commercially available (*R*)- or (*S*)-pyroglutamic acid (Scheme 92, **A**).[157] The ester of the lactam is reduced to the equivalent 5-hydroxymethyl lactam (Scheme 92, **C**).[158] Conversion of the alcohol to the tosylate (Scheme 92, **D**) followed by treatment with tributyltin hydride (Bu_3SnH) and AIBN affords 5-methyl 2-pyrrolidinone,[157a] or alternatively, higher alkyl substituents can be introduced by treatment of the tosylate with an appropriate lithium dialkylcuprate (Scheme 92, **E**).[157b] The stereochemistry of the original lactam is retained throughout this sequence of reactions.



A B C D E

(i) $SOCl_2$, MeOH, -25°C (ii) $NaBH_4$, EtOH, RT (iii) TsCl, NEt_3, CH_2Cl_2, RT
(iv) R = H, Bu_3SnH, AIBN, toluene, 80°C or R = alkyl, R_2CuLi, DME, -40°C

Scheme 92

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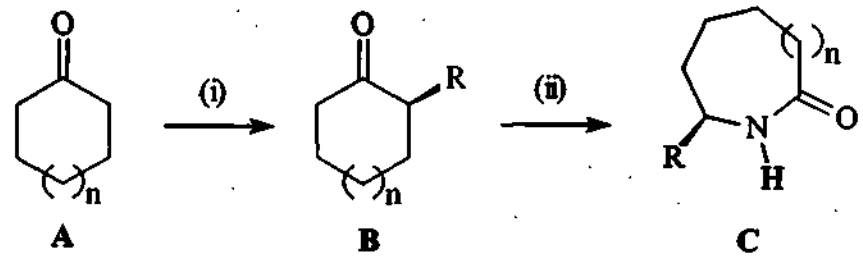
[157] a) Smith, M.B., Dembofsky, B.T., Son, Y.C., *J. Org. Chem.*, 1994, *59*, 1719-1725. b) Smith, A.L., Williams, S.F., Holmes, A.B., Hughes, L.B., Lidert, Z., Swithenbank, C., *J. Am. Chem. Soc.*, **1988**, *110*, 8696-8698.

[158] Acevedo, C.M., Kogut, E.F., Lipton, M.A., *Tetrahedron*, **2001**, *57*, 6353-6359.

Enantiomerically pure δ-valerolactams (n = 2) and ε-caprolactams (n = 3) are harder to prepare. Chiral precursors to the corresponding lactams are not available commercially and, therefore, need to be prepared *via* asymmetric synthesis. This can be accomplished by using the chiral auxiliary (*S*)- or (*R*)-1-amino-2-methoxymethyl-pyrrolidine (SAMP or RAMP), which allows for enantioselective preparation of α-alkyl cyclic ketones (Scheme 93, **B**).[159] The ketones prepared in this fashion can then undergo Beckmann rearrangement to afford the desired chiral lactams (Scheme 93, **C**).[160]



A **B** **C**

n = 0,1

(i) RAMP, LDA, RBr, HCl (ii) H_2NOSO_3H, HCO_2H

Scheme 93

13.3 Model studies of fluoride-induced alkyl substitution

Although all the steps of the proposed synthetic route have literature precedent, the most ambitious of these is the, fluoride-induced, alkyl substitution of the trimethylsilyl group and, therefore, model studies were carried out to determine the likelihood of this reaction being successful. 3-Bromo-1-trimethylsilylpropyne was prepared by treating propargyl bromide with LDA, trimethylsilyl chloride and hexamethylphosphoramide (HMPA).[155] *C*-Propargylation using this substituted propargyl bromide afforded both the desired compound (Scheme 94, **A**) and the bisadduct (Scheme 94, **B**). This result is contrary to that obtained for reaction of the same vinylogous carbamate and unsubstituted propargyl bromide, perhaps indicating that the trimethylsilyl group increases the reactivity of propargyl bromide.

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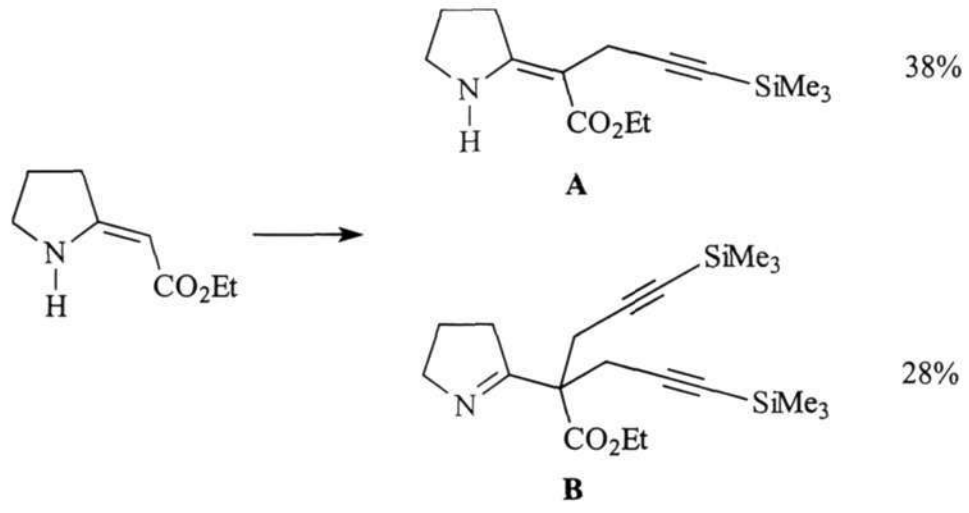
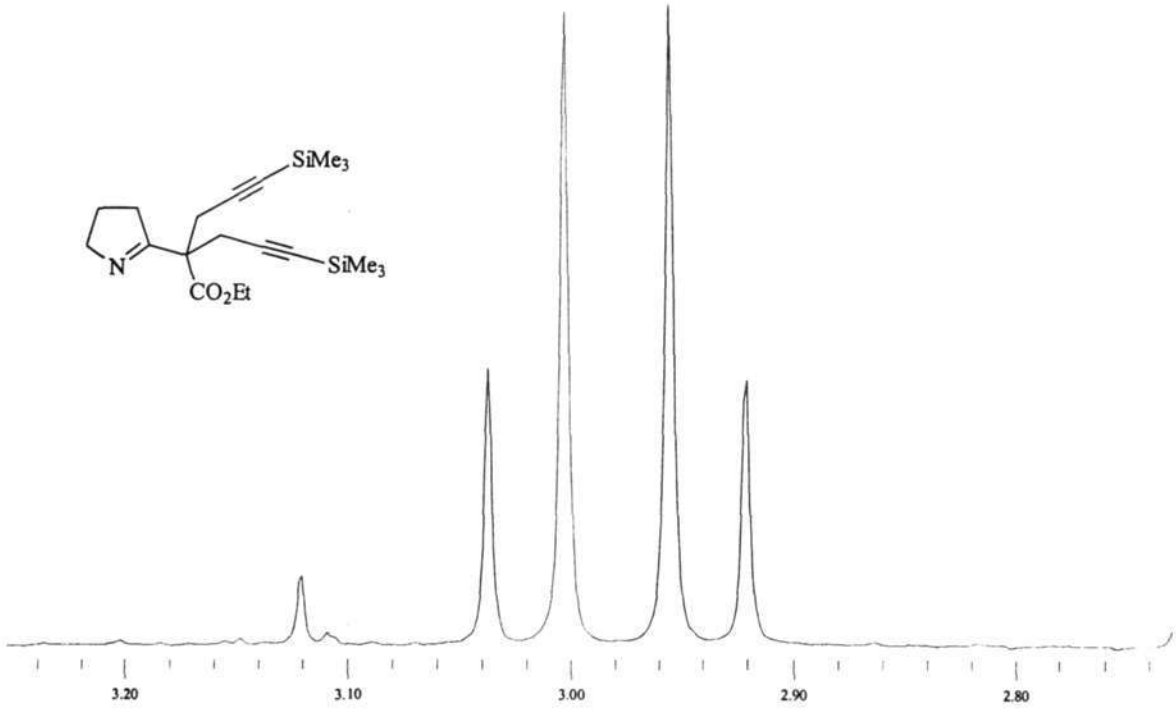
[159] a) Enders, D., Eichenauer, H., Baus, U., Schubert, H., Kremer, K.A.M., *Tetrahedron*, **1984**, *40*, 1345-1359. b) Enders, D., Eichenauer, H., *Chem. Ber.*, **1979**, *112*, 2933-2960.

[160] For example see Duhamel, P., Kotera, M., Marabout, B., *Tetrahedron: Asymmetry*, **1991**, *2*, 203-206.



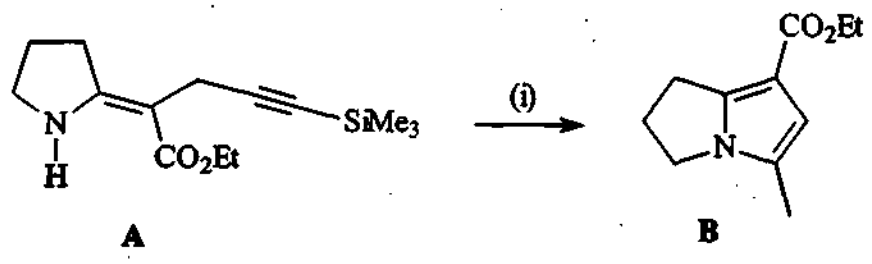
Scheme 94

The ^{1}H NMR spectrum of the bisadduct shows the same splitting pattern as similar bisadducts prepared previously (Spectrum 15). However, the appropriate signal appears as a pair of doublets (J = 17.0 Hz), but is not split further due to the substitution at the terminal position.



Spectrum 15

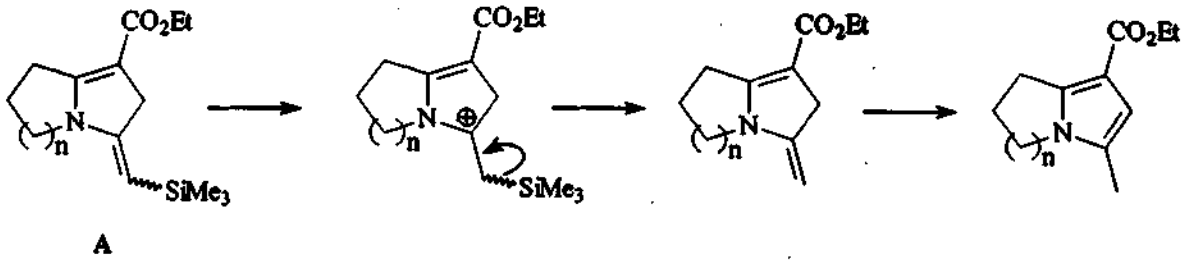
However, treating the *C*-propargyl compound (Scheme 95, **A**) with silver nitrate, using standard conditions, did not afford the desired trimethylsilyl substituted *N*-bridgehead pyrrole but rather the *N*-bridgehead pyrrole derived from the unsubstituted *C*-propargyl compound (Scheme 95, **B**).



(i) $AgNO_3$, CH_3CN, 30%

Scheme 95

It was, subsequently, found that silver salts have been used to deprotect alkynes protected with silyl groups, although the mechanism of this deprotection has not been specified.[161] The yield observed for the reaction (30%) and the quantity of silver nitrate present (0.2 eq) indicate that the cyclisation is still catalytic with respect to silver nitrate and presumably occurs *via* an analogous mechanism. The absence of the silyl group in the final product could arise from substitution of the silicon atom with an electrophile (H^+) after formation of a vinyl silane intermediate (Scheme 96, **A**). The relatively low yield of product could be due to deactivation of the catalyst deprotection of the alkynyl silane, forming an inactive σ-bonded silver complex.



Scheme 96

[161] a) Jackson, W.P., Ley, S.V., *J. Chem. Soc., Perkin Trans. 1*, **1981**, 1516-1519. b) Corey, E.J., Kirst, H.A., *Tetrahedron Lett.*, **1968**, *9*, 5041-5043.

13.4 Alternative methods of introducing an alkyl side-chain

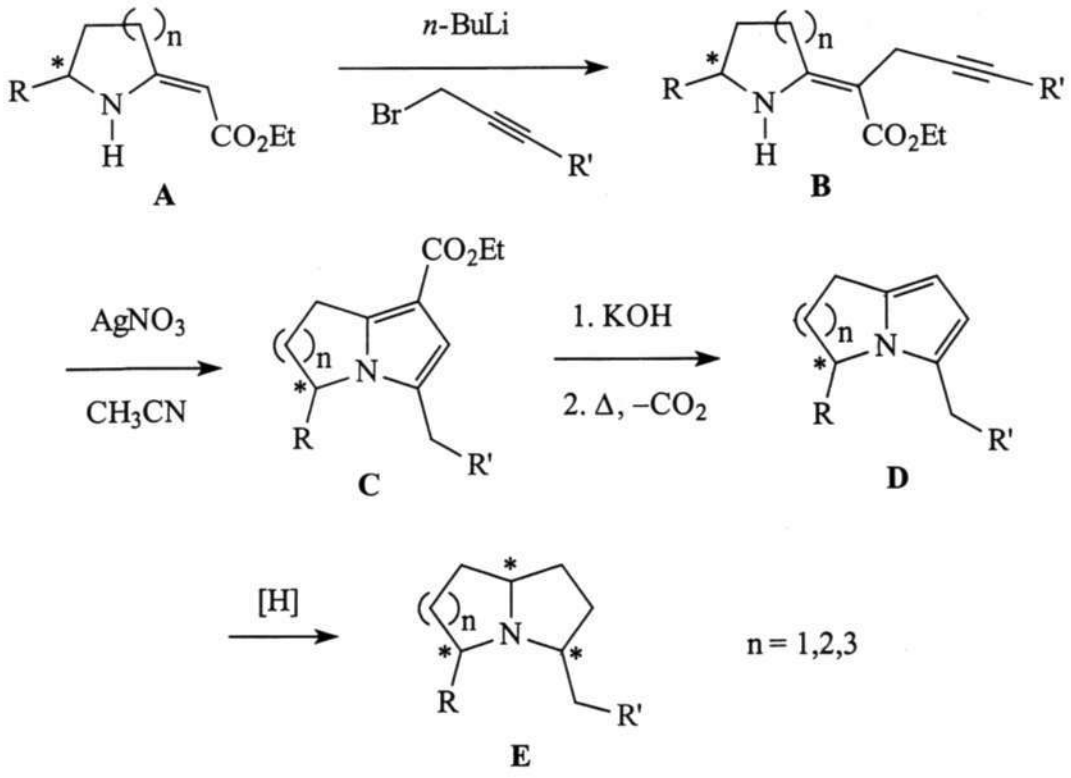
Fluoride-induced alkyl substitution is an attractive means of introducing the desired alkyl group as 1-trimethylsilyl propargyl bromide can be employed as a general reagent and the appropriate alkyl group can be introduced at a later stage. Nonetheless, due to the trimethylsilyl group's failure to survive hydroamination, another method needs to be found to introduce the desired alkyl group. A possible, although laborious, alternative is to employ an appropriately substituted 1-alkyl propargyl bromide in the synthetic sequence. These compounds can be prepared over two steps from propargyl alcohol (Scheme 97).[162]

(i) 2 *n*-BuLi, RBr, THF (ii) CBr_4, PPh_3, benzene

Scheme 97

As 1-bromo-2-pentyne has been shown to undergo the required hydroamination to afford an appropriately substituted pyrrole (p79), this methodology appears exploitable. Therefore, a revised, general preparation of 3,5-disubstituted 'izidine' alkaloids is shown below (Scheme 98).

[162] a) Makabe, H., Tanaka, A., Oritani, T., *J. Chem. Soc., Perkin Trans. 1*, **1994**, 1975-1982. b) Cao, X., Yang, Y., Wang, X., *J. Chem. Soc., Perkin Trans. 1*, **2002**, 2485-2489.



Scheme 98

14 Conclusions

The aim of this project was to develop general methods for the preparation of nitrogen-containing heterocycles. In addition to this, general synthetic precursors were identified as target compounds, and we believe that our endeavours have gone a long way toward satisfying these goals. It must be said that the work described above has been a journey rather than a destination and, as such, a number of aspects of the investigation remain unfinished. Nevertheless, we believe that several important contributions have been made therein.

Although our primary goal, the mechanism of indolizinone formation, was not determined, other interesting observations were made during these studies. *N*-Allenyl enaminones were identified as extremely interesting compounds even though their presence as intermediates in indolizinone formation was not substantiated. The factors influencing the preparation of *N*-allenyl enaminones as well their chemical reactivity could be, in hindsight, the subject of a large independent study.

Secondary enaminones, both cyclic and acyclic, have shown themselves to be extremely complex compounds. Ironically, this complexity is not betrayed by their appearance. The manipulation of such systems has, unintentionally, been the subject of most of our work, whether it be *C*-propargylation or preparation of cyclic vinylogous carbamates. Again, methods for controlling the reactivity of such systems could be the subject of a substantial investigation.

Without a doubt, the focus of the work discussed above is the preparation of functionalised pyrroles. The one-pot reaction that provides these compounds is an extremely interesting one and, we believe, its full potential has still not been realised. The two-step methodology provides overall improvement to the process although the *C*-propargylation reaction still limits the efficiency of the procedure.

Future work, in the form of a general procedure for the preparation of 3,5-disubstituted 'izidine' alkaloids, has been proposed. The extent to which this procedure has been investigated has been limited by time constraints and, if the formation of functionalised

pyrroles can be optimised further, this route may become a practical method for the preparation of important and exciting alkaloids.

Experimental

General

Instrumentation:

NMR spectra were recorded using either a 500 MHz Varian Unity Inova spectrometer equipped with an Oxford magnet (11.744T) and a switchable 5mm probe or a 200 MHz Varian Gemini-200 instrument.

^{1}H NMR spectra were recorded at either 500 or 200 MHz, ^{13}C NMR spectra were recorded at either 125 or 50 MHz and ^{11}B NMR spectra were recorded at 160 MHz.

Spectra were referenced against either the $CDCl_3$ singlet at 7.26 ppm, the central line of the $CDCl_3$ triplet at 77.0 ppm or the D_2O singlet at 4.26 ppm.

IR spectra were recorded as thin films (chloroform) using a Perkin Elmer Spectrum One spectrometer.

Low resolution (Electron Impact) mass spectra were recorded using a ThermoFinnigan Polaris / GCQ Plus instrument or a Hewlett-Packard gas chromatographic mass specrometer (HP5988A).

High resolution mass spectra were obtained by the Mass Spectrometry Unit of the Cape Technikon on a double-focusing Kratos MS 80RF mass spectrometer, the Mass Spectrometry Service at the School of Chemistry at the University of the Witwatersrand using a Micromass VG 70 SEQ mass spectrometer and the Mass Spectrometry Unit of the University of the North West using an Autospec-TOF (Micromass) mass spectrometer.

X-ray diffraction data were collected on an Oxford Diffraction Xcalibur2 CCD 4-circle diffractometer equipped with an Oxford Instruments Cryojet.

Melting points were determined using a Kofler hot-stage melting point apparatus.

Microwave reactions were carried out using a National 700 W domestic microwave oven.

Solvents:

Solvents were dried using the agents described hereafter and were distilled before use.

THF and Et_2O from Na / benzophenone. CH_3CN from CaH_2. CH_2Cl_2 from P_2O_5. MeOH from Mg turnings. $CHCl_3$ and CCl_4 were filtered through a short plug of basic Al_2O_3. EtOAc and hexane were distilled for use in chromatography.

Chromatography:

Silica gel 60 PF_{254} was used for column and radial chromatography. Thin layer chromatography was carried out using silica gel 60 F_{254} aluminium backed plates. The plates were viewed under UV light and developed in iodine thereafter.

Explanation of NMR abbreviations:

s – singlet; d – doublet; t – triplet; q – quartet; m – multiplet (Any, non-first order, signal with a multiplicity greater than a quartet. The chemical shift of a symmetrical multiplet is quoted as the midpoint of that multiplet, whereas the chemical shift of a complex, unsymmetrical multiplet is quoted as a range.); br – broad (Any signal for which a multiplicity cannot be assigned).

Miscellaneous:

Silica gel 60, 230-400 mesh, was used as an inert support for microwave reactions.

The concentrations of *n*- and *t*-BuLi solutions were determined by titration against a standard solution of *n*-BuOH (2.00M) using bipyridyl as indicator.

t-BuOK and KHMDS powders were weighed and delivered using the inert atmosphere provided by a glove box.

Meldrum's acid was prepared using a literature procedure.[163]

NaOEt was freshly prepared from Na metal and absolute EtOH.

Dynamic ^{11}B NMR experiments were carried out in quartz NMR tubes using $NaB(Ph)_4$ as external standard.

Spectra:

All spectra referred to in the 'Discussion' have been included within the text. Supplementary spectra have been included in electronic format (enclosed CD). NMR spectra have been included as FIDs and Mestrec and Spinworks software packages have been included to facilitate viewing of these spectra. IR, MS and HRMS spectra, as well as X-ray data tables for compound 9.15, have been included as word documents. Each folder has been assigned the same number as the compound whose spectra are found therein. The compounds are numbered roughly according to the section, and order, they appear in the text.

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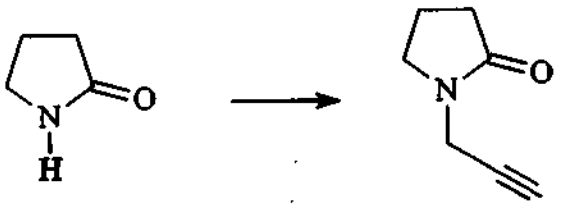
[163] Davidson, D., Bernhard, S.A., *J. Am. Chem. Soc.*, **1948**, *70*, 3426-3428.

5.1 1-Prop-2-ynyl pyrrolidin-2-one (*N*-propargyl pyrrolidinone)[100]



C_7H_9NO
123.15

NaH (50% w/w suspension in mineral oil, 2.05 g, 42.7 mmol) was added to a stirred solution of pyrrolidin-2-one (2.70 ml, 3.02 g, 35.5 mmol) and propargyl bromide (80% w/w solution in toluene, 4.80 ml, 5.13 g, 43.1 mmol) in THF (20 ml) at 0°C. The solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched by the addition of water (10 ml) and extracted with EtOAc (3 × 20 ml). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to afford 1-prop-2-ynyl pyrrolidin-2-one as a yellow oil (3.99 g, 32.4 mmol, 91%) after column chromatography (EtOAc/Hex 1:1); R_f 0.45 (EtOAc/Hex 1:1).

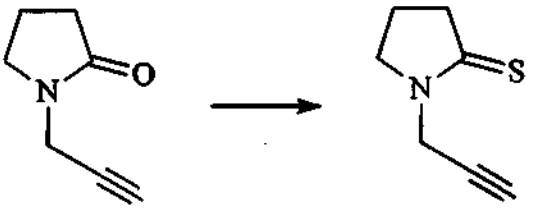
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 4.05 (2H, d, J = 2.7 Hz, $C\underline{H}_2C{\equiv}CH$), 3.45 (2H, t, J = 7.3 Hz, $NC\underline{H}_2CH_2$), 2.35 (2H, t, J = 8.2 Hz, $C\underline{H}_2C{=}O$), 2.20 (1H, t, J = 2.1 Hz, $C{\equiv}C\underline{H}$), 2.01 (2H, m, $NCH_2C\underline{H}_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 174.6 (C=O), 77.5 ($\underline{C}{\equiv}CH$), 72.1 ($C{\equiv}\underline{C}H$), 46.2 $N\underline{C}H_2CH_2$), 31.8 ($\underline{C}H_2C{\equiv}CH$), 30.5 ($\underline{C}H_2C{=}O$), 17.4 ($NCH_2\underline{C}H_2$).

MS (EIMS): *m/z* (%) = 123 [M^+] (16), 95 (100), 67 (38).

HRMS: found *m/z* = 123.0685 [M^+], C_7H_9NO requires 123.0684.

5.2 1-Prop-2-ynyl pyrrolidine-2-thione (*N*-propargyl pyrrolidinethione)[101]



C_7H_9NS
139.21

Na_2CO_3 (3.51 g, 33.1 mmol) was added, slowly, to a suspension of P_4S_{10} (14.70 g, 33.07 mmol) in dry THF (30 ml) and stirred at ambient temperature until the mixture became homogeneous (typically 20-30 minutes). 1-Prop-2-ynyl pyrrolidin-2-one (3.38 g, 27.4

mmol) was added thereafter and stirred for a further 4 hours. The reaction was quenched by the addition of 10% $Na_3PO_{4(aq)}$ solution (20 ml) and extracted with EtOAc (3 × 50 ml). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to afford 1-prop-2-ynyl pyrrolidine-2-thione as a colourless oil (1.56 g, 11.2 mmol, 41%) after column chromatography (EtOAc/Hex 3:1); R_f 0.60 EtOAc/Hex 3:1.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 4.59 (2H, d, J = 1.8 Hz, $C\underline{H}_2C{\equiv}CH$), 3.83 (2H, t, J = 7.4 Hz, $NC\underline{H}_2CH_2$), 3.03 (2H, t, J = 8.2 Hz, $C\underline{H}_2C{=}S$), 2.31 (1H, t, J = 1.9 Hz, $C{\equiv}C\underline{H}$), 2.08 (2H, m, $NCH_2C\underline{H}_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 201.9 (C=S), 76.1 ($\underline{C}{\equiv}CH$), 73.4 ($C{\equiv}\underline{C}H$), 53.7 ($N\underline{C}H_2CH_2$), 44.6 ($\underline{C}H_2C{=}S$), 37.1 ($\underline{C}H_2C{\equiv}CH$), 29.6 ($NCH_2\underline{C}H_2$).

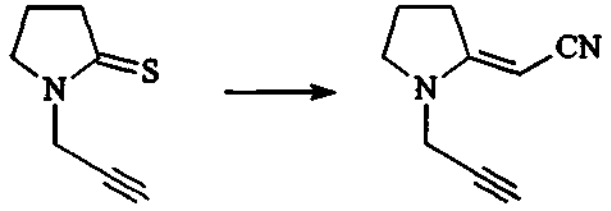
MS (EIMS): *m/z* (%) = 139 [M^+] (100), 106 (53), 79 (24), 69 (20).

HRMS: found *m/z* = 139.0450 [M^+], C_7H_9NS requires 139.0456.

Preparation of *N*-propargyl enaminones: General procedure (Eschenmoser coupling)[97]

The appropriate bromo compound (6 mmol) was added dropwise to a solution of 1-prop-2-ynyl pyrrolidine-2-thione (4 mmol) in dry CH_3CN (2 ml). Reaction progress was monitored by TLC analysis until salt formation was complete (typically 5-10 hrs). When salt formation was complete, PPh_3 (6 mmol) and NEt_3 (6 mmol) were added, as a solution in CH_2Cl_2 (5 ml), and stirred for 2 hours. The reaction was quenched with water (20 ml) and extracted with CH_2Cl_2 (3 × 20ml). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo* to afford the desired *N*-propargyl enaminones after chromatography.

5.3 (2*E*)-(1-Prop-2-ynylpyrrolidin-2-ylidene)acetonitrile



$C_9H_{10}N_2$
146.19

1-Prop-2-ynyl pyrrolidine-2-thione (0.56 g, 4.0 mmol) was treated with bromoacetonitrile (0.45 ml, 0.75 g, 6.3 mmol), PPh_3 (1.60 g, 6.10 mmol) and NEt_3 (0.85 ml, 0.62 g, 6.1 mmol) to afford (2*E*)-(1-prop-2-ynylpyrrolidin-2-ylidene)acetonitrile as a yellow oil (0.28 g, 1.9 mmol, 48%) after radial chromatography (CH_2Cl_2/Hex 1:1); R_f 0.39 (EtOAc/Hex 1:1).

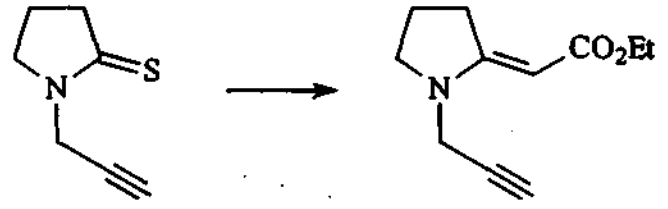
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 3.82 (2H, d, *J* = 2.6 Hz, C$\underline{H}_2$C≡CH), 3.75 (1H, s, C=C$\underline{H}$), 3.46 (2H, t, *J* = 6.4 Hz, NC$\underline{H}_2$CH$_2$), 2.82 (2H, t, *J* = 7.8 Hz, C$\underline{H}_2$C=CH), 2.26 (1H, t, *J* = 1.8 Hz, C≡C$\underline{H}$), 1.96 (2H, m, NCH$_2$C$\underline{H}_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 165.3 ($\underline{C}$=CH), 122.1 (C≡N), 76.6 ($\underline{C}$≡CH), 73.4 (C≡$\underline{C}$H), 56.2 (C=$\underline{C}$H), 53.4 (N$\underline{C}$H$_2$CH$_2$), 35.8 ($\underline{C}$H$_2$C≡CH), 32.7 ($\underline{C}$H$_2$C=CH), 20.8 (NCH$_2\underline{C}$H$_2$).

MS (EIMS): *m/z* (%) = 146 [M^+] (40), 145 (100), 118 (28), 91 (17), 78 (15), 52 (13).

HRMS: found *m/z* = 146.0836 [M^+], $C_9H_{10}N_2$ requires 146.0844.

5.4 Ethyl (2*E*)-(1-prop-2-ynylpyrrolidin-2-ylidene)acetate



$C_{11}H_{15}NO_2$
193.24

1-Prop-2-ynyl pyrrolidine-2-thione (0.57 g, 4.0 mmol) was treated with ethyl bromoacetate (0.70 ml, 1.1 g, 6.3 mmol), PPh_3 (1.66 g, 6.33 mmol) and NEt_3 (0.90 ml, 0.65 g, 6.5 mmol) to afford ethyl (2*E*)-(1-prop-2-ynylpyrrolidin-2-ylidene)acetate as a colourless oil (0.27 g, 1.4 mmol, 34%) after radial chromatography (CH_2Cl_2/Hex 1:1); R_f 0.48 (EtOAc/Hex 1:3).

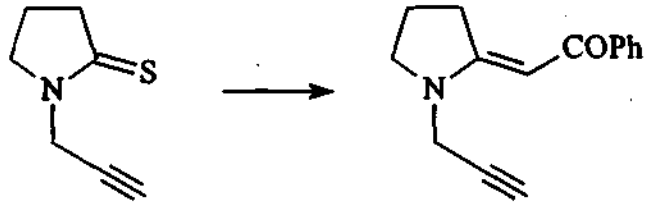
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 4.63 (1H, s, C=C$\underline{H}$), 4.09 (2H, t, *J* = 7.3 Hz, OC$\underline{H}_2$CH$_3$), 3.91 (2H, d, *J* = 2.6 Hz, C$\underline{H}_2$C≡CH), 3.42 (2H, t, *J* = 7.3 Hz, NC$\underline{H}_2$CH$_2$), 3.14 (2H, t, *J* = 8.0 Hz, C$\underline{H}_2$C=CH), 2.24 (1H, t, *J* = 1.8 Hz, C≡C$\underline{H}$), 1.96 (2H, m, NCH$_2$C$\underline{H}_2$), 1.25 (3H, t, *J* = 7.4 Hz, OCH$_2$C$\underline{H}_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 169.0 (C=O), 164.2 ($\underline{C}$=CH), 80.1 (C=$\underline{C}$H), 77.1 ($\underline{C}$≡CH), 72.5 (C≡$\underline{C}$H), 58.5 (O$\underline{C}$H$_2$CH$_3$), 51.9 (N$\underline{C}$H$_2$CH$_2$), 35.6 ($\underline{C}$H$_2$C≡CH), 32.3 ($\underline{C}$H$_2$C=CH), 20.8 (NCH$_2\underline{C}$H$_2$), 14.7 (OCH$_2\underline{C}$H$_3$).

MS (EIMS): *m/z* (%) = 194 [M^+ + 1] (6), 193 [M^+] (8), 148 (35), 121 (24), 120 (100), 92 (11), 85 (13), 57 (21), 43 (18).

HRMS: found *m/z* = 193.1098 [M^+], $C_{11}H_{15}NO_2$ requires 193.1103.

5.5 (2*E*)-1-Phenyl-2-(1-prop-2-ynylpyrrolidin-2-ylidene)ethanone



$C_{15}H_{15}NO$
225.29

1-Prop-2-ynyl pyrrolidine-2-thione (0.10 g, 0.71 mmol) was treated with phenacyl bromide (0.33 g, 1.7 mmol), PPh_3 (0.45 g, 1.7 mmol) and NEt_3 (0.24 ml, 0.17 g, 1.7 mmol) to afford (2*E*)-1-phenyl-2-(1-prop-2-ynylpyrrolidin-2-ylidene)ethanone as a brown oil (51 mg, 0.23 mmol, 32%) after radial chromatography (CH_2Cl_2/Hex 1:1 → EtOAc/Hex 1:3); R_f 0.12 (EtOAc/Hex 1:2).

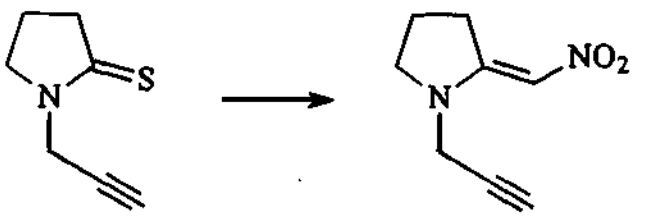
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.89-7.87 (2H, m, *o*-$C_6\underline{H}_5$), 7.42-7.37 (3H, m, *m*- and *p*-$C_6\underline{H}_5$), 5.82 (1H, s, C=C$\underline{H}$), 4.05 (2H, d, *J* = 2.4 Hz, $C\underline{H}_2C{\equiv}CH$), 3.50 (2H, t, *J* = 7.3 Hz, $NC\underline{H}_2CH_2$), 3.37 (2H, t, *J* = 7.3 Hz, $C\underline{H}_2C{=}CH$), 2.31 (1H, t, *J* = 1.8 Hz, C≡C$\underline{H}$), 2.02 (2H, m, $NCH_2C\underline{H}_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 188.1 (C=O), 166.0 ($\underline{C}$=CH), 141.7 (*ipso*-$\underline{C}_6H_5$), 130.5 (*p*-$\underline{C}_6H_5$), 128.0 (2C, *m*-$\underline{C}_6H_5$), 127.2 (2C, *o*-$\underline{C}_6H_5$), 87.7 (C=$\underline{C}$H), 76.6 ($\underline{C}{\equiv}CH$), 72.9 (C≡$\underline{C}$H), 52.1 ($N\underline{C}H_2CH_2$), 35.8 ($\underline{C}H_2C{\equiv}CH$), 33.5 ($\underline{C}H_2C{=}CH$), 20.7 ($NCH_2\underline{C}H_2$).

MS (EIMS): *m/z* (%) = 225 [M^+] (22), 224 (100), 196 (22), 120 (82), 105 (19), 77 (43).

HRMS: found *m/z* = 224.1079 [M^+-H], $C_{15}H_{14}NO$ requires 224.1075.

5.6 (2*E*)-2-(Nitromethylene)-1-prop-2-ynylpyrrolidine[103]



$C_8H_{10}N_2O_2$
166.17

MeI (0.24 ml, 0.55 g, 3.9 mmol) was added to a stirred solution of 1-prop-2-ynyl pyrrolidine-2-thione (0.18 g, 1.3 mmol) in dry $CHCl_3$ (5 ml). Reaction progress was monitored by TLC analysis until salt formation was complete (5 hours). CH_3NO_2 (0.15 ml, 0.17 g, 2.8 mmol) was added along with K_2CO_3 (anhydrous, 0.77 g, 5.6 mmol) and the mixture was stirred overnight. The reaction was quenched with water (20 ml) and extracted with CH_2Cl_2 (3 × 20ml). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to afford (2*E*)-2-(nitromethylene)-1-prop-2-ynylpyrrolidine as a yellow crystalline solid (m.p. 143-144°C) (21 mg, 0.13 mmol, 10%) after preparative TLC (EtOAc/Hex 1:1); R_f 0.67 (EtOAc/Hex 3:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 6.77 (1H, s, C=C<u>H</u>), 3.95 (2H, br, C<u>H</u>$_2$C≡CH), 3.63 (2H, t, J = 7.4 Hz, NC<u>H</u>$_2$CH$_2$), 3.45 (2H, t, J = 7.7 Hz, C<u>H</u>$_2$C=CH), 2.35 (1H, br, C≡CH), 2.09 (2H, m, NCH$_2$C<u>H</u>$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 163.4 (<u>C</u>=CH), 110.6 (C=<u>C</u>H), 75.4 (<u>C</u>≡CH), 74.6 (C≡<u>C</u>H), 53.9 (N<u>C</u>H$_2$CH$_2$), 36.8 (<u>C</u>H$_2$C≡CH), 34.6 (<u>C</u>H$_2$C=CH), 20.6 (NCH$_2$<u>C</u>H$_2$).

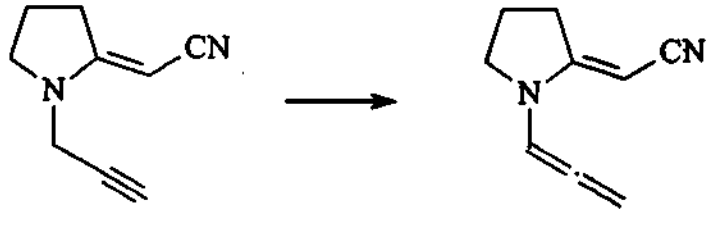
MS (EIMS): *m/z* (%) = 166 [M^+] (1), 120 (100), 119 (47), 118 (27), 92 (63), 65 (27).

HRMS: found *m/z* = 166.0744 [M^+], $C_8H_{10}N_2O_2$ requires 166.0742.

Preparation of *N*-allenyl compounds: General procedure[5a]

t-BuOK (1 mmol) was added to a solution of the appropriate *N*-propargyl enaminone (1 mmol) in dry THF (2 ml) and stirred at room temperature for 30 minutes. The solvent was removed *in vacuo* and the residue was dissolved in a minimum amount of CH_2Cl_2 and filtered (EtOAc) through a short plug of basic Al_2O_3 to afford the desired *N*-allenyl enaminones.

7.1 (2*E*)-(1-Propa-1,2-dienylpyrrolidin-2-ylidene)acetonitrile



$C_9H_{10}N_2$
146.19

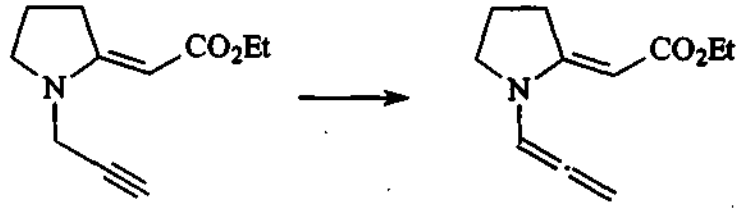
(2*E*)-(1-Prop-2-ynylpyrrolidin-2-ylidene)acetonitrile (41 mg, 0.28 mmol) was treated with *t*-BuOK (32 mg, 0.29 mmol) to afford (2*E*)-(1-propa-1,2-dienylpyrrolidin-2-ylidene)acetonitrile as a yellow oil (27 mg, 0.18 mmol, 66%); R_f 0.45 (EtOAc/Hex 1:3).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 6.40 (1H, t, J = 6.4 Hz, $\underline{H}C{=}C{=}CH_2$), 5.40 (2H, d, J = 6.4 Hz, $HC{=}C{=}C\underline{H}_2$), 3.98 (1H, s, $NC{=}C\underline{H}$), 3.42 (2H, t, J = 7.4 Hz, $NC\underline{H}_2$), 2.88 (2H, t, J = 7.9 Hz, $C\underline{H}_2C{=}CH$), 1.97 (2H, m, $NCH_2C\underline{H}_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 203.2 ($C{=}\underline{C}{=}CH$), 162.2 ($N\underline{C}{=}CH$), 121.5 ($C{\equiv}N$), 97.8 ($\underline{C}{=}C{=}CH_2$), 87.3 ($C{=}C{=}\underline{C}H_2$), 58.1 ($NC{=}\underline{C}H$), 52.0 ($N\underline{C}H_2$), 32.8 ($\underline{C}H_2C{=}CH$), 20.3 ($NCH_2\underline{C}H_2$).

HRMS: found *m/z* = 146.0844 [M^+], $C_9H_{10}N_2$ requires 146.0844.

7.2 Ethyl (2*E*)-(1-propa-1,2-dienylpyrrolidin-2-ylidene)acetate



$C_{11}H_{15}NO_2$
193.24

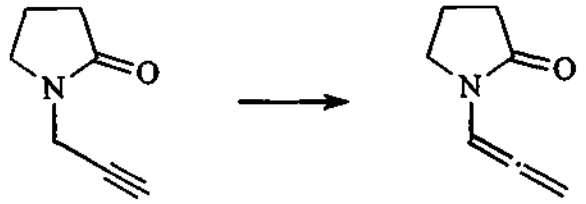
(2*E*)-(1-Prop-2-ynylpyrrolidin-2-ylidene)acetonitrile (41 mg, 0.28 mmol) was treated with *t*-BuOK (32 mg, 0.29 mmol) to afford (2*E*)-(1-Propa-1,2-dienylpyrrolidin-2-ylidene)acetonitrile as a yellow oil (27 mg, 0.18 mmol, 66%); R_f 0.45 (EtOAc/Hex 1:3).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 6.61 (1H, t, J = 6.4 Hz, $\underline{H}C{=}C{=}CH_2$), 5.37 (2H, d, J = 6.3 Hz, $HC{=}C{=}C\underline{H}_2$), 4.77 (1H, s, $NC{=}C\underline{H}$), 4.05 (2H, q, J = 7.2 Hz, $O\underline{C}H_2CH_3$), 3.33 (2H, t, J = 7.5 Hz, $NC\underline{H}_2$), 3.15 (2H, t, J = 7.8 Hz, $C\underline{H}_2C{=}CH$), 1.93 (2H, $NCH_2C\underline{H}_2$), 1.20 (3H, t, J = 7.4 Hz, $OCH_2C\underline{H}_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 203.5 ($C{=}\underline{C}{=}CH$), 168.9 ($C{=}O$), 160.9 ($N\underline{C}{=}CH$), 98.1 ($\underline{C}{=}C{=}CH_2$), 86.5 ($NC{=}\underline{C}H$), 81.7 ($C{=}C{=}\underline{C}H_2$), 58.5 ($O\underline{C}H_2CH_3$), 50.3 ($N\underline{C}H_2$), 32.3 ($\underline{C}H_2C{=}CH$), 20.4 ($NCH_2\underline{C}H_2$), 14.5 ($OCH_2\underline{C}H_3$).

HRMS: found *m/z* = 193.1110 [M^+], $C_{11}H_{15}NO_2$ requires 193.1103.

7.3 1-Propa-1,2-dienylpyrrolidin-2-one



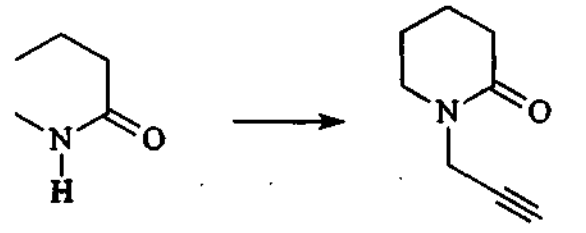
C_7H_9NO
123.15

1-Prop-2-ynyl pyrrolidin-2-one (0.35 g, 2.8 mmol) was treated with *t*-BuOK (1M solution in *t*-BuOH, 2.84 ml, 2.84 mmol) to afford 1-propa-1,2-dienylpyrrolidin-2-one as a colourless oil (0.27 g, 2.2 mmol, 77%).

^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 6.99 (1H, t, J = 6.2 Hz, $\underline{H}C=C=CH_2$), 5.29 (2H, d, J = 6.1 Hz, $HC=C=C\underline{H}_2$), 3.33 (2H, t, J = 7.4 Hz, $NC\underline{H}_2$), 2.39 (2H, t, J = 7.8 Hz, $C\underline{H}_2C=O$), 1.99 (2H, m, $NCH_2C\underline{H}_2$).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 203.3 ($C=\underline{C}=CH$), 173.6 (C=O), 96.4 ($\underline{C}=C=CH_2$), 87.2 ($C=C=\underline{C}H_2$), 46.4 ($N\underline{C}H_2$), 31.8 ($\underline{C}H_2C=O$), 18.0 ($NCH_2\underline{C}H_2$).

8.1 1-Prop-2-ynylpiperidin-2-one[100]



$C_8H_{11}NO$
137.18

NaH (50% w/w suspension in mineral oil, 1.88 g, 39.2 mmol) was added to a stirred solution of piperidin-2-one (δ-valerolactam) (3.19 g, 32.2 mmol) and propargyl bromide (80% w/w solution in toluene, 4.30 ml, 4.59 g, 38.6 mmol) in THF (20 ml) at 0°C. The solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched by the addition of water (10 ml) and extracted with EtOAc (3 × 20 ml). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to afford 1-prop-2-ynylpiperidin-2-one as a yellow oil (3.47 g, 25.3 mmol, 79%) after column chromatography (EtOAc/Hex 1:4 → EtOAc/Hex 1:1); R_f 0.34 (EtOAc/Hex 1:1).

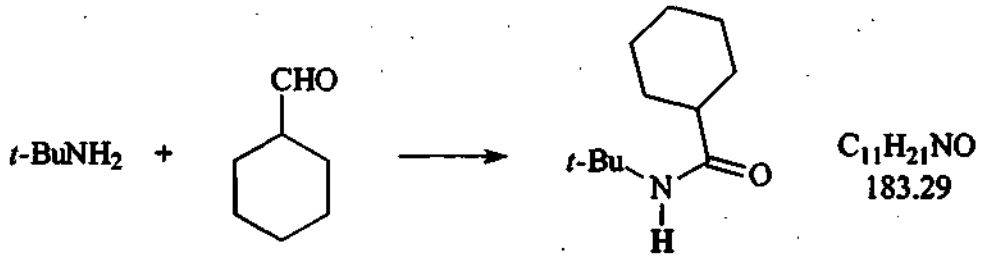
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 4.21 (2H, d, J = 2.7 Hz, $C\underline{H}_2C\equiv CH$), 3.38 (2H, t, J = 5.5 Hz, $NC\underline{H}_2CH_2$), 2.37 (2H, t, J = 6.4 Hz, $C\underline{H}_2C=O$), 2.18 (1H, t, J = 2.7 Hz, $C\equiv C\underline{H}$), 1.83 (2H, m, $NCH_2C\underline{H}_2$) 1.78 (2H, m, $NCH_2CH_2C\underline{H}_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 169.6 (C=O), 78.6 (C≡CH), 71.6 (C≡CH), 47.1 (NCH_2CH_2), 35.5 ($CH_2C{\equiv}CH$), 32.3 ($CH_2C{=}CH$), 23.0 (NCH_2CH_2), 21.2 ($NCH_2CH_2CH_2$). MS (EIMS): *m/z* (%) = 137 [M^+] (100), 108 (24), 95 (64), 84 (32), 80 (31), 68 (40).

Preparation of secondary amides: General procedure

N-Bromosuccinimide (NBS) (13 mmol) and AIBN (1 mol%) was added to a solution of the appropriate aldehyde (10 mmol) in dry CCl_4 (30 ml) and heated under reflux until the orange colouration had disappeared (~15 minutes). The reaction mixture was cooled to 0°C and the appropriate amine (23 mmol) was added. The resulting suspension was stirred at room temperature for a further 15 minutes, filtered, washed with water (20 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford the desired secondary amides after chromatography.

8.2 *N*-(*tert*-Butyl)cyclohexanecarboxamide



Cyclohexanecarboxaldehyde (2.00 ml, 1.85 g, 16.5 mmol) was treated with NBS (3.87 g, 21.7 mmol), AIBN (50 mg, 0.30 mmol) and *t*-$BuNH_2$ (4.00 ml, 2.77 g, 37.9 mmol) to afford *N*-(*tert*-butyl)cyclohexanecarboxamide as a white crystalline solid (m.p. 155-159°C) (lit.[164] 162°C) (1.11 g, 6.05 mmol, 37%) after column chromatography (EtOAc/Hex 1:3); R_f 0.55 (EtOAc/Hex 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 5.22 (1H, br, NH), 1.97-1.90 (1H, m, CH), 1.83-1.62 and 1.44-1.19 (10H, m, CHC_5H_{10}), 1.33 [9H, s, $NC(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 175.7 (C=O), 50.8 [$NC(CH_3)_3$], 46.3 (CH), 29.8 [2C, $CH(CH_2)_2$], 28.9 [3C, $NC(CH_3)_3$], 25.7 [3C, $(CH_2)_2CH_2$].

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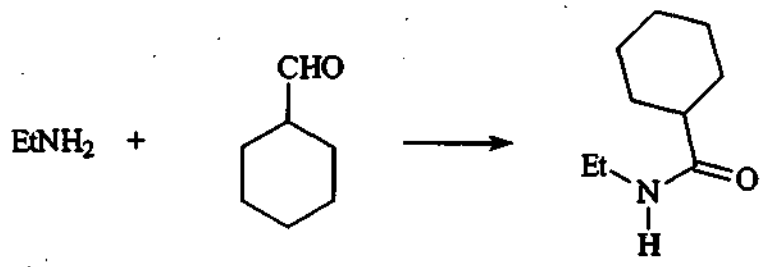
[164] De Kimpe, N., Verhe, R., De Buyck, L., Chys, J., Schamp, N., *Org. Prep. Proced. Int.*, **1978**, *10*, 149-156.

MS (EIMS): *m/z* (%) = 183 [M^+] (44), 168 (11), 128 (100), 111 (16), 83 (46), 58 (60).

8.3 *N*-Ethylcyclohexanecarboxamide



$C_9H_{17}NO$
155.24

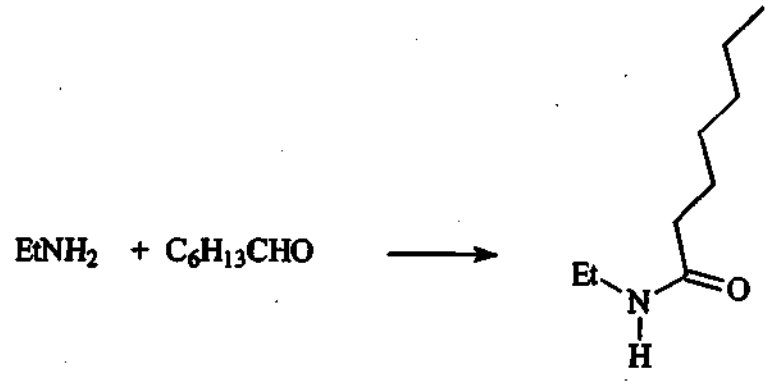
Cyclohexanecarboxaldehyde (3.50 ml, 3.24 g, 28.9 mmol) was treated with NBS (6.69 g, 37.6 mmol), AIBN (80 mg, 0.49 mmol) and $EtNH_2$ (70% w/w solution in water, 4.00 ml, 2.77 g, 37.9 mmol) to afford *N*-(*tert*-butyl)cyclohexanecarboxamide as a white crystalline solid (m.p. 91-96°C) (lit.[165] 98-99.5°C) (1.92 g, 12.4 mmol, 43%) after column chromatography (EtOAc/Hex 1:4); R_f 0.33 (EtOAc/Hex 1:4).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 6.34 (1H, br, NH), 3.14 (2H, m, $NC\underline{H}_2CH_3$), 2.03-1.96 (1H, m, C<u>H</u>), 1.73-1.61 [4H, m, $CH(C\underline{H}_2)_2$], 1.56-1.51 and 1.36-1.26 and 1.17-1.06 [6H, m, $(C\underline{H}_2)_2C\underline{H}_2$], 1.00 (3H, t, J = 7.3 Hz, $NCH_2C\underline{H}_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 176.1 (C=O), 45.1 (<u>C</u>H), 33.8 ($N\underline{C}H_2CH_3$), 29.4 [2C, $CH(\underline{C}H_2)_2$], 25.5 [3C, $(\underline{C}H_2)_2\underline{C}H_2$], 14.5 ($NCH_2\underline{C}H_3$).

MS (EIMS): *m/z* (%) = 155 [M^+] (57), 126 (22), 100 (100), 87 (42), 83 (35), 72 (36).

8.4 *N*-Ethylheptanamide



$C_9H_{19}NO$
157.25

[165] Gassman, P.G., Fox, B.L., *J. Org. Chem.*, **1967**, *32*, 3670-3680.

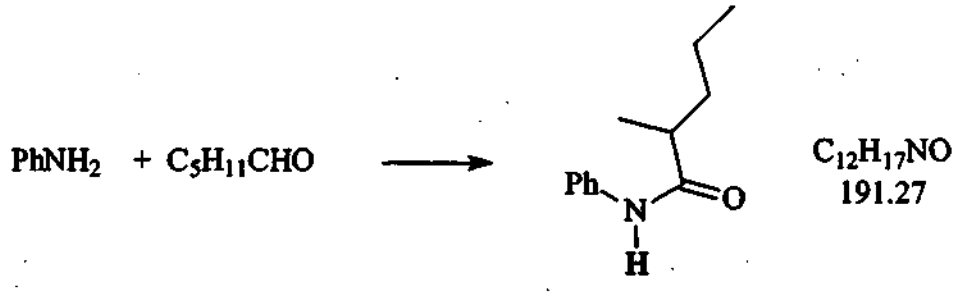
Heptaldehyde (4.00 ml, 3.27 g, 28.7 mmol) was treated with NBS (6.67 g, 37.5 mmol), AIBN (0.12 g, 0.73 mmol) and $EtNH_2$ (70% w/w solution in water, 5.60 ml, 3.57 g, 79.0 mmol) to afford *N*-ethylheptanamide as a colourless oil (2.57 g, 16.3 mmol, 57%) after distillation under reduced pressure (b.p. 105-115°C, 10 mmHg) (lit.[166] 154°C, 15 mmHg); R_f 0.17 (EtOAc/Hex 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 6.14 (1H, br, NH), 3.24 (2H, m, $NC\underline{H}_2$), 2.15 (2H, m, $C\underline{H}_2C{=}O$), 1.58 (2H, m, $C\underline{H}_2CH_2C{=}O$), 1.30-1.20 (6H, br, $C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 1.10 (3H, t, J = 6.9 Hz, $NCH_2C\underline{H}_3$), 0.83 (3H, t, J = 7.3 Hz, $CH_2CH_2C\underline{H}_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 173.4 (C=O), 36.6 ($\underline{C}H_2C{=}O$), 34.4 ($N\underline{C}H_2$), 31.5 ($\underline{C}H_2CH_2CH_3$), 28.9 ($\underline{C}H_2CH_2CH_2CH_3$), 25.8 ($\underline{C}H_2CH_2C{=}O$), 22.4 ($CH_2\underline{C}H_2CH_3$), 14.7 ($NCH_2\underline{C}H_3$), 13.9 ($CH_2CH_2\underline{C}H_3$).

MS (EIMS): *m/z* (%) = 157 [M^+] (2), 128 (2), 114 (9), 100 (23), 87 (100), 72 (49).

8.5 2-Methyl-*N*-phenylpentanamide



2-Methylpentaldehyde (3.52 ml, 2.84 g, 28.4 mmol) was treated with NBS (6.57 g, 36.9 mmol), AIBN (0.10 g, 0.60 mmol) and aniline (7.20 ml, 7.36 g, 79.0 mmol) to afford 2-methyl-*N*-phenylpentanamide as a white crystalline solid (m.p. 94-98°C) (lit.[167] 96°C) (1.01 g, 5.28 mmol, 19%) after column chromatography (EtOAc/Hex 1:4); R_f 0.29 (EtOAc/Hex 1:4).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.91 (1H, br, NH), 7.56 (2H, m, *o*-$C_6\underline{H}_5$), 7.28 (2H, m, *m*-$C_6\underline{H}_5$), 7.08 (1H, m, *p*-$C_6\underline{H}_5$), 2.39 (1H, m, $C\underline{H}C{=}O$), 1.75-1.64 (2H, m, $C\underline{H}_2CH_2CH_3$), 1.43-1.29 (2H, m, $C\underline{H}_2CH_3$), 1.20 (3H, d, J = 7.3 Hz, $CHC\underline{H}_3$), 0.90 (3H, t, J = 7.0 Hz, $CH_2C\underline{H}_3$).

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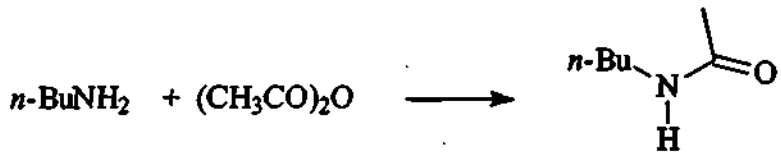
[166] Heymons, A., *Chem. Ber.*, **1932**, *65*, 320-329.

[167] Duggleby, P.M., Holt, G., Hope, M.A., Lewis, A., *J. Chem. Soc. Perkin Trans. 1*, **1972**, 3020-3024.

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 175.6 (C=O), 138.2 (*ipso*-$\underline{C}_6H_5$), 128.9 (2C, *o*-$\underline{C}_6H_5$), 124.1 (*p*-$\underline{C}_6H_5$), 120.1 (2C, *m*-$\underline{C}_6H_5$), 42.2 ($\underline{C}HC$=O), 36.6 ($\underline{C}H_2CH_2CH_3$), 20.7 ($\underline{C}H_2CH_3$), 17.9 ($CH\underline{C}H_3$), 14.1 ($CH_2\underline{C}H_3$).

8.6 *N*-Butylacetamide

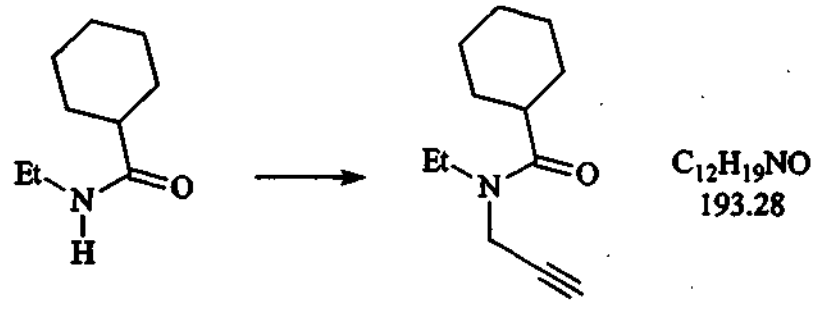


Acetic anhydride (10.40 ml, 11.25 g, 110.1 mmol) was added to a mixture of *n*-$BuNH_2$ (9.90 ml, 7.33 g, 100 mmol) and pyridine (8.10 ml, 7.92 g, 100 mmol) and stirred for 30 minutes at room temperature. The reaction mixture was washed with water (50 ml), saturated $NaHCO_{3(aq)}$ (3 × 20 ml) and dilute HCl (3M, 50 ml) to afford *N*-butylacetamide as a yellow oil (7.23 g, 62.8 mmol, 63%); R_f 0.29 (EtOAc/Hex 3:1).

^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 7.22 (1H, br, NH), 2.97 (2H, m, $NC\underline{H}_2$), 1.76 (3H, s, $COC\underline{H}_3$), 1.24 (2H, m, $NCH_2C\underline{H}_2$), 1.12 (2H, m, $NCH_2CH_2C\underline{H}_2$), 0.69 (3H, t, J = 7.4 Hz, $CH_2C\underline{H}_3$).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 171.3 (C=O), 39.7 ($N\underline{C}H_2$), 31.8 ($NCH_2\underline{C}H_2$), 23.1 ($CO\underline{C}H_3$), 20.4 ($\underline{C}H_2CH_3$), 14.0 ($CH_2\underline{C}H_3$).

8.7 *N*-Ethyl-*N*-prop-2-ynylcyclohexanecarboxamide[122]



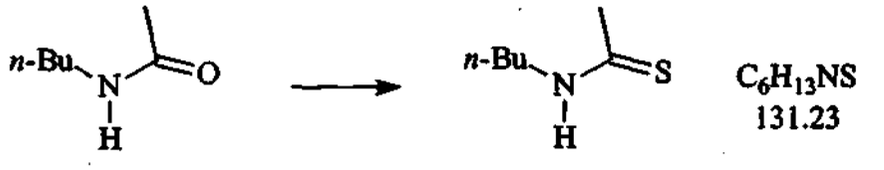
t-BuLi (1.7M solution in pentane, 4.17 ml, 7.08 mmol) was added to a solution of *N*-ethylcyclohexanecarboxamide (1.00 g, 6.44 mmol) in dry THF (50 ml) at –78°C and stirred for 30 minutes. Propargyl bromide (80% w/w solution in toluene, 1.45 ml, 1.54 g, 13.0

mmol) was added and the mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was washed with dilute HCl (3M, 50 ml) and saturated $NaHCO_3$ (3 × 20 ml) and extracted with CH_2Cl_2 (3 × 50 ml). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo* to afford *N*-ethyl-*N*-prop-2-ynylcyclohexanecarboxamide as a yellow oil (0.33 g, 1.7 mmol, 26%) after column chromatography (EtOAc/Hex 1:9); R_f 0.29 (EtOAc/Hex 1:4).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 4.15 (2H, d, J = 2.0 Hz, $C\underline{H}_2C{\equiv}CH$), 3.45 (2H, q, J = 7.4 Hz, $NC\underline{H}_2CH_3$), 2.42-2.36 (1H, m, $NC\underline{H}$), 2.12 (1H, t, J ≈ 1.8 Hz, $C{\equiv}C\underline{H}$), 1.77-1.43 (10H, m, $NCHC_5\underline{H}_{10}$), 1.18 (3H, t, J = 7.2 Hz, $NCH_2C\underline{H}_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 175.6 (C=O), 79.5 ($\underline{C}{\equiv}CH$), 71.1 ($C{\equiv}\underline{C}H$), 41.4 ($N\underline{C}H_2CH_3$), 40.6 ($N\underline{C}H$), 33.6 ($\underline{C}H_2C{\equiv}CH$), 29.4 [2C, $NCH(\underline{C}H_2)_2$], 25.7 [3C, $(\underline{C}H_2)_2\underline{C}H_2$], 14.3 ($NCH_2\underline{C}H_3$).

8.8 *N*-Butylethanethioamide[101]



$C_6H_{13}NS$
131.23

N-Butylacetamide (3.30 g, 28.6 mmol) was treated with P_4S_{10} (17.33 g, 39.0 mmol) and Na_2CO_3 (4.13 g, 39.0 mmol) using Brillon's procedure (see above p130) to afford *N*-butylethanethioamide as a white crystalline solid (m.p. 89-94°C) (lit.[168] 93-94°C) (1.39 g, 10.6 mmol, 40%) after column chromatography (EtOAc/Hex 1:1); R_f 0.60 (EtOAc/Hex 3:1).

^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 8.20 (1H, br, NH), 3.48 (2H, m, $NC\underline{H}_2$), 2.44 (3H, s, $COC\underline{H}_3$), 1.52 (2H, $NCH_2C\underline{H}_2$), 1.28 (2H, m, CH_2CH_3), 0.82 (3H, t, J = 7.3 Hz, $CH_2C\underline{H}_3$).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 200.1 (C=S), 46.2 ($N\underline{C}H_2$), 33.7 ($NCH_2\underline{C}H_2$), 29.8 ($CO\underline{C}H_3$), 20.1 ($\underline{C}H_2CH_3$), 13.7 ($CH_2\underline{C}H_3$).

MS (EIMS): *m/z* (%) = 131 [M^+] (100), 102 (13), 98 (16), 89 (40), 59 (65).

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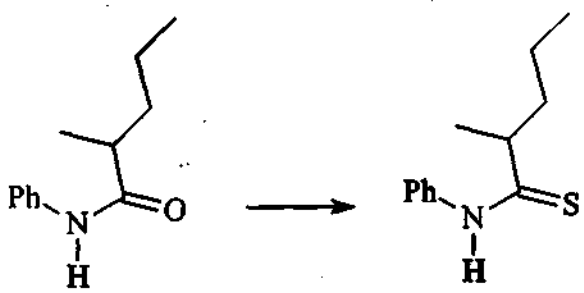
[168] Reynaud, P., Moreau, R.C., *Bull. Soc. Chim. Fr*, **1965**, *12*, 3623-3628.

8.9 2-Methyl-*N*-phenylpentanethioamide[101]



$C_{12}H_{17}NS$
207.33

2-Methyl-*N*-phenylpentanamide (0.98 g, 5.12 mmol) was treated with P_4S_{10} (3.52 g, 7.92 mmol) and Na_2CO_3 (0.54 g, 5.1 mmol) using Brillon's procedure (see above p130) to afford 2-methyl-*N*-phenylpentanethioamide as a yellow crystalline solid (m.p. 48-51°C) (0.19 g, 0.92 mmol, 18%) after column chromatography (EtOAc/Hex 1:4); R_f 0.36 (EtOAc/Hex 1:4).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.57 (1H, br, NH), 7.68 (2H, m, *o*-$C_6\underline{H}_5$), 7.41 (2H, m, *m*-$C_6\underline{H}_5$), 7.27 (1H, m, *p*-$C_6\underline{H}_5$), 2.78 ($C\underline{H}C$=S), 1.89-1.82 and 1.44-1.37 (2H, m, $C\underline{H}_2CH_2CH_3$), 1.63-1.57 (2H, m, $C\underline{H}_2CH_3$), 1.35 (3H, d, J = 6.4 Hz, $CHCH_3$), 0.95 (3H, t, J = 7.4 Hz, $CH_2C\underline{H}_3$).

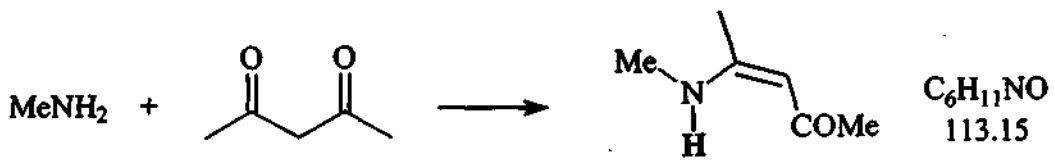
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 210.6 (C=S), 138.5 (*ipso*-$\underline{C}_6H_5$), 128.9 (2C, *o*-$\underline{C}_6H_5$), 126.9 (*p*-$\underline{C}_6H_5$), 124.1 (2C, *m*-$\underline{C}_6H_5$), 52.1 ($\underline{C}HC$=S), 39.5 ($\underline{C}H_2CH_2CH_3$), 21.2 ($\underline{C}H_2CH_3$), 20.7 ($CH\underline{C}H_3$), 14.1 ($CH_2\underline{C}H_3$).

MS (EIMS): *m/z* (%) = 207 [M^+] (82), 174 (46), 164 (100), 132 (42), 104 (52), 77 (98).

Preparation of acyclic vinylogous amides and carbamates: General procedure

The appropriate primary amine (3.33-6.66 mmol) was mixed with the appropriate β-dicarbonyl compound (3.33 mmol) and poured on to a bed of silica gel (1 g) in a small beaker. The mixture was placed in a domestic microwave oven and irradiated for 3 min (700 W, low). The mixture was extracted with CH_2Cl_2 (10 ml), filtered and the silica gel washed with CH_3OH (2 × 10ml). The solvent was removed *in vacuo* to afford the desired vinylogous amides and carbamates without further purification.

9.1 (*Z*)-4-(Methylamino)pent-3-en-2-one



Methylamine (33% w/w solution in ethanol, 0.31 g, 3.3 mmol) and acetylacetone (0.34 g, 3.4 mmol) were mixed and irradiated to afford (*Z*)-4-(methylamino)pent-3-en-2-one as a yellow crystalline solid (m.p. 38-40°C) (lit.[169] 37-39°C) (0.30 g, 2.7 mmol, 80%); R_f 0.27 (EtOAc/Hex 1:1).

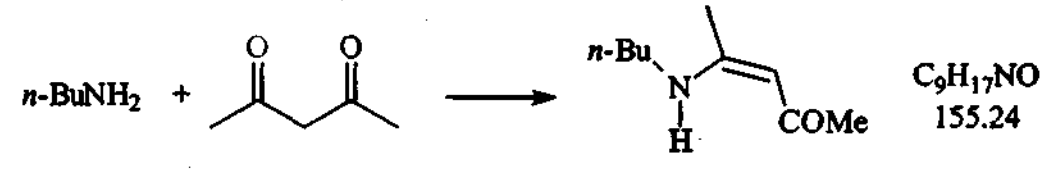
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 10.65 (1H, br, NH), 4.93 (1H, s, C=C<u>H</u>), 2.87 (3H, d, J = 5.4 Hz, NC<u>H</u>$_3$), 1.93 (3H, s, COC<u>H</u>$_3$), 1.86 (3H, s, C<u>H</u>$_3$C=C).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 194.5 (C=O), 164.0 (<u>C</u>=CH), 94.9 (C=<u>C</u>H), 29.3 (CO<u>C</u>H$_3$), 28.5 (N<u>C</u>H$_3$), 18.5 (<u>C</u>H$_3$C=C).

IR (thin film, $CHCl_3$): 3072, 2961, 2928, 1610, 1572, 1297 cm^{-1}.

MS (EIMS): *m/z* (%) = 113 [M$^+$] (62), 98 (100), 56 (61).

9.2 (*Z*)-4-(Butylamino)pent-3-en-2-one



n-Butylamine (0.37 g, 5.1 mmol) and acetyl acetone (0.34 g, 3.4 mmol) were mixed and irradiated to afford (*Z*)-4-(butylamino)pent-3-en-2-one as a yellow oil (0.40 g, 2.6 mmol, 76%); R_f 0.49 (EtOAc/Hex 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 10.83 (1H, br, NH), 4.91 (1H, s, C=C<u>H</u>), 3.19 (2H, q, J = 7.5 Hz, NC<u>H</u>$_2$), 1.96 (3H, s, COC<u>H</u>$_3$), 1.88 (3H, s, C<u>H</u>$_3$C=C), 1.53 (2H, m, NCH$_2$C<u>H</u>$_2$), 1.38 (2H, m, C<u>H</u>$_2$CH$_3$), 0.90 (3H, t, J = 7.5 Hz, CH$_2$C<u>H</u>$_3$).

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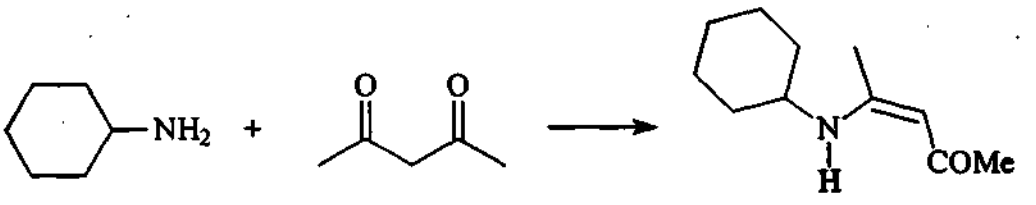
[169] Braibante, M.E.F., Braibante, H.S., Missio, L., Andricopulo, A., *Synthesis*, **1994**, 898-900.

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 194.5 (C=O), 163.1 (C=CH), 94.9 (C=CH), 42.6 (NCH_2), 32.0 (NCH_2CH_2), 28.6 ($COCH_3$), 19.9 (CH_2CH_3), 18.7 (CH_3C=C), 13.6 (CH_2CH_3).

IR (thin film, $CHCl_3$): 3071, 2956, 2928, 2868, 1610, 1574, 1294, 735 cm^{-1}.

MS (EIMS): *m/z* (%) = 155 [M^+] (100), 140 (85), 126 (36), 112 (51), 98 (26), 84 (42), 70 (21).

9.3 (*Z*)-4-(Cyclohexylamino)pent-3-en-2-one



$C_{11}H_{19}NO$
181.27

Cyclohexylamine (0.50 g, 5.0 mmol) and acetylacetone (0.34 g, 3.4 mmol) were mixed and irradiated to afford (*Z*)-4-(cyclohexylamino)pent-3-en-2-one as a yellow oil (0.49 g, 2.7 mmol, 88%); R_f 0.52 (EtOAc/Hex 1:1).

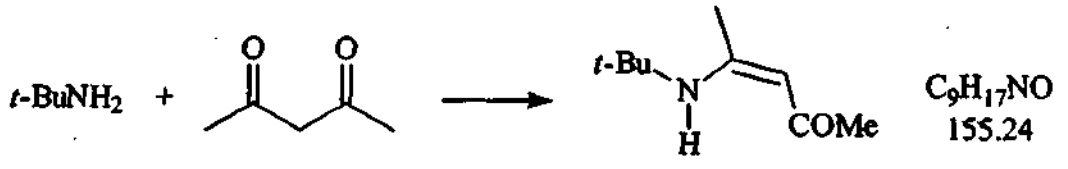
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 10.9 (1H, br, NH), 4.85 (1H, s, C=CH), 3.32 (1H, m, NCH), 1.92 (3H, s, $COCH_3$), 1.88 (3H, s, CH_3C=C), 1.82-1.77 and 1.72-1.67 and 1.55-1.48 and 1.34-1.17 (10H, m, $NCHC_5H_{10}$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 194.2 (C=O), 161.7 (C=CH), 94.7 (C=CH), 51.3 (NCH), 33.6 [2C, $NCH(CH_2)_2$], 28.5 ($COCH_3$), 25.2 [2C, $NCH(CH_2)_2(CH_2)_2$], 24.2 [$(CH_2)_2CH_2$], 18.4 (CH_3C=C).

IR (thin film, $CHCl_3$): 3080, 2934, 2857, 1610, 1580, 1300, 732 cm^{-1}.

MS (EIMS): *m/z* (%) = 181 [M^+] (100), 166 (37), 138 (57), 100 (44), 84 (48).

9.4 (*Z*)-4-(*t*-Butylamino)pent-3-en-2-one



$C_9H_{17}NO$
155.24

t-Butylamine (0.37 g, 5.1 mmol) and acetylacetone (0.34 g, 3.4 mmol) were mixed and irradiated to afford (*Z*)-4-(*t*-butylamino)pent-3-en-2-one as a yellow oil (32 mg, 0.21 mmol, 6%); R_f 0.47 (EtOAc/Hex 1:1).

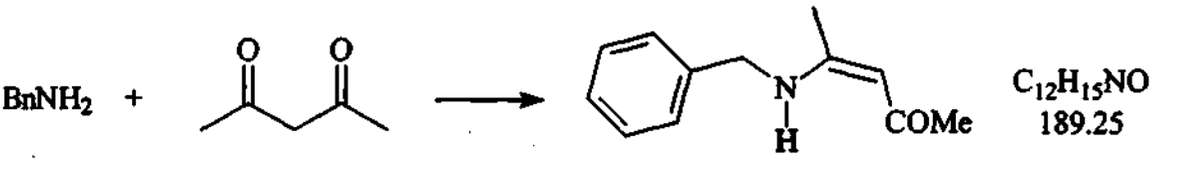
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 11.34 (1H, br, NH), 4.88 (1H, s, C=C<u>H</u>), 2.04 (3H, s, COC<u>H</u>$_3$), 1.97 (3H, s, C<u>H</u>$_3$C=C), 1.38 [NC(C<u>H</u>$_3$)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 193.9 (C=O), 163.2 (<u>C</u>=CH), 96.2 (C=<u>C</u>H), 52.2 [<u>C</u>(CH$_3$)$_3$], 30.7 [C(<u>C</u>H$_3$)$_3$], 28.6 (CO<u>C</u>H$_3$), 20.4 (<u>C</u>H$_3$C=C).

IR (thin film, $CHCl_3$): 3065, 2972, 2928, 1610, 1591 cm^{-1}.

MS (EIMS): *m/z* (%) =155 [M$^+$] (38), 140 (16), 84 (100).

9.5 (*Z*)-4-(Benzylamino)pent-3-en-2-one



Benzylamine (0.37 g, 3.5 mmol) and acetylacetone (0.34 g, 3.4 mmol) were mixed and irradiated to afford (*Z*)-4-(benzylamino)pent-3-en-2-one as a yellow oil (0.32 g, 3.2 mmol, 95%); R_f 0.51 (EtOAc/Hex 1:1).

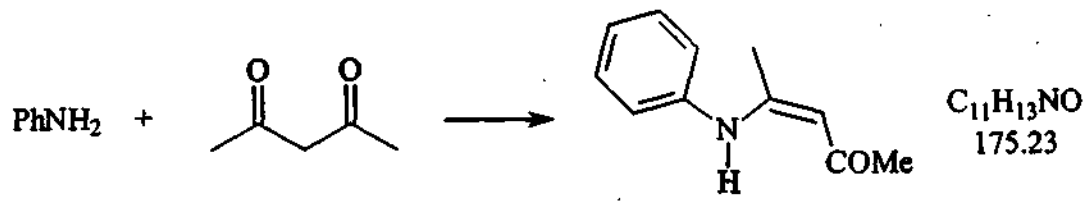
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 11.16 (1H, br, NH), 7.33-7.22 (5H, m, C$_6$<u>H</u>$_5$), 5.03 (1H, s, C=C<u>H</u>), 4.42 (2H, d, *J* = 6.8 Hz, C$_6$H$_5$C<u>H</u>$_2$), 2.01 (3H, s, COC<u>H</u>$_3$), 1.89 (3H, s, C<u>H</u>$_3$C=C).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 195.2 (C=O), 162.9 (<u>C</u>=CH), 137.9 (*ipso*-<u>C</u>$_6$H$_5$), 128.6 (2C, *m*-<u>C</u>$_6$H$_5$), 127.2 (*p*-<u>C</u>$_6$H$_5$), 126.5 (2C, *o*-<u>C</u>$_6$H$_5$), 95.7 (C=<u>C</u>H), 46.5 (C$_6$H$_5$<u>C</u>H$_2$), 28.7 (CO<u>C</u>H$_3$), 18.7 (<u>C</u>H$_3$C=C).

IR (thin film, $CHCl_3$): 3027, 1607, 1572, 1289, 735 cm^{-1}.

MS (EIMS): *m/z* (%) = 189 [M$^+$] (69), 174 (32), 91 (100).

9.6 (*Z*)-4-(Phenylamino)pent-3-en-2-one



Aniline (0.32 g, 3.4 mmol) and acetylacetone (0.34 g, 3.4 mmol) were mixed and irradiated to afford (*Z*)-4-(phenylamino)pent-3-en-2-one as a yellow oil (0.56 g, 3.2 mmol, 94%); R_f 0.59 (EtOAc/Hex 1:1).

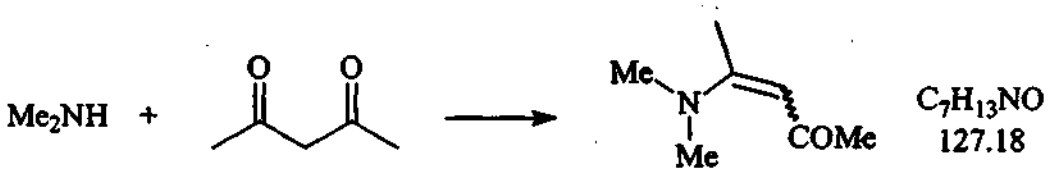
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 12.48 (1H, br, NH), 7.33-6.69 (5H, m, $C_6\underline{H}_5$), 5.19 (1H, s, C=C$\underline{H}$), 2.10 (3H, s, COC$\underline{H}_3$), 1.98 (3H, s, C$\underline{H}_3$C=C).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 196.4 (C=O), 160.5 (C=CH), 139.0 (*ipso*-$\underline{C}_6H_5$), 129.3 (2C, *m*-$\underline{C}_6H_5$), 125.8 (*p*-$\underline{C}_6H_5$), 125.0 (2C, *o*-$\underline{C}_6H_5$), 97.9 (C=$\underline{C}$H), 29.4 (CO$\underline{C}H_3$), 20.1 ($\underline{C}H_3$C=C).

IR (thin film, $CHCl_3$): 2923, 1613, 1572, 1278, 749 cm^{-1}.

MS (EIMS): *m/z* (%) = 175 [M$^+$] (41), 161 (100), 132 (32), 77 (22).

9.7 (3*E*)- and (3*Z*)-4-(Dimethylamino)pent-3-en-2-one

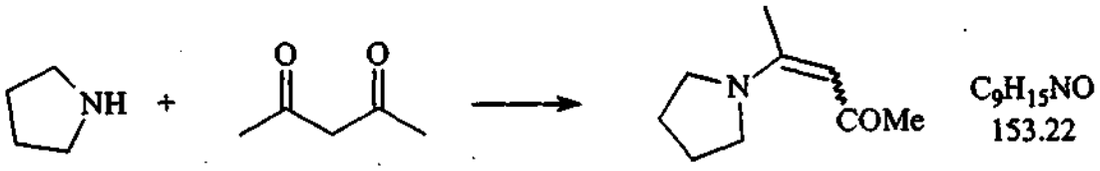


Dimethylamine (40% w/w solution in water, 0.38 g, 3.4 mmol) and acetylacetone (0.33 g, 3.3 mmol) were mixed and irradiated to afford (3*E*)- and (3*Z*)-4-(dimethylamino)pent-3-en-2-one as a yellow oil (*Z*:*E* 3:2) (0.15 g, 1.2 mmol, 36%); R_f 0.65 (EtOAc/Hex 2:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = (*E*-isomer) 4.98 (1H, s, C=C$\underline{H}$), 2.92 (6H, s, N(C$\underline{H}_3$)$_2$), 2.45 (3H, s, COC$\underline{H}_3$), 2.02 (3H, s, C$\underline{H}_3$C=C). (*Z*-isomer) 5.46 (1H, s, C=C$\underline{H}$), 2.92 (6H, s, N(C$\underline{H}_3$)$_2$), 2.45 (3H, s, COC$\underline{H}_3$), 1.99 (3H, s, C$\underline{H}_3$C=C).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = (*E*-isomer) 191.0 (C=O), 161.9 ($\underline{C}$=CH), 94.9 (C=$\underline{C}$H), 39.6 (2C, N($\underline{C}H_3$)$_2$), 31.6 (CO$\underline{C}H_3$), 15.7 ($\underline{C}H_3$C=C). (*Z*-isomer) 194.5 (C=O), 161.9 ($\underline{C}$=CH), 100.3 (C=$\underline{C}$H), 39.6 (2C, N($\underline{C}H_3$)$_2$), 31.6 (CO$\underline{C}H_3$), 24.7 ($\underline{C}H_3$C=C).

9.8 (3*E*)- and (3*Z*)-4-Pyrrolidin-1-ylpent-3-en-2-one

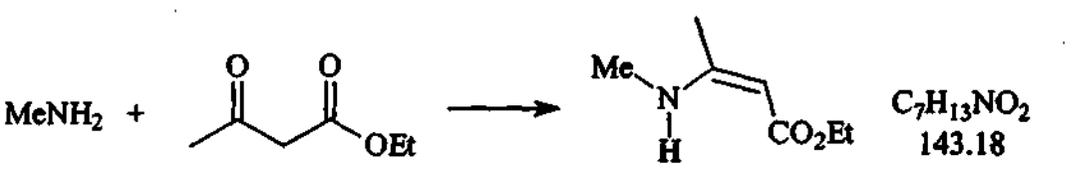


Pyrrolidine (0.32 g, 4.5 mmol) and acetylacetone (0.34 g, 3.4 mmol) were mixed and irradiated to afford (3*E*)- and (3*Z*)- 4-pyrrolidin-1-ylpent-3-en-2-one as a yellow crystalline solid (m.p. 105-109°C) (lit.[125] 115°C) (*E*:*Z* 11:1) (0.33 g, 2.2 mmol, 63%); R_f 0.57 (EtOAc/Hex 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = (*E*-isomer) 4.92 (1H, s, C=C<u>H</u>), 3.45-3.37 and 3.24-3.16 [4H, m, N(C<u>H</u>$_2$)$_2$], 2.49 (3H, s, COC<u>H</u>$_3$), 2.03 (3H, s, C<u>H</u>$_3$C=C), 1.95-1.90 [4H, m, N(CH$_2$)$_2$(C<u>H</u>$_2$)$_2$). (*Z*-isomer) 5.48 (1H, s, C=C<u>H</u>), 3.45-3.37 and 3.24-3.16 [4H, m, N(C<u>H</u>$_2$)$_2$], 2.49 (3H, s, COC<u>H</u>$_3$), 2.02 (3H, s, C<u>H</u>$_3$C=C), 1.95-1.90 [4H, m, N(CH$_2$)$_2$(C<u>H</u>$_2$)$_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = (*E*-isomer) 194.1 (C=O), 159.7 (<u>C</u>=CH), 95.0 (C=<u>C</u>H), 47.8 [2C, N(<u>C</u>H$_2$)$_2$], 31.4 (CO<u>C</u>H$_3$), 25.0 [N(CH$_2$)$_2$(<u>C</u>H$_2$)$_2$], 17.2 (<u>C</u>H$_3$C=C). (*Z*-isomer) 189.9 (C=O), 159.7 (<u>C</u>=CH), 100.4 (C=<u>C</u>H), 47.8 [2C, N(<u>C</u>H$_2$)$_2$], 31.4 (CO<u>C</u>H$_3$), 25.0 [N(CH$_2$)$_2$(<u>C</u>H$_2$)$_2$], 22.5 (<u>C</u>H$_3$C=C).

9.9 Ethyl (*Z*)-3-(methylamino)but-2-enoate



Methylamine (33% w/w solution in ethanol, 1.24 g, 13.3 mmol) and ethyl acetoacetate (0.88 g, 6.8 mmol) were mixed and irradiated to yield ethyl (*Z*)-3-(methylamino)but-2-enoate as a colourless oil (0.79 g, 5.5 mmol, 82%); R_f 0.58 (EtOAc/Hex 1:1).

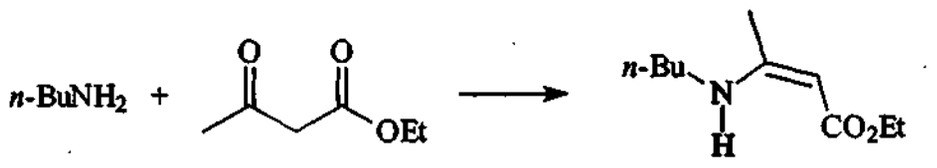
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.43 (1H, br, NH), 4.42 (1H, s, C=C<u>H</u>), 4.03 (2H, q, *J* = 7.0 Hz, OC<u>H</u>$_2$CH$_3$), 2.86 (3H, d, *J* = 5.5 Hz, NC<u>H</u>$_3$), 1.87 (3H, s, C<u>H</u>$_3$C=C), 1.20 (3H, t, *J* = 7.0 Hz, OCH$_2$C<u>H</u>$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 170.5 (C=O), 162.6 (C=CH), 81.7 (C=CH), 58.1 (OCH_2CH_3), 29.4 (NCH_3), 19.0 (CH_3C=C), 14.5 (OCH_2CH_3).

IR (thin film, $CHCl_3$): 3296, 2978, 2934, 1651, 1610, 1273, 1166, 781 cm^{-1}.

MS (EIMS): *m/z* (%) = 143 [M$^+$] (59), 98 (100), 82 (20), 71 (57), 56 (37).

9.10 Ethyl (*Z*)-3-(*n*-butylamino)but-2-enoate



$C_{10}H_{19}NO_2$
185.26

n-Butylamine (0.49 g, 6.7 mmol) and ethyl acetoacetate (0.44 g, 3.4 mmol) were mixed and irradiated to yield ethyl (*Z*)-3-(*n*-butylamino)but-2-enoate as a colourless oil (0.44 g, 2.4 mmol, 70%); R_f 0.59 (EtOAc/Hex 1:1).

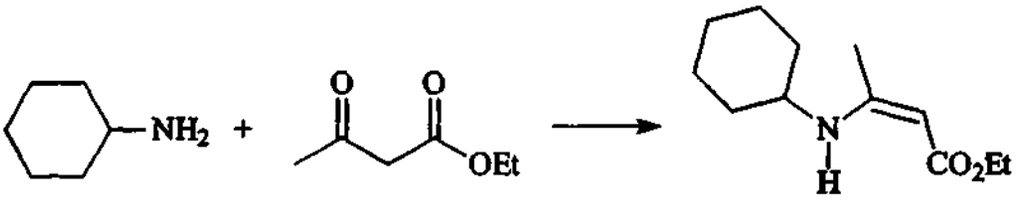
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.51 (1H, br, NH), 4.37 (1H, s, C=CH), 4.03 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.15 (2H, q, *J* = 6.9 Hz, NCH_2), 1.86 (3H, s, CH_3C=C), 1.50 (2H, m, NCH_2CH_2), 1.35 (2H, m, CH_2CH_3), 1.19 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 0.88 (3H, t, *J* = 7.1 Hz, CH_2CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 170.5 (C=O), 161.8 (C=CH), 81.5 (C=CH), 58.0 (OCH_2CH_3), 42.5 (NCH_2CH_2), 32.3 (NCH_2CH_2), 19.9 (CH_2CH_3), 19.2 (CH_3C=C), 14.5 (OCH_2CH_3), 13.6 (CH_2CH_3).

IR (thin film, $CHCl_3$): 3285, 2961, 2934, 1648, 1607, 1270, 1171, 1144, 781 cm^{-1}.

MS (EIMS): *m/z* (%) = 185 [M$^+$] (60), 142 (25), 130 (37), 124 (56), 84 (100), 57 (67).

9.11 Ethyl (*Z*)-3-(cyclohexylamino)but-2-enoate



$C_{12}H_{21}NO_2$
211.30

Cyclohexylamine (0.67 g, 6.8 mmol) and ethyl acetoacetate (0.44 g, 3.4 mmol) were mixed and irradiated to yield ethyl (*Z*)-3-(cyclohexylamino)but-2-enoate as a colourless oil (0.54 g, 2.6 mmol, 76%); R_f 0.54 (EtOAc/Hex 1:1).

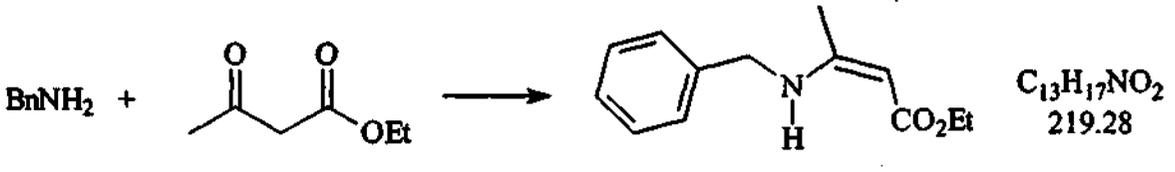
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.58 (1H, br, NH), 4.32 (1H, s, C=C<u>H</u>), 4.01 (2H, q, *J* = 7.5 Hz, OC<u>H</u>$_2$CH$_3$), 3.25 (1H, m, NC<u>H</u>), 1.87 (3H, s, C<u>H</u>$_3$C=C), 1.83-1.77 and 1.72-1.66 and 1.56-1.49 and 1.32-1.20 (10H, m, NCHC$_5$<u>H</u>$_{10}$), 1.18 (3H, t, *J* = 7.5 Hz, OCH$_2$C<u>H</u>$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 170.4 (C=O), 160.6 (<u>C</u>=CH), 81.5 (C=<u>C</u>H), 57.9 (O<u>C</u>H$_2$CH$_3$), 51.2 (N<u>C</u>H), 34.1 [2C, NCH(<u>C</u>H$_2$)$_2$], 25.2 [2C, NCH(CH$_2$)$_2$(<u>C</u>H$_2$)$_2$], 24.5 [(CH$_2$)$_2$<u>C</u>H$_2$], 19.0 (<u>C</u>H$_3$C=C), 14.5 (OCH$_2$<u>C</u>H$_3$).

IR (thin film, $CHCl_3$): 3274, 2928, 2857, 1648, 1607, 1270, 781 cm^{-1}.

MS (EIMS): *m/z* (100) = 211 [M$^+$] (73), 166 (34), 138 (23), 130 (100), 84 (55).

9.12 Ethyl (*Z*)-3-(benzylamino)but-2-enoate



Benzylamine (0.72 g, 6.7 mmol) and ethyl acetoacetate (0.44 g, 3.4 mmol) were mixed and irradiated to yield ethyl (*Z*)-3-(benzylamino)but-2-enoate as a colourless oil (0.72 g, 3.3 mmol, 97%); R_f 0.54 (EtOAc/Hex 1:1).

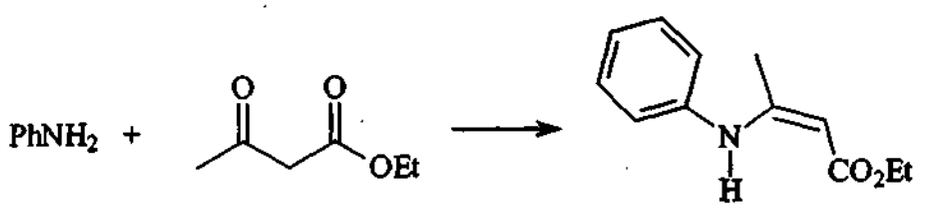
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.97 (1H, br, NH), 7.34-7.24 (5H, m, C$_6$<u>H</u>$_5$), 4.54 (1H, s, C=C<u>H</u>), 4.40 (2H, d, *J* = 7.5 Hz, C$_6$H$_5$C<u>H</u>$_2$), 4.10 (2H, q, *J* = 7.1 Hz, OC<u>H</u>$_2$CH$_3$), 1.89 (3H, s, C<u>H</u>$_3$C=C), 1.25 (3H, t, *J* = 7.0 Hz, OCH$_2$C<u>H</u>$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 170.3 (C=O), 161.6 (<u>C</u>=CH), 138.5 (*ipso*-<u>C</u>$_6$H$_5$), 128.5 (2C, *m*-<u>C</u>$_6$H$_5$), 127.1 (*p*-<u>C</u>$_6$H$_5$), 126.5 (2C, *o*-<u>C</u>$_6$H$_5$), 83.0 (C=<u>C</u>H), 58.1 (O<u>C</u>H$_2$CH$_3$), 46.5 (N<u>C</u>H$_2$), 19.1 (<u>C</u>H$_3$C=C), 14.4 (OCH$_2$<u>C</u>H$_3$).

IR (thin film, $CHCl_3$): 3291, 2978, 1648, 1607, 1171, 784 cm^{-1}.

MS (EIMS): *m/z* (%) = 219 [M$^+$] (46), 190 (22), 172 (48), 146 (32), 91 (100).

9.13 Ethyl (*Z*)-3-(phenylamino)but-2-enoate



Aniline (0.62 g, 6.7 mmol) and ethyl acetoacetate (0.44 g, 3.4 mmol) were mixed and irradiated to yield ethyl (*Z*)-3-(phenylamino)but-2-enoate as a colourless oil (0.46 g, 2.3 mmol, 70%); R_f 0.68 (EtOAc/Hex 1:1).

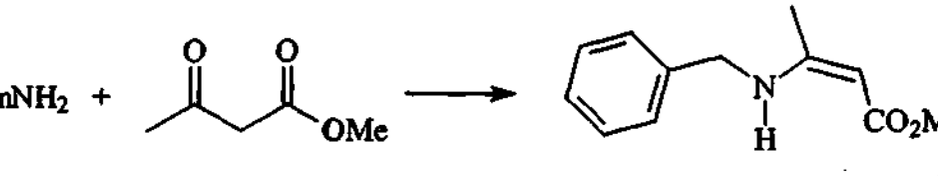
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 10.47 (1H, br, NH), 7.34-6.66 (5H, m, $C_6\underline{H}_5$), 4.75 (1H, s, C=C$\underline{H}$), 4.19 (2H, q, J = 7.2 Hz, OC$\underline{H}_2$CH$_3$), 2.00 (3H, s, C$\underline{H}_3$C=C), 1.31 (3H, t, J = 7.1 Hz, OCH$_2$C$\underline{H}_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 170.1 (C=O), 158.7 (C=CH), 139.0 (*ipso*-$\underline{C}_6$H$_5$), 128.8 (2C, *m*-$\underline{C}_6$H$_5$), 124.0 (2C, *o*-$\underline{C}_6$H$_5$), 114.7 (*p*-$\underline{C}_6$H$_5$), 85.8 (C=$\underline{C}$H), 58.5 (O$\underline{C}$H$_2$CH$_3$), 19.9 ($\underline{C}$H$_3$C=C), 14.3 (OCH$_2\underline{C}$H$_3$).

IR (thin film, $CHCl_3$): 3258, 2972, 1651, 1613, 1270, 1157 cm^{-1}.

MS (EIMS): *m/z* (%) = 205 [M$^+$] (83), 160 (57), 130 (69), 118 (100), 77 (55).

9.14 Methyl (2*Z*)-3-(benzylamino)but-2-enoate



Benzylamine (0.39 g, 3.7 mmol) and methyl acetoacetate (0.39 g, 3.3 mmol) were mixed and irradiated to yield methyl (*Z*)-3-(benzylamino)but-2-enoate as a colourless oil (0.65 g, 3.2 mmol, 95%); R_f 0.55 (EtOAc/Hex 1:1).

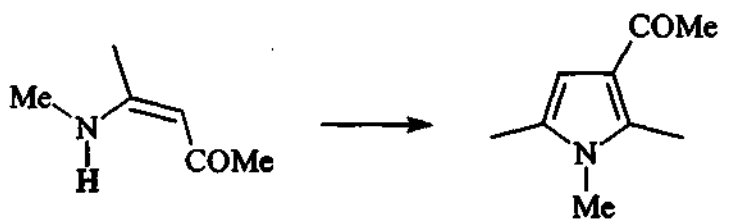
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.94 (1H, br, NH), 7.35-7.24 (5H, m, $C_6\underline{H}_5$), 4.54 (1H, s, C=C$\underline{H}$), 4.41 (2H, d, J = 6.8 Hz, $C_6H_5C\underline{H}_2$), 3.63 (3H, s, OC$\underline{H}_3$), 1.91 (3H, s, C$\underline{H}_3$C=C).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 170.8 (C=O), 161.8 (C=CH), 138.6 (*ipso*-C_6H_5), 128.7 (2C, *m*-C_6H_5), 127.2 (*p*-C_6H_5), 126.6 (2C, *o*-C_6H_5), 82.7 (C=CH), 49.9 (OCH_3), 46.6 (NCH_2), 19.2 (CH_3C=C).

Preparation of functionalised pyrroles: General procedure (one-pot)

$AgNO_3$ (1.2-2 mmol) was added to a stirred solution of the appropriate vinylogous amide or carbamate (1 mmol) and propargyl bromide (1.2-2 mmol) in dry CH_3CN (2 ml) and stirred overnight. The organic layer was washed with $NaI_{(aq)}$, dried ($MgSO_4$) and concentrated *in vacuo* to afford the desired *N*-bridgehead pyrroles after radial chromatography.

9.15 1-(1,2,5-Trimethyl-1*H*-pyrrol-3-yl)ethanone



$C_9H_{13}NO$
151.20

(*Z*)-4-(Methylamino)pent-3-en-2-one (1.00 g, 8.84 mmol) was treated with propargyl bromide (80% w/w solution in toluene, 1.97 ml, 2.10 g, 17.7 mmol) and $AgNO_3$ (3.01 g, 17.7 mmol) to afford 1-(1,2,5-trimethyl-1*H*-pyrrol-3-yl)ethanone as a white crystalline solid (mp 37-38 °C) (lit.[170] 51-54°C) (0.43 g, 2.8 mmol, 32%) after radial chromatography (EtOAc/Hex 1:4); R_f 0.40 (EtOAc/Hex 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 6.19 (1H, s, C=CH), 3.38 (3H, s, NCH_3), 2.52 (3H, s, CH_3C=$CCOCH_3$), 2.34 (3H, s, $COCH_3$), 2.19 (3H, s, CH_3C=CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 194.8 (C=O), 135.0 (C=$CCOCH_3$), 127.6 (C=CH), 119.7 ($CCOCH_3$), 107.7 (C=CH), 29.9 (NCH_3), 28.4 ($COCH_3$), 12.2 (CH_3C=CH), 11.8 (CH_3C=$CCOCH_3$).

IR (thin film, $CHCl_3$): 2933, 1646, 1522, 1410, 1229 cm^{-1}.

MS (EI): *m/z* (%) = 151 [M^+] (40), 136 (100), 56 (9).

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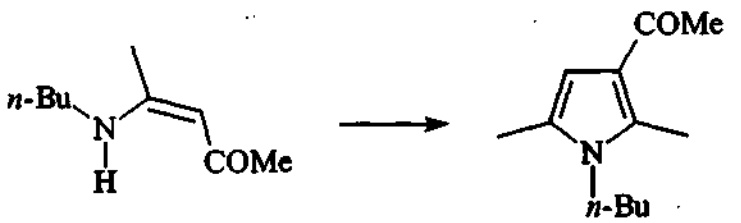
[170] Moon, M.W. and Wade, R.A., *J. Org. Chem.*, **1984**, *49*, 2663-2669.

HRMS: found *m/z* = 151.1003 [M^+], $C_9H_{13}NO$ requires 151.0997.

9.16 1-(1-Butyl-2,5-dimethyl-1*H*-pyrrol-3-yl)ethanone



$C_{12}H_{19}NO$
193.28

(*Z*)-4-(*n*-Butylamino)pent-3-en-2-one (0.20 g, 1.3 mmol) was treated with propargyl bromide (80% w/w solution in toluene, 0.22 ml, 0.23 g, 2.0 mmol) and $AgNO_3$ (0.33 g, 1.9 mmol) to afford 1-(1-butyl-2,5-dimethyl-1*H*-pyrrol-3-yl)ethanone as a yellow oil (59 mg, 0.31 mmol, 24%) after radial chromatography (EtOAc/Hex 1:4); R_f 0.56 (EtOAc/Hex 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 6.16 (1H, s, C=C<u>H</u>), 3.72 (2H, t, *J* = 7.8 Hz, NC<u>H</u>$_2$), 2.51 (3H, s, C<u>H</u>$_3$C=CCOCH$_3$), 2.32 (3H, s, COC<u>H</u>$_3$), 2.18 (3H, s, C<u>H</u>$_3$C=CH), 1.56 (2H, m, NCH$_2$C<u>H</u>$_2$), 1.34 (2H, m, C<u>H</u>$_2$CH$_3$), 0.93 (3H, t, *J* = 7.3 Hz, CH$_2$C<u>H</u>$_3$).

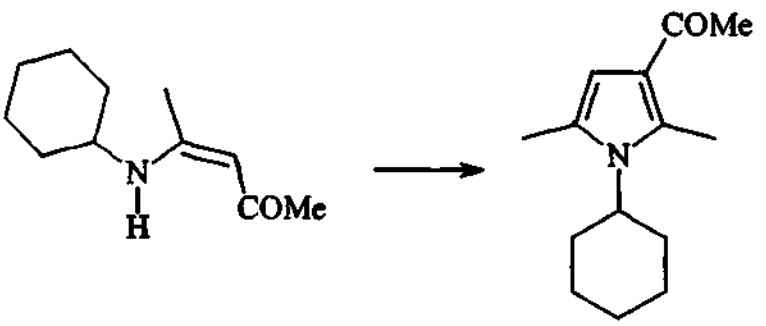
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 194.7 (C=O), 134.4 (<u>C</u>=CCOCH$_3$), 127.0 (<u>C</u>=CH), 119.7 (<u>C</u>COCH$_3$), 108.0 (C=<u>C</u>H), 43.1 (N<u>C</u>H$_2$), 32.4 (NCH$_2$<u>C</u>H$_2$), 28.3 (CO<u>C</u>H$_3$), 19.9 (<u>C</u>H$_2$CH$_3$), 13.6 (<u>C</u>H$_3$C=CH), 12.1 (<u>C</u>H$_3$C=CCOCH$_3$), 11.7 (CH$_2$<u>C</u>H$_3$).

IR (thin film, $CHCl_3$): 2956, 2934, 1648, 1517, 1418 cm^{-1}.

MS (EI): *m/z* (%) = 193 [M^+] (98), 178 (100), 150 (18), 136 (37), 122 (30), 108 (46), 43 (28).

HRMS: found *m/z* = 193.1464 [M^+], $C_{12}H_{19}NO$ requires 193.1467.

9.17 1-(1-Cyclohexyl-2,5-dimethyl-1*H*-pyrrol-3-yl)ethanone



$C_{14}H_{21}NO$
219.32

(*Z*)-4-(Cyclohexylamino)pent-3-en-2-one (0.20 g, 1.1 mmol) was treated with propargyl bromide (80% w/w solution in toluene, 0.18 ml, 0.19 g, 1.6 mmol) and $AgNO_3$ (0.28 g, 1.7 mmol) to afford 1-(1-cyclohexyl-2,5-dimethyl-1*H*-pyrrol-3-yl)ethanone as a red/brown oil (25%) after radial chromatography (EtOAc/Hex 1:4); R_f 0.56 (EtOAc/Hex 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 6.17 (1H, s, C=C<u>H</u>), 3.96 (1H, m, NC<u>H</u>), 2.62 (3H, s, C<u>H</u>$_3$C=CCOCH$_3$), 2.33 (3H, s, COC<u>H</u>$_3$), 2.28 (3H, s, C<u>H</u>$_3$C=CH), 2.00-1.72 and 1.41-1.17 (10H, m, NCHC$_5$<u>H</u>$_{10}$).

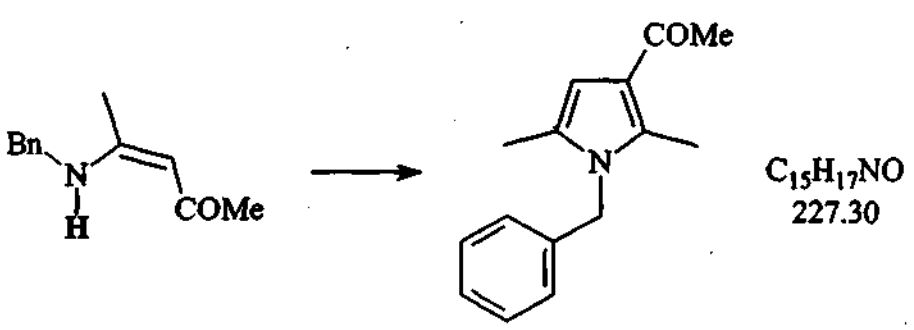
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 194.9 (C=O), 134.9 (<u>C</u>=CCOCH$_3$), 127.4 (<u>C</u>=CH), 109.7 (<u>C</u>COCH$_3$), 106.0 (C=<u>C</u>H), 56.5 (N<u>C</u>H), 31.8 [2C, NCH(<u>C</u>H$_2$)$_2$], 28.5 (CO<u>C</u>H$_3$), 26.4 [2C, NCH(CH$_2$)$_2$(<u>C</u>H$_2$)$_2$], 25.3 [(CH$_2$)$_2$<u>C</u>H$_2$], 14.2 (<u>C</u>H$_3$C=CH), 13.0 (<u>C</u>H$_3$C=CCOCH$_3$).

IR (thin film, $CHCl_3$): 2928, 2850, 1648, 1517, 1415 cm^{-1}.

MS (EI): *m/z* (%) = 219 [M$^+$] (95), 204 (35), 138 (28), 137 (91), 122 (100), 55 (42), 41 (25).

HRMS: found *m/z* = 219.1627 [M$^+$], $C_{14}H_{21}NO$ requires 219.1623.

9.18 1-(1-Benzyl-2,5-dimethyl-1*H*-pyrrol-3-yl)ethanone



$C_{15}H_{17}NO$
227.30

(*Z*)-4-(Benzylamino)pent-3-en-2-one (0.20 g, 1.1 mmol) was treated with propargyl bromide (80% w/w solution in toluene, 0.24 ml, 0.25 g, 2.1 mmol) and $AgNO_3$ (0.36 g, 2.1 mmol) to afford 1-(1-benzyl-2,5-dimethyl-1*H*-pyrrol-3-yl)ethanone as a colourless oil (50 mg, 0.22 mmol, 21%) after radial chromatography (EtOAc/Hex 1:3); R_f 0.58 (EtOAc/Hex 1:1).

^{1}H NMR (500 MHz, CDCl3): δ (ppm) = 7.33-7.23 and 6.90-6.88 (5H, m, $C_6\underline{H}_5$), 6.30 (1H, s, C=C$\underline{H}$), 5.04 (2H, s, $C_6H_5C\underline{H}_2$), 2.49 (3H, s, $C\underline{H}_3C$=CCOCH$_3$), 2.40 (3H, s, COC$\underline{H}_3$), 2.13 (3H, s, $C\underline{H}_3C$=CH).

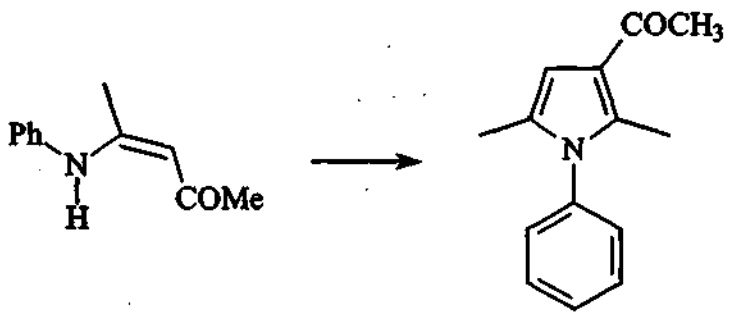
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 195.0 (C=O), 136.7 (*ipso*-$\underline{C}_6H_5$), 135.1 ($\underline{C}$=CCOCH$_3$), 128.8 (2C, *m*-$\underline{C}_6H_5$), 127.8 ($\underline{C}$=CH), 127.4 (*p*-$\underline{C}_6H_5$), 125.5 (2C, *o*-$\underline{C}_6H_5$), 120.2 ($\underline{C}$COCH$_3$), 108.3 (C=$\underline{C}$H), 46.5 ($C_6H_5\underline{C}H_2$), 28.5 (CO$\underline{C}$H$_3$), 12.1 ($\underline{C}$H$_3$C=CH), 11.7 ($\underline{C}$H$_3$C=CCOCH$_3$).

IR (thin film, $CHCl_3$): 2912, 1651, 1522, 1415, 1242 cm^{-1}.

MS (EI): *m/z* (%) = 227 [M$^+$] (100), 212 (68), 91 (80).

HRMS: found *m/z* = 227.1302 [M$^+$], $C_{15}H_{17}NO$ requires 227.1310.

9.19 1-(2,5-Dimethyl-1-phenyl-1*H*-pyrrol-3-yl)ethanone



$C_{14}H_{15}NO$
213.27

(*Z*)-4-(Phenylamino)pent-3-en-2-one (0.20 g, 1.1 mmol) was treated with propargyl bromide (80% w/w solution in toluene, 0.25 ml, 0.27 g, 2.3 mmol) and $AgNO_3$ (0.39 g, 2.3 mmol) to afford 1-(2,5-dimethyl-1-phenyl-1*H*-pyrrol-3-yl)ethanone as an inseparable mixture of starting material and product (SM : prod 1:1) (7% from ^{1}H NMR integral values) after radial chromatography (EtOAc/Hex 1:4); R_f 0.59 (EtOAc/Hex 1:1).

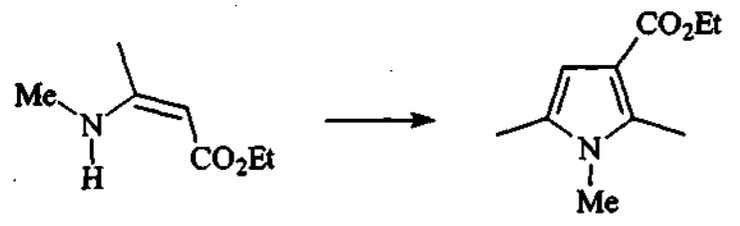
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.51-7.32 (5H, m, $C_6\underline{H}_5$), 6.32 (1H, s, C=C$\underline{H}$), 2.42 (3H, s, $C\underline{H}_3C$=CCOCH$_3$), 2.30 (3H, s, COC$\underline{H}_3$), 1.99 (3H, s, $C\underline{H}_3C$=CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 196.4 (C=O), 139.0 (*ipso*-$\underline{C}_6H_5$), 137.6 ($\underline{C}$=CCOCH$_3$), 136.0 ($\underline{C}$=CH), 129.7 (2C, *m*-$\underline{C}_6H_5$), 128.9 (*p*-$\underline{C}_6H_5$), 128.3 (2C, *o*-$\underline{C}_6H_5$), 120.7 ($\underline{C}$COCH$_3$), 108.3 (C=$\underline{C}$H), 29.4 (CO$\underline{C}$H$_3$), 13.2 ($\underline{C}$H$_3$C=CH), 12.9 ($\underline{C}$H$_3$C=CCOCH$_3$).

MS (EI): *m/z* (%) = 213 [M$^+$] (34), 198 (100).

HRMS: found *m/z* = 213.1144 [M$^+$], $C_{14}H_{15}NO$ requires 213.1154.

9.20 Ethyl 1,2,5-trimethyl-1*H*-pyrrole-3-carboxylate



$C_{10}H_{15}NO_2$
181.23

Ethyl (*Z*)-3-(methylamino)but-2-enoate (0.25 g, 1.8 mmol) was treated with propargyl bromide (80% w/w solution in toluene, 0.39 ml, 0.42 g, 3.5 mmol) and $AgNO_3$ (0.59 g, 3.5 mmol) to afford ethyl 1,2,5-trimethyl-1*H*-pyrrole-3-carboxylate as a colourless oil (68 mg, 0.38 mmol, 21%) after radial chromatography (EtOAc/Hex 1:4); R_f 0.59 (EtOAc/Hex 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 6.22 (1H, s, C=C<u>H</u>), 4.22 (2H, q, J = 7.3 Hz, OC<u>H</u>$_2$CH$_3$), 3.36 (3H, s, NC<u>H</u>$_3$), 2.48 (3H, s, C<u>H</u>$_3$C=CC=O), 2.16 (3H, s, C<u>H</u>$_3$C=CH), 1.31 (3H, t, J = 7.2 Hz, OCH$_2$C<u>H</u>$_3$).

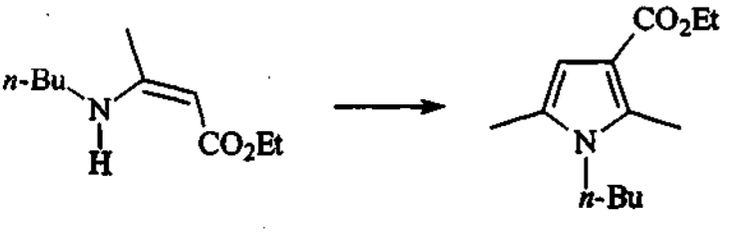
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 165.6 (C=O), 135.2 (<u>C</u>=CC=O), 127.6 (<u>C</u>=CH), 110.3 (<u>C</u>C=O), 106.9 (C=<u>C</u>H), 58.9 (O<u>C</u>H$_2$CH$_3$), 30.0 (N<u>C</u>H$_3$), 14.4 (<u>C</u>H$_3$C=CH), 12.1 (OCH$_2$<u>C</u>H$_3$), 11.2 (<u>C</u>H$_3$C=CC=O).

IR (thin film, $CHCl_3$): 2983, 2923, 1695, 1533, 1415, 1223, 1061 cm^{-1}.

MS (EI): *m/z* (%) = 181 [M$^+$] (80), 152 (100), 136 (58).

HRMS: found *m/z* = 181.1110 [M$^+$], $C_{10}H_{15}NO_2$ requires 181.1103.

9.21 Ethyl 1-butyl-2,5-dimethyl-1*H*-pyrrole-3-carboxylate



$C_{13}H_{21}NO_2$
223.31

Ethyl (*Z*)-3-(*n*-butylamino)but-2-enoate (0.12 g, 0.65 mmol) was treated with propargyl bromide (80% w/w solution in toluene, 0.30 ml, 0.32 g, 2.7 mmol) and $AgNO_3$ (0.46 g, 2.7 mmol) to afford ethyl 1-butyl-2,5-dimethyl-1*H*-pyrrole-3-carboxylate as a yellow oil (71

mg, 0.32 mmol, 24%) after radial chromatography (EtOAc/Hex 1:4); R_f 0.60 (EtOAc/Hex 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 6.24 (1H, s, C=C<u>H</u>), 4.23 (2H, q, J = 7.1 Hz, OC<u>H</u>$_2$CH$_3$), 3.73 (2H, t, J = 7.4 Hz, NC<u>H</u>$_2$), 2.50 (3H, s, C<u>H</u>$_3$C=CC=O), 2.18 (3H, s, C<u>H</u>$_3$C=CH), 1.58 (2H, m, NCH$_2$C<u>H</u>$_2$), 1.36 (2H, m, CH$_2$C<u>H</u>$_2$CH$_3$), 1.31 (3H, t, J = 7.1 Hz, OCH$_2$C<u>H</u>$_3$), 0.94 (3H, t, J = 7.5 Hz, CH$_2$CH$_2$C<u>H</u>$_3$).

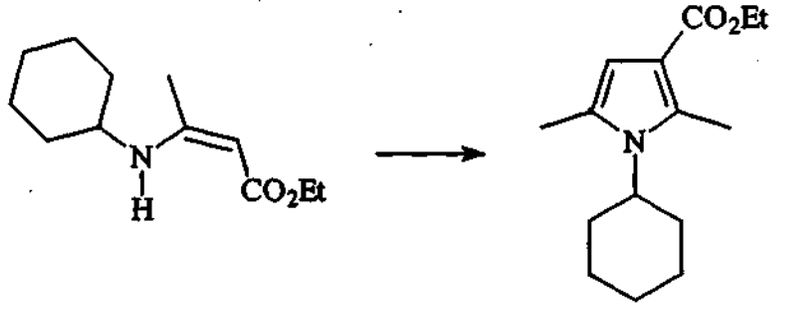
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 165.7 (C=O), 134.8 (<u>C</u>=CC=O), 127.2 (<u>C</u>=CH), 110.5 (<u>C</u>C=O), 107.4 (C=<u>C</u>H), 58.9 (O<u>C</u>H$_2$CH$_3$), 43.4 (N<u>C</u>H$_2$), 32.6 (NCH$_2$<u>C</u>H$_2$), 20.0 (CH$_2$<u>C</u>H$_2$CH$_3$), 14.5 (<u>C</u>H$_3$C=CH), 13.7 (CH$_2$CH$_2$<u>C</u>H$_3$), 12.1 (OCH$_2$<u>C</u>H$_3$), 11.2 (<u>C</u>H$_3$C=CC=O).

IR (thin film, $CHCl_3$): 2961, 2928, 1698, 1533, 1421, 1229, 1061, 770 cm^{-1}.

MS (EI): *m/z* (%) = 223 [M$^+$] (100), 194 (56), 181 (31), 178 (40), 108 (20).

HRMS: found *m/z* = 223.1578 [M$^+$], $C_{13}H_{21}NO_2$ requires 223.1572.

9.22 Ethyl 1-cyclohexyl-2,5-dimethyl-1*H*-pyrrole-3-carboxylate



$C_{15}H_{23}NO_2$
249.35

Ethyl (*Z*)-3-(cyclohexylamino)but-2-enoate (0.27 g, 1.3 mmol) was treated with propargyl bromide (80% w/w solution in toluene, 0.29 ml, 0.31 g, 2.6 mmol) and $AgNO_3$ (0.44 g, 2.6 mmol) to afford ethyl 1-cyclohexyl-2,5-dimethyl-1*H*-pyrrole-3-carboxylate as a yellow oil (75 mg, 0.30 mmol, 24%) after radial chromatography (EtOAc/Hex 1:9); R_f 0.55 (EtOAc/Hex 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 6.22 (s, 1H, C=C<u>H</u>), 4.22 (2H, q, J = 7.1 Hz, OC<u>H</u>$_2$CH$_3$), 3.95 (1H, m, NC<u>H</u>), 2.60 (3H, s, C<u>H</u>$_3$C=CC=O), 2.27 (3H, s, C<u>H</u>$_3$C=CH), 1.99-1.73 and 1.41-1.17 (10H, m, NCHC$_5$<u>H</u>$_{10}$), 1.31 (3H, t, J = 7.1 Hz, OCH$_2$C<u>H</u>$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 165.7 (C=O), 135.3 (<u>C</u>=CC=O), 127.5 (<u>C</u>=CH), 110.6 (<u>C</u>C=O), 108.8 (C=<u>C</u>H), 58.9 (O<u>C</u>H$_2$CH$_3$), 56.6 (N<u>C</u>H), 31.9 [2C, NCH(<u>C</u>H$_2$)$_2$], 26.4

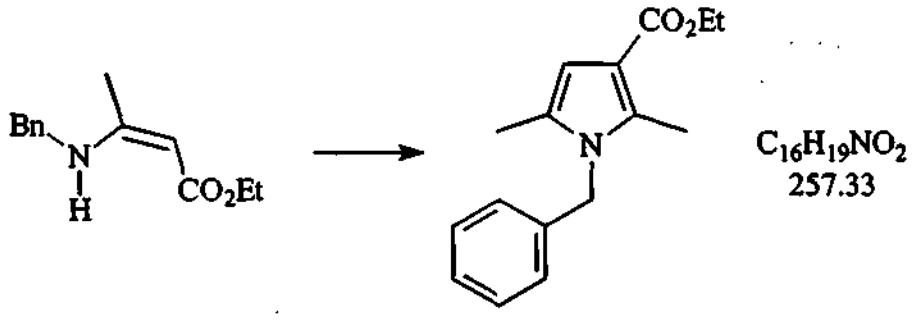
[2C, NCH$(CH_2)_2(\underline{C}H_2)_2$], 25.4 [$(CH_2)_2\underline{C}H_2$], 14.5 (2C, $\underline{C}H_3C$=CH and $OCH_2\underline{C}H_3$), 12.3 ($\underline{C}H_3C$=CC=O).

IR (thin film, $CHCl_3$): 2928, 2857, 1698, 1530, 1421, 1220, 1185, 1067, 770 cm^{-1}.

MS (EI): *m/z* (%) = 249 [M^+] (100), 220 (19), 204 (21), 167 (35), 139 (24), 138 (71), 122 (27).

HRMS: found *m/z* = 249.1740 [M^+], $C_{15}H_{23}NO_2$ requires 249.1729.

9.23 Ethyl 1-benzyl-2,5-dimethyl-1*H*-pyrrole-3-carboxylate



$C_{16}H_{19}NO_2$
257.33

Ethyl (*Z*)-3-(benzylamino)but-2-enoate (0.25 g, 1.1 mmol) was treated with propargyl bromide (80% w/w solution in toluene, 0.25 ml, 0.27 g, 2.2 mmol) and $AgNO_3$ (0.39 g, 2.3 mmol) to afford ethyl 1-benzyl-2,5-dimethyl-1*H*-pyrrole-3-carboxylate as an inseparable mixture of starting material and product (SM : prod 1.3:1) (14% from ^1H NMR integral values) after radial chromatography (EtOAc/Hex 1:4); R_f 0.54 (EtOAc/Hex 1:1).

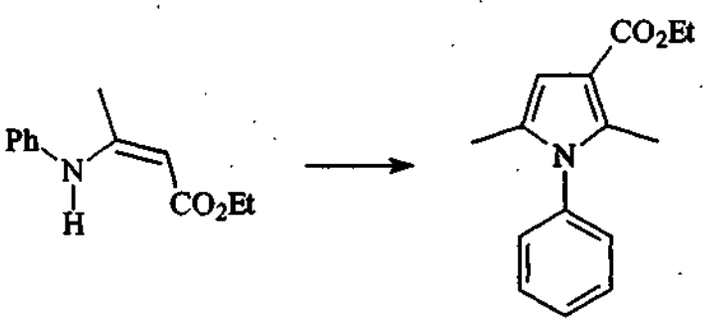
^1H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.35-7.27 and 6.90-6.88 (5H, m, $C_6\underline{H}_5$), 6.37 (1H, s, C=C$\underline{H}$), 5.03 (2H, s, $C_6H_5C\underline{H}_2$), 4.27 (2H, q, *J* = 7.1 Hz, $OC\underline{H}_2CH_3$), 2.46 (3H, s, $C\underline{H}_3C$=CC=O), 2.12 (3H, s, $C\underline{H}_3C$=CH), 1.35 (3H, s, *J* = 7.0 Hz, $OCH_2C\underline{H}_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 165.6 ($\underline{C}$=O), 136.9 (*ipso*-$\underline{C}_6H_5$), 135.4 ($\underline{C}$=CC=O), 128.7 (2C, *m*-$\underline{C}_6H_5$), 127.8 ($\underline{C}$=CH), 127.2 (*p*-$\underline{C}_6H_5$), 125.4 (2C, *o*-$\underline{C}_6H_5$), 111.2 ($\underline{C}$C=O), 107.6 (C=$\underline{C}$H), 59.1 ($O\underline{C}H_2CH_3$), 46.7 ($N\underline{C}H_2$), 14.5 ($\underline{C}H_3C$=CH), 12.0 ($OCH_2\underline{C}H_3$), 11.2 ($\underline{C}H_3C$=CC=O).

MS (EI): *m/z* (%) = 257 [M^+] (74), 228 (19), 212 (20), 91 (100).

HRMS: found *m/z* = 257.1402 [M^+], $C_{16}H_{19}NO_2$ requires 257.1416.

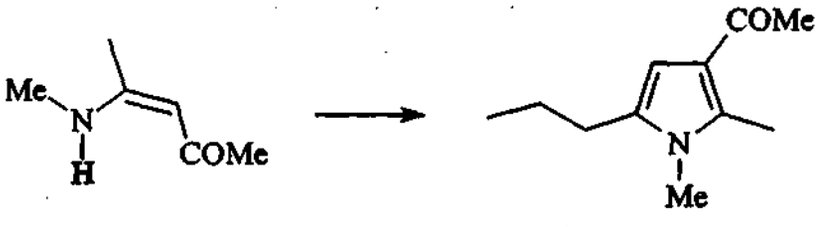
9.24 Ethyl 2,5-dimethyl-1-phenyl-1*H*-pyrrole-3-carboxylate



$C_{15}H_{17}NO_2$
243.30

Ethyl (*Z*)-3-(phenylamino)but-2-enoate (0.25 g, 1.2 mmol) was treated with propargyl bromide (80% w/w solution in toluene, 0.27 ml, 0.29 g, 2.4 mmol) and $AgNO_3$ (0.41 g, 2.4 mmol) to afford ethyl 2,5-dimethyl-1-phenyl-1*H*-pyrrole-3-carboxylate in a **trace** quantity (determined by ^{1}H NMR) after radial chromatography (EtOAc/Hex 1:9).

10.1 1-(1,2-Dimethyl-5-propyl-1*H*-pyrrol-3-yl)-ethanone



$C_{11}H_{17}NO$
179.26

(*Z*)-4-(Methylamino)pent-3-en-2-one (0.15 g, 1.3 mmol) was treated with 1-bromopent-2-yne (0.16 ml, 0.23 g, 1.6 mmol) and $AgNO_3$ (0.27 g, 1.6 mmol) to afford 1-(1,2-dimethyl-5-propyl-1*H*-pyrrol-3-yl)ethanone as a colourless oil (30 mg, 0.17 mmol, 13%) after radial chromatography (EtOAc/Hex 1:4); R_f 0.51 (EtOAc/Hex 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 6.20 (1H, s, C=C$\underline{H}$), 3.40 (3H, s, NC$\underline{H}_3$), 2.56 (3H, s, COC$\underline{H}_3$), 2.44 (2H, t, J = 7.0 Hz, C$\underline{H}_2$CH$_2$CH$_3$), 2.39 (3H, s, C$\underline{H}_3$C=CH), 1.64 (2H, m, CH$_2$C$\underline{H}_2$CH$_3$), 1.02 (3H, t, J = 7.2 Hz, CH$_2$CH$_2$C$\underline{H}_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 194.9 (C=O), 135.2 (C=CCOCH$_3$), 132.1 (C=CH), 119.8 (CCOCH$_3$), 106.9 (C=CH), 30.0 (NCH$_3$), 28.6 (CH$_2$CH$_2$CH$_3$), 28.4 (COCH$_3$), 21.7 (CH$_2$CH$_2$CH$_3$), 13.9 (CH$_2$CH$_2$CH$_3$), 11.8 (CH$_3$C=CCOCH$_3$).

MS (EI): *m/z* (%) = 179 [M$^+$] (32), 164 (13), 150 (100), 107 (22).

10.2 1-(2,5-Dimethyl-3-furyl)ethanone

$C_8H_{10}O_2$
138.16

R = Me, Bn

(*Z*)-4-(Methylamino)pent-3-en-2-one (1.00 g, 8.84 mmol) was treated with propargyl bromide (80% w/w solution in toluene, 1.97 ml, 2.10 g, 17.7 mmol) and $AgNO_3$ (3.01 g, 17.7 mmol) to afford 1-(2,5-dimethyl-3-furyl)ethanone as a colourless oil (98 mg, 0.71 mmol, 8%) after radial chromatography (EtOAc/Hex 1:4); R_f 0.64 (EtOAc/Hex 1:1).

(*Z*)-4-(Benzylamino)pent-3-en-2-one (0.20 g, 1.1 mmol) was treated with propargyl bromide (80% w/w solution in toluene, 0.24 ml, 0.25 g, 2.1 mmol) and $AgNO_3$ (0.36 g, 2.1 mmol) to afford 1-(2,5-dimethyl-3-furyl)ethanone as a colourless oil (16 mg, 0.12 mmol, 11%) after radial chromatography (EtOAc/Hex 1:3).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 6.18 (1H, s, C=C<u>H</u>), 2.53 (3H, s, C<u>H</u>$_3$C=CCOCH$_3$), 2.35 (3H, s, COC<u>H</u>$_3$), 2.24 (3H, s, C<u>H</u>$_3$C=CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 194.2 (C=O), 156.9 (<u>C</u>=CCOCH$_3$), 149.8 (<u>C</u>=CH), 122.1 (<u>C</u>COCH$_3$), 106.1 (C=<u>C</u>H), 29.2 (CO<u>C</u>H$_3$), 14.1 (<u>C</u>H$_3$C=CH), 13.2 (<u>C</u>H$_3$C=CCOCH$_3$).

IR (thin film, $CHCl_3$): 2923, 2857, 1673, 1572, 1229 cm^{-1}.

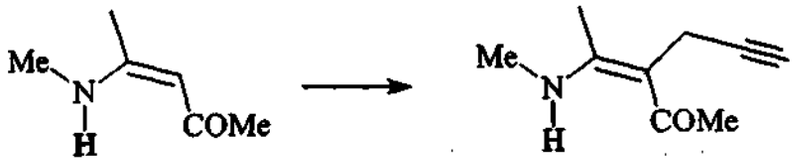
MS (EI): *m/z* (%) = 138 [M$^+$] (67), 123 (100), 81 (33), 53 (37).

Preparation of *C*-propargyl vinylogous amides: General procedure

n-BuLi (2.2 mmol) was added to a solution of the appropriate vinylogous amide (2 mmol) in dry THF (10 ml) at 0°C and allowed to warm to room temperature over 30 minutes. Propargyl bromide (3 mmol) was added thereafter and the reaction mixture was stirred overnight. The reaction was quenched by addition of $NH_4Cl_{(aq)}$ (5 ml), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 ml). The organic layers were combined, dried

($MgSO_4$) and concentrated *in vacuo* to afford the desired *C*-propargyl vinylogous amides after chromatography.

11.1 (3*Z*)-3-[1-(Methylamino)ethylidene]hex-5-yn-2-one



$C_9H_{13}NO$
151.20

(*Z*)-4-(Methylamino)pent-3-en-2-one (0.50 g, 4.4 mmol) was treated with *n*-BuLi (1.6M solution in hexane, 3.04 ml, 4.86 mmol) and propargyl bromide (80% w/w solution in toluene, 0.74 ml, 0.79 g, 6.6 mmol) to afford (3*Z*)-3-[1-(methylamino)ethylidene]hex-5-yn-2-one as a colourless oil (0.37 g, 2.5 mmol, 55%) after radial chromatography (EtOAc/Hex 1:3), R_f 0.43 (EtOAc/Hex 2:1).

^{1}H NMR (500 MHz, CDCl3): δ (ppm) = 11.87 (1H, br, NH), 3.09 (2H, d, J = 2.7 Hz, $C\underline{H}_2C{\equiv}CH$), 2.93 (3H, d, J = 5.4 Hz, $NC\underline{H}_3$), 2.20 (3H, s, $COC\underline{H}_3$), 2.06 (3H, s, $C\underline{H}_3C{=}C$), 1.97 (1H, t, J = 2.6 Hz, $C{\equiv}C\underline{H}$).

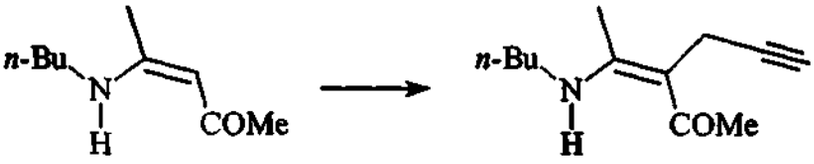
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 193.8 (C=O), 163.9 ($N\underline{C}{=}C$), 99.5 ($NC{=}\underline{C}$), 83.8 ($\underline{C}{\equiv}CH$), 67.5 ($C{\equiv}\underline{C}H$), 29.8 ($N\underline{C}H_3$), 27.7 ($CO\underline{C}H_3$), 18.9 ($\underline{C}H_2C{\equiv}CH$), 14.7 ($\underline{C}H_3C{=}C$).

IR (thin film, $CHCl_3$): 3285, 2109, 1602, 1486, 1275 cm^{-1}.

MS (EIMS): m/z = 151 [M^+], 136, 108 (100), 56.

Note: This compound was found to be exceptionally unstable and, hence, acquiring HRMS data was not possible.

11.2 (3*Z*)-3-[1-(Butylamino)ethylidene]hex-5-yn-2-one



$C_{12}H_{19}NO$
193.28

(*Z*)-4-(Butylamino)pent-3-en-2-one (0.86 g, 5.5 mmol) was treated with *n*-BuLi (0.75M solution in hexane, 8.15 ml, 6.10 mmol) and propargyl bromide (80% w/w solution in toluene, 0.93 ml, 0.99 g, 8.3 mmol) to afford (3*Z*)-3-[1-(butylamino)ethylidene]hex-5-yn-2-one as a colourless oil (0.55 g, 2.9 mmol, 51%) after column chromatography (EtOAc/Hex 1:4), R_f 0.62 (EtOAc/Hex 1:1).

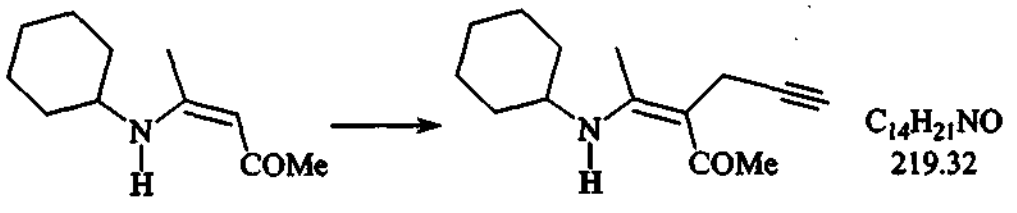
^{1}H NMR (500 MHz, CDCl3): δ (ppm) = 12.02 (1H, br, NH), 3.21 (2H, q, J = 6.5 Hz, NC$\underline{H}_2$), 3.05 (2H, d, J = 2.7 Hz, C$\underline{H}_2$C≡CH), 2.15 (3H, s, COC$\underline{H}_3$), 2.02 (3H, s, C$\underline{H}_3$C=C), 1.94 (1H, t, J = 2.7 Hz, C≡C$\underline{H}$), 1.53 (2H, m, NCH$_2$C$\underline{H}_2$), 1.37 (2H, m, C$\underline{H}_2$CH$_3$), 0.88 (3H, t, J = 7.3 Hz, CH$_2$C$\underline{H}_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 193.4 (C=O), 162.9 (N$\underline{C}$=C), 99.1 (NC=$\underline{C}$), 83.7 ($\underline{C}$≡CH), 67.4 (C≡$\underline{C}$H), 43.0 (N$\underline{C}$H$_2$), 31.8 (NCH$_2\underline{C}$H$_2$), 27.6 (CO$\underline{C}$H$_3$), 19.9 ($\underline{C}$H$_2$CH$_3$), 18.7 ($\underline{C}$H$_2$C≡CH), 14.8 ($\underline{C}$H$_3$C=C), 13.6 (CH$_2\underline{C}$H$_3$).

IR (thin film, $CHCl_3$): 3280, 2950, 2868, 2109, 1599, 1566, 1275 cm^{-1}.

HRMS: found m/z = 193.1467 [M$^+$], $C_{12}H_{19}NO$ requires 193.1467.

11.3 (3*Z*)-3-[1-(Cyclohexylamino)ethylidene]hex-5-yn-2-one



(*Z*)-4-(Cyclohexylamino)pent-3-en-2-one (0.83 g, 4.6 mmol) was treated with *n*-BuLi (0.75M solution in hexane, 6.71 ml, 5.04 mmol) and propargyl bromide (80% w/w solution in toluene, 0.76 ml, 0.82 g, 6.9 mmol) to afford (3*Z*)-3-[1-(cyclohexylamino)ethylidene]hex-5-yn-2-one as a colourless oil (0.52 g, 2.4 mmol, 52%) after radial chromatography (EtOAc/Hex 1:9), R_f 0.49 (EtOAc/Hex 1:1).

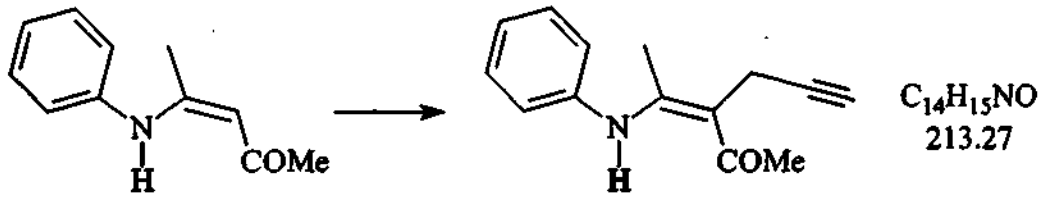
^{1}H NMR (500 MHz, CDCl3): δ (ppm) = 12.19 (1H, br, NH), 3.40 (1H, m, NC$\underline{H}$), 3.06 (2H, d, J = 2.0 Hz, C$\underline{H}_2$C≡CH), 2.17 (3H, s, COC$\underline{H}_3$), 2.06 (3H, s, C$\underline{H}_3$C=C), 1.95 (1H, t, J = 2.9 Hz, C≡C$\underline{H}$), 1.88-1.69 and 1.36-1.28 (10H, m, NCHC$_5\underline{H}_{10}$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 193.2 (C=O), 161.7 (N<u>C</u>=C), 98.9 (NC=<u>C</u>), 83.8 (<u>C</u>≡CH), 67.5 (C≡<u>C</u>H), 51.7 (N<u>C</u>H), 33.7 [2C, NCH(<u>C</u>H_2)$_2$], 27.7 (CO<u>C</u>H_3), 25.2 [2C, NCH(CH_2)$_2$(<u>C</u>H_2)$_2$], 24.2 [(CH_2)$_2$<u>C</u>H_2], 18.8 (<u>C</u>H_2C≡CH), 14.7 (<u>C</u>H_3C=C).

IR (thin film, $CHCl_3$): 3285, 2934, 2851, 2109, 1593, 1566, 1289 cm^{-1}.

HRMS: found *m/z* = 219.1622 [M^+], $C_{14}H_{21}NO$ requires 219.1623.

11.4 (3*Z*)-3-[1-(Phenylamino)ethylidene]hex-5-yn-2-one



(*Z*)-4-(Phenylamino)pent-3-en-2-one (1.00 g, 5.71 mmol) was treated with *n*-BuLi (0.75M solution in hexane, 8.37 ml, 6.28 mmol) and propargyl bromide (80% w/w solution in toluene, 0.95 ml, 1.0 g, 8.6 mmol) to afford (3*Z*)-3-[1-(phenylamino)ethylidene]hex-5-yn-2-one as a colourless oil (0.26 g, 1.2 mmol, 21%) after column chromatography (EtOAc/Hex 1:9), R_f 0.50 (EtOAc/Hex 1:1).

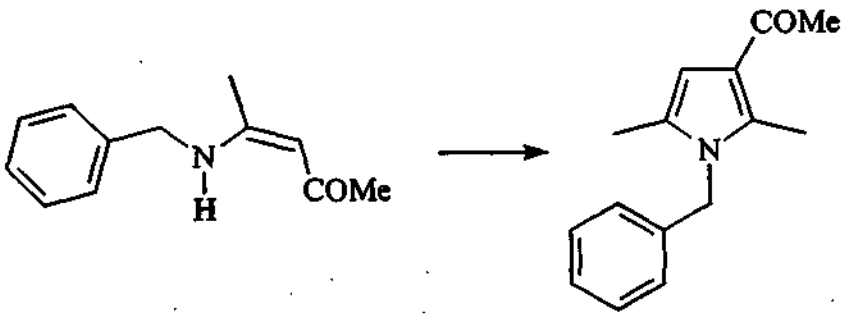
^{1}H NMR (500 MHz, CDCl3): δ (ppm) = 13.49 (1H, br, NH), 7.34-7.06 (5H, m, C_6<u>H</u>$_5$), 3.18 (2H, d, *J* = 2.0 Hz, C<u>H</u>$_2$C≡CH), 2.31 (3H, s, COC<u>H</u>$_3$), 2.11 (3H, s, C<u>H</u>$_3$C=C), 2.02 (1H, t, *J* = 2.7 Hz, C≡C<u>H</u>).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 195.6 (C=O), 159.7 (N<u>C</u>=C), 138.7 (*ipso*-<u>C</u>$_6$H$_5$), 129.0 (2C, *m*-<u>C</u>$_6$H$_5$), 125.6 (*p*-<u>C</u>$_6$H$_5$), 125.3 (2C, *o*-<u>C</u>$_6$H$_5$), 101.8 (NC=<u>C</u>), 83.1 (<u>C</u>≡CH), 68.0 (C≡<u>C</u>H), 27.9 (CO<u>C</u>H_3), 18.9 (<u>C</u>H_2C≡CH), 16.4 (<u>C</u>H_3C=C).

IR (thin film, $CHCl_3$): 3285, 2109, 1588, 1563, 1273 cm^{-1}.

HRMS: found *m/z* = 213.1145 [M^+], $C_{14}H_{15}NO$ requires 213.1154.

11.5 1-(1-Benzyl-2,5-dimethyl-1*H*-pyrrol-3-yl)ethanone



$C_{15}H_{17}NO$
227.30

(*Z*)-4-(Benzylamino)pent-3-en-2-one (1.00 g, 5.28 mmol) was treated with *n*-BuLi (0.75M solution in hexane, 7.75 ml, 5.81 mmol) and propargyl bromide (80% w/w solution in toluene, 0.65 ml, 0.69 g, 7.9 mmol) to afford 1-(1-benzyl-2,5-dimethyl-1*H*-pyrrol-3-yl)ethanone as a colourless oil (0.52 g, 2.3 mmol, 43%) after column chromatography (EtOAc/Hex 1:9), R_f 0.58 (EtOAc/Hex 1:1).

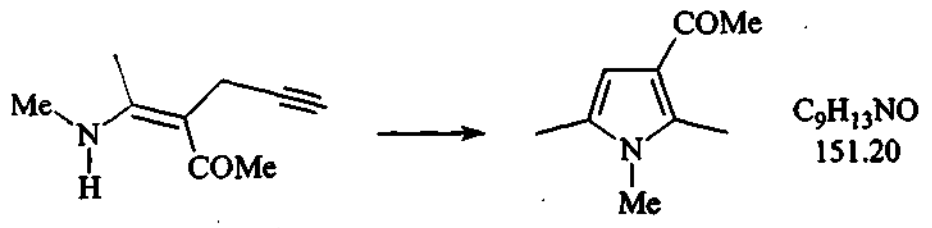
Note: Spectral and physical data for this compound matched those acquired for the same compound in a prior reaction (p153).

Preparation of functionalised pyrroles: General procedure (two step)

Room temperature: $AgNO_3$ (0.2 mmol) was added to a solution of the appropriate *C*-propargyl vinylogous amide (1 mmol) in dry CH_3CN (1 ml) and stirred overnight. The organic layer was washed with $NaI_{(aq)}$, dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was filtered (MeOH) through a short plug of silica gel to afford the desired pyrroles.

Microwave: $AgNO_3$ (0.2 mmol) was added to a Pyrex test tube containing a solution of the appropriate *C*-propargyl vinylogous amide or carbamate (1 mmol) in dry CH_3CN (1 ml). The test tube was sealed and subjected to microwave irradiation (700 W, low) for 60 seconds (2 × 30s). Work up as above.

11.6 1-(1,2,5-Trimethyl-1*H*-pyrrol-3-yl)ethanone

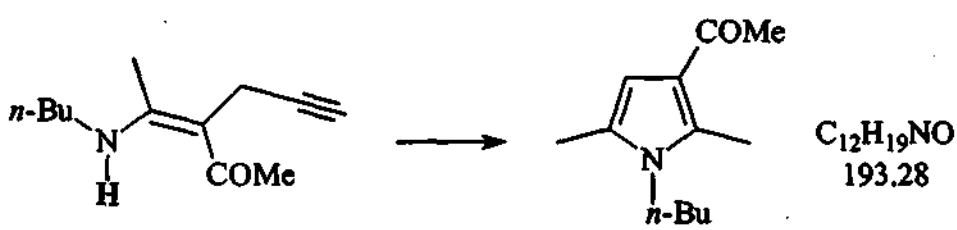


(3*Z*)-3-[1-(Methylamino)ethylidene]hex-5-yn-2-one (0.10 g, 0.66mmol) was treated with $AgNO_3$ (22 mg, 0.13 mmol) at room temperature to afford 1-(1,2,5-trimethyl-1*H*-pyrrol-3-yl)ethanone as a pale yellow oil (93 mg, 0.62 mmol, 93%).

(3*Z*)-3-[1-(Methylamino)ethylidene]hex-5-yn-2-one (0.14 g, 0.93mmol) was treated with $AgNO_3$ (31 mg, 0.19 mmol) and irradiated to afford 1-(1,2,5-trimethyl-1*H*-pyrrol-3-yl)ethanone as a pale yellow oil (0.13 g, 0.86 mmol, 93%).

Note: Spectral and physical data for this compound matched those acquired for the same compound in a prior reaction (p151).

11.7 1-(1-Butyl-2,5-dimethyl-1*H*-pyrrol-3-yl)ethanone

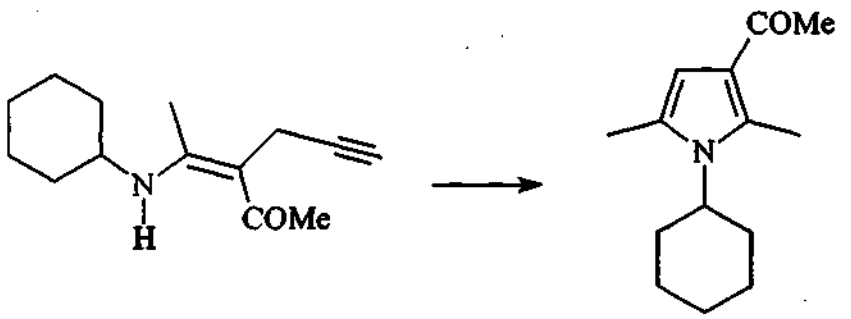


(3*Z*)-3-[1-(Butylamino)ethylidene]hex-5-yn-2-one (0.10 g, 0.52 mmol) was treated with $AgNO_3$ (18 mg, 0.10 mmol) at room temperature to afford 1-(1-butyl-2,5-dimethyl-1*H*-pyrrol-3-yl)ethanone as a yellow oil (95 mg, 0.49 mmol, 95%).

(3*Z*)-3-[1-(Butylamino)ethylidene]hex-5-yn-2-one (0.10 g, 0.52 mmol) was treated with $AgNO_3$ (18 mg, 0.10 mmol) and irradiated to afford 1-(1-butyl-2,5-dimethyl-1*H*-pyrrol-3-yl)ethanone as a yellow oil (91 mg, 0.47 mmol, 91%).

Note: Spectral and physical data for this compound matched those acquired for the same compound in a prior reaction (p152).

11.8 1-(1-Cyclohexyl-2,5-dimethyl-1*H*-pyrrol-3-yl)ethanone



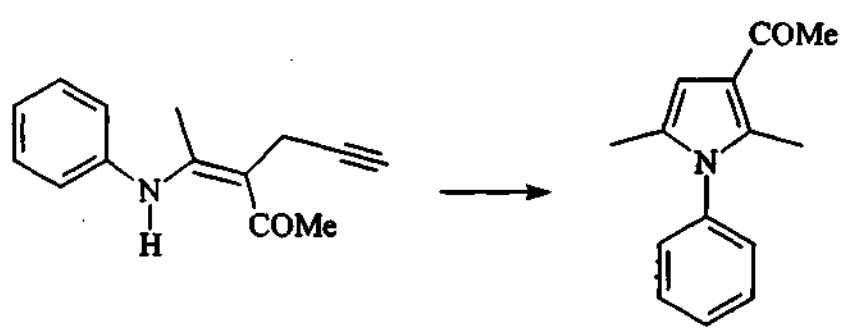
$C_{14}H_{21}NO$
219.32

(3*Z*)-3-[1-(Cyclohexylamino)ethylidene]hex-5-yn-2-one (0.13 g, 0.59 mmol) was treated with $AgNO_3$ (20 mg, 0.12 mmol) at room temperature to afford 1-(1-cyclohexyl-2,5-dimethyl-1*H*-pyrrol-3-yl)ethanone as a red / brown oil (0.11 g, 0.52 mmol, 87%).

(3*Z*)-3-[1-(Cyclohexylamino)ethylidene]hex-5-yn-2-one (0.20 g, 0.91 mmol) was treated with $AgNO_3$ (20 mg, 0.12 mmol) and irradiated to afford 1-(1-cyclohexyl-2,5-dimethyl-1*H*-pyrrol-3-yl)ethanone as a red / brown oil (0.19 g, 0.88 mmol, 96%).

Note: Spectral and physical data for this compound matched those acquired for the same compound in a prior reaction (p152).

11.9 1-(2,5-Dimethyl-1-phenyl-1*H*-pyrrol-3-yl)ethanone



$C_{14}H_{15}NO$
213.27

(3*Z*)-3-[1-(Phenylamino)ethylidene]hex-5-yn-2-one (0.10 g, 0.47 mmol) was treated with $AgNO_3$ (16 mg, 0.09 mmol) at room temperature to afford 1-(2,5-dimethyl-1-phenyl-1*H*-pyrrol-3-yl)ethanone as a red / brown oil (75 mg, 0.35 mmol, 75%).

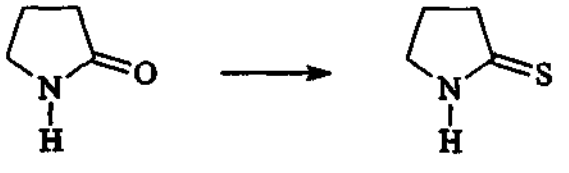
(3*Z*)-3-[1-(Phenylamino)ethylidene]hex-5-yn-2-one (0.11 g, 0.52 mmol) was treated with $AgNO_3$ (18 mg, 0.10 mmol) and irradiated to afford 1-(2,5-dimethyl-1-phenyl-1*H*-pyrrol-3-yl)ethanone as a red / brown oil (86 mg, 0.40 mmol, 78%).

Note: Spectral and physical data for this compound matched those acquired for the same compound in a prior reaction (p154). In this instance, however, the compound was obtained in pure form.

Preparation of thiolactams: General procedure[151]

Lawesson's reagent (10 mmol) and the appropriate lactam (20 mmol) were mixed in a small beaker, which was placed in a larger beaker containing neutral Al_2O_3 and subjected to microwave irradiation (700 W, low) until the mixture became homogeneous. The crude material was purified using column or radial chromatography to afford the desired thiolactams.

12.1 Pyrrolidine-2-thione



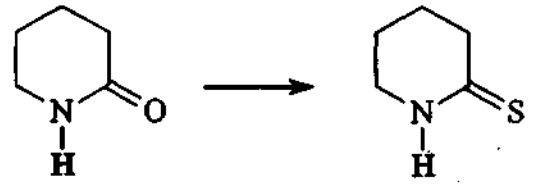
C_4H_7NS
101.16

Lawesson's reagent (2.38 g, 5.87 mmol) and pyrrolidin-2-one (1.00 g, 11.7 mmol) were mixed and irradiated for 30 seconds to afford pyrrolidine-2-thione as a white crystalline solid (m.p. 108-110°C) (lit.[101] m.p. 109-110°C) (1.15 g, 11.4 mmol, 97%) after radial chromatography (EtOAc/Hex 1:2); R_f 0.24 (EtOAc/Hex 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 9.08 (NH), 3.60 (2H, m, $NC\underline{H}_2$), 2.85 (2H, m, $C\underline{H}_2C{=}S$), 2.14 (2H, m, NCH2C$\underline{H}_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 205.6 (C=S), 49.6 (N$\underline{C}H_2$), 43.2 ($\underline{C}H_2$C=S), 22.7 (NCH$_2\underline{C}H_2$).
MS (EIMS): *m/z* (%) = 101 [M^+] (100), 71 (10), 67 (11).

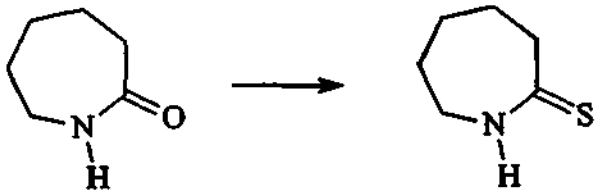
12.2 Piperidine-2-thione



C_5H_9NS
115.19

Lawesson's reagent (4.08 g, 10.1 mmol) and piperidin-2-one (δ-valerolactam) (2.00 g, 20.2 mmol) were mixed and irradiated for 30 seconds to afford piperidine-2-thione as a white crystalline solid (m.p. 90-92°C) (lit.[101] m.p. 92-92°C) (2.12 g, 18.4 mmol, 91%) after column chromatography (EtOAc/Hex 1:3); R_f 0.29 (EtOAc/Hex 1:1).
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.68 (1H, br, NH), 3.38 (2H, m, N$\underline{CH_2}$), 2.90 (2H, t, *J* = 6.5 Hz, $\underline{CH_2}$C=S), 1.83 (2H, m, NCH$_2\underline{CH_2}$), 1.77 (2H, m, NCH$_2$CH$_2\underline{CH_2}$).
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 202.6 (C=S), 44.9 (N$\underline{C}H_2$), 38.8 ($\underline{C}H_2$C=S), 20.8 (NCH$_2\underline{C}H_2$), 20.1 (NCH$_2$CH$_2\underline{C}H_2$).
MS (EIMS): *m/z* (%) = 115 [M^+] (100), 100 (24), 81 (13), 58 (12).

12.3 Azepane-2-thione



$C_6H_{11}NS$
129.22

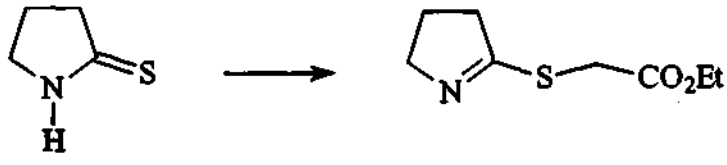
Lawesson's reagent (1.79 g, 4.42 mmol) and azepane-2-one (ε-caprolactam) (1.00 g, 8.84 mmol) were mixed and irradiated for 1 minute to afford azepane-2-thione as a white crystalline solid (m.p. 103-105°C) (lit.[101] m.p. 103-104°C) (1.02 g, 7.90 mmol, 89%) after column chromatography (EtOAc/Hex 1:2); R_f 0.43 (EtOAc/Hex 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 9.16 (1H, br, NH), 3.35 (2H, m, $NC\underline{H}_2$), 2.95 (2H, m, $C\underline{H}_2C{=}S$), 1.76 (2H, m, $C\underline{H}_2CH_2C{=}S$), 1.69 (2H, m, $NCH_2CH_2C\underline{H}_2$), 1.62 (2H, m, $NCH_2C\underline{H}_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 209.9 (C=S), 46.9 ($N\underline{C}H_2$), 44.7 ($\underline{C}H_2C{=}S$), 30.1 ($\underline{C}H_2CH_2C{=}S$), 27.8 ($NCH_2\underline{C}H_2$), 24.3 ($NCH_2CH_2\underline{C}H_2$).

MS (EIMS): *m/z* (%) = 129 [M^+] (100), 100 (55), 71 (28), 58 (32).

12.4 Ethyl (3,4-dihydro-2*H*-pyrrol-5-ylthio)acetate[148]



$C_8H_{13}NO_2S$
187.25

Ethyl bromoacetate (1.21 ml, 1.82 g, 10.9 mmol) was added to a solution of pyrrolidine-2-thione (1.03 g, 10.2 mmol) in dry CH_2Cl_2 (10 ml) at 0°C. The mixture was warmed to room temperature and stirred for 4 hours. The organic phase was washed with saturated $NaHCO_3$ solution (10 ml) and water (10 ml), dried (MgSO4) and concentrated *in vacuo* to afford ethyl (3,4-dihydro-2*H*-pyrrol-5-ylthio)acetate (1.87 g, 9.97 mmol, 98%) as a colourless oil; R_f 0.41 (EtOAc/Hex 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 4.16 (2H, q, J = 7.1 Hz, $OC\underline{H}_2CH_3$), 3.86 (2H, $SC\underline{H}_2$), 3.79 (2H, t, J = 7.1 Hz, $NC\underline{H}_2$), 2.61 (2H, t, J = 7.5 Hz, $NCH_2CH_2C\underline{H}_2$), 1.98 (2H, m, $NCH_2C\underline{H}_2$), 1.23 (3H, t, J = 7.2 Hz, $OCH_2C\underline{H}_3$).

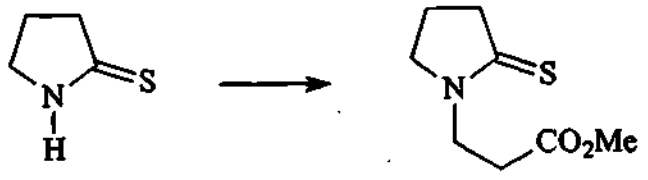
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 171.0 (C=O), 168.9 (N=C), 61.6 ($O\underline{C}H_2CH_3$), 60.3 ($N\underline{C}H_2$), 38.0 ($NCH_2CH_2\underline{C}H_2$), 33.1 ($S\underline{C}H_2$), 23.6 ($NCH_2\underline{C}H_2$), 14.0 ($OCH_2\underline{C}H_3$).

MS (EIMS): *m/z* (%) = 187 [M^+] (4), 141 (50), 140 (61), 114 (81), 113 (100), 72 (51).

Preparation of thiolactam adducts *via* conjugate addition: General procedure

Crushed NaOH pellets (1 mmol) were added to a solution of the appropriate thiolactam (10 mmol) and methyl acrylate (20 mmol) in *undried* THF (50 ml) and stirred at room temperature for 2 hours. The reaction was quenched by the addition of water (5 ml) and extracted with CH_2Cl_2 (3 × 50 ml). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to afford the desired thiolactam adducts without further purification.

12.5 Methyl 3-(2-thioxopyrrolidin-1-yl)propanoate



$C_8H_{13}NO_2S$
187.25

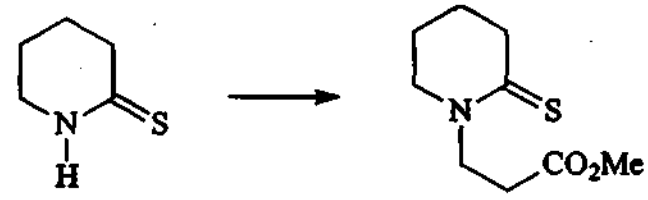
Pyrrolidine-2-thione (0.67 g, 6.6 mmol) and methyl acrylate (1.20 ml, 1.14 g, 13.3 mmol) were treated with NaOH (~30 mg, 0.66 mmol) to afford methyl 3-(2-thioxopyrrolidin-1-yl)propanoate as a colourless oil (0.87 g, 4.7 mmol, 70%); R_f 0.32 (EtOAc/Hex 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 3.84 (2H, t, J = 6.8 Hz, $NC\underline{H}_2CH_2CO_2CH_3$), 3.66 (2H, t, J = 7.5 Hz, $NC\underline{H}_2CH_2CH_2$), 3.54 (3H, s, $OC\underline{H}_3$), 2.84 (2H, t, J = 8.0 Hz, $C\underline{H}_2C{=}S$), 2.62 (2H, t, J = 6.8 Hz, $C\underline{H}_2CO_2CH_3$), 1.92 (2H, m, $NCH_2C\underline{H}_2CH_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 201.1 (C=S), 171.4 (C=O), 55.4 ($N\underline{C}H_2CH_2CH_2$), 51.5 ($O\underline{C}H_3$), 44.5 ($\underline{C}H_2C{=}S$), 43.3 ($N\underline{C}H_2CH_2CO_2CH_3$), 30.3 ($\underline{C}H_2CO_2CH_3$), 19.5 ($NCH_2\underline{C}H_2CH_2$).

MS (EIMS): *m/z* (%) = 187 [M^+] (89), 128 (100), 100 (21), 85 (91), 71 (23).

12.6 Methyl 3-(2-thioxopiperidin-1-yl)propanoate



$C_9H_{15}NO_2S$
201.28

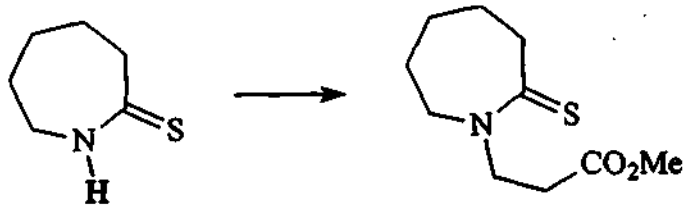
Piperidine-2-thione (1.47 g, 12.8 mmol) and methyl acrylate (2.30 ml, 2.20 g, 25.6 mmol) were treated with NaOH (~50 mg, 1.3 mmol) to afford methyl 3-(2-thioxopyrrolidin-1-yl)propanoate as a colourless oil (1.50 g, 7.46 mmol, 58%); R_f 0.37 (EtOAc/Hex 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 4.09 (2H, t, J = 7.5 Hz, $NC\underline{H}_2CH_2CO_2CH_3$), 3.60 (3H, s, $CO_2C\underline{H}_3$), 3.43 (2H, t, J = 6.2 Hz, $NC\underline{H}_2CH_2CH_2$), 2.87 (2H, t, J = 6.2 Hz, $C\underline{H}_2C{=}S$), 2.77 (2H, t, J = 7.5 Hz, $C\underline{H}_2CO_2CH_3$), 1.80 (2H, m, $NCH_2C\underline{H}_2CH_2$), 1.63 (2H, m, $NCH_2CH_2C\underline{H}_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 199.8 (C=S), 171.8 (C=O), 51.7 ($N\underline{C}H_2CH_2CH_2$), 51.6 ($O\underline{C}H_3$), 50.5 ($\underline{C}H_2C$=S), 41.5 ($C\underline{H}_2CO_2CH_3$), 30.2 ($NCH_2\underline{C}H_2CH_2$), 22.7 ($NCH_2CH_2\underline{C}H_2$).

MS (EIMS): *m/z* (%) = 201 [M^+] (88), 186 (100), 142 (31), 82 (34).

12.7 Methyl 3-(2-thioxoazepan-1-yl)propanoate



$C_{10}H_{17}NO_2S$
215.31

Azepane-2-thione (0.99 g, 7.7 mmol) and methyl acrylate (1.38 ml, 1.33 g, 15.3 mmol) were treated with NaOH (~30 mg, 0.77 mmol) to afford methyl 3-(2-thioxopyrrolidin-1-yl)propanoate as a colourless oil (1.49 g, 6.92 mmol, 90%); R_f 0.46 (EtOAc/Hex 1:1).

^1H NMR (500 MHz, $CDCl_3$): δ (ppm) = 4.17 (2H, t, J = 6.8 Hz, $NC\underline{H}_2CH_2CO_2CH_3$), 3.68 (2H, m, $NC\underline{H}_2CH_2CH_2$), 3.62 (3H, s, $OC\underline{H}_3$), 3.04 (2H, m, $C\underline{H}_2C$=S), 2.75 (2H, t, *J* = 6.9 Hz, $C\underline{H}_2CO_2CH_3$), 1.69-1.62 (4H, m, $NCH_2CH_2C\underline{H}_2C\underline{H}_2$), 1.62-1.57 (2H, m, $NCH_2C\underline{H}_2$).

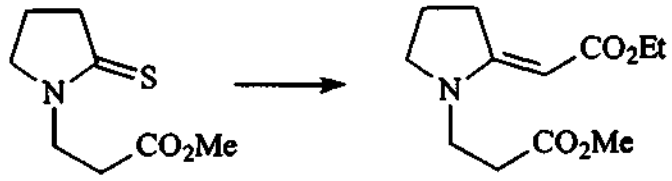
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 206.3 (C=S), 171.8 (C=O), 54.9 ($N\underline{C}H_2CH_2CH_2$), 52.6 ($O\underline{C}H_3$), 51.6 ($N\underline{C}H_2CH_2CO_2CH_3$), 46.9 ($\underline{C}H_2C$=S), 30.9 ($\underline{C}H_2CO_2CH_3$), 28.9 ($\underline{C}H_2CH_2C$=S), 26.8 ($NCH_2\underline{C}H_2CH_2$), 24.3 ($NCH_2CH_2\underline{C}H_2$).

MS (EIMS): *m/z* (%) = 215 [M^+] (94), 200 (100), 182 (28), 129 (44), 96 (75).

Preparation of vinylogous carbamate acrylate adducts: General procedure[149a]

Ethyl bromoacetate (10 mmol) was added to a solution of the appropriate thiolactam adduct (5 mmol) in dry CH_3CN (10 ml) and the resulting solution was stirred overnight at room temperature to ensure salt formation. A solution of NEt_3 (6 mmol) and PPh_3 (6 mmol) in dry CH_2Cl_2 (2 ml) was added to the reaction mixture and stirred until the reaction was complete according to TLC analysis (1-2 hours). The reaction was quenched with water (5 ml) and extracted with CH_2Cl_2 (3 × 20 ml). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to afford the desired vinylogous carbamate acrylate adducts after chromatography.

12.8 Methyl 3-[(2*E*)-2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl]propanoate



$C_{12}H_{19}NO_4$
241.28

Methyl 3-(2-thioxopyrrolidin-1-yl)propanoate (0.50 g, 2.7 mmol) was treated with ethyl bromoacetate (0.60 ml, 0.90 g, 5.4 mmol), NEt_3 (0.45 ml, 0.32 g, 3.2 mmol) and PPh_3 (0.84 g, 3.20 mmol) to afford methyl 3-[(2*E*)-2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl]propanoate as a colourless oil (0.54 g, 2.2 mmol, 83%) after radial chromatography (CH_2Cl_2/Hex 1:1 → EtOAc/Hex 1:3); R_f 0.31 (EtOAc/Hex 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 4.51 (1H, s, C=C<u>H</u>), 4.07 (2H, q, *J* = 7.1 Hz, OC<u>H</u>$_2$CH$_3$), 3.68 (3H, s, OC<u>H</u>$_3$), 3.48 (2H, t, *J* = 7.1 Hz, NC<u>H</u>$_2$CH$_2$CO$_2$CH$_3$), 3.38 (2H, t, *J* = 7.2 Hz, NC<u>H</u>$_2$CH$_2$CH$_2$), 3.12 (2H, t, *J* = 7.9 Hz, C<u>H</u>$_2$C=CH), 2.57 (2H, t, *J* = 6.9 Hz, C<u>H</u>$_2$CO$_2$CH$_3$), 1.91 (2H, m, NCH$_2$C<u>H</u>$_2$CH$_2$), 1.23 (3H, t, *J* = 7.1 Hz, OCH$_2$C<u>H</u>$_3$).

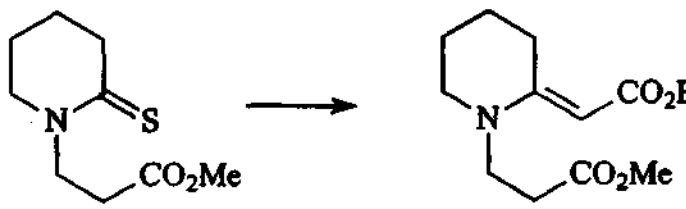
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 171.9 (<u>C</u>O$_2$CH$_3$), 169.2 (<u>C</u>O$_2$CH$_2$CH$_3$), 164.4 (<u>C</u>=CH), 78.3 (C=<u>C</u>H), 58.3 (O<u>C</u>H$_2$CH$_3$), 52.8 (N<u>C</u>H$_2$CH$_2$CH$_2$), 51.8 (O<u>C</u>H$_3$), 41.9 (N<u>C</u>H$_2$CH$_2$CO$_2$CH$_3$), 32.5 (<u>C</u>H$_2$CO$_2$CH$_3$), 30.7 (<u>C</u>H$_2$C=CH), 21.1 (NCH$_2$<u>C</u>H$_2$CH$_2$), 14.7 (OCH$_2$<u>C</u>H$_3$).

IR (thin film, $CHCl_3$): 2934, 1736, 1682, 1594, 1130 cm^{-1}.

MS (EIMS): *m/z* (%) = 241 [M$^+$] (78), 196 (77), 182 (77), 169 (79), 154 (40), 136 (50), 110 (100).

HRMS: found *m/z* = 241.1314 [M$^+$], $C_{12}H_{19}NO_4$ requires 241.1314.

12.9 Methyl 3-[(2*E*)-2-(2-ethoxy-2-oxoethylidene)piperidin-1-yl]propanoate



$C_{13}H_{21}NO_4$
255.31

Methyl 3-(2-thioxopyrrolidin-1-yl)propanoate (1.32 g, 6.56 mmol) was treated with ethyl bromoacetate (1.46 ml, 2.19 g, 13.1 mmol), NEt_3 (1.10 ml, 0.80 g, 7.9 mmol) and PPh_3 (2.06 g, 7.87 mmol) to afford methyl 3-[(2*E*)-2-(2-ethoxy-2-oxoethylidene)piperidin-1-yl]propanoate as a colourless oil (1.40 g, 5.48 mmol, 84%) after radial chromatography (CH_2Cl_2/Hex 1:1); R_f 0.43 (EtOAc/Hex 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 4.49 (1H, s, C=C<u>H</u>), 4.01 (2H, q, *J* = 7.2 Hz, OC<u>H</u>$_2$CH$_3$), 3.65 (3H, s, OC<u>H</u>$_3$), 3.45 (2H, t, *J* = 7.2 Hz, NC<u>H</u>$_2$CH$_2$CO$_2$CH$_3$), 3.21 (2H, t, *J* = 6.3 Hz, NC<u>H</u>$_2$CH$_2$CH$_2$), 3.04 (2H, t, *J* = 6.8 Hz, C<u>H</u>$_2$C=CH), 2.59 (2H, t, *J* = 7.2 Hz, C<u>H</u>$_2$CO$_2$CH$_3$), 1.71 (2H, m, NCH$_2$C<u>H</u>$_2$CH$_2$), 1.58 (2H, m, NCH$_2$CH$_2$C<u>H</u>$_2$), 1.19 (3H, t, *J* = 7.1 Hz, OCH$_2$C<u>H</u>$_3$).

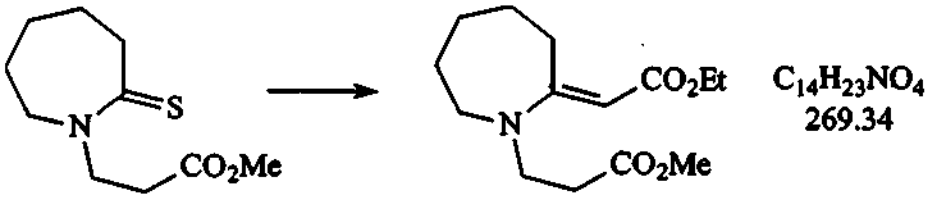
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 172.0 (<u>C</u>O$_2$CH$_3$), 168.7 (<u>C</u>O$_2$CH$_2$CH$_3$), 161.3 (<u>C</u>=CH), 82.1 (C=<u>C</u>H), 58.1 (O<u>C</u>H$_2$CH$_3$), 51.7 (O<u>C</u>H$_3$), 50.0 (N<u>C</u>H$_2$CH$_2$CH$_2$), 47.4 (N<u>C</u>H$_2$CH$_2$CO$_2$CH$_3$), 30.1 (<u>C</u>H$_2$CO$_2$CH$_3$), 26.3 (<u>C</u>H$_2$C=CH), 23.2 (NCH$_2$<u>C</u>H$_2$CH$_2$), 19.4 (NCH$_2$CH$_2$<u>C</u>H$_2$), 14.6 (OCH$_2$<u>C</u>H$_3$).

IR (thin film, $CHCl_3$): 2945, 1736, 1679, 1569, 1133, 1050 cm^{-1}.

MS (EIMS): *m/z* (%) = 255 [M$^+$] (84), 210 (68), 196 (65), 182 (100), 150 (60), 122 (67), 97 (87).

HRMS: found *m/z* = 255.1471 [M$^+$], $C_{13}H_{21}NO_4$ requires 255.1471.

12.10 Methyl 3-[(2*E*)-2-(2-ethoxy-2-oxoethylidene)azepan-1-yl]propanoate



$C_{14}H_{23}NO_4$
269.34

Methyl 3-(2-thioxopyrrolidin-1-yl)propanoate (1.40 g, 6.51 mmol) was treated with ethyl bromoacetate (1.49 ml, 2.25 g, 13.5 mmol), NEt_3 (1.13 ml, 0.82 g, 8.09 mmol) and PPh_3 (2.12 g, 8.09 mmol) to afford methyl 3-[(2*E*)-2-(2-ethoxy-2-oxoethylidene)azepan-1-yl]propanoate as a colourless oil (0.40 g, 1.5 mmol, 23%) after radial chromatography (EtOAc/Hex 1:3); R_f 0.52 (EtOAc/Hex 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 4.46 (1H, s, C=C<u>H</u>), 4.04 (2H, q, *J* = 7.1 Hz, OC<u>H</u>$_2$CH$_3$), 3.67 (3H, s, OC<u>H</u>$_3$), 3.53 (2H, t, *J* = 7.1 Hz, NC<u>H</u>$_2$CH$_2$CO$_2$CH$_3$), 3.40 (2H, m,

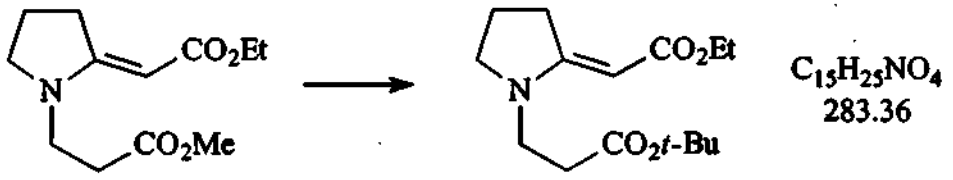
$NC\underline{H}_2CH_2CH_2$), 3.21 (2H, br, $C\underline{H}_2C{=}CH$), 2.60 (2H, t, J = 7.1 Hz, $C\underline{H}_2CO_2CH_3$), 1.61 (4H, br, $NCH_2CH_2C\underline{H}_2C\underline{H}_2$), 1.53 (2H, br, $NCH_2C\underline{H}_2$), 1.22 (3H, t, J = 7.1 Hz, $OCH_2C\underline{H}_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 172.1 ($\underline{C}O_2CH_3$), 169.0 ($\underline{C}O_2CH_2CH_3$), 166.3 ($\underline{C}{=}CH$), 82.9 ($C{=}\underline{C}H$), 58.2 ($O\underline{C}H_2CH_3$), 53.0 ($N\underline{C}H_2CH_2CH_2$), 51.7 ($O\underline{C}H_3$), 48.5 ($N\underline{C}H_2CH_2CO_2CH_3$), 31.3 ($\underline{C}H_2CO_2CH_3$), 29.3 ($\underline{C}H_2CH_2C{=}CH$), 28.7 ($NCH_2\underline{C}H_2CH_2$), 27.0 ($\underline{C}H_2C{=}CH$), 25.9 ($NCH_2CH_2\underline{C}H_2$), 14.6 ($OCH_2\underline{C}H_3$).

IR (thin film, $CHCl_3$): 2923, 1733, 1681, 1572, 1443, 1135 cm^{-1}.

HRMS: found m/z = 269.1628 [M^+], $C_{14}H_{23}NO_4$ requires 269.1627.

12.11 *tert*-Butyl 3-[(2*E*)-2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl]propanoate[150]



$C_{15}H_{25}NO_4$
283.36

t-BuOK (1M solution in *t*-BuOH, 1.40 ml, 1.40 mmol) was added to a solution of methyl 3-[(2*E*)-2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl]propanoate (0.17 g, 0.70 mmol) in dry THF (5 ml) and stirred at room temperature for 30 minutes. The reaction was quenched with water (2 ml) and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 ml). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to afford *tert*-butyl 3-[(2*E*)-2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl]propanoate as a colourless oil (20 mg, 0.071 mmol, 10%) after radial chromatography (EtOAc/Hex 1:4); R_f 0.60 (EtOAc/Hex 2:1).

^1H NMR (500 MHz, $CDCl_3$): δ (ppm) = 4.51 (1H, s, $C{=}C\underline{H}$), 4.07 (2H, q, J = 7.2 Hz, $OC\underline{H}_2CH_3$), 3.43 (2H, t, J = 7.1 Hz, $NC\underline{H}_2CH_2CO_2C(CH_3)_3$), 3.37 (2H, t, J = 7.0 Hz, $NC\underline{H}_2CH_2CH_2$), 3.12 (2H, t, J = 7.7 Hz, $C\underline{H}_2C{=}CH$), 2.47 [2H, t, J = 7.0 Hz, $C\underline{H}_2CO_2C(CH_3)_3$], 1.90 (2H, m, $NCH_2C\underline{H}_2CH_2$), 1.43 [9H, s, $C(C\underline{H}_3)_3$], 1.23 (3H, t, J = 7.2 Hz, $OCH_2C\underline{H}_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 171.0 [$\underline{C}O_2C(CH_3)_3$], 169.6 ($\underline{C}O_2CH_2CH_3$), 164.7 ($\underline{C}{=}CH$), 81.3 [$\underline{C}(CH_3)_3$], 78.4 ($C{=}\underline{C}H$), 58.5 ($O\underline{C}H_2CH_3$), 53.0 ($N\underline{C}H_2CH_2CH_2$), 42.3 [$N\underline{C}H_2CH_2CO_2C(CH_3)_3$], 32.8 [$\underline{C}H_2CO_2C(CH_3)_3$], 32.5 ($\underline{C}H_2C{=}CH$), 28.3 [$C(\underline{C}H_3)_3$], 21.4 ($NCH_2\underline{C}H_2CH_2$), 15.0 ($OCH_2\underline{C}H_3$).

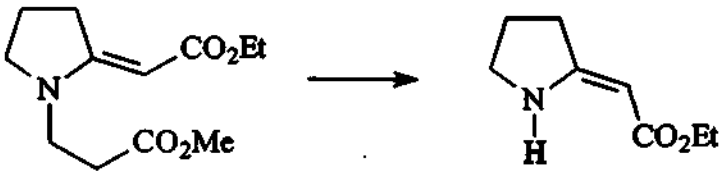
IR (thin film, $CHCl_3$): 2978, 1725, 1681, 1591, 1130 cm^{-1}.

MS (EIMS): *m/z* (%) = 283 [M^+] (42), 182 (71), 154 (32), 110 (100).

Removal of acrylate group: General procedure

KHMDS (1.2 or 2.0 mmol) was added to a stirred solution of the appropriate vinylogous carbamate (1 mmol) in dry THF (2 ml) and stirred for 15 minutes at room temperature. The reaction mixture was quenched with water (10 ml) and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 ml). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to afford the, spectroscopically pure, secondary vinylogous carbamates.

12.12 Ethyl (2*Z*)-pyrrolidin-2-ylideneacetate



$C_8H_{13}NO_2$
155.19

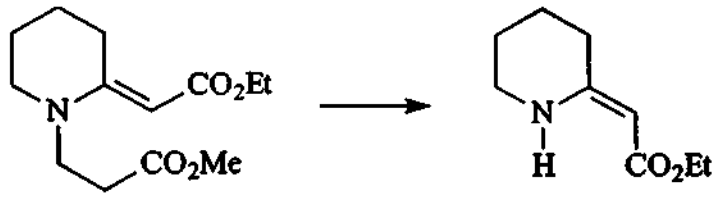
Methyl 3-[(2*E*)-2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl]propanoate (0.27 g, 1.1 mmol) was treated with KHMDS (0.47 g, 2.2 mmol) to afford ethyl (2*Z*)-pyrrolidin-2-ylideneacetate as a white crystalline solid (m.p. 60-62°C) (lit.[147] m.p. 61-62°C) (0.11 g, 0.71 mmol, 63%); R_f 0.57 (EtOAc/Hex 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.90 (1H, br, NH), 4.52 (1H, s, C=C<u>H</u>), 4.09 (2H, q, *J* = 7.2 Hz, OC<u>H</u>$_2$CH$_3$), 3.50 (2H, t, *J* = 6.2 Hz, NC<u>H</u>$_2$), 2.57 (2H, t, *J* = 7.5 Hz, C<u>H</u>$_2$C=CH), 1.96 (2H; m, NCH$_2$C<u>H</u>$_2$), 1.24 (2H, t, *J* = 7.4 Hz, OCH$_2$C<u>H</u>$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 170.8 (C=O), 166.4 (<u>C</u>=CH), 76.6 (C=<u>C</u>H), 58.4 (O<u>C</u>H$_2$CH$_3$), 47.0 (N<u>C</u>H$_2$), 32.2 (<u>C</u>H$_2$C=CH), 22.0 (NCH$_2$<u>C</u>H$_2$), 14.7 (OCH$_2$<u>C</u>H$_3$).

MS (EIMS): *m/z* (%) = 155 [M^+] (22), 110 (79), 83 (95), 82 (100), 80 (43), 54 (19).

12.13 Ethyl (2*Z*)-piperidin-2-ylideneacetate



$C_9H_{15}NO_2$
169.22

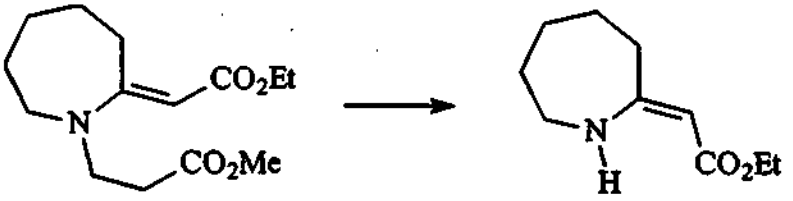
Methyl 3-[(2*E*)-2-(2-ethoxy-2-oxoethylidene)piperidin-1-yl]propanoate (0.70 g, 2.7 mmol) was treated with KHMDS (0.63 g, 3.0 mmol) to afford ethyl (2*Z*)-piperidin-2-ylideneacetate as a colourless oil (0.40 g, 2.4 mmol, 86%); R_f 0.84 (EtOAc/Hex 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.70 (1H, br, NH), 4.32 (1H, s, C=C<u>H</u>), 4.05 (2H, q, *J* = 7.4 Hz, OC<u>H</u>$_2$CH$_3$), 3.26 (2H, dt, *J* = 5.8 and 2.4 Hz, NC<u>H</u>$_2$), 2.32 (2H, t, *J* = 6.2 Hz, C<u>H</u>$_2$C=CH), 1.74 (2H, m, NCH$_2$C<u>H</u>$_2$), 1.66 (2H, m, NCH$_2$CH$_2$C<u>H</u>$_2$), 1.21 (3H, t, *J* = 6.8 Hz, OCH$_2$C<u>H</u>$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 170.7 (C=O), 162.7 (<u>C</u>=CH), 80.1 (C=<u>C</u>H), 58.1 (O<u>C</u>H$_2$CH$_3$), 41.2 (N<u>C</u>H$_2$), 29.1 (<u>C</u>H$_2$C=CH), 22.7 (NCH$_2$CH$_2$<u>C</u>H$_2$), 19.9 (NCH$_2$<u>C</u>H$_2$), 14.6 (OCH$_2$<u>C</u>H$_3$).

MS (EIMS): *m/z* (%) = 169 [M^+] (56), 124 (59), 97 (100), 82 (36).

12.14 Ethyl (2*Z*)-azepan-2-ylideneacetate



$C_{10}H_{17}NO_2$
183.25

Methyl 3-[(2*E*)-2-(2-ethoxy-2-oxoethylidene)azepan-1-yl]propanoate (0.32 g, 1.2 mmol) was treated with KHMDS (0.30 g, 1.4 mmol) to afford ethyl (2*Z*)-azepan-2-ylideneacetate as a white crystalline solid (m.p. 47-50°C) (lit.[147] m.p. 55-56°C) (0.18 g, 0.98 mmol, 83%); R_f 0.68 (EtOAc/Hex 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.76 (1H, br, NH), 4.35 (1H, s, C=C<u>H</u>), 4.00 (2H, q, *J* = 6.8 Hz, OC<u>H</u>$_2$CH$_3$), 3.22 (2H, br, NC<u>H</u>$_2$), 2.21 (2H, br, C<u>H</u>$_2$C=CH), 1.63-1.49 (6H, m, NCH$_2$C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$), 1.16 (3H, t, *J* = 6.9 Hz, OCH$_2$C<u>H</u>$_3$).

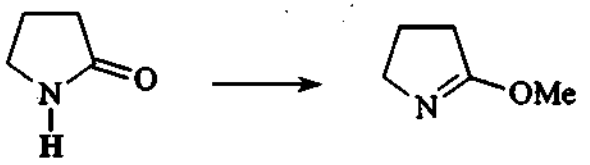
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 170.6 (C=O), 168.2 (C=CH), 80.4 (C=CH), 58.0 (OCH_2CH_3), 43.9 (NCH_2), 34.9 (CH_2C=CH), 30.2 (CH_2CH_2C=CH), 29.9 (NCH_2CH_2), 26.3 ($NCH_2CH_2CH_2$), 14.3 (OCH_2CH_3).

MS (EIMS): *m/z* (%) = 184 [M^+ + 1] (100), 183 [M^+] (68), 138 (55), 111 (83), 96 (28).

Preparation of lactim ethers: General procedure[153]

The appropriate lactam (100 mmol) was added, slowly, to dimethyl sulfate (100 mmol). The mixture was warmed to ~60°C (water bath) and stirred overnight. The mixture was poured over ice and saturated Na_2CO_3 solution and extracted with Et_2O (3 × 50 ml). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to afford the desired lactim ethers after distillation.

12.15 5-Methoxy-3,4-dihydro-2*H*-pyrrole



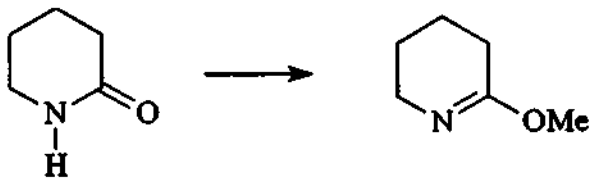
C_5H_9NO
99.13

Pyrrolidin-2-one (8.93 ml, 10.0 g, 117 mmol) was treated with dimethyl sulfate (11.12 ml, 14.81 g, 117 mmol) to afford 5-methoxy-3,4-dihydro-2*H*-pyrrole as a colourless liquid (b.p. 115-116°C) (lit.[153] 24°C, 11 mmHg) (5.98 g, 60.3 mmol, 52%) after distillation.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 3.65 (3H, s, OCH_3), 3.51 (2H, t, *J* = 6.8 Hz, NCH_2), 2.29 (2H, t, *J* = 8.0 Hz, N=CCH_2), 1.88 (2H, m, NCH_2CH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 173.4 (N=C), 54.9 (NCH_2), 54.7 (OCH_3), 30.5 (N=CCH_2), 23.0 (NCH_2CH_2).

12.16 6-Methoxy-2,3,4,5-tetrahydropyridine



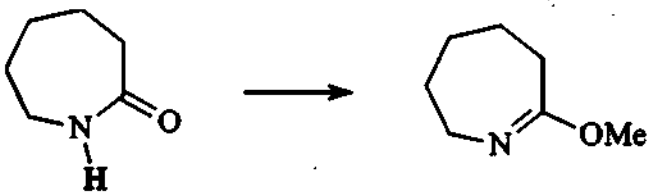
$C_6H_{11}NO$
113.15

Piperidin-2-one (δ-valerolactam) (5.22 g, 52.7 mmol) was treated with dimethyl sulfate (4.98 ml, 6.64 g, 52.7 mmol) to afford 6-methoxy-2,3,4,5-tetrahydropyridine as a colourless liquid (b.p. 38-42°C, 15 mmHg) (lit.[171] 68-71°C, 45 mmHg) (1.10 g, 9.73 mmol, 18%) after distillation under reduced pressure.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 3.45 (3H, s, $OC\underline{H}_3$), 3.32 (2H, t, J = 6.4 Hz, $NC\underline{H}_2$), 2.00 (2H, t, J = 7.4 Hz, $N{=}CC\underline{H}_2$), 1.57 (2H, m, $NCH_2CH_2C\underline{H}_2$), 1.41 (2H, m, $NCH_2C\underline{H}_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 162.6 (N=C), 51.5 ($O\underline{C}H_3$), 46.4 ($N\underline{C}H_2$), 25.5 ($N{=}C\underline{C}H_2$), 22.2 ($NCH_2\underline{C}H_2$), 20.1 ($NCH_2CH_2\underline{C}H_2$).

12.17 7-Methoxy-3,4,5,6-tetrahydro-2*H*-azepine



$C_7H_{13}NO$
127.18

Azepane-2-one (ε-caprolactam) (10.00 g, 88.42 mmol) was treated with dimethyl sulfate (8.36 ml, 11.2 g, 88.4 mmol) to afford 7-methoxy-3,4,5,6-tetrahydro-2*H*-azepine as a colourless liquid (b.p. 59.5-61.5°C, 20 mmHg) (lit.[172] 60-61°C, 20 mmHg) (6.84 g, 53.8 mmol, 61%) after distillation under reduced pressure.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 3.48 (3H, s, $OC\underline{H}_3$), 3.32 (2H, m, $NC\underline{H}_2$), 2.30 (2H, m, $N{=}C\underline{C}H_2$), 1.67 (2H, m, $NCH_2CH_2C\underline{H}_2$), 1.48 (2H, m, $NCH_2C\underline{H}_2$), 1.42 (2H, m, $N{=}CCH_2C\underline{H}_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 169.5 (N=C), 52.3 ($O\underline{C}H_3$), 48.5 ($N\underline{C}H_2$), 32.0 ($N{=}C\underline{C}H_2$), 31.1 ($NCH_2CH_2\underline{C}H_2$), 27.8 ($NCH_2\underline{C}H_2$), 23.3 ($N{=}CCH_2\underline{C}H_2$).

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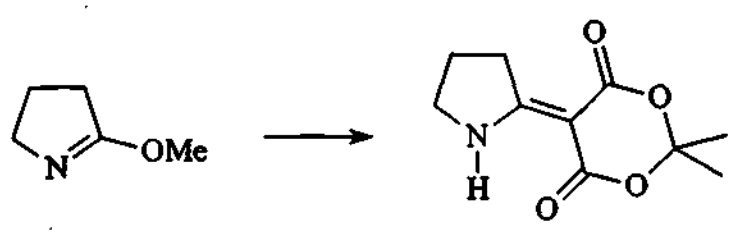
[171] Jones, K., Newton, R.F., Yarnold, C.J., *Tetrahedron*, **1996**, *52*, 4133-4140.

[172] Ulrich, H., Tucker, B., Richter, R., *J. Org. Chem.*, **1978**, *43*, 1544-1546.

Preparation of cyclic diester adducts: General procedure[144]

The appropriate lactim ether (50 mmol), 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) (50 mmol) and the appropriate base (10 mmol) were heated under reflux overnight in benzene (50 ml). The solvent was removed *in vacuo* to afford the desired cyclic diester adducts after recrystallisation.

12.18 2,2-Dimethyl-5-pyrrolidin-2-ylidene-1,3-dioxane-4,6-dione



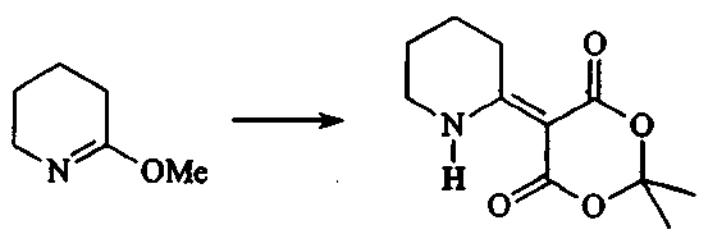
$C_{10}H_{13}NO_4$
211.21

5-Methoxy-3,4-dihydro-2*H*-pyrrole (5.35 g, 54.0 mmol), Meldrum's acid (7.78 g, 54.0 mmol) and NEt_3 (1.51 ml, 1.09 g, 10.8 mmol) were heated under reflux overnight to afford 2,2-dimethyl-5-pyrrolidin-2-ylidene-1,3-dioxane-4,6-dione as a white crystalline solid (m.p. 160-165°C) (lit.[144] 171°C) (2.01 g, 9.52 mmol, 17%) after recrystallisation from abs. EtOH; R_f 0.16 (EtOAc/Hex 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 10.12 (1H, br, NH), 3.73 (2H, t, J = 7.4 Hz, $NC\underline{H}_2$), 3.37 (2H, t, J = 7.5 Hz, $C\underline{H}_2C{=}C$), 2.15 (2H, m, $NCH_2C\underline{H}_2$), 1.66 [6H, s, $C(C\underline{H}_3)_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 176.9 ($N\underline{C}{=}C$), 166.5 (C=O), 163.1 (C=O---H), 103.1 [$\underline{C}(CH_3)_2$], 81.7 (NC=$\underline{C}$), 48.3 ($N\underline{C}H_2$), 34.9 ($\underline{C}H_2C{=}C$), 26.6 [2C, $C(\underline{C}H_3)_2$], 20.8 ($NCH_2\underline{C}H_2$).

12.19 2,2-Dimethyl-5-piperidin-2-ylidene-1,3-dioxane-4,6-dione



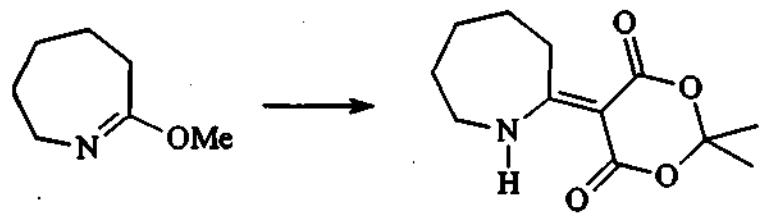
$C_{11}H_{15}NO_4$
225.24

6-Methoxy-2,3,4,5-tetrahydropyridine (1.70 g, 15.0 mmol), Meldrum's acid (2.17 g, 15.0 mmol) and NEt_3 (0.42 ml, 0.30 g, 3.0 mmol) were heated under reflux overnight to afford 2,2-dimethyl-5-piperidin-2-ylidene-1,3-dioxane-4,6-dione as a white crystalline solid (m.p. 108-110°C) (lit.[144] 116°C) (1.30 g, 5.77 mmol, 38%) after column chromatography (EtOAc/Hex 1:2); R_f 0.44 (EtOAc/Hex 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 11.60 (1H, br, NH), 3.48 (2H, br, NCH_2), 3.18 (2H, t, J = 6.6 Hz, $CH_2C{=}C$), 1.85-1.76 (2H, m, $NCH_2CH_2CH_2$), 1.64 [6H, s, $C(CH_3)_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 174.1 ($NC{=}C$), 167.5 (C=O), 162.8 (C=O---H), 102.3 [$C(CH_3)_2$], 83.0 ($NC{=}C$), 42.4 (NCH_2), 29.0 ($CH_2C{=}C$), 26.3 [2C, $C(CH_3)_2$], 20.5 ($NCH_2CH_2CH_2$), 18.5 (NCH_2CH_2).

12.20 5-Azepan-2-ylidene-2,2-dimethyl-1,3-dioxane-4,6-dione



$C_{12}H_{17}NO_4$
239.27

7-Methoxy-3,4,5,6-tetrahydro-2*H*-azepine (2.00 g, 15.7 mmol), Meldrum's acid (2.27 g, 15.7 mmol) piperidine (0.15 ml, 1.51 mmol) and glacial acetic acid (0.30 ml) were heated under reflux overnight to afford 5-azepan-2-ylidene-2,2-dimethyl-1,3-dioxane-4,6-dione as a white crystalline solid (m.p. 146-150°C) (lit.[144] 147°C) (2.50 g, 10.4 mmol, 67%) after recrystallisation from MeOH; R_f 0.44 (EtOAc/Hex 1:1).

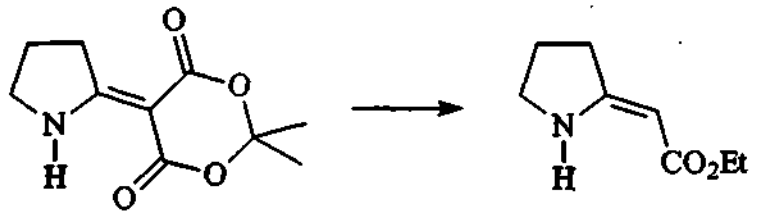
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 11.35 (1H, br, NH), 3.50 (2H, m, NCH_2), 3.22 (2H, m, $CH_2C{=}C$), 1.75 (2H, m, $CH_2CH_2C{=}C$), 1.65-1.57 (4H, m, $NCH_2CH_2CH_2$), 1.58 [6H, s, $C(CH_3)_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 179.8 ($NC{=}C$), 167.0 (C=O), 162.9 (C=O---H), 101.9 [$C(CH_3)_2$], 83.5 ($NC{=}C$), 44.4 (NCH_2), 29.8 ($CH_2CH_2C{=}C$), 29.5 ($CH_2C{=}C$), 27.2 ($NCH_2CH_2CH_2$), 26.0 [2C, $C(CH_3)_2$], 23.1 (NCH_2CH_2).

Opening of cyclic diesters: General procedure[144]

The appropriate cyclic diester (10 mmol) was added to a solution of NaOEt (10 mmol) in abs. EtOH (10 ml) and heated under reflux overnight. The solvent was removed *in vacuo* and the residue was dissolved in water. The pH of the aqueous phase was adjusted to 6 by the addition of dil. HCl (3M) and extracted with CH_2Cl_2 (3 × 20 ml). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to afford the desired vinylogous carbamates after chromatography.

12.21 Ethyl (2*Z*)-pyrrolidin-2-ylideneacetate

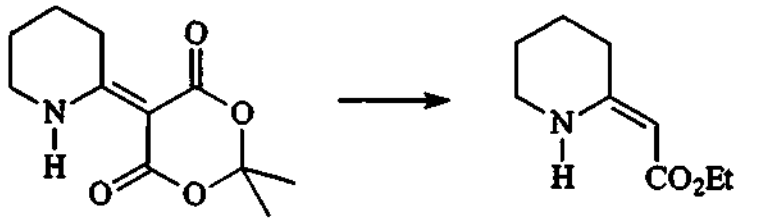


$C_8H_{13}NO_2$
155.19

2,2-Dimethyl-5-pyrrolidin-2-ylidene-1,3-dioxane-4,6-dione (1.97 g, 9.33 mmol) was treated with NaOEt (Na metal [0.24 g, 10 mmol] in absolute EtOH [10 ml]) to afford ethyl (2*Z*)-pyrrolidin-2-ylideneacetate as a white crystalline solid (0.87 g, 5.6 mmol, 60%) after radial chromatography (EtOAc/Hex 1:4); R_f 0.57 (EtOAc/Hex 1:1).

Note: Spectral and physical data for this compound matched those acquired for the same compound in a prior reaction (p174).

12.22 Ethyl (2*Z*)-piperidin-2-ylideneacetate



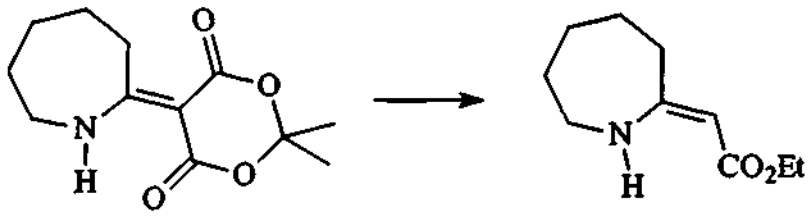
$C_9H_{15}NO_2$
169.22

2,2-Dimethyl-5-piperidin-2-ylidene-1,3-dioxane-4,6-dione (1.29 g, 5.73 mmol) was treated with NaOEt (Na metal [0.13 g, 5.7 mmol] in absolute EtOH [5 ml]) to afford ethyl (2*Z*)-

piperidin-2-ylideneacetate as a colourless oil (0.37 g, 2.2 mmol, 38%) after column chromatography (EtOAc/Hex 1:9); R_f 0.84 (EtOAc/Hex 1:1).

Note: Spectral and physical data for this compound matched those acquired for the same compound in a prior reaction (p174).

12.23 Ethyl (2*Z*)-azepan-2-ylideneacetate



$C_{10}H_{17}NO_2$
183.25

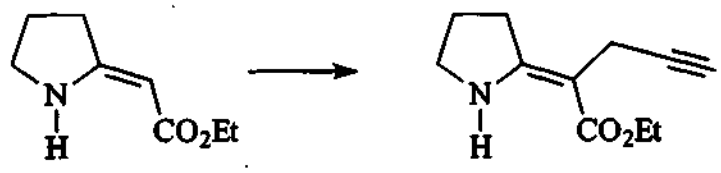
5-Azepan-2-ylidene-2,2-dimethyl-1,3-dioxane-4,6-dione (2.40 g, 10.0 mmol) was treated with NaOEt (Na metal [0.23 g, 10 mmol] in absolute EtOH [10 ml]) to afford ethyl (2*Z*)-azepan-2-ylideneacetate as a white crystalline solid (0.34 g, 1.9 mmol, 19%) after column chromatography (EtOAc/Hex 1:2); R_f 0.68 (EtOAc/Hex 1:1).

Note: Spectral and physical data for this compound matched those acquired for the same compound in a prior reaction (p175).

Preparation of cyclic *C*-propargyl vinylogous carbamates: General procedure

n-BuLi (2.2 mmol) was added to a solution of the appropriate vinylogous carbamate (2 mmol) in dry THF (10 ml) at 0°C and allowed to warm to room temperature over 30 minutes. Propargyl bromide (3 mmol) was added thereafter and the reaction mixture was stirred overnight. The reaction was quenched by addition of $NH_4Cl_{(aq)}$ (5 ml), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 ml). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to afford the desired cyclic *C*-propargyl vinylogous carbamates after chromatography.

12.24 Ethyl (2*Z*)-2-pyrrolidin-2-ylidenepent-4-ynoate



$C_{11}H_{15}NO_2$
193.24

Ethyl (2*Z*)-pyrrolidin-2-ylideneacetate (0.35 g, 2.3 mmol) was treated with *n*-BuLi (1.6M solution in hexane, 1.55 ml, 2.48 mmol) and propargyl bromide (80% w/w solution in toluene, 0.38 ml, 0.40 g, 3.4 mmol) to afford ethyl (2*Z*)-2-pyrrolidin-2-ylidenepent-4-ynoate as a colourless oil (0.29 g, 1.5 mmol, 66%) after radial chromatography (EtOAc/Hex 1:3); R_f 0.61 (EtOAc/Hex 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.14 (1H, br, NH), 4.14 (2H, q, J = 7.3 Hz, $OC\underline{H}_2CH_3$), 3.51 (2H, t, J = 7.0 Hz, $NC\underline{H}_2$), 3.08 (2H, d, J = 2.6 Hz, $C\underline{H}_2C{\equiv}CH$), 2.72 (2H, t, J = 7.8 Hz, $NCH_2CH_2C\underline{H}_2$), 2.00 (2H, m, $NCH_2C\underline{H}_2$), 1.90 (1H, t, J = 2.6 Hz, $C{\equiv}C\underline{H}$), 1.26 (3H, t, J = 7.1 Hz, $OCH_2C\underline{H}_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 169.4 (C=O), 165.2 ($N\underline{C}$=C), 84.5 (NC=$\underline{C}$), 84.2 ($\underline{C}{\equiv}CH$), 66.4 ($C{\equiv}\underline{C}H$), 58.9 ($O\underline{C}H_2CH_3$), 47.2 ($N\underline{C}H_2$), 30.8 ($CH_2\underline{C}H_2C$=C), 21.8 ($NCH_2\underline{C}H_2$), 17.0 ($\underline{C}H_2C{\equiv}CH$), 14.6 ($OCH_2\underline{C}H_3$).

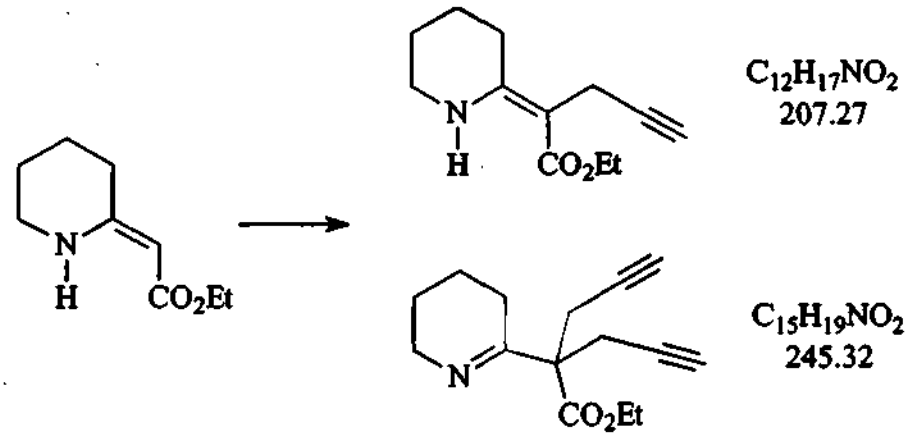
IR (thin film, $CHCl_3$): 3362, 3307, 2972, 2104, 1654, 1596, 1248, 1212 cm^{-1}.

MS (EIMS): *m/z* (%) = 193 [M^+] (35), 164 (100), 120 (74), 118 (46), 91 (22).

HRMS: found *m/z* = 193.1091 [M^+], $C_{11}H_{15}NO_2$ requires 193.1103.

12.25 Ethyl (2*Z*)-2-piperidin-2-ylidenepent-4-ynoate and

12.26 Ethyl 2-prop-2-ynyl-2-(3,4,5,6-tetrahydropyridin-2-yl)pent-4-ynoate



Ethyl (2*Z*)-piperidin-2-ylideneacetate (0.38 g, 2.3 mmol) was treated with *n*-BuLi (1.6M solution in hexane, 1.54 ml, 2.47 mmol) and propargyl bromide (80% w/w solution in toluene, 0.38 ml, 0.40 g, 3.4 mmol) to afford ethyl (2*Z*)-2-piperidin-2-ylidenepent-4-ynoate as a colourless oil (0.16 g, 0.79 mmol, 35%) and ethyl 2-prop-2-ynyl-2-(3,4,5,6-tetrahydropyridin-2-yl)pent-4-ynoate as a colourless oil (70 mg, 0.29 mmol, 13%) after radial chromatography (EtOAc/Hex 1:9); R_f 0.37 and 0.30 (EtOAc/Hex 1:4) respectively.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 9.65 (1H, br, NH), 4.13 (2H, q, *J* = 7.4 Hz, $OC\underline{H}_2CH_3$), 3.31 (2H, m, $NC\underline{H}_2$), 3.12 (2H, d, *J* = 2.4 Hz, $C\underline{H}_2C{\equiv}CH$), 2.58 (2H, t, *J* = 6.2 Hz, $CH_2C\underline{H}_2C{\equiv}C$), 1.91 (1H, t, *J* = 2.5 Hz, $C{\equiv}C\underline{H}$), 1.78-1.72 (4H, m, $NCH_2C\underline{H}_2C\underline{H}_2$), 1.27 (3H, t, *J* = 7.4 Hz, $OCH_2C\underline{H}_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 169.7 (C=O), 161.2 ($N\underline{C}{=}C$), 85.3 ($NC{=}\underline{C}$), 84.8 ($\underline{C}{\equiv}CH$), 66.3 ($C{\equiv}\underline{C}H$), 58.7 ($O\underline{C}H_2CH_3$), 41.3 ($N\underline{C}H_2$), 25.9 ($CH_2\underline{C}H_2C{=}C$), 22.0 ($NCH_2CH_2\underline{C}H_2$), 19.8 ($NCH_2\underline{C}H_2$), 15.6 ($\underline{C}H_2C{=}CH$), 14.6 ($OCH_2\underline{C}H_3$).

IR (thin film, $CHCl_3$): 3280, 2939, 2857, 2109, 1690, 1637, 1591, 1207 cm^{-1}.

MS (EIMS): *m/z* (%) = 207 [M^+] (44), 178 (100), 162 (23), 134 (60), 132 (33).

HRMS: found *m/z* = 207.1245 [M^+], $C_{12}H_{17}NO_2$ requires 207.1259.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 4.20 (2H, q, *J* = 7.3 Hz, $OC\underline{H}_2CH_3$), 3.66 (2H, t, *J* = 6.0 Hz, $NC\underline{H}_2$), 2.98 and 2.89 (2H, dd, *J* = 17.0 Hz 2.5 Hz and 2H, dd, *J* = 17.0 Hz 2.5 Hz, $(C\underline{H}_2C{\equiv}CH)_2$), 2.09 (2H, t, *J* = 6.5 Hz, $N{=}CC\underline{H}_2$), 1.97 [2H, t, *J* = 2.5 Hz, $(CH_2C{\equiv}C\underline{H})_2$], 1.66 (2H, m, $NCH_2CH_2C\underline{H}_2$), 1.56 (2H, m, $NCH_2C\underline{H}_2$), 1.25 (3H, t, *J* = 7.1 Hz, $OCH_2C\underline{H}_3$).

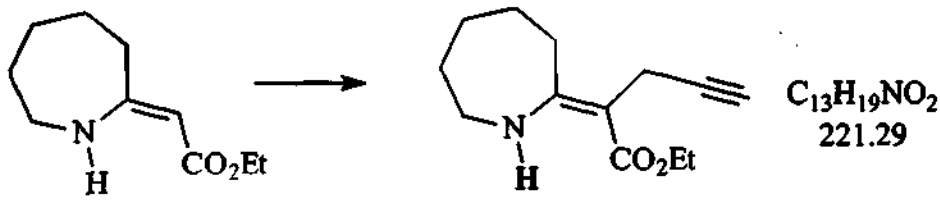
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 171.7 (C=O), 165.8 (N=C), 80.1 (2C, $(CH_2\underline{C}{\equiv}CH)_2$), 70.9 (2C, $(CH_2C{\equiv}\underline{C}H)_2$), 61.5 ($O\underline{C}H_2CH_3$), 57.6 ($N{=}C\underline{C}$), 49.4 ($N\underline{C}H_2$),

26.1 (N=C$\underline{C}$H$_2$), 22.8 [2C, ($\underline{C}$H$_2$C≡CH)$_2$], 21.7 (NCH$_2$$\underline{C}H_2$), 19.4 (NCH$_2CH_2$$\underline{C}H_2$), 14.1 (OCH$_2$$\underline{C}H_3$).

IR (thin film, $CHCl_3$): 3285, 2934, 2115, 1728, 1198 cm^{-1}.

MS (EIMS): *m/z* (%) = 245 [M$^+$] 206 (100), 178 (71), 172 (65), 134 (58).

12.27 Ethyl (2*Z*)-2-azepan-2-ylidenepent-4-ynoate



Ethyl (2*Z*)-azepan-2-ylideneacetate (0.34 g, 1.9 mmol) was treated with *n*-BuLi (1.6M solution in hexane, 1.28 ml, 2.04 mmol) and propargyl bromide (80% w/w solution in toluene, 0.31 ml, 0.33 g, 2.8 mmol) to afford ethyl (2*Z*)-2-azepan-2-ylidenepent-4-ynoate as a colourless oil (0.10 g, 0.45 mmol, 24%) after radial chromatography (EtOAc/Hex 1:9); R_f 0.69 (EtOAc/Hex 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 9.67 (1H, br, NH), 4.13 (2H, q, *J* = 7.1 Hz, OC$\underline{H}_2$CH$_3$), 3.32 (2H, m, NC$\underline{H}_2$), 3.21 (2H, d, *J* = 2.8 Hz, C$\underline{H}_2$C≡CH), 2.59 (2H, m, CH$_2$C$\underline{H}_2$C≡C), 1.92 (1H, t, *J* = 2.6 Hz, C≡C$\underline{H}$), 1.73-1.66 (4H, m, NCH$_2$CH$_2$C$\underline{H}_2$C$\underline{H}_2$), 1.61-1.56 (2H, m, NCH$_2$C$\underline{H}_2$), 1.27 (3H, t, *J* = 7.1 Hz, OCH$_2$C$\underline{H}_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 170.2 (C=O), 167.8 (N$\underline{C}$=C), 86.2 (NC=$\underline{C}$), 85.6 ($\underline{C}$≡CH), 66.5 (C≡$\underline{C}$H), 59.0 (O$\underline{C}$H$_2$CH$_3$), 44.0 (N$\underline{C}$H$_2$), 30.4 ($\underline{C}$H$_2$CH$_2$C=C), 30.0 (NCH$_2$$\underline{C}H_2$), 29.1 (CH$_2$$\underline{C}H_2$C=C), 25.3 (NCH$_2CH_2$$\underline{C}H_2$), 16.6 ($\underline{C}H_2$C≡CH), 14.6 (OCH$_2$$\underline{C}H_3$).

IR (thin film, $CHCl_3$): 3291, 2928, 2109, 1643, 1591, 1248, 1196 cm^{-1}.

MS (EIMS): *m/z* (%) = 221 [M$^+$] (42), 192 (100), 148 (84), 146 (41), 120 (32).

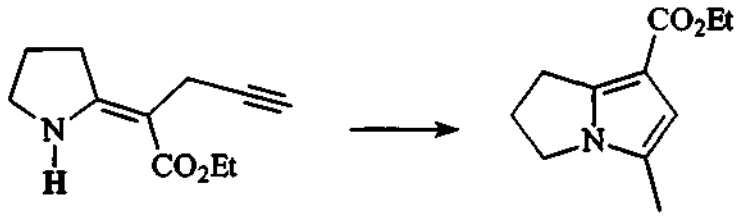
HRMS: found *m/z* = 221.1401 [M$^+$], $C_{13}H_{19}NO_2$ requires 221.1416.

Preparation of *N*-bridgehead pyrroles: General procedure (two step)

$AgNO_3$ (0.2 mmol) was added to a Pyrex test tube containing a solution of the appropriate *C*-propargyl vinylogous amide or carbamate (1 mmol) in dry CH_3CN (1 ml). The test tube

was sealed and subjected to microwave irradiation (700 W, low) for 60 seconds (2 × 30s). The organic layer was washed with $NaI_{(aq)}$, dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was filtered (MeOH) through a short plug of silica gel to afford the desired *N*-bridgehead pyrroles.

12.28 Ethyl 5-methyl-2,3-dihydro-1*H*-pyrrolizine-7-carboxylate



$C_{11}H_{15}NO_2$
193.24

Ethyl (2*Z*)-2-pyrrolidin-2-ylidenepent-4-ynoate (0.25 g, 1.3 mmol) was treated with $AgNO_3$ (44 mg, 0.26 mmol) and irradiated to afford ethyl 5-methyl-2,3-dihydro-1*H*-pyrrolizine-7-carboxylate as a colourless crystalline solid (m.p. 54-56°C) (lit.[142a] m.p. 58°C) (0.19 g, 0.97 mmol, 75%); R_f 0.57 (EtOAc/Hex 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 6.26 (1H, s, C=C<u>H</u>), 4.22 (2H, q, *J* = 7.1 Hz, OC<u>H</u>$_2$CH$_3$), 3.83 (2H, t, *J* = 7.1 Hz, NC<u>H</u>$_2$CH$_2$), 3.05 (2H, t, *J* = 7.4 Hz, NCH$_2$CH$_2$C<u>H</u>$_2$), 2.51 (2H, m, NCH$_2$C<u>H</u>$_2$), 2.17 (3H, s, NCC<u>H</u>$_3$), 1.30 (3H, t, *J* = 7.2 Hz, OCH$_2$C<u>H</u>$_3$).

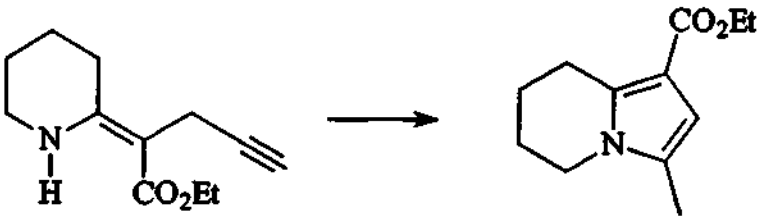
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 165.4 (C=O), 142.6 (N<u>C</u>=CCO$_2$CH$_2$CH$_3$), 124.0 (N<u>C</u>=CH), 110.0 (NC=<u>C</u>H), 106.3 (<u>C</u>CO$_2$CH$_2$CH$_3$), 59.1 (O<u>C</u>H$_2$CH$_3$), 44.9 (N<u>C</u>H$_2$), 26.9 (NCH$_2$<u>C</u>H$_2$), 25.9 (NCH$_2$CH$_2$<u>C</u>H$_2$), 14.6 (OCH$_2$<u>C</u>H$_3$), 11.7 (NC<u>C</u>H$_3$).

IR (thin film, $CHCl_3$): 2978, 1698, 1209, 1078 cm^{-1}.

MS (EIMS): *m/z* (%)= 193 [M$^+$] (44), 164 (100), 148 (41), 120 (33).

HRMS: found *m/z* = 193.1103 [M$^+$], $C_{11}H_{15}NO_2$ requires 193.1103.

12.29 Ethyl 3-methyl-5,6,7,8-tetrahydro-1-indolizinecarboxylate



$C_{12}H_{17}NO_2$
207.27

Ethyl (2*Z*)-2-piperidin-2-ylidenepent-4-ynoate (48 mg, 0.23 mmol) was treated with $AgNO_3$ (8 mg, 0.05 mmol) and irradiated to afford ethyl 3-methyl-5,6,7,8-tetrahydro-1-indolizinecarboxylate as a colourless oil (36 mg, 0.17 mmol, 75%); R_f 0.56 (EtOAc/Hex 1:2).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 6.26 (1H, s, C=C<u>H</u>), 4.23 (2H, q, J = 7.2 Hz, OC<u>H</u>$_2$CH$_3$), 3.75 (2H, t, J = 6.0 Hz, NC<u>H</u>$_2$CH$_2$), 3.06 (2H, t, J = 6.6 Hz, <u>C</u>H$_2$C=C), 2.15 (3H, s, NCC<u>H</u>$_3$), 1.96 (2H, m, NCH$_2$C<u>H</u>$_2$), 1.80 (2H, m, NCH$_2$CH$_2$C<u>H</u>$_2$), 1.31 (3H, t, J = 7.0 Hz, OCH$_2$C<u>H</u>$_3$).

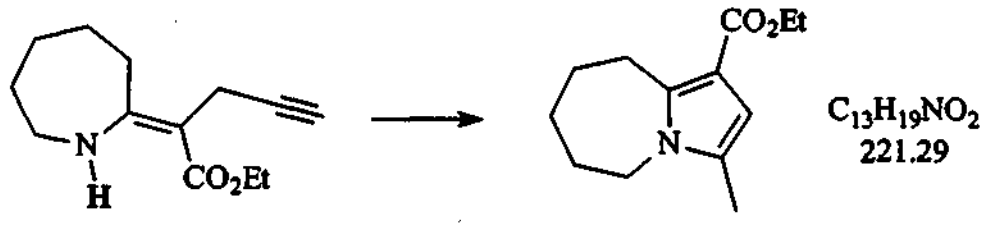
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 165.5 (C=O), 136.2 (N<u>C</u>=CCO$_2$CH$_2$CH$_3$), 127.1 (N<u>C</u>=CH), 109.4 (<u>C</u>CO$_2$CH$_2$CH$_3$), 107.0 (NC=<u>C</u>H), 59.0 (O<u>C</u>H$_2$CH$_3$), 42.9 (N<u>C</u>H$_2$), 23.9 (NCH$_2$<u>C</u>H$_2$), 23.0 (<u>C</u>H$_2$C=C), 19.9 (NCH$_2$CH$_2$<u>C</u>H$_2$), 14.6 (OCH$_2$<u>C</u>H$_3$), 11.6 (NC<u>C</u>H$_3$).

IR (thin film, $CHCl_3$): 2923, 1692, 1218, 1185 cm^{-1}.

MS (EIMS): *m/z* (%) = 207 [M$^+$] (40), 178 (100), 134 (79).

HRMS: found *m/z* = 207.1257 [M$^+$], $C_{12}H_{17}NO_2$ requires 207.1259.

12.30 Ethyl 3-methyl-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-1-carboxylate



$C_{13}H_{19}NO_2$
221.29

Ethyl (2*Z*)-2-azepan-2-ylidenepent-4-ynoate (98 mg, 0.44 mmol) was treated with $AgNO_3$ (15 mg, 0.088 mmol) and irradiated to afford ethyl 3-methyl-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-1-carboxylate as a colourless oil (70 mg, 0.32 mmol, 71%); R_f 0.67 (EtOAc/Hex 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 6.15 (1H, s, C=C<u>H</u>), 4.20 (2H, q, J = 7.2 Hz, OC<u>H</u>$_2$CH$_3$), 3.84 (2H, m, NC<u>H</u>$_2$CH$_2$), 3.20 (2H, br, <u>C</u>H$_2$C=C), 2.15 (3H, s, NCC<u>H</u>$_3$), 1.80 (2H, m, NCH$_2$C<u>H</u>$_2$), 1.64 (2H, m, NCH$_2$CH$_2$C<u>H</u>$_2$C<u>H</u>$_2$), 1.29 (3H, t, J = 7.1 Hz, OCH$_2$C<u>H</u>$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 165.7 (C=O), 141.7 (N<u>C</u>=CCO$_2$CH$_2$CH$_3$), 126.9 (N<u>C</u>=CH), 109.3 (<u>C</u>CO$_2$CH$_2$CH$_3$), 106.8 (NC=<u>C</u>H), 58.9 (O<u>C</u>H$_2$CH$_3$), 45.3 (N<u>C</u>H$_2$), 31.1

($NCH_2\underline{C}H_2$), 28.6 ($NCH_2CH_2CH_2\underline{C}H_2$), 26.8 ($NCH_2CH_2\underline{C}H_2$), 25.2 ($\underline{C}H_2C{=}C$), 14.4 ($OCH_2\underline{C}H_3$), 12.2 ($NC\underline{C}H_3$).

IR (thin film, $CHCl_3$): 2928, 1695, 1651, 1602, 1253, 1168, 1116, 1053 cm^{-1}.

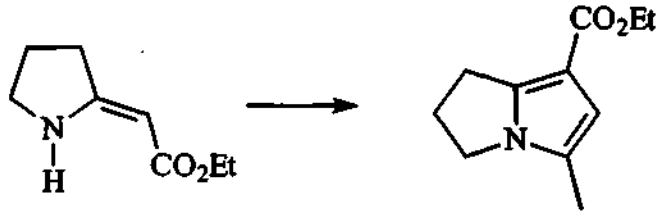
MS (EIMS): *m/z* (%) = 221 [M^+] (54), 191 (77), 148 (100).

HRMS: found *m/z* = 221.1416 [M^+], $C_{13}H_{19}NO_2$ requires 221.1416.

Preparation of *N*-bridgehead pyrroles: General procedure (one pot)

$AgNO_3$ (1.2 mmol) was added to a stirred solution of the appropriate vinylogous carbamate (1 mmol) and propargyl bromide (1.2 mmol) in dry CH_3CN (2 ml) and stirred overnight. The organic layer was washed with $NaI_{(aq)}$, dried ($MgSO_4$) and concentrated *in vacuo* to afford the desired *N*-bridgehead pyrroles after radial chromatography.

12.31 Ethyl 5-methyl-2,3-dihydro-1*H*-pyrrolizine-7-carboxylate

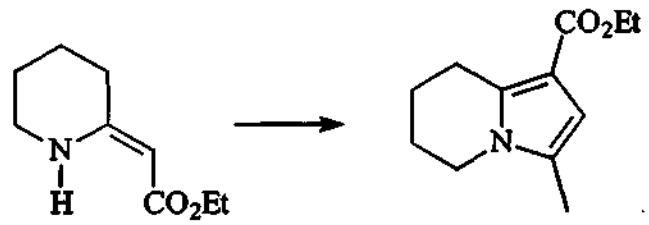


$C_{11}H_{15}NO_2$
193.24

Ethyl (2*Z*)-pyrrolidin-2-ylideneacetate (0.10 g, 0.64 mmol) was treated with $AgNO_3$ (0.13 g, 0.77 mmol) and propargyl bromide (80% w/w solution in toluene, 0.09 ml, 0.09 g, 0.8 mmol) to afford ethyl 5-methyl-2,3-dihydro-1*H*-pyrrolizine-7-carboxylate as a colourless crystalline solid (16 mg, 0.083 mmol, 13%) after radial chromatography (EtOAc/Hex 1:3).

Note: Spectral and physical data for this compound matched those acquired for the same compound in a prior reaction (p185).

12.32 Ethyl 3-methyl-5,6,7,8-tetrahydro-1-indolizinecarboxylate

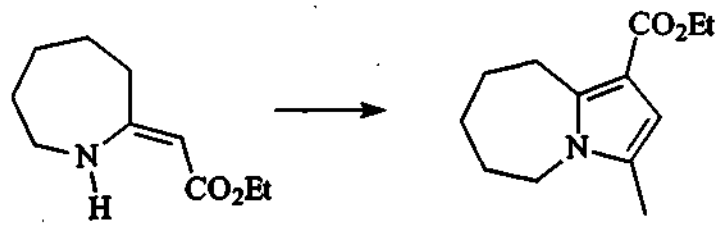


$C_{12}H_{17}NO_2$
207.27

Ethyl (2*Z*)-piperidin-2-ylideneacetate (75 mg, 0.44 mmol) was treated with $AgNO_3$ (90 mg, 0.53 mmol) and propargyl bromide (80% w/w solution in toluene, 0.06 ml, 0.06 g, 0.5 mmol) to afford ethyl 3-methyl-5,6,7,8-tetrahydro-1-indolizinecarboxylate as a colourless oil (16 mg, 0.077 mmol, 19%) after radial chromatography (EtOAc/Hex 1:3).

Note: Spectral and physical data for this compound matched those acquired for the same compound in a prior reaction (p185).

12.33 Ethyl 3-methyl-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-1-carboxylate

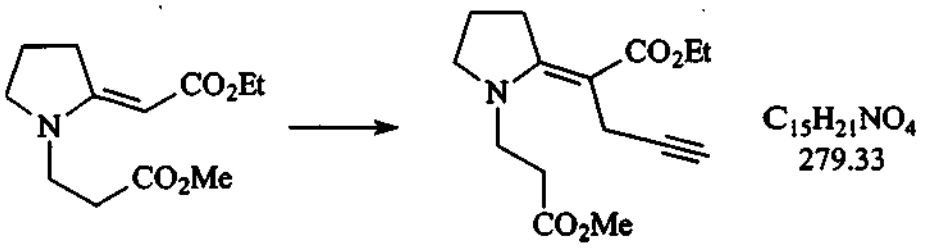


$C_{13}H_{19}NO_2$
221.29

Ethyl (2*Z*)-azepan-2-ylideneacetate (0.18 g, 0.98 mmol) was treated with $AgNO_3$ (0.20 g, 1.2 mmol) and propargyl bromide (80% w/w solution in toluene, 0.13 ml, 0.14 g, 1.2 mmol) to afford ethyl 3-methyl-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-1-carboxylate as an inseparable mixture of starting material and product (SM : prod 2:1) (14% from ^1H NMR integral values) after radial chromatography (EtOAc/Hex 1:3).

Note: Spectral and physical data for this compound matched those acquired for the same compound in a prior reaction (p186).

12.34 Ethyl (2*E*)-2-[1-(3-methoxy-3-oxopropyl)pyrrolidin-2-ylidene]pent-4-ynoate[149b]



$C_{15}H_{21}NO_4$
279.33

Propargyl bromide (80% w/w solution in toluene, 0.51 ml, 0.55 g, 4.6 mmol) was added to a solution of methyl 3-[(2*E*)-2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl]propanoate (0.74 g, 3.1 mmol) in dry CH_3CN (10 ml) and heated under reflux overnight to afford ethyl (2*E*)-2-[1-(3-methoxy-3-oxopropyl)pyrrolidin-2-ylidene]pent-4-ynoate as a crude red oil (0.81 g, ~2.9 mmol, >90%) after filtration through a short silica gel plug (MeOH); R_f 0.30 (EtOAc/Hex 1:1).

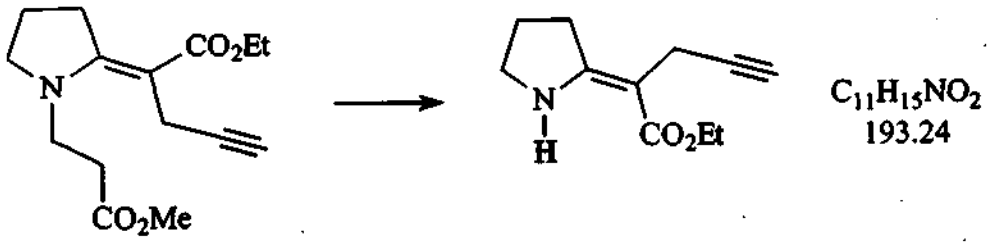
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 4.15 (2H, q, J = 7.1 Hz, $OC\underline{H}_2CH_3$), 3.84 (2H, t, J = 7.6 Hz, $NC\underline{H}_2CH_2CO_2CH_3$), 3.70 (3H, s, $OC\underline{H}_3$), 3.34 (2H, t, J = 7.0 Hz, $NC\underline{H}_2CH_2CH_2$), 3.24 (2H, d, J = 2.1 Hz, $C\underline{H}_2C{\equiv}CH$), 3.03 (2H, t, J = 7.6 Hz, $NCH_2CH_2C\underline{H}_2$), 2.66 (2H, t, J = 7.2 Hz, $C\underline{H}_2CO_2CH_3$), 1.98 (1H, t, J = 2.7 Hz, $CH_2C{\equiv}C\underline{H}$), 1.86 (2H, m, $NCH_2C\underline{H}_2CH_2$), 1.27 (3H, t, J = 7.1 Hz, $OCH_2C\underline{H}_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 171.9 ($\underline{C}O_2CH_3$), 169.1 ($\underline{C}O_2CH_2CH_3$), 163.8 ($N\underline{C}$=C), 90.5 ($\underline{C}CO_2CH_2CH_3$), 84.4 ($\underline{C}{\equiv}CH$), 67.8 ($CH_2C{\equiv}\underline{C}H$), 59.4 ($O\underline{C}H_2CH_3$), 54.6 ($N\underline{C}H_2CH_2CH_2$), 51.8 ($O\underline{C}H_3$), 46.1 ($N\underline{C}H_2CH_2CO_2CH_3$), 35.7 ($NCH_2CH_2\underline{C}H_2$), 33.4 ($\underline{C}H_2CO_2CH_3$), 21.9 ($NCH_2\underline{C}H_2CH_2$), 18.0 ($\underline{C}H_2C{\equiv}CH$), 14.5 ($OCH_2\underline{C}H_3$).

MS (EIMS): *m/z* (%) = 279 [M^+] (40), 207 (44), 206 (100), 192 (37), 174 (45), 146 (38), 133 (37).

Note: The crude material was of sufficient purity to, unambiguously, assign NMR spectra and was used in the next step without further purification.

12.35 Ethyl (2*Z*)-2-pyrrolidin-2-ylidenepent-4-ynoate

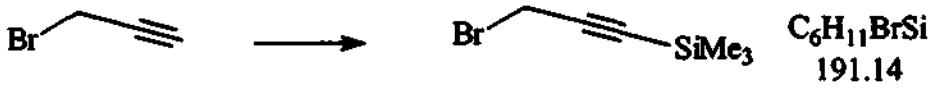


KHMDS (0.11 g, 0.52 mmol) was added to a stirred solution of ethyl (2*E*)-2-[1-(3-methoxy-3-oxopropyl)pyrrolidin-2-ylidene]pent-4-ynoate (0.13 g, 0.47 mmol) in dry THF (5 ml) and stirred for **10 minutes** at room temperature. The reaction mixture was quenched with water (10 ml) and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 ml). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to afford ethyl (2*Z*)-2-pyrrolidin-2-ylidenepent-4-ynoate as a colourless oil (14 mg, 0.072 mmol, 15%) after column chromatography (EtOAc/Hex 1:4).

KHMDS (0.18 g, 0.83 mmol) was added to a stirred solution of ethyl (2*E*)-2-[1-(3-methoxy-3-oxopropyl)pyrrolidin-2-ylidene]pent-4-ynoate (0.21 g, 0.75 mmol) in dry THF (5 ml) and stirred for **30 minutes** at room temperature. Work up as above to afford ethyl (2*Z*)-2-pyrrolidin-2-ylidenepent-4-ynoate as a colourless oil (22 mg, 0.11 mmol, 15%) after column chromatography (EtOAc/Hex 1:4).

Note: Spectral and physical data for this compound matched those acquired for the same compound in a prior reaction (p182).

13.1 (3-Bromo-prop-1-ynyl)trimethylsilane[155]



i-Pr_2NH (7.71 ml, 5.57 g, 55.0 mmol) was added to a solution of *n*-BuLi (0.75M solution in hexane, 66.7 ml, 50.0 mmol) in ether (40 ml) at 0°C. The solution was cooled to <-85°C (hexane / liquid N_2) and propargyl bromide (80% w/w solution in toluene, 5.57 ml, 5.95 g, 50.0 mmol), TMSCl (12.69 ml, 10.86 g, 100.0 mmol) and HMPA (5 ml) were added at this temperature. The reaction mixture was warmed to 10°C over 40 minutes and poured over

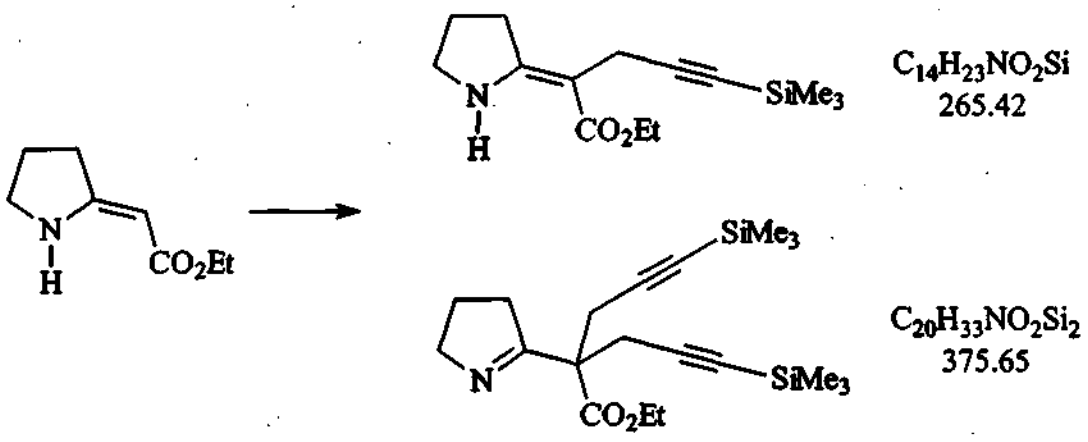
ice water (150 ml). The mixture was extracted with Et_2O (3 × 50 ml) and the organic layers were combined, washed with dilute HCl (3M, 2 × 50 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford (3-bromo-prop-1-ynyl)trimethylsilane (b.p. 55-62°C, 15 mmHg) (lit.[155] 58°C, 15 mmHg) (6.17 g, 32.3 mmol, 65%) after distillation under reduced pressure.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 3.91 [2H, s, $C\underline{H}_2C{\equiv}CSi(CH_3)_3$], 0.17 [9H, s, $CH_2C{\equiv}CSi(C\underline{H}_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 100.0 [$CH_2\underline{C}{\equiv}CSi(CH_3)_3$], 92.3 [$CH_2C{\equiv}\underline{C}Si(CH_3)_3$], 14.6 [$\underline{C}H_2C{\equiv}CSi(CH_3)_3$], 0.38 [3C, $CH_2C{\equiv}CSi(\underline{C}H_3)_3$].

13.2 2-Pyrrolidin-2-ylidene-5-trimethylsilanyl-pent-4-ynoic acid ethyl ester and

13.3 2-(4,5-Dihydro-3*H*-pyrrol-2-yl)-5-trimethylsilanyl-2-(3-trimethylsilanyl-prop-2-ynyl)-pent-4-ynoic acid ethyl ester



n-BuLi (1.5M solution in hexane, 2.41 ml, 3.62 mmol) was added to a solution of ethyl (2*Z*)-pyrrolidin-2-ylideneacetate (0.51 g, 3.3 mmol) in dry THF (10 ml) at 0°C and allowed to warm to room temperature over 30 minutes. (3-Bromo-prop-1-ynyl)trimethylsilane (0.80 ml, 0.94 g, 4.9 mmol) was added thereafter and the reaction mixture was stirred overnight. The reaction was quenched by addition of $NH_4Cl_{(aq)}$ (5 ml), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 ml). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to afford 2-pyrrolidin-2-ylidene-5-trimethylsilanyl-pent-4-ynoic acid ethyl ester as a colourless oil (0.33 g, 1.2 mmol, 38%) and 2-(4,5-dihydro-3*H*-pyrrol-2-yl)-5-trimethylsilanyl-2-(3-trimethylsilanyl-prop-2-ynyl)-pent-4-

ynoic acid ethyl ester as a colourless oil (0.35 g, 0.93 mmol, 28%); R_f 0.71 and 0.78 (EtOAc/Hex) respectively.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.16 (1H, brs, NH), 4.15 (2H, q, J = 7.4 Hz, OCH_2CH_3), 3.53 (2H, t, J = 6.8 Hz, NCH_2), 3.14 [2H, s, $CH_2C{\equiv}CSi(CH_3)_3$], 2.73 (2H, t, J = 7.9 Hz, $NCH_2CH_2CH_2$), 2.01 (2H, m, NCH_2CH_2), 1.28 (3H, t, J = 7.4 Hz, OCH_2CH_3), 0.12 [9H, s, $Si(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 169.6 (C=O), 165.3 (NC=C), 107.2 [$C{\equiv}CSi(CH_3)_3$], 84.6 (NC=C), 82.4 [$C{\equiv}CSi(CH_3)_3$], 58.9 (OCH_2CH_3), 47.3 (NCH_2), 30.9 ($NCH_2CH_2CH_2$), 22.0 (NCH_2CH_2), 18.5 [$CH_2C{\equiv}CSi(CH_3)_3$], 14.7 (OCH_2CH_3), 0.18 [3C, $Si(CH_3)_3$].

IR (thin film, $CHCl_3$): 3346, 2956, 2164, 1659, 1588, 1204, 839 cm^{-1}.

MS (EIMS): *m/z* (%) = 265 [M^+] (19), 236 (100), 192 (91), 162 (52), 73 (21).

HRMS: found *m/z* = 265.1401 [M^+], $C_{14}H_{23}NO_2Si$ requires 265.1498.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 4.17 (2H, q, J = 7.0 Hz, OCH_2CH_3), 3.84 (2H, t, J = 7.4 Hz, NCH_2), 3.02 and 2.94 {2H, d, J = 17.0 Hz and 2H, d, J = 17.0 Hz, [$CH_2C{\equiv}CSi(CH_3)_3]_2$}, 2.48 (2H, t, J = 7.9 Hz, $NCH_2CH_2CH_2$), 1.86 (2H, m, NCH_2CH_2), 1.24 (3H, t, J = 6.8 Hz, OCH_2CH_3), 0.10 {18H, [$CH_2C{\equiv}CSi(CH_3)_3]_2$}.

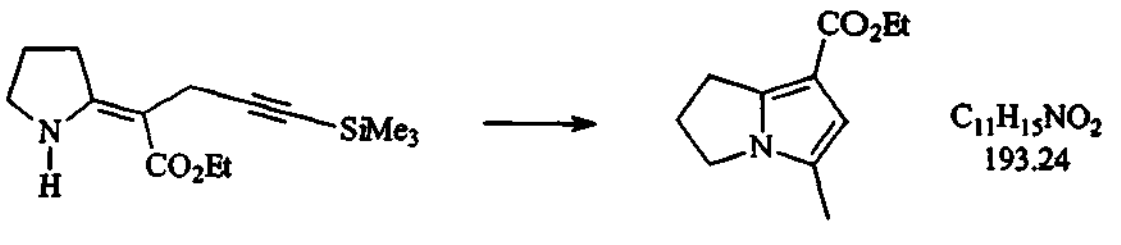
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 174.7 (N=C), 170.8 (C=O), 102.3 {2C, [$CH_2C{\equiv}CSi(CH_3)_3]_2$}, 87.5 {2C, [$CH_2C{\equiv}CSi(CH_3)_3]_2$}, 61.6 ($OCH_2CH_3$), 60.7 ($NCH_2$), 54.3 (N=CC), 34.9 ($NCH_2CH_2CH_2$), 24.7 {2C, [$CH_2C{\equiv}CSi(CH_3)_3]_2$}, 22.8 ($NCH_2CH_2$), 14.1 ($OCH_2CH_3$), 0.07 {6C, [$CH_2C{\equiv}CSi(CH_3)_3]_2$}.

IR (thin film, $CHCl_3$): 2956, 2175, 1736, 1248, 1196, 842 cm^{-1}.

MS (EIMS): *m/z* (%) = 375 [M^+] (72), 302 (22), 264 (100), 190 (13).

HRMS: found *m/z* = 375.2074 [M^+], $C_{20}H_{33}NO_2Si_2$ requires 375.2050.

13.4 Ethyl 5-methyl-2,3-dihydro-1*H*-pyrrolizine-7-carboxylate



$C_{11}H_{15}NO_2$
193.24

2-Pyrrolidin-2-ylidene-5-trimethylsilanyl-pent-4-ynoic acid ethyl ester (0.17 g, 0.64 mmol) was treated with $AgNO_3$ (22 mg, 0.13 mmol) and irradiated to afford ethyl 5-methyl-2,3-dihydro-1*H*-pyrrolizine-7-carboxylate as a colourless crystalline solid (37 mg, 0.19 mmol, 30%).

Note: Spectral and physical data for this compound matched those acquired for the same compound in a prior reaction (p185).