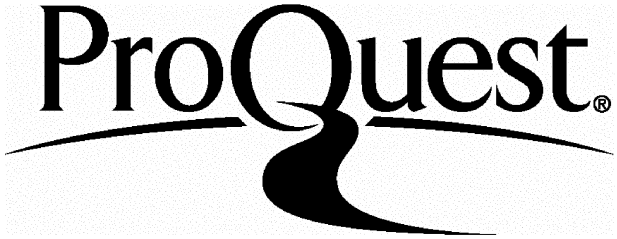
Amidoalkylations and Cyclisations Involving Hydroxamic Acids and Their Derivatives

A thesis presented to the University of London in partial fulfillment for the degree of doctor of philosophy

Sabrina Pucci

University College London
Christopher Ingold Laboratories

2004



To my mum

Contents

Chapter3

New Condensations of Hydroxamic Acids to give N-Heterocycles

Chapter 4

Preparation and Use of Acyl Hydrazines in Multicomponent Reactions and in New Cyclisations

Acknowledgements

First I would like to thank my supervisor, Dr Charles Marson for giving me the opportunity to work on this interesting subject and for many helpful suggestions throughout my PhD. Also, I would like to thank my second supervisor Prof. William Motherwell for his help during my PhD.

I am very grateful for technical assistance, in particular from Dr Abil Aliev (NMR), John Hill and Steve Firth (Mass Spectroscopy), Jill Maxwell (Microanalysis). Many thanks to all my friends in the UCL Chemistry Department, in particular those in the Marson group, past and present, for friendship, support and for making my time in London very enjoyable. I would like also to thank Dr Pascal Savy and Dr Sarah Bregant for their helpful suggestions as well as Dr Stéphane Sengmany and James Morrell for their patience in reading this thesis and finally to Mike for his support over the past years.

Receipt of financial support from the EPSRC and the Graduate School of UCL is gratefully acknowledged.

Abstract

Amidoalkylations and Cyclisations involving Hydroxamic Acids and Their Derivatives

Sabrina Pucci, PhD Thesis, 2004

Amidoalkylations are multicomponent reactions, which proceed via a highly reactive intermediate such as the *N*-acyliminium species. Amidoalkylations involving hydroxamic acids are rare and their reactivity in three-component condensations with carbonyl compounds is almost unknown.

The development of new synthetic routes to both natural and novel cyclic hydroxamic acids is of primary importance in view of their potential in a wide range of biological applications. A new ring-closure reaction involving unsaturated hydroxamic acids has been investigated.

In *Chapter 1* is depicted a complete introduction to hydroxamic acids, including their biological and physical properties, structure and preparation. A variety of unsaturated and *O*-protected hydroxamic acids were prepared in order to test the scope of the three-component amidoalkylation condensation and the acid-catalysed cyclisation.

In *Chapter 2* is described a new amidoalkylation that furnishs acyclic aliphatic β-hydroxamic acids aldehydes for the first time. Unique features include: (a) *in situ* formation of the presumed imine substrate (from a hydroxamic acid and an aldehyde) (b) subsequent amidoalkylation by an aldehyde, in an overall one-pot process to give (c) an isolable β-hydroxamic acid aldehyde as the product.

Chapter 3 describes attempts to generate heterocycles by treating unsaturated hydroxamic acids with trifluoromethanesulfonic acid (TfOH). At 30% concentration of TfOH this was largely successful.

Chapter 4 describes attempts to broaden the scope of the multicomponent reactions and to uncover new cyclisations. Hydrazides were prepared in the hope that their enhanced nucleophilicity would assist in carbonyl condensations.

Abbreviations

BOC	*t*-Butoxycarbonyl
Bn	Benzyl
Bz	Benzoyl
DBU	1,8-diazobicyclo[5.4.0.]undec-7-ene
DCC	1,3-Dicyclohexylcarbodiimide
DEAD	Diethyl azodicarboxylate
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
LDA	Lithium diisopropylamine
*m*CPBA	*meta*-Chloroperbenzoic acid
MCR	Multicomponent reactions
NMM	*N*-Methylmorpholine
NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear Magnetic Resonance
MMP	Matrix metalloproteinases
NOE	Nuclear Overhauser Effect
$Pd_2(dba)_2$	Tris(dibenzylideneacetone)dipalladium
PIFA	[Bis(trifluoroacetoxy)iodo]benzene
PPA	Polyphosphoric acid
PPE	Polyphosphoric ester
TEBA	Triethylbenzylammonium chloride
p-TsOH	*para*-Toluenesulfonic acid
THF	Tetrahydrofuran
TIMP	Tissue inhibitor metalloproteinase
t.l.c.	Thin-layer chromatography
TMS	Trimethylsilyl
Triflic	Trifluoromethanesulfonic
TfOH	Trifluoromethanesulfonic acid

Chapter 1

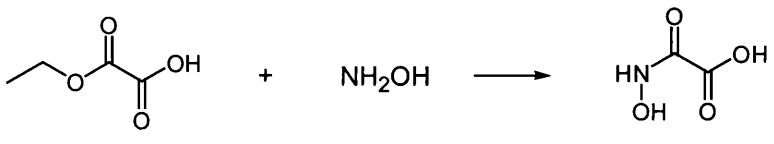
Preparation and Use of Hydroxamic Acids

1.1 Introduction

This thesis is mainly concerned with the reaction of carbonyl compounds with hydroxamic acids. Subsequently, the participation of hydroxamic acids was examined in ring closure reactions where the nitrogen atom of the hydroxamic acid moiety can react intramolecularly with an unactivated double bond in the presence of an acid catalyst. This work is based on previous research, which was carried out in our group that involved amides rather than hydroxamic acids. This chapter contains a description of the structure, reactivity, properties and in particular the synthesis of hydroxamic acids.

1.1.1 Hydroxamic acids

The RCONHOH derivatives of hydroxylamine are generally referred to as hydroxamic acids. Accounts of the chemistry of hydroxamic acids began in 1869 when *H. Lossen*, working in *W. Lossen's* laboratory, isolated oxalohydroxamic acid from the reaction of ethyl oxalate with hydroxylamine[1] (scheme 1.1).



Scheme 1.1: Reaction of ethyl oxalate with hydroxylamine

At that time, in the absence of spectral data, the structure of the oxo form (I) (fig 1.1) was difficult to establish; many chemists of the era believed that the hydroximic acid (II) correctly represented hydroxamic acids. It was only after X-ray analysis that it was proved that structure (I) represents hydroxamic acids in the solid state. It had long been known that complexation of metal ions with hydroxamic acids formed the basis of analytical determinations; for example, Fe^{3+} gives complexes of a beautiful purple colour.

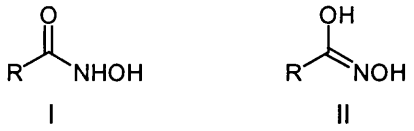


Fig 1.1

Hydroxamic acids belong to an important class of reagents in organic and inorganic chemistry,[2] and are also valuable intermediates in pharmaceutical applications.[3-5] Moreover they manifest interesting properties as iron chelators (siderophores),[6] photochemical reactions[7] and enzyme inhibitors.[8-12] As the name implies, hydroxamic acids behave as weak acids and this is one of their most important features.

1.1.2 Chemical Properties of Hydroxamic Acids

1.1.2.1 Site of Ionization and pK_a values

The structure-function relationships of hydroxamic acids still present some unresolved questions[13] concerning their exceptionally low pK_a values (pK_a ≈ 8-9), when compared with their structurally similar amide derivatives (pK_a ≈ 11-15) and the evaluation of the structural features of their conjugated bases[14;15]. In fact, the identification of the site of deprotonation has not yet been clearly defined, either in solution or in gas phase, because different experimental techniques lead to different results.

In the gas phase a molecule of acetohydroxamic acid possess four stable neutral forms (fig 1.2) and shows three electrophilic centres, of which the carbonyl oxygen and the nitrogen atom are prone to protonation.[16] Without including solvent effects, the acetohydroxamic acid could adopt any of the four stable neutral forms but the most stable ones are the amide tautomer I and the Z imide isomer II (figure 1.2),[16] because of the hydrogen bonds established between the hydroxyl and the carbonyl groups. The energy difference between both stable structures has been evaluated to be 0.9 Kcal mol^{-1}, in favour of the amide tautomer I.[16] On the other hand, when the effect of the solvent is taken into account, the relative energy of the two tautomers changes considerably.

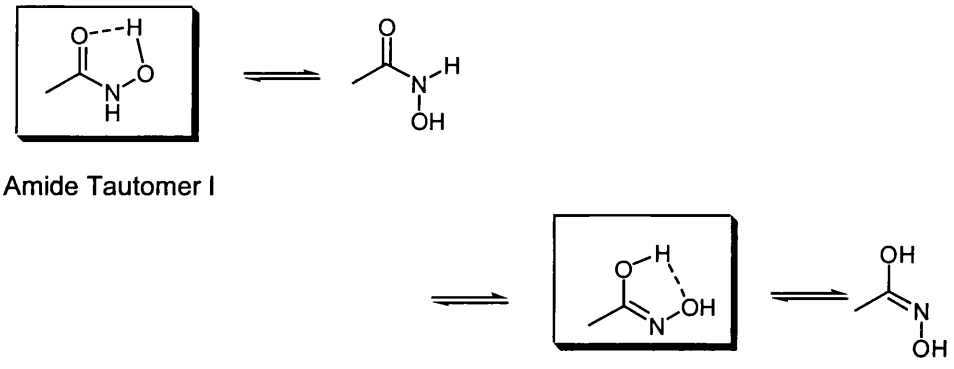


Fig 1.2. The four stable neutral forms of hydroxamic acid in the gas phase.

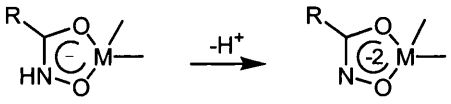
Past and recent reports have shown that both the OH and NH groups are possible ionization sites in solution.[17-20] A study of oxidation potentials[21] and cation complexation experiments in alkaline media[22;23] of the hydroxamate moiety imply that the NH group is the preferred ionization site in DMSO and aprotic polar solvents, whereas the hydroxylic function acts as a proton donor in water and protic solvents.[24;25] Moreover, extended spectroscopic experiments[13] and theoretical calculations (*ab initio* methods)[26] have demonstrated that the acidity of both NH and OH functions is strongly affected by the structural characteristics of the substrate and also depends upon the solvent.

Hydroxamic acids are acidic but can also behave as weak bases owing to the NC=O moiety;[27] despite their importance, there are only a few experimental contributions concerning their acid-base behaviour. In theory, protonation can occur

at nitrogen, the carbonyl oxygen or the oxygen of the OH group but theoretical calculations performed on the isolated acetohydroxamic acid show only two stable cations (fig. 1.2). By analogy with the chemical behaviour of amides, it is usually accepted that the site of protonation is the carbonyl oxygen atom.[13;28]

1.1.2.2 Chelating Properties

Hydroxamate-containing compounds, one of the major classes of naturally occurring metal complexing agents, have been thoroughly studied as ligands. Numerous papers show that hydroxamic acids adopt a typical binding mode in which the oxygen atoms belonging to the carbonyl and NHOH groups are the ones chelated to the metal.[29] Investigation of complex formation with simple primary hydroxamic ligands in aqueous solution demonstrated clearly that, depending on the pH, the monoanion (III) arises from the first deprotonation step and involves the coordination of the metal (O,O) to NHO^- moiety and to the carbonyl oxygen (**III**, Scheme 1.2). The dianion (IV) form of the ligand is produced by further metal-induced deprotonation of NHO^- (**IV**).[30] The anions of the hydroxamic acids and their *N*-substituted derivatives may serve as bidentate ligands toward metal ions such as Fe(III), Ni(II) and Cu(II).



III IV

Scheme 1.2

1.1.2.3 Comparison of Reactivity of Hydroxamic Acids with that of Amides

The unexpectedly high acidity of hydroxamic acids is one of their most remarkable properties, and is one of the main differences between their amide counterparts. In fact, the pK_a values of hydroxamic acids are approximately 6 units more acidic than the corresponding amide.[14] On the other hand, an early study[16]

showed that hydroxamic acids behave as weaker bases than amides. However, one of the most interesting properties on which this entire work is based is the nucleophilic nature of the nitrogen atom of hydroxamic acids compared to amides especially towards *N*-alkylation. Much less is known about the nucleophilicity of hydroxamic acids; nevertheless it can be assumed that the nitrogen atom of the hydroxamic acid moiety would be likely to have a higher nucleophilicity compared to the amides, owing to the *alpha effect*. In general, the presence of an OH group adjacent to the nitrogen atom confers the latter with higher nucleophilicity. Moreover the positive charge formed during *N*-alkylation is better sustained by the neighbouring atoms of hydroxamic acids than those of the corresponding amides. Relevant are literature observations that describe the oxygen of the NHOH group participating as a nucleophile.[31;32]

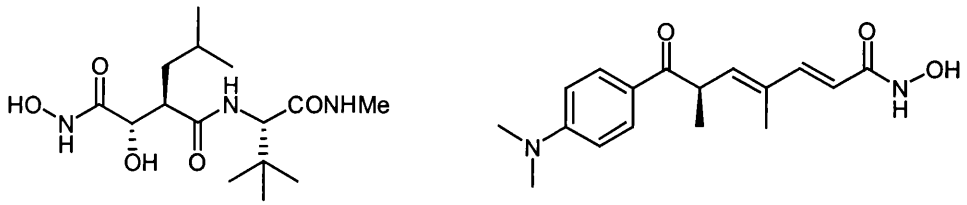
1.1.3 Biological Properties of Hydroxamic Acids

As already mentioned, hydroxamic acids possess useful biological properties and important medical applications; much of their biological activity is related to their ability to form very stable chelates with a wide range of metal ions, especially iron.[33] They possess a wide spectrum of biological activities such as anti-inflammatory,[34] anti-asthmatic,[35] psychotropic[36] antibiotic insecticidal,[37] acaricidal and nematocidal activities.[38] Naturally occurring hydroxamic acids can be low-molecular weight iron chelators in the microbial transport of iron (siderophores)[6] and play a key role in facilitating the proper function of enzymes in electron and oxygen transport and other life-sustaining processes.[39] They are also inhibitors of urease activity and have been used therapeutically in the treatment of hepatic coma.[6]

Their strong ability to chelate metals makes hydroxamic acids efficient inhibitors of a large class of enzymes called metallo-enzymes, the matrix metalloproteins being important anticancer targets.[40]

Matrix metalloproteinases (MMP) require zinc ion at their active sites and are responsible for connective tissue remodelling and have emerged as interesting targets for a wide array of disease process where the remodelling process plays a key role.[41] Treatment of osteoarthritis,[42;43] rheumatoid arthritis, tumour metastasis,[44-46] multiple sclerosis,[47] among many others, holds promise. Eighteen kinds of MMP have been

isolated and cloned and are collectively termed the MMP family.[48;49] In figure 1.3 are depicted two potent enzyme inhibitors, Marimastat and Trichostatin A. Marimastat is a potent inhibitor of the series of matrix metalloproteinases involved in the tumour necrosis factor α convertase[50] while Trichostatin A is a potent inhibitor of the histone deacetylase family of enzymes integrally associated with DNA.[51]



Marimastat Trichostatin A (TSA 1)

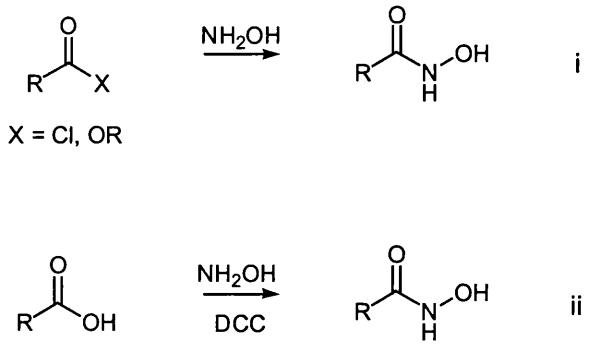
Fig. 1.3: Two potent inhibitors: Marimastat for Matrix metalloproteinases and Trichostatin A as an inhibitor of histone deacetylase

The molecular mechanism underlying the enzyme activity of the MMP family has been revealed on the basis of their molecular interaction with their specific inhibitors. Although their physiological activities are not yet fully understood, they are postulated to regulate the homeostasis of a variety of tissues under the control of the tissue inhibitor metalloproteinase (TIMP), which associates with and inhibits the activity of MMP. Therefore, it is thought that production of MMP and stoichiometric imbalance between TIMP and MMPs could result in a variety of morbid states, including tumour metastasis[52] or multiple sclerosis[53] or rheumatoid arthritis.[54] Moreover, certain MMP inhibitors have recently been shown to exert antitumor activity other than antitumour metastasis.[55]

1.1.4 Preparation of Hydroxamic Acids

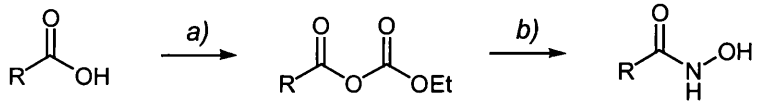
Several well-documented literature methods are available for the preparation of hydroxamic acids.[56-60] The most common method for the preparation of these compounds is by reaction of hydroxylamine with esters or acid chlorides[2] (scheme 1.3 eq i). In contrast, the direct formation of hydroxamic acids from a carboxylic acid and hydroxylamine is unfavourable owing to the equilibrium position which makes significant the reverse reaction of solvolysis of the hydroxamic acid. Formation of a hydroxamic acid from a carboxylic acid requires the activation of the latter using a

coupling agent of the sort used in peptide synthesis, such as DCC (dicyclohexylcarbodiimmide) or a similar reagent[2] (scheme 1.3 eq ii).



Scheme 1.3.

Preparation of hydroxamic acids from acid chlorides can be troublesome and where an ester is used to prepare a hydroxamic acid, reaction does not proceed under neutral conditions; in fact, strong basic conditions are often required. Moreover when DCC is used, it is usually difficult to isolate the product without traces of the side product DCU. In contrast, a very simple and straightforward method has been adopted for the preparation of the hydroxamic acids in one step and under neutral conditions. The carboxylic acid is reacted with ethyl chloroformate in the presence of a mild base, such *N*-methylmorpholine, to form, *in situ,* the anhydride that reacts with a solution of hydroxylamine previously prepared (scheme 1.4).[61]



Scheme 1.4. *a)* Ethyl chloroformate, NMM, Et_2O, 0 °C, 15 min. *b)* NH_2OH in MeOH, 0°C, 25 min

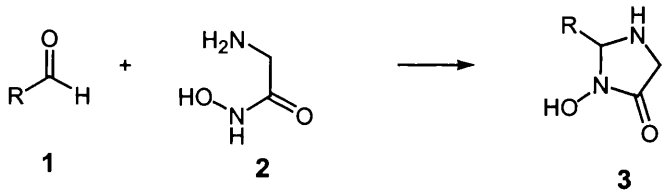
This procedure was successfully used in the preparation of all the classes of hydroxamic acids considered in this thesis.

1.2 Results and Discussion

This chapter describes various methods for preparing hydroxamic acids with the purpose of finding one general procedure. Classical and well-documented routes were tried before discovering that the method of Reddy[61] was suitable for all the classes of hydroxamic acids required.

1.2.1 Synthesis of α-Amino Hydroxamic Acids

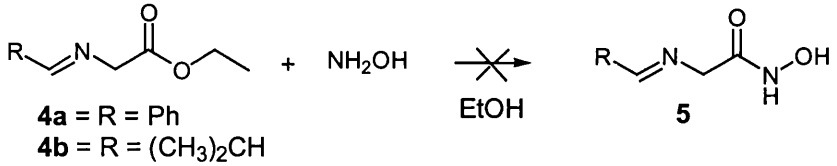
A class of hydroxamic acid that has been extensively investigated in the present multicomponent amidoalkylations is that of α-amino hydroxamic acids. Such compounds are known to condense with aldehydes to give the five-membered ring system, 3-hydroxyimidazolidin-4-ones (**3**) (scheme 1.5).[62]



Scheme 1.5

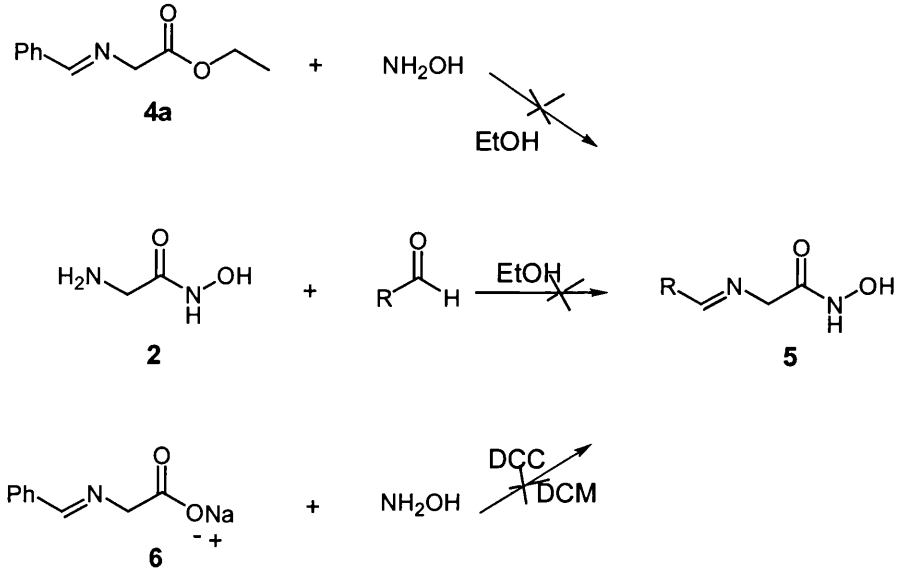
Since the formation of the intermediate imine from reaction of the aldehyde **1** with the amino group of hydroxamic acid **2** is primarily favoured, and as our aim was to evaluate the reaction of aldehydes with the hydroxamic acid moiety (scheme 1.5), protection of the amine appeared to be the only way to prevent reaction at this functionality. Accordingly, some *N-Boc*, *N*-aryl and *N*-acyl glycine hydroxamic acids were prepared.

Hydroxamic acid **2** has been readily prepared from the corresponding *β*-aminoesters and hydroxylamine under neutral conditions,[62] but when the nitrogen atom of the ester bears a protecting group it was found that the hydroxamic acid could not be formed (scheme 1.6).



Scheme 1.6

Our first attempt to protect the amine function as an imine was achieved by treating the glycine ester with benzaldehyde in dry dichloromethane in the presence of magnesium sulfate as a dehydrating agent.[63] However this approach was rapidly abandoned when the coupling of *N*-phenylglycine ethyl ester **4a** with hydroxylamine did not give the desired hydroxamic acid and only hydrolysis of the imine was observed. Consequently, alternative preparation of the desired compounds were attempted, (scheme 1.7), but in no case could the hydroxamic acid be isolated.

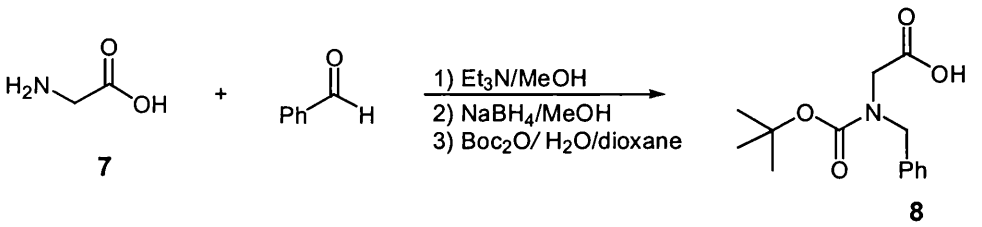


Scheme 1.7

When **2** was treated with benzaldehyde in ethanol no reaction occurred and the hydroxamic acid was quantitatively recovered unchanged. This suggests that either the amine is less reactive, owing to the electron-withdrawing effect of the hydroxamic acid moiety, or that the imine (formed from the reaction of the aldehyde with the amine) is rapidly hydrolysed as soon as it is produced.

The reaction of the more activated carboxylate **6** with hydroxylamine in presence of 1,3-dicyclohexylcarbodiimide (DCC) did not provide the protected hydroxamic acid. Although the sodium salt **6** reacts faster with DCC due to the

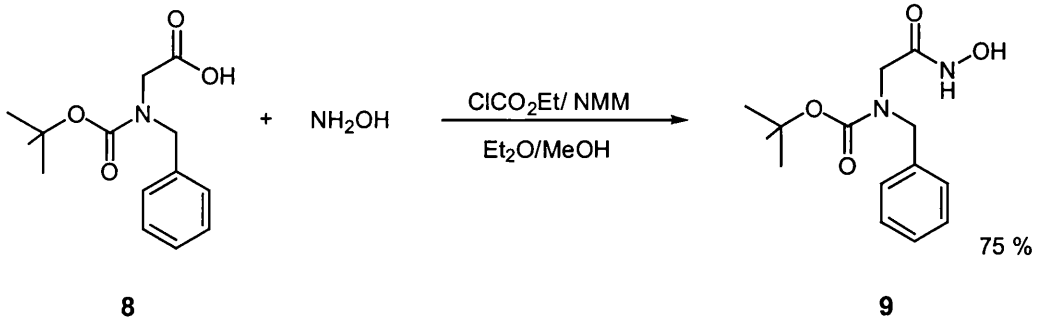
increased nucleophilicity of the negatively charged oxygen, the desired **5** could not be detected, and glycine was the only product isolated. The idea of the imine as a protecting group was then abandoned and other protecting groups were considered such as acyl and benzyl. In such cases in order to avoid double protection on nitrogen with the same group a specific synthetic pathway was devised (scheme 1.8).



Scheme 1.8

The formation of the imine and its reduction and protection with di-*tert*-butyl dicarbonate was achieved in a one-pot reaction in 55% overall yield.

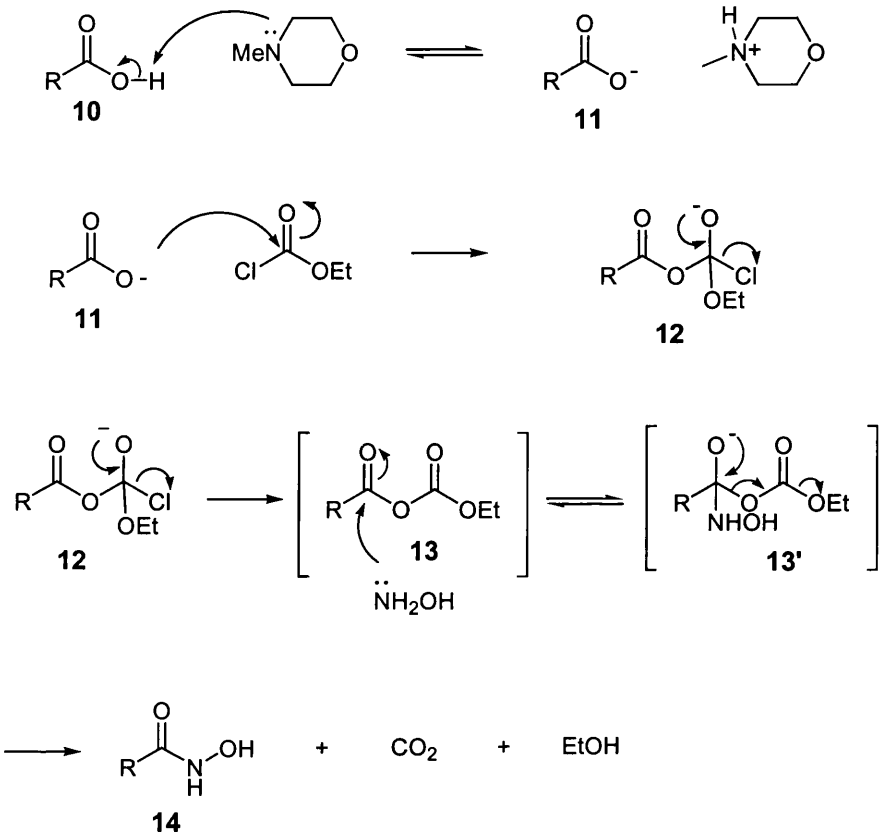
Coupling of **8** with hydroxylamine using DCC was carried but unfortunately only starting material was recovered. It was at this stage that the method of Reddy [61] was used, affording the hydroxamic acid **9** (equation 1.5) in 75% yield (scheme 1.9).



Scheme 1.9

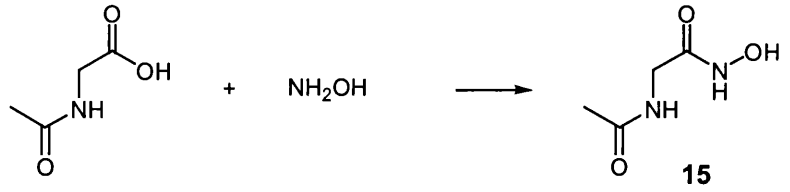
The mechanism involves the formation of an anhydride *in situ* that is subsequently displaced by hydroxylamine to give the hydroxamic acid **9**. Deprotonation of the acid **10** by *N*-methylmorpholine (NMM) generates the carboxylate **11** (scheme 1.10), which reacts with the ethyl chloroformate to form a tetrahedral intermediate **12**. The latter eliminates chloride to form the anhydride **13** that by subsequent attack of the nucleophilic nitrogen atom of hydroxylamine affords the hydroxamic acid **14**. The formation from **10** of the ethyl ester, a major side-

product, could be attributed to the fact that as the amount of hydroxamic acid produced increases, so does the amount of ethoxide; this leads to a competitive reaction in which the ethyl ester is formed as a side-product.



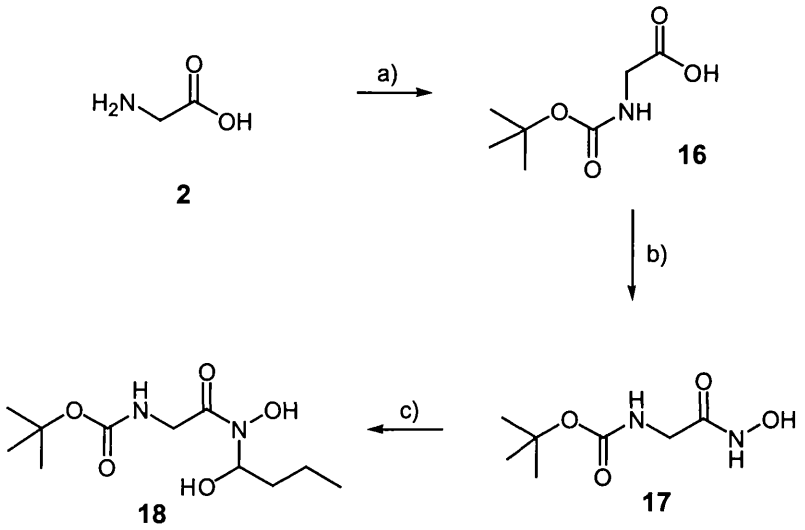
Scheme 1.10 Mechanism of the formation of hydroxamic acids *via* chloroformate activation

The method used to prepare hydroxamic acid **9** (scheme 1.9) was then applied to other related hydroxamic acids and in most of the cases the products were obtained in satisfactory yields. In this way, several other *N*-protected glycine hydroxamic acids were prepared and reacted with carbonyl compounds. In particular, *N-Boc* glycine hydroxamic acid **16** and *N*-acetylglycine hydroxamic acid **18** (scheme 1.12) were envisaged. The latter was synthesised from the commercially available *N*-acetyl glycine; **16** was obtained from the precursor *N-Boc* glycine, prepared using standard *Boc*-protection.[64]



Scheme 1.11

When acid **16** was reacted with butyraldehyde an intermediate hemiaminal **18** was isolated (scheme 1.12); this is, to our knowledge, the first amidoalkylation to deliver this class of acyclic hemiaminal.



Scheme 1.12: *a)* 1M NaOH, Boc_2O dioxane/H_2O, 0 °C, pH =9-10, 25 min; 20 °C, pH =9; 16 h. *b)* NMM, ethyl chloroformate, Et_2O/MeOH, rt, 25 min. *c)* Butyraldehyde, EtOH, rt, 16 h.

The product was isolated in low yield and although various conditions had been examined, the yield could be little improved (see Table 1).

Table 1.1. Attempted Optimisation of the Preparation of Hemiaminal **18**

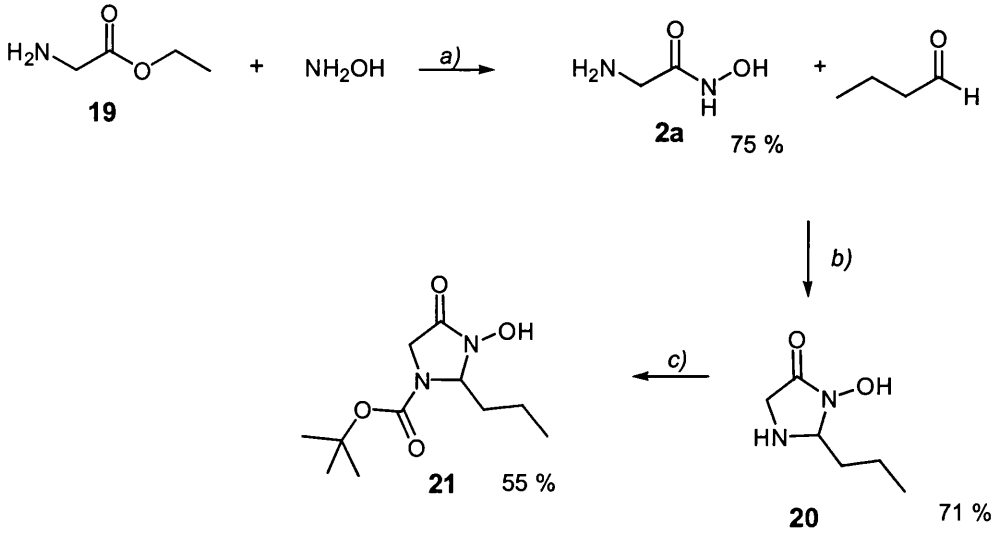
Entry	15 (eq)	Butyr-aldehyde(eq)	Conditions	Yield %
1	1	1	EtOH, rt	33
2	1	2	EtOH, rt	35
3	1	2	EtOH, 70°C	0
4	1	-	$CuSO_4$, butyraldehyde, rt	0
5	1	1	CH_2Cl_2, rt	37
6	1	1	CF_3CH_2OH	38

The yield was not improved by employing more butyraldehyde (entry 2, table 1.1); also the change in temperature did not seem to make any difference (entry 3). It was thought that addition of copper sulfate as dehydrating agent could have driven the reaction towards the formation of the hemiaminal, the latter being water-sensitive. However, no conversion was observed and only starting material was

recovered (entry 4). Moreover, the use of polar and aprotic solvents such as dichloromethane and trifluoroethanol did not seem to make significant changes (entry 5 and 6).

For a better understanding of the results two comments should be made, firstly that the equilibrium, leading to the formation of the hemiaminal **17** may lie in favour of the reactants, and secondly that the electron-withdrawing protecting group on the nitrogen atom can considerably enhance the stability of the hemiaminal. Consistent with this hypothesis *N*-acetylglycine hydroxamic acid was prepared but no hemiaminal derived from it was observed.

The NMR and infrared spectra are in agreement with the structure proposed for the hemiaminal **18**; the mass spectrum does not show any peak at M+1 but instead a peak for M-H_2O. The major concern was to verify that the structure was the hemiaminal **18** and not the five-membered ring 3-hydroxy-4-imidazolidinones **3**. In accordance to that a parallel synthesis was carried on (scheme 1.13). The glycine ethyl ester **19** was converted into the hydroxamic acid **2a** by stirring the ester with hydroxylamine in ethanol, following the procedure described by Horman.[62] Since condensation of **2** with butyraldehyde gave the five-membered ring 3-hydroxy-4-imidazolidinone **20**, the ring was protected using di-*tert*-butyl dicarbonate to give the final compound **21**. At this point ^{13}C NMR comparison of the two compounds was made and it was clear that in the hemiaminal system the carbon atom attached to the nitrogen atom of the hydroxamic acid had a chemical shift of 80.1 ppm while the corresponding carbon atom of the ring system showed a chemical shift of 72.4 ppm. This unequivocally established that the hemiaminal **18** had been isolated in the first place.



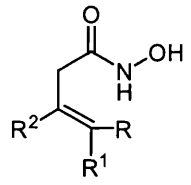
Scheme 1.13 a) EtOH, -5 °C, 16 h; b) *i*-PrOH, reflux, 4 h; c) Boc_2O, H_2O/dioxane, 5 h.

The condensation of butyraldehyde with glycine hydroxamic acid was carried out by heating at reflux in isopropanol although the method described by Horman[62] recommended conducting the reaction in ethanol at room temperature; however using the latter conditions **20** could not be obtained in good yield; hence different conditions needed to be investigated and finally the 3-hydroxy-2-propyl-imidazolidin-4-one (**20**) was obtained in satisfactory yield (71%).

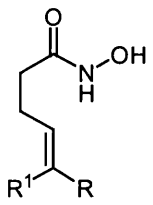
1.2.2 Preparation of β,γ- and γ,δ-Unsaturated Hydroxamic Acids

Reactions of these types of hydroxamic acid are extensively discussed in chapter three; the aim was to achieve an intramolecular cyclisation involving the nucleophilic nitrogen atom of the hydroxamic acid moiety and the electrophilic carbocation formed *in situ* by the attack of the acid catalyst on the unactivated double bond. The hydroxamic acids **22** to **29** (figure 1.4) were prepared following the same procedure described in section 1.2.1, the yields being between 22 and 68%.

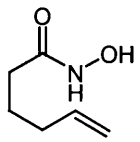
β,γ-Unsaturated **γ,δ-Unsaturated** **δ,ε-Unsaturated**



R=H R^1=CH_3 R^2=H **22**
R=CH_3, R^1=CH_3 R^2=H **23**
R= H R^1=R^2=C_4H_8 **24**
R=H R^1=C_2H_5 R^2=H **25**



R = CH_3, R^1 = H **26**
R = CH_3, R^1 = CH_3 **27**
R = Ph, R^1 = H **28**



29

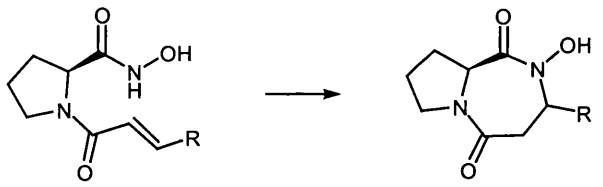
Fig 1.4

Preparations of the precursor carboxylic acids that led to the hydroxamic acids shown in figure 1.4 are described and discussed in chapter three. In the present chapter is presented a general understanding of the different classes of hydroxamic acids investigated, as well as the difficulties encountered in finding a general method suitable for all the hydroxamic acids required. Although there are different ways of

preparing hydroxamic acids, it seems that each hydroxamic acid requires a specific procedure. Consequently, considerable investigation was needed in order to master how to prepare each different hydroxamic acid required for the condensations that formed the principal aim of the work.

1.2.3 Synthesis of Proline-Type Hydroxamic Acids

This class of hydroxamic acids is further discussed in chapter three; they could in principle react in the same manner as acyclic ones, giving seven-membered rings **32** (eqn 1.6) which have important pharmaceutical properties. The double bond of the unsaturated amide function, if sufficiently activated, reacts with the nitrogen atom of the hydroxamic acid moiety to form the desired seven-membered rings **32.** Also in this case the hydroxamic acids were prepared by the method of Reddy.[61]

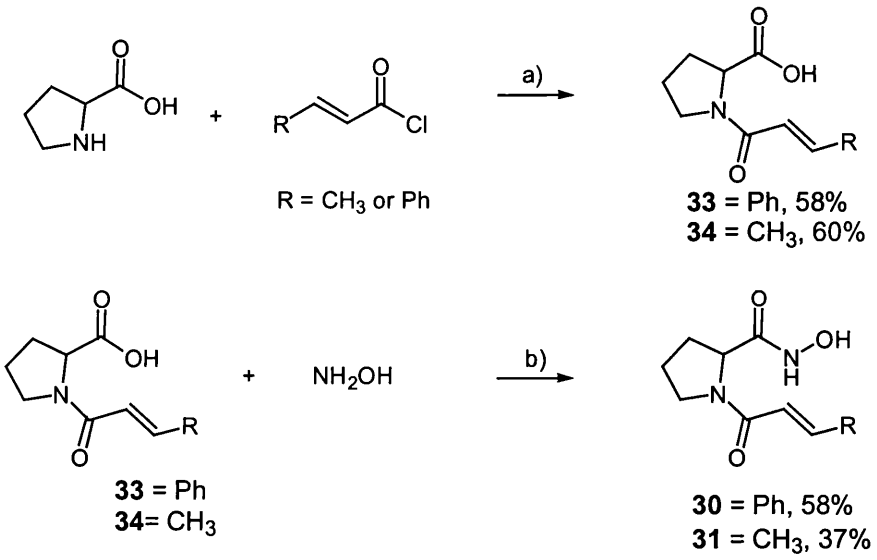


R = Ph **30**
R = CH_3 **31**

32

Scheme 1.14

The preparation of **30** and **31** (scheme 1.15) did not present any particular difficulties; the coupling of the acid chloride with *L*-proline was indeed achieved by following the literature procedure,[65] and the *N*-protected *L*-proline was converted into the hydroxamic acid **30** by the procedure discussed above. A relevant observation is that an amide bond is created without difficulty when the acid chloride contains no trace of chlorinating agents; the latter can inhibit the formation of the amide bond to the extent that low conversion is sometimes observed.



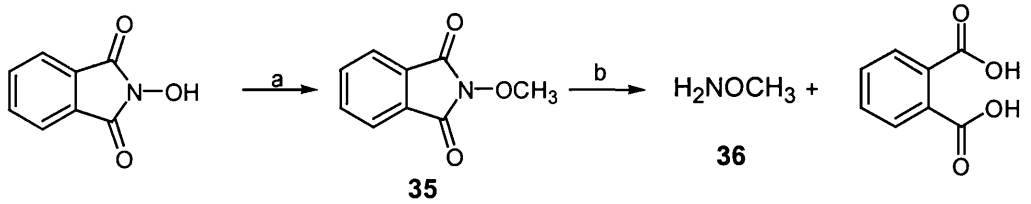
Scheme 1.15 *a)* Formation of the amide bond **33-34**, *Reagents:* NaOH 2 M, acetone, 0 °C, 3 h. *b)* Conversion into the hydroxamic acids **30-31**, *Reagents:* Ethyl chloroformate, NMM, Et_2O, 0 °C, 25 min.

1.2.4 Synthesis of O-Protected Hydroxamic Acids

This section contains a large number of hydroxamic acids of different structure. They were employed in multicomponent condensations involving carbonyl compounds. The condensation reactions are extensively discussed in chapter two.

The oxygen atom of the hydroxamic acid moiety required protection to prevent competitive alkylation of both NH and OH functionalities by the carbonyl group of the aldehyde; with such protection, the reaction could only occur at the nitrogen atom. Although benzyl was a suitable protecting group, side effects encouraged us to consider an *O*-methyl group instead of *O*-benzyl group.

Conversion of the carboxylic acid into the *O*-methylated hydroxamic acid was in most of the cases achieved using *O*-methylhydroxylamine. The latter was prepared by following the procedure of Bhat and Clegg[66] in which *N*-hydroxyphthalimide is methylated with methyl iodide in the presence of potassium carbonate to give **35** in 92% yield (scheme 1.16). Deprotection of the phthaloyl group using hydrochloric acid and subsequent drying under a high vacuum gave *O*-methylhydroxylamine hydrochloride **36** in reasonable yield (63%).

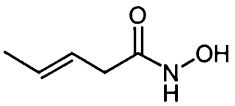
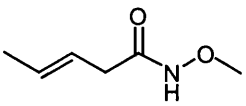
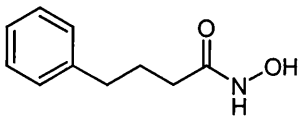
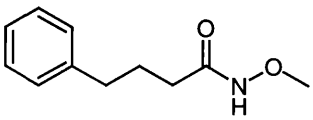
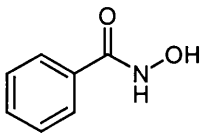
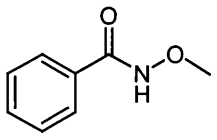


35 36

Scheme 1.16: *a)* K_2CO_3, DMSO, MeI, 30 °C, 25 min, rt 24 h, 0 °C, 4 h. *b)* 6M HCl, reflux 30 min.

The *O*-methylated hydroxamic acids that have been prepared to test the scope reaction of this thesis are shown in Tables 1.2 and Table 1.3. Some were prepared by a different route which involved methylation of the hydroxamic acid with methyl iodide in the presence of potassium carbonate as a base[19] (table 1.2); this route was used because some of the hydroxamic acids, such as pent-3-enoic hydroxamic acid **22** and the 4-phenylbutyric hydroxamic acid **38**, had already been prepared. *O*-Methylbenzoic hydroxamic acid **40** was prepared from the commercially available benzoic hydroxamic acid.

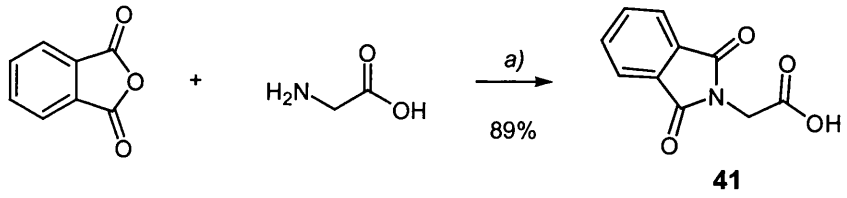
Table 1.2: Preparation of *O*-Methylated Hydroxamic Acids prepared by methylation of the *O*-free Hydroxamic Acid

Entry	Hydroxamic Acids	Conditions	Products	Yields (%)
1	 **22**	CH_3I, K_2CO_3 20 h	 **37**	51
2	 **38**	CH_3I, K_2CO_3 24 h	 **39**	54
3		CH_3I, K_2CO_3 16 h	 **40**	38

^{13}C NMR showed that both *O*-methylated (64 ppm) and *N*,*O*-dimethylated (35 and 64 ppm) products were formed. Those products were separated by column chromatography.

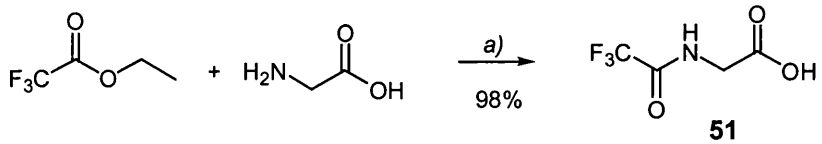
Treatment of benzoic hydroxamic acid with 1 equivalent of methyl iodide in the presence of potassium carbonate afforded the *O*-methylated hydroxamic acid **39** in only 38% yield (entry 3, table 1.2). This result suggests that *N*-methylation was preferred to *O*-methylation. On the other hand, for the hydroxamic acids **22** and **38** *O*-methylation was more favoured (entries 1 and 2, table 1.2).

The *O*-methylated hydroxamic acids **42** and **43** were prepared in very good yield from *N*-phthaloylglycine **41** using the procedure of Reyes and co-workers[67] (scheme 1.17).



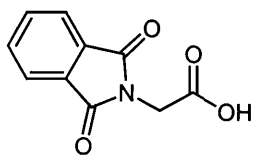
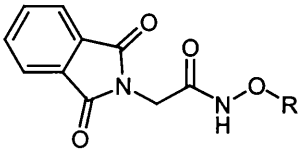
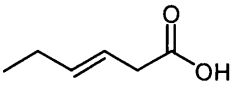
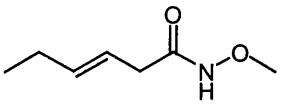
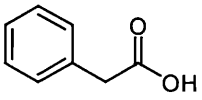
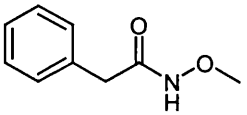
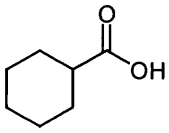
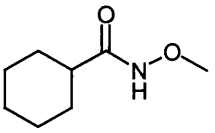
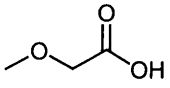
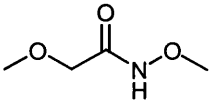
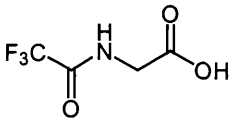
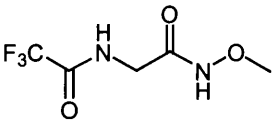
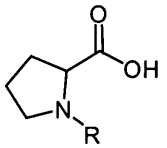
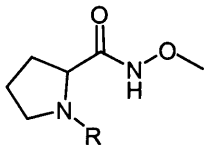
Scheme 1.17: *a)* Pyridine, 95 °C, 20 h.

Hydroxamic acid **48** was prepared from the (2,2,2-trifluoroacetylamino)-acetic acid **51**, obtained from a literature procedure[68] (Scheme 1.18).

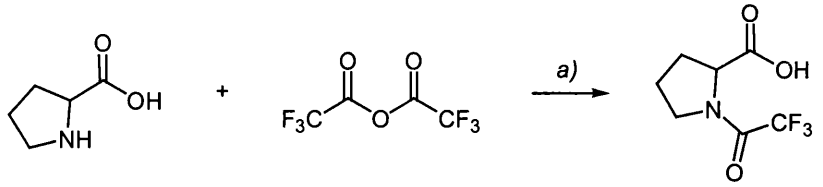


Scheme 1.18: *a)* Methanol, triethylamine, 24 h, r.t.

Table 1.3: *O*-Methylated Hydroxamic Acids prepared using NMM and ethyl chloroformate.

Entry	Substrate	Conditions	Products	Yields (%)
1	 **41**	NH_2OR $NMM/ClCO_2Et$ 1 h 1.5 h	 R = CH_3, **42** R = Bn, **43**	62 61
2		NH_2OCH_3 $NMM/ClCO_2Et$ 24 h	 **44**	51
3		NH_2OCH_3 $NMM/ClCO_2Et$ 24 h,	 **45**	52
4		NH_2OCH_3 $NMM/ClCO_2Et$ 30 min	 **46**	82
5		NH_2OCH_3 $NMM/ClCO_2Et$ 20 min	 **47**	96
6	 **51**	NH_2OCH_3 $NMM/ClCO_2Et$ 1 h	 **48**	98
7	 **52**	NH_2OCH_3 $NMM/ClCO_2Et$ 20 min 15 min	 R = Boc, **49** R = CF_3CO, **50**	83 72

Hydroxamic acids **49** and **50** were prepared respectively from the commercially available *N-Boc* proline and from *N*-trifluoroacetyl proline **52** which was obtained from a literature procedure[69] as shown in scheme 1.19.



52

Scheme 1.19: *a)* 0 °C 10 min, 80 °C 2 h.

1.3 Experimental

General methods: Melting points were measured on an Electrothermal 9100 hot stage micro melting point apparatus and are uncorrected. Reaction flasks were flame-dried and then allowed to cool under a stream of argon. All reactions involving air-sensitive reagents were carried out under argon atmosphere. ^{1}H NMR and ^{13}C chemical data were recorded on a Bruker spectrometer (operating at 300, 400 and 500 MHz for ^{1}H NMR spectra and 75, 100, 125 for ^{13}C) with tetramethylsilane as the internal reference. Coupling constants are quoted in Hz. NMR spectra were run in $CDCl_3$ unless otherwise stated. ^{1}H and ^{13}C chemical shifts were measured in parts per million (ppm) relative to the tetramethylsilane or by calibration of the central signal $CDCl_3$. The following abbreviations are used to describe the NMR signals: s, singlet; d, doublet; t, triplet; q, quadruplet; qt, quintuplet; m, multiplet; dd, doublet of doublets; dt, doublets of triplets, br s, broad singlet. In ^{13}C NMR spectra *o* = ortho, *m*= meta, *p* = para, *i* = ipso.

Infrared spectra were recorded on a Shimadzu FTIR-8700 and compounds that were solids were prepared as potassium bromide discs while liquids were applied neat onto a surface of sodium chloride.

Microanalytical data were obtained in the Microanalytical Laboratory of UCL Chemistry Department.

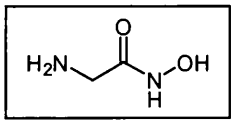
Mass spectra were obtained on a VG ZAB 2SE operating in FAB MS or electron impact (EI) mode, as specified in the text.

Thin-layer chromatography was performed on Merck 0.2 mm aluminium backed silica plates and visualised using ultraviolet light or developed using either an alkaline solution of potassium permanganate or an acidic solution of dinitrophenylhydrazine.

Column chromatography was carried out using Sorbsil C60 40/60H silica gel under flash conditions.

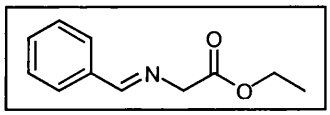
Acetonitrile was distilled from phosphorus pentoxide; dichloromethane from calcium hydride and THF from sodium and benzophenone.

Glycine hydroxamic acid (2)[62]



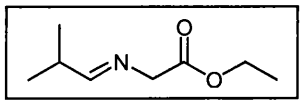
A solution of glycine ethyl ester hydrochloride (1.0 g, 7.16 mmol) in methanol (3.0 mL) was mixed with a solution of potassium hydroxide (0.30 g, 7.16 mmol) in methanol (3.0 mL) and kept at –5 °C for 16 h. A solution of hydroxylamine hydrochloride (0.75 g, 10.7 mmol) in methanol (5.0 mL) was added to a solution of potassium hydroxide (0.44 g, 10.7 mmol) and methanol (5.0 mL) and cooled to –5 °C overnight. The filtrates from the two reactions were mixed together and kept at –5 °C for 16 h. The solution was concentrated to about 10 mL, cooled again and kept at –5 °C. Filtration led to **2** (0.46 g, 75%) as a white prisms: mp 139-141 °C (lit[62] mp 140 °C); ^{1}H NMR (D_2O) 3.49 (2H, s, $C\underline{H}_2C{=}O$); ^{13}C NMR (D_2O) 168.8 ($\underline{C}{=}O$) 41.4 ($\underline{C}H_2C{=}O$).

***N*-Benzylideneglycine ethyl ester (4a).**[63]



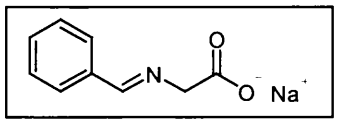
The procedure of Muller[63] for the preparation of *N*-benzylidene glycine ethyl ester was suitably adapted. Triethylamine (2.0 mL, 14.3 mmol), magnesium sulfate (0.6 g, 5.0 mmol) and freshly distilled benzaldehyde (0.75 mL, 7.16 mmol) were added to a solution of glycine ethyl ester hydrochloride in dichloromethane (25 mL) and stirred at 20 °C for 3 days. The magnesium sulfate was filtered off and the solvent removed under reduced pressure. The pale yellow oil was dissolved in diethyl ether (25 mL), washed with water (25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to give **4a** (1.12 g, 81%) as pale yellow oil: ^{1}H NMR 8.40 (1H, s, CH=N), 7.79 (2H, m, H_o), 7.20 (3H, m, $H_{m,p}$), 4.28 (2H, s, CH_2) 4.28 (2H, q, J = 6 Hz, $C\underline{H}_2CH_3$), 1.32 (3H, t J = 6 Hz, $CH_2C\underline{H}_3$); ^{13}C NMR 170.5($\underline{C}{=}O$), 165.1 ($C\underline{H}{=}N$), 136.1 (C_i), 131.6 (C_m), 129.0 (C_o), 128.9 (C_p), 61.8 (CH_2), 60.8 ($\underline{C}H_2CH_3$), 14.0 ($CH_2\underline{C}H_3$).

_N-Iso_butyideneglycine ethyl ester (4b)[63]



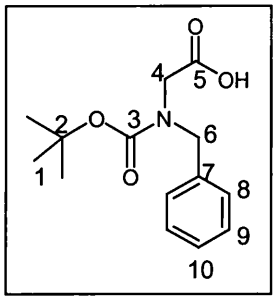
Triethylamine (2.0 mL, 14.3 mmol), magnesium sulfate (0.60 g, 5.0 mmol) and freshly distilled isobutyraldehyde (0.60 mL, 7.16 mmol) were added to a solution of glycine ethyl ester hydrochloride in dichloromethane (25 mL) and stirred at 20 °C for 3 days. The magnesium sulfate was filtered off and the solvent removed under reduced pressure. The pale yellow oil was dissolved in diethyl ether (25 mL), washed with water (25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to give **4a** (0.60 g, 54%) as pale yellow oil: ^{1}H NMR 7.51 (1H, s, CH=N), 4.14 (2H, s, CH_2) 4.06 (2H, q J = 6 Hz, $C\underline{H}_2CH_3$), 2.44 (1H, m, CH), 1.16 (3H, t J = 6 Hz, 3.67 $CH_2C\underline{H}_3$), 1.01 (6H, d, J = 9 Hz, $(CH_3)_2$); ^{13}C NMR 174.2($\underline{C}$=O), 169.8 ($C\underline{H}$=N), 60.4 (CH_2), 60.3 ($\underline{C}H_2CH_3$), 33.8 ($C\underline{H}(CH_3)_2$), 18.7 (($CH_3)_2$), 13.7 ($CH_2\underline{C}H_3$).

Sodium-_N_-benzylidene glycinate (6)[70]



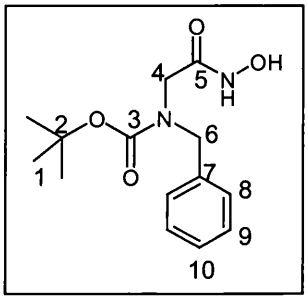
Glycine (0.75 g, 10.0 mmol) was dissolved in aqueous sodium hydroxide (1 M, 10.0 mL). The solution was then concentrated under reduced pressure until solid began to appear at which time benzaldehyde (1.02 mL, 10.0 mmol) was added and stirred for 30 min. The solvent was then evaporated under reduced pressure until it became a solid. The solid was suspended in diethyl ether (150.0 mL), filtered and washed thoroughly with diethyl ether and dried under reduced pressure to give **6** (1.85 g, 97%) as a white prisms: ^{1}H NMR (DMSO) 8.16 (1H, s, CH=Ph), 7.70 (2H, m, H_o), 7.43 (3H, m, $H_{m,p}$), 4.02 (2H, s, CH_2); ^{13}C NMR could not be taken because of the low solubility of the salt in DMSO.

***N-Boc-N'*-benzylglycine (8)[63;64]**



To a solution of glycine (0.75 g, 10.0 mmol), in anhydrous methanol were successively added benzaldehyde (1.02 mL, 10.0 mmol) and triethylamine (2.79 mL, 20.0 mmol). The solution was stirred at 20 °C until t.l.c. showed the absence of glycine (2 h). Sodium borohydride (0.76 g, 20.0 mmol) was then added in portions to the reaction mixture cooled to –5 °C, which was vigorously stirred for 3.5 h. The methanol was evaporated under reduced pressure and the residue dissolved in water/dioxane (1:2 30 mL). A solution of di-*tert*-butyl dicarbonate (2.4 g, 11.0 mmol) in dioxane/water (2:1 30 mL) was added dropwise to the stirred solution of benzylglycine at 0 °C, at such a rate that the pH was maintained at 9-10 by careful addition of 1 M sodium hydroxide. The mixture was allowed to warm to 20 °C and the pH was checked periodically and maintained at 9.0, if necessary by addition of further 1 M sodium hydroxide. Stirring was continued for 16 h and then the solvent was evaporated. The residual oil was dissolved in water (40 mL) and the solution extracted with diethyl ether (3 x 35 mL). The aqueous layer was acidified with citric acid to pH 3 and then extracted with ethyl acetate. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 1:1 ethyl acetate:petroleum ether) to give **8** (1.17 g, 71%) as white microprisms: mp 134 °C; ^{1}H NMR 7.26 (5H, m, Ph), 4.45 (2H, s, H_4), 3.77 (2H, s, H_6), 1.41 (9H, s, H_1); ^{13}C NMR 175.5 (C_5), 156.6 (C_3), 137.6 (C_7), 128.9 (C_9), 128.8 (C_8), 127.8 (C_{10}), 81.1 (C_2), 51.6 (C_6), 47.6 (C_4), 28.2 (C_1).

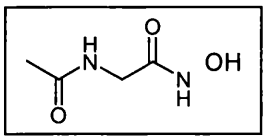
***N-Boc-N'*-benzylglycine hydroxamic acid (9)**



Hydroxylamine hydrochloride (0.63 g, 9.10 mmol) in methanol (9.0 mL) was added to a stirred solution of potassium hydroxide (0.53 g, 9.10 mmol) in methanol (5.0 mL) at 0 °C and stirred for 15 min. Potassium chloride was removed and the filtrate was used as such. To a solution of *N*-(*t*-butoxy)-benzylglycine (0.80 g, 4.80

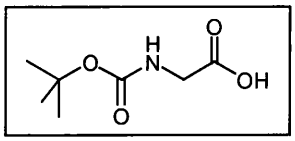
mmol) in diethyl ether (20.0 mL) at 0 °C were added ethyl chloroformate (0.55 mL, 5.70 mmol) and *N*-methylmorpholine (0.69 mL, 6.24 mmol) and the mixture was stirred for 15 min. The solid was filtered off and the filtrate was added to the freshly prepared hydroxylamine in methanol. The mixture was stirred at 20 °C for 4 h. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (silica gel, 3:7 ethyl acetate:petroleum ether) to give **9** (0.87 g, 65%) as pale yellow oil: IR ν_{max} (cm^{-1}) 3237 (N-OHr), 2982 (NH), 1749 (CO), 1687 (CO); ^1H NMR 9.92 (1H, br s, N-OH), 7.39 (5H, m, Ar), 4.66 (2H, s, CH_2Ph), 3.82 (2H, s, CH_2CO), 1.58 (($C\underline{H}_3)_3$); ^{13}C NMR 167.8 (C_5), 156.6 (C_3), 137.6 (C_7), 128.9 (C_9), 128.8 (C_8), 127.8 (C_{10}), 81.7 (C_2), 60.8 (C_6), 48.0 (C_4), 28.6 (C_1). LRMS M/Z (EI): 224 (M-$C(CH_3)_3$, 43%), 180 (20), 164 (38), 91 (73). HRMS Found: 280.14276 ($C_{14}H_{20}N_2O_4$ requires 280.14231).

_N_-Acetylglycine hydroxamic acid (15)



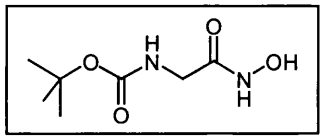
Hydroxylamine hydrochloride (4.40 g, 64.0 mmol) in methanol (50 mL) was added to a stirred solution of potassium hydroxide (3.6 g, 64.0 mmol) in methanol (40 mL) at 0 °C and stirred for 15 min. Potassium chloride was removed and the filtrate was used as such. To a solution of *N*-acetylglycine (5.0 g, 42.5 mmol) in diethyl ether (125 mL) at 0 °C were added ethyl chloroformate (4.8 mL, 50.9 mmol) and *N*-methylmorpholine (6.9 mL, 8.16 mmol) and the mixture was stirred for 15 min. The solid was filtered off and the filtrate was added to the freshly prepared hydroxylamine in methanol. The mixture was stirred at 20 °C for 2 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography 1 (silica gel, 1:1 ethyl acetate:petroleum ether) to give **18** (1.6 g, 30%) as white prisms: mp 124 °C; IR ν_{max} (cm^{-1}) (KBr) 3137 (N-OH), 2887 (N-H), 1665 (CO), 1635 (CO); ^1H NMR (D_2O) 3.92 (2H, s, CH_2), 2.15 (3H, s, CH_3); ^{13}CNMR (D_2O) 175.2 (C_2), 168.7 (C_4), 40.9 (C_3), 22.2 (C_1); LRMS M/Z (Fab +) 133 (MH^+, 100), 117 (30), 100 (55). Found C, 34.59, H, 5.75, N, 20.12, ($C_4H_8N_2O_3$ + ½ H_2O requires: C, 34.09, H, 5.67, N, 19.85).

***N-Boc* glycine (16)[64]**



A mixture of di-*tert*-butyl dicarbonate (3.0 g, 14.65 mmol) in a 2:1 ratio of dioxane:water (40.0 mL) was added dropwise to the stirred solution of glycine in 2:1 ratio of dioxane:water (40.0 ml) at 0 °C. The pH was maintained at 9-10 by careful addition of 1 M sodium hydroxide. The mixture was allowed to warm to 20 °C and the pH was checked periodically and adjusted at 9.0, if necessary, by the addition of further 1 M sodium hydroxide. Stirring was continued for 16 h, and the solvent was evaporated. The residual oil was dissolved in water and the solution extracted with diethyl ether (3 x 35 mL). The aqueous layer was acidified with citric acid to pH 3 and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and the solvent was evaporated to give **15** (2.33 g, 95%) as white prisms: mp 86-87 °C (lit[64] 87-88 °C); ^{1}H NMR 4.16 (2H, br. s, C$\underline{H_2}$C=O), 1.65 (9H, s, Boc), ^{13}C NMR 174.8 ($\underline{C}$=O), 156.4 (*t-boc* $\underline{C}$=O), 80.8 ($\underline{C}(CH_3)_3$), 42.6 ($\underline{C}H_2C$=O), 28.6 (C($\underline{C}H_3)_3$).

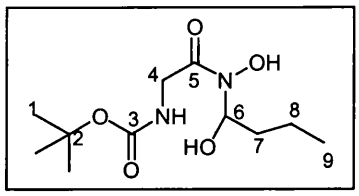
***N-Boc* glycine hydroxamic acid (17)**



Hydroxylamine hydrochloride (0.63 g, 9.50 mmol) in methanol (6.0 mL) was added to a stirred solution of potassium hydroxide (1.10 g, 9.50 mmol) in methanol (4.0 mL) at 0 °C. The mixture was stirred for 15 min at the same temperature. The precipitate of potassium chloride was removed and the filtrate was used as such. To a solution of *N*-(*t*-butoxy) glycine (1.10 g, 6.28 mmol) in diethyl ether (20.0 mL) at 0 °C were added ethyl chloroformate (0.72 mL, 7.53 mmol) and *N*-methylmorpholine (0.89 mL, 8.16 mmol) and the mixture was stirred for 15 min. The solid was filtered off and the filtrate was added to the freshly prepared hydroxylamine in methanol. The mixture was stirred at 20 °C for 30 min. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (silica gel, 1:1 ethyl acetate:petroleum ether first, pure ethyl acetate then) to give **16** (0.80 g, 68%) as white microprisms: mp 115-116 °C; IR ν_{max} (cm^{-1}) 3325 (NH str), 3179 (N-OH), 1670 (CO), 1663 (CO); ^{1}H NMR 3.95 (1H, s, C$\underline{H_2}$C=O conformer b), 3.77 (1H,

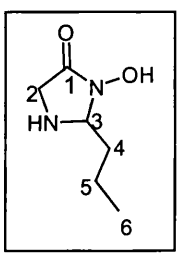
s, C<u>H</u>$_2$C=O conformer a), 1.37 (9H, s, Boc), ^{13}C NMR 169.9 (<u>C</u>=O), 157.7 (*t-boc* <u>C</u>=O), 80.7 (<u>C</u>(CH$_3$)$_3$), 52.6 (CH_2C=O), 28.6 (C(<u>C</u>H$_3$)$_3$). M/Z (EI): 190 (M-C(CH$_3$)$_3$, 35%), 146 (23), 130 (32), 86 (36), 57 (100). Found C, 43.94, H, 7.52, N, 14.24, ($C_9H_{22}N_2O_4$ requires C, 44.20, H, 7.42, N, 14.73).

{[Hydroxy-(1-hydroxybutyl)-carbamoyl]-methyl}-carbamic acid *tert* butyl ester (18).



To a solution of *N-Boc*-glycine hydroxamic acid (0.10 g, 0.57 mmol) in chloroform (5.0 mL), was added butyraldehyde (0.05 mL, 0.57 mmol). The mixture was stirred at 20 °C for 24 h. The solvent was removed under reduced pressure and the residue purified by column chromatography eluting with ethyl acetate and petroleum ester (1:1) to give **17** (40 mg, 35%) as a clear yellow oil: IR ν_{max} (cm^{-1}) 3235 (NH), 3219 (N-OH), 1686 (CO), 1628 (CO); ^{1}H NMR 9.48 (1H, br s, N-OH), 8.42 (1H, br s, NH), 6.10 (1H, m, H_6), 4.81 (1H, m, H_{4a}), 4.50 (1H, m, H_{4b}), 3.45 (1H, m, H_{7a}), 3.00 (1H, m, H_{7b}), 2.79 (1H, m, H_{8a}), 2.73 (9H, s, H_1), 2.62 (1H, m, H_{8b}). 2.33 (3H, t J = 6.7 Hz, H_9); ^{13}C NMR 172.6 (C_3), 156.8 (C_5), 88.6 (C_6), 80.8 (C_2), 42.4 (C_4), 30.7 (C_7), 28.7 (C_1), 19.7 (C_8), 13.9 (C_9). LRMS M/Z (Fab +) 245 (M-H_2O, 3 %), 189 (13), 158 (14), 88 (62), 57 (100). HRMS Found 245.15005 ($C_{11}H_{22}N_2O_5$ + H_2O requires 245.15013).

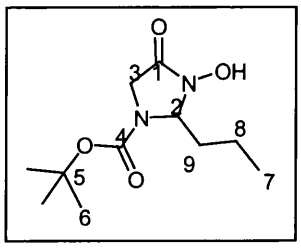
3-Hydroxy-2-butyl-5-methylimidazolidin-4-one (20)[62]



Glycine hydroxamic acid **2** (0.10 g, 1.20 mmol) was added to a solution of butyraldehyde (0.10 mL, 1.20 mmol) in isopropanol (15 mL). The mixture was heated at reflux for 4 h, filtered while hot and the filtrate concentrated under reduce pressure. Recrystallisation from ethanol gave **20** (0.10 g, 71%) as white prisms: mp 124 °C; IR ν_{max} (cm^{-1}) (KBr) 3186 (N-OH), 2872 (N-H), 1699 (CO); ^{1}H NMR (D_2O) 4.67 (1H,

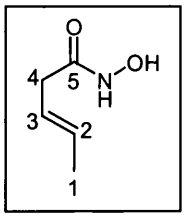
m, H_3), 3.56 (1H, d, J = 16 Hz, H_2), 3.64 (1H, d J = 16 Hz, $H_{2'}$), 2.01 (1H, m, H_4) 1.70 (1H, m, $H_{4'}$), 1.51 (2H. m. H_5), 1.14 (3H, t J = 6.5 Hz, H_6); ^{13}CNMR (D_2O) 172.1 (C_1), 75.5 (C_3), 46.1 (C_2), 34.5 (C_4), 24.2 (C_5), 16.9 (C_6). LRMS M/Z (Fab+) 145 (MH^+, 100), 127 (10), 84 (15), 44 (35). Found C, 44.86, H, 8.75, N, 17.48, ($C_4H_8N_2O_3$ + ½ H_2O requires: C, 44.43, H, 8.70, N, 17.27).

3-hydroxy-5-methyl-4-oxo-2-propylimidazilidine-1-carboxylic acid *tert* butyl ester (21)



To a solution of 3-hydroxy-2-methylimidazolidin-4-one (0.10 g, 0.63 mmol) in tetrahydrofuran (25 mL) the di-*tert*-butyl dicarbonate (0.15 mL, 0.69 mmol) was added dropwise and at such a rate the pH was maintained at 9-10 by addition of triethylamine (0.12 mL, 0.82 mmol). The mixture was stirred at room temperature for 12 h. The solvent was evaporated and the crude product purified by column chromatography (silica gel, 1:4:95/ water:methanol:ethyl acetate) to give **21** (80 mg, 50%) as pale yellow oil: IR ν_{max} (cm^{-1}) (KBr) 3186 (N-OH), 1780 (CO), 1699 (CO); ^{1}H NMR 5.72 (1H, t J = 6 Hz, H_2), 4.57 (1H, d J = 16 Hz, H_3), 4.45 (1H, d J= 16 Hz, $H_{3'}$) 1.62 (2H, m, H_9), 1.43 (9H, s, H_6), 1.23 (2H, m, H_9), 0.97 (3H, t J = 6.5 Hz, H_7); ^{13}C NMR 166.7 (C_1), 153.3 (C_4), 81.4 (C_5), 72.1 (C_2), 48.0 (C_3), 34.8 (C_9), 28.5 (C_8), 18.1 (C_6), 13.8 (C_7); LRMS M/Z (Fab+) 245 (MH^+, 18%), 188 (55), 168 (25), 98 (13), 57 (100); HRMS Found 244.14265 ($C_{11}H_{22}N_2O_4$ requires 244.14231).

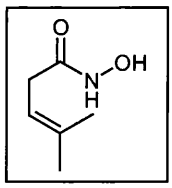
(*E*)-3-Pentenoic hydroxamic acid (22)



Hydroxylamine hydrochloride (1.03 g, 14.9 mmol) in methanol (15 mL) was added to a stirred solution of potassium hydroxide (0.8 g, 14.9 mmol) in methanol (12 mL) at 0 °C and stirred for 15 min. The potassium chloride was removed and the filtrate was used as such. To a solution of (*E*)-3-pentanoic acid (1.0 g, 9.9 mmol) in diethyl ether

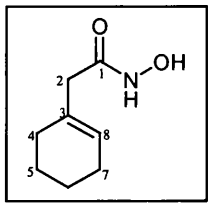
(25 mL) at 0 °C were added ethyl chloroformate (1.4 mL, 11. mmol) and *N*-methylmorpholine (1.52 mL, 12.9 mmol) and the mixture was stirred for 15 min. The solid was filtered off and the filtrate was added to the freshly prepared hydroxylamine in methanol. The mixture was stirred at 20 °C for 2 h. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (silica gel, 1:1 ethyl acetate: petroleum ether) to give **22** (0.70 g, 61%) as white microprisms: mp 92 °C; IR ν_{max} (cm^{-1}) (KBr) 3217 (N-OH), 3218 (N-H), 2367 (C=C), 1623 (CO str); ^{1}H NMR 5.61 (1H, m, H_2), 5.40 (1H, m, H_3), 2.79 (2H, d J = 8.0, Hz, H_4), 1.58 (3H, d J = 1.5 Hz, H_1); ^{13}C NMR 168.2 (C_5), 131.7 (C_3), 122.6 (C_2), 36.7 (C_4), 17.6 (C_1); LRMS M/Z (Fab) 116 (MH^+, 100), 102 (13), 54 (35). Found C, 51.88, H, 7.02, N, 12.54, ($C_5H_9NO_2$ requires C, 52.18, H, 6.80, N, 12.17).

4-Methylpent-3-enoic hydroxamic acid (23)



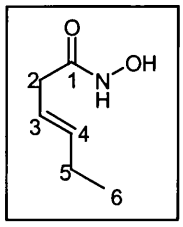
Hydroxylamine hydrochloride (0.54 g, 7.89 mmol) in methanol (5.0 mL) was added to a stirred solution of potassium hydroxide (0.44 g, 7.89 mmol) in methanol (2.0 mL) at 0 °C and stirred for 15 min. The potassium chloride was removed and the filtrate was used as such. To a solution of 4-methyl-3-pentenoic acid (0.60 g, 5.26 mmol) in diethyl ether (15 mL) at 0 °C were added ethyl chloroformate (0.6 mL, 6.31 mmol) and *N*-methylmorpholine (0.71 mL, 6.84 mmol) and the mixture was stirred for 15 min. The solid was filtered off and the filtrate was added to the freshly prepared hydroxylamine in methanol. The mixture was stirred at 20 °C for 25 min. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (silica gel, 1:1 ethyl acetate: petroleum ether) to give **23** (0.34g, 50%) as white microprisms: mp 97 °C; IR ν_{max} (cm^{-1}) (KBr) 3217 (N-OH str), 3218 (NH), 2367 (C=C), 1623 (CO); ^{1}H NMR 5.23 (2H, m, CH), 2.88 (2H, br d, CH_2), 1.67 (3H, br s, CH_3), 1.57 (3H, br s, CH_3); ^{13}C NMR 169.2 (CO) 138.4 (C), 115.4 (CH), 33.2 (CH_2), 26.5 (CH_3), 18.3 (CH_3). Found C, 55.60, H, 7.96, N, 10.44, ($C_6H_{11}NO_2$ requires C, 55.78, H, 8.59, N, 10.85).

Cyclohex-1-enyl-*N*-hydroxyacetamide (24)



Hydroxylamine hydrochloride (1.96 g, 28.4 mmol) in methanol (4.5 mL) was added to a stirred solution of potassium hydroxide (1.65 g, 28.4 mmol) in methanol (1.8 mL) at 0 °C and stirred for 15 min. Potassium chloride was removed and the filtrate was used as such. To a solution of cyclohex-1-eneacetic acid (2.65 g, 18.9 mmol) in diethyl ether (14.0 mL) at 0 °C were added ethyl chloroformate (1.99 mL, 20.8 mmol) and *N*-methylmorpholine (2.15mL, 20.8 mmol) and the mixture was stirred for 25 min. The solid was filtered off and the filtrate was added to the freshly prepared hydroxylamine in methanol. The mixture was stirred at 20 °C for 1.5 h. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (silica gel, 7:3 ethyl acetate:petroleum ether) to give **23** (1.32 g, 22%) as white microprisms: mp 114-115 °C; IR ν_{max} (cm^{-1}) (KBr) 3224 (N-OH str), 3228 (N-H str), 1621 CO str; ^{1}H NMR 6.21 (1H, br m, H_8), 5.06 (1H, br s, N-H), 2.94 (2H, br s, CH_2CO), 2.21 (4H, br,m, H_4 + H_7), 1.82 (4H, br m, H_5 + H_6); ^{13}C NMR 171.4 (C1), 133.3 (C3), 126.9 (C8), 43.5 (C2), 29.5 (C4), 26.7 (C7), 24.3 (C6), 23.6 (C5). Found C, 61.47 H, 8.24, N, 8.57, ($C_8H_{13}NO_2$ requires C, 61.89, H, 8.45, N, 9.03).

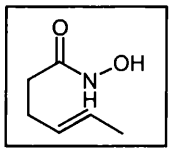
Hex-3-enoic hydroxamic acid (25)



Hydroxylamine hydrochloride (2.72 g, 39.4 mmol) in methanol (25 mL) was added to a stirred solution of potassium hydroxide (2.30 g, 39.4 mmol) in methanol (12.0 mL) at 0 °C and stirred for 15. Potassium chloride was removed and the filtrate was used as such. To a solution of hex-3-enoic acid (3.4 g, 29.8 mmol) in diethyl ether (75 mL) at 0 °C were added ethyl chloroformate (2.75 mL, 28.7 mmol) and *N*-methylmorpholine (3.46 mL, 31.5 mmol) and the mixture was stirred for 15 min. The solid was filtered off and the filtrate was added to the freshly prepared hydroxylamine in methanol. The mixture was stirred at 20 °C for 30 min.

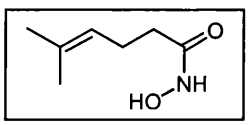
The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (ssilica gel, 3:7 ethyl acetate:petroleum ether) to give **25** (1.8 g, 48%) as white microprisms: mp 78-80 °C (lit[71] mp 75-77 °C); ^{1}H NMR 8.14 (1H, br s, N-O<u>H</u>), 5.74 (1H, m, H_3), 5.37 (1H, m, H_2), 2.85 (2H, d, J = 3 Hz, H_2), 1.98 (2H, m, H_5), 0.91 (3H, t, J = 6 Hz, H_6); ^{13}C NMR 170.4 (C_1), 138.9 (C_3), 120.2 (C_4), 37.4 (C_2), 25.9 (C_5). 13.7 (C_6).

Hex-4-enoic hydroxamic acid (26)



Hydroxylamine hydrochloride (0.35 g, 5.3 mmol) in methanol (3.0 mL) was added to a stirred solution of potassium chloride (0.3 g, 5.3 mmol) in methanol (1.0 mL) at 0°C and stirred for 15 min. Potassium chloride was removed and the filtrate was used as such. To a solution of 5-methylpentenoic acid (0.40 g, 3.5 mmol) in diethyl ether (26 mL) at 0 °C were added ethyl chloroformate (0.40 mL, 4.2 mmol) and *N*-methylmorpholine (0.46 mL, 4.2 mmol) and the mixture was stirred for 15 min. The solid was filtered off and the filtrate was added to the freshly prepared hydroxylamine in methanol. The mixture was stirred at 20 °C for 15 min. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (3:7 ethyl acetate:petroleum ether) to give **26** (0.16 g, 37%) as white plates: mp 76-78°C; IR ν_{max} (cm^{-1}) (KBr) 1633 (CO); ^{1}H NMR 9.51 (N-OH), 5.60 (2H, m, CH=CH), 2.44 (2H, s bd, CHC<u>H</u>$_2$), 2.37 (2H, s bd, CH_2CO), 1.79 (3H, s br, CH_3); ^{13}C NMR 171.85 (CO), 129.3 (CH_3<u>C</u>H), 127.1 (<u>C</u>HCH_2), 33.4 (<u>C</u>H_2CO), 28.6 (CH<u>C</u>H_2), 18.2 (CH_3). Found C, 55.14, H, 8.51, N, 10.69, ($C_6H_{11}NO_2$ requires C, 55.78, H, 8.58, N, 10.84).

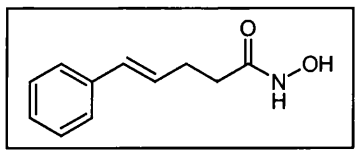
5-Methylhex-4-enoic-hydroxamic acid (27)



Hydroxylamine hydrochloride (0.76 g, 11.7 mmol) in methanol (6.0 mL) was added to a stirred solution of potassium hydroxide (0.70 g, 11.7 mmol) in methanol (2.0 mL) at 0 °C and

stirred for 15 min. Potassium chloride was removed and the filtrate was used as such. To a solution of 5-methylhex-4-enoic acid (1.0 g, 7.8 mmol) in diethyl ether (52 mL) at 0 °C were added ethyl chloroformate (0.80 mL, 8.4 mmol) and *N*-methylmorpholine (1.0 mL, 9.1 mmol) and the mixture was stirred for 15 min. The solid was filtered off and the filtrate was added to the freshly prepared hydroxylamine in methanol. The mixture was stirred at 20 °C for 1 h. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (silica gel, 1:1 ethyl acetate:petroleum ether) to give **27** (0.71 g, 68%) as white microprisms: mp 60-61 °C; IR ν_{max} (cm^{-1}) (KBr) 1645 (C=C), 1622 (CO); ^{1}H NMR 9.12 (OH), 5.22 (1H, m, CH=C), 2.48 (2H, m, CH=C$\underline{H_2}$), 2.31 (2H, m, CH_2CO), 1.83 (3H, s, *cis* CH_3), 1.76 (3H, s, *trans* CH_3); ^{13}C NMR 172.1 (CO), 133.9 ($\underline{C}$=CH_2), 122.4 (C=$\underline{C}H_2$), 33.5 ($\underline{C}H_2CO$), 25.9 (CH_3 *cis*), 24.4 ($CH\underline{C}H_2$), 17.9 (*trans* CH_3); LRMS M/Z: (Fab +): 147 (20), 130 (100), 114 (25), 69 (50). Found C, 57.82, H, 8.83, N, 9.76, ($C_7H_{13}NO_2$ + 1/3 H_2O requires C, 57.53, H, 8.94, N, 9.39).

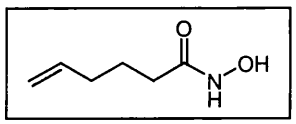
5-Phenylpent-4-enoic hydroxamic acid (28)



Hydroxylamine hydrochloride (0.53 g, 7.7 mmol) in methanol (5.1 mL) was added to a stirred solution of potassium hydroxide (0.43 g, 7.7 mmol) in methanol (2.0 mL) at 0 °C and stirred for 15 min. Potassium chloride was removed and the filtrate was used as such. To a solution of 5-phenylpent-4-enoic acid (0.90 g, 5.1 mmol) in diethyl ether (15 mL) at 0 °C were added ethyl chloroformate (0.54 mL, 5.6 mmol) and *N*-methylmorpholine (0.67 mL, 6.1 mmol) and the mixture was stirred for 15 min. The solid was filtered off and the filtrate was added to the freshly prepared hydroxylamine in methanol. The mixture was stirred at 20 °C for 15 min. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (silica gel, 7:3 ethyl acetate:petroleum ether) to give **28** (0.28 g, 50%) as white needles: mp 107-109 °C; IR ν_{max} (cm^{-1}) (KBr) 3223 (Ar), 1658 (CO); ^{1}H NMR 8.75 (1H, br s, OH), 7.25 (5H, m, Ar), 6.43 (1H, d, J = 6 Hz, CH-Ph), 6.10 (1H, m, CH=CH), 2.52 (2H, m, CH $C\underline{H_2}$), 2.34-2.17 (2H, m, CH_2-CO); ^{13}C NMR 172.2 (CO), 138.9 (CH-Ph), 133.6 (C_i), 131.2 (CH=$\underline{C}$H), 128.8 (C_m), 127.5

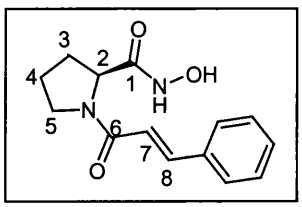
(C_o), 126.5 (C_p), 30.2 ($\underline{C}H_2$-CO), 28.6 (CH-$\underline{C}H_2$). Found C, 63.44, H, 7.51, N, 8.01, ($C_{11}H_{13}NO_2$ + ½ H_2O requires C, 63.14, H, 7.23, N, 7.69).

Hex-5-enoic acid hydroxyamide (29)



Hydroxylamine hydrochloride (0.47 g, 6.8 mmol) in methanol (4.6 mL) was added to a stirred solution of potassium hydroxide (0.51 g, 6.8 mmol) in methanol (1.8 mL) at 0 °C and stirred for 15 min. Potassium chloride was removed and the filtrate was used as such. To a solution of hex-5-enoic acid (0.52 g, 4.6 mmol) in diethyl ether (15 mL) at 0 °C were added ethyl chloroformate (0.48 mL, 5.0 mmol) and *N*-methylmorpholine (0.60 mL, 5.5 mmol) and the mixture was stirred for 15 min. The solid was filtered off and the filtrate was added to the freshly prepared hydroxylamine in methanol. The mixture was stirred at 20 °C for 30 min. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (silica gel, 7:3 ethyl acetate:petroleum ether) to give **29** (0.28 g, 50%) as a colourless oil: IR ν_{max} (cm^{-1}) (KBr) 1667 (CO), 1654 (CO); ^{1}H NMR 9.15 (N-OH), 5.68 (1H, m, CH_2=C$\underline{H}$), 4.91 (2H, t, J = 6 Hz, $C\underline{H_2}$=CH), 2.08 (2H, t, J = 6 Hz, CH_2=CH-C$\underline{H_2}$), 1.99 (CH_2CO), 1.61 (2H, m, $C\underline{H_2}$-CH_2CO); ^{13}C NMR 172.4 (CO), 137.9 (CH_2=$\underline{C}$H), 115.9 ($\underline{C}H_2$=CH), 33.3 (CH_2=CH-$C\underline{H_2}$), 32.6 (CH_2CO), 24.9 ($C\underline{H_2}$-CH_2CO). HRMS Found 129.07877 ($C_6H_{11}NO_2$ requires 129.07898).

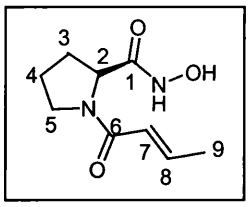
(*S*)-Cinnamoylproline hydroxamic acid (30)



Hydroxylamine hydrochloride (55.0 mg, 0.8 mmol) in methanol (0.5 mL) was added to a stirred solution of potassium hydroxide (45.0 mg, 0.8 mmol) in methanol (0.2 mL) at 0 °C and stirred for 15 min. Potassium chloride was removed and the filtrate was used as such. To a solution of (*S*)-cinnamoylproline (0.19 g, 0.5 mmol) in diethyl ether (2.0 mL) at 0 °C were added ethyl chloroformate

(0.06 mL, 0.6 mmol) and *N*-methylmorpholine (0.08 mL, 0.70 mmol) and the mixture was stirred for 15 min. The solid was filtered off and the filtrate was added to the freshly prepared hydroxylamine in methanol. The mixture was stirred at 20 °C for 1.5 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (silica gel, 7:3 ethyl acetate:petroleum ether) to give **30** (92.3 mg, 58%) as a white microprisms: mp 176-178 °C; IR ν_{max} (cm^{-1}) 3128 (N-OH str), 1656 (C=O str); ^{1}H NMR (CD_3OD): 7.95 (1H, d, J = 15 Hz, H_7), 7.561 (5H, m, Ph), 7.14 (1H, d, J = 15 Hz, H_8), 4.61 (1H, br d, J = 6 Hz, H_2), 4.03 (2H, m, H_5), 3.49 (1H, m, H_3), 2.18-2.35 (3H, m, H_3 and H_4); ^{13}C NMR (CD_3OD): 172.1 (C_6), 167.9 (C_1), 144.3 (C_7), 136.8 (C_i), 131.5 (C_m), 130.7(C_p), 129.5 (C_o), 119.6 (C_8), 60.2 (C_2), 47.9 (C_5), 31.2 (C_3), 26.2 (C_4). LRMS M/Z (Fab +) 261 (M+1, 55%), 228 (25), 200 (19). Found C, 63.03, H, 6.36, N, 10.54, ($C_{14}H_{16}N_2O_3$ + 1/3 H_2O requires: C, 63.15, H, 6.26, N, 10.52).

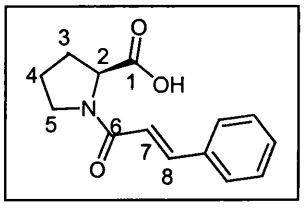
(*S*)-*N*-Crotonylproline hydroxamic acid (31)



Hydroxylamine hydrochloride (55.0 mg, 0.8 mmol) in methanol (0.5 mL) was added to a stirred solution of potassium hydroxide (45.0 mg, 0.8 mmol) in methanol (0.2 mL) at 0 °C and stirred for 15 min. Potassium chloride was removed and the filtrate was used as such. To a solution of (*S*)-crotonylproline (0.10 g, 0.5 mmol) in diethyl ether (2.0 mL) at 0 °C were added ethyl chloroformate (0.06 mL, 0.6 mmol) and *N*-methylmorpholine (0.08 mL, 0.7 mmol) and the mixture was stirred for 15 min. The solid was filtered off and the filtrate was added to the freshly prepared hydroxylamine in methanol. The mixture was stirred at 20 °C for 1.5 h. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (silica gel, 7:3 ethyl acetate:petroleum ether) to give **31** (40 mg, 37%) as white microprims: mp 112-114 °C; IR ν_{max} (cm^{-1}) 3298 (N-OH str), 1685 (C=O str); ^{1}H NMR 8.69 (1H, br s, NH), 7.78 (1H, m, H_7), 6.14 (1H, d, J = 15 Hz, H_8), 5.08 (1H, br s, OH), 4.56 (1H, br d, J = 6 Hz, H_2), 3.58 (2H, m, H_5), 2.22 (3H, m, H_3 and H_4), 2.07 (1H, m, H_3), 1.88 (3H, dd, J = 6.9 Hz, J= 1.5 Hz H_9); ^{13}C NMR 169.7 (C_6), 166.7 (C_1), 143.6 (C_7), 122.6 (C_8), 57.9 (C_2), 47.8 (C_5), 28.1 (C_3), 25.3

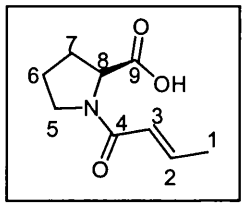
(C_4), 18.6 (C_9). LRMS M/Z (Fab +) 199 (M+1, 100%), 166 (85). Found C, 54.23, H, 7.12, N, 14.13, ($C_{14}H_{16}N_2O_3$ requires: C, 54.53, H, 6.96, N, 14.58).

(*S*)-*N*-Cinnamoylproline (33)[65]



A solution of (*S*)-proline (0.10 g, 0.9 mmol) in 2 M aqueous sodium hydroxide (0.60 mL 1,1 mmol,) was cooled in an ice-bath and diluted with acetone (0.6 mL). An acetone solution (0.6 mL) of cinnamoyl chloride (0.16 g, 0.9 mmol) and 2 M aqueous sodium hydroxide (1.22 mmol, 0.7 mL) were simultaneously added over 20 min with good stirring to the aqueous proline in the ice-bath. After 3 h at room temperature, the mixture was evaporated under reduced pressure to remove the acetone. The residual solution was extracted with diethyl ether (2 x 5 mL) and then acidified (pH 2) with conc. hydrochloric acid. The acidic mixture, after saturation with sodium chloride, was extracted with ethyl acetate (3 x 15 mL); the combined extracts were washed with brine and evaporated. Recrystallization of the crude product from methanol gave **33** (0.12 g, 58%) as white needles: mp 187-189 °C (lit[72] 184-185 °C); ^{1}H NMR 9.42 (1H, br s, H_1), 7.78 (1H, d, J = 15 Hz, H_7), 7.37 (5H, m, Ph), 6.61 (1H, d, J = 15 Hz, H_8), 4.52 (1H, br d, J = 6 Hz, H_2), 3.60 (2H, m, H_5), 2.31 (1H, m, H_3), 1.85-2.07 (3H, m, H_3 and H_4); ^{13}C NMR 172.9 (C_6), 167.9 (C_1), 145.3 (C_7), 135.0 (C_i), 130.8 (C_m), 129.1 (C_p), 128.4 (C_o), 117.0 (C_8), 60.7 (C_2), 48.2 (C_5), 28.0 (C_3), 25.2 (C_4).

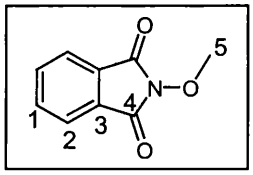
(*S*)-*N*-Crotonylproline (34)[65]



A solution of (*S*)-proline (1.0 g, 8.7 mmol) in 2 M aqueous sodium hydroxide (5.1 mL, 10.4 mmol) was cooled in an ice-bath and diluted with acetone (5.3 mL). An acetone solution (5.3 mL) of crotonyl chloride (0.83 mL, 9.5 mmol) and 2 M aqueous sodium hydroxide (6.3 mL, 12.2 mmol) were simultaneously added over 20 min with good stirring to the aqueous proline in the ice-bath. After 3 h at room temperature,

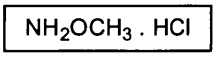
the mixture was evaporated under reduced pressure to remove the acetone. The residual solution was extracted with diethyl ether (2 x 25 mL) and then acidified (pH 2) with conc. hydrochloric acid. The acidic mixture, after saturation with sodium chloride, was extracted with ethyl acetate (3 x 25 mL); the combined extracts were washed with brine and evaporated. Recrystallization of the crude product from methanol gave **34** (0.95 g, 60%) as white plates: mp 132 °C (lit[72] mp 132-134 °C); ^{1}H NMR 6.90 (1H, m, H_2), 6.07 (1H, dd, J = 15 Hz, J = 1.5 Hz, H_3), 4.58 (1H, m, H_8), 3.58 (2H, m, H_5), 2.38 (1H, m, H_7), 1.99 (3H, m, H_7, H_8), 1.86 (3H, dd J = 6.9 Hz, J = 1.5 Hz, H_1); ^{13}C NMR 174.0 (C_9), 165.6 (C_4), 142.2 (C_3), 122.3 (C_2), 59.3 (C_8), 47.1 (C_5), 27.6 (C_7), 24.6 (C_6), 17.8 (C_1).

2-Methoxyisoindole-1,3-dione (35)[66]



Anhydrous potassium carbonate (2.21 g, 16.0 mmol) was added slowly to a stirred solution of *N*-hydroxyphthalimide (4.10 g, 25.0 mmol) in dimethyl sulfoxide (30 mL). Iodomethane (1.70 mL, 42.5 mmol) was added dropwise to the reddish brown solution at the rate such that the temperature did not exceed 30 °C. The mixture was stirred at room temperature for 24 h, then poured into cold water (20 mL) and left to stand at 0 °C for 4 h. The crystals were filtered, washed with water and dried under vacuum to recover **35** (4.41 g, 92 %) as white microprisms: mp 129 °C (lit[66] mp 132 °C); ^{1}H NMR 7.88 (2H, m, H_2), 7.74 (2H, m, H_1), 4.06 (3H, s, H_5); ^{13}C NMR 163.2 (C_4), 134.5 (C_2), 128.8 (C_3), 123.5 (C_1), 65.7 (C_5).

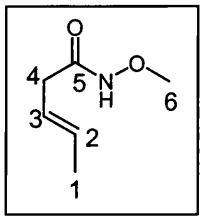
***O*-Methylhydroxylamine (36)[66]**



A solution of *N*-methoxyphthalimide (4.10 g, 23.0 mmol), in aqueous hydrochloric acid (6 M, 42.0 mL) was heated at reflux for 30 min. The mixture was allowed to cool, then kept below 0 °C for 12 h. The white precipitate

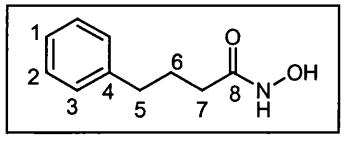
was filtered and washed with cold water (2 x 20 mL). The filtrate and washings were combined and extracted with dichloromethane (3 x 100 mL). The water was then evaporated under reduced pressure and the residual crystals were dried under vacuum to a constant weight. Recrystallization from ethanol and diethyl ether (1:9) gave **36** (1.20 g, 63 %) as white plates: mp 150 °C (lit[73] mp 148 °C); ^{1}H NMR (D_2O) 4.83 (NH_3 +H_2O), 3.96 (CH_3).

Pent-3-enoic acid methoxyamide (37)



The pent-3-enoic hydroxamic acid (0.64 g, 5.6 mmol) was dissolved in methanol (15.0 mL), potassium carbonate (0.84 g, 6.1 mmol) and iodomethane (0.34 mL, 5.6 mmol) were added and the mixture was stirred for 28 h. The solution was then concentrated under reduced pressure and the remaining oil was dissolved in ethyl acetate (25 mL) and water (25 mL). The organic layer was washed with water (2 x 25 mL) then brine, dried, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 3:7 ethyl acetate:petroleum ether) to give **37** (0.37 g, 51 %) as a colourless oil: IR: ν_{max} (cm^{-1}) (KBr) 1622 (CO); ^{1}H NMR 9.69 (1H, br s, NH), 5.83-5.66 (2H, m, H_3, H_2), 3.92 (3H, s, H_6), 3.06 (2H, br s, H_4), 1.85 (3H, d, J = 6 Hz, H_1); ^{13}C NMR 169.6 (C_5), 130.1 (C_2), 123.1 (C_3), 64.1 (C_6), 37.3 (C_4), 17.9 (C_1). HRMS Found 129.07845 ($C_6H_{11}NO_2$ requires 129.07898).

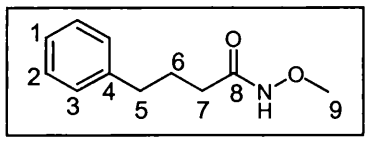
***N*-Hydroxy-4-phenylbutyramide (38)**



Hydroxylamine hydrochloride (0.63 g, 9.5 mmol) in methanol (6.0 mL) was added to a stirred solution of potassium hydroxide (0.51 g, 9.5 mmol) in methanol (3.0 mL) at 0 °C and stirred for 15 min. Potassium chloride was removed and the filtrate was used as such. To a solution of 4-phenylbutyric acid (1.0 g, 6.1 mmol) in diethyl

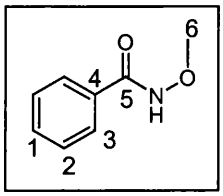
ether (20 mL) at 0 °C were added ethyl chloroformate (0.70 mL, 7.3 mmol) and *N*-methylmorpholine (0.87 mL, 7.9 mmol) and the mixture was stirred for 15 min. The solid was filtered off and the filtrate was added to the freshly prepared hydroxylamine in methanol. The mixture was stirred at 20 °C for 30 min. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (silica gel, 4:95:1 methanol:ethyl acetate:water) to give **38** (0.70 g, 63%) as a white solid: mp 82 °C; IRν_{max} (cm^{-1}) (KBr) 2856 (Ar), 1689 (CO); ^{1}H NMR 9.09 (1H, br s, NH), 7.23-7.00 (5H, m, Ph), 2.55 (2H, t J = 6.2 Hz, H_7), 2.06 (2H, t, J = 6.7 Hz, H_5), 1.87 (2H, m, H_6); ^{13}C NMR 169.6 (C_8), 141.5 (C_4), 128.8 (C_3 + C_2), 126.4 (C_1), 35.5 (C_7), 32.7 (C_5), 27.2 (C_6). Found C, 67.45, H, 7.24, N, 7.86, ($C_{10}H_{13}NO_2$ requires C, 67.02, H, 7.31, N, 7.82).

_N_-Methoxy-4-phenylbutyramide (39)



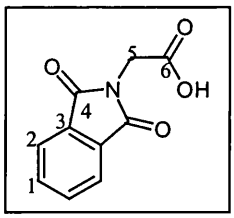
4-Phenylbutyric hydroxamic acid (1.0 g, 5.6 mmol) was dissolved in methanol (15 mL), potassium carbonate (0.85 g, 6.1 mmol) and iodomethane (0.35 mL, 5.6 mmol) were added and the mixture was stirred for 24 h. The solution was then concentrated under reduced pressure and the remaining oil was dissolved in ethyl acetate (25 mL) and water (25 mL). The organic layer was washed with water (2 x 25 mL) brine, dried, filtered and concentrated under reduced pressure. The crude was purified by column chromatography (silica gel, 5:95 methanol:chloroform) to give **39** (0.57 g, 54%) as white microprisms: mp 60-62 °C (lit[19] mp 58-60 °C); ^{1}H NMR 8.11 (1H, br s, NH), 7.27 (2H, m, Ar), 7,18 (3H, m, Ar), 3.96 (3H, s, H_9), 2.67 (2H, t, J = 6 Hz, H_5), 2.13 (2H, br m, H_7), 1.98 (2H, m, H_6); ^{13}C NMR 169.5 (C_8), 141.06 (C_4), 128.38 (C_1), 128.31 (C_2), 125.8 (C_3), 64.3 (C_9), 34.8 (C_5), 33.0 (C_7), 26.2 (C_6).

N-Methoxybenzamide (40)



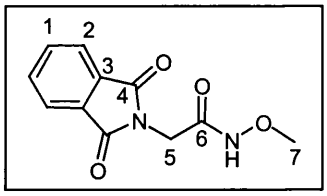
Benzoic hydroxamic acid (1.10 g, 8.0 mmol) was dissolved in methanol (20 mL), potassium carbonate (1.22 g, 8.8 mmol) and iodomethane (0.50 mL, 8.0 mmol) were added and the mixture was stirred for 16 h. The solution was then concentrated under reduced pressure and the remaining solid was dissolved in ethyl acetate (35 mL) and water (35 mL). The organic layer was washed with water (2 x 35 mL) brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 2:8 ethyl acetate:toluene) to give **40** (0.45 g, 38 %) as white microprisms: mp 102-104 °C (lit[56] mp 102 °C); ^{1}H NMR 9.96 (1H, br s, NH), 7.60 (2H, d, J = 6 Hz, H_3), 7.34 (1H, m, H_1), 7.23 (2H, m, H_2), 3.78 (3H, s, CH_3); ^{13}C NMR 166.5 (C_5), 131.7 (C_4), 128.5 (C_3, C_2), 127.1 (C_1), 64.2 (C_6).

N-Phthaloylglycine (41)[67]



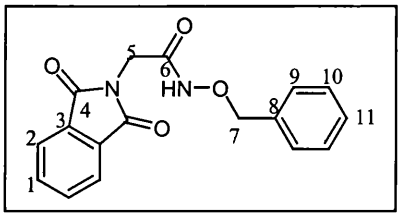
A suspension of phthalyc anhydride (3.70 g, 25.0 mmol), glycine (2.25 g, 30.0 mmol), and pyridine (5.0 mL) was heated at 95 °C for 20 hours. The mixture was then allowed to cool to ambient temperature before the sequential addition of 50 mL of water and 5 mL of conc. hydrochloric acid. The resulting mixture was extracted with ethyl acetate (3 x 15 mL) and the combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Recrystallisation from benzene gave **41** (4.56 g, 89 %) as white microprisms: mp 189-192 °C; (lit[67] mp 190-192 °C); ^{1}H NMR (DMSO) 7.86 (2H, m, H_1), 7.74 (2H, m, H_2), 4.47 (2H, s, H_5); ^{13}C NMR (DMSO) 169.2 (C_6), 167.6 (C_4), 135.2 (C_3), 131.8 (C_1), 123.7 (C_2), 39.3 (C_5).

2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-*N*-methoxyacetamide (42)



O-Methylhydroxylamine hydrochloride (1.0 g, 11.9 mmol) in methanol (8.2 mL) was added to a stirred solution of potassium hydroxide (0.70 g, 11.9 mmol) in methanol (3.3 mL) at 0 °C and stirred for 15 min. Potassium chloride was removed and the filtrate was used as such. To a solution of *N*-phthaloylglycine (1.60 g, 7.9 mmol) in diethyl ether (28 mL) at 0 °C were added ethyl chloroformate (0.91 mL, 9.6 mmol) and *N*-methylmorpholine (1.15 mL, 10.4 mmol) and the mixture was stirred for 15 min. The solid was filtered off and the filtrate was added to the freshly prepared hydroxylamine in methanol. The mixture was stirred at 20 °C for 1 h. The hydroxamic acid **42** (1.10 g, 62%) precipitated from the reaction as white microprisms: mp 196-198 °C; IR ν_{max} (cm^{-1}) (KBr) 3150 (Ar), 2877 (NH), 1669 (CO), 1612 (CO); ^{1}H NMR (DMSO) 7.73(4H, m, Ar), 3.44 (3H, s, H_7), 3.14 (2H, s, H_5); ^{13}C NMR (DMSO) 167.7 (C_4), 163.5 (C_6), 135.0 (C_2), 132.0 (C_3), 123.6 (C_1), 63.7 (C_7), 38.6 (C_5). Found C, 54.51, H, 4.17, N, 11.66, ($C_{11}H_{10}N_2O_4$ + 1/3 H_2O requires C, 55.00, H, 4.44, N, 11.66)

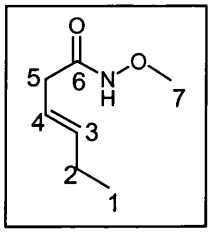
***N*-Benzyloxy-2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-acetamide (43)**



Benzylhydroxylamine hydrochloride (0.34 g, 2.2 mmol) in methanol (1.5 mL) was added to a stirred solution of potassium hydroxide (0.13 g, 2.2 mmol) in methanol (0.6 mL) at 0 °C and stirred for 15 min. Potassium chloride was removed and the filtrate was used as such. To a solution of *N*-phthaloylglycine (0.30 g, 1.5 mmol) in diethyl ether (5.0 mL) at were added 0 °C ethyl chloroformate (0.17 mL, 1.7 mmol) and *N*-methylmorpholine (0.19 mL, 1.8 mmol) and the mixture was stirred for 15 min. The solid was filtered off and the filtrate was added to the freshly prepared hydroxylamine in methanol. The mixture was stirred at 20 °C for 1 h. The hydroxamic acid **43** (0.25 g, 61%) precipitated from the reaction as white plates: mp 198-199 °C; IR ν_{max} (cm^{-1}) (KBr) 3143 (Ar), 2853 (NH), 1680 (CO); ^{1}H NMR

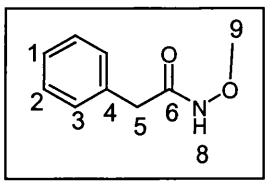
(DMSO 100 °C) 11.01 (1H, s, NH), 7.86 (4H, m, H_3 H_4), 7.37 (5H, m, Ph), 4.86 (2H, s, H_7), 4.25 (2H, s, H_5); ^{13}C NMR 166.6 (C_6), 163.9 (C_4), 135.2 (C_8), 133.8 (C_{11}), 128.1 (C_1), 127.6 (C_2), 127.6 (C_{10}), 122 .4 (C_9), 76.9 (C_7), 37.8 (C_5). Found C, 65.45, H, 4.29, N, 9.76, ($C_{17}H_{14}N_2O_4$ requires C, 65.80, H, 4.55, N, 9.03).

Hex-3-enoic acid methoxyamide (44)



Hex-3-enoic hydroxamic acid (1.0 g, 7.7 mmol) was dissolved in methanol (20 mL), potassium carbonate (2.14 g, 15.5 mmol) and iodomethane (0.48 mL, 7.7 mmol) were added and the mixture was stirred for 24 h. The solution was then concentrated under reduced pressure and the remaining solid was dissolved in ethyl acetate (35 mL) and water (35 mL). The organic layer was washed with water (2 x 35 mL) brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 1:1 ethyl acetate:petroleum ether) to give **44** (0.70 g, 64%) as colourless oil: IR ν_{max} (cm^{-1}) (KBr) 2133 (NH), 1654 (CO); ^{1}H NMR 9.96 (1H, br s, NH), 5.54 (1H, m, H_4), 5.42 (1H, m, H_3), 3.64 (3H, br s, H_7), 2.7 (2H, br s, H_5), 1.95 (br d, J = 6 Hz, 2H, H_2), 0.87 (3H, br t, J = 7 Hz, H_1). ^{13}C NMR 169.4 (C_6), 136.9 (C_4), 120.7 (C_3), 63.9 (C_7), 37.0 (C_5), 25.4 (C_2), 13.3 (C_1). LRMS M/Z (EI): 142 (15), 96 (65), 69 (100), 41 (100). HRMS = 142.08664. ($C_{14}H_{21}NO_3$ requires 142.08686).

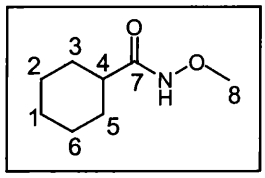
***N*-Methoxy-2-phenylacetamide (45)**



Phenylacetic hydroxamic acid (0.30 g, 1.9 mmol) was dissolved in methanol (5.0 mL), potassium carbonate (0.30 g, 2.2 mmol) and iodomethane (0.12 mL, 1.9 mmol) were added and the mixture was stirred for 24 h. The solution was then concentrated under reduced pressure and the remaining solid was dissolved in ethyl

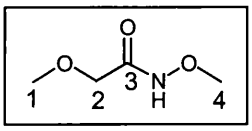
acetate (15 mL) and water (15 mL). The organic layer was washed with water (2 x 15 mL) brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude was purified by column chromatography (silica gel, 3:7 ethyl acetate:petroleum ether) to give **45** (0.17 g, 52%) as white prisms: mp 92-94 °C (lit[74] mp 90-92 °C); ^{1}H NMR 9.80 (1H, br s, H_8), 7.31 (5H, br s, Ar), 3.71 (3H, s, CH_3), 3.46 (2H, s, CH_2); ^{13}C NMR 169.3 (C_6), 134.8 (C_4), 129.5 (C_1), 129.0 (C_2), 127.4 (C_3), 64.3 (C_9), 40.5 (C_5).

Cyclohexanecarboxylic acid methoxyamide (46)



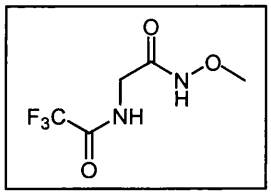
O-Methylhydroxylamine hydrochloride (0.97 g, 11.7 mmol) in methanol (7.0 mL) was added to a stirred solution of potassium hydroxide (0.65 g, 11.7 mmol) in methanol (2.6 mL) at 0 °C and stirred for 15 min. Potassium chloride was removed and the filtrate was used as such. To a solution of cyclohexane carboxylic acid (1.0 g, 7.8 mmol) in diethyl ether (28 mL) at 0 °C were added ethyl chloroformate (0.89 mL, 9.3 mmol) and *N*-methylmorpholine (1.11 mL, 10.1 mmol) and the mixture was stirred for 20 min. The solid was filtered off and the filtrate was added to the freshly prepared hydroxylamine in methanol. The mixture was stirred at 20 °C for half an hour and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 3:7 ethyl acetate:toluene) to give **46** (0.99 g, 82%) as white microprisms: mp 75-78 °C (lit[75] 77-79 °C); ^{1}H NMR 8.87 (1H, br s, NH), 3.72 (3H, s, H_8), 2.33 (1H, br, m, H_4), 1.77 (6H, br, m, H_2, H_6, H_1), 1.28 (4H, m, H_3, H_5); ^{13}C NMR 173.9 (C_7), 64.3 (C_8), 42.5 (C_4), 33.9 (C_1), 29.2 (C_3), 25.0 (C_2).

2, *N*-Dimethoxyacetamide (47)



O-Methylhydroxylamine hydrochloride (1.1 g, 13.3 mmol) in methanol (8.0 mL) was added to a stirred solution of potassium hydroxide (0.75 g, 13.3 mmol) in methanol (3.0 mL) at 0 °C and stirred for 15 min. Potassium chloride was removed and the filtrate was used as such. To a solution of methoxyacetic acid (0.85 mL, 11.1 mmol) in diethyl ether (40 mL) at 0 °C ethyl chloroformate (1.27 mL, 13.3 mmol) and *N*-methylmorpholine (1.58 mL, 14.4 mmol) were added and the mixture was stirred for 20 min. The solid was filtered off and the filtrate was added to the freshly prepared hydroxylamine in methanol. The mixture was stirred at 20 °C for ½ h. The crude was purified by column chromatography (3:7 toluene:ethyl acetate) to give **44** (1.20 g, 96%) as a colourless oil: IR ν_{max} (cm^{-1}) (KBr) 2628 (NH), 1623 (CO); ^{1}H NMR 9.29 (1H, br s, NH), 3.87 (2H, s, H_2), 3.68 (3H, s, H_4), 3.30 (3H, s, H_1); ^{13}C NMR 166.6 (C_3), 71.7 (C_2), 64.4 (C_4), 59.3 (C_1); LRMS M/Z (EI): 119 (45), 73 (60), 45 (100). HRMS Found 119.05785 ($C_4H_9NO_3$ requires 119.05824).

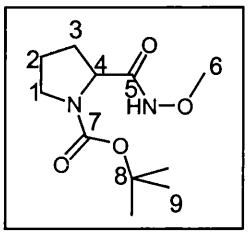
2,2,2,-Trifluoro-*N*-(methoxycarbamoyl methyl)-acetamide (48)



O-Methylhydroxylamine hydrochloride (1.0 g, 11.9 mmol) in methanol (8.2 mL) was added to a stirred solution of potassium hydroxide (0.70 g, 11.9 mmol) in methanol (3.3 mL) at 0 °C and stirred for 15 min. Potassium chloride was removed and the filtrate was used as such. To a solution of (2,2,2-Trifluoroacetylamino)-acetic acid (0.84 g, 7.9 mmol) in diethyl ether (28 mL) at 0 °C were added ethyl chloroformate (0.91 mL, 9.6 mmol) and *N*-methylmorpholine (1.15 mL, 10.5 mmol) and the mixture was stirred for 15 min. The solid was filtered off and the filtrate was added to the freshly prepared hydroxylamine in methanol. The mixture was stirred at 20 °C for 1 h. The residue was purified by column chromatography (silica gel, 7:3 ethyl acetate:petroleum ether) to give **48** (0.51 g, 48 %) as white microprisms: mp 124-126 °C; IR ν_{max} (cm^{-1}) (KBr) 3265 (NH), 2904 (NH), 1674 (CO), 1562 (CO); ^{1}H NMR 4.96 (3H, s, $OC\underline{H_3}$), 3.91 (2H, s, CH_2); ^{13}C

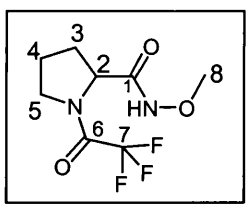
NMR (CD_3OD) 167.3 (CO), 159.7 (q, $^2J_{C-F}$ = 37 Hz, $COCF_3$), 117.8 (q, $^1J_{C-F}$ = 285 Hz, CF_3), 64.9 (s, CH_3), 41.5 (s, CH_2). Found C, 34.59, H, 5.75, N, 20.12, ($C_{11}H_{10}N_2O_4$ + 1/2 H_2O requires C, 34.04, H, 5.71, N, 19.87).

Methoxycarbamoylpyrrolidine-1-*tert*-butyl ester (49)



O-Methylhydroxylamine hydrochloride (0.29 g, 3.5 mmol) in methanol (2.0 mL) was added to a stirred solution of potassium hydroxide (0.2 g, 3.5 mmol) in methanol (0.9 mL) at 0 °C and stirred for 15 min. Potassium chloride was removed and the filtrate was used as such. To a solution of pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (0.50 g, 2.3 mmol) in diethyl ether (9.0 mL) at 0 °C were added ethyl chloroformate (0.26 mL, 2.8 mmol) and *N*-methylmorpholine (0.33 mL, 3.0 mmol) and the mixture was stirred for 20 min. The solid was filtered off and the filtrate was added to the freshly prepared hydroxylamine in methanol. The mixture was stirred at 20 °C for 30 min and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 3:7 petroleum ether:ethyl acetate) to give **49** (0.45 g, 83 %) as white microprisms: mp 112 °C (lit[76] 116-118 °C); ^{1}H NMR 4.02 (1H, br m, H_4), 3.87 (3H, s, H_6), 3.57-3.21 (2H, m, H_1), 2.06 (1H, m, H_3), 1.74 (3H, m, H_3 H_4), 1.33 (s, 9H, H_9); ^{13}C NMR 174.4 (C_7), 158.2 (C_5), 83.8 (C_8), 68.2 (C_4), 62.7 (C_6), 51.6 (C_1), 36.1 (C_3), 33.3 (C_9), 28.3 (C_2).

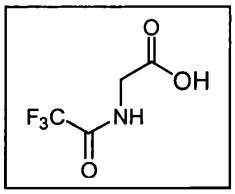
1-(2,2,2-Trifluoroacetyl)-pyrrolidine-2-carboxylic acid methoxyamide (50)



O-Methylhydroxylamine hydrochloride (0.5 g, 5.9 mmol) in methanol (3.6 mL) was added to a stirred solution of potassium hydroxyde (0.32 g, 5.9 mmol) in methanol (1.5 mL) at 0 °C and stirred for 15 min. Potassium chloride was removed and the filtrate was used as such. To a solution of 1-(2,2,2-trifluoroacetyl)-pyrrolidine-2-carboxylic acid (1.0 g, 4.7 mmol) in diethyl ether (17 mL) at 0 °C were

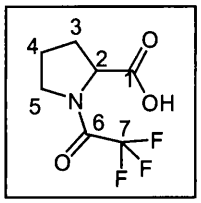
added ethyl chloroformate (0.54 mL, 5.7 mmol) and *N*-methylmorpholine (0.68 mL, 6.2 mmol) and the mixture was stirred for 15 min. The solid was filtered off and the filtrate was added to the freshly prepared hydroxylamine in methanol. The mixture was stirred at 20 °C for 30 min. The residue was purified by column chromatography eluting with 1:1 ethyl acetate and petroleum ether to give **48** as white prisms (0.82 g, 72%): mp 108-110 °C; IR ν_{max} (cm^{-1}) (KBr) 2877 (NH), 1679 (CO), 1525 (CO); ^{1}H NMR 9.82 (1H, br s, NH), 4.34 (1H, br d, J = 4.5 Hz, H_2), 3.75 (5H, br s, H_5, H_8), 2.15 (2H, m, H_3), 1.97 (2H, m, H_4); ^{13}C NMR 167.9 (C_1), 156 (q, $^{2}J_{C\text{-}F}$ = 36.7 Hz, C_6), 115.2 (q, $^{1}J_{C\text{-}F}$ = 285.3 Hz, C_7), 64.0 (C_8), 58.9 (C_2), 57.5 (C_5), 47.5 (C_4), 27.6 (C_4). Found C, 39.87, H, 4.54, N, 11.21 ($C_8H_{11}F_3N_2O_3$ requires C, 39.99, H, 4.62, N, 11.66).

(2,2,2- Trifluoro-acetylamino) acetic acid (51) [68]



The compound was prepared by following the procedure described by Chambers.[68] Triethylamine (9.30 mL, 66.0 mmol) was added to a solution of glycine (5.0 g, 66.0 mmol) in methanol (33 mL). After 5 min ethyl trifluoroacetate (9.90 mL, 86.0 mmol) was added and the reaction was allowed to stir for 24 h. The solvent was removed under reduced pressure; the residue that remained was dissolved in water (75 mL) and acidified with conc. hydrochloric acid (12 mL). After stirring for 15 min, the mixture was extracted with ethyl acetate (4 x 90 mL) and the organic layers were combined and washed with brine (75 mL), dried over $MgSO_4$, filtered and concentrated by rotary evaporation to give **50** (10.1 g, 98%) as a white microprisms: mp 119 °C (lit[68] 119 °C); ^{1}H NMR 9.44 (1H, s, OH); 4.13 (2H, s, CH_2); ^{13}C NMR 171.93 (s, COOH); 159.92 (q, $^{2}J_{C\text{-}F}$ = 37 Hz, $COCF_3$), 117.82 (q, $^{1}J_{C\text{-}F}$ = 285 Hz, CF_3), 42.28 (s, CH_2).

1-(2,2,2-Trifluoroacetyl)-pyrrolidine-2-carboxylic acid (52)[69]



Trifluoroacetic anhydride (12.8 mL, 90.5 mmol) was added dropwise over 5 min to *(S)*-proline (8.0 g, 69.0 mmol) with vigorous stirring at 0 °C. The solution was stirred at 0 °C for 10 min then heated at 80 °C for 2 h. The mixture was allowed to cool down before diluting it with hydrochloric acid (100 mL, 2 M). The aqueous layer was extracted with diethyl ether (3 x 100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography eluting with diethyl ether and hexane (1:1) to give **52** (5.0 g, 34%) as white microprisms: mp 45-47 °C (lit[69] mp 46-48 °C); ^{1}H NMR 4.52 (1H, m, H_2), 3.81-3.58 (2H, m, H_5), 2.25 (1H, m, H_{3a}), 2.13-1.89 (3H, m, H_{3b}, H_4); ^{13}H NMR 175.0 (C_1), 155.1 (q, $^2J_{6\text{-}F}$ = 34 Hz, C_6), 115.1 (q, $^1J_{7\text{-}F}$ = 285.4 Hz, C_7), 58.9 (C_5), 46.3 (C_2), 30.4 (C_4), 23.8 (C_3).

1.4 References

(1) Lossen, H. *Liebigs.Ann.Chem.* **1969**, *150*, 314.

(2) Munson, J. W. *Hydroxamic Acids In the Chemistry of Acid Derivatives*; J. Wiley and Sons: New York, 1992; p 849.

(3) Summers, J. B.; Caruer, G. W.; Dyer, R. D.; Maxdiyasni, H.; Holm, J. H.; Ratajcxyk, J. D. *J.Med.Chem.* **1997**, *30*, 574.

(4) Kurzak, B.; Koxlowski, H.; Farkas, E. *Coord.Chem.Rev.* **2003**, *114*, 169.

(5) Kazmierski, W. M.; Wolberg, J. G.; Smith, S. R.; Thorp, H. H.; Molina, L. *Proc.Natl.Acad.Sci.USA* **1996**, *93*, 9138.

(6) Miller, M. J. *Chem.Rev.* **1989**, *89*, 1563.

(7) Lipczynska-Kochany, E. *Chem.Rev.* **1991**, *91*, 477.

(8) Stewart, O. A.; Martin, G. J. *J.Org.Chem.* **1989**, *54*, 1221.

(9) Arnold, M.; Brown, D. A.; Deeg, O.; Errington, W.; Haase, W.; Herdlhy, K.; Nimir, H.; Werner, R. *J. Inorg.Chem* **1998**, *37*, 2920.

(10) Inabka, Y.; Takahashi, S.; Kinoshita, T. *J.Antibiotc.* **1986**, *39*, 1378.

(11) Brown, D. A.; Cuffe, L. P.; Deeg, O.; Errington, W.; Fitzpatrick, N. J.; Glass, W. K.; Herlihyk, J. *Chem.Commun.* **1998**, 2433.

(12) Dobosz, A.; Karaczyn, A.; Kozlowski, H.; Sliva, T. Y.; Swiate-Kozlowski, J. *J.Chem.Soc.,Dalton Trans.* **1998**, 1089.

(13) Bagno, A.; Comuzzi, C.; Scorrano, G. *J.Am.Chem.Soc.* **1994**, *116*, 916.

(14) Bauer, L.; Exner, O. *Angew.Chem.,Int.Ed.Engl.* **1974**, *13*, 376.

(15) PothBrink, C.; Crumbliss, A. L. *J.Org.Chem.* **1982**, *47*, 1171.

(16) Garcia, B.; Ibeas, S.; Hoyuelos, F. J.; Leal, J. M. *J.Org.Chem.* **2001**, *66*, 7986.

(17) Plapinger, R. E. *J.Org.Chem.* **1959**, *24*, 802.

(18) Stelberg, G. M.; Swidler, R. *J.Org.Chem.* **1965**, *30*, 2362.

(19) Glover, S. A.; Goosen, A.; McLelland, C. W.; Schoonraad, J. L. *Tetrahedron* **1987**, *43*, 2577.

(20) Gerstein, J.; Jencks, W. P. *J.Am.Chem.Soc.* **1967**, *86*, 4655.

(21) Bordwell, F. G.; Harrelson, J. A.; Jr Linch, T. Y. *J.Org.Chem.* **1990**, *55*, 3337.

(22) Chatterjee, B. *Coord.Chem.Rev.* **1978**, *26*, 281.

(23) Chang, C. A.; Sekhar, V. C.; Garrg, B. S.; Guziec, F. S.; Carrera Russo, T *Inorg.Chem.Acta* **1987**, *135*, 11.

(24) Exner, O.; Holubeck, J. *Collect.Czech.Chem.Commun.* **1965**, *30*, 940.

(25) Exner, O.; Simon, W. *Collect.Czech.Chem.Commun.* **1965**, *30*, 4078.

(26) Ventura, O. N.; Rama, J. B.; Turi, L.; Dannenberg, J. J. *J.Am.Chem.Soc.* **1993**, *115*, 5754.

(27) Tanaka, K.; Matsuo, K.; Nakanishi, K.; Kataoka, Y.; Takase, K.; Otsuki, S. *Chem.Pharm.Bull.* **1988**, *36*, 2323.

(28) Levi, A.; Modena, G.; Scorrano, G. *J.Am.Chem.Soc.* **1974**, *96*, 6585.

(29) Lindner, H. J.; Goettlicher, S. *Acta Crystallogr., Sect.B* **1969**, *25*, 832.

(30) Farkas, E.; Enyedy, E. A.; Garriba, E.; Micera, G. *Polyhedron* **2000**, *19*, 1727.

(31) Kametani, T.; Nemoto, H. *Chem.Pharm.Bull.* **1971**, *19*, 1325.

(32) Takahashi, H.; Hitomi, Y.; Iwai, Y.; Ikegami, S. *J.Am.Chem.Soc.* **2000**, *122*, 2995.

(33) Fishbein, W. N.; Strecter, C. L.; Daly, J. E. *J.Pharmacol.Exp.Ther.* **1973**, *186*, 173.

(34) Nagarajan, K.; Rajappa, S.; Rajagopala, P.; Talwalkar, P. K. *Ind.J.Chem* **1991**, *30 B*, 222.

(35) Hodgson, S. T., Davies, D. E., and Smith, S. *Chem.Abstr.* **1994**, 121, 280396a.

(36) Scott, A. W.; Wood, B. L. *J.Org.Chem.* **1942**, *7*, 508.

(37) Nakamura, S. and Inouye, Y. *Chem.Abstr.* **1989**, 111, 224693b.

(38) Lafon, L. *Chem.Abstr.* **1983**, 98, 106999w.

(39) Brown, D. A.; Chidambaram, M. V. *Metal Ions in Biological Systems*; New York, 1982.

(40) Pirrung, M. C.; Cao, J. *J.Org.Chem.* **1995**, *60*, 5790.

(41) Whittaker, M.; Floyd, C. D. *Chem.Rev.* **1999**, *99*, 2735.

(42) Leff, R. L. *Austr.J.Chem., EN* **2004**, *878*, 201.

(43) Shlopov, B. V.; Lie, W. R.; Mainardi, C. L.; Cole, A. A. *Austr.J.Chem., EN* **1997**, *40*, 2065.

(44) Brown, D. A.; Chidambaram, M. V. *Int.J.Pancreat* **1997**, *21*, 1.

(45) Lafleur, M.; Underwood, J. L.; Rappolee, D. A.; Werb, Z. *J.Exp.Med* **1996**, *184*, 2311.

(46) Wojtowicz-Praga, S. M.; Dickson, R. B.; Hawkins, M. J. *Invest.New Drugs* **1997**, *15*, 61.

(47) Matyszak, M. K.; Perry, V. H. *J.Neuroimmunol.* **1996**, *69*, 141.

(48) Cossins, J.; Dudgeon, T. J.; Catlin, G.; Gearing, A. J. H.; Clements, J. M. *Biochim.Biophys.Res.Commun* **1996**, *228*, 494.

(49) Pendas, A. M.; Knauper, V.; Puente, X. S.; Llano, E.; Mattei, M. G.; Apote, S.; Murphy, G. L. *J.Biol.Chem.* **1997**, *272*, 4281.

(50) Black, R. A. *Nature* **1997**, *385*, 729.

(51) Tsuji, N.; Kobayashi, M.; Nagashima, K.; Wakisaka, Y.; Koizumi, K. *J.Antibiotc.* **1976**, *29*, 1.

(52) Pyke, C.; Ralfkiaer, E.; Huhtala, P.; Hurskainenen, T.; Dano, K.; Tryggvason, K. *Cancer Res.* **1992**, *52*, 1336.

(53) Gjibels, K.; Masure, S.; Carton, H.; Opdenakker, G. *J.Neuroimmunol.* **1992**, *41*, 29.

(54) Walakovits, L. A.; Moore, V. L.; Bhardwaj, N.; Gallick, G. S.; Lark, M. W. *Arthritis Rheumatism* **1992**, *35*, 35.

(55) Ries, C. L.; Petrides, P. E. *Biol.Chem.Hoppe-Seyler* **1995**, *376*, 345.

(56) Bachman, G. B.; Goldmacher, J. E. *J.Org.Chem.* **1964**, *29*, 2576.

(57) Sosnovsky, G.; Krogh, J. A. *Synthesis* **1980**, 654.

(58) Bashiardes, G.; Bodwell, G. J.; Davies, S. G. *J.Chem.Soc.,Perkin Trans.1* **1993**, 459.

(59) Prirrung, M. C.; Chau, J. H.-L. *J.Org.Chem.* **1995**, *60*, 8084.

(60) Thomas, A.; Rajappa, S. *Tetrahedron* **1995**, *13*, 1053.

(61) Reddy, A. S.; Kumar, S. M.; Reddy, R. *Tetrahedron Lett.* **2000**, *41*, 6285.

(62) Horman, R. E.; Rizzo, V. L.; Gupta, S. K. *J.Heterocycl.Chem.* **1970**, *7*, 439.

(63) Muller, D. M.; Zeltser, I.; Bitan, G.; Gilon, C. *J.Org.Chem.* **1977**, *62*, 411.

(64) Walter, M. G.; Adlington, R. M.; Baldwin, J. E.; Schofield, C. J. *J.Org.Chem.* **1998**, *63*, 5179.

(65) Chung, S.; Jeong, T.; Kang, D. *J.Chem.Soc.,Perkin Trans.1* **1998**, 969.

(66) Bhat, J. I.; Clegg, W.; Maskill, H.; Elsegood, M. R. J.; Menneer, I. D.; Miatt, P. C. *J.Chem.Soc.,Perkin Trans.II* **2002**, *7*, 1435.

(67) Reyes, A.; Juaristi, E. *Tetrahedron Asymm.* **2000**, *11*, 1411.

(68) Chambers, J. J.; Kurrasch-Orbough, D. M.; Parker, M. A.; Nichols, D. E. *J.Med.Chem.* **2001**, *44*, 1003.

(69) Clark, J. S.; Hodgson, P. B.; Goldsmith, M. D.; Blake, A. J.; Cooke, P. A. *J.Chem.Soc.,Perkin Trans.II* **2001**, *24*, 3325.

(70) Dunn, G.; Elvidge, J. A.; Newbold, G. T.; Ramsay, D. W. C.; Spring, F. S.; Sweeny, W. *J.Chem.Soc.* **1949**, *2*, 707.

(71) Tiecco, M.; Testaferri, L.; Marini, F.; Sternativo, S.; Bagnoli, L.; Temperini, A. *Tetrahedron Asymm.* **2001**, *12*, 1493.

(72) Babidge, P. J.; Shiengthong, D.; Massy-Westropp, R. A.; Pyne, S. G.; Ungphakorn, A. *Aus.J.Chem., EN* **1980**, *33*, 1841.

(73) Sigma-Aldrich. catalogue **2000**.

(74) Schneider, W. P.; Murray, H. C. *J.Org.Chem.* **1973**, *38*, 396.

(75) Noland, T.; Sundberg, S. *J.Org.Chem.* **1963**, *28*, 3150.

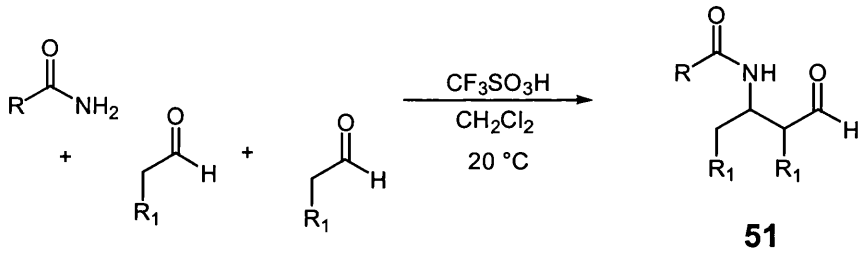
(76) Kisfaludy, K. J., Richter, S. L., Gedeon, K. S., and Vegyeszeti, D. F. *Chem.Abstr.* **1970**, 73, 45856g.

Chapter 2

New Multicomponent Amidoalkylations

2.1 Introduction

In 1998 in our group was reported a new three-component reaction in which a molecule of amide reacts with two molecules of an aliphatic aldehyde to deliver, for the first time, acyclic aliphatic β-amido aldehydes of type **51**[75] (Scheme 2.1).



51

Scheme 2.1

Unique features include (a) *in situ* formation of the presumed *N*-acyliminium ion substrate (from the amide and the aldehyde), (b) subsequent amidoalkylation by the enolic form of the other molecule of aldehyde to give (c) an isolable *β*-amido aldehyde as a product. The reaction occurs under mild condition of acid and at 20 °C.

This reaction offers a flexible route to the synthesis of β-amido aldehydes which otherwise are not easy to access. Those compounds are important building blocks in synthesis and are precursors of 3-amino alcohols, common units in many biologically important compounds. Moreover, compounds **51** are protected forms of β-amino aldehydes, key intermediates in synthesis.

Several approaches to the synthesis of β-amido aldehydes have been reported; they can be classified according to the bond formed (figure 2.1).

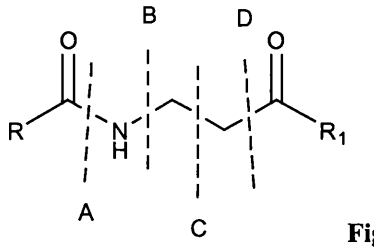
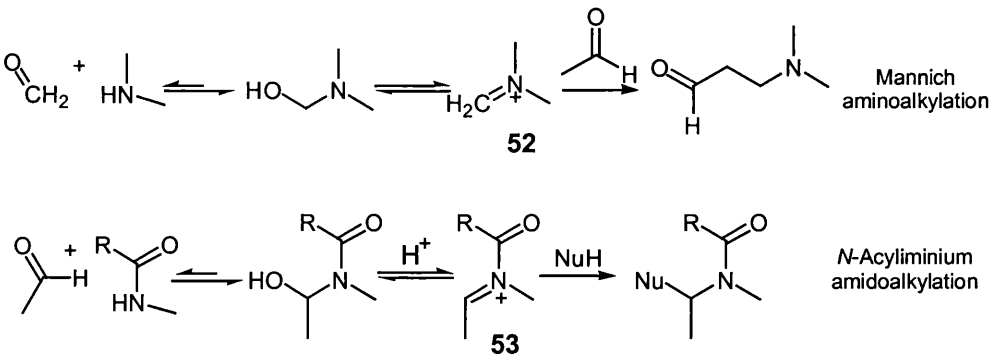


Fig. 2.1

β-Amido aldehydes can be prepared by formation of (i) the A bond by acylation of a *β*-amino aldehydes,[76] or (ii) the B bond by Michael addition to a α,β-unsaturated ketone[77] or (iii) the D bond by photolysis of a phthalimide.[78] However most of the β-amino ketones are prepared by forming the C bond; in fact Iqbal and co-workers reported a cobalt-catalysed synthesis of these compounds[79] and experiments involving Lewis acid catalysts[80] showed that 4-acetoxyazetidin-2-one reacts with various silyl enol ethers to give β-amino ketones. Amidoalkylations which are widely used in organic synthesis,[81;82] have provided many β-amidocarbonyl compounds[81;83], through formation of the N-C bond. *N*-Acyliminium ions are key intermediates of multicomponent reactions and consequently their general features are discussed in the following section.

2.1.1 Iminium *versus* *N*-Acyliminium Ions in Synthesis

The development of *N*-acyliminium ion chemistry (Scheme 2.2) is relatively recent in contrast to that involving iminium cations. The reactions using the iminium ion are largely Mannich amidoalkylations, Carl Mannich was the first to recognise the enormous significance of these reactions, whereas reactions proceeding *via* *N*-acyliminium ions are referred to Mannich-type condensations owing to the structural analogy with Mannich condensations. Both *N*-acyliminium and iminium ion intermediates have been extensively employed in the synthesis of numerous pharmaceutical and natural products. Significantly, the present work is based entirely on the reactivity of *N*-acyliminium intermediates.



Scheme 2.2

2.1.2 Iminium salts

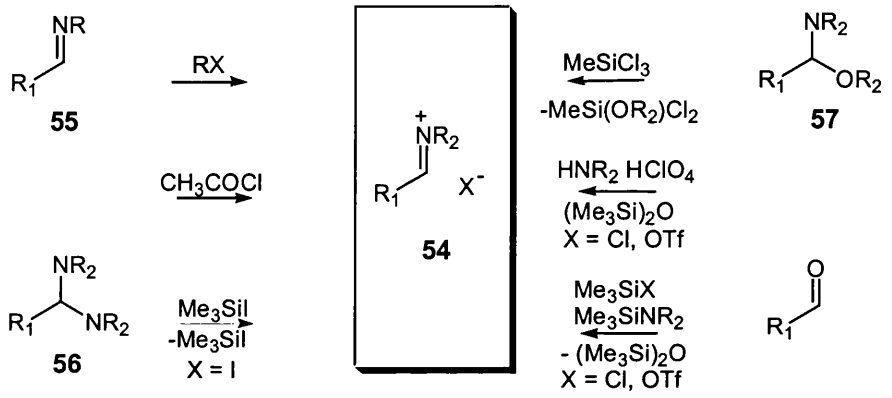
Iminium salts are commonly obtained by alkylation of imines[84], by cleavage of aminals (*e.g.* with CH_3COCl),[85;86] or from *N,O*-acetals (*e.g.* with $MeSiCl_3$).[87] Aldehydes can be also converted into iminium salts by direct reaction with a secondary amine in the presence of a Lewis acid[88] (scheme 2.3). Another important synthetic method is the treatment of enamines with protic acids such as HCl.[89] Iminium salts are commonly employed as Mannich reagents in the synthesis of β-amino aldehydes because they are more powerful electrophiles than imines, *N,O*-acetals or aminals.

Iminium salts are normally hygroscopic and sensitive towards hydrolysis. In the absence of moisture the salts can be stored over a long period, even though it is quite common to generate them in *situ*.[90-92] The reactivity of **54** towards nucleophiles decreases,[93;94] as would be expected, in the sequence R_1 = H >aryl>alkyl because, although there is no rule that determines the reactivity of an ion, differences in reactivity are likely to be influenced by solubility;[95] consequently to achieve the best possible solubility of the iminium salts, the use of polar aprotic solvents such as acetonitrile or dimethylformamide is recommended.

2.1.3 Imines, Aminals and *N,O*-Acetals

Imines **55** (scheme 2.3) are generally much less electrophilic than the corresponding aldehydes. Imines are usually generated *in situ* and have often been

used with success in the stereoselective aminoalkylation of carboxylic acid derivatives[96]. Aminals **56** and *N,O*-acetals **57** resemble imines in terms of their electrophilicity. A Lewis acid is needed in order that they react with nucleophiles; the formation of the iminium intermediate is considered to be an S_N1-type process. Only aminals and *N,O*-acetals which are derived from non-enolizable aldehydes have been used in the Mannich reaction owing to their instability under acid catalysis.



Scheme 2.3

2.1.4 General Aspects of *N*-Acyliminium Ion

This section concerns the chemistry of the *N*-acyliminium ions (**53**, scheme 2.2) and their reactivity towards nucleophiles. There are several synthetic ways of forming **53**: (i) acylation of imines, (ii) *N*-protonation of *N*-acylimines, (iii) electrophilic addition to *N*-acylimines, (iv) heterolysis of amides bearing a leaving group X on the α-carbon with respect to the nitrogen group and (v) oxidation of amides[97]. In all those circumstances the iminium ions are generated *in situ* owing to their high reactivity, and usually by an acid catalyst. It was suggested without any experimental evidence that there is an equilibrium between the *N*-acyliminium ion (**53**) and its precursor (see scheme 2.2) and also that attack by the nucleophile is essentially irreversible.

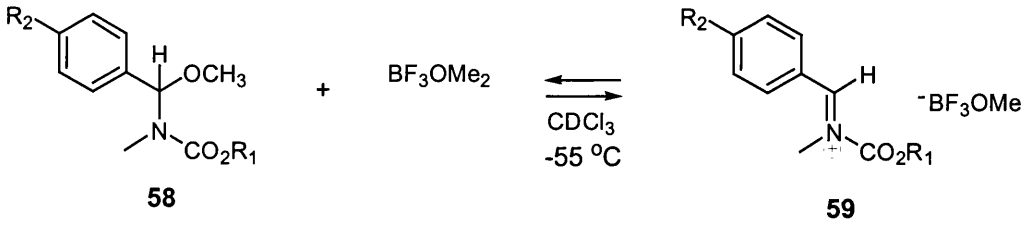
2.1.5 Reactivity and Experimental Conditions

It has been well established that an electron-withdrawing group at nitrogen renders the Mannich intermediate (**54**, scheme 2.2) considerably more reactive by enhancing its cationic character. However the introduction of an acyl group not only confers higher electrophilicity but also prevent the reverse reaction of the *N*-acyliminium ion formation, once it reacts with the nucleophile.[97]

Protic acids as well as Lewis acids have been used to effect bond formation. For sensitive nucleophiles the use of protic acid is possible only if the rate of bond formation is sufficiently high compared to the rate of the alternative nucleophilic decomposition, which limits the reaction to the intramolecular variant.[98] The Lewis acids that are often used for both convenience and good results are: BF_3OEt_2, $SnCl_4$, and $TiCl_4$; sometimes also metal halides such as $FeCl_3$, $ZnBr_2$, and $LiClO_4$ are used. For enol ethers, trimethylsilyl triflate is often appropriate.[98]

2.1.6 Evidence for the Formation of *N*-Acyliminium Species

The existence of *N*-acyliminium species is, in many cases is inferred from the nature of the reaction product. Recently however, it has been shown that *N*-acyliminium salts generated from α-alkoxycarbamates (**58**, scheme 2.4) in the presence of BF_3OMe_2, can be detected by ^1H and ^{13}C NMR spectroscopy.[99] It was shown that an equilibrium exists between **58** and **59** and that the position of this equilibrium depends on the type of Lewis acid used.



Scheme 2.4 α-Alkoxycarbamates-acyliminium ion equilibrium

Furthermore, treatment of **58** with one equivalent of trifluoromethanesulfonic anhydride afforded the acyliminium ion exclusively, demonstrating that the position

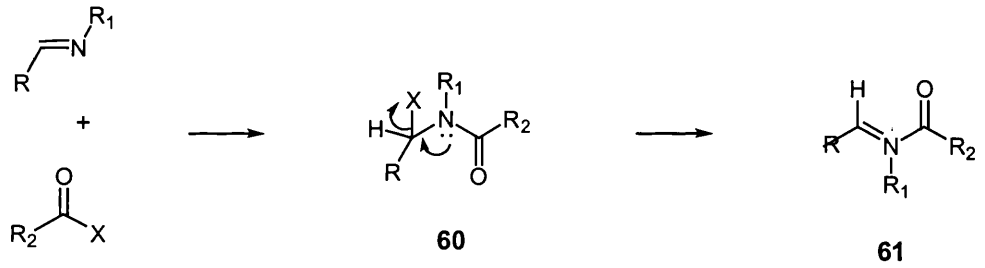
of the equilibrium depends not only on the quantity but also the type of Lewis acid used.

2.1.7 Formation of *N*-Acyliminium Ions

Since *N*-acyliminium ions are generated *in situ*, a number of precursors have been used to form such highly reactive species.[97;100] Five major synthetic pathways are outlined below:

2.1.7.1 N-Acylation of Imines

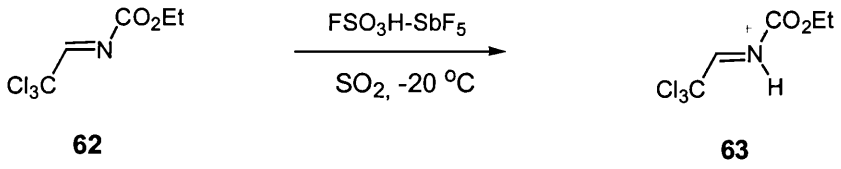
Imines can react with an acid chloride or an anhydride to give adduct **60** which will readily form an *N*-acyliminium ion species (**61** scheme 2.5)[97]



Scheme 2.5 *N*-Acylation of Imines

Depending on the nature of the product, the adduct can go on to form an enamide,[101] a β-lactam,[102] or undergo trapping with nucleophilic carbon atoms or heteroatoms.[103]

2.1.7.2 N-Protonation of N-Acylimines

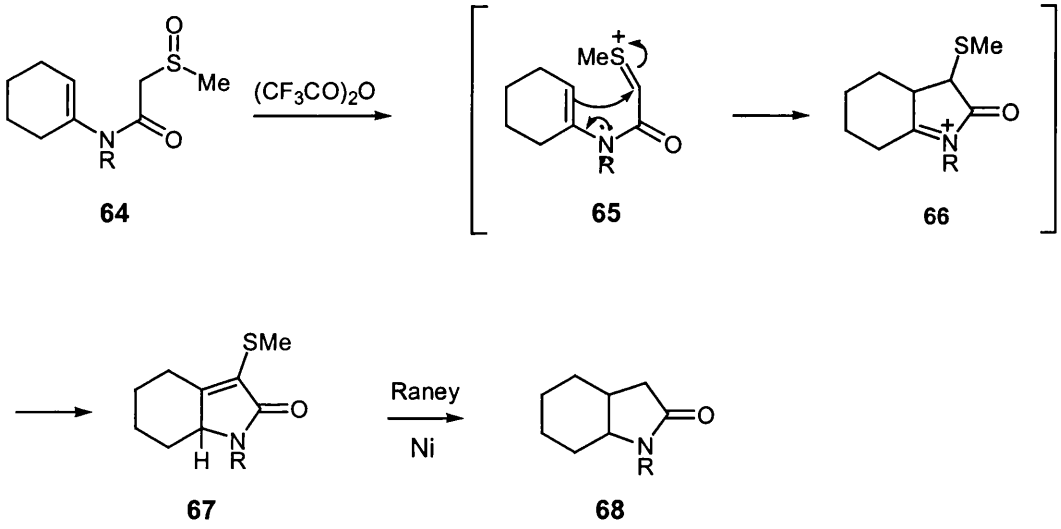


Scheme 2.6 Formation of *N*-Acyliminium from Acylimines

N-Acylimines undergo protonation in strong acidic media to give *N*-acyliminium ions,[97] but because *N*-acylimines are rather unstable species, undergoing tautomerism to the corresponding enamides, this is not a general method. It is generally possible to isolate the *N*-acylimine only when an electron-withdrawing group is present (*e.g.* **62**) which, in presence of fluorosulfonic acid-antimony pentafluoride, will give the *N*-acyliminium ion **63** detectable by ^{1}H NMR. [104]

2.1.7.3 Electrophilic Addition to Enamides

Enamides, which can be prepared by using a variety of methods [101], are useful precursors of *N*-acyliminium ions, the latter being generated by protonation or acylation.

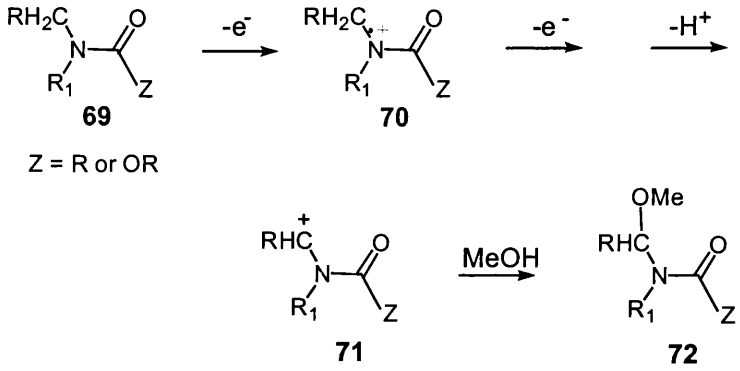


Scheme 2.7 Formation of lactams from Enamides via the Pummerer Reaction

The reaction of enamide **64** under Pummerer conditions to give the lactam **68** (scheme 2.7)[105] provides an example of *N*-acyliminium ion formation. The reaction is thought to proceed through an intermediate **65**, which *via* a 5-*endo*-trigonal cyclisation gives the *N*-acyliminium ion **66**.

2.1.7.4 *Oxidation of Amides*

Expulsion of a hydride from the α-carbon of an amide leads to an *N*-acyliminium ion. This conversion is mainly carried out electrochemically and can be used for a wide range of amides and carbamates.[106]



Scheme 2.8 Electrochemical Oxidation of Amides and Carbamates

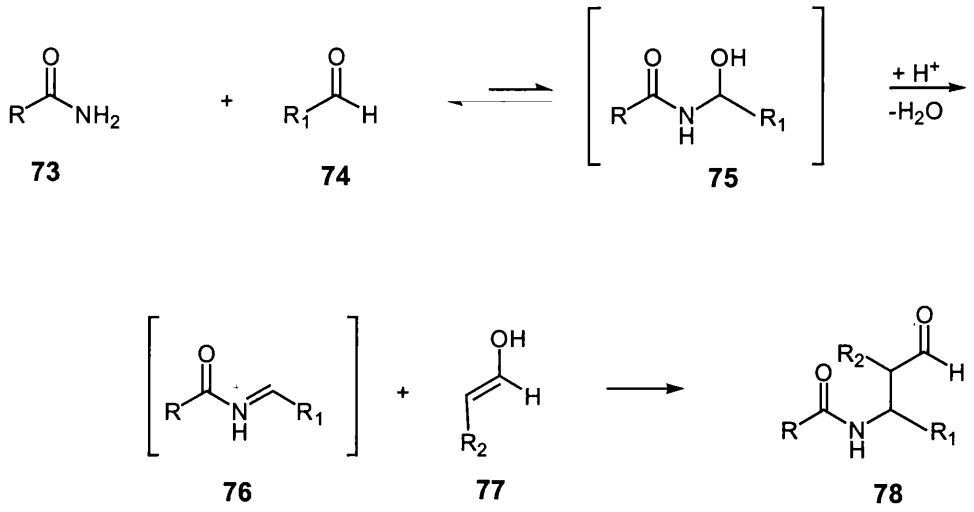
The mechanism has been shown to involve direct removal of one electron from the nitrogen lone pair in the initial step (scheme 2.8).[106] Loss of an electron and a proton from **70** generates the *N*-acyliminium ion **71**, which is trapped by a nucleophile, usually a molecule of solvent.

2.1.7.5 *Heterolysis of α-Substituted Amides*

The method most frequently used to generate *N*-acyliminium ions is the heterolysis of an α-substituted amide.[97;98;106] The α-substitutent is normally an oxygen function that becomes the leaving group on protonation; however other groups have been used including bisamides, (α-chloroalkyl amides) and (α-thioalkyl amides).[97]

The preparation of α-alkoxyamides can be carried using other routes, the most common methods being the condensation of an aldehyde or ketone with an amide to generate an *N*-acyliminium ion which is readily trapped by a nucleophile. One reason for the extensive use of this method is its versatility in application to variously substituted amides, as well as the high regioselectivity.[98] One such example is given in scheme 2.9.

Reactions of this type are discussed in greater depth in section 1.4.



Scheme 2.9 Amide-aldehyde condensation followed by addition of an enol.

An aliphatic amide **73** reacts with an aliphatic aldehyde **74** to form the α-alkoxyamide intermediate, which in acidic media provides the *N*-acyliminium ion that reacts with the enolic form of the aldehyde **77**, to deliver an α-amido aldehyde **78**.

2.2 Multicomponent Reactions and Their Features

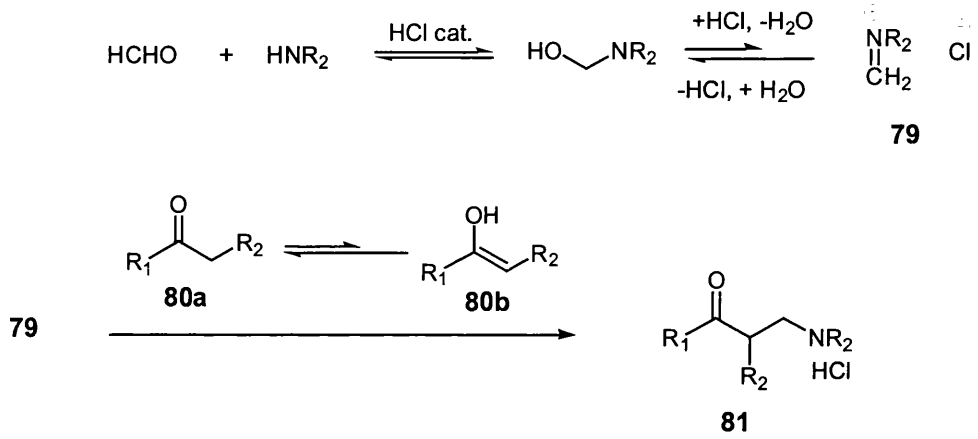
2.2.1 General Aspects

Multicomponent reactions are an area of special interest in organic chemistry since three or more reactants combine together in a single reaction vessel to form new products that contain a portion of all the components used.[107] Therefore multicomponent reaction strategies offer significant advantages over conventional linear-type syntheses, where two or more steps are required to achieve what it is otherwise possible in a one-pot process.

Since the present work tries to combine the chemistry of hydroxamic acids together with amidoalkylation in a multicomponent reaction context, an outline is provided of previously known multicomponent reactions.

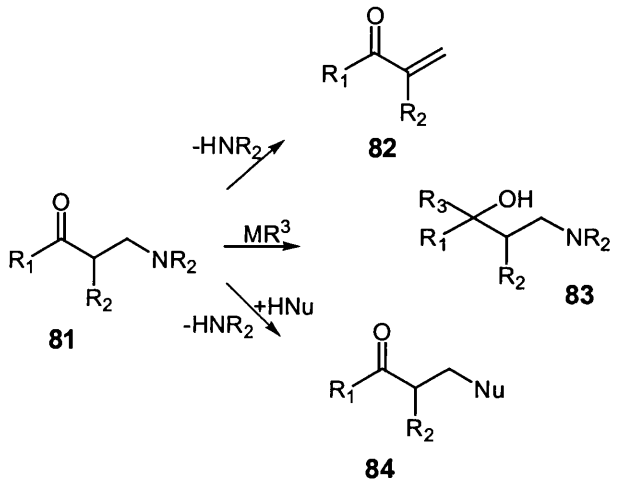
2.2.2 Mannich Reaction

In section 2.1.1 was described one of the most powerful three-component reaction to prepare β-amino ketones and aldehydes, namely the Mannich reaction. The mechanism is given in scheme 2.10.



Scheme 2.10 Simplified Mechanism of the Mannich Reaction

It is assumed that methyleneiminium salts **79** are formed in low concentration, by a series of equilibrium reactions. These then react with the enol tautomer **80b** of the carbonyl compound **80a**, also present in low concentration, to give the hydrochloride of the β-amino carbonyl compounds **81**. These so-called Mannich bases are synthetic building blocks which can be converted into a series of useful derivatives, such as Michael acceptors **82** (scheme 2.11), 1,3-amino alcohols **83** and functionalised carbonyl compound **84**.



Scheme 2.11 Mannich bases as synthetic building blocks

The classic Mannich reaction possesses several disadvantages, owing to the drastic reaction conditions and the long reaction times. One of the major problems is the formation of the bisketone **85**. The monoamino-methylated product **81** is formed only if secondary amines are used, because the use of a primary amine or ammonia permits the reaction to continue until all the hydrogen atoms on the nitrogen atom have been replaced (*e.g.* **86**). Other Mannich bases such as **87** and **88** are also observed as side-products; to avoid the formation of **88** a large excess of ketone needs to be employed. In the case of unsymmetrical ketones further problems are encountered.

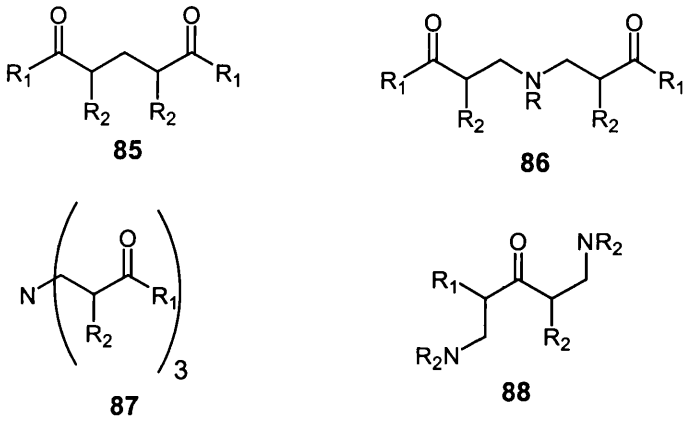


Fig 2.2

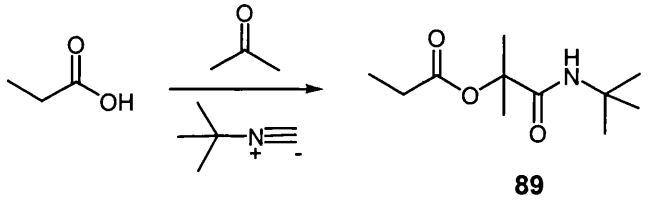
Other limitations of the Mannich reaction are that (a) the regioselectivity cannot be controlled to any significant extent (b) only ketones and aldehydes can be used and (c) other carbonyl compounds such as carboxylic acids and their derivatives cannot be aminomethylated.

Owing to the power of the Mannich reaction different variations have been pursued in order to find alternative routes without altering the basic classical procedure. Modern versions of the Mannich reaction normally employ preformed electrophiles (iminium salts or imines) and nucleophiles (enolates, enol ethers and enamines) to achieve the desired β-aminocarbonyl compound. The use of preformed reagents guarantee a higher concentration of electrophile, leading to shorter times of reaction and less drastic conditions.[108]

2.2.3 Passerini Reaction

This classic reaction between carboxylic acids, oxo compounds and C-isocyanides, described by Passerini in 1921 provides access to α-acyloxy carboxamides such as **89** (scheme 2.12).

The Passerini reaction as well as the Ugi reaction, which is extensively discussed in the following section, belongs to the large and important class of multicomponent reactions that employ isocyanides, formerly known as isonitriles; since they possess peculiar properties an introduction to their chemistry is given below.



89

Scheme 2.12 The Passerini Reaction

The chemistry of isocyanides is characterised by three properties: the α-acidity, the α-addition and the ease of formation of radicals. The α-acidity is a striking feature of isocyanide and increases when electron-withdrawing substituents are present at the α-position such as carboxylic esters, nitriles, sulfonyl compounds and phosphonic esters. However the most important synthetic property is the α-addition reaction with both nucleophiles and electrophiles at the isocyanide carbon atom. Isocyanides are the only class of compounds with a formally divalent carbon atom together with carbenes and carbon monoxide.[109]

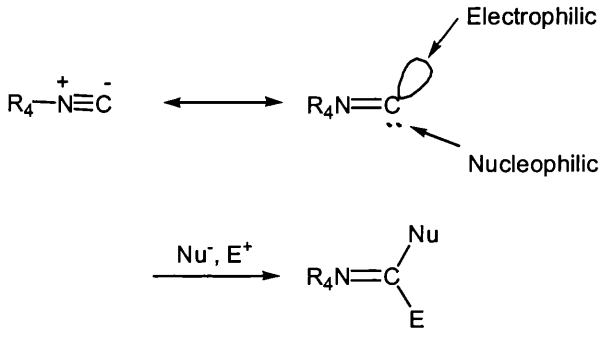
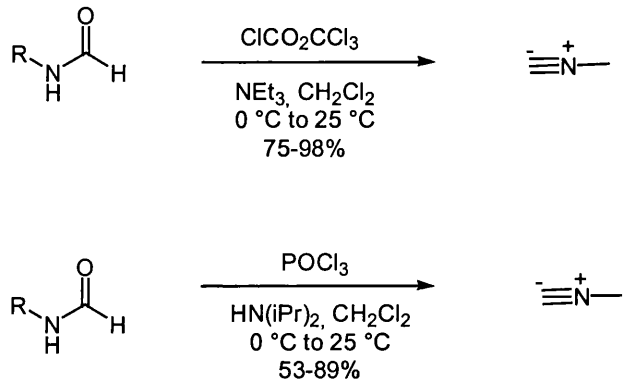


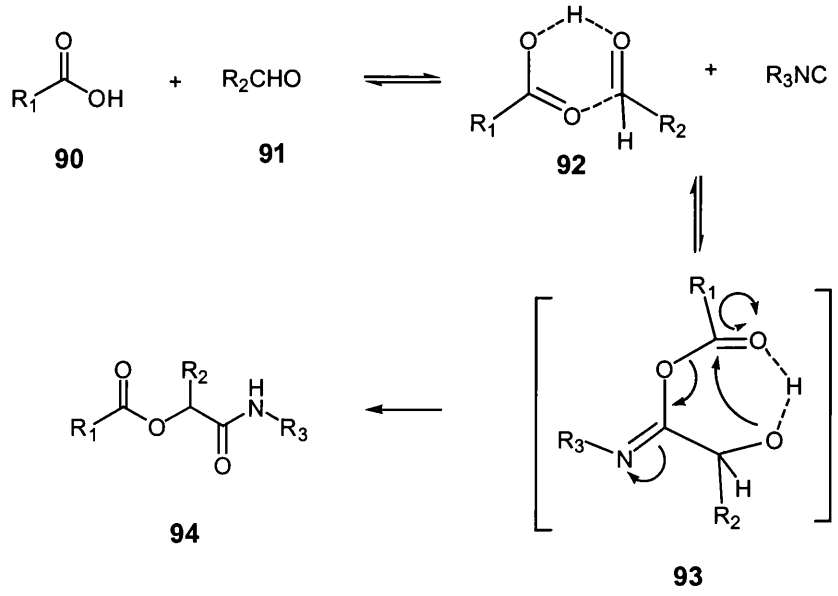
Fig 2.3

Isocyanides can be prepared by dehydration of formamide or derivatization of another isocyanide (scheme 2.13).[110]



Scheme 2.13

Going back to the Passerini reaction a mechanism, which agrees with experimental data, postulates a hydrogen-bonded intermediate **92** formed from the aldehyde **91** and the carboxylic acid **90**, followed by the insertion of the isocyanide to form a cyclic transition state **93** comprised of all three compounds. The α-adduct rearranges in an intramolecular transacylation to the stable acyloxy carboxamide **94**.

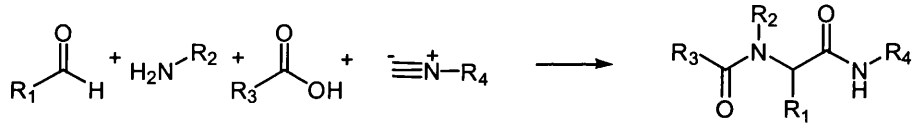


Scheme 2.14 Mechanism of the Passerini reaction

In contrast with the Ugi reaction, the Passerini reaction is accelerated by aprotic solvents, which indicates a non-ionic mechanism.[109] The reaction is generally carried out at high concentration of the starting materials and in inert solvents and below room temperature. Chiral isocyanides have usually no influence on the diastereoselectivity of the multicomponent reaction.

2.2.4 Ugi Reaction

The Ugi reaction is a four-component reaction in which an aldehyde, an amine, a carboxylic acid and an isocyanide unite to form an α-amino acylamide as shown in Scheme 2.15.[109]

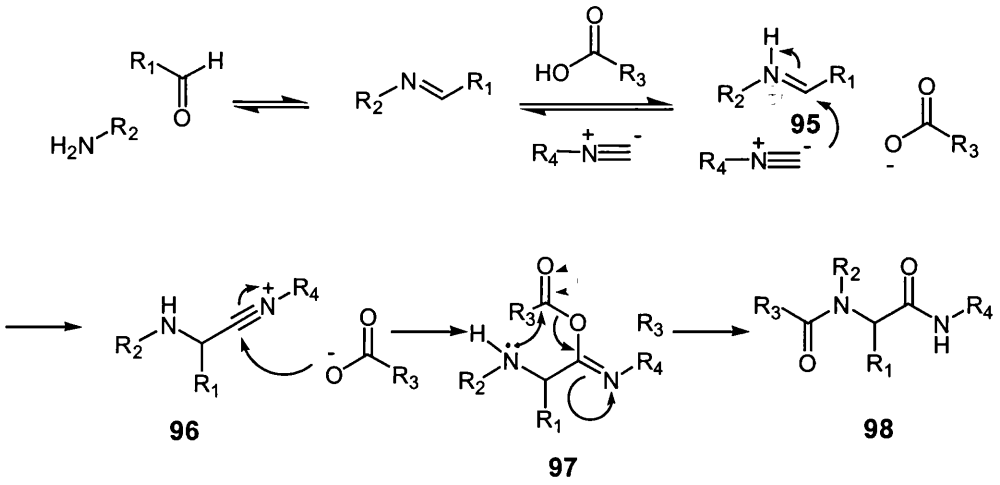


Scheme 2.15 The Ugi Reaction

The exothermic reactions are generally run in methanol or ethanol at high reagent concentrations (0.2 to 2 M). Lewis acids can accelerate the reaction and the yields can be improved by precondensation of the amine with the aldehyde.

The mechanism proposed for the Ugi reaction is illustrated in scheme 2.16. The coupling occurs between the isocyanide that traps the reversibly formed iminium ion and the carboxylate, followed by an acyl migration to give the desired α-amino acylamide **98**. In the first step the carbonyl component and the amine condense to give an imine or Schiff base. Like most imine reactions, the Ugi reaction runs better if the Schiff base is activated; indeed, the carboxylic acid protonates the nitrogen atom of the imine, enhancing the electrophilicity of the N=C bond. Another way of increasing the electrophilicity of the imine is by using Lewis acids such as $TiCl_4$ or $BF_3{\cdot}OEt_2$.

The electrophilic iminium ion and the nucleophilic acid anion add to the isocyanide carbon atom. The α-adduct undergoes intramolecular acylation and subsequent rearrangement to give the Ugi product **98** (scheme 2.16).



Scheme 2.16 Mechanism of the Ugi Reaction

It is instructive to follow the changes in nucleophilicity and electrophilicity of the components during the Ugi reaction. During the individual steps the reactive centres of the acid and the imine change the sign of their reactivity several times. In the first step the imine behaves as a base towards the acid component, then the protonated iminium ion **95** reacts as an electrophile and the acid anion as a nucleophile component at the α-addition. After α-addition to the isocyanide, intramolecular acyl transfer occurs from the imidate to the amine function in **97**. In the course of the cycloaddition and elimination the reactive centres change their nucleophilic nature.

Both the Passerini and Ugi reactions employ isocyanide species together with carboxylic acids and carbonyl compounds, but while the Ugi is a four-component reaction, the Passerini reaction is a three-component one. In the Passerini reaction, the electrophilic carbon atom of the carbonyl compound and the nucleophilic oxygen of the carboxylic acid are employed in the α-addition to the isocyanide. On the other hand, in the Ugi reaction the carbonyl compound participates in the formation of the imine that after protonation by the acid counterpart reacts, as electrophile, in the α-addition to the isocyanide together with the nucleophilic anion of the carboxylic acid. In contrast to the Ugi reaction that uses low-molecular weight alcohols as solvents, the Passerini reaction is accelerated by aprotic solvents, indicating a non-ionic mechanism. Both reactions are exothermic and are conducted at high concentration of reactants.

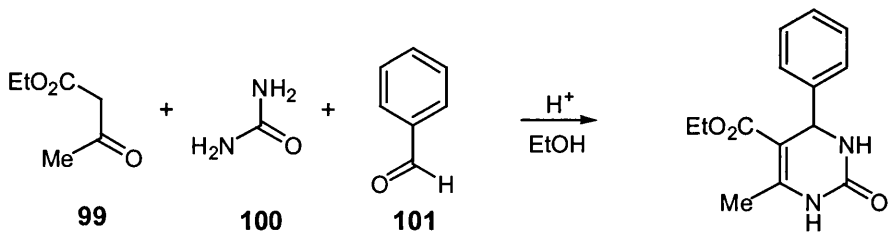
2.2.5 Formation of Heterocyclic Rings

The multicomponent reactions observed in the previous sections have two things in common: first, they involve formation of iminium ion intermediates and secondly, although subsequent applications in the synthesis of heterocycles exist, they are mostly involved in the synthesis of acyclic compounds.

On the other hand multicomponent reactions in which the final product leads to the formation of functionalised heterocycles are gaining progressively more interest in organic chemistry, as useful pharmaceutical properties can often be attributed to them. Accordingly, examples of multicomponent reactions of this type are discussed below.

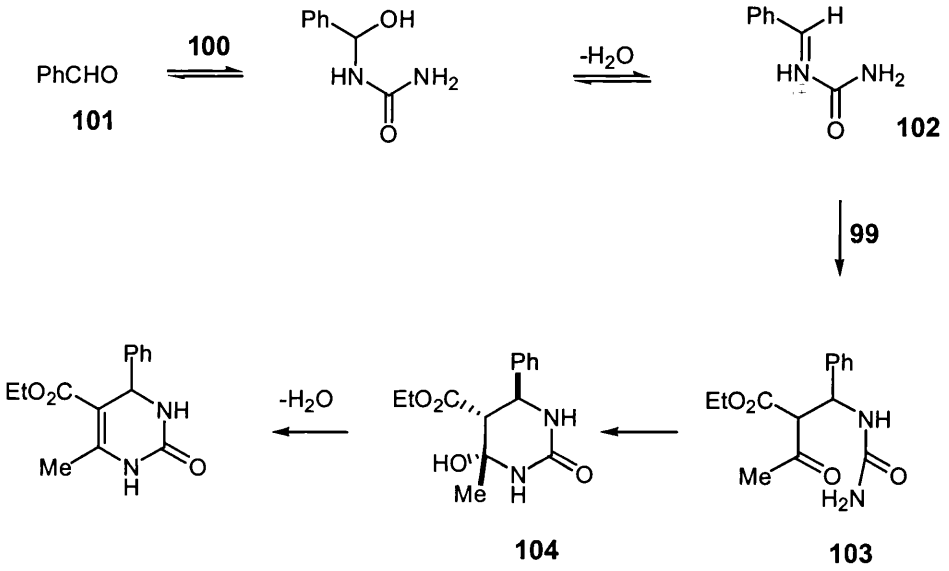
2.2.5.1. Biginelli Reaction

In 1893 an Italian chemist, Pietro Biginelli, reported the synthesis of functionalised 3,4-dihydropyrimidine-2(1*H*)-ones *via* a three-component condensation reaction involving an aromatic aldehyde, a urea and ethyl acetoacetate (scheme 2.17). The reaction was carried out simply by heating the mixture of the three components dissolved in ethanol with a catalytic amount of HCl at reflux. The product of the novel one-pot three-component reaction precipitated from the reaction mixture on cooling. Although the reaction has been known for a long time, only recently has it been reconsidered in view of the fact that functionalised 3,4-dihydropyrimidin-2(1*H*)-ones belong to a class of heterocycles that possess remarkable pharmacological properties, such as antiviral, antitumour, antibacterial and anti-inflammatory[111] activity.



Scheme 2.17: The Biginelli reaction

The mechanism of the Biginelli reaction has been subject of debate in recent years. However work conducted by Kappe[112] established that the key step of the reaction involves the acid-catalysed formation of the *N*-acyliminium ion intermediate of type **102** (scheme 2.18) from an aldehyde **101** and urea **100**. Interception of the iminium ion by ethyl acetoacetate produces an open-chain ureide **103**, which cyclises to the hexahydropyrimidine **104**. Acid-catalysed elimination of water leads to the final compound.



Scheme 2.18: Proposed mechanism of the Biginelli Reaction

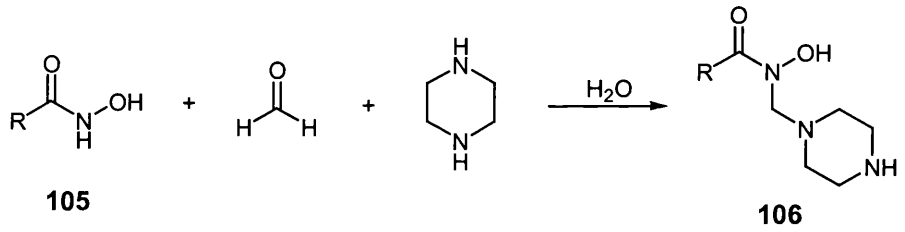
In the Biginelli reaction, the generation of the acyliminium ion is a key step and this can be facilitated by selection of the appropriate Lewis or Brönsted acid (including polyphosphate ester, PPE) usually leading to improved yields.[113]

2.3 Results and Discussion

2.3.1 Adaptation of the Amide-Aldehyde Multicomponent Reaction to a Hydroxamic Acid-Aldehyde Process

The scope of this work is to broaden the three-component amidoalkylation recently discovered in our group to reactions involving hydroxamic acids derivatives.

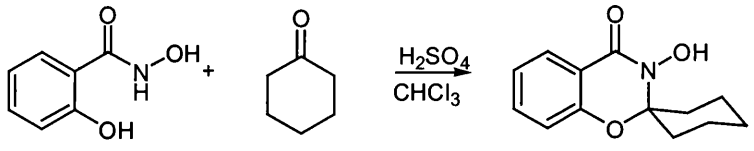
Very little is known concerning *N*-amidoalkylations of acyclic hydroxamic acids. A study reported by Hellmann[114] in 1989 described a condensation in water of some hydroxamic acids **105** with formaldehyde and piperazine, (scheme 2.19). The formaldehyde condenses with the piperazine to form an iminium ion which reacts with the nucleophilic nitrogen of the hydroxamic acid to give the adduct **106**. This reaction illustrates the important theme of the nucleophilicity of the nitrogen atom of a hydroxamic acid.



105 106

Scheme 2.19

Another example regarding the nucleophilicity of the nitrogen atom is given in scheme 2.20.[115]

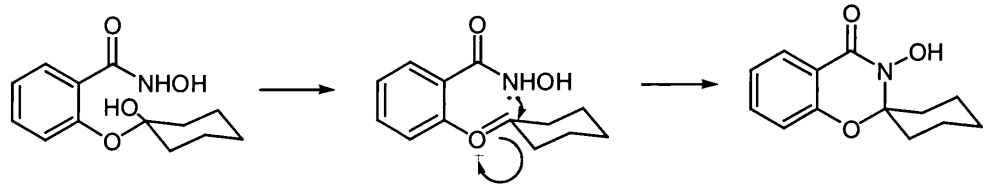


107 108

Scheme 2.20

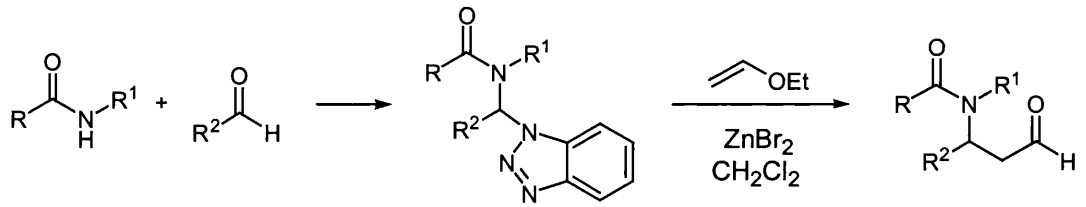
The mechanism postulated for the formation of hydroxamic acid **108** suggests that the oxonium ion, generated from the condensation of the phenoic hydroxyl

group with the ketone is the intermediate that, as soon it is formed, reacts rapidly with the nitrogen atom of the hydroxamic acid to afford the cyclic system **108** (scheme 2.21).



Scheme 2.21

Another line of research conducted by Katritzky and co-workers[116] showed that amides as well as hydroxamic acids can undergo amidoalkylation in a very general way, simply by preparing a bulky *N*-acyliminium ion precursor **109** that under the right reaction conditions forms the *N*-acyliminium ion itself that reacts rapidly with a nucleophile present in the reaction (scheme 2.22).



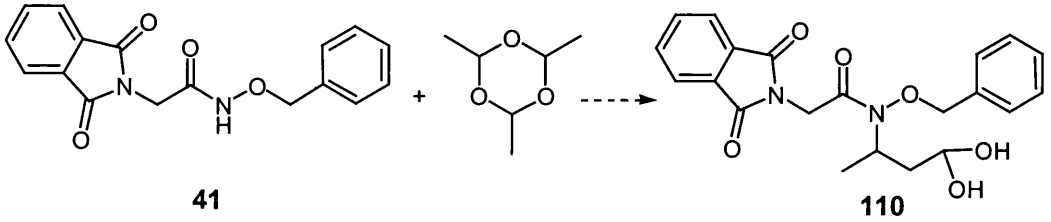
109

Scheme 2.22

Consequently as there was evidence that the nitrogen atom of the hydroxamic acid moiety can form an *N*-acyliminium ion intermediate which can then react with carbanions to form *N*-alkylated hydroxamic acids, an extensive study was made of their reactivity towards carbonyl compounds.

2.3.2 Condensation of Hydroxamic Acids with Aldehydes *via* *N*-Acyliminium Ions

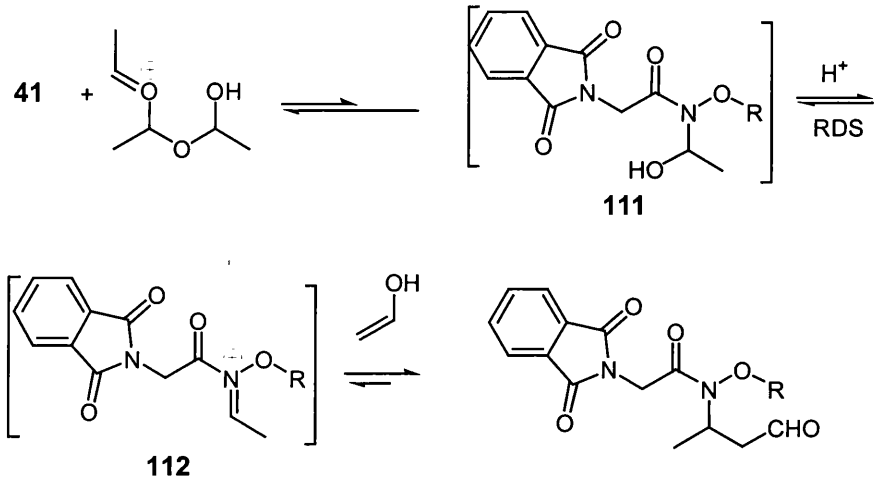
To evaluate the three-component *N*-amidoalkylation discussed in section 2.1, the α-amino hydroxamate **41** and paraldehyde were chosen as model reactants. The hydroxamate **41** was prepared from *N*-phthaloyl glycine which was obtained by heating phthalic anhydride and glycine in pyridine[117] (scheme 2.23).



41 **110**

Scheme 2.23

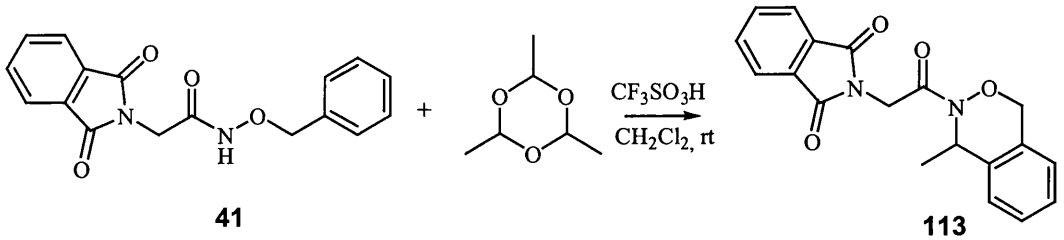
The three-component amidoalkylation proceeds at room temperature in dry dichloromethane and in the presence of trifluoromethanesulfonic acid as acid catalyst. The mechanism suggested for the one-pot amidoalkylation involves the activation of the trioxane form of the acetaldehyde by the acid with consequent formation of the hemiaminal **111** (scheme 2.15). Acid-catalysed elimination of water from **111** leads to the *N*-acyliminium ion complex **112**, which reacts spontaneously with the enolic form of the acetaldehyde to deliver the final β-aldehydic hydroxamic acid. The rate-determining step of the α-amidoalkylation is the formation of the *N*-acyliminium ion **112** formed by the acid-catalysed elimination of water from **111**.



111 **112**

Scheme 2.24 Suggested mechanism of the α-amidoalkylation of hydroxamic acids by aldehydes and their equivalents.

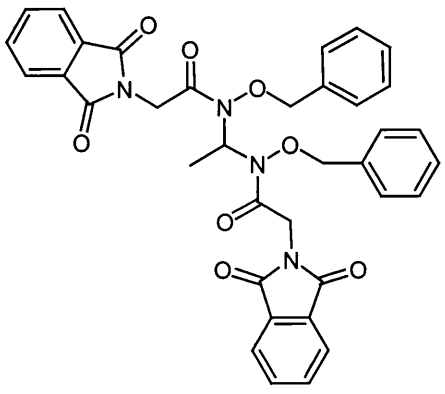
When hydroxyamide **41** reacted with paraldehyde in presence of 2% v/v trifluoromethanesulfonic acid at room temperature none of the expected β-carbonyl hydroxamic acid was observed, the bicyclic system **113** (scheme 2.25) being recovered together with the unreacted starting material. Although unexpected, this result was nonetheless encouraging since it showed that the *N*-acyliminium ion was definitely formed in the conditions proposed and also reacted with the nucleophilic benzene ring.



41 **113**

Scheme 2.25

At that time two strategies could have been undertaken; either to change the conditions to drive the reaction towards an intermolecular pathway instead of intramolecular one, or to change the protecting group at oxygen. For a better understanding of the reaction and conditions, we decided to investigate both features. Different conditions were tried (table 2.1) in order to shift the reaction towards an intermolecular pathway; however unexpected results were encountered. In fact, different kinds of products were obtained depending upon the conditions employed. In only a few cases was the desired *β*-aldehyde hydroxamic acid **110** obtained (scheme 2.23) and although different conditions were examined, none led to **110** in satisfactory yield. Furthermore a dimeric form **114** of **41** was identified (fig 2.4).



114

Fig 2.4.

The results resumed in Table 2.1 suggested that in the reaction three nucleophiles could in theory react with the *N*-acyliminium ion formed *in situ*: the first is the desired enolic form of the paraldehyde; the second is the benzene ring and the last is the hydroxamic acid itself.

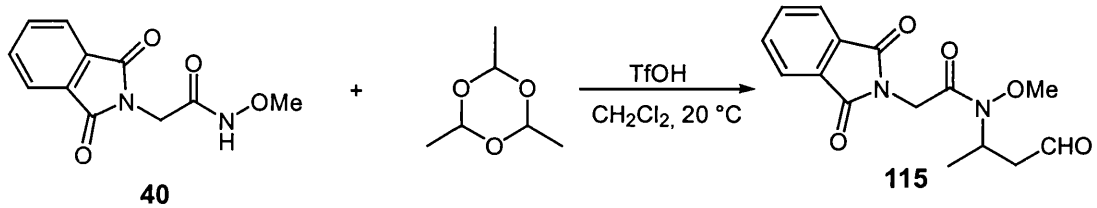
Table 2.1: Different reaction conditions of the three component condensation involving **41** and paraldehyde.

Entry	**41** (eq)	**Paraldehyde** (eq)	**Vol (%)/eq of TfOH**	**Products**	**Yield %**
1	1	1	2/1.2	**113**	60
				110	13
2	1	1	2/0.2	**114**	35
				110	19
3	1	3	9/0.6	**114**	10
				110	19
4	1	1	11/1.2	**114**	1
				110	24
5	1	3	11/1.2	**114**	12
				110	20
6	1	1	16/2.5	**113**	12
7	1	1	8/5	**113**	60
8	1	1	44/10	**113**	60

We discovered that in conditions where the mixture is too acidic or very dilute the 6-membered ring closure is generally favoured; on the other hand when trifluoromethanesulfonic acid is present in catalytic amount the desired compound **110** is formed but always together with the dimeric form **114** (obtained by condensation of the hydroxamic acid itself with the *N*-acyliminium ion). Although the amount of paraldehyde as well as the amount of the catalyst and the concentration was varied, the reaction never led to the desired compound **110** in satisfactory yield. The reason could be that a considerable amount of acid is required in the reaction, not only to form the *N*-acyliminium ion itself but also to produce the enolic form of acetaldehyde and to generate free acetaldehyde from paraldehyde. On the other hand when the conditions of reaction were too acidic, the paraldehyde polymerised, giving side-products. Since the yield of the desired compound could not

be significantly improved, the plan of driving the reaction towards an intermolecular pathway instead of an intramolecular one could not be investigated.

To change the protecting group on oxygen seemed to be the preferred solution to the problem. Thus, *N*-phthaloyl-*N'*-methoxyglycine hydroxamic acid **40** was prepared by following the same procedure described for the synthesis of **41**. The hydroxamic acid **40** was employed in the multicomponent reaction in presence of 2% v/v of trifluoromethanesulfonic acid as previously described (scheme 2.26)



40 **115**

Scheme 2.26

Treatment of **40** and paraldehyde with trifluoromethanesulfonic acid gave the aldehydic hydroxamic acid **115** in only 23% yield while the major product formed from the aldol condensation reaction were the α,β-unsaturated aldehyde (2-butenal), unreacted starting material and aldehyde polymerization products. In an effort to favour the three-component amidoalkylation (formation of **115** instead of aldol condensation products, different condition were used. First, the amount of trifluoromethanesulfonic acid was increased, but unfortunately ^{1}H NMR evidence showed that the formation of the aldol product (2-butenal) was even more favored. Secondly, variation of the temperature was more promising (entry 2 table 2.2); although the yield of the three-component amidoalkylation was still low, only a small amount of aldol product was recovered. Even though the low temperature was preventing side reactions such as polymerization of the aldehydes and aldol condensation reaction, the formation of the *N*-acyliminium ion was still not significant. Hence other strategies needed to be developed. Thirdly, a drying agent was added with the idea of removing water formed *in situ* from the reaction of **111** leading to the *N*-acyliminium **112** (scheme 2.24). This was the most promising variation (entry 3, Table 2.2) and gave the best results. The reason why two drying agents were combined together was simply due to experimental requirements. Neither phosphorus pentoxide nor sodium sulfate alone promoted the reaction, but only the combination of both led to the desired compound.

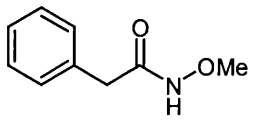
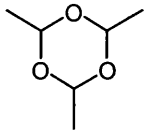
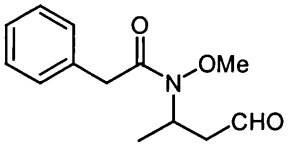
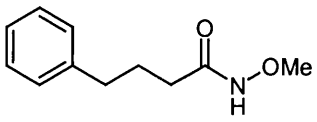
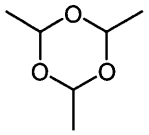
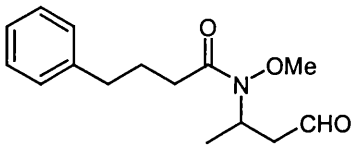
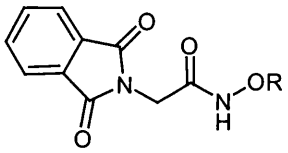
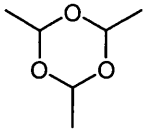
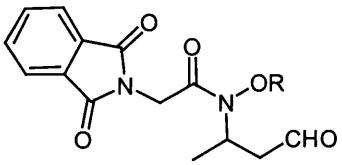
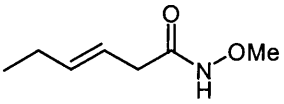
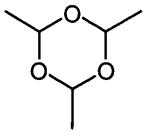
Table 2.2: Different reaction conditions in the three-component amidoalkylation involving **116** and paraldehyde.

Entry	40 (eq)	aldehyde (eq)	Catalyst	Conditions	Yield %
1	1	1	TfOH (2.5eq)	25 °C CH_2Cl_2	23
2	1	1	TfOH (2.5eq)	0 °C CH_2Cl_2	29
3	1	1	TfOH (2% v)	-55 °C P_2O_5/Na_2SO_4 CH_2Cl_2	52
4	1	1	$BF_3OEt_2/AlCl_3$ $ZnCl_2/TiCl_4$	-78 °C CH_2Cl_2	0
5	1	1	BF_3OEt_2	-40 °C CH_3CN	46

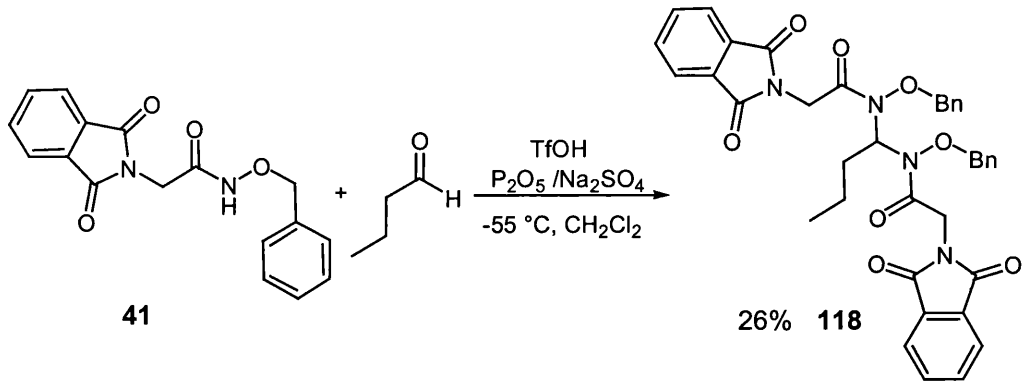
However, still not completely satisfied with the results, other conditions were examined, including modifying the nature of the catalyst by opting for a Lewis acid. Initially, the classical Lewis acids (entry 4, table 2.2) were used but no product was obtained; later was found a literature report that hemiaminals such as **111**-like can form *N*-acyliminium ions when treated with boron trifluoride-diethyl etherate in acetonitrile at –40 °C.[118] In fact when **40** was treated with boron trifluoride-diethyl etherate in the conditions described by Robins[118] **115** was obtained in 46%.

Since many possibilities to improve the yield had been tried we accepted the result of entry 3 (table 2.2) as the best obtainable result. Consequently as the amidoalkylation of **40** had been achieved the aim was to generalize the reaction by changing the substrate and the aldehyde. Accordingly, other hydroxamic acids were prepared and exposed to the three-component amidoalkylation in the presence of trifluoromethanesulfonic acid (entry 3 table 2.2); the results are shown in table 2.3. As the table shows (entry 1 and 2), the hydroxamic acids employed in the three-component reaction did not react as well as **40**. However, when the hydroxamic acid **41** was exposed to the three-component reaction under those conditions, a better result was achieved. The product **110** was obtained in 35% yield compared with 19% previously (table 2.1, entry 2).

Table 2.3: Condensation of *O*-Methyl Hydroxamic Acids with Paraldehyde (2 v/v TfOH, in CH_2Cl_2 with Na_2SO_4 (5 eq) and P_2O_5 (5eq) at –55 °C.

Entry	Hydroxamic Acid	Paraldehyde	Product
1	 **43**		 **116** 27 %
2	 **38**		 **117** 12 %
3	 R = CH_3 **40** R = Bz **41**		 R = Bz 35 % **110** R = CH_3 52 % **115**
4	 **42**		Hydrolysis of the amide bond

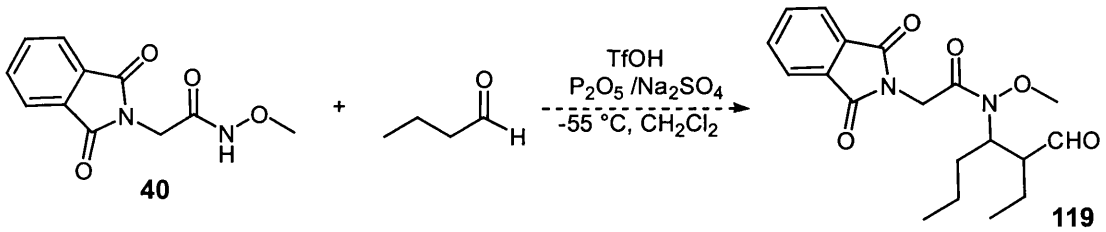
The process of generalization was carried on by changing the nature of the aldehyde. When butyraldehyde was employed in the multicomponent reaction together with the hydroxamic acid **41**, the dimeric system **118** was isolated although in considerably lower yield (scheme 2.27). Moreover it was noticed that conditions that had previously favoured the three-component product now gave only dimerisation and aldol condensation products.



41 26% **118**

Scheme 2.27

To prevent the formation of the dimeric system **118** and to determine whether the use of butyraldehyde was affecting the course of the reaction, hydroxamic acid **40** was selected. Thus starting hydroxamic acid unreacted together with the aldol condensation product were detected (Scheme 2.28). These results could suggest that when butyraldehyde is used, the aldehyde is mostly consumed in the aldol condensation reaction before the *N*-acyliminium ion concentration is significant. Conversely, if the paraldehyde is used, since it is a slower source of acetaldehyde, the aldol reaction occurs competitively with the formation of *N*-acyliminium ion.



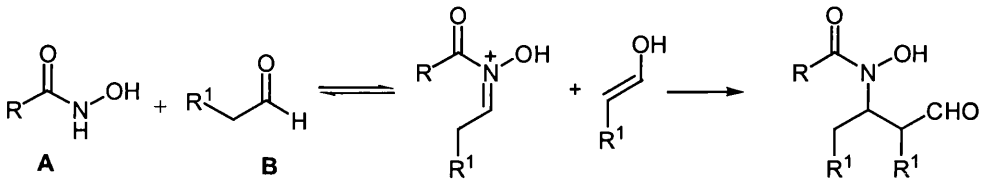
40 **119**

Scheme 2.28

Since the use of aldehydes gave side reactions it was decided to employ their trioxane equivalents. Accordingly, the preparation of trioxane derivative of butyraldehyde according to the procedure of Reddy[119] using tantalum pentachloride as catalyst was attempted. Unfortunately the trioxane derivative could not be detected and only butyraldehyde was recovered, so the dimethyl acetals of acetaldehyde and butyraldehyde were prepared and employed in the three-component amidoalkylation.

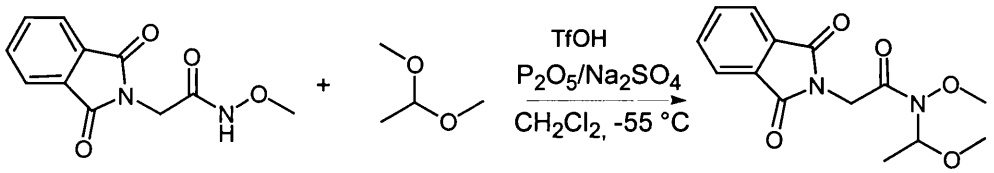
2.3.2.1 Multicomponent Condensations to give ABB-Type Products

This section describes an extensive investigation of the three-component condensation of hydroxamic acids with aldehydes, in particular three-component condensations that lead to ABB-type products derived from one molecule of hydroxamic acid (A) and two molecules of the same aldehyde (B) (scheme 2.29).



Scheme 2.29

When acetaldehyde dimethyl acetal was reacted with hydroxamic acid **40** in presence of phosphorus pentoxide, sodium sulfate and trifluoromethanesulfonic acid in dichloromethane, the hemiaminal **120** was the major product (95% yield, scheme 2.30).

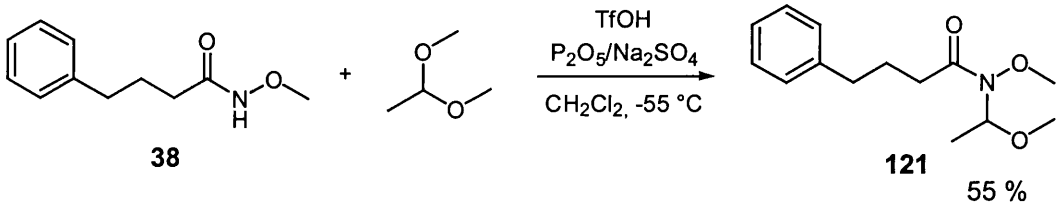


Scheme 2.30

This result suggested that either the conditions adopted were not strong enough to generate the *N*-acyliminium ion or that the protic acid was not suitable when acetals were employed; when more acid catalyst was added only more side-products from the aldol condensations and polymerizations were obtained. Even when more acetal was added, the reaction never led to the ABB product, and the hemieminal was always recovered in high yield.

Although the reaction did not give the desired compound, it was anyway interesting to discover the novel class of acyclic hemiaminals of type **120**. However since the aim was the production of a general route to aldehydic hydroxamic acids in one-pot reaction, the investigation of this new class of compounds was not pursued.

Nevertheless a further example was obtained along the course of this work, in which 4-phenylbutyric hydroxamic **38** acid and acetaldehyde dimethyl acetal react to give the hemiaminal **121** (scheme 3.31).

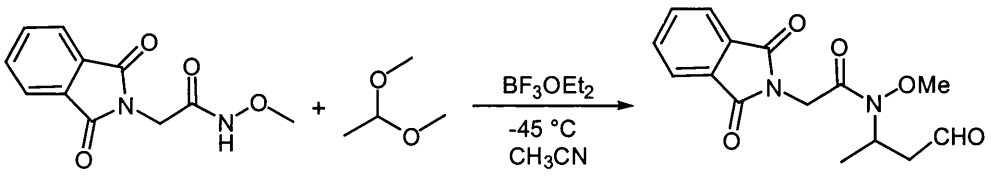


38 **121** 55 %

Scheme 2.31

Since trifluoromethanesulfonic acid in the presence of drying agents was not giving the desired three-component products when acetals were employed and since the trioxane form of butyraldehyde could not be prepared, other conditions needed to be found. Seeing that hydroxamic acid **40** together with paraldehyde in the presence of BF_3OEt_2 (entry 5, table 2.2) gave the three-component product **115** in a reasonable yield (46%), it was decided to apply the same reaction conditions to acetals. It was found that the condensation of **40** with acetaldehyde dimethyl acetal in the presence of $BF_3{\cdot}OEt_2$ gave the desired aldehydic hydroxamic acid **115** (scheme 2.32).

Although we had not yet examined the reaction of other hydroxamic acids with other acetals, it was reasonable to expect that this method could be applied in a general way.

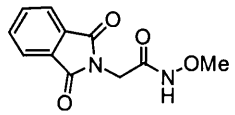
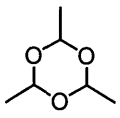
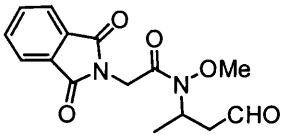
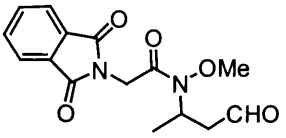
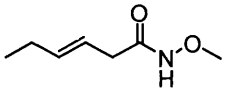
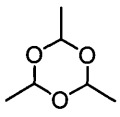
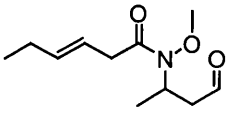
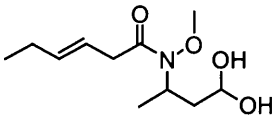
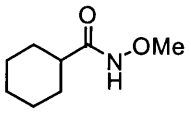
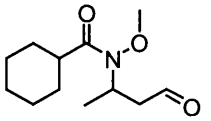
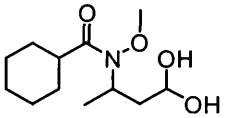


40 **115**

Scheme 2.32

These considerations prompted us to try the reaction using a variety of other hydroxamic acids bearing functional groups such as double bonds, heterocycles and acid-labile groups. It was shown that several of them were successfully converted into the corresponding β-aldehydic hydroxamic acid together with the hydrate form (table 2.4).

Table 2.4: Products from the three-component reaction of various hydroxamic acids with acetaldehyde.

Hydroxamic acid	Aldehyde	Conditions	Product	Yield %
 **40**		CF_3SO_3H/CH_2Cl_2 P_2O_5/Na_2SO_4 -55 °C	 **(115)**	55
		BF_3OEt_2/CH_3CN - 40 °C	 **(115)**	46
 **42**		CF_3SO_3H/CH_2Cl_2 P_2O_5/Na_2SO_4 -55 °C	Amide Bond Hydrolysis	-
		BF_3OEt_2/CH_3CN - 40 °C	 **(122)**	60
			 **(123)**	20
 **44**		BF_3OEt_2/CH_3CN - 40 °C	 **(124)**	48
			 **(125)**	12

When the three-component reaction was tried on **42** (entry 2, table 2.4), the *β*-aldehydic hydroxamic **122** was obtained in equilibrium with the hydrate form **123** in 78% yield as 3:1 ratio favouring aldehyde **122**. 4A Molecular sieves were employed to remove water from the hydrate form of the aldehyde; however NMR spectra showed the unchanged equilibrium of the two.

While the condensation of **42** with paraldehyde in trifluoromethanesulfonic acid led to hydrolysis of the amide bond (entry 4, table 2.3), the combination of acetaldehyde dimethyl acetal and $BF_3{\cdot}OEt_2$ gave in this case aldehyde **122** in good yield (60%), and **123** in 20% yield. The yields were estimated from the integration of NMR signals.

Evidently, intermolecular attack by an enol form of an aldehyde or an acetal is faster than the intramolecular attack by the C=C double bond in unsaturated in hydroxamic acids such as **42**. Participation of the double bond of **122** in a cyclisation was not observed although stereocontrolled intramolecular processes were observed with similar amides when condensed with aromatic aldehydes.[120] In the latter work, the aldehydes used could not enolise (lacking *α*-hydrogen atoms), and so various intermolecular processes were not possible.

These experiments showed that not only the three-component condensation proceeded *via* the intermolecular attack since **122** was observed, but also that the intermolecular condensation was especially favourable, as **122** was recovered in 60% yield.

When *O*-methyl hydroxamic acid **40** was reacted with paraldehyde and trifluoromethanesulfonic acid in presence of drying agents, aldehyde **115** was obtained in 55% yield but when $BF_3{\cdot}OEt_2$ was used the yield decreased to 46% (table 2.4). A reason for that could be that in the reaction with the hydroxamic acid **40,** two more equivalents of $BF_3{\cdot}OEt_2$ were needed because of the oxygen atoms of the phthaloyl group; this could cause a higher hindrance of the complex with consequent lower reactivity. Since six equivalents of $BF_3{\cdot}OEt_2$ were used, the conditions of reaction could have became unsuitably acidic.

The three-component condensation of hydroxamic **44** with acetaldehyde dimethyl acetal was carried out in acetonitrile at –40 °C in the presence of $BF_3{\cdot}OEt_2$, as already described (entry 3, table 2.4). Also in this case the *β*-aldehydic hydroxamic **124** was obtained in equilibrium with the hydrate form **125** where the ratio was 3:1 favouring the desired aldehyde; all the attempts either to separate or

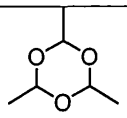
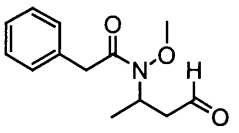
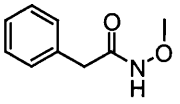
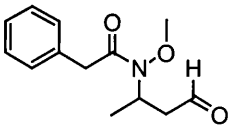
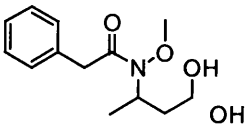
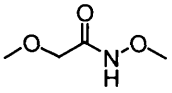
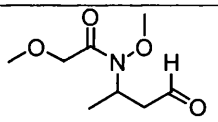
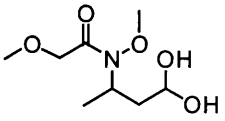
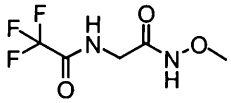
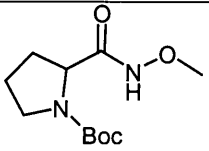
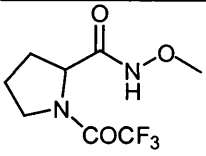
convert **125** into **124** were unsuccessful. The yields were estimated by ^{1}H NMR spectroscopy in this case, as previously. Although the compounds were always recovered in equilibrium with their hydrate form, this was not considered as a negative result since the hydrate form of an aldehyde should react similarly to the aldehyde.

To render the reaction more general various other hydroxamic acids bearing acid labile groups, heterocycles, heteroatoms or aromatic functions were investigated in the three-component reaction (table 2.5). The original idea was to apply the three-component reaction to the synthesis of highly substituted heterocycles of biological interest such as diazepinones, which is why glycine and proline were chosen first. A complete overview of the synthesis and the problems encountered along is given in section **2.3.3**.

Hydroxamic acid **45** was employed in the three-component reaction and gave the expected compound **127** together with **128** in reasonable yields (entry 2, table 2.5).

N-Protected proline hydroxamic acids **47** and **48** were investigated in the three-component reaction for the purpose of synthesising highly substituted heterocyclic system. The nitrogen atom *alpha* to the hydroxamic acid moiety needed to be protected to prevent it reacting intramolecularly with the *N*-acyliminium ion. *Boc* was selected as the protecting group; it was hoped that the three-component reaction and the removal of the *Boc* group could have been achieved all in a one-pot process. Unfortunately the *Boc* was lost and proline hydroxamic acid was detected unreacted. Similar treatment of substrate **48** (entry 4, table 2.5) gave an unidentified compound together with the product of the aldol condensation reaction of the aldehyde. These results can be rationalised by assuming that the nitrogen atom of the hydroxamic acid is inaccessible owing to restrained conformations of the protecting group within the rest of the molecule. Abandoning the idea of using proline hydroxamic acid derivatives to synthesise heterocyclic systems, it was decided to focus on the glycine derivatives only and to change the protecting group on the α-nitrogen atom by replacing the phthaloyl group with a trifluoroacetyl group. Hydroxamic acid **46** was subjected to the three-component reaction, but only unidentified compounds were observed together with the aldol condensation product. In view of this the synthesis of diazepinones derivatives, which is amply discussed in section **2.3.3**, was attempted using only the β-aldehydic hydroxamic acid **115** (entry 1, table 2.4).

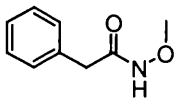
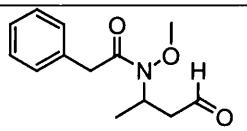
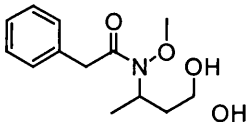
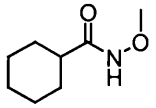
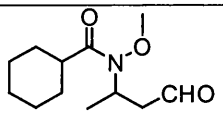
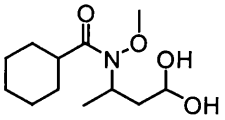
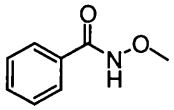
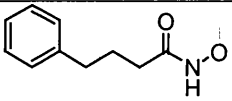
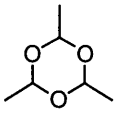
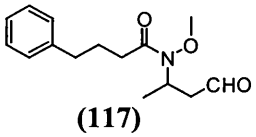
Table 2.5: Products from the three-component reaction of various hydroxamic acids with acetaldehyde equivalents

Hydroxamic acid	Aldehyde	Conditions	Product	Yield %
		CF_3SO_3H/CH_2Cl_2 P_2O_5/Na_2SO_4 -55 °C	 **(116)**	35
 **43**		BF_3OEt_2/CH_3CN - 40 °C	 **(116)**	33
			 **(126)**	18
 **45**		BF_3OEt_2/CH_3CN - 40 °C	 **(127)**	34
			 **(128)**	34
 **46**		BF_3OEt_2/CH_3CN - 40 °C	No reaction	-
 **47**		BF_3OEt_2/CH_3CN - 40 °C	Loss of the Boc group	-
		BF_3OEt_2/CH_3CN - 40 °C	Unidentified compounds and aldol condensation product	-

48

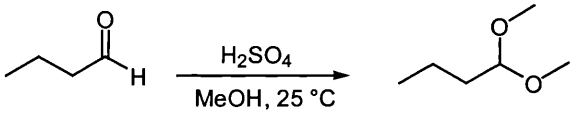
Hydroxamic acid **43** was reacted with acetaldehyde dimethyl acetals in the presence of $BF_3 \cdot OEt_2$ (entry 1, table 2.5) and paraldehyde in the presence of trifluoromethanesulfonic acid (entry 1 table 2.3); in both cases **116** was recovered in the same yield; when BF_3OEt_2 was employed, **116** was found in equilibrium with its hydrate form **126** as already observed for related compounds. When aromatic hydroxamic acids were employed, results were never satisfactory and the yields decreased in the order phenylacetic hydroxamic acid > 4-phenylbutyric hydroxamic > benzoic hydroxamic acid. (Table 2.6).

Table 2.6: Products from the three-component reaction of various hydroxamic acids with acetaldehyde equivalents

Hydroxamic acid	Aldehyde	Conditions	Product	Yield %
 **43**		BF_3OEt_2/CH_3CN - 40 °C	 **(116)**	35
			 **(126)**	18
 **44**		BF_3OEt_2/CH_3CN - 40 °C	 **(124)**	48
			 **(125)**	12
 **37**		BF_3OEt_2/CH_3CN - 40 °C	No reaction	-
 **38**		CF_3SO_3H/CH_2Cl_2 P_2O_5/Na_2SO_4 -55 °C	 **(117)**	12

The Lewis-acid mediated three-component reaction of benzoic hydroxamic acid **37** with acetaldehyde dimethyl acetal did not lead to the desired β-aldehydic hydroxamic acid. This may be due to conjugation of the aromatic ring with the hydroxamic acid moiety, decreasing the reactivity of the nitrogen atom owing to π-overlapping interactions. To confirm this hypothesis, cyclohexyl hydroxamic acid **44** (entry2, table 2.6) was employed and as expected the reaction proceeded to the three-component compound in satisfactory yield (38%). Additionally, the aromatic hindered **38** and **43** reacted with acetaldehyde as expected.

The process of generalisation of the three-component reaction was continued using other acetals. Butyraldehyde dimethyl acetal **129** (see table 2.7) was prepared according to the method of Chen and co-workers[121] (scheme 2.33)



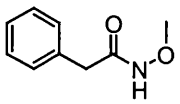
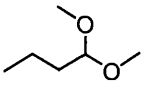
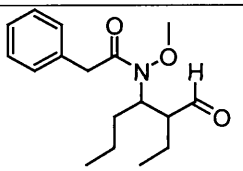
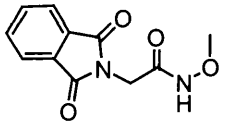
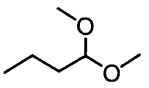
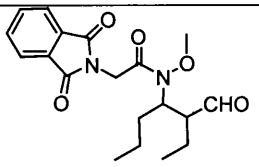
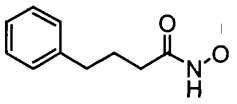
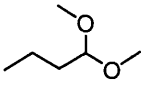
129 40 %

Scheme 2.33

Acetal **129** was reacted with hydroxamic acids **38**, **40**, and **43** that in the previous reaction with acetaldehyde dimethyl acetal gave the three-component product in a reasonable yield **43** and in a low yield **38**. The phthaloyl glycine derivative was selected because the preparation of other diazepinones was desired.

Phenylacetic hydroxamic acid **43** reacted with the acetal **129** to give the desired compound **130**. On the other hand when 4-phenylbutyric acid was employed, no compound could be detected and only decomposition products from the hydroxamic acid together with the products from the aldol condensation reaction were recovered. In continuing these studies, it was also found that the condensation reaction of the glycine hydroxamic acid derivative **40** with butyraldehyde dimethyl acetal afforded the desired compound in lower yield (33%) compared to the reaction where acetaldehyde dimethyl acetal was employed (55%). One possible explanation for this could be the steric hindrance of the butyraldehyde in the presence of the already bulky phthaloyl group, which will impede the approach of another molecule of aldehyde to the reactive intermediate.

Table 2.7: The three-component reaction using butyraldehyde dimethyl acetal.

Hydroxamic acid	Aldehyde	Conditions	Product	Yield %
 **43**	 **129**	BF_3OEt_2/CH_3CN - 40 °C	 **(130)**	35
 **40**		BF_3OEt_2/CH_3CN - 40	 **(131)**	33
 **38**		BF_3OEt_2/CH_3CN - 40 °C	No reaction	-

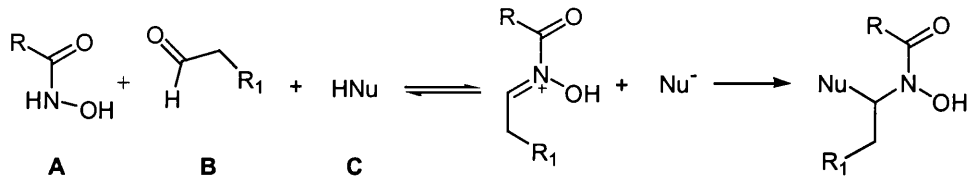
So far, it was revealed that the Lewis acid-mediated three-component reaction proceeded in moderate to excellent yield to give the corresponding *β*-aldehydic hydroxamic acids together with the hydrate form in a reasonably general way.

A mechanistic study could be undertaken to understand why boron trifluoro etherate leads the formation of the hydrate form of the aldehyde, which is not otherwise observed.

2.3.2.2 Multicomponent Condensations to give ABC-Type Products

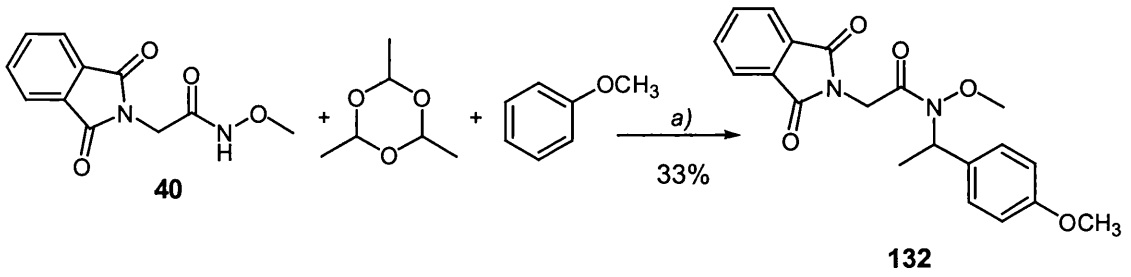
In this section is investigated three-component condensations that lead to ABC-type products, derived from one molecule each of hydroxamic acid (A) aldehyde (B)

and a nucleophile (C), the latter being either the enol form of another aldehyde or a more general nucleophile (scheme 2.34).



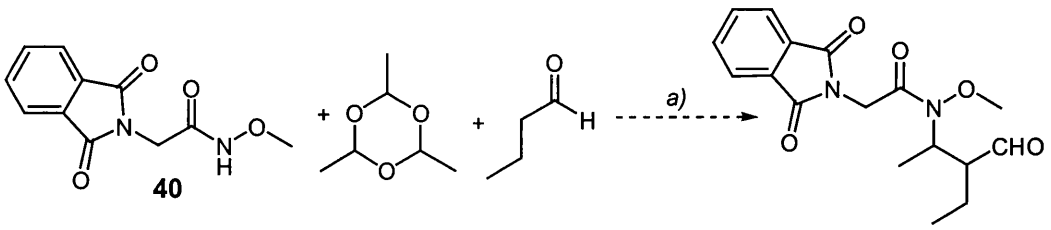
Scheme 2.34

In work conducted previously in our group, no condensations of the ABC-type were reported; nevertheless attempts to effect the three-component reaction were pursued. The reaction was tried using the *N*-phthaloyl glycine hydroxamic acid **40** with paraldehyde and anisole in a 1:1:1 ratio in the presence of trifluoromethanesulfonic acid and a dehydrating agents as already described in paragraph 2.4.2. The strategy for the synthesis described in scheme 2.35 assumes that under the reaction conditions the anisole will be ready to attack the *N*-acyliminium ion. Since it had already been shown that the *N*-acyliminium ion was formed in the presence of trifluoromethanesulfonic acid and a dehydrating agent, the course of the reaction would have been determined only by the ability of anisole to react faster than the enolic form of the acetaldehyde.



Scheme 2.35: Triflic acid, P_2O_5/Na_2SO_4; CH_2Cl_2; -78 °C; 5 h

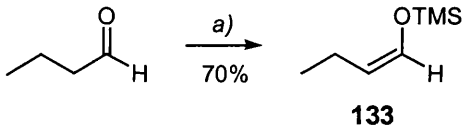
The three-component product **132** from the condensation ABC was obtained in 33% yield together with the aldol condensation product and unreacted starting material (25%). This is, to our knowledge, the first ABC-type reaction involving a hydroxamic acid. Encouraged by this result, the condensation was attempted on a more challenging situation where C is a different aldehyde (scheme 2.36).



Scheme 2.36: Triflic acid, P_2O_5/Na_2SO_4; CH_2Cl_2; -78 °C; 5 h

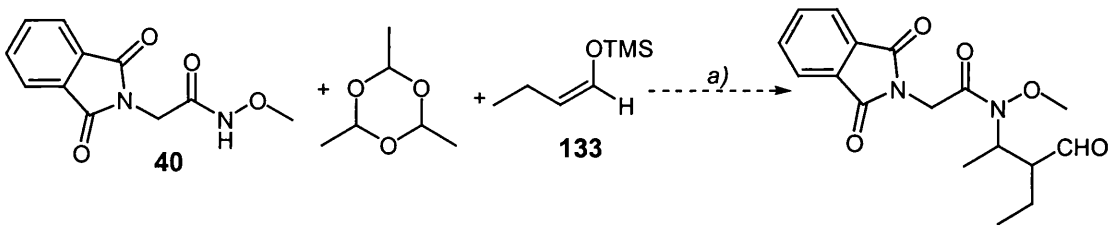
The reaction did not lead to the desired compound and only decomposition of the hydroxamic acid together with products from various side reactions of aldehydes were observed.

Next, we investigated the reaction in the same conditions employing butyl-1-enyloxytrimethylsilane **133** instead of butyraldehyde. The enol **133** was prepared according to the procedure described by Aggarwal and co-workers[122] (scheme 2.37).



Scheme 2.37: *a)* Et_3N, $(CH_3)_3SiCl$, DMF; 80 °C, 12 h.

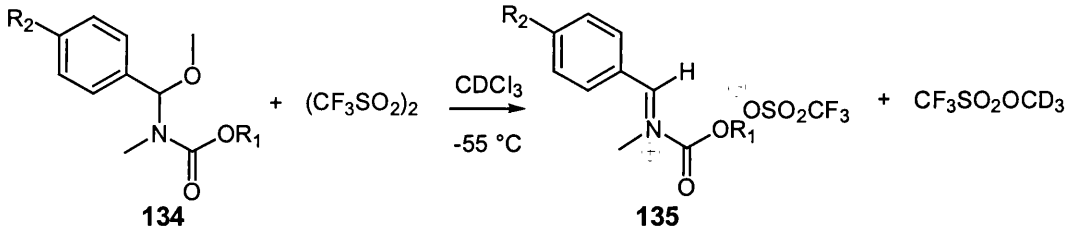
The reaction was initiated by adding a solution of the paraldehyde to the acid mixture and ended by adding **133** (scheme 2.38), no ABC-type product was observed and only side products were recovered.



Scheme 2.38: Triflic acid, P_2O_5/Na_2SO_4; CH_2Cl_2; -78 °C; 5 h

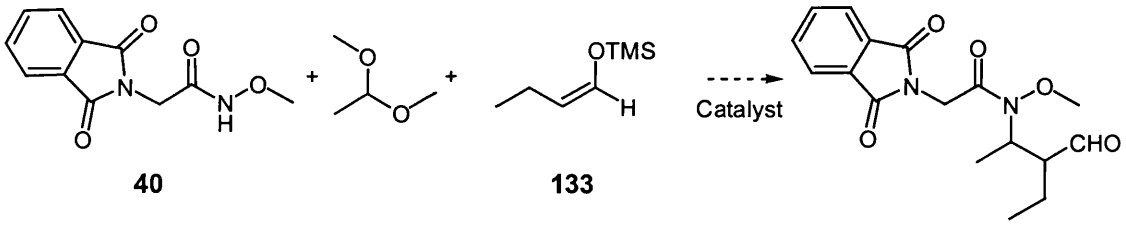
To explore the ABC-type condensation further, it was carried out another variation of the conditions using trifluoromethanesulfonic anhydride as catalyst. Yamamoto[99] showed that treatment of the hemiaminal **134** (scheme 2.39) with 1 equivalent of triflic anhydride at -55 °C afforded the *N*-acyliminium ion **135** almost quantitatively. Moreover, ^1H NMR studies carried out in deuterated chloroform showed that not only trifluoromethanesulfonic anhydride but also boron trifluoride

etherate or trimethylsilyl triflate would generate an equilibrium between **134** and **135** (scheme 3.39).[99]



Scheme 2.39

In view of these studies attempts were made to optimise the reaction conditions of the ABC-type condensation of hydroxamic acid **40** with acetaldehyde dimethyl acetal and **133** (scheme 2.40, table 2.8).



Scheme 2.40

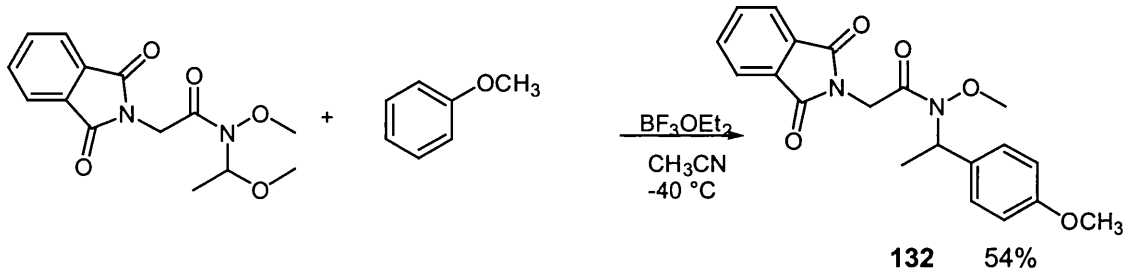
Table 2.8

Entry	Catalyst	Solvent	Temp °C	Result
1	$(CF_3SO_2)_2O$	DCM	-55 °C	Aldol condensation product and starting material unreacted
2	TMSOTf	DCM	-55 °C	Aldol condensation product and starting material unreacted
3	BF_3OEt_2	CH_3CN	-40 °C	Hemiaminal **120** and aldol condensation product

When dichloromethane and trifluoromethanesulfonic anhydride were used as solvent and catalyst respectively, the products from the aldol condensation reaction of the aldehydes and the unreacted hydroxamic acid **40** predominated (entry 1, table 2.8). Nor was trimethylsilyl trifluoromethanesulfonate in dichloromethane (entry 2, table 2.8) effective and it resulted in significant recovery of the starting material together with aldol condensation products. On the other hand when the reaction was

conducted in acetonitrile in the presence of boron trifluoride etherate, although the hydroxamic acid reacted with acetaldehyde dimethyl acetal to form the hemiaminal **120**, the reaction did not proceed to give the desired product; the butyraldehyde reacted with itself to give the aldol condensation product.

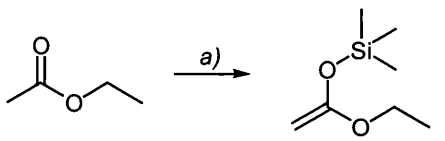
However, when the hemiaminal **120** was reacted with anisole in presence of boron trifluoride etherate in the conditions of entry 3, table 2.8 the compound **132** (scheme 2.41) was obtained in 54% yield; this result suggested that the butyraldehyde had already undergone self-condensation prior to the formation of *N*-acyliminium ion.



132 54%

Scheme 2.41

To investigate the reaction further the less reactive nucleophile (1-ethoxy vinyloxy)-trimethylsilane **136** and vinyl acetate were used. The ketene acetal **136** was prepared using the literature procedure of Mikami[122] (scheme 2.42).

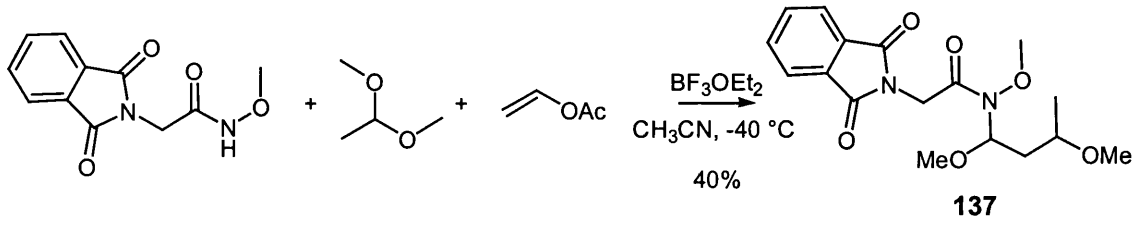


136 70%

Scheme 2.42: *a)* Diisopropylamine, 1.6 M BuLi in hexane, TMSCl; THF, -78°C-rt, 3h.

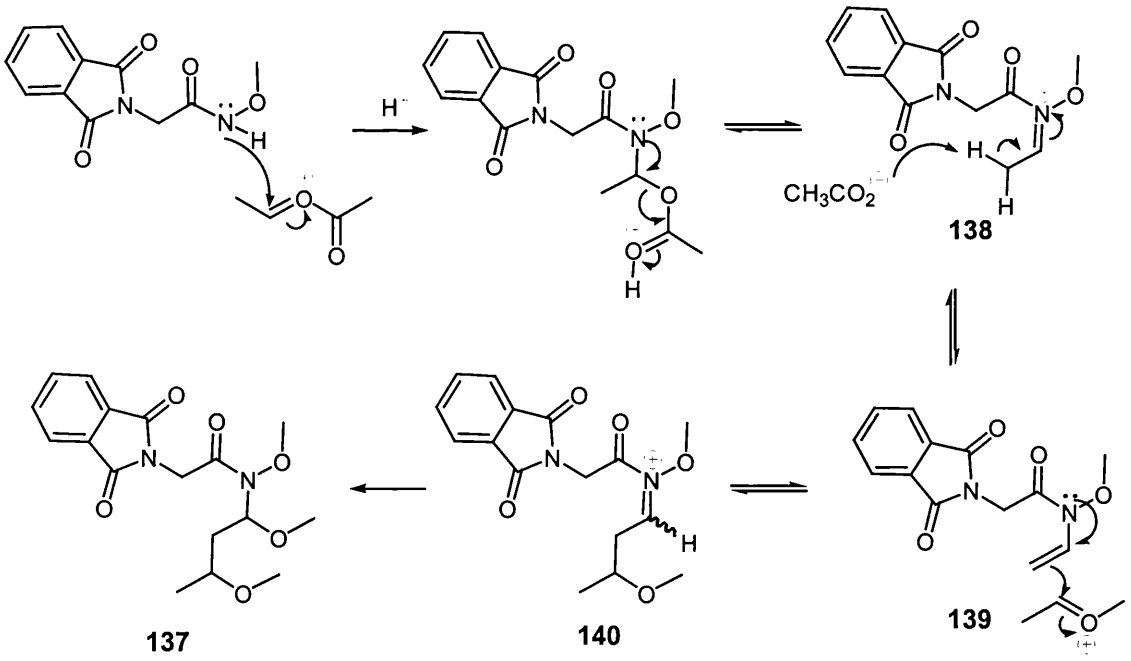
The use of such nucleophiles was particularly important for the approach planned because it was hoped that their self-condensation would occur more slowly than that of **136** and that the *N*-acyliminium ion would react with the nucleophile before the latter had time to undergo self-condensation. Unfortunately, the desired product could not be observed in any of the cases examined; nevertheless a rather interesting product was observed when hydroxamic acid **40** was reacted with vinyl

acetate and acetaldehyde dimethyl acetal in boron trifluoride diethyl etherate (scheme 2.43).



Scheme 2.43

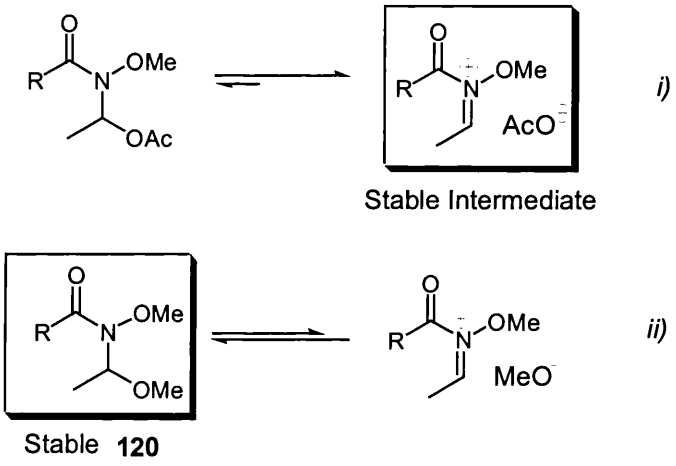
^{1}H and ^{13}C NMR studies together with mass spectrometry confirmed that the major product was **137** instead of the expected hemiaminal **120**. A plausible mechanism is shown is scheme 2.44.



Scheme 2.44

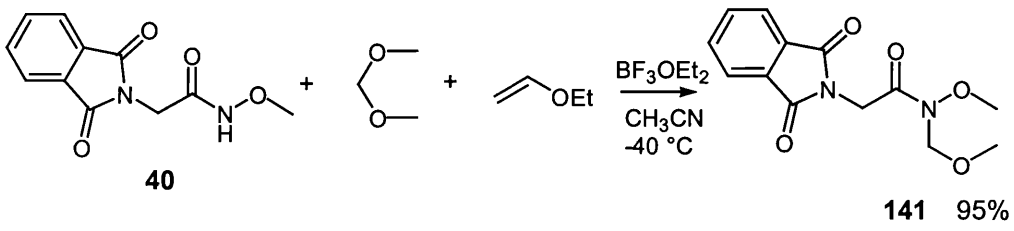
The mechanism involves an initial attack of the nitrogen atom of the hydroxamic acid moiety on the protonated form of the vinyl acetate (scheme 2.44) followed by loss of the acetyl group, to give the *N*-acyliminium ion **138**. The next step involves deprotonation to give intermediate **139**. Subsequent attack of **139** by the oxonium ion derived from the dimethyl acetal gives the *N*-acyliminium ion **140**, which will readily react with methanol present in solution to give **137**. Importantly, when vinyl acetate was omitted from the reaction, **137** was not observed. Also

important is that when acetaldehyde dimethyl acetal is used, no **137** is observed. In the case reactions conducted in presence of methanol it is considered that the ionisation to give the corresponding *N*-acyliminium cation is significantly lower than for the acetic acetate reactions (see scheme 2.45). Thus, methanol effectively traps cations such as **138**, forming the isolable intermediates of type **120**. Conversely, ionisation of acetated-derived hemiaminals is more ready (*i.e. i* in scheme 2.45) and so further reactions can occur, especially deprotonation and subsequent reactions (scheme 2.44).



Scheme 2.45

However to reproduce the same conditions of the three-component reaction showed in scheme 2.35 where acetaldehyde dimethyl acetal and anisole were reacted, it was decided to carry out our last experiment on the hydroxamic acid **40** with dimethoxymethane and ethyl vinyl ether in acetonitrile in the presence of boron trifluoride etherate (scheme 2.46).



40 **141** 95%

Scheme 2.46

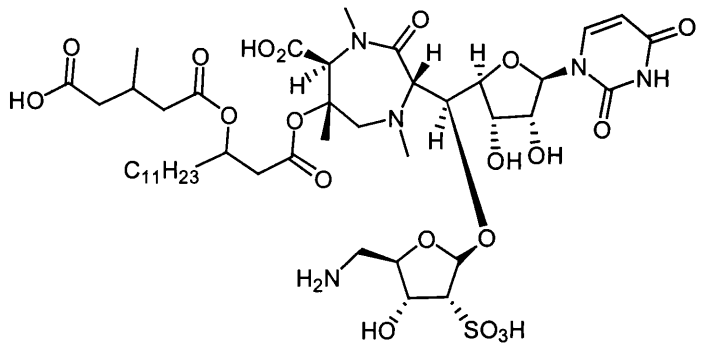
Unfortunately, there was no evidence of the desired product; a substantial quantity of the hemiaminal **141** was recovered together with polymers derived from ethyl vinyl ether.

In conclusion, the three-component reaction of hydroxamic acids with two different aldehydes did not furnish the ABC system by a mechanism that involves an initial attack of the first molecule of aldehyde followed by nucleophilic attack of the enol of the second aldehyde to the *N*-acyliminium ion. While it is believed this could be achieved, the conditions and especially relative reactivity of the two aldehyde components need to be finely balanced.

2.3.3 Reaction of Multicomponent Products

Nitrogen-containing heterocycles are abundant in nature and exhibit diverse and important properties.[123] Accordingly, novel strategies for the synthesis of ring systems of diazepines and related structures such as [1,4] diazepanones would be most useful. A variety of preparative methods have been developed[124-126] and there are many reviews on their biological properties.[127-129]

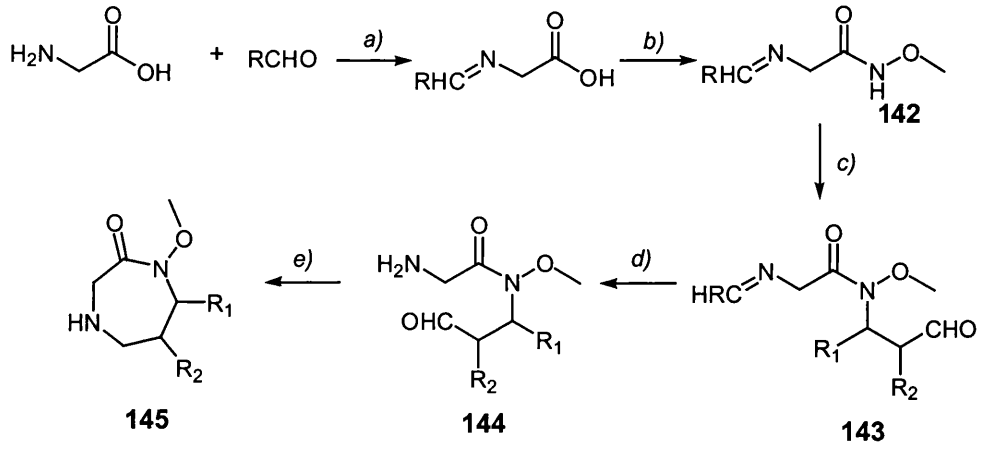
The seven-membered ring [1,4] diazepanone is found in the core structure of a variety of antibiotic such as the liposidomycin C (fig. 2.5), which is an important nucleoside antibiotics isolated from *Streptomyces grisoeosporeus*.[130] Liposidomycins A and B show variation only in the lipid portion.[125] They all inhibit the formation of the lipid intermediate in some bacterial reproductive synthesis. The growing emergency of drug resistance by specific bacterial strains to current antibiotics is becoming a problem of profound importance around the world and has prompted the need for the synthesis new antibiotics with novel mechanisms of action.



liposidomycin C

Fig 2.5

The elaboration of a novel synthesis of [1,4]diazepanones obtainable by combining the chemistry of *N*-acyliminium ions and the ring closure reductive amination offers an interesting application of the three-component reactions discussed above. In scheme 2.47 is proposed a route to various [1,4] diazepanones **145** that involves (i) protection of the *alpha* amine group (ii) formation of the aldehydic α-amino hydroxamic acids **144** followed by (iii) reductive amination to give [1,4] diazepanone derivatives.

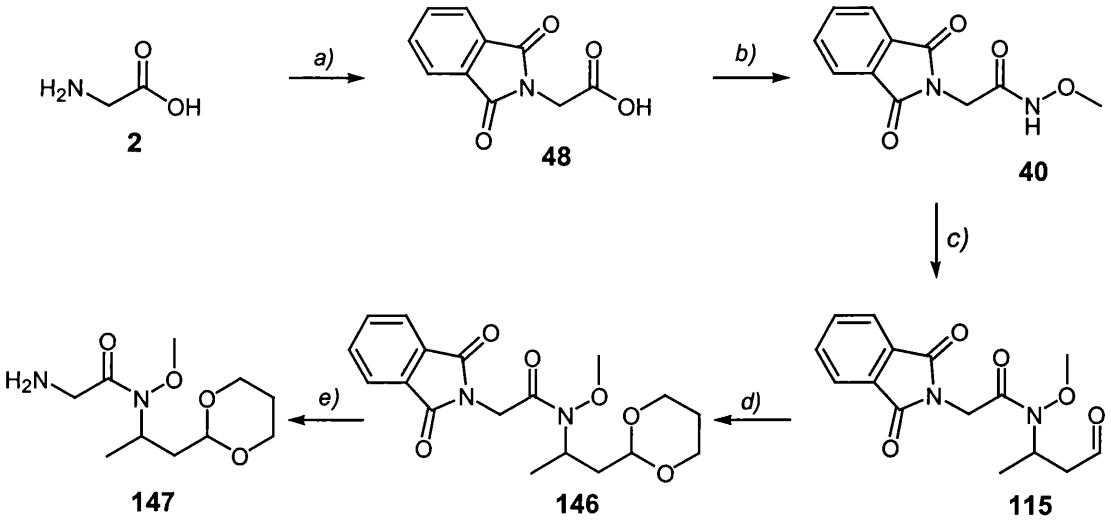


Scheme 2.47: *a)* Mg SO_4; MeOH; 25 °C; 24 h. *b)* NH_2OMe, Ethyl chloroformate, NMM; Et_2O; 0-25 °C; 1 h. *c)* $CH_3CH(OCH_3)_2$, BF_3OEt_2, CH_3CN, -40 °C, 1-4 h. *d)* 1.0 M HCl, H_2O; 25 °C, 3 h. *e)* $NaBH_3CN$, THF, 20 °C.

The original idea was to attach the α-amino hydroxamic acid either to an aldehydic polymer support or else to an aromatic aldehyde to form in both cases a Schiff base. However, it was found that the Schiff base would not stand the conditions where the carboxylic acid was converted into the hydroxamic acid (step *b)* scheme 2.47).

2.3.3.1 An Approach to [1,4] Diazepan-2-ones

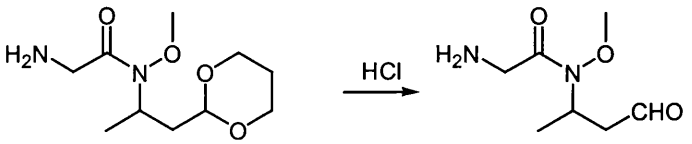
It was envisaged that attachment of an α-amino hydroxamic acid to either an aldehydic polymer support or to an aromatic aldehyde would give the protected imine which could be subjected to the three-component amidoalkylation prior to reductive cyclisation to [1,4] diazepan-2-ones. The latter heterocycles are analogous to the well-known and widely used [1,4] benzodiazepines which have found extensive use as tranquillisers and antidepressant.[131] However, although imines could be formed from aromatic aldehydes, such imines did not behave as protective groups even at the stage of conversion of the carboxylic acid into the hydroxamic acid. It proved difficult to handle the amine nitrogen while inducing reaction at the amidic nitrogen. Nor was monoprotection with benzylic or acyl groups helpful since both led to reaction at the amine nitrogen atom, usually with the formation of 3-hydroxy-4-imidazolidinones **3** (scheme 1.5, section **1.2.1** chapter 1). Complete protection on nitrogen was found to be necessary and the use of the phthaloyl group was shown to be effective. However, protection of aldehyde **115** (scheme 2.48) as an acetal was necessary in order to permit deprotection of the phthaloyl group.



Scheme 2.48: *a)* Phthalyc anhydride, pyridine, 90 °C, 20 h. *b)* NH_2OCH_3, NMM, ethylchloroformate; diethyl ether, 0 °C, 30min. *c)* $CH_3CH(OCH_3)_2$, BF_3OEt_2; acetonitrile, -40 °C, 4 h. *d)* 1,3-propanediol, *p*-TsOH; toluene; 120 °C, 5 h. *e*) NH_2NH_2, ethanol, 100 °C, 1 h.

When **147** was subjected to acetal cleavage under conditions described by Kirkovsky,[132] only polymers from the aldehyde were detected by mass spectroscopy.

Therefore various attempts to optimise the conditions of reaction were made (table 2.9).



147 148

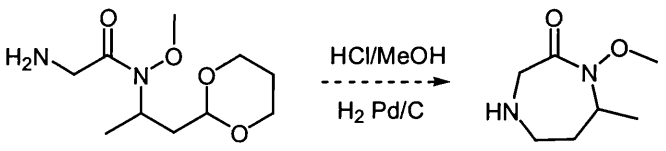
Scheme 2.50

Table 2.9

Entry	Conditions	Solvent	Results
1	1.5 M	THF	Mixture of products
2	0.4 M	THF	Mixture of products
3	1 M	H_2O /EtOH	Mixture of products
4	1 M	MeOH	Mixture of products

To steer the reaction towards an intramolecular pathway, it was decided to use more dilute conditions (entry 2, table 2.9) and different solvents, but the desired compound could not be detected either by NMR spectroscopy or mass data and only a complex mixture of products was observed.

Consequently, a thorough literature research revealed a suitable method by Andres[133] in which the deprotection step and the reductive ammination were achieved in a one-pot procedure, as depicted in scheme 2.51. Also in this case cyclisation could not be achieved and a complex mixture of inseparable products was obtained.



Scheme 2.51

By appropriate selection of the reaction conditions, it was hoped to produce the seven-membered ring of structure **145** (scheme 2.47). Surprisingly it did not prove to be easy to cleave the acetal, probably because of interference by the amino group. A variety of experiments, involving varying concentrations and solvents did not reveal an obvious trend or way forward.

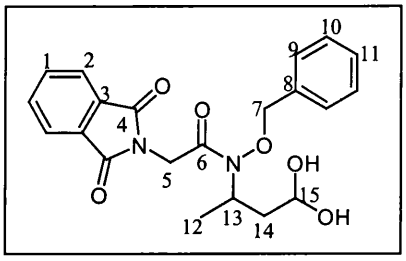
2.4 Conclusions

In this chapter, a new three-component between ABB-type condensation involving an *O*-protected hydroxamic acid and two molecules of the same aldehyde has been developed in moderate yield to give the corresponding *β*-aldehydic hydroxamic acid. Since we have shown that the *β*-aldehydic hydroxamic acids can be obtained by employing suitable aldehyde dimethyl acetals, this methodology offers a useful approach to the synthesis of these important intermediates. Efforts were made to extend this approach to the synthesis of ABC-type systems in which two different aldehydes are employed, but unfortunately no experimental conditions could be found to achieve the desired product. In addition, attempts were made to clarify the parameters governing the three-component reaction.

Further application of the three-component reaction to the synthesis of [1,4] diazepan-2-ones, an important class of biologically interesting heterocycles, was undertaken. Difficulties encountered in the last step of deprotection and consecutive cyclisation precluded the formation of the ring. An alternative strategy, involving a different protecting group on the amine nitrogen atom, may be successful.

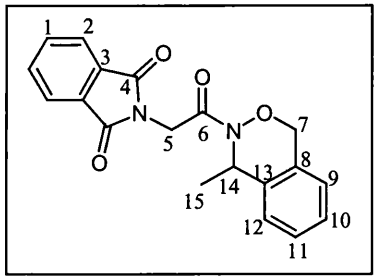
2.5 Experimental

_N_-Benzyloxy-_N_-(3,3-dihydro-1-methylpropyl)-2-(1,3-dioxoisoindol-2-yl)-acetamide (110)



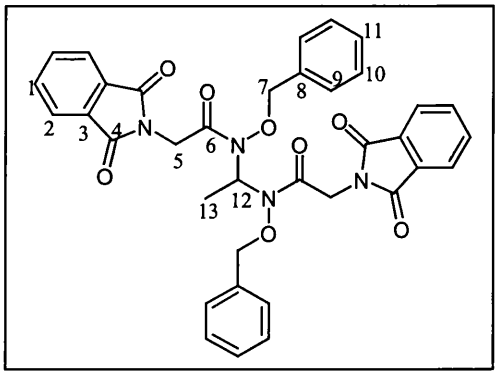
To a solution of _N_-phthalic glycine-_N_-benzylic hydroxamic acid (0.30 g, 1.0 mmol) and paraldehyde (0.14 mL, 1.0 mmol) in dichloromethane (1.0 mL), was added trifluoromethanesulfonic acid (20 μL). After stirring for an hour the mixture was poured over ice, made alkaline with sodium hydroxide 1.0 M, extracted with dichloromethane (3 x 5 mL) and dried over $MgSO_4$. The residue was purified by flash chromatography (5:95 ethyl acetate:toluene) to give **110** (73.0 mg, 19%) as a white powder: mp 163-165 °C; IR ν_{max} (cm^{-1}) (KBr) 3294 (Ar), 3178 (Ar), 1678 (CO); ^{1}H NMR 7.85 (2H, m, H_1), 7.71 (2H, m, H_2), 7.47 (1H, m, H_{11}) 7.43 (4H, m, H_9;H_{10}), 5.84 (1H, dd, J = 11.1, Hz J = 2.4 Hz, H_{15}), 5.33 (1H, d, J = 10.7 Hz, $H_{7a,}$), 5.11 (1H, d, J = 10.7 Hz, H_{7b}), 4.65 (1H, d, J = 17.3 Hz, H_{5a}), 4.38 (1H, d, J = 17.3 Hz, H_{5b}) 3.82 (1H, m, H_{13}), 2.01 (1H, dt, J = 12.9, J = 2.4 Hz, H_{14}), 1.65 (1H, dt, J = 12.9, J = 2.4 Hz, H_{14a}), (1H, dt, J = 12.9, J = 11.1 Hz, H_{14b}), 1.30 (3H, d, J = 5 Hz, H_{12}); ^{13}C NMR 167.8 (C_4), 164.4 (C_6), 134.2 (C_8), 134.0 (C_3), 132.1 (C_1), 129.4 (C_{10}), 129.2 (C_9), 128.8 (C_{11}), 123.4 (C_2), 98.1 (C_{15}), 80.4 (C_7), 71.7 (C_{13}), 39.2 (C_5),34.5 (C_{14}), 20.1(C_{12}). LRMS M/Z (EI) 380 (M-18, 2%), 230 (7), 160 (55), 115 (54), 91 (47). Found C, 64.67, H, 5.68, N, 6.48, ($C_{21}H_{22}N_2O_6$ + ½ H_2O requires C, 64.78, H, 5.91, N, 7.09).

2-[2-(1,4-Dihydrobenzo[d][1,2]oxazin-3-yl)-2-oxoethyl]-isoindole-1,3-dione (113)



To a solution of *N*-phthalic glycine-*N*-benzylic hydroxamic acid (0.15 g, 0.53 mmol) and paraldehyde (0.07 mL, 0.53 mmol) in dichloromethane (2.65 mL), was added trifluoromethanesulfonic acid (53 μL). After stirring for an hour the mixture was poured over ice, made alkaline with sodium hydroxide 1 M, extracted with dichloromethane (3 x 5 mL) and dried over $MgSO_4$. The residue was purified by flash chromatography (2:8 ethyl acetate: petroleum ether) to give **113** (0.10 g, 60%) as a white microprisms: mp 196-199 °C; IR ν_{max} (cm^{-1}) (KBr) 3150 (Ar), 2877 (Ar), 1669 (CO); ^{1}H NMR 7.84 (2H, m, H_1), 7.70 (2H, m, H_2), 7.24 (2H, m, H_{10};H_{11}), 7.10 (1H, d, J = 4.5 Hz, H_9), 6.92 (1H, d, J = 4.5 Hz, H_{12}), 5.37 (1H, q, J = 5 Hz, H_{14}), 5.30 (1H, d, J = 15 Hz, H_{7a}), 5.01 (1H, d, J = 15 Hz, H_{7b}), 4.77 (1H, d, J = 20 Hz, H_{5a}), 4.60 (1H, d, J = 20 Hz, H_{5b}), 1.53 (3H, d J = 5 Hz, H_{15}); ^{13}C NMR 167.9 (C_4), 164.4 (C_6), 134.8 (C_8), 133.9 (C_3), 132.1 (C_2), 130.3 (C_1), 127.4 (C_{12}), 126.9 (C_{11}), 126.6 (C_9), 124.3 (C_{10}), 123.4 (C_1), 72.3 (C_7), 49.8 (C_{14}), 38.9 (C_5), 20.5 (C_{15}); LRMS M/Z (Fab +): 337 (15), 225 (10), 160 (30), 133 (26), 91 (11). Found C, 66.66, H, 5.06, N, 8.20, ($C_{19}H_{16}N_2O_4$ + ½ H_2O requires C, 66.08, H, 4.92, N, 8.11).

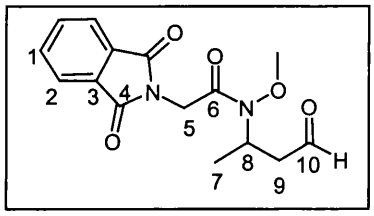
***N*-Benzyloxy-*N*-(1-{benzyloxy-[2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-acetyl]-amino}-ethyl)-2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-acetamide (114)**



To a solution of *N*-phthalic glycine-*N*-benzylic hydroxamic acid (0.30 g, 1.0 mmol) and paraldehyde (0.14 mL, 1.0 mmol) in dichloromethane (1.0 mL), was added trifluoromethanesulfonic acid (20 μL). After stirring for an hour the mixture was poured over ice, made alkaline with sodium hydroxide 1 M, extracted with dichloromethane (3 x 5 mL) and dried over $MgSO_4$.

The residue was purified by flash chromatography (5:95 ethyl acetate:toluene) to give **114** (0.23 g, 35%) as a colourless oil: IR ν_{max} (cm^{-1}) (KBr) 3388 (Ar), 2997 (Ar), 1778 (CO), 1665 (CO); ^{1}H NMR 7.86 (4H, m, H_2), 7.69 (4H, m, H_1), 7.23 (10H, s, Ph), 6.28 (1H, q J = 3 Hz, H_{12}), 5.02 (4H, d, J = 9 Hz, H_{5a}), 4.96 (4H, d, J = 9 Hz, H_{5b}), 4.56 (4H, s, H_7), 1.74 (2H, d J = 3 Hz, H_{13}); ^{13}C NMR 171.4 (C_4), 168.1 (C_6), 134.2 (C_8), 134.4 (C_2), 132.7 (C_3), 129.9 (C_{10}), 129.5 (C_{11}), 129.2 (C_9), 123.9 (C_1), 79.5 (C_7), 68.9 (C_{12}), 39.8 (C_5), 16.7 (C_{13}); LRMS M/Z (Fab +) 669 (M + Na, 25%), 333 (19), 160 (66), 133 (25), 91 (60). HRMS Found 669.19798 ($C_{36}H_{30}N_4O_8$ + Na requires 669.19612).

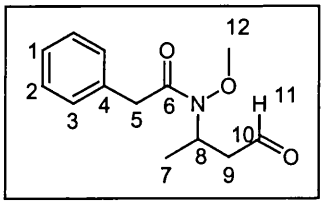
2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-*N*-methoxy-*N*-(1-methyl-3-oxopropyl)-acetamide (115)



To a solution of 2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-*N*-methoxyacetamide (0.20 g, 0.85 mmol), phosphorus pentoxide (0.40 g, 4.27 mmol) and sodium sulfate (1.20 g, 8.54 mmol) in dry dichloromethane (3.0 mL) was added, at –78 °C, trifluoromethanesulfonic acid (91 μL, 1.02 mmol). After 2 min a solution of paraldehyde (0.13 mL, 0.9 mmol) in dry dichloromethane (1.0 mL) was added dropwise over 1 h. The mixture was allowed to warm to –50 °C and stirred for 3 h. The reaction was quenched and neutralized at –20 °C, with saturated sodium hydrogen carbonate and slowly allowed to warm to 25 °C. The aqueous layer was extracted with dichloromethane (3 x 10 mL). The organic layers were washed with brine, dried over $MgSO_4$, filtered and then evaporated under reduced pressure to give a pale yellow oil. Purification by column chromatography (9:1 toluene:ethyl acetate) gave **115** (0.11 g; 55%) as colourless oil: IR ν_{max} (cm^{-1}) (KBr) 3430 (Ar), 1707 (CO), 1746 (CO), 1645 (CO); ^{1}H NMR 9.70 (1H, t, J = 1.5 Hz, CHO), 7.84 (2H, m, Ar), 7.23-7.70 (2H, m, Ar), 4.70 (1H, q, J = 8 Hz, H_8), 4.60 (1H, d, J = 16 Hz, H_{5a}), 5.53 (1H, d, J = 16 Hz, H_{5b}), 3.87 (3H, s, CH_3), 2.90 (1H, ddd, J = 16 Hz, J = 4 Hz, J = 8 Hz, H_{9a}), 2.68 (1H, ddd, J = 16 Hz, J = 4 Hz, J = 1.5 Hz, ^{3}J = 5 Hz, H_{9b}), 1.34 (3H, d J = 8 Hz, H_7); ^{13}C NMR 199.8 (C_{10}), 169.3 (C_6), 168.2 (C_4), 134.3 (C_2), 132.6 (C_3),

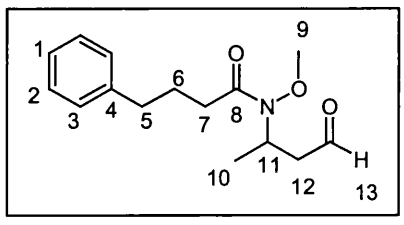
123.8 (C_1), 65.1 (C_{11}), 50.9 (C_8), 47.9 (C_9), 39.7 (C_5), 21.7 (C_7). HRMS Found 305.11346 ($C_{15}H_{16}N_2O_5$ requires 305.11374).

_N_-Methoxy-_N_-(1-methyl-3-oxopropyl)-2-phenylacetamide (116)



To a solution of _N_-methoxy-2-phenyl acetamide (0.20 g, 1.2 mmol), phosphorus pentoxide (0.52 g, 3.68 mmol) and sodium sulfate (1.70 g, 12.1 mmol) in dry dichloromethane (6.0 mL) was added, at –78 °C, trifluoromethanesulfonic acid (0.13 mL, 1.4 mmol). After 2 min a solution of paraldehyde (0.16 mL, 1.2 mmol) in dry dichloromethane (1.0 mL) was added dropwise over 1 h. The mixture was allowed to warm to –50 °C and stirred for 5 h. The reaction was quenched and neutralized at –20 °C, with saturated sodium hydrogen carbonate. The aqueous layer was extracted with dichloromethane (3 x 15 mL) then washed with brine. The organic layers were dried over magnesium sulfate, filtered and evaporated under reduced pressure to give a yellow oil. Purification by column chromatography (7:3 toluene:ethyl acetate) gave **116** (75 mg; 27%) as colourless oil: IR ν_{max} (cm^{-1}) (KBr) 3230 (Ar), 1699 (CO), 1634 (CO); ^{1}H NMR 9.72 (1H, t J = 3 Hz, CHO), 7.26 (5H, m, Ar), 4.80 (1H, q, J = 6 Hz, H_8), 3.77 (1H, d, J = 9 Hz, H_{5b}), 3.73 (3H, s, H_{12}), 3.69 (1H, d J = 9 Hz, H_{5a}) 2.81 (1H, ddd J = 21 Hz, J = 12 Hz J = 3 Hz, H_{9a}), 1.27 (3H, d, J = 6 Hz, H_7); ^{13}C NMR 199.8 (C_{10}), 168.7 (C_6), 134.4 (C_4), 129.2 (C_2), 128.5 (C_3), 126.8 (C_1), 64.5 (C_{12}), 49.8 (C_8), 47.8 (C_9), 40.1 (C_5), 18.1 (C_7). HRMS Found 235.12008 ($C_{13}H_{17}NO_3$ requires 235.12084).

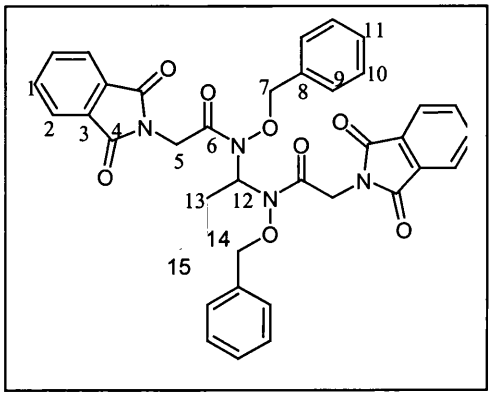
_N_-methoxy-_N_-(1-methyl-3-oxopropyl)-4-phenylbuyramide (117)



To a solution of _N_-Methoxy-4-butyramide (0.20 g, 1.0 mmol), phosphorus pentoxide (0.40 g, 4.3 mmol) and sodium sulfate (1.47 g, 10.0 mmol) in dry dichloromethane (4.0 mL) was added, at –78 °C, trifluoromethanesulfonic acid (110.0 μL, 1.2 mmol). After 2 min a solution of

paraldehyde (0.15 mL, 1.0 mmol) in dry dichloromethane (1.0 mL) was added dropwise over 1 h. The mixture was allowed to warm to –50 °C and stirred for 3.5 h. The reaction was quenched and neutralized at –20 °C, with saturated sodium hydrogen carbonate. The aqueous layer was extracted with dichloromethane (3 x 15 mL) then washed with brine. The combined organic layers were dried over magnesium sulfate filtered and evaporated under reduced pressure to give a yellow oil. Purification by column chromatography (9:1 toluene:ethyl acetate) gave **117** (41 mg; 15%) as colourless oil: IR ν_{max} (cm^{-1}) (KBr) 3323 (Ar), 1701 (CO), 1698 (CO); ^{1}H NMR 9.70 (1H, t, J = 1.5 Hz, H_{13}), 7.21 (5H, m, Ar), 5.27 (1H, br m, H_{11}), 3.65 (3H, s, H_9), 2.66 (1H, ddd, J = 22 Hz, J = 1.6 Hz, J = 7.6 Hz, H_{12a}), 2.63 (2H, m, H_5), 2.38 (2H,m, H_6), 1.92 (2H, m, H_7), 1.25 (3H, d, J = 8 Hz, H_{10}); ^{13}C NMR 199.9 (C_{13}), 170 (br, C_8), 141.6 (C_4), 128.5 (C_2), 128.3 (C_3), 64.5 (C_9), 49.4 (C_{11}), 47.8 (C_{12}), 35.2 (C_5), 32.4 (C_7), 25.8 (C_6), 18.2 (C_{10}). HRMS Found 264.15578 ($C_{15}H_{21}NO_3$ + H requires 264.15550).

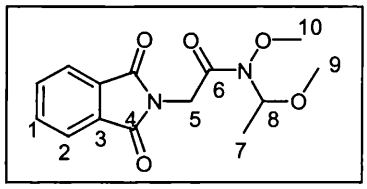
_N_-Benzyloxy-_N_-(1-{benzyloxy-[2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-acetyl]-amino}-butyl)-2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-acetamide (118)



_N_-Benzyloxy-2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-acetamide (0.15 g, 0.5 mmol) was dissolved in dry dichloromethane (1.6 mL) and cooled to –30 °C when trifluoromethanesulfonic acid (23.0 μL, 0.3 mmol) was added. A solution of butyraldehyde (0.10 mL, 1.1 mmol) in dry dichloromethane (1.0 mL) was added dropwise over a period of 30 min and the mixture stirred for 2 h. The mixture was quenched at –15 °C with saturated sodium hydrogen carbonate to pH = 7. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the collected organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude was purified by column chromatography (3:7 ethyl acetate:toluene) to give the **118** (36%, 0.13 g) as a colourless oil: IR ν_{max} (cm^{-1})

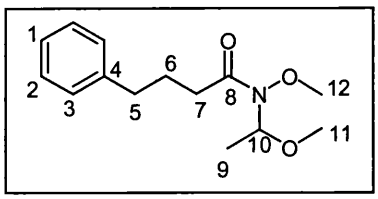
(KBr) 3398 (Ar), 2997 (Ar), 1789 (CO), 1645 (CO); ^{1}H NMR 7.86 (4H, m, H_2), 7.69 (4H, m, H_1), 7.37 (10H, s, Ph), 6.08 (1H, br s, H_{12}), 5.02 (4H, br d, J = 9 Hz, H_5), 4.56 (4H, s, H_7), 2.34 (2H, br s, H_{13}), 1.46 (2H, m, H_{14}), 0.95 (3H, t, J = 6 Hz, H_{15}); ^{13}C NMR 168.6 (C_2), 167.7 (C_4), 134.0 (C_2), 132.3 (C_8), 130.0 (C_1), 129.1 (C_9), 128.8 ($C_{9,15}$), 123.5 (C_3), 78.9 (C_{14}), 60.4 (C_7), 39.5 (C_5), 34.2 (C_{13}), 19.2 (C_{12}), 13.6 (C_{11}). M/Z (EI): 674 (3%), 365 (85), 188 (100), 160 (80), 91 (100). HRMS Found 674.23743 ($C_{38}H_{34}N_4O_8$ requires 674.23767).

2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-*N*-methoxy-*N*-(1-methoxy-ethyl)-acetamide (120)



To a suspension of 2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-*N*-methoxy-acetamide (50.0 mg, 0.2 mmol), phosphorus pentoxide (0.15 g, 1.1 mmol) and sodium sulfate (0.15 g, 1.1 mmol) in dry dichloromethane (1.0 mL) was added, at –50 °C, trifluoromethanesulfonic acid (21.0 µL). After 2 min a solution of acetaldehyde dimethyl acetal (47.0 µL, 0.4 mmol) in dry dichloromethane (0.52 mL) was added dropwise over 1 h. The mixture was allowed to stir at –50 °C and stirred for 3 h. The reaction was quenched and neutralized at –20 °C, with saturated sodium hydrogen carbonate. The aqueous layer was extracted with dichloromethane (3 x 10 mL) then washed with brine. The organic layers were dried over magnesium sulfate filtered and evaporated under reduced pressure to give a viscous solid. Purification by column chromatography (9:1 toluene:ethyl acetate) gave **120** (51 mg; 82%) as white powder: mp 114-116 °C; IR ν_{max} (cm^{-1}) (KBr) 3479 (Ar), 1776 (CO), 1716 (CO); ^{1}H NMR 7.85 (2H, m, H_2), 7.72 (2H, m, H_1), 5.52 (1H, q, J = 6 Hz, H_8), 4.69 (1H, d, J = 17 Hz, H_{5a}), 4.58 (1H, d, J = 17 Hz, H_{5b}), 3.98 (3H, s, H_{10}), 3.34 (3H, s, H_9), 1.44 (3H,d, J = 6 Hz, H_7); ^{13}C NMR 168.2 (C_6), 167.9 (C_4), 134.0 (C_2), 132.2 (C_3), 123.5 (C_1), 84.8 (C_8), 65.6 (C_{10}), 56.0 (C_9), 39.0 (C_5), 17.6 (C_7). Found C, 56.51, H, 5.49, N, 9.02, ($C_{14}H_{16}N_2O_5$ + 1/3 H_2O requires C, 56.37, H, 5.59, N, 9.39).

_N_-Methoxy-_N_-(1-methoxyethyl)-4-phenylbutyramide (121)

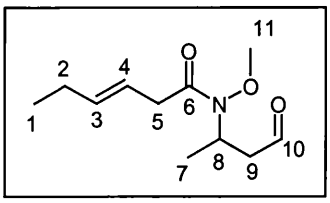


A suspension of _N_-methoxy-4-phenyl butyramide (0.15 g, 0.8 mmol), phosphorus pentoxide (0.55 g, 3.9 mmol), sodium sulfate (0.55 g, 3.9 mmol) in dichloromethane (2.8 mL) was prepared and cooled at –50 °C. A solution of acetaldehyde dimethyl acetal (0.18 mL, 1.7 mmol) in dichloromethane (1.0 mL) was added dropwise over a period of 1 h and the mixture was stirred at –35 °C for 4 h. The temperature was lowered to –15 °C and the reaction quenched with saturated sodium hydrogen carbonate. The aqueous layer was extracted with dichloromethane (2 x 10 mL) and the combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. Column chromatography (5:95 ethyl acetate:toluene) of the residue gave **121** (0.10 g, 53%) as a colourless oil: IR ν_{max} (cm^{-1}) (KBr) 3324 (Ar), 1678 (CO). ^{1}H NMR 7.25 (2H, s, Ar), 7.19 (3H, m, Ar), 5.62 (1H, br, s, H_{10}), 3.76 (3H, s, H_{11}), 3.33 (3H, s, H_{12}), 2.69 (2H, t, J = 9 Hz, H_7), 2.55-2.37 (2H, m, H_6), 1.96 (2H, m, H_5), 1.38 (3H, d, J = 6 Hz, H_9); ^{13}C NMR 175.5 (C_8), 141.7 (C_4), 128.4 (C_2), 128.3 (C_3), 83.9 (C_{11}), 65.1 (C_{12}), 55.7 (C_{10}), 35.3 (C_7), 31.9 (C_6), 25.9 (C_5), 17.8 (C_9). LRMS M/Z (ES +): 233 (100), 203 (5), 156 (15). HRMS Found 252.15524 ($C_{14}H_{21}NO_3$ + H requires 252.15550).

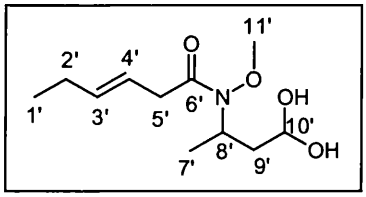
Hex-3-enoic acid methoxy-(1-methyl-3-oxopropyl)-amide (122) and Hex-3-enoic acid (3,3-dihydroxy-1-methylpropyl)-methoxyamide (123).

Hex-3-enoic hydroxamic acid (0.10 g, 0.7 mmol) was dissolved in dry acetonitrile (3.5 mL) and cooled to –35 °C where upon boron trifluoride diethyl etherate (0.55 mL, 4.52 mmol) was added. At this temperature the acetaldehyde dimethyl acetal (0.28 mL, 2.3 mmol) was added dropwise and the mixture stirred for 24 h. The mixture was then allowed to warm to 0 °C and quenched with saturated sodium hydrogen carbonate. The organic layer was washed with water, then with brine after and finally dried, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (1:9 ethyl acetate:toluene) to give

an inseparable mixture (3:1) of the aldehyde in equilibrium with the hydrate form, as colourless oil (78%, 110 mg 16% of the hydrate form): For **122**: ν_{max} (cm^{-1}) (KBr) 2965 (C=C), 1689 (CO), 1634 (CO); ^{1}H NMR: 9.60 (1H, t, J = 2.1 Hz, H_{10}), 5.56 (2H, m, H_3, H_4,), 4.80 (1H, m, H_8), 3.72 (3H, s, H_{11}), 3.33 (1H, d, J = 10.5 Hz, H_{5a}), 3.28 (1H, d, J = 10.5 Hz, H_{5b}), 2.81 (1H, ddd, J = 12.5 Hz, J = 8.3 Hz, J = 2.4 Hz, H_{9a}), 2.63 (1H, ddd, J = 12.5 Hz, J = 6.1 Hz, J = 1.5 Hz, H_{9b}), 2.03 (2H, m, H_2), 1.30 (3H, d, J = 6.9 Hz, H_7), 0.96 (3H, t, J = 7.5 Hz, H_1). ^{13}C NMR: 200.1 (C_{10}), 173.2 (C_6) 136.2 (C_3), 121.0 (C_4), 64.7 (C_{11}), 55.8 (C_8), 47.8 (C_9), 36.9 (C_5), 25.6 (C_2), 18.1 (C_7), 13.5 (C_1); LRMS M/Z (EI) 214 (M+1; 10), 117 (35), 69 (87), 59 (100). HRMS Found 214.14414 ($C_{11}H_{19}NO_3$ + 1 requires 214.14431).



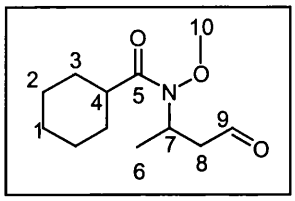
For **123**: ^{1}H NMR 5.66 (2H,m, $H_{3'}$, $H_{4'}$,), 4.80 (1H, m, H_8), 3.82 (3H, s, $H_{11'}$), 3.33 (1H, d, J = -10.5 Hz, $H_{5a'}$), 3.21 (1H, m, $H_{8'}$), 3.28 (1H, d, J = -10.5 Hz, $H_{5b'}$), 2.031 (2H, m, H_2), 2.81 (1H, m, $H_{9a'}$), 2.63 (1H, m, $H_{9b'}$), 1.11 (3H, d, J = 6.3 Hz, H_7), 0.96 (3H, t, J = 7.5 Hz, $H_{1'}$). ^{13}C NMR 173.2 ($C_{6'}$) 136.3 ($C_{3,}$), 121.1 (C_4), 102.5 ($C_{10'}$), 65.3 ($C_{11'}$), 56.1 ($C_{8'}$) 49.5 ($C_{9'}$), 38.6 ($C_{5'}$), 25.6 ($C_{2'}$), 18.7 ($C_{7,}$), 13.5 ($C_{1'}$).



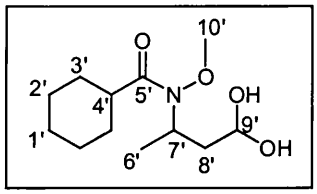
Cyclohexanecarboxylic acid methoxy-(1-methyl-3-oxopropyl)-amide (124) and cyclohexanecarboxylic acid (3,3,-dihydro-1-methylpropyl)-methoxyamide (125)

Cyclohexanecarboxylic acid methoxy amide (0.20 g, 1.3 mmol) was dissolved in dry acetonitrile (6.0 mL) and cooled to –35 °C when boron trifluoride diethyl etherate (0.52 mL, 4.2 mmol) added. At this temperature the acetaldehyde dimethyl acetal (0.32 mL, 3.1 mmol) was added dropwise and the mixture stirred for 24 h. The mixture was then allowed to warm to 0 °C and quenched with saturated sodium hydrogen carbonate. The organic layer was washed with water, then with brine and finally dried, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (5:95 ethyl acetate:toluene) to give an

inseparable mixture (3:1) of the aldehyde in equilibrium with the hydrate form, as colourless oil (48%, 140 mg 12% of the hydrate form):



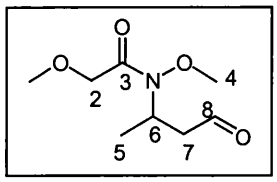
For **124**: ν_{max} (cm^{-1}) (KBr dis)1698 (CO), 1667 (CO); ^{1}H NMR 9.67 (1H, t, J = 1.7 Hz, H_8), 4.35 (1H, m, H_7), 3.71 (3H, s, H_{10}), 2.76 (1H, ddd, J = -16.5 Hz, J = 7.8 Hz, J = 2.4 Hz, H_{8a}), 2.57 (1H, ddd, J = -16.5 Hz, J = 6.2 Hz, J = 1.7 Hz, H_{10b}), 1.76-1.69 (7H, m, H_1, H_2, H_3, H_4), 1.27 (3H, d, J = 7.0 Hz, H_6); ^{13}C NMR 202.6 (C_9), 171.5 (C_5), 64.5 (C_{10}), 46.3 (C_8), 40.1 (C_7), 34.4 (C_4), 27.8 (C_3), 26.7 (C_1), 23.9 (C_2), 15.1 (C_6). LRMS M/Z (EI+): 228 (M+1), 226 (15), 83 (100), 55 (89). HRMS Found 228.15553 ($C_{12}H_{21}NO_3$ + H requires 228.15550).



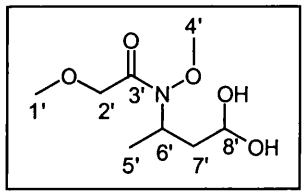
For **125**: ^{1}H NMR 5.25 (1H, br s, $H_{9'}$), 3.71 (3H, s, $H_{10'}$), 3.26 (1H, m, $H_{7'}$), 2.52 (1H, m, H_{8a}), 2.00 (1H, ddd, J = -14.0 Hz, J = 8.4 Hz, J = 4.7 Hz, $H_{8b'}$), 1.73 (7H, m, $H_{1'}$, $H_{2'}$, $H_{3'}$, $H_{4'}$), 1.27 (3H, d, J = 7.0 Hz, $H_{6'}$); ^{13}C NMR 171.5 ($C_{5'}$), 100.2 ($C_{9'}$) 63.5 ($C_{10'}$), 37.7 ($C_{8'}$), 43.1 ($C_{7'}$), 34.4 ($C_{4'}$), 27.8 ($C_{3'}$), 26.7 ($C_{1'}$), 23.9 ($C_{2'}$), 15.9 ($C_{6'}$). LRMS M/Z (EI+) 228 (M+1), 226 (15), 83 (100), 55 (89).

2, *N*-Dimethoxy-*N*-(1-methyl-3-oxopropyl)-acetamide (127) and *N*-(3,3-Dihydroxy-1-methylpropyl)-2,*N*-dimethoxyacetamide (128).

2, *N*-Dimethoxyacetamide (0.20 g, 1.4 mmol) was dissolved in dry acetonitrile (6.8 mL) and cooled to –30 °C when boron trifluoride diethyl etherate (0.55 mL, 4.5 mmol) was added. At this temperature the acetaldehyde dimethyl acetal (0.32 mL, 3.0 mmol) was added dropwise and the mixture stirred for 3 h. The mixture was then allowed to warm to 0 °C and quenched with saturated sodium hydrogen carbonate. The organic layer was washed first with water then with brine, dried, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (45:55 ethyl acetate:toluene) to give **127** and **128** (100 mg, 68%) as an inseparable 1:1 mixture of a colourless oil:

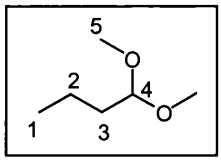


For **127**: IR ν_{max} (cm^{-1}) (KBr dis) 1701 (CO), 1678 (CO); ^{1}H NMR 9.72 (1H, t, J = 8 Hz, H_9), 4.75 (1H, m, H_6), 4.17 (2H, d, J = -15.8 Hz, H_{2a}), 4.13 (2H, d, J = -15.8 Hz, H_{2b},), 3.74 (3H, s, H_4), 3.43 (3H, s, H_1), 2.87 (1H, ddd, J = -16.8 Hz, J = 7.8 Hz, J = 2.4, H_{7a}), 2.63 (1H, ddd, J = -16.8 Hz, J = 6.2 Hz, J = 1.5, H_{7b}) 1.32 (3H, d, J = 6.5 Hz, H_5); ^{13}C NMR 199.1 (C_8), 172.3 (C_3), 70.4 (C_2), 59.4 (C_4), 53.4 (C_1), 50.0 (C_6), 36.5 (C_7), 18.0 (C_5). HRMS Found 190.10337 ($C_8H_{15}NO_4$ requires 190.10346).



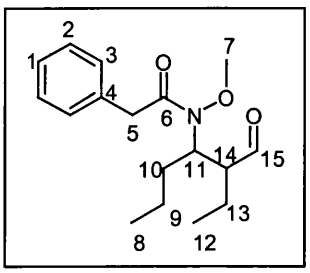
For **128**: ^{1}H NMR 4.36 (1H, dd, J = 6.2 Hz, J = 5.3 Hz, $H_{8'}$), 4.17 (2H, d, J = -15.8 Hz, $H_{2a'}$), 4.13 (2H, d, J = -15.8 Hz, $H_{2b'}$), 3.75 (3H, s, $H_{4'}$), 3.44 (3H, s, $H_{1'}$), 2.08 (1H, ddd, J = -14.2 Hz, , = 8.9 Hz, J = 5.3 Hz, $H_{7a'}$), 1.71 (1H, ddd, J = -14.2 Hz, J = 8.9 Hz, J = 5.7, $H_{7b'}$); ^{13}C NMR 172.3 ($C_{3'}$), 102.4 ($C_{8'}$), 70.4 ($C_{2'}$), 64.8 ($C_{4'}$), 52.6 ($C_{1'}$) 51.6 ($C_{6'}$), 47.6 ($C_{7'}$), 18.5 ($C_{5'}$).

1,1-Dimethoxy-butane (129)[121]



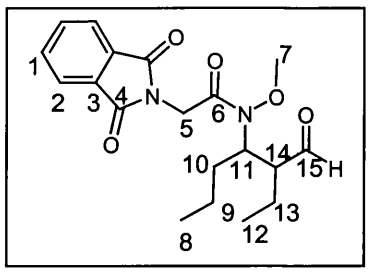
Butyraldehyde (5.0 mL, 55.5 mmol) was dissolved in methanol (12.0 mL) and concentrated sulfuric acid (0.70 mL) was added dropwise at 25 °C with vigorous stirring. This solution was then stirred for 1 h. The solution was washed with saturated sodium hydrogen carbonate and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuum. The crude was distilled (33 mmHg; 75 °C). As methanol was still present the oil was dissolved in dichloromethane washed with water, dried, filtrated and concentrated under reduced pressure to give **129** (40% 10 mL) as a colourless oil: ^{1}H NMR 4.35 (1H, t, J = 6 Hz, H_4), 3.29 (6H, s, H_5), 1.55 (2H, m, H_3), 1.37 (2H, m, H_2), 0.91 (3H, t, J = 6 Hz, H_1); ^{13}C NMR 104.3 (C_4), 52.5 (C_5), 34.5 (C_3), 17.8 (C_2), 13.9 (C_1).

_N_-4-(3-Formylheptyl)-_N_-methoxy-2-phenylacetamide (130)



_N_-Methoxy-2-phenylacetamide (0.20 g, 1.3 mmol) was dissolved in dry acetonitrile (4.0 mL) and cooled to –35 °C whereupon boron trifluoride diethyl etherate (1.1 mL, 8.74 mmol) was added. At this temperature a solution of butyraldehyde dimethyl acetal (0.62 g, 5.29 mmol) in acetonitrile (2.0 mL) was added over 1 h and the mixture stirred for 3 h. The mixture was then allowed to warm to 0 °C and quenched with saturated sodium hydrogen carbonate. The organic layer was washed first with water then with brine, dried, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (5:95 ethyl acetate:toluene) to give **130** (35%, 0.12 mg) as a colourless oil: IR ν_{max} (cm^{-1}) (KBr) 3444 (Ar), 1705 (CO), 1665 (CO); ^{1}HNMR 9.57 (1H, t, J = 3.9 Hz, H_{15}), 7.31 (5H, m, Ar), 4.43 (1H, br t, J = 9 Hz, H_{11}) 3.89 (1H, d, J = 15 Hz, H_{5a}), 3.82 (1H, d, J = 15 Hz, H_{5b},), 3.79 (3H, s, H_7), 2.61 (1H, m, H_{14}), 1.0 (2H, m, H_{13}), 1.63 (2H, m, H_{10}), 1.40 (2H, m, H_9), 0.92 (6H, t J = 6 Hz, H_8 +H_{12}); ^{13}C NMR 203.7 (C_{15}), 170.8 (C_6), 134.5 (C_4), 129.6 (C_3), 128.5 (C_2) 126.9 (C_1), 64.6 (C_7), 58.6 (C_{11}), 57.1 (C_5), 39.9 (C_{14}), 32.7 (C_{13}), 20.0 (C_{10}), 19.6 (C_9), 13.7 (C_8), 11.2 (C_{12}). HRMS Found 291.18369 ($C_{17}H_{25}NO_3$ requires 291.18344).

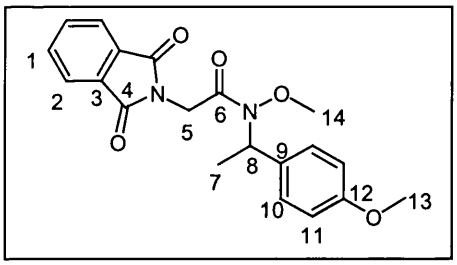
2-(Dioxo-1,3-dihydroisoindol-2-yl)-_N_-4-(3-formylheptyl)-_N_-methoxyacetamide (131)



2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-_N_-methoxy-_N_-(1-methoxyethyl)-acetamide (0.20 g, 0.8 mmol) was dissolved in dry acetonitrile (3.2 mL) and cooled to –35 °C when boron trifluoride diethyl etherate (0.69 mL, 5.6 mmol) was added. At this temperature the butyraldehyde dimethyl acetal (0.24 g, 2.0 mmol) in dry acetonitrile (1.0 mL) was added dropwise and the mixture stirred for 4 h. The mixture was then allowed to warm to 0 °C and quenched with saturated sodium hydrogen carbonate. The organic layer was washed with water, then with brine, dried, filtrated and

concentrated under reduced pressure. The residue was purified by column chromatography (5:95 ethyl acetate:toluene) to give **131** (0.10 g, 33%) as a white powder: IR: ν_{max} (cm^{-1}) (KBr) 3440 (Ar), 1700 (CO), 1756 (CO), 1645 (CO); ^{1}H NMR 9.59 (1H, t, J = 3.9 Hz, H_{15}), 7.86 (2H, m, H_2), 7.73 (2H, m, H_1), 4.67 (1H, d, J = 15 Hz, H_{5a}), 4.62 (1H, d, J = 15 Hz, H_{5b},), 4.43 (1H, br t, J = 9 Hz, H_{11}) 3.89 (3H, s, H_7), 2.63 (1H, m, H_{14}), 1.83 (2H, m, H_{13}), 1.64 (2H, m, H_{10}), 1.40 (2H, m, H_9), 0.92 (6H, t J = 6 Hz, H_8 + H_{12}); ^{13}C NMR 202.9 (C_{15}), 169.3 (C_4), 167.9 (C_6), 134.1 (C_2), 132.2 (C_3), 123.5 (C_1), 64.6 (C_7), 58.8 (C_{11}), 56.8 (C_5), 38.9 (C_{14}), 32.7 (C_{13}), 20.2 (C_{10}), 19.6 (C_9), 13.7 (C_8), 11.2 (C_{12}). LRMS M/Z (CI+) 361 (M + 1, 100), 235 (25), 188 (75), 160 (50). Found C, 59.80, H, 6.91, N, 6.40, ($C_{19}H_{16}N_2O_4$ + 3/4 H_2O requires C, 59.37, H, 6.25, N, 7.29).

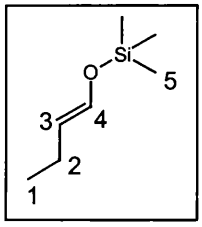
2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-*N*-methoxy-*N*-[1-(4-methoxyphenyl)-ethyl]-acetamide (132)

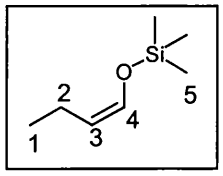


2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-*N*-methoxy-*N*-(1-methoxyethyl)-acetamide (90.0 mg, 0.3 mmol) was dissolved in dry acetonitrile (1.5 mL) and cooled at –10 °C when boron trifluoride diethyl etherate (0.25 mL, 2.03 mmol) was added. At this temperature anisole (0.13 mL, 1,2 mmol) was added dropwise and the mixture stirred for 3 h. The mixture was then allowed to warm to 0 °C and quenched with saturated sodium hydrogen carbonate. The organic layer was washed first with water (15 mL) then with brine (15 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (1:9 ethyl acetate:toluene) to give **132** (60 mg, 54%) as colourless oil: IR ν_{max} (cm^{-1}) (KBr) 3003 (Ar), 2976 (Ar), 1674 (CO); ^{1}H NMR 7.86 (2H, m, H_2), 7.70 (2H, m, H_1), 7.45 (2H, dd J = 9 Hz, J = 3 Hz, H_{10}), 6.87 (2H, d, J = 9 Hz, H_{11}), 5.81 (1H, br s, H_8), 4.56 (1H, d, J = 9.6 Hz, H_{5a}), 4.50 (1H, d, J = 9.6 Hz, H_{5b}), 3.85 (3H, s, H_{13}), 3.52 (3H, s, H_{14}), 1.61 (3H, d, J = 9 Hz, H_7); ^{13}C NMR 168.0 (C_4), 157.3 (C_6), 133.9 (C_2), 132.3 (C_3), 129.2 (C_{12}), 1127.2

(C_9), 123.4 (C_1), 120.4 (C_{10}), 110.3 (C_{11}), 64.7 (C_{13}), 55.5 (C_{14}), 51.4 (C_8), 39.3 (C_5), 16.5 (C_7). HRMS Found 369.1442 ($C_{20}H_{20}N_2O_5$ +1 requires 369.1445).

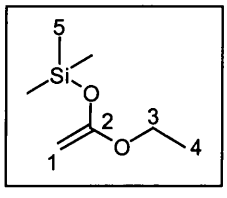
Butyl-1-enyloxy-trimethyl-silane (133)[122]





Butanal (3.75 mL), triethylamine (13.8 mL), trimethylchlorosilane (6.3 mL) were heated in dimethylformamide (15 mL) at 80 °C for 12 h. The mixture was then allowed to cool to room temperature and pentane (200 mL) was added. The solution was quickly washed with cold dilute hydrochloric acid (2 x 30 mL), saturated sodium hydrogen carbonate and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Distillation under reduced pressure (180 mmHg, 75 °C) afforded **133** (4.2 g, 70%) as an inseparable 3:7 mixture of *cis*- and *trans*-isomers: ^{1}H NMR 6.12 (1H, dt, J = 12 Hz, J= 1.5 Hz H_{4cis}), 6.04 (1H, dt, J = 12 Hz, J = 1.5 Hz H_{4trans}), 4.95 (1H, dt J = 12 Hz, J = 9 Hz H_{3cis}), 4.42 (1H, q, J = 6 Hz H $_{3trans}$), 2.01 (2H, dq J= 7.2 Hz, J=1.5 Hz, H_{2trans}), 1.84 (2H, dq, J= 7.2 Hz, J =1.5 Hz, H_{2cis}), 0.90 (3H, t J = 7.2 Hz, H_{3trans}), 0.88 (3H, t J = 7.2 Hz, H_{3cis}), 0.11 (18H, s, $Si(CH_3)_3$).

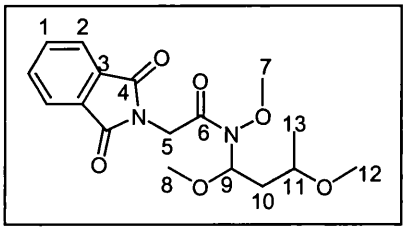
(1-Ethoxy-vinyloxy)-trimethylsilane (136)[134]



To a solution of diisopropylamine (3.1 mL, 22.0 mmol), in tetrahydrofuran (20 mL), at 0 °C, was added 1.6 M hexane solution of *n*-butyllithium and stirred for 20 min at that temperature. To the mixture was added ethyl acetate (1.95 mL, 20.0 mmol) at -78 °C. After 30 min, chlorotrimethylsilane (3.0 mL, 24.0 mmol) was added at that temperature. After stirring for additional 30 min, the mixture was allowed to warm at room temperature and stirred for 1 h. The reaction mixture was then poured into a solution of hexane (80 mL) and water (40 mL). The organic layer was washed with brine and dried over magnesium sulfate. After evaporation under

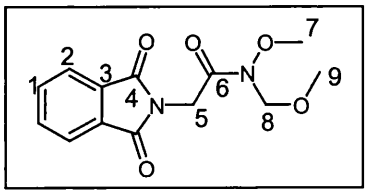
reduced pressure, the residue was distilled (50 °C/ 75 mmHg) to give **136** as colorless oil (2.2 g, 70%): ^{1}H NMR (C-Si/O-Si 75:25), 3.75 (2H, q, J= 7.2 Hz, H_3) 3.20 (1H, d, J= 2.7 Hz, H_{1a}), 3.05 (1H, d, J= 2.7 Hz, H_{1b}), 1.30 (3H, t J= 7.2 Hz, H_4), 0.22 (9H, s, H_5).

_N_-(1,3.Dimethoxy butyl)-2-(1,3-dioxo indan-2-yl)-_N_-methoxyacetamide (137)



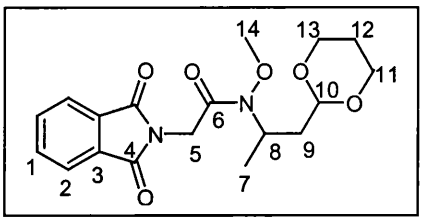
2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-*N*-methoxy-*N*-(1-methoxyethyl)-acetamide (0.10 g, 0.4 mmol) was dissolved in dry dichloromethane (3.0 mL) and cooled to –55 °C when trifluoromethanesulfonic anhydride (72 μL, 0.4 mmol) was added. At this temperature acetaldehyde dimethyl acetal (90 μL, 3.1 mmol) was added dropwise and the mixture stirred for 30 min. Vinyl acetate (80 μL, 0.8 mmol) in dry dichloromethane (1.0 mL) was added to the cold mixture over a period of 20 min. After for 4 h, the mixture was allowed to warm to 0 °C and quenched with saturated sodium hydrogen carbonate. The organic layer was washed first with water then with brine, dried, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (1:9 ethyl acetate:toluene) to give **137** (60 mg, 40%) as inseparable mixture of diastereoisomers: IR ν_{max} (cm^{-1}) (KBr) 2972 (Ar), 1776 (CO), 1722 (CO ald), 1693 (CO); ^{1}H NMR 7.85 (4H, m, H_1 + H_{1diast}), 7.71 (4H, m, H_2 + $H_{2\ diast}$), 5.54 (1H, dd J= 8.1 Hz, J= 5.2 Hz, H_9) 5.51 (1H, dd, J= 8.1 Hz J= 5.2 Hz, $H_{9\ diast}$), 4.72 (1H, d, J= 17.3 Hz, H_{5a}), 4.57 (1H, d, J= 17.3 Hz, H_{5b}), 4.69 (1H, d, J= 17.3 Hz, $H_{5a\ diast}$), 4.56 (1H, d, J= 17.3 Hz, $H_{5b\ diast}$), 3.42 (2H, m, H_{11}), 3.35 (3H, s, H_7), 3.34 (3H, s, $H_{7\ diast}$), 3.29 (3H, s, H_{12}), 3.28 (1H, m, $H_{11diast}$), 3.23 (3H, m, $H_{12\ diast}$), 1.99 (1H, m, H_{10}), 1.95 (1H, m, $H_{10\ diast}$), 1.12 (3H, d, J = 4 Hz, H_{13}), 1.11 (3H, d, J = 4 Hz, $H_{13\ diast}$); ^{13}C NMR 169.3 (C_4), 167.9 (C_6), 134.4 (C_2), 132.2 (C_3), 123.5 (C_1), 86.4 (C_9), 86.3 ($C_{9\ diast}$), 73.8 (C_7), 73.6 ($C_{7\ diast}$), 65.6 (C_{11}), 65.5 ($C_{11\ diast}$), 56.3 (C_{12}), 56.2 ($C_{12\ diast}$), 56.1 (C_8), 55.9 ($C_{8\ diast}$), 39.0 (C_5), 38.9 ($C_{5\ diast}$), 38.7 (C_{10}), 38.4 ($C_{10\ diast}$), 19.2 (C_{13}), 19.0 ($C_{13\ diast}$),. LRMS M/Z (CI +) 351 (M+H, 45 %), 31(80) 287 (70), 261 (100), 188 (100). HRMS Found 351.15718 ($C_{10}H_{21}NO_5$ + H requires 351.15560).

2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-*N*-methoxy-*N*-methoxymethylacetamide (141)



2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-*N*-methoxy-*N*-(1-methoxyethyl)-acetamide (0.10 g, 0.4 mmol) was dissolved in dry acetonitrile (2.2 mL) and cooled to –35 °C when boron trifluoride diethyl etherate (0.35 mL, 2.82 mmol) was added. Dimethoxymethane (91 μl g, 1.1 mmol) in dry acetonitrile (1.0 mL) was then added dropwise and the mixture stirred for 4 h. The mixture was then allowed to warm to 0 °C and quenched with saturated sodium hydrogen carbonate. The organic layer was washed with water, then with brine, dried, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (2:8 ethyl acetate:toluene) to give **141** (0.10 g, 95%) as a white powder: mp 101-104 C; IR ν_{max} (cm^{-1}) (KBr) 3389 (Ar), 1787 (CO), 1707 (CO). ^{1}H NMR 7.87 (2H, m, H_2), 7.73 (2H, m, H_1), 5.00 (2H, s, H_8), 4.74 (2H, s, H_5), 3.95 (3H, s, H_7), 3.37 (3H, s, H_9); ^{13}C NMR 168.9 (C_6), 167.9 (C_4), 134.1 (C_2), 132.2 (C_3), 123.5 (C_1), 77.9 (C_8), 64.1 (C_7), 56.9 (C_9), 38.8 (C_5). Found C, 57.11, H, 5.11, N, 9.55, ($C_{14}H_{16}N_2O_5$ + 1/2 CH_3OH requires C, 57.32, H, 5.46, N, 9.55).

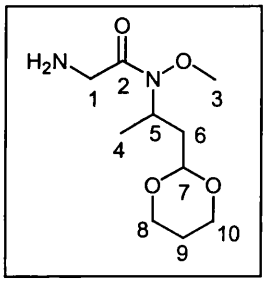
***N*-(2-[1,3]Dioxan-2-yl-1-methylethyl)-2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-*N*-methoxyacetamide 146[135]**



2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-*N*-methoxy-*N*-(1-methyl-3-oxopropyl)-acetamide (1.96 g, 6.5 mmol), was added to a solution of 1,3-propanediol (0.70 mL, 9.7 mmol) in toluene (100 mL). A catalytic amount of *p*-toluenesulfonic acid (25.0 mg) was added and the mixture was warmed to reflux with removal of water by a Dean-Stark trap. After 4 h the mixture was cooled to room temperature and extracted with saturated sodium hydrogen carbonate (3 x 150 mL) followed by brine (1 x 150 mL). Drying over Na_2SO_4 followed by evaporation of the solvent gave an oil, which was purified by column chromatography (3:7 ethyl acetate:toluene) to give **146** (2.2 g, 95 %) as a

colourless oil: IR ν_{max} (cm^{-1}) (KBr) 3435 (Ar), 1720 (CO); ^{1}H NMR 7.80 (2H, m, H_2), 7.66 (2H, m, H_1), 4.51 (4H, m, H_{13} H_{11}), 4.12 (3H, m, H_{10} H_5), 3.86 (3H, s, H_{14}), 3.71 (1H, br, m, H_8), 2.14 (1H, td, J (12_{eq}, 11) = 10 Hz, J (12_{eq}, 12_{ax}) = 4.5 Hz, H_{12eq}), 2.02 (2H, m, H_9), 1.67 (1H, td, J (12_{ax}, 12_{eq}) = 4.5 Hz J (12_{ax}, 11) = 10 Hz, H_{12ax}) 1.27 (3H, d, J = 6 Hz, H_7); ^{13}C NMR 168.6 (C_6), 167.9 (C_4), 133.9 (C_2), 132.3 (C_3), 123.3 (C_1), 100.2 (C_{10}), 66.9 ($C_{11,}$ C_{13}), 65.0 (C_{14}), 51.3 (C_8), 39.3 (C_{12}), 38.7 (C_5), 25.7 (C_9), 19 (C_7). HRMS Found 362.14765 ($C_{18}H_{22}N_2O_6$ requires 362.14779).

2-Amino-*N*-(2-1-[1,3]dioxan-2-yl)propyl-*N*-methoxyacetamide (147) [136]



N-(2-1-[1,3]Dioxan-2-yl)propyl-2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-*N*-methoxyacetamide (0.57 g, 1.6 mmol), was dissolved in ethanol (20 mL). Hydrazine monohydrate (0.15 mL, 3.1 mmol) was added and the mixture was heated at reflux for 1 h. A white precipitate was formed, so the mixture was left to cool at room temperature, the precipitate was filtered and the ethanol was evaporated under vacuum. The residue was then dissolved in dichloromethane (25 mL) and the white precipitated filtered off. The filtrate was concentrated under reduced pressure to give **147** (0.32 g, 90%,) as a yellow oil: IR ν_{max} (cm^{-1}) (KBr) 1664 (CO); ^{1}H NMR 4.44 (1H, t, J = 6 Hz, H_7), 3.95 (2H, m, H_5 H_1), 3.66 (3H, s, H_3), 3.59 (3H, m, H_1 H_8), 3.48 (2H, br s, H_9), 2.29 (2H, br s, NH_2), 1.98 (3H, m, H_6 + $H_{9\,eq}$), 1.63 (1H, dt, J = 12 Hz, J = 6 Hz, $H_{9\,ax}$); ^{13}C NMR 163.9 (C_2), 100.1 (C_7), 66.7 (C_3), 64.5 (C_5), 51.0 (C_1), 42.9 (C_6), 38.8 ($C_{8,10}$), 25.6 (C_9), 18.5 (C_4). LRMS M/Z (ES +): 233 (100), 203 (5), 156 (15). HRMS Found 233.14221 ($C_{10}H_{20}N_2O_4$ requires 232.14231).

2.6 Reference

(75) Marson, C. M.; Fallah, A. *J. Chem. Soc., Chem.Commun.* **1998**, 83.

(76) Dallemagne, P.; Rault, S.; Sevricourt, M.; Hassan, Kh. M.; Robba, M. *Tetrahedron Lett.* **1986**, *27*, 2607.

(77) Jeff, P. W.; Redfearn, R.; Wolfram, J. *J.Org.Chem.* **1983**, *48*, 3861.

(78) Paleo, M.; Dominiguez, D.; Castedo, L. *Tetrahedron* **1993**, *34*, 2369.

(79) Bhatia, B.; Reddy, M. M.; Iqbal, J. *J.Chem. Soc. Chem.Commun.* **1994**, 713.

(80) Reider, P. J.; Rayford, R.; Grabowski, E. J. J. *Tetrahedron Lett.* **1982**, *23*, 379.

(81) Bott, K. *Angew.Chem.,Int.Ed.Engl.* **1980**, *19*, 171.

(82) Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am.Chem.Soc.* **1981**, *103*, 1172.

(83) Krauss, G. A.; Neuenschwand, K. *Tetrahedron lett* **1980**, *21*, 3841.

(84) Bohme, H.; Haake, M. *Adv.Org.Chem.* **1976**, *9*, 107.

(85) Bohme, H.; Hartke, M. *Chem.Ber.* **1960**, *93*, 1305.

(86) Kinast, G.; Tietze, L. F. *Angew.Chem.* **1976**, *88*, 261.

(87) Rochin, C.; Babot, O.; Dunoguès, J.; Duboudin, F. *Synthesis* **1986**, 228.

(88) Leonard, N. J.; Klainer, J. R. *J.Org.Chem.* **1963**, *28*, 3021.

(89) Opitz, G.; Hellmann, H.; Schubert, H. W. *Justus Liebigs Ann.Chem.* **1959**, *623*, 117.

(90) Arend, M. and Risch, N. 11th Int. Conf. Org. Chem. Abstr Pap. 1996. Amsterdam (The Netherlands).

(91) Ofial, A. R.; Mayr, H. *Angew.Chem.* **1997**, *109*, 145.

(92) Ofial, A. R.; Mayr, H. *Angew.Chem.,Int.Ed.Engl.* **1997**, *36*, 143.

(93) Mayr, H.; Patz, M. *Angew.Chem.* **1994**, *106*, 990.

(94) Mayr, H.; Patz, M. *Angew.Chem.,Int.Ed.Engl.* **1994**, *33*, 938.

(95) Holy, N.; Fowler, R.; Burnett, E.; Lorenz, R. *Tetrahedron* **1979**, *35*, 613.

(96) Davis, F. A.; Szewczyk, J. M.; Reddy, R. E. *J.Org.Chem.* **1996**, *61*, 2222.

(97) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.

(98) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817.

(99) Yamamoto, Y.; Nakada, T.; Nemoto, H. *J.Am.Chem.Soc.* **1992**, *114*, 121.

(100) Zaugg, H. E.; Martin, W. B. *Org. React.* **1965**, *14*, 52.

(101) Lenz, G. R. *Synthesis* **1978**, 489.

(102) Sheehan, J. C.; Ryan, J. J. *J.Am.Chem.Soc.* **1951**, *73*, 1204, 4367.

(103) Bohme, H.; Hartke, M. *Chem.Ber.* **1963**, *96*, 600.

(104) Krow, G. R.; Pyun, C.; Leith, C.; Ramey, K. *J.Org.Chem.* **1974**, *39*, 2449.

(105) Tamura, Y.; Maeda, H.; Akai, S.; Ishibashi, H. *Tetrahedron Lett.* **1982**, *23*, 2209.

(106) Shono, T. *Tetrahedron* **1984**, *40*, 811.

(107) Ugi, I.; Domling, A.; Horl, W. *Endeavour* **1994**, *18*, 115.

(108) Arend, M.; Westermann, B.; Risch, N. *Angew.Chem.,Int.Ed.Engl.* **1998**, *37*, 1044.

(109) Domling, A.; Ugi, I. *ACIEE* **2000**, *39*, 3169.

(110) Skorna, G.; Ugi, I. *ACIEE* **1977**, *16*, 259.

(111) Kappe, C. O. *Acc.Chem.Res.* **2000**, *33*, 879.

(112) Kappe, C. O. *J.Org.Chem* **1997**, *62*, 7201.

113) Kappe, C. O.; Falsone, S. F. *Synlett* **1998**, 718.

(114) Hellmann, F. *Chem.Ber.* **1989**, -1134.

(115) Knegel, O. R. *J.Chem.Soc.* **1990**, *68*, 69.

(116) Katritzky, A.R; Denisko, V. O.; Busont, S. *J.Org.Chem.* **2000**, *65*, 8066.

(117) Reyes, A.; Juaristi, E. *Tetrahedron Asymm.* **2000**, *11*, 1411.

(118) Lin, X.; Robins, J. M. *Org.Lett.* **2002**, *2*.

(119) Chandrasekhar, S.; Takhi, M.; Mohapatra, S.; Rao, C. R.; Reddy, k. V. *Tetrahedron* **1997**, *53*, 14997.

(120) Marson, C. M., Grabowska, U., Fallah, A. *J.Org.Chem.* **1994**, *59,* 291.

(121) Chen, C. Y.; Senanayake, C. H.; Bill, T. J.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J.Org.Chem.* **1994**, *59*, 3738.

(122) Aggarwal, V. K.; Eames, J.; McIntyre, S.; Sansbury, F. H.; Warren, S.; Villa, M. J. *J.Chem.Soc.,Perkin Trans.1* **2000**, 533.

(123) Katritzky, A.R; Rees, C.W.; Scriven, E.F.V. Elsevier Science: Oxford, UK, 1996.

(124) Drouillat, B.; Poupardin, O.; Bourdreux, Y.; Greck, C. *Tetrahedron Lett.* **2003**, *44*, 2781.

(125) Dini, C.; Didier-Laurent, N.; Drochon, S.; Feteanu, J. C.; Guillot, F.; Monti, F.; Uridat, E.; Zhang, J.; Aszodi, J. *Bioorg.Med.Chem.Lett.* **2002**, *12*, 1209.

(126) Knapp, S.; Morriello, J. G.; Doss, A. G. *Tetrahedron Lett.* **2003**, *44*, 2645.

(127) Sieghart, W. *Pharmacol.Rev.* **1995**, *47*, 181.

(128) Gardner, C. R. *Prog.Neurobiol.* **1988**, *31*, 425.

(129) Smith, G. B.; Olsen, R. W. *Trends Pharmacol.Sci.* **1995**, *16*, 162.

(130) Ison, K.; Kusakabe, M.; Kimura, K.; Nelson, C.; McCloskey, J. A. *J.Antibiot.* **1985**, *38*, 1617.

(131) Balkenhohl, C.; Bussche-Huennfeld, C.; Lansky, A.; Zeche, C *Angew.Chem.Int.Ed.Engl.* **1996**, *61*, 7242..

(132) Kirkovsky, L.; Mukherjee, A.; Donghua, Y.; Dalton, J. T.; Miller, D. D. *J.Med.Chem.* **2000**, *43*, 581.

(133) Andres, J. M.; Herraiz-Sierra, I.; Pedrosa, R.; Perez-Encabo, A. *Eur.J.Org.Chem.* **2000**, *9*, 1719.

(134) Mikami, K.; Matsumoto, S.; Ispida, A.; Takamuku, S.; Suenobu, T.; Fukuzumi, S. *J.Am.Chem.Soc.* **1995**, *117*, 11134.

(135) Belliotti, T. R.; Wustrow, D. J.; Brink, K. T.; Shih, Y. H.; Whetzel, S. Z.; Wise, L. D. *J.Med.Chem.* **1999**, *42*, 5181.

(136) Abe, Y. *J.Med.Chem.* **1998**, *41*, 4062.

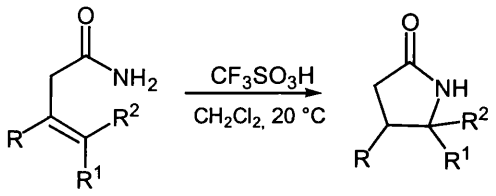
Chapter 3

New Condensations of Hydroxamic Acids to give N-Heterocycles

3.1 Introduction

In chapter two we examined the nucleophilic behaviour of the hydroxamic acid moiety in the three-component condensation with carbonyl compounds. In this chapter are described the nucleophilic reactions of hydroxamic acids in cyclisation where an isolated double bond participates as electrophile in presence of trifluoromethanesulfonic acid.

Some years ago,[137] it was shown that unsaturated amides cyclise to give γ- and δ-lactams (scheme 3.1); accordingly, investigations have been undertaken in order to achieve the analogous cyclisations using hydroxamic acids rather than amides.



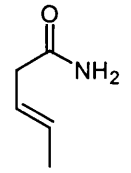
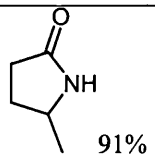
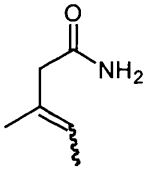
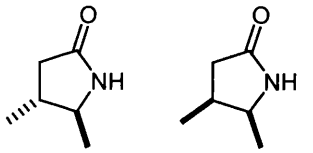
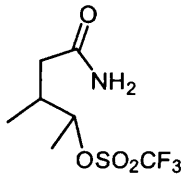
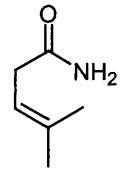
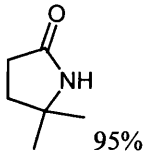
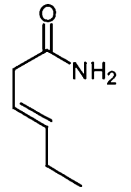
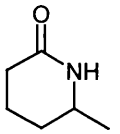
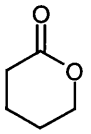
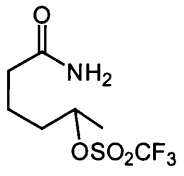
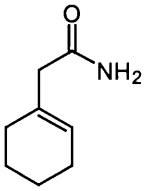
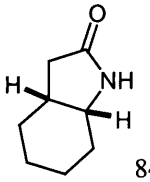
Scheme 3.1

There are several ways of preparing cyclic hydroxamic acids which usually also apply to lactams. However, acid-catalysed cyclisations of an amidic-type nitrogen onto double bonds are rare and chiefly or exclusively confined to the

formation of a quaternary carbon centre *alpha* to the nitrogen atom of the resulting ring.[138;139]

Our group established that the cyclisation of β,γ-unsaturated amides in trifluoromethanesulfonic acid is a general method for the preparation of a variety γ-lactams[137] (table 3.1).

Table 3.1 Cyclisation of Unsaturated Amides using Trifluoromethanesulfonic Acid[137]

Entry	Amide	Reaction time (h)	Products
1		0.75	 91%
2		16	 1:3 72%  23%
3		2	 95%
4		4	 69%  11%  14%
5		16	 84%

A notable feature of cyclisations giving lactams (table 3.1) is the efficient formation of a tertiary carbon centre, which can be competitively attacked intramolecularly by the amidic termini (entries 1, 4, and 5) or intermolecularly by the

trifluoromethanesulfonate anion (entries 2 and 4). Indeed the formation of trifluoromethanesulfonates indicates competition for attack at the cationic centre: intermolecularly by attack of trifluoromethanesulfonate anion *versus* internally by the amide group. The difference in behaviour of the two unsaturated amides in entries 2 and 5 suggests that the size of the ring being formed governs the fine balance that determines the constitution of the cyclised products. Considering the initial location of the alkenic double bond, the formation of the six-membered ring is consistent with acid-catalysed migration of the double bond, in certain cases (*e.g.* entry 4).

The formation of the lactams may proceed through alkyl iminotrifluoromethanesulfonates or their salts **155** (fig 3.1). The formation of the lactones most probably proceeds through salts of cyclic imino-ethers such as **156**.

155 **156**

Fig 3.1

Given the success in preparing γ- and δ-lactams from unsaturated acyclic amides in the presence of trifluoromethanesulfonic acid, it appeared worthwhile to investigate the same cyclisation using the corresponding hydroxamic acids.

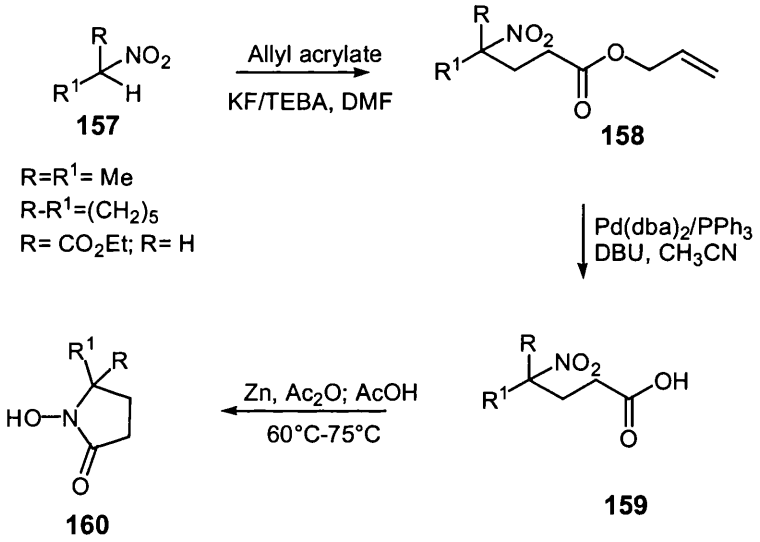
3.1.1 Syntheses of Cyclic Hydroxamic Acids by Ring Closure of Unsaturated Acyclic Hydroxamic Acids

Few methods for generating cyclic hydroxamic acids are known and there are very few cases where cyclisation proceeds onto an inactivated double bond. Generally, activation is achieved by using PhSeBr together with AgOTf (section **3.1.1.4**). Kametani and co-workers[140] reported cyclisations of hydroxamic acids onto

an aromatic double bond in the presence of polyphosphoric acid (section **3.1.2.4**), even though only a specific class of hydroxamic acids reacted successfully.

3.1.1.1 Reductive Cyclisation of Nitro Carboxylic Acids

Reductive cyclisation of the nitrocarboxylic acids **159** over Zn in the presence of acetic anhydride and acetic acid afforded the 1-hydroxy-2-substituted-5-oxoproline derivatives **160**, which being derivatives of pyroglutamic acids, hold great interest in restoring the balance of glutamate receptors in CNS disorders.[141]



Scheme 3.2

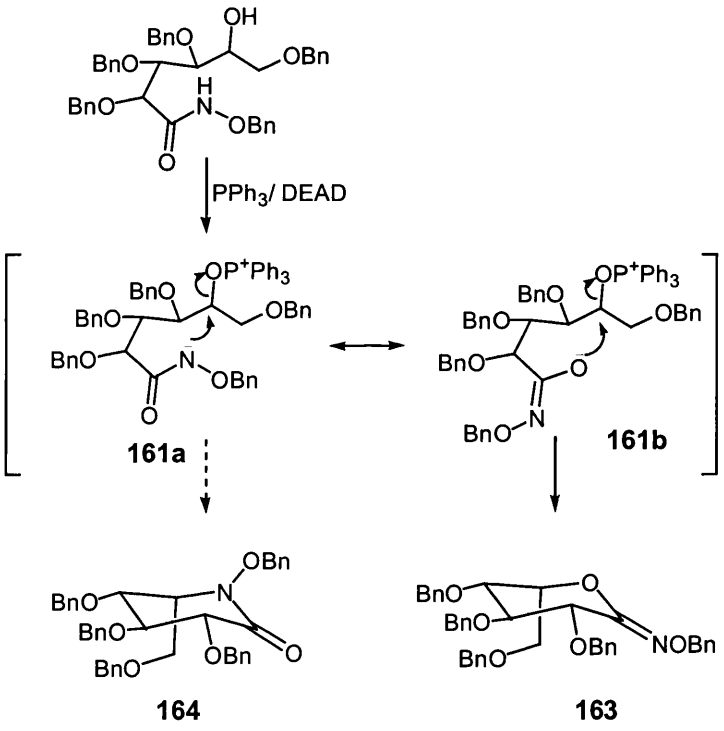
The structure of these products presents a rare combination of three desirable features: i) a pyroglutamate skeleton, ii) the possibility of creating a quaternary α-carbon atom on the proline ring and iii) incorporation of a cyclic hydroxamic acid moiety.

The methodology involves Michael addition of compounds **157** to allyl acrylate to give esters **158** followed by saponification of compounds **158** and subsequent reductive cyclisation of the nitro carboxylic acids **159** to give the cyclic hydroxamic acids **160** in excellent yield. The disadvantage of this method is that no stereocontrol accompanies the reaction and although chiral reagents have been used,[141] no significant e.e's were observed.

3.1.1.2 Cyclisation of Hydroxamic Acids *via* Mitsunobu Reactions

Ikegami and co-workers[142] reported a new and interesting cyclisation of *δ*-hydroxy hydroxamic acids under Mitsunobu conditions (scheme 3.3).

The cyclisation of the *δ*-hydroxy hydroxamic acids can be rationalised by assuming the formation of anion **161a** and **161b** as shown in scheme 3.3. Deprotonation of the amide NH by the DEAD anion present in the Mitsunobu reaction mixture generates the anion **161a** which undergoes *O*-alkylation.

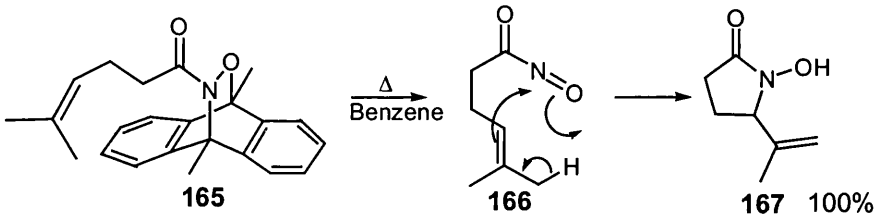


Scheme 3.3

The stereochemistry of the starting material did not affect the ratio of *O-/N*-alkylation; additionally, cyclisation occurred on the oxygen atom only, no *N*-alkylation product being observed. Cyclisation always proceeded with complete inversion at C5. This is the first reported application of the Mitsunobu-type reaction to the synthesis of cyclic hydroxamic acids.

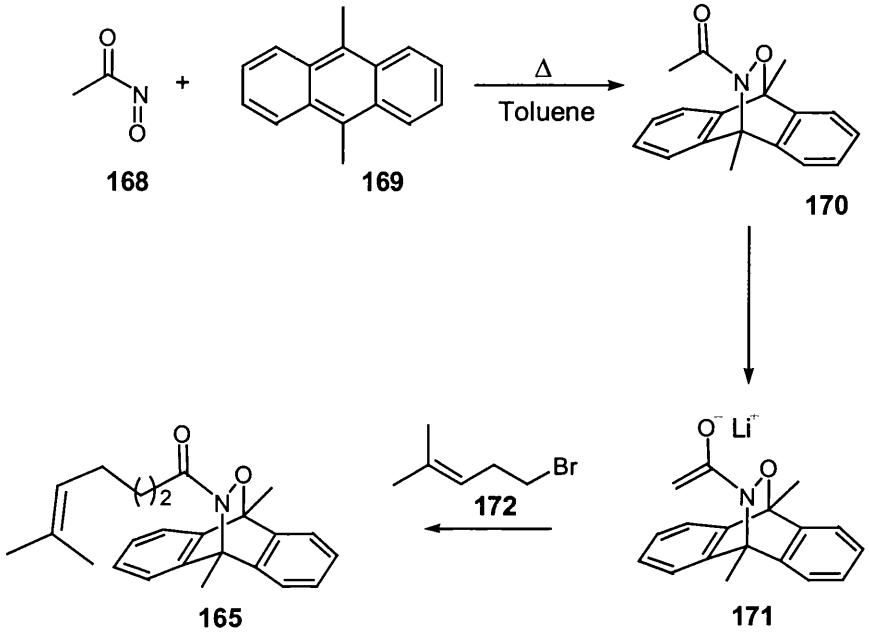
3.1.1.3 Cyclisation *via* Ene Processes

Ene cyclisations of acyl nitroso compounds can afford cyclic hydroxamic acids (scheme 3.4).[143] Acyl nitroso compounds are exceptionally reactive species and have never been directly observed or isolated owing to their extreme reactivity. The intramolecular ene process can give five and six-membered cyclic hydroxamic acids in excellent yields.[143]



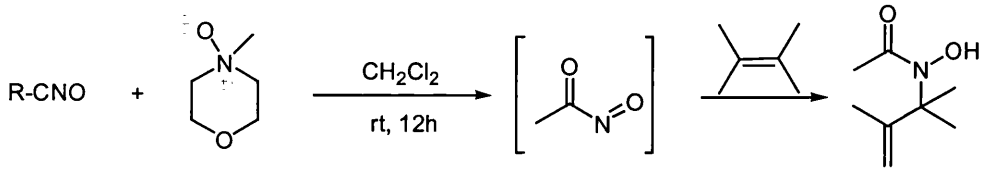
Scheme 3.4

The hydroxamic acid **170** was prepared by a Diels-Alder reaction between nitrosocarbonylmethane **168** and 9,10-dimethylanthracene **169** (scheme 3.5).[144] The former was then converted into its lithium enolate by treatment with lithium diisopropylamide, followed by condensation with 1-bromo-3-methyl-2-butene to give **165** in 76% yield. The intramolecular ene process was achieved simply by heating **165** in benzene solution for a few hours. The cyclic hydroxamic acids were generally obtained in good yields (60-80%).



Scheme 3.5

The method of Quadrelli and co-workers[145] also affords ene products such as **166** in high yields[145] (scheme 3.6). A nitrile oxide is oxidized *in situ* by *N*-methylmorpholine *N*-oxide giving an intermediate acyl nitroso compound that reacts with an olefin.

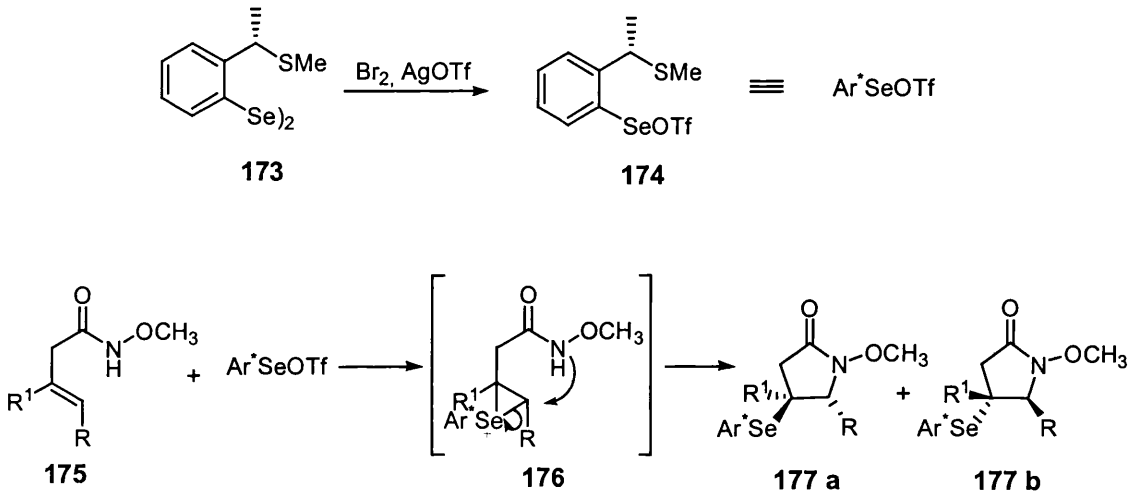


Scheme 3.6

Unfortunately, the precursors are cumbersome to prepare for both methods, and the olefinic partner for the ene reaction must be used in large excess. However, Waldemar and co-workers[146] described a new method of preparing unsaturated hydroxamic acids in a one-pot reaction involving *in situ* oxidation of hydroxamic acids with iodosobenzene and iodosobenzene acetate followed by a [2 + 2] cycloaddition of the acyl nitroso compound with an olefinic component.

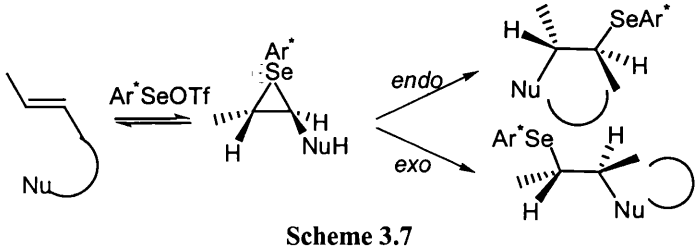
3.1.1.4 Cyclisation of β,γ-Unsaturated Hydroxamic Acids *via* Sulfur-containing Diselenides

The only reported example of an intramolecular cyclisation of β,γ-unsaturated hydroxamic acids to give a cyclic hydroxamic acids is shown in scheme 3.8[147]. Tiecco and co-workers[147] showed that β,γ-unsaturated hydroxamic acids can readily cyclise to the five-membered ring if treated with phenylselenyl triflate as the electrophilic reagent.



Scheme 3.8

Treatment of **173** with bromine and silver triflate afforded the corresponding selenyl triflate **174** which was employed to effect very efficient asymmetric selenohydroxylations of alkenes.[147] The addition of **174** to the double bond of compound **175** afforded a mixture of the two diastereomeric seleniranium intermediates **176** which were trapped by the nucleophilic nitrogen atom to give a mixture of enantiomerically pure diastereisomeric addition products **177a** and **177b**. The reaction involves a stereospecific *anti*-addition.



Scheme 3.7

As indicated in scheme 3.7, depending on the relative position of the double bond and the nucleophilic group, the products can be the result of an *exo*- or an *endo*-cyclisation.

The trapping of the seleniranium intermediate **176** by the oxygen atom, leading to an imidate product (fig 3.2) is faster than trapping by nitrogen (which leads to lactam product). However, under the conditions employed, the formation of the cyclic *N*-hydroxyimidate is reversible and appropriate conditions *N*-hydroxy-γ-lactam were found to be the sole product of the reaction.

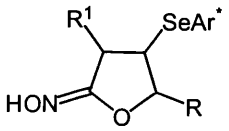
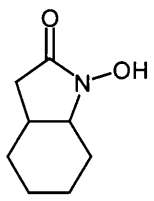


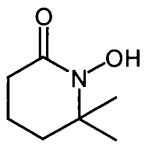
Fig 3.2

3.1.2 Syntheses and Biological Activities of 1-Hydroxypyrrolidin-2-ones, 1-Hydroxypiperidin-2-ones, [1,2] Oxazepan-3-ones and [1,2] Oxazinan-3-ones

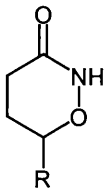
The cyclisation of unsaturated hydroxamic acids in presence of trifluoromethanesulfonic acid discussed in this chapter afforded to five, six- and seven-membered rings (fig 3.3) where, depending of the starting material and the conditions employed, either the nitrogen or the oxygen atom of the hydroxamic acid moiety participates in the ring-closure step.



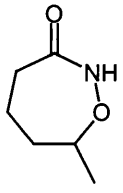
178



179



R= CH_3, **180**
R = CH_3CH_2, **181**



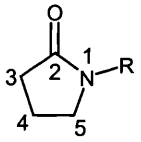
182

Fig 3.3

The biological properties of these compounds are related not only to the presence of the hydroxamic acids moiety but also to the structure of the ring itself, being analogous to pyrrolidinones piperidones, and oxazinanones.

3.1.2.1 1-Hydroxypyrrolidin-2-ones

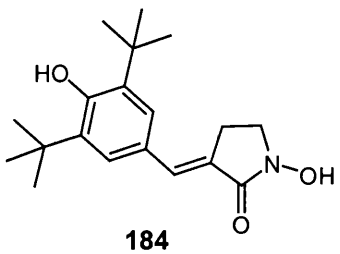
Polysubstituted pyrrolidinones **183** (fig 3.4) are common structural sub-units in many natural products and drugs; because they exhibit a wide range of biological activities,[148] investigation of a general method to synthesise them was considered to be of particular interest.



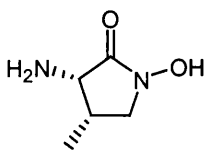
183

Fig 3.4

1-Hydroxypyrrolidin-2-one derivatives provide a diverse range of pharmacological activity such as antitumour[149] and anti-inflammatory properties[150] and many others related to CNS disorders in the form of cognitive defects,[151] epilepsy,[152] schizophrenia[153] and depression.[154] Indeed, the 1-hydroxypyrrolidin-2-one **184** (fig 3.4) belongs to a new class of nonsteroidal anti-inflammatory agents with antioxidant properties, being potent dual inhibitors of both cyclooxygenase and 5-lypooxygenase.[150] Nonsteroidal anti-inflammatory drugs are usually used in the treatment of a number of arthritic conditions, including rheumatoid arthritis and osteoarthritis.[150] Their primary mode of action is thought to be related to inhibition of prostaglandin biosynthesis.[155]



184



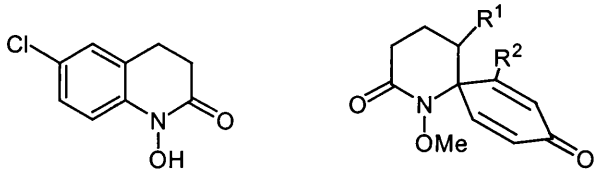
185

Fig 3.5

1-Hydroxypyrrolidin-2-one **185** is representative of a strychnine-insensitive glycine partial agonist,[156] mainly because of the rigid framework of the structure that permits a precise delineation of the spatial orientation of acidic and basic pharmacophores. [157] Indeed, the (basic) nitrogen of the amine group and the (acidic) proton of the hydroxamic acid moiety are located on opposite sites, conferring a distinctive activity to the compound.

3.1.2.2 1-Hydroxypiperidin-2-ones

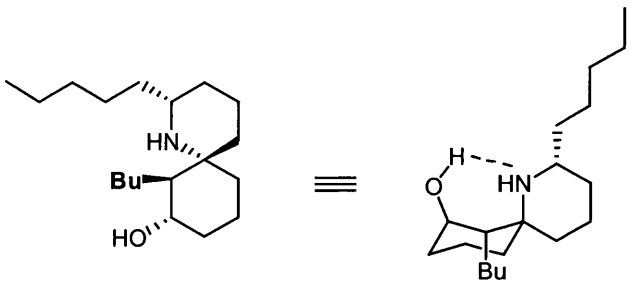
Diverse biological properties have been found for 1-hydroxypiperidin-2-ones, *e.g.* **179**, which can be intermediates in the synthesis more complex molecules containing the piperidone skeleton. For example 1-hydroxypyrrolidin-2-one **186** (fig 3.6) was shown to be a potent and selective inhibitor of the growth of DU-145 human prostate cancer cells, [149] and induced cell death. Treatment of DU-145 with **186** substantially decreased the number of viable cells within 2 days, and no viable cells remained in culture after 4 days. DU-145 cells constitute an androgen-insensitive human prostate cell line derived from a brain metastasis of prostate cancer.



186 **187**

Fig 3.6

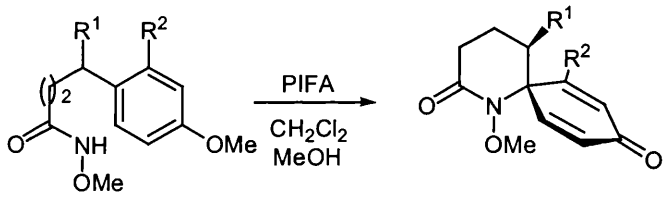
1-Azaspiroundecandienones **187** (fig 3.6)[158] were prepared because of the considerable importance of 1-azaspiroundecanes ring system present in a number of bioactive natural products.[159-161] The alkaloid perhydrohistrionicotoxin **188** is one such example, and is an important natural neurotoxic alkaloid.[162]



188 188

Fig 3.7

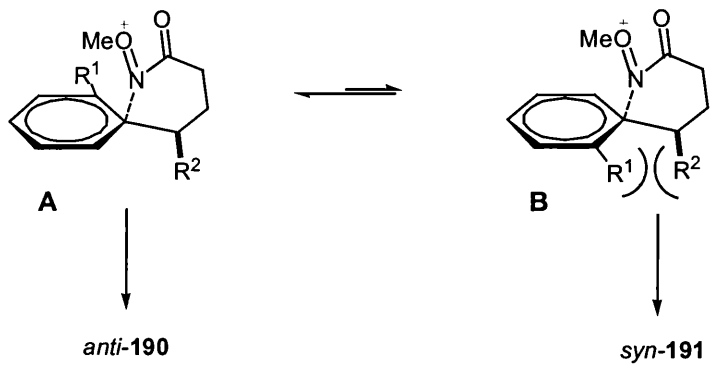
Compounds **187** were prepared by heating the acyclic hydroxamic acids **189** with phenyliodine (III) bis(trifluoroacetate) (scheme 3.8).[163]



189 187

Scheme 3.8

Spirocyclisation of the nitrenium ion generated from **189** would preferentially proceed via a transition state resembling **A** to form *anti*-**190** (scheme 3.9). Conformer **B**, on the other hand, would be destabilised owing to nonbonding interaction between the substituent on the side-chain and the *ortho* position at the aromatic ring.



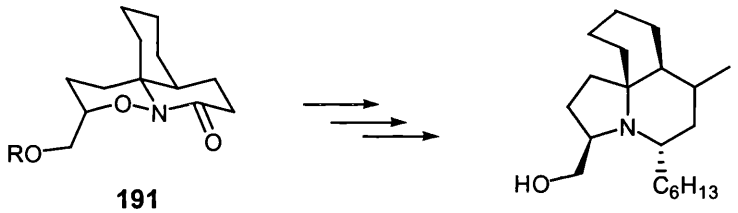
anti-**190** *syn*-**191**

Scheme 3.9: Stereochemical course for the Spirocyclisation of **189**

This approach provides a general route to such cyclic hydroxamic acids, which have shown to be useful building blocks for the preparation of a range of biologically active compounds.

3.1.2.3 [1,2] Oxazinan-3-ones

Oxazinanones such as **180** and **181** (fig 3.3) are rare, being synthetic intermediates, as shown in scheme 3.10 and 3.12 show.

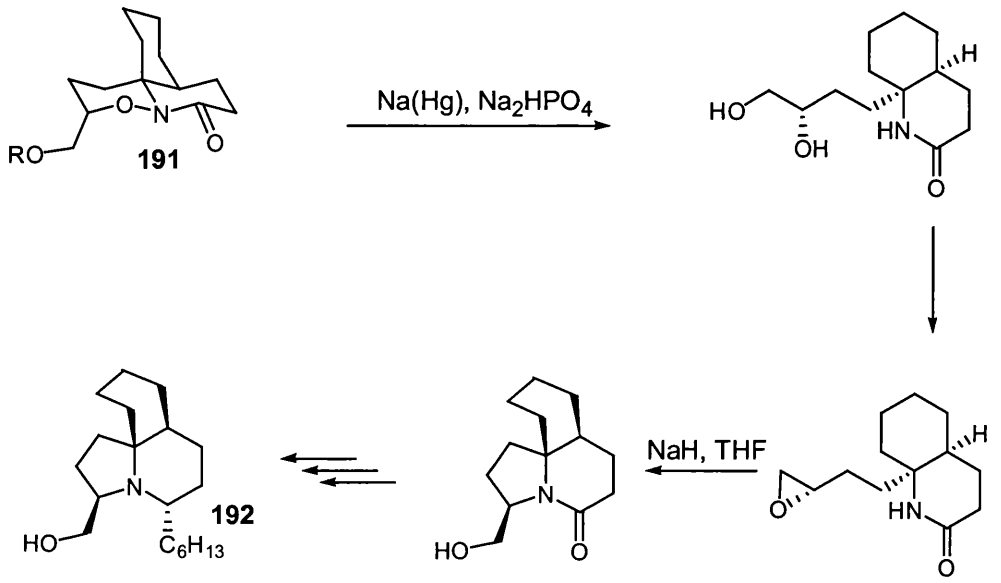


191 **192**

Scheme 3.10: Conversion of oxazinanone **191** in the marine alkaloid **192**.

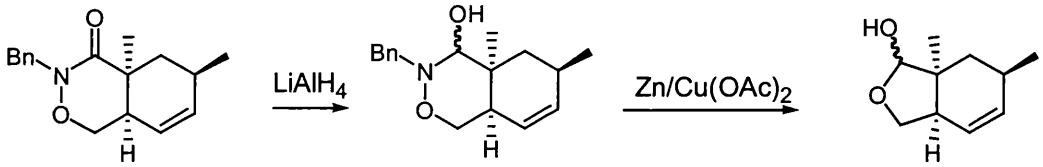
Reduction of such oxazinanones at the carbonyl group affords oxazines, or else to the corresponding lactams by cleavage of the N-O bond upon reductive treatment (*e.g* Na-Hg, Na_2HPO_4).

Lactam **191** (scheme 3.10) was subjected to reductive cleavage of the N-O bond with consequent ring opening followed ring closure to an epoxide that underwent intramolecular alkylation. Reduction of the carbonyl group then gave the fused ring **192** (scheme 3.11).[164]



Scheme 3.11

In scheme 3.12 is represented the conversion of the 6,6-fused system **193** to a stable hemiaminal using lithium aluminium hydride in THF at –78 °C. Subsequently, the bond N-O was cleaved reductivly (Zn, $Cu(OAc)_2$/AcOH-H_2O) to give the hemiacetal **194** in 65 % yield.[165]

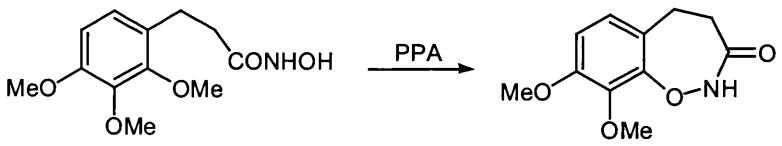


193 **194**

Scheme 3.12

3.1.2.4 [1,2] Oxazepan-3-ones

[1,2] Oxazepan-3-ones such as **182** are very little known; indeed only one example was found. Kametani and co-workers[140] showed that cyclisation of **195** with polyphosphoric acid gave the seven-membered ring **196** where the oxygen atom of the hydroxamic acid participated in the ring closure (scheme 3.12).



195 **196**

Scheme 3.12

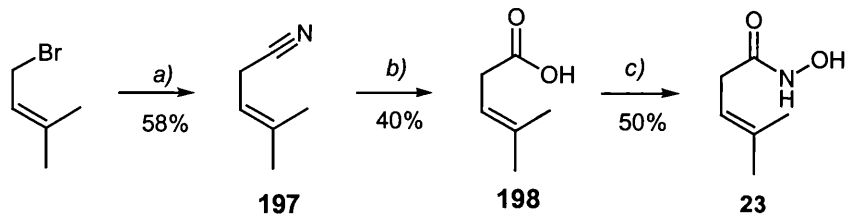
In the search for a general method of preparing such seven-membered rings as present in **196**, ring-closure reactions of unsaturated hydroxamic acids using trifluoromethanesulfonic acid were examined.

3.2 Results and Discussion

The reactions discussed above show that cyclisation of unsaturated hydroxamic acids can be achieved under various conditions and that the hydroxamic acid moiety can react with double bonds under appropriate conditions. Our interest was to try the ring closure reaction of hydroxamic acids onto unactivated double bonds by employing trifluoromethanesulfonic acid as thr catalyst. Since previous work in our group had established that trifluoromethanesulfonic acid effectively activated the double bond of unsaturated amides towards cyclisation,[137] various unsaturated hydroxamic acids were prepared and subjected to ring-closure conditions.

3.2.1 Preparation of β,γ-Unsaturated Hydroxamic Acids

Our initial foray into the acid-catalysed cyclisations required preparation of suitable substrates; 4-methyl-3-pentenoic hydroxamic acid **23** was initially chosen. It was thought that the presence of two methyl groups on the double bond could enhance the ring closure reaction, owing to an electron-rich C=C bond. The synthesis of **23** is shown in scheme 3.13.

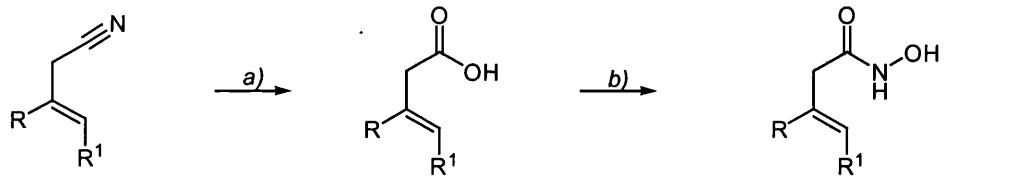


Scheme 3.13: *a)*: CuCN, KI; benzene; 25 °C; 48 h. *b)*: H_2O_2, NaOH, Bu_4NI; CH_2Cl_2; 0-25 °C; 5 days. *c)* NMM, $ClCO_2Et$, NH_2OH;Et_2O; 0-25 °C; 25 min.

Hydroxamic acid **23** was conveniently prepared from the corresponding carboxylic acid **198** by following the procedure of Reddy[166] (section **1.2.2**), in which

ethyl chloroformate and *N*-methylmorpholine activated the carboxylic acid *in situ* prior to reaction with hydroxylamine. The carboxylic acid **198** (scheme 3.13) was in turn prepared from 4-methyl-3-pentenenitrile **197** via a modification of Cacchi's for the preparation of pent-3-enamide,[167] using a phase-transfer catalysed reaction in hydrogen peroxide.[168] Nitrile **197** was obtained from the reaction of the commercial available 1-bromo-3-methyl-2-butene with copper cyanide in benzene catalysed by potassium iodide.[169]

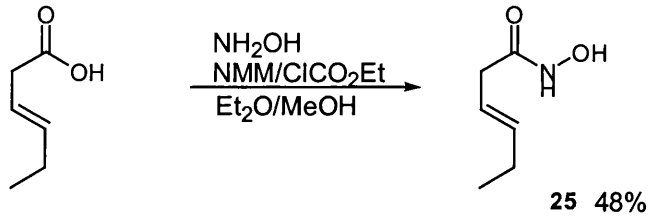
In a similar way the reaction of (*E*)-pent-3-enoic acid **199** and cyclohex-1-enyl acid **200** with hydroxylamine in the presence of ethyl chloroformate and *N*-methylmorpholine gave the expected hydroxamic acids **22** and **25** in 61% and 22% yields respectively. The carboxylic acids were in turn prepared from hydrolysis of the commercially available nitriles (scheme 3.14).



R = H, R^1 = CH_3, R = R^1= $(CH_2)_4$	R = H, R^1 = CH_3, **199**, 47% R = R^1= $(CH_2)_4$, **200**, 60%	R = H, R^1 = CH_3, **22**, 61% R = R^1= $(CH_2)_4$, **25**, 22%

Scheme 3.14: *a)*: H_2O_2, NaOH, Bu_4NI; CH_2Cl_2; 0-25 °C; 5 days. *b)*: NMM, $ClCO_2Et$, NH_2OH; Et_2O; 0-25 °C; 25 min.

(*E*)-Hex-3-enoic hydroxamic acid **25** was prepared by the reaction of (*E*)-hex-3-enoic acid with hydroxylamine, as described in chapter one (scheme 3.13).

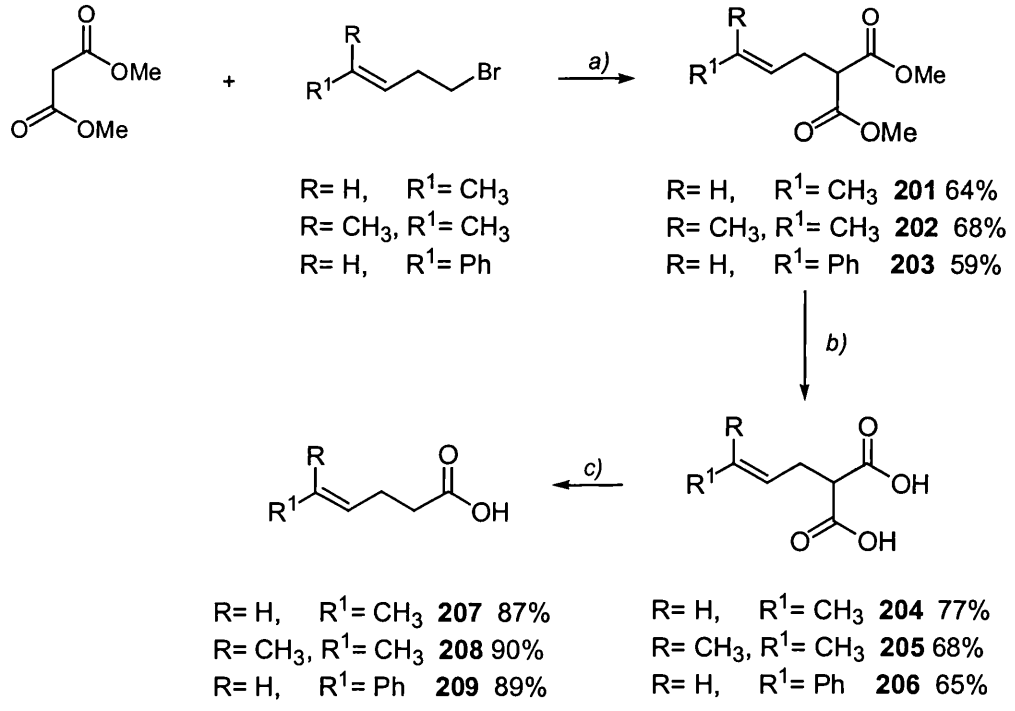


Scheme 3.13

The *β,γ*-unsaturated hydroxamic acids **22-25** were subjected to the cyclisations conditions as used for the corresponding amides.[137]

3.2.2 Preparation of γ,δ- and δ,ε-Unsaturated Hydroxamic Acids

Both γ,δ- and δ,ε-unsaturated hydroxamic acids were obtained by reaction of the corresponding carboxylic acids with hydroxylamine in the presence of ethyl chloroformate and *N*-methylmorpholine (section **1.2.2**). The γ,δ-unsaturated carboxylic acids were prepared as shown in scheme 3.14.

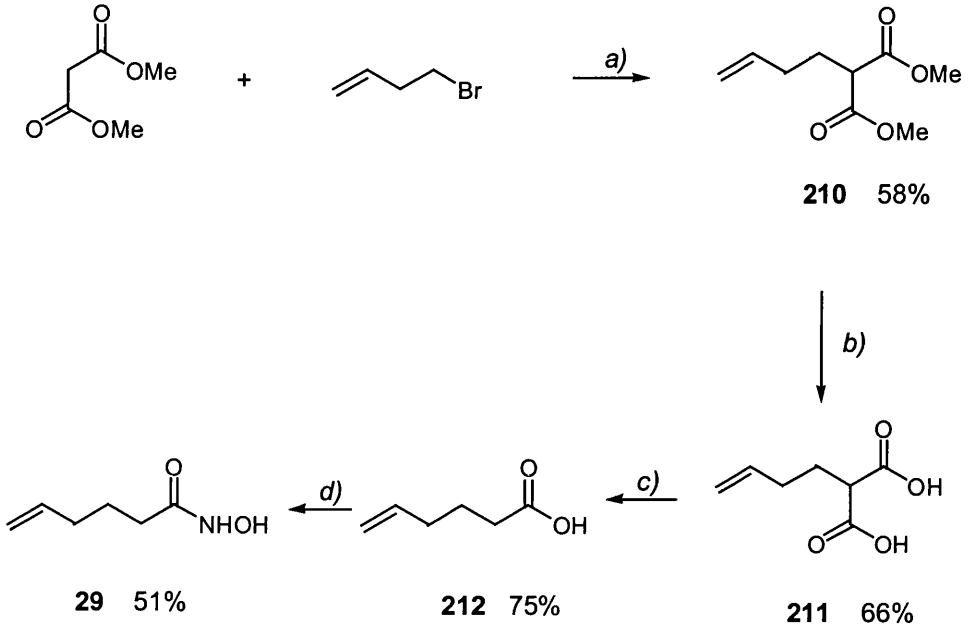


Scheme 3.14: *a)* NaH, THF; 25 °C; 12 h. *b)* NaOH, H_2O, THF; 25 °C; 48 h. *c)* DMF; 150 °C; 2 h.

The sequence involved the formation of diesters **201-203** by the reaction of the anionic dimethyl malonate with bromoalkenes as described by Shengming and co-workers.[170] Hydrolysis of the diesters **201-203**[171] afforded the corresponding diacids **204-206** in good yields that were converted into the desired carboxylic acids **207-209** by heating at reflux in dimethylformamide.[172]

A similar synthetic approach furnished the δ,ε-unsaturated hydroxamic acid **29** (scheme 3.15). The anion of dimethyl malonate was reacted with 5-bromopent-1-ene to give **210** as previously described.[170] The diester **210** was then converted into the

diacid **211** which was decarboxylated in dimethylformamide at reflux to give the acid **212**.



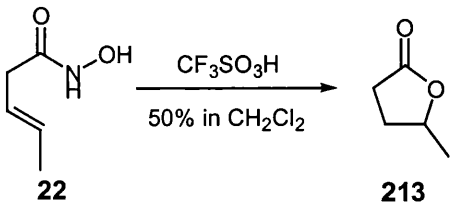
Scheme 3.15: *a)* NaH, THF; 25 °C; 12 h. *b)* NaOH, H_2O, THF; 25 °C; 48 h. *c)* DMF; 150 °C; 2 h. *d)* $ClCO_2Et$, NMM, NH_2OH, Et_2O ; 0→25 °C; 25 min.

When the reaction of malonate anion with various bromoalkenes was attempted in dimethylformamide, as described by McNamara and co-workers,[171] only unreacted starting material was recovered; therefore other conditions needed to be found and it was at that point that heated at reflux in tetrahydrofuran was found to be successful.

Moreover, when decarboxylation of the diacid **211** was conducted in 6 M hydrochloric acid at reflux, as described by McNamara and co-workers,[171] the main product was the corresponding lactone. The hydrochloric acid was promoting the undesired cyclisation to form the corresponding lactone.

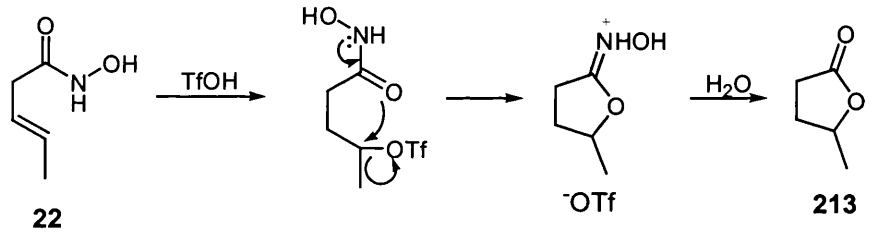
3.2.3 Cyclisation of *βγ*-Unsaturated Hydroxamic Acids

When (*E*)-pent-3-enoic hydroxamic acid was treated with 50% v/v trifluoromethanesulfonic acid in dichloromethane (2 h at 0 °C) an immediate formation of insoluble polymeric material together with lactone **205** was observed (scheme 3.16).



Scheme 3.16

A mechanism for the formation of the lactone **213** proceeds *via* intramolecular cyclisation of the hydroxamic acid **22** in which the oxygen atom of the carbonyl moiety reacts with the carbocation instead of the nitrogen atom. Subsequent hydrolysis of the oxime afforded **213** (scheme 3.17), in analogy with the reaction of amides with trifluoromethanesulfonic acid described above (section **3.1.1**).[137]



Scheme 3.17: Formation of Lactone **205**

In an endeavour to avoid problems of decomposition and the formation of side products, less trifluoromethanesulfonic acid was employed. That led to the six-membered [1,2] oxazinan-3-one **214** being isolated (entry 1, table 3.2) when 30% v/v of trifluoromethanesulfonic acid was employed. ^{1}H NMR studies confirmed the structure of [1,2] oxazinan-3-one **214**; appropriate coupling constants for axial and equatorial hydrogen atoms in a distorted chair conformation of a six-membered ring were observed.

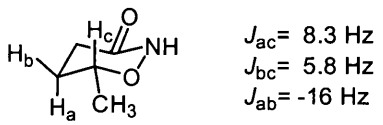


fig 3.7

Additionally, a line at 81.2 ppm in the ^{13}C NMR spectrum of **214** unequivocally confirmed that the methine carbon atom was bonded to oxygen rather

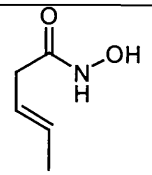
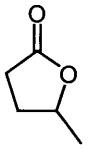
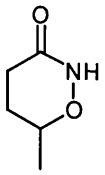
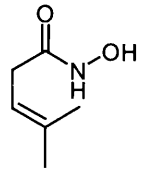
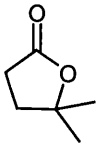
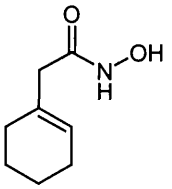
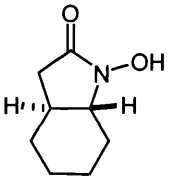
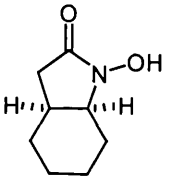
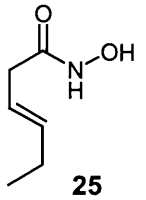
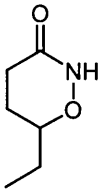
than nitrogen. Although the expected *N*-hydroxy γ-lactam was not detected, the reaction appeared to open a novel route for the synthesis of such compounds.

To clarify the formation of the six-membered ring instead of the expected five-membered ring, two aspects need to be considered: firstly the formation of a six-membered ring is more thermodynamically favorable and secondly the oxygen and nitrogen atoms of the hydroxamic acid moiety can both participate to the ring closure, being both nucleophilic. Indeed, various literature examples[140;164;165] were uncovered that show participation of the oxygen atom of the hydroxamic acid moiety instead of the nitrogen atom, when reacted with electrophiles. Similar treatment of substrate **25** with 30% v/v trifluoromethanesulfonic acid in dichloromethane gave the [1,2] oxazinan-3-one **217** in 60% yield (entry 4, table 3.2).

Next, we investigated the cyclisation reaction of 4-methylpent-3-enoic hydroxamic acid **23**. It was thought that the presence of a second methyl substituent on the double bond would render it more nucleophilic and therefore more reactive. Surprisingly, no [1,2] oxazinan-3-one was observed and the reaction led to the formation of lactone **215** as the exclusive product (entry 2). This result might be explained on the basis that the lactone is thermodynamically more stable than the [1,2] oxazinan-3-one ring.

Conversely, subjection of the sterically hindered hydroxamic acid **24** to the acidic conditions of above resulted in the formation of the five-membered ring, 1-hydroxyoctahydroindol-2-one **216**, as a 4:1 ratio of diastereoisomers in an overall yield of 50% (entry 3, table 3.2).

Table 3.2 Cyclisation of β,γ-Unsaturated Hydroxamic Acids (30% CF_3SO_3H in CH_2Cl_2)

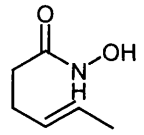
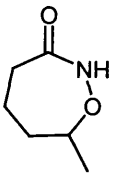
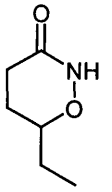
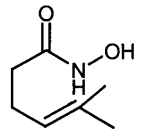
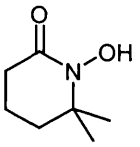
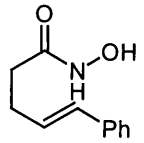
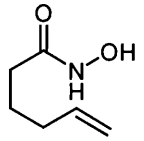
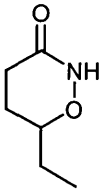
Entry	Hydroxamic Acid	Reaction time (h) and yields %	Products
1	 **22**	5 days 54%	 **213** +  **214** 1 : 4
2	 **23**	-	 **215**
3	 **24**	4 days 50%	  1 : 4 **216**
4	 **25**	5 days 60%	 **217**

3.2.4 Cyclisation of γ,δ- and δ,ε-Unsaturated Hydroxamic Acids

Seeing that β,γ-unsaturated hydroxamic acids cyclised to give mostly six-membered rings where the oxygen rather then the nitrogen attacked the carbocation, it was decided to investigate the ring closure reaction of various unsaturated hydroxamic acids with the double bond in different location. Accordingly, γ,δ- and δ,ε-unsaturated hydroxamic acids were prepared, and cyclisations attempted.

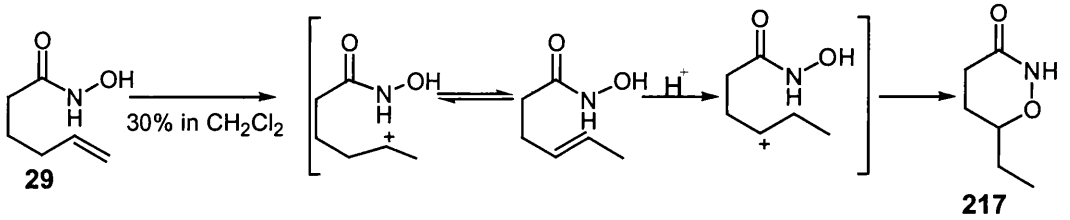
Hydroxamic acid **26** afforded a mixture of the seven-membered ring **218** and the six-membered ring **217** in a 3: 1 ratio (entry 1, table 3.3) while no product of *N*-cyclisation was detected. Conversely, cyclisation of hydroxamic acid **27**, in 30% v/v trifluoromethanesulfonic acid and dichloromethane (5 days, rt) led exclusively to the six-membered ring **219** where the nitrogen atom of the hydroxamic acid moiety instead of the oxygen atom attacks the carbocation (entry 2, table 3.3).

Table 3.3 Cyclisation of γ,δ and δ,ε-Unsaturated Hydroxamic Acids in Trifluoromethanesulfonic Acid

Entry	Hydroxamic Acid	Reaction time (h)	Products
1	 **26**	5 days 52%	 **218** 3:1  **217**
2	 **27**	5 days 73%	 **219**
3	 **28**	5 days	Unreacted Starting Material
4	 **29**	5 days 63%	 **217**

Cyclisation of **29** proceeded via C=C double bond migration as observed in an analogous case for the amide.[137] Indeed isomerisation of the double bond from δ-position to the γ-position had occurred, leading to the six-membered ring **217** as the exclusive product in 63% yield. While conclusive predictions concerning *O*- and *N*-

cyclisation are not possible, it is likely that the *N*-cyclised product is the result of kinetic control (e.g. **219**), whereas *O*-cyclised products such as **217** would be more thermodynamically formed over their *O*-cyclised counterparts, since in the former is amide resonance stabilisation possible ($^{-}OC=N^{+}(OH)R$ being a poor resonance hybrid).

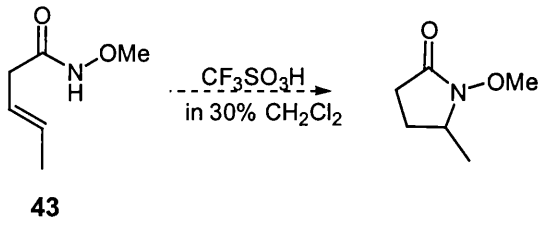


Scheme 3.18

Acid-induced cyclisation of hydroxamic acid **28** (entry 2) did not occur, possibly because the ring closure was sufficiently hindered by the phenyl substituent.

3.2.5 Cyclisation of *O*-Protected Unsaturated Hydroxamic Acids

Since cyclisation proceeded predominantly *via* the attack of oxygen rather than nitrogen, it was thought that *O*-protection might induce cyclisation such that the nitrogen would attack exclusively. Accordingly, hydroxamic acid **43** was prepared and treated with trifluoromethanesulfonic acid (scheme 3.28). Unfortunately, no *N*-hydroxy γ-lactam could be isolated and only a variety of inseparable products was obtained.

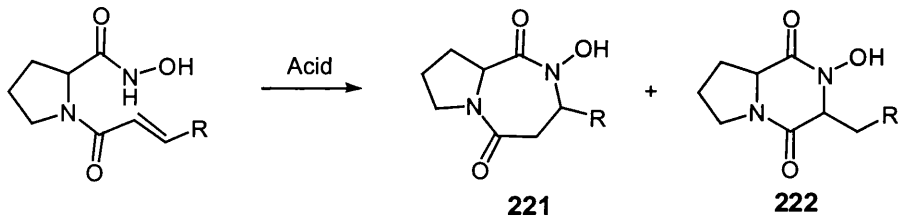


Scheme 3.19

The use of milder conditions (5% trifluoromethanesulfonic acid in dichloromethane at −10 °C) was not beneficial. It seemed that protection of the oxygen atom did not appear to direct the reaction towards the desired *N*-cyclisation.

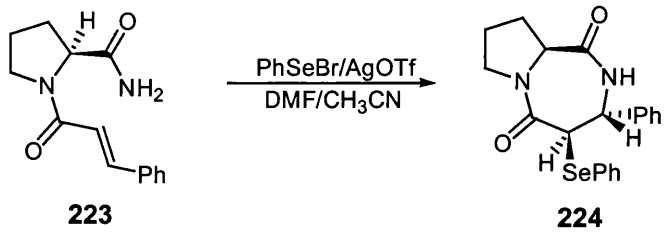
3.2.6 Cyclisation of Proline-Derivated Hydroxamic Acids

Extension of the above methodology to the synthesis of diazepinones **210** was attempted (scheme 3.20). Proline hydroxamic acids could in fact cyclise to form either the seven-membered ring **221** or the six-membered **222**, depending upon which carbocation participates during the reaction. However, **222** would proceed via a strongly destabilised carbocation, so it was hoped that only **221** would result.



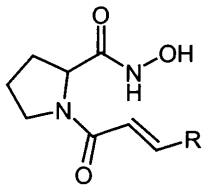
Scheme 3.20

Chung and co-workers[168] have described an efficient route to lactams **224** with a high degree of chirality transfer using PhSeBr and AgOTf (scheme 3.21).



Scheme 3.21

To test our approach to the synthesis of diazepinones **221** (scheme 3.20), two differently substituted hydroxamic acids **30** and **31** (fig 3.4) were synthesised from appropriate carboxylic acids (scheme 1.7, section **1.2.3**).



R = Ph **30**
R = CH_3 **31**

Fig 3.4

The hydroxamic acid **30** was selected for the cyclisation reaction of proline-type hydroxamic acids, because Chung and co-workers[168] obtained good results with the corresponding amide. However, when **30** was treated with 30% v/v trifluoromethanesulfonic acid in dichloromethane (rt, 2 days), only starting material could be recovered; the use of stronger conditions (50% trifluoromethanesulfonic acid) was of no benefit. Since the bulk of the benzene ring on the double bond might have prevented cyclisation of the hydroxamic acid, a less bulky substituent was investigated; methyl substituted hydroxamic acid **31** was prepared and treated with acid. Unfortunately no cyclised products were isolated.

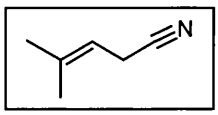
Cyclisation of proline-type hydroxamic acids **30** and **31** did not occur possibly because of the substantial deactivation of the double bond by the amide functionality. Trifluoromethanesulfonic acid, even in high concentration, was not found to be effective.

3.2.7 Conclusions

It was shown that unsaturated hydroxamic acids undergo cyclisation using 30% trifluoromethanesulfonic acid as a catalyst to give heterocycles linked through C-O bonds. Although the cyclisation reaction did not proceed predominantly through attack of the nitrogen atom as expected, it was nevertheless interesting to observe that novel heterocycles could be synthesised.

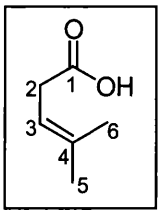
3.3 Experimental

4-Methyl-3-pentenenitrile (197)[173]



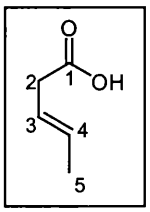
Copper (I) cyanide (3.0 g, 34 mmol) was added to dry benzene (10 mL). 4-Bromo-2-methyl-2-butene (3.0 g, 20 mmol) and potassium iodide (0.30 g, 2.0 mmol) were then added. The mixture was stirred for 48 h at 20 °C. Benzene was distilled at atmospheric pressure and the residue was then distilled at reduced pressure to give **197** (1.57 g, 58%); ^{1}H NMR 5.05 (1H, t J = 6 Hz, CH), 2.92 (2H, d J = 9 Hz, CH_2), 1.58 (3H, br s, *cis*-CH_3), 1.53 (3H, br s, *trans*-CH_3); ^{13}C NMR 139.0 (CH), 128.7 (C), 112.2 (CN), 25.7 (CH_2), 16.6 (*cis* CH_3), 18.2 (*trans* CH_3).

4-Methylpent-3-enoic acid (198)[168]



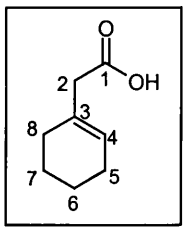
To a solution of 4-methyl-3-pentenentrile (1.39 g, 14.63 mmol), in dichloromethane (6.0 mL) cooled in a ice-bath were added 30% w/v aqueous hydrogen peroxide (0.12 mol), tetra-*n*-butylammonium iodide (4.55 g, 12.3 mmol) and an aqueous solution of 20% w/v sodium hydroxide (74 mmol). The mixture was allowed to warm to 20 °C and vigorously stirred for 5 days. The organic and the aqueous layers were separated. The aqueous layer was extracted with dichloromethane (3 x 30 mL) to remove the phase transfer catalyst. The aqueous layer was acidified with dilute hydrochloric acid, extracted with dichloromethane (5 x 30 mL), and the combined layers were dried (Na_2SO_4) and evaporated. Flash chromatography (ethyl acetate/petroleum ether 1:1) afforded **198** (1.0 g, 40%) as clear yellow liquid; ^{1}H NMR 11.3 (1H, br s, COOH) 5.14 (1H, m, H_3), 2.93 (2H, br d J = 9Hz, H_2), 1.60 (3H, br s, H_6), 1.50 (3H, br s, H_5); ^{13}C NMR 179.2 (CO) 136.5 (C_4), 115.5 (C_3), 33.9 (C_2), 25.9 (C_6), 17.8 (C_5).

(*E*)-3-Pentenoic acid (199)[168]



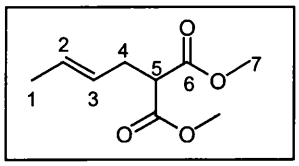
To a solution of (*E*)-3-pentenenitrile (2.39 mL, 24.65 mmol) in dichloromethane (50 mL) cooled in an ice-bath, were added 30% w/v aqueous hydrogen peroxide (0.12 mol), tetra-*n*-butylammonium iodide (4.55 g, 12.3 mmol), and an aqueous solution of 20% w/v sodium hydroxide (74.0 mmol). The mixture was allowed to warm to 20 °C and vigorously stirred for 5 days. The organic and the aqueous layers were separated. The aqueous layer was extracted with dichloromethane (3 x 30 mL) to remove the phase transfer catalyst. The aqueous layer was acidified with dilute hydrochloric acid, extracted with dichloromethane (5 x 30 mL), and the combined layers dried over Na_2SO_4. Evaporation of the solvent afforded **199** (1.0 g, 47%) as clear yellow liquid and used without further purification. ^{1}H NMR 5.86-5.67 (m, 2H H_3, H_4), 3.22 (dd, J = 6 Hz, J = 2.1 Hz, 2H, H_2), 1.68 (dd, J = 8 Hz, J = 1.2 Hz, 3H, H_5); ^{13}C NMR 179.0 (C_1), 130.0 (C_3), 121.9 (C_4), 37.8 (C_2), 17.8 (C_5).

Cyclohex-1-enylacetic acid (200)[168]



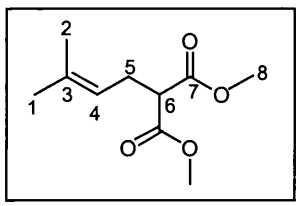
To a solution of cyclohex-1-ene acetonitrile (5.0 g, 41.3 mmol) in dichloromethane (21.0 mL) cooled in an ice-bath were added 30% w/v aqueous hydrogen peroxide (0.20 mol), tetra-*n*-butylammonium iodide (4.55 g, 0.20 mmol) and an aqueous solution of 20% w/v sodium hydroxide (0.12 mmol). The mixture was allowed to warm to 20 °C and vigorously stirred for 5 days. The organic and the aqueous layers were separated. The aqueous layer was extracted with dichloromethane (3 x 50 mL) to remove the phase-transfer catalyst. The aqueous layer was acidified with dilute hydrochloric acid and extracted with dichloromethane (5 x 50 mL). The combined layers were dried over Na_2SO_4 and evaporated. Flash chromatography (4:6 ethyl acetate:petroleum ether) gave **200** (3.4 g, 60%); ^{1}H NMR 5.88 (1H, br s, H_4), 2.13 (2H, s, H_2), 1.76 (8H, m, H_5, H_6, H_7, H_8); ^{13}C NMR 178.3 (C_1), 131.0 (C_3), 127.8 (C_4), 43.7 (C_2), 37.7 (C_8), 25.7 (C_5), 23.1 (C_6), 22.3 (C_7).

2-But-2-enyl malonic acid dimethyl ester (201)[170]



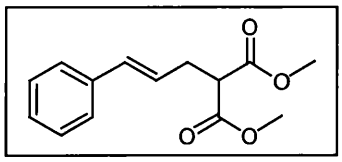
To an ice-cold suspension of sodium hydride (1.1 g, 27.5 mmol) in dry tetrahydrofuran (25 mL) was added slowly dimethyl malonate (4.0 g, 25.0 mmol). The mixture was stirred for 15 min at 20 °C. The crotyl bromide was added dropwise and the mixture stirred overnight at room temperature. The mixture was quenched with water (15 mL) and the tetrahydrofuran removed under reduced pressure. The aqueous layer was extracted with diethyl ether (3 x 25 mL) and the combined organic layers were dried over $MgSO_4$. The crude product was purified by flash chromatography (ethyl acetate: petroleum ether/1:9) to give the mixture of *cis*- and *trans*-**201** (3.0 g; 64%) as a colourless oil; ^{1}H NMR 5.59 (1H, m, H_3), 5.43 (1H, m, H_2), 3.77 (6H, s, H_7), 3.44 (1H, t, J = 6 Hz, H_5), 2.69 (1H, t bd, J = 6 Hz J = 3 Hz,, H_4), 1.68 (3H, d J = 3 Hz, H_1); ^{13}C NMR 169.5 (C_6), 128.6 (C_2), 126.7 (C_3), 52.2 (C_7), 51.8 (C_5), 32.1 (C_4), 18.0 (C_1).

2-(3-Methyl but-2-enyl) malonic acid dimethyl ester (202)[170]



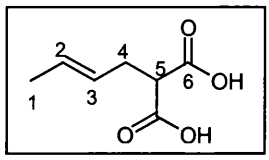
To a stirred solution of sodium hydride (0.14 g, 3.50 mmol) in dry tetrahydrofuran (3.0 mL) was slowly added dimethyl malonate (0.47 mL, 3.12 mmol) at 20 °C. The mixture was stirred for 15 min, 4-bromo-2-methylbut-2-ene (0.35 mL, 3.12 mmol) was then added dropwise. After stirring the mixture for 12 h, it was quenched with water and the tetrahydrofuran was evaporated under reduced pressure. The aqueous layer was extracted with diethyl ether (3 x 15 mL) and the combined extracts were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography (1:9 diethyl ether:petroleum ether) to give the diester **202** (0.42 g; 68 %) as a colourless oil; ^{1}H NMR 5.25 (m, 1H, H_4), 3.93 (s, 6H, H_8), 3.56 (t J = 7.5 Hz, 1H, H_6), 2.79 (br t, J = 7.4 Hz, 2H, H_5), 1.88 (br s, 3H, H_1), 1.83 (br s, 3H, H_2); ^{13}C NMR 169.7 (C_7), 135.2 (C_3), 119.5 (C_4), 52.5 (C_8), 52.0 (C_6), 27.7 (C_5), 25.8 (C_1), 17.8 (C_2).

2-(3-Phenylallyl)-malonic acid dimethyl ester (203)[170]



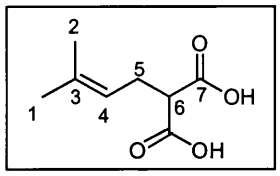
To a stirred solution of sodium hydride (0.60 g, 15.2 mmol) in dry tetrahydrofuran (12 mL) was slowly added dimethyl malonate (1.9 mL, 12.7 mmol) at 20 °C. The mixture was stirred for 15 min and the cinnamyl bromide (1.9 mL, 12.7 mmol) was added dropwise. After stirring the mixture for 12 h, the reaction was quenched with water (20 mL) and the tetrahydrofuran was evaporated under reduced pressure. The aqueous layer was extracted with diethyl ether (3 x 15 mL) and the combined extracts were washed with brine, dried over $MgSO_4$ and evaporated under vacuum. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether 15: 75) to give **203** (1.85 g; 59 %) as a colourless oil; ^{1}H NMR 7.40-7.25 (5H, m, Ar), 6.55 (1H, d J = 15 MHz, PhCH), 6.21 (1H, m, PhCH=CH), 3.75 (6H, s, OCH_3), 3.51 (1H, t, J = 6 MHz, CHCO), 2.90-2.84 (2H, m, CH_2); ^{13}C NMR 169.6 (CO), 137.5 (PhCH), 133.3 (C_i), 128.9 (C_m), 127.8 (PhCH=CH), 126.6 (C_p), 125.84 (C_o), 52.9 (OCH_3), 52.1 (CH), 33.7 (CH_2).

2-But-2-enylmalonic acid (204)[171]



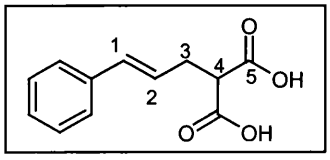
To a stirred solution of 2-but-2-enylmalonic acid dimethyl ester (2.6 g, 14.0 mmol) in tetrahydrofuran (10 mL) and water (10 mL) was added sodium hydroxide (1.1 g, 28.0 mmol) and the mixture was stirred for 2 days at 20 °C. The solvent was removed *in vacuo* and the resulting white solid was added to hydrochloric acid (2 M, 2.0 mL). The aqueous layer was saturated with sodium chloride and then extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure to give **204** (1.7 g, 77%) as colourless oil; ^{1}H NMR 8.69 (br s, OH), 5.60 (1H, m, H_3), 5.34 (1H, m, H_2), 3.47 (t, J = 7.5 Hz, 1H, H_5), 2.61 (t, 2H, H_4), (br s, 3H, H_1); ^{13}C NMR 174.3 (C_6), 129.4 (C_3), 125.6 (C_2), 51.8 (C_5), 31.7 (C_4), 18.0 (C_1).

2-(3-Methylbut-2-enyl)-malonic acid (205)[171]



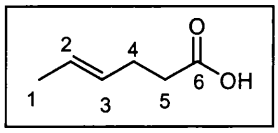
To a stirred solution of 2-(3-methylbut-2-enyl)-malonic ester (0.27 g, 1.38 mmol) in tetrahydrofuran (1.0 mL) and water (1 mL) was added sodium hydroxide (0.11 g, 2.76 mmol) and the mixture was stirred for 2 days at 20 °C. The solvent was removed *in vacuo* and the resulting white solid was added to hydrochloric acid (2 M, 2.0 mL). The aqueous layer was saturated with sodium chloride and then extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure to give **205** (0.16 g, 68%)as colourless oil; ^{1}H NMR 4.95 (m, 1H, H_3), 3.28 (1H, t, J = 6 Hz, H_4), 2.49 (2H, t, J = 6 Hz, H_5), 1.68 (3H, br s, H_1), 1.48 (3H, br s, H_2); ^{13}C NMR 174.6 (C_7), 136.0 (C_3), 119.4 (C_4), 52.1 (C_6), 28.0 (C_5), 26.0 (C_1), 18.0 (C_2).

2-(3-Phenylallyl)-malonic acid (206)



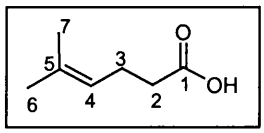
To a stirred solution of 2-(3-phenylallyl) malonic ester (1.75 g, 7.05 mmol) in tetrahydrofuran (2.0 mL) and water (2.0 mL) was added sodium hydroxide (0.56 g, 14.11 mmol) and the mixture was stirred for 2 days at 25 °C. The solvent was removed under reduced pressure and the resulting white solid was added to hydrochloric acid (2 M, 10.0 mL). The aqueous layer was saturated with sodium chloride and then extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure to give **206** (1.0 g, 65%)as white microprisms; mp 129-131 °C (lit[174] mp 131 °C); ^{1}H NMR 9.78 (2H, s, OH), 7.19 (5H, m, Ar), 6.43(1H, m, H_1), 6.13-5.95 (1H, m, H_2), 3.51 (1H, t, J = 6 Hz, H_4), 2.76 (2H, m, H_3); ^{13}C NMR 173.6 (C_5), 137.2 (C_1), 133.8 (C_i), 128.9 (C_m), 127.9 (C_2), 126.7 (C_o), 125.1 (C_p), 51.8 (C_4), 32.5 (C_3).

Hex-4-enoic acid (207)[172]



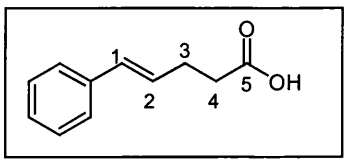
2-But-2-enylmalonic acid (2.21 g, 13.9 mmol) was heated at reflux in dry dimethylformamide (50 mL) for 2 h. The cooled mixture was acidified with 1 M hydrochloric acid to pH = 5 and extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with water (2 x 30 mL), dried over $MgSO_4$ and evaporated under reduced pressure to give **207** (1.41 g, 87%) as a colourless oil; ^{1}H NMR 5.75-5.59 (2H, m, H_2 H_3), 2.63 (2H, m, H_5), 2.54 (2H, m, H_4), 1.81 (3H, br s, H_1); ^{13}C NMR 179.4 (C_6), 128.9 (C_3), 126.4 (C_2), 34.1 (C_5), 27.5 (C_4), 17.8 (C_1).

5-Methylhex-4-enoic acid (208)[172]



2-(3-Methylbut-2-enyl)malonic acid (0.10 g, 0.5 mmol) was heated at reflux in dry dimethylformamide (2.0 mL) for 2 h. The cooled mixture was acidified with 1 M hydrochloric acid to pH = 5 and extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with water (2 x 10 mL), dried over $MgSO_4$ and evaporated under reduced pressure to give **208** (0.74 mg, 90%) as a colourless oil; ^{1}H NMR 5.09 (1H, m, H_4), 2.33 (4H, m, H_3, H_2), 1.67 (3H, br s, H_7), 1.61 (3H, br s, H_6); ^{13}C NMR 177.0 (C_1), 133.9 (C_5), 122.5 (C_4), 36.1 (C_2), 25.3(C_7), 21.3 (C_3) 19.3 (C_7).

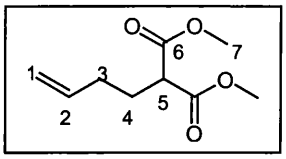
5-Phenylpent-4-enoic acid (209)[175]



2-(3-Phenylpent-4-enoic)malonic acid (1.1 g, 5.0 mmol) was heated at reflux in dry dimethylformamide (20 mL) for 2 h. The cooled mixture was acidified with 1 M hydrochloric acid to pH 5 and extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with water (2 x 30 mL), dried over $MgSO_4$ and evaporated under reduced pressure to give **209** (0.74 g, 89%) as a clear yellow

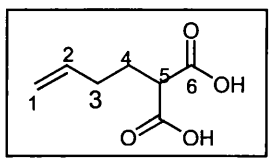
solid; mp 87-89 °C (lit[175] 90-91 °C); ^{1}H NMR 8.75 (1H, s, OH), 7.25 (5H, m, Ar), 6.43 (1H, d, J = 6 Hz, H_1), 6.21 (1H, m, H_2), 2.82 (2H, m, H_3), 2.50 (2H, m, H_4). ^{13}C NMR 177.2 (C_5), 137.8 (C_1), 132.6 (C_i), 131.2 (C_2), 128.9 (C_m), 127.5 (C_o), 126.5 (C_p), 35.3 (C_3), 28.5 (C_4).

2-But-3-enylmalonic acid dimethyl ester (210)[170]



To an ice-cold solution of sodium hydride (0.65 g, 16.3 mmol) in dry tetrahydrofuran (13 mL) was slowly added dimethyl malonate (2.25 mL, 14.81 mmol). The mixture was stirred for 15 min and 4-bromo-1-butene (1.5 mL = 14.8 mmol) was added dropwise. The mixture was stirred overnight, and was then quenched with water (30 mL). The aqueous layer was extracted with diethyl ether (5 x 20 mL) and the combined extracts were washed with brine, dried over $MgSO_4$ and evaporated under vacuum. The crude product was purified by flash chromatography (ethyl acetate:petroleum ether 1:9) to give the diester **210** (1.5 g; 58 %) as a colourless oil; ^{1}H NMR 5.81 (1H, m, H_2), 5.07 (2H, m, H_1), 3.77 (6H, s, H_7), 3.44 (H_5), 2.08 (4H, m, H_3, H_4); ^{13}C NMR 170.1 (C_6), 137.1 (C_2), 116.3 (C_1), 52.8 (C_7), 51.2 (C_5), 31.6 (C_3), 28.3 (C_4).

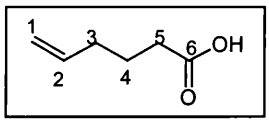
2-But-3-enylmalonic acid (211)[177]



To a stirred solution of 2-but-3-enylallylmalonic ester (1.8 g, 9.7 mmol) in tetrahydrofuran (2.5 mL) and water (2.5 mL) was added sodium hydroxide (0.77 g, 19.35 mmol) and the mixture was stirred for 2 days at 20 °C. The solvent was removed *in vacuo* and the resulting white solid was added to hydrochloric acid (2.0 M, 12.0 mL). The aqueous layer was saturated with sodium chloride and extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and then evaporated under reduced pressure to give **211** (1.0 g, 66%) as white solid; mp 90 °C

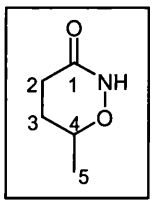
(lit[176] mp 92 °C); ^{1}H NMR 5.64 (1H, m, H_2), 4.88 (2H, m, H_1), 3.31 (1H, t, J = 6 Hz, H_5), 2.00 (2H, m, H_4), 1.90 (2H, m, H_3); ^{13}C NMR 175.28 (C_6), 136.6 (C_2), 116.9 (C_1), 51.1 (C_5), 31.4 (C_4), 28.1 (C_3).

Hex-5-enoic acid (212)[172]



2-But-3-enylmalonic acid (1.0 g, 6.0 mmol) was heated at reflux in dry dimethylformamide (21 mL) for 2 h. The cooled mixture was acidified with 1 M hydrochloric acid to pH = 5 and extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with water (2 x 30 mL), dried over $MgSO_4$ and evaporated under reduced pressure to give **212** (0.54g, 75%) as a colourless oil; ^{1}H NMR 8.93 (1H, s, OH), 5.00 (1H, m, H_2), 4.93 (2H, td, J = 6 Hz, J= 3 Hz, H_1), 2.27 (2H, t, J = 6 Hz, H_3), 2.00 (H_5), 1.62 (2H, m, H_4); ^{13}C NMR 179.5 (C_6), 137.9 (C_2), 115.8 (C_1), 33.7 (C_3), 33.3 (C_5), 24.1 (C_4).

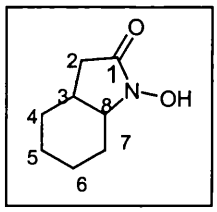
6-Methyl-[1,2]oxazinan-3-one (214)



Pent-3-enoic hydroxamic acid (0.20 g, 1.74 mmol) was dissolved in a mixture of dichloromethane (2.0 mL) and trifluoromethanesulfonic acid (0.65 mL) under an inert atmosphere. After 5 days the residue was cooled at -20 °C and neutralized to pH 7 with saturated sodium hydrogen carbonate. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic layers dried over $MgSO_4$. The crude product was purified by column chromatography eluting with petroleum ether:ethyl acetate (1:1) to give the oxazinan-3-one **214** (0.11 g, 54 %) as white microprisms: mp 132-133 °C; IR ν_{max} (cm^{-1}) (KBr) 3148 (NH), 2921 (N-O), 1695 (CO); ^{1}H NMR: 8.28 (NH), 4.64 (qdd, J (4ax, 5) = 6.2 Hz, J (4ax, 3eq) = 5.8 Hz J (4ax, 3ax) = 8.3 Hz, 1H, H_{4ax}), 2.66 (ddd, J (2eq, 2ax) = -16 Hz, J (2eq, 3ax) = 8.9 Hz J (2eq, 3eq) = 4.5, 2H, H_{2eq}), 2.61 (ddd, J (2ax, 2eq) = -16 Hz, J (2ax, 3ax) = 9.6

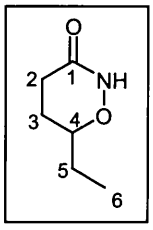
Hz J (2ax, 3eq) = 8.1, 2H, H_{2ax}), 2.23 (dddd, J (3eq, 3ax) = -12 Hz, J (3eq, 2ax) = 8.1 Hz J (3eq, 4ax) = 5.8 J (3eq, 2eq) = 4.5 Hz, 1H, H_{3eq}), 1.73 (dddd, ^2J (3ax, 3eq) = -12 Hz, J (3ax, 2ax) = 9.6 Hz J (3ax, 2eq) = 8.9 J (3ax, 4ax) = 8.3 Hz, 1H, H_{3ax}), 1.41 (d, J (5, 4ax) = 6.2 Hz; ^{13}C NMR 159.9 (C_3), 80.8 (C_6), 30.8 (C_4), 26.6 (C_5), 20.4 (C_7). Found C, 52.49, H, 8.13, N, 11.83, ($C_5H_9NO_2$ requires C, 52.16, H, 7.88, N, 12.17).

1-Hydroxy-octahydroindol-2-one (216)



Cyclohex-1-ene acetohydroxamic acid (0.13 g, 0.84 mmol) was dissolved in a mixture of trifluoromethanesulfonic acid (1.0 mL) and dichloromethane (2.0 mL) and stirred at 20 °C under an atmosphere of nitrogen for 5 days. The mixture was cooled to – 20 °C, neutralized with saturated aqueous sodium carbonate (dropwise initially), and extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (90:8:2 ethyl acetate: methanol: water) to give **216** (0.65 mg, 50%) as a white pellets: mp 132-134° C; IR ν_{max} (cm^{-1}) 3134 (N-OH str), 1676 (C=O str); ^{1}H NMR 8.01 (N-H), 2.58 (1H, m, H_8), 2.38 (1H, s, H_3), 2.10 (2H, m, H_2), 1.94 (2H, m, H_7), 1.67 (2H, m, H_4), 1.45 (4H, br s, H_5, H_6); ^{13}C NMR 166.7 (C_1), 68.8 (C_8), 44.7 (C_2), 41.0 (C_3), 37.7 (C_7), 33.0 (C_4), 30.3 (C_6), 20.74 (C_5). Found C, 61.44, H, 8.30, N, 8.97, ($C_8H_{13}N_1O_2$ requires C, 61.89, H, 8.45, N, 9.03).

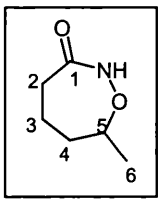
6-Ethyl-[1,2]oxazinan-3-one (217)



Hex-3-enoic hydroxamic acid (0.20 g, 1.74 mmol) was dissolved in a mixture of trifluoromethanesulfonic acid (2.3 mL) and dichloromethane (7.0 mL) and stirred at 20 °C under an atmosphere of nitrogen for 4 days. Ice was then added to the mixture which was then cooled to – 20 °C, neutralized with saturated aqueous sodium carbonate (dropwise initially), and extracted with dichloromethane (3 x 10 mL). The

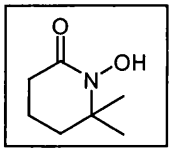
combined organic extracts were dried over $MgSO_4$, the solvent removed and the residue purified by flash chromatography (ethyl acetate:petroleum ether 1:1) to give **217** (90 mg, 60%) as white microprisms: mp 82-83 °C; IR ν_{max} (cm^{-1}) (KBr) 3130 (NH str), 2926(N-O), 1680 (CO); ^1H NMR 8.20 (N-H), 4.62-4.33 (1H, m, H_4), 2.60 (2H, t, H_2), 2.14 (1H, m, H_3), 1.80 (1H, m, $H_{3'}$), 1.71-1.58 (2H, m, H_5), 0.92 (3H, t, J = 6 Hz, H_6); ^{13}C NMR 160.4 (C_1), 86.2 (C_4), 28.9 (C_2), 28.1 (C_3), 26.8 (C_5), 9.9 (C_6). LRMS M/Z (EI) 130 (100), 97 (45), 69 (80), 55 (60). Found C, 54.94, H, 8.45, N, 10.47, ($C_6H_{11}NO_2$ + 1/6 H_2O requires C, 54.54, H, 8.63, N, 10.60).

7-Methyl-[1,2]oxazepan-3-one (218)



5-Methyl pent-3-enoic hydroxamic acid (0.90 g, 0.69 mmol) was dissolved in a mixture of dichloromethane (1.0 mL) and trifluoromethanesulfonic acid (0.3 mL) under nitrogen. After 5 days the mixture was cooled at -20 °C and neutralized with saturated sodium hydrogen carbonate. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic layers dried over $MgSO_4$. Evaporation gave a crude product which was purified by column chromatography (ethyl acetate /petroleum ether 7:3) to give **218** (0.46 g, 52 %) as a white solid: mp 68-69 °C; IR ν_{max} (cm^{-1}) (KBr) 3232 (NH str), 2946 (N-O), (1612 (CO); ^1H NMR 8.96 (N-H), 4.15 (1H, m, H_5), 2.33 (1H, m, H_{4a}), 2.20 (1H, m, H_{4b}), 1.85 (2H, m, H_2), 1.81 (1H, m, H_{3a}), 1.70 (m, 1H, H_{3b}), 1.36 (d J = 6 Hz, H_6); ^{13}C NMR 155.6 (C_1), 75.9 (C_5), 31.0 (C_4), 24.5 (C_2), 21.5 (C_3), 19.4 (C_6). Found C, 55.61, H, 8.65, N, 10.72, ($C_7H_{13}NO_2$ requires C, 55.78, H, 8.59, N, 10.85).

1-Hydroxy-6,6-dimethylpiperidin-2-one (219)



The procedure of Marson[137] for the preparation of 1-Hydroxy-6,6-dimethylpiperidin-2-one was suitably adapted.

6-Methylhex-4-enoic hydroxamic acid (0.15 g, 1.05 mmol) was dissolved in a mixture of trifluoromethanesulfonic acid (0.6

mL) and dichloromethane (2.0 mL) and stirred at 20 °C under an atmosphere of nitrogen for 5 days. The mixture was then cooled in ice, treated with saturated aqueous sodium hydrogen carbonate (dropwise initially), then extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, the solvent removed and the residue purified by flash chromatography (ethyl acetate:petroleum ether 4:6) to give **219** (0.11 g, 73%) as microprisms: mp 81 °C (lit[177] 79 °C); ^{1}H NMR 2.36 (2H, t J = 6 Hz, $C\underline{H}_2CO$), 1.73 (4H, m, CH_2), 1.31 (6H, s, CH_3); ^{13}C NMR 164.3 (CO), 60.1 (CH-N), 38.2 ($\underline{C}H_2CO$), 31.39 (CH_2), 26.52 ($\underline{C}H_2CH$), 17.32 (CH_3).

3.4 References

(137) Marson, C. M.; Fallah, A. *Tetrahedron Lett.* **1994**, *35*, 293.

(138) Hill, R. K. *J.Org.Chem.* **1957**, *22*, 830.

(139) Tilley, J. W.; Clader, J. W.; Blount, J. F. *J.Org.Chem.* **1985**, *50*, 2220.

(140) Kametani, T.; Nemoto, H. *Chem.Pharm.Bull.* **1971**, *19*, 1325.

(141) Moody, C. M.; Young, D. W. *Tetrahedron Lett.* **1993**, *34*, 4667.

(142) Takahashi, H.; Hitomi, Y.; Iwai, Y.; Ikegami, S. *J. Am.Chem.Soc.* **2000**, *122*, 2995.

(143) Keck, G. E.; Webb, R. *Tetrahedron Lett.* **1979**, *14*, 1185.

(144) Keck, G. E. *Tetrahedron Lett.* **1978**, 4767.

(145) Quadrelly, P.; Mella, M.; Caramella, P. *Tetrahedron Lett.* **1998**, *39*, 3233.

(146) Waldemar, A.; Bottke, N.; Krebs, O.; Saha-Moller, R. C. *Eur. J. Org.Chem.* **1999**, 1963.

(147) Tiecco, M.; Testaferri, L.; Marini, F.; Sternativo, S.; Bagnoli, L.; Temperini, A. *Tetrahedron Asymm.* **2001**, *12*, 1493.

(148) Schneider, M. J. *Alkaloids: Chemical and Biological Perspectives*; Oxford, 1996; p 155.

(149) Roberts, K. P.; Iyer, A.; Prasad, G.; Liu, L. T.; Lind, E. R.; Hanna, P. E. *The Prostate* **1998**, *34*, 92.

(150) Ikuta, H.; Shirota, H.; Kobayashi, S.; Yamagishi, Y.; Yamada, K.; Yamatsu, L.; Katayama, K. *J. Med.Chem.* **1987**, *30*, 1995.

(151) Monahan, J. B.; Handelman, G. E.; Hood, W. F.; Cordi, A. A. *Pharmacol.Biochem.and Behav.* **1989**, *34*, 649.

(152) Smith, S. E.; Meldrum, B. S. *Eur. J. Pharmacol.* **1992**, 445.

(153) Waziri, R. *Biol. Psychiatry* **1988**, *23*, 210.

(154) Nowak, G.; Trullas, R.; Layer, R. T.; Skolnick, P.; Paul, I. A. *J. Pharmacol. Exp. Ther.* **1993**, *265*, 1380.

(155) Flower, R. *Pharmacol. Rev.* **1974**, *26*, 33.

(156) Leeson, P. D.; William, B. J.; Ladduwahetty, T.; Moore, K. W.; Rowley, M. *J.Chem.Soc., Chem.Commun.* **1990**, 1578.

(157) Cordi, A.; Lacoste, J. M.; Audinot, V.; Millan, M. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1409.

(158) Babidge, P. J.; Shiengthong, D.; Massy-Westropp, R. A.; Pyne, S. G.; Ungphakorn, A. *Aus. J. Chem., EN* **1980**, *33*, 1841.

(159) Kim, D.; Shim, P. J.; Lee, J.; Park, C. W.; Hong, S. W.; Kim, S. *J.Org.Chem.* **2000**, *65*, 4864.

(160) Luzzio, F.; Fitch, R. W. *J.Org.Chem.* **1999**, *64*, 5485.

(161) Stockmann, R. A. *Tetrahedron* **2000**, *41*, 9163.

(162) Tanner, D.; Hagberg, L.; Poulsen, S. *Tetrahedron* **1999**, *55*, 1427.

(163) Wardrop, D. J.; Burge, M. S.; Zhang, W.; Ortiz, J. A. *Tetrahedron Lett.* **2003**, *44*, 2587.

(164) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am.Chem.Soc.* **2000**, *122*, 4583.

(165) Shireman, T. B.; Miller, M. J. *J.Org.Chem.* **2001**, *66*, 4809.

(166) Reddy, A. S.; Kumar, S. M.; Reddy, R. *Tetrahedron Lett.* **2000**, *41*, 6285.

(167) Cacchi, S.; Misiti, D.; La Torre, F. *Synthesis* **1980**, 243.

(168) Marson, C. M.; Brooks, P. *Tetrahedron* **1998**, *54*, 9613.

(169) Katagiry, T.; Agata, A.; Takabe, K.; Tanaka, J. *Bull.Chem.Soc.Japan* **1976**, *49*, 3715.

(170) Chambers, J. J.; Kurrasch-Orbough, D. M.; Parker, M. A.; Nichols, D. E. *J. Med.Chem.* **2001**, *44*, 1003.

(171) MC Namara, C. M.; Box, S.; Crowforth, J. M.; Hickman, B. S.; Norwood, T. J.; Rowlings, B. J. *J.Chem.Soc.,Perkin Trans.1* **1998**, 83.

(172) Hudlicky, T.; Koszyk, F.; Kutchan, T. M. *J.Org.Chem.* **1980**, *25*, 5020.

(173) Brandsma, L.; Verkruijsse, H. D. *Synthesis of Acetylenes, Allenes and Cumulenes*; Amsterdam, 1981; p 225.

(174) Farmer, S. J.; Hose, B. U. *J.Chem.Soc.* **1933**.

(175) Beard, S.; Burger, J. M. *J.Org.Chem.* **1961**, *26*, 2335.

(176) Linstead, J. M.; Rydon, L. K. *J.Chem.Soc.* **1998**, 34.

(177) Arend, M. and Risch, N. 11th Int. Conf. Org. Chem. Abstr Pap. 1996. Amsterdam (The Netherlands).

Chapter 4

Preparation and Use of Acyl Hydrazines in Multicomponent Reactions and in New Cyclisations

4.1 Introduction

This chapter is mainly focused on the preparation of acyl hydrazines **212** (fig 4.1) and their reactions with aldehydes in regard to new three-component processes and new cyclisations in which the acyl hydrazones **213** could be key intermediates. Acyl hydrazines were prepared in the hope that their enhanced nucleophilicity would assist in the condensations with aldehydes. Moreover it was planned to examine the participation of acyl hydrazines in ring closure reactions where the NH_2 group, directly attached to the amidic function, reacts intramolecularly with an unactivated double bond in presence of trifluoromethanesulfonic acid.

212 **213**

Fig 4.1

Acyl hydrazines **212** exhibit several interesting biological properties not only because they can complex metals,[179-182] but also because they can be precursors of nitrogen-containing heterocycles, such pyrroles, pyrrolidines, piperazines and their derivatives.[182;183]

Acyl hydrazines are nucleophilic species and are known to react with aldehydes to give compounds such as **213** which are stable surrogates of imines in Mannich-type reactions.[184] Imines are often difficult to isolate and usually decompose when stored for long periods, so acyl hydrazones are usually used as good replacements. A drawback of using acyl hydrazones as electrophiles is their lower reactivity when compared with the corresponding imines; however several examples of their reactions have been reported.[184-188] The aim of this work was to find the right conditions that would drive the reaction towards the three-component condensation and related cyclisations.

4.1.1 Comparison of the Reactivity of Acyl Hydrazines with that of Hydroxamic Acids

Since there are many similarities between hydroxamic acids and acyl hydrazines, the idea was to compare their behaviour in three-component reactions and in new cyclisations. Since acyl hydrazines as well as acyl hydrazones can complex metals, inhibition of metallo-enzymes is often central to their biological activity. Like hydroxamic acids, acyl hydrazines bind to metals in similar way, the oxygen atom of the carbonyl group and the nitrogen atom of the NH_2 group, being chelated to the metal (fig 4.2). However acyl hydrazines form less stable complex with metals than do hydroxamic acids, owing to the ability of oxygen atoms to form stronger bond with metals than nitrogen atoms.

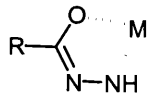


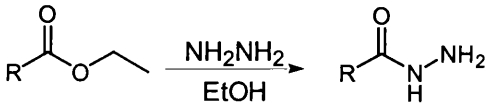
Fig 4.2

An interesting difference between hydroxamic acids and acyl hydrazines is that despite the nitrogen atom next to the carbonyl in an acyl hydrazines being more nucleophilic than that in the corresponding hydroxamic acid,[189] it is the NH_2 group which reacts predominantly with electrophiles. The carbonyl group strongly deactivates the adjacent nitrogen atom in both acyl hydrazines and hydroxamic acids.

Therefore unless the NH_2 group of acyl hydrazines is protected reaction will occur exclusively at the NH_2 nitrogen atom.

4.1.2 Preparation of Acyl Hydrazines

Acyl hydrazines **212** are usually prepared by the reaction of hydrazine with an ester, the reactions proceeding in high yields and with almost any type of ester. However hydroxamic acids require an activated ester or equivalent for a successful reaction with hydroxylamine (eqn 4.1).



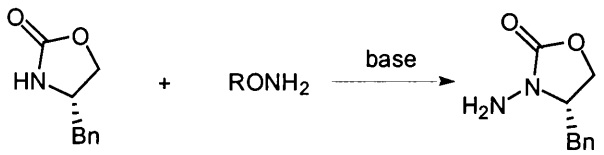
212

Scheme 4.1

The reaction is generally conducted under neutral conditions, by heating in ethanol. The acyl hydrazine usually precipitates from the reaction mixture and filtration generally provides the compound in high yield.

Acylhydrazines can be also prepared by *N*-amination of the corresponding amides.[190] Amination can be achieved either *via* nitrosation followed by reduction[191] which is always accompanied by significant side-reactions.[192] This latter reaction is more used for amination of amines than amides.

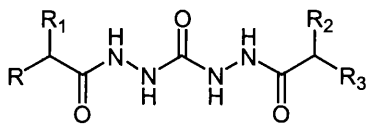
Amination can also be achieved by reaction of an amide with hydroxylamine derivatives that are powerful electrophilic NH_2^+ equivalents, such as *O*-(*p*-nitrobenzoyl) hydroxylamine, *O*-(diphenylphosphinyl) hydroxylamine and many others (scheme 4.2).



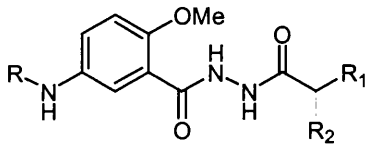
Scheme 4.2

4.1.3 Biological Properties of Acyl Hydrazines and Acyl Hydrazones

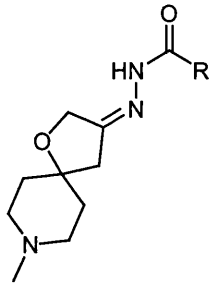
Acyl hydrazines as well as acyl hydrazones possess a wide range of biological activities such as anti-bacterial, anti-parasitic and antitumour activity and can be β-strand mimics, metallo-enzyme inhibitors, osteoarthritis regulators among many others.[193-197] Their activity is mainly related to the high ability of these compounds to interact with the active site of the enzyme by coordination to the metal and by hydrogen bonding. Additionally, since acyl hydrazines and acyl hydrazones possess a peptide-like structure, they can mimic interactions of peptides with enzymes; for example the class of compounds **214** (fig 4.3) are inhibitors of cathepsin K, an enzyme belonging to the superfamily of papain enzymes implicated in bone resorption.[193]



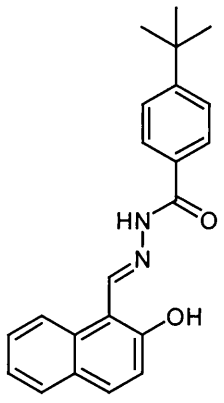
214



215



216



217

Fig 4.3

Hydrazones such as **215** (fig 4.3) are used as β-strand mimics. β-Strand interactions have been hypothesised to be involved in cell signalling and oncogene expression[198-202] as well as in binding with the major groove of DNA.[203] Many proteins aggregate to form insoluble β-strands that are associated with Alzheimer's disease,[204;205] other prion diseases and progressive neurodegenerative disorders.[206-208] The therapeutic activities of these compounds are based on their ability to replace

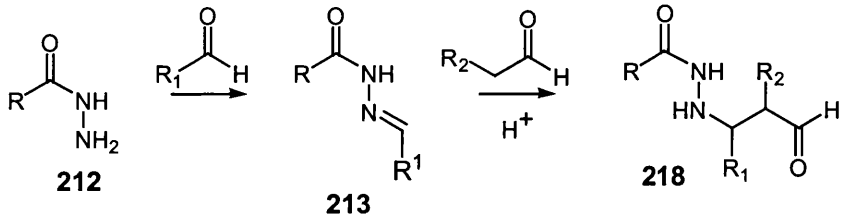
amino acid side-chains as well as achieving an alternating array of hydrogen bond donors and acceptors.

Acyl hydrazones such as **216** have shown activity as M1-selective muscarinic agonists, which are compounds involved in cognitive deficits as Alzheimer disease.[209] Moreover, acyl hydrazone **217** was shown to be a potent inhibitor of HIV-1 ribonuclease with which it binds *via* two major interactions, coordination to the metals (Mg^{2+} and Mn^{2+}) and aromatic stacking interactions.[197] HIV-1 ribonuclease activity is considered to be responsible for human immunodeficiency virus HIV-1 reverse transcriptase.[197]

4.2 Reactions of Acyl Hydrazines with Aldehydes in Acidic Media

4.2.1 Introduction

It is well known that acyl hydrazines **212** react with aldehydes to form acyl hydrazones **213** (fig 4.1) under neutral conditions. The objective was to investigate whether acyl hydrazones could be subjected to further reaction with another molecule of aldehyde in presence of an acid catalyst to form β-aldehydic hydrazines **218** (scheme 4.3).



Scheme 4.3

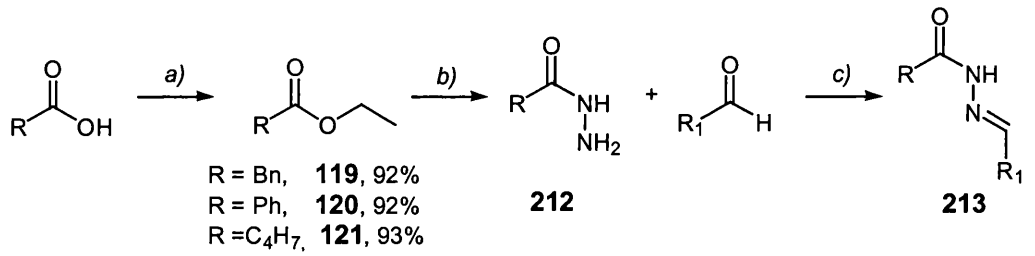
There are several examples of acyl hydrazones reacting with allylsilanes in Mannich-type reactions[184-188] catalysed by Lewis acids. Given that acyl hydrazones such as **213** can undergo nucleophilic attack at the imine type carbon atom, it was of interest to investigate how they might react with enolates. Kobayashi and co-workers

[183] showed that acyl hydrazones react with silyl enolates in the presence of rare earth trifluoromethanesulfonates such as scandium trifluoromethanesulfonate or ytterbium trifluoromethanesulfonate to give *β-N'*-acylhydrazino esters in high yields. Those reactions prompted us to try the three-component reaction involving acylhydrazines. Before attempting the one-pot reaction using acylhydrazines the reactivity of some acylhydrazones was first studied.

4.2.2 Preparation of *N*-Acylhydrazones

Several *N*-acylhydrazones were prepared in the hope that their similarity with imines would permit the reaction with aldehydes analogous to those described previously (chapter 2). Although examples of acylhydrazones reacting with silyl enolates of ketones and esters are known,[183] no reactions involving enolates of aldehydes appear to have been described. Therefore it was decided to investigate reactions involving aldehydes.

Acylhydrazones were generally prepared by condensation of the appropriate acylhydrazine with an aldehyde or ketone under neutral conditions (scheme 4.4, table 4.1).



Scheme 4.4: *a)* conc.H_2SO_4, EtOH, 90 °C, 4 h. *b)* NH_2NH_2, EtOH, 90 °C, 5 h. *c)* MeOH, rt, 12 h.

Table 4.1 Preparation of Acylhydrazines and Acylhydrazones

Entry	R	Acyl Hydrazine	Yield %	R_1	Acyl Hydrazone	Yield %
1	Bn	**222**	87	C_4H_7	**223**	82
2	Bn	**222**	87	PhCO	**224**	60
3	Ph	**225**	23	PhCO	**226**	50
4	C_4H_7	**227**	82	C_4H_7	**228**	55

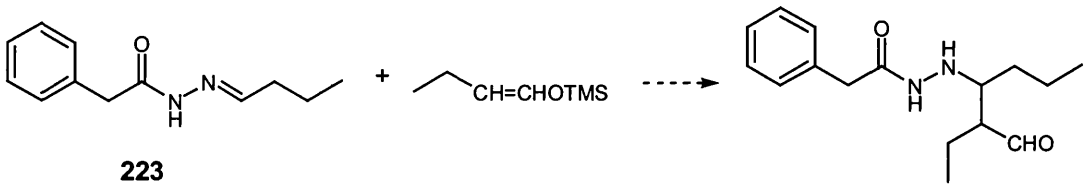
Table 4.1:

Acylhydrazones are aldehyde or ketone equivalents, as are imines. Their stability is much higher than that of imines, and they are often crystalline and can be isolated and stored at room temperature. However their reactivity as electrophiles is low, and there are many fewer reports of reactions of hydrazones with nucleophiles than those of imines.[210;211]

It was found that hydrazones with electron-donating groups were less reactive towards nucleophiles than hydrazones bearing electron-withdrawing groups.[183] Hence hydrazones derived from phenyl glyoxal were investigated, the additional *β*-group making them more electrophilic than the corresponding hydrazone derived from butyraldehyde.

4.2.3 Reaction of *N*-Acylhydrazones with Aldehydes

The reaction of acyl hydrazone **223** (scheme 4.5) with butyraldehyde trimethylsilane was investigated under various conditions (scheme 4.5, table 4.2).



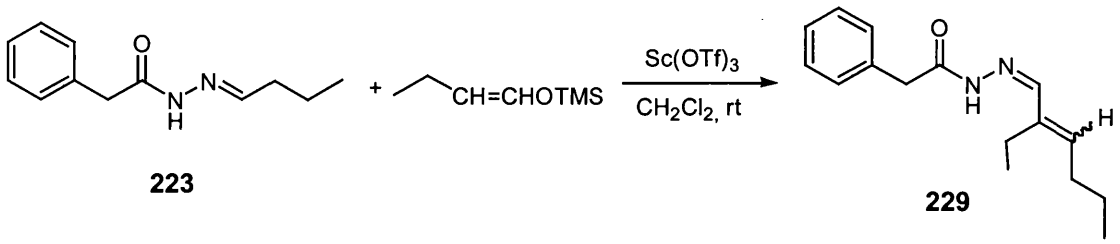
223

Scheme 4.5

Table 4.2: Reactions with acyl hydrazone **220** and butyraldehyde trimethylsilane.

Entry	Catalyst	Solvent	Temp °C	Time (h)	Result
1	CF_3SO_3H (2% v/V)	CH_2Cl_2	0 →20	4	Decomposition
2	CF_3SO_3H (0.2% v/V)	CH_2Cl_2	0 →20	4	SM unreacted + Aldol product
3	CF_3SO_3H (0.2% v/V)	CH_2Cl_2	-50	8	SM unreacted + Aldol product
4	BF_3OEt_2	CH_3CN	-40	6	Decomposition
5	BF_3OEt_2	CH_2Cl_2	-78	8	SM unreacted + Aldol product

When the conditions (entry 1 and 4, table 4.2) optimised for the three-component reaction using hydroxamic acids (chapter 2) were employed on the acyl hydrazone **223**, decomposition was mainly observed. Therefore new conditions needed to be found and when less trifluoromethanesulfonic acid at either 0 °C or –50 °C (entry 3 and 4, table 4.2) was used only unreacted starting material and aldol condensation product were recovered. Similar treatment of substrate **223** with boron trifluorodiethyl etherate in dichloromethane at a lower temperature (entry 5, table 4.2) gave predominantly unreacted starting material and aldol condensation product. Since there was no evidence of the desired compound under any of the conditions adopted, it was decided to test the reaction using scandium trifluoromethanesulfonate, as described by Kobayashi (scheme 4.6).

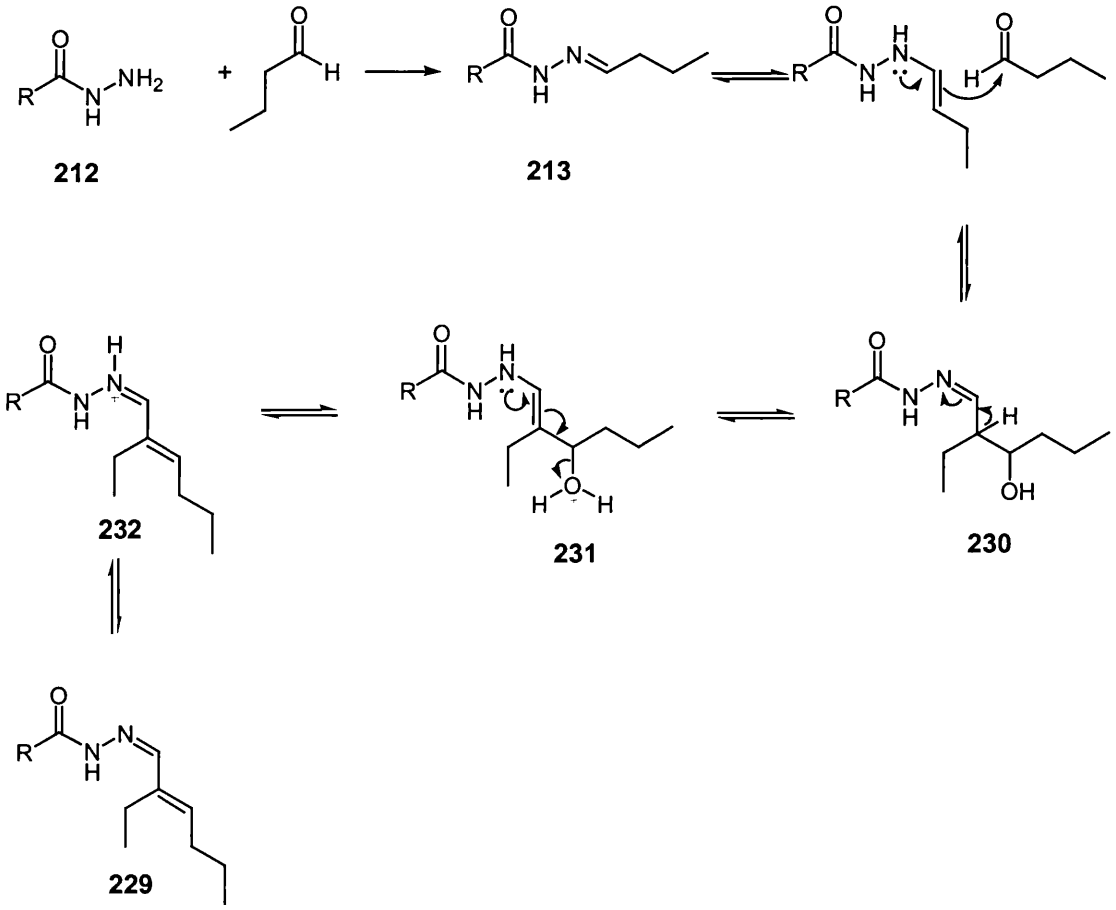


223 **229**

Scheme 4.6

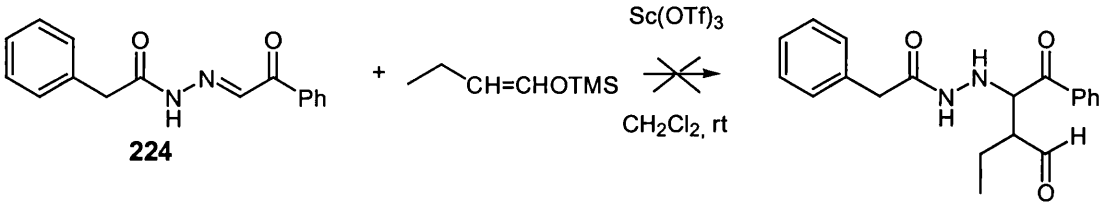
It was found that compound **229** was produced in high yield using scandium trifluoromethanesulfonate. This result can be explained by assuming that, under

those conditions, isomerisation of the double bond in acyl hydrazone **213** occurs; presumably, condensation of the adduct with a second molecule of butyraldehyde produces the intermediate **230**, which after α elimination of the hydrogen atom followed by isomerisation of the double bond affords **231**. The latter, after loss of water and subsequent rearrangement gives the acylhydrazone **229** (scheme 4.7).



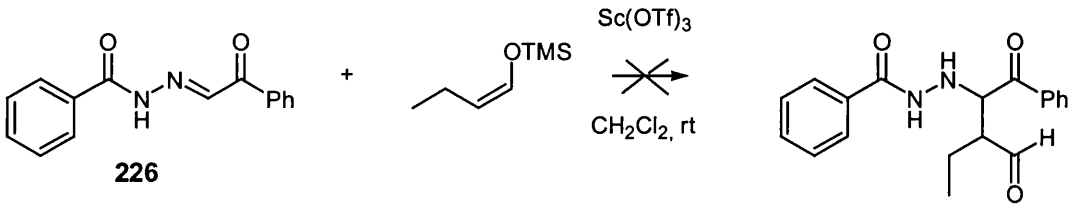
Scheme 4.7: Suggested mechanism for the formation of acylhydrazone **229**.

To optimise the conditions we tried the coupling on a different acylhydrazone **224** (scheme 4.8). Mindful that electron-withdrawing groups render acylhydrazones more reactive,[183] it was decided to use phenylglyoxal.



Scheme 4.8

Unfortunately only the starting material and the product from the aldol condensation reaction of butyraldehyde were recovered. Although no evidence of the α-amidoalkylation product was found, this result is consistent with the presumed mechanism of formation of acylhydrazone **229** (scheme 4.7).



226

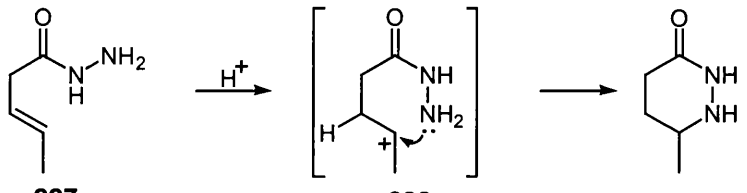
Scheme 4.10

Acylhydrazone **226** was then examined in the hope that the benzene ring directly attached to the acyl hydrazine moiety would render the acylhydrazone more reactive towards nucleophiles. However, only the aldol condensation product and starting material were observed.

It appeared that acyl hydrazones do not react with aldehydes to give β-aldehydic acylhydrazines under the conditions used for hydroxamic acids. Additionally, hydroxamic acids seem to undergo the three-component reaction much more readily than do acylhydrazines.

4.3 Attempted Cyclisations of β,γ-Unsaturated Acylhydrazines in Acidic Media

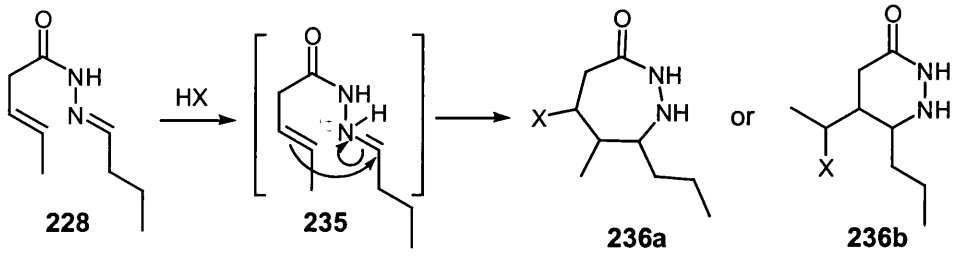
This section describes the preparation and attempted cyclisation of unsaturated acyl hydrazine **227** *via* nucleophilic attack of the amino group of the hydrazine moiety onto the activated electrophilic double bond (scheme 4.11).



227 **233** **234**

Scheme 4.11

The unsaturated acylhydrazone **228** was prepared in the hope that in acidic media the nucleophilic double bond would attack the electrophilic N=C of the acylhydrazone moiety to afford a six or seven-membered ring of structure **236a** or **236b** (scheme 4.12).

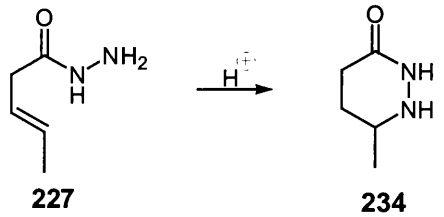


Scheme 4.12

Acyl hydrazine **227** was prepared by heating the corresponding ester and hydrazine in ethanol at reflux; precipitation on cooling afforded **227** in 82% yield. The acylhydrazine was then reacted with butyraldehyde in ethanol at reflux to give **228** in 55% yield. Both substrates were subjected to the optimized conditions of the cyclisation previously described.

4.3.1 Cyclisation of 3-Pentenoic Acid Hydrazide

Treatment of hydrazide **227** with trifluoromethanesulfonic acid (20% v/v in dichloromethane), monitored by t.l.c., afforded a complex mixture of uncyclised products and insoluble polymeric material. Accordingly, the cyclisation of acylhydrazine **227** was investigated under different concentrations, using trifluoromethanesulfonic acid (scheme 4.13, table 4.3).

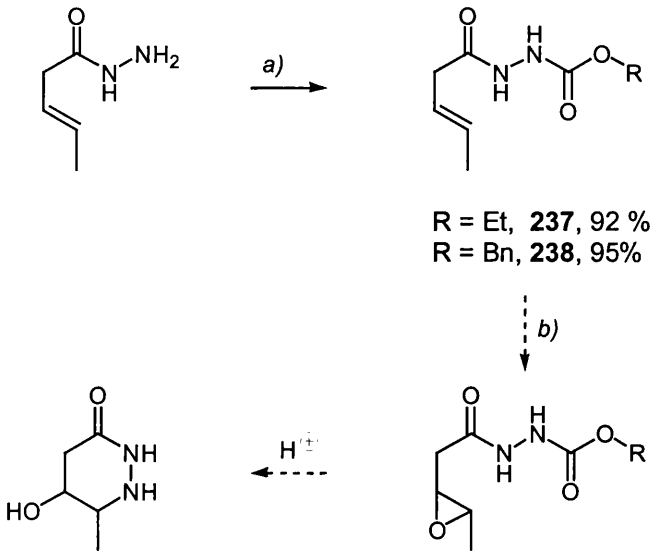


Scheme 4.13

Table 4.3: Attempts to achieve the cyclisation of hydrazide **227**

Entry	Catalyst	Solvent	Temp °C	Time (h)	Result
1	CF_3SO_3H (20 % v/v)	CH_2Cl_2	0 →20	2	Decomposition
2	CF_3SO_3H (10 % v/v)	CH_2Cl_2	0 →20	5	Mixture of products
3	CF_3SO_3H (2 % v/v)	CH_2Cl_2	0 →20	12	Mixture of products

Although decomposition and polymeric materials were not observed using triflic acid in lower concentration, the reaction was not useful since it appeared from tlc analysis that many compounds were formed (entry 2 and 3, table 4.3). At that point a different strategy had to be found and epoxidation of acyl hydrazine **227** appeared to be a possible way forward. Attempts to epoxidise **227** were not successful and even protection of the nitrogen atom of the NH_2 group to preclude side reactions did not lead to the desired product (scheme 4.14). Ethyl chloroformate and benzyl chloroformate were employed as protecting groups to give **237** and **238** substrates, because it was thought that the epoxidation was prevented by steric hindrance. Unfortunately in neither case were suitable intermediates obtained. No further investigations of the cyclisation of acylhydrazines were attempted.



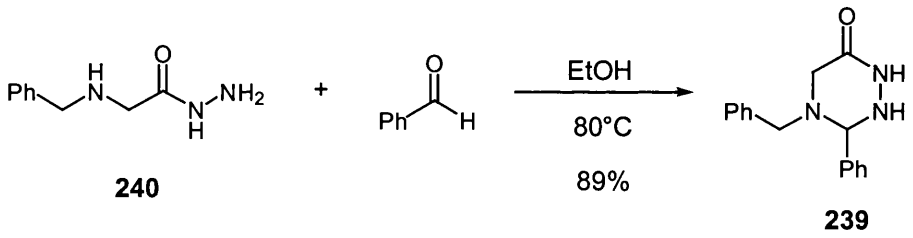
Scheme 4.14: *a)* Et_3N, $ClCO_2R$; diethyl ether; 20 °C; 25 min. *b)* *m*-CPBA, K_2HPO_4; dichloromethane; 20 °C; 12 h.

4.3.2 Cyclisation of 3-Pentenoic Acid Butylidene Hydrazide

Having synthesised a suitable substrate, the cyclisation step was examined. Cyclisation was attempted using 20% of trifluoromethanesulfonic acid in dichloromethane (rt, 12 h) but immediate formation of polymeric materials was observed and the use of milder conditions was not found to be beneficial since a complex mixture of apparently uncyclised products was formed.

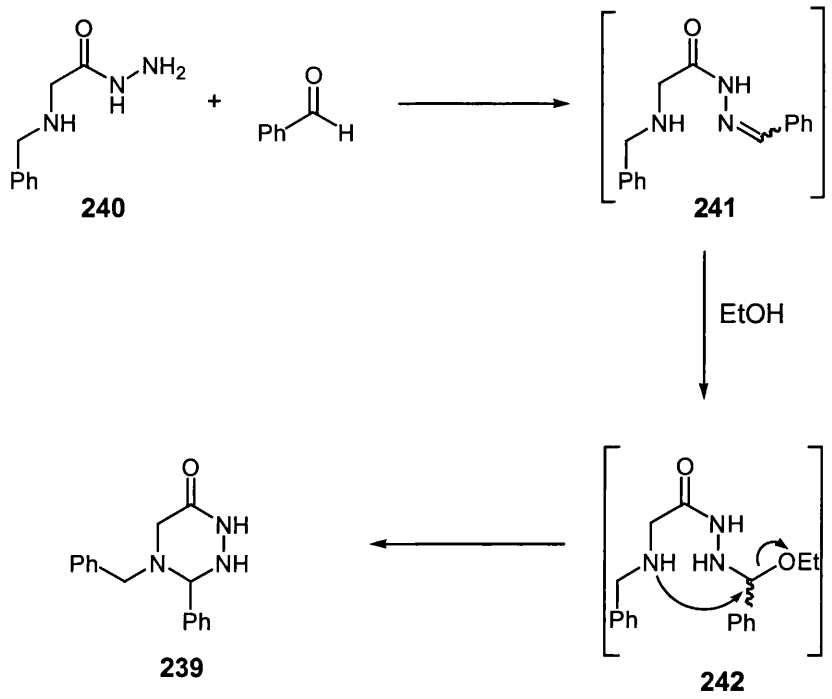
4.4 Cyclisation of Benzylamino Acetic Acid Hydrazide with Benzaldehyde

In this section is detailed the synthesis of a simple but new heterocycle ring system **239** (scheme 4.15) from the condensation of benzylamino acetic acid hydrazide **240** with benzaldehyde. The cyclisation was accomplished in ethanol and under neutral conditions (scheme 4.15).



Scheme 4.15

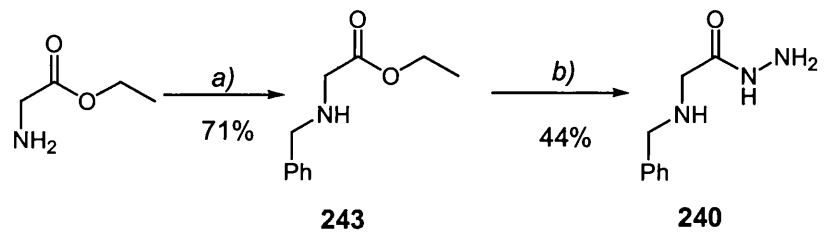
A plausible mechanism that agrees with the experimental data is the formation of a Schiff base **241**, from the reaction of **240** with benzaldehyde, followed by a slow addition of a molecule of ethanol to the double bond to give the adduct **242** which after displacement of the ethoxy group by the nitrogen atom in position α affords the heterocycle **239** in high yield (scheme 4.16).



Scheme 4.16: Postulated mechanism for the formation of the heterocycle **239**

^{1}H NMR studies confirmed the structure of [1,2,4]-triazinan-6-one **239** since appropriate coupling constants for geminal hydrogen atoms in two isolated AB systems generated from the new chiral centre were observed. Additionally, a line at 83.3 ppm in the ^{13}C NMR spectrum of **239** unequivocally confirmed that the methine carbon atom was bonded to two nitrogen atoms in a six-membered ring.

The acylhydrazine **240** was prepared from the reaction of the corresponding ester **242** with hydrazine, which was in turn prepared from the reaction of glycine ethyl ester with benzaldehyde followed by reduction with sodium borohydride (scheme 4.17).



Scheme 4.17: *a)* 1. PhCHO, Et_3N, EtOH, 25 °C, 2.5 h, 2. $NaBH_4$, -5 °C, 2.5 h; *b)* NH_2NH_2, EtOH, 80 °C, 12 h.

4.5 Conclusions

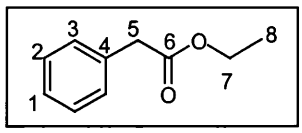
Neither acid-catalyzed cyclisations nor three-component condensations of acylhydrazines or acylhydrazones could be achieved in the time available. However it was confirmed that hydroxamic acids are better substrates for those reactions than the corresponding acyl hydrazines.

One of the reasons for the unsuccessful three-component reaction could be that acylhydrazones, being less reactive than *N*-acyliminium ions, are not activated in the conditions used; consequently, it seems that the optimized conditions for the cyclisations of hydroxamic acids are too strong for the corresponding reactions involving acyl hydrazines.

A successful synthesis of a new heterocycle ring system was achieved but unfortunately lack of time did not allow us to investigate the generality of the methodology; however, the result seems to open a route for the synthesis of a new and appealing class of heterocycles.

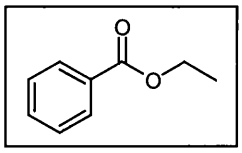
4.6 Experimental

Phenylacetic acid ethyl ester (219)[212]



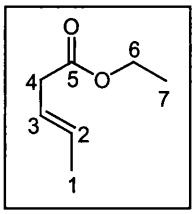
To a solution of phenylacetic acid (3.0 g, 36.8 mmol) in ethanol (50 mL), 5 drops of concentrated sulfuric acid were added and the mixture heated at reflux for 2 h. After cooling to 0 °C, the mixture was treated with saturated sodium hydrogen carbonate and the ethanol removed under reduced pressure. The aqueous layer was extracted with diethyl ether (3 x 30 mL) and the combined organic extracts washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give the **219** (3.6 g, 92 %) as a clear oil: ^{1}H NMR 7.52 (5H, m, Ar), 4.39 (2H, q J = 6 Hz, H_7), 3.85 (2H, s, H_5), 1.49 (3H, t J = 6 Hz, H_8); ^{13}C NMR 171.9 (C_6), 134.6 (C_4), 129.6 (C_3), 128.9 (C_1), 127.4 (C_2), 61.2 (C_7), 41.8 (C_5), 14.5 (C_8).

Ethyl benzoate (220)[212]



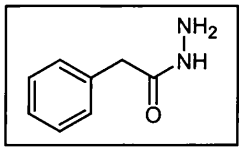
To a solution of benzoic acid (5.0 g, 40.9 mmol) in ethanol (50 mL), 5 drops of concentrated sulfuric acid were added and the mixture heated at reflux for 2 h. After cooling to 0 °C, the mixture was treated with saturated sodium hydrogen carbonate and the ethanol removed under reduced pressure. The aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic extracts washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give **220** (5.6 g, 92 %) as a clear oil: ^{1}H NMR 8.24 (2H, m, Ar), 7.74 (1H, m, Ar), 7.63 (2H, m, Ar), 3.67 (2H, q J = 6 Hz, CH_2), 1.40 (3H, t J = 6 Hz, CH_3); ^{13}C NMR 166.9 (CO), 133.1 (C_i), 130.9(C_o), 129.9 (C_p), 128.6(C_m), 67.2 (CH_2), 15.6 (CH_3).

Pent-3-enoic acid ethyl ester (221)[212]



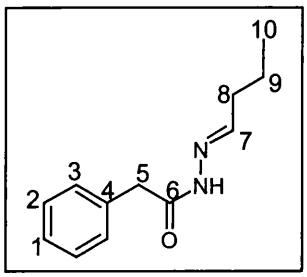
To a solution of (*E*)-pent-3-enoic acid (6.0 g, 60 mmol) in ethanol (50 mL), 5 drops of concentrated sulfuric acid were added and the mixture heated at reflux for 2 h. After cooling to 0 °C, the mixture was treated with saturated sodium hydrogen carbonate and the ethanol removed under reduced pressure. The aqueous layer was extracted with diethyl ether (3 x 30 mL) and the combined organic extracts washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give **221** (6.0 g, 93%) as a clear oil: ^{1}H NMR 6.13 (2H, m, H_2 + H_3), 3.88 (2H, q J = 6 Hz, H_6), 3.20 (2H, dd, J = 1.8 Hz, J = 4.2 Hz, H_4), 1.90 (3H, dd, J = 1.2 Hz, J = 3.6, H_1), 1.43 (3H, t, J = 6 Hz, H_7); ^{13}C NMR 172.8 (C_5), 129.7 (C_3), 123.0 (C_2), 66.2 (C_6), 38.5 (C_4), 18.2 (C_1), 14.5 (C_7).

Phenylacetic acid hydrazide (222)[196]



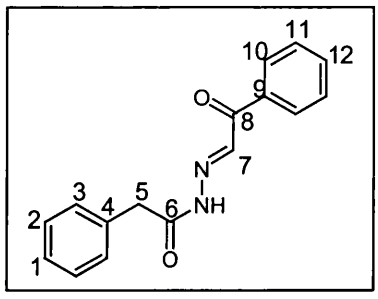
Phenylacetic acid ethyl ester (2.0 g, 12.2 mmol) and hydrazine hydrate (1.1 mL, 36.6 mmol) were dissolved in ethanol (5.0 mL) and heated at reflux for 8 h. Ethanol was then evaporated under reduced pressure. The residue was dissolved in toluene and the latter evaporated to remove unreacted hydrazine. The residue was recrystallised from ethanol to give **222** (1.57 g, 87 %) as prisms: mp 116 °C, (lit[213] mp 114-116 °C); ^{1}H NMR 7.42-7.13 (5H, m, Ar), 6.76 (1H, s, NH), 3.66 (2H, s, NH_2), 3.45 (2H, s, CH_2); ^{13}C NMR 172.0 (CO), 134.4 (C_i), 129.7 (C_o), 129.4 (C_m), 127.9 (C_p), 42.3 (CH_2).

Phenylacetic acid butylidene hydrazide (223)



A solution of phenylacetic hydrazide (0.20 g, 1.33 mmol) in ethanol (4.0 mL) was added dropwise to a solution of butyraldehyde (0.36 mL) in ethanol (2.0 mL) and the mixture heated at reflux for 5 h. The ethanol was evaporated under reduced pressure and the residue triturated in ethyl acetate and petroleum ether (1:1). The precipitate was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, ethyl acetate:petroleum ether 7:3) to give **223** (0.22 g, 82 %) as prisms: mp 109-110 °C; IR ν_{max} (cm^{-1}) (KBr) 3328 (NH), 3125 (Ar), 1708 (CO), 1413 (C=C); ^{1}H NMR 9.43 (1H, s, NH), 7.51-7.36 (5H, m, Ar), 7.28 (1H, t J = 6 Hz, H_7), 4.12 (2H, s, H_5), 2.48 (2H, m, H_8), 1.70 (2H, m, H_9), 1.13 (3H, t, J = 6 Hz, H_{10}); ^{13}C NMR 173.8 (CO), 148.1 (C_7), 135.6 (C_4), 129.9 (C_3), 128.7 (C_2), 127.0 (C_1), 39.8 (C_5), 34.5 (C_8), 19.9 (C_9), 14.0 (C_{10}). Found C, 70.66, H, 8.02, N, 13.75, ($C_{12}H_{16}N_2O$ requires C, 70.56, H, 8.02, N, 13.71).

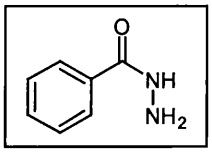
Phenylacetic acid (2-oxo-2-phenyl-ethylidene)-hydrazide (224)



A solution of phenylacetic hydrazide (0.20 g, 1.33 mmol) in methanol (0.50 mL) was added to a solution of phenylglyoxal hydrate (0.21 g, 1.33 mmol) in methanol (0.3 mL) and the whole was stirred for 12 h at 20 °C. The solution was concentrated under reduced pressure and the residue was purified by chromatography (silica gel, 1:1/ ethyl acetate:petroleum ether) to give **224** (0.21 g, 60 %) as a white prisms: mp 162-164 °C; IR ν_{max} (cm^{-1}) (KBr) 3377 (NH), 3092 (Ar), 1715 (CO), 1608 (CO), 1513 (C=C); ^{1}H NMR 10.26 (1H, s, NH), 7.98 (2H, d J = 6 Hz, H_{10}), 7.64 (1H, s, H_7), 7.46 (3H, m, H_{11} + H_{12}), 7.23 (5H, m, Ph), 3.97 (2H, s, H_5); ^{13}C NMR 189.9 (C_8), 175. 1 (C_6), 141.2 (C_7), 136.2 (C_9), 134.1 (C_{12}), 133.6 (C_4), 130.4 (C_{10}), 129.7 (C_{11}), 129.1 (C_2), 128.7 (C_1), 127.5 (C_3),

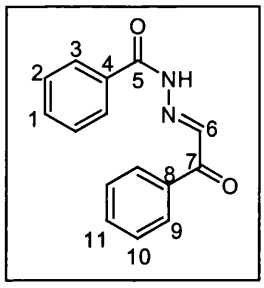
41.2 (C_5). Found C, 71.81, H, 5.37, N, 10.08, ($C_{16}H_{14}N_2O_2$ requires C, 72.16, H, 5.30, N, 10.52).

Benzoic acid hydrazide (225)[214]



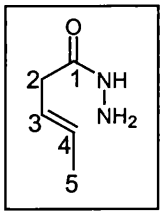
A mixture of benzoic acid ethyl ester (5.0 g, 33.3 mmol), and hydrazine hydrate (3.1 mL, 0.10 mol) in ethanol (10 mL) was heated at reflux for 8 h. The ethanol was evaporated under reduced pressure. The residue was dissolved in toluene and the latter evaporated to remove unreacted hydrazine. The residue was recrystallised from ethanol to give **225** (1.02 g, 23 %) as white needles: mp 113-115 °C (lit[214] mp = 115 °C); ^{1}H NMR 7.93 (2H, m, Ar), 7.60 (3H, m, Ar); ^{13}C NMR 170.1 (CO), 133.1 (C_p), 130.9 (C_i), 130.2 (C_m), 128.6 (C_o).

Benzoic acid (2-oxo-2-phenyl-ethylidene)-hydrazide (226)[215]



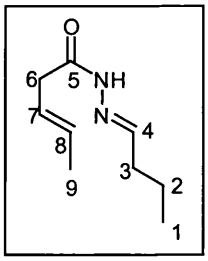
A solution of benzoic hydrazide (0.50 g, 3.68 mmol) in methanol (1.5 mL) was added to a solution of phenylglyoxale hydrate (0.56 g, 3.68 mmol) in methanol (0.9 mL) and the mixture was stirred for 8 h at 20 °C. Benzoic acid (2-oxo-2-phenyl-ethylidene)-hydrazide **226** (0.51 g, 50%) precipitated from the reaction mixture as a yellow solid: mp 168-170 °C (lit[215] mp 168-169 °C); ^{1}H NMR 8.28 (3H, br s, H_9 + NH), 7.96 (2H, br d J = 7.5 Hz, H_3), 7.65 (2H, m, H_{11} + H_6), 7.55 (5H, m, H_1 + H_2 +H_{10}); ^{13}C NMR 188.9 (C_7), 174. 1 (C_5), 145.4 (C_6), 136.7 (C_8), 134.6 (C_{11}), 133.5 (C_4), 130.4 (C_2), 129.1 (C_9), 128.7 (C_{10}), 127.7 (C_1), 127.5 (C_3).

3-Pentenoic acid hydrazide (227)



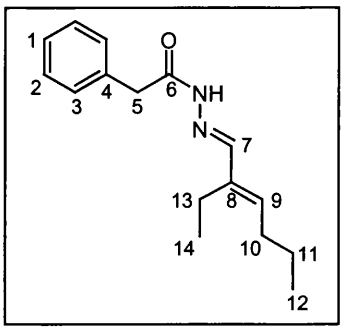
3-Pentenoic acid ethyl ester (1.10 g, 8.59 mmol) and hydrazine hydrate (0.30 mL, 9.45 mmol) were dissolved in ethanol (2.0 mL) and heated at reflux for 24 h. Ethanol was then evaporated under reduced pressure. The residue was dissolved in toluene and the latter evaporated to remove unreacted hydrazine. The residue was recrystallised from diethyl ether to give **227** (0.80 g, 82%) as white prisms: mp 79-80 °C; IR ν_{max} (cm^{-1}) (KBr) 3243 (NH), 1697 (CO), 1414 (C=C); ^{1}H NMR 7.43 (1H, s, NH), 5.89 (1H, m, H_3), 5.76 (1H, m, H_4), 4.13 (2H, s, NH_2), 3.16 (2H, dd, J = 6 Hz, J = 1.2 Hz, H_2), 1.96 (3H, dd, J = 6 Hz, J = 3 Hz, H_5); ^{13}C NMR 172.4 (C_1), 131.5 (C_3), 123.2 (C_4), 38.9 (C_2), 18.3 (C_5). Found C, 52.71, H, 8.83, N, 25.19, ($C_5H_{10}N_2O_1$ requires C, 55.59, H, 8.83, N, 24.55).

3-Pentenoic acid butylidene hydrazide (228)



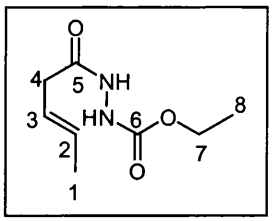
A solution of butyraldehyde (0.08 mL, 0.87 mmol) in ethanol (4.0 mL) was added dropwise to a solution of 3-pentenoic acid hydrazide (0.10 g, 0.87 mmol) in ethanol (10 mL). The mixture was heated at reflux for 12 h and then concentrated until precipitation of the product occurred. The ethanol was decanted and the precipitate washed with pentane (2 x 2 mL) to give **228** (0.24 g, 55 %) as white pellets: mp 69-70 °C; IR ν_{max} (cm^{-1}) (KBr) 3243 (NH), 1614 (CO), 1445 (C=C), 1434 (C=C); ^{1}H NMR 9.40 (1H, br s, NH), 7.47 (1H, t, J = 6 Hz, H_4), 5.60 (2H, m, H_7, H_8), 3.37 (2H, br d, J = 3 Hz, H_6), 2.27 (2H, q, J = 6 Hz, H_3), 1.73 (3H, br s, H_9), 1.62 (2H, m, H_2), 1.00 (3H, t, J = 6 Hz, H_1); ^{13}C NMR 174.7 (C_5), 148.1 (C_4), 128.8 (C_7), 123.3 (C_8), 36.6 (C_6), 34.1 (C_3), 19.5 (C_2), 18.9 (C_9), 13.7 (C_1). Found C, 64.30, H, 9.78, N, 16.53, ($C_9H_{16}N_2O$ requires C, 64.25, H, 9.59, N, 16.55).

Phenylacetic acid (2-ethyl-hept-3-enylidene) hydrazide (229)



Phenylacetic acid butylidene hydrazide (0.15 g, 0.73 mmol) was dissolved in dry dichloromethane (4.0 mL) and then trifluoromethanesulfonic acid (80.0 μl) was added. A solution of but-1-enyloxy trimethylsilane (0.16 g, 1.10 mmol) in dichloromethane (1.0 mL) was added to the over a period of 20 min and the mixture was stirred at 25 °C for 3 h. Ice was then added to the mixture, which was cooled to – 10 °C, neutralised with saturated aqueous sodium hydrogen carbonate, and extracted with dichloromethane (3 x 30 mL). The combined extracts were dried over magnesium sulfate, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, ethyl acetate:petroleum ether/ 9:1) to give **229** (0.10 g, 62%) as a clear oil: ^{1}H NMR 9.34 (1H, br s, NH), 7.33 (2H, m, H_3), 7.27 (3H, m, H_1; H_2), 7.22 (1H, s, H_7), 5.71 (1H, t J = 7.5 Hz, H_9), 3.94 (2H, s, H_5), 2.39 (2H, q J = 7.4 Hz, H_{13}), 2.19 (2H, m, H_{10}), 1.45 (2H, m, H_{11}) 1.04 (3H, t J = 7.4 Hz, H_{14}), 0.92 (3H, t, J = 7 Hz, H_{12}); ^{13}C NMR 173.5 (C_6), 148.4 (C_7), 141.8 (C_9), 138.9 (C_4), 135.1 (C_8), 130.1(C_3), 128.9 (C_2), 127.9 (C_1) 39.6 (C_5), 30.2 (C_{13}), 22.5 (C_{10}), 19.2 (C_{11}), 12.8 (C_{14}), 12.5 (C_{12}). LRMS M/Z (EI) 259 (100), 133 (20), 91 (41). HRMS Found 259.1769 ($C_{16}H_{22}N_2O$ requires 259.1766).

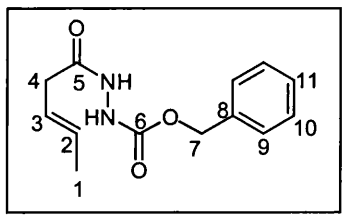
***N*-Pent-3-enoylhydrazinecarboxylic acid ethyl ester (237)**



To a solution of 3-pentenoic acid hydrazide (0.20 g, 1.75 mmol) and diethyl ether (4.0 mL) was prepared, sodium carbonate (93 mg, 0.88 mmol) and ethyl chloroformate (0.17 mL, 1.7 mmol) were added to the prepared solution and the mixture was stirred for 8 h at 20 °C. The diethyl ether was evaporated under reduced pressure; the residue was dissolved in dichloromethane and the sodium chloride filtered off. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, ethyl

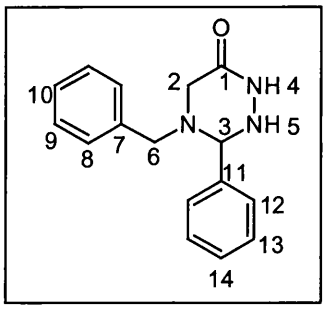
acetate:petroleum ether/ 1:1) to give **237** (0.3 g, 91 %) as microprisms: mp 62 °C; IR ν_{max} (cm^{-1}) (KBr) 3321 (NH) 3217 (NH), 1716 (CO) 1651 (CO); ^{1}H NMR 7.83 (1H, s, NH-COOEt), 6.96 (1H, s, NH-CO), 5.57 (1H, m, H_3), 5.46 (1H, m, H_2), 4.10 (2H, q J = 6 Hz, H_7), 2.91 (2H, d J = 3 Hz, H_4), 1.63 (3H, d J = 6 Hz, H_1), 1.20 (3H, t J = 6 Hz, H_8); ^{13}C NMR 171.5 (C_6), 157.0 (C_5), 131.5 (C_3), 122.8 (C_2), 62.6 (C_7), 38.5 (C_4), 18.3 (C_8). Found C, 50.92, H, 7.64, N, 14.71, ($C_8H_{14}N_2O_3$ requires C, 51.60, H, 7.58, N, 15.04).

3-Pentenoylhydrazine carboxylic acid benzyl ester (238)



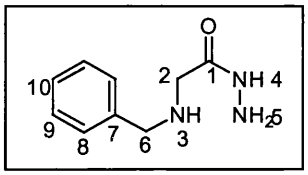
To a solution of 3-pentenoic acid hydrazide (0.20 g, 1.75 mmol) and diethyl ether (4.0 mL) was prepared, sodium carbonate (95 mg, 0.88 mmol) and benzyl chloroformate (0.25 mL, 1.75 mmol)) were added to the prepared solution and the mixture was stirred for 8 h at 20 °C. The diethyl ether was evaporated under reduced pressure, the residue was dissolved in dichloromethane and the sodium chloride was filtered off. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, ethyl acetate:petroleum ether 1:1) to give **228** (0.3 g, 95 %) as white prisms: mp 162-163 °C; IR ν_{max} (cm^{-1}) (KBr) 3401 (NH) 3332 (NH), 3109 (Ar) 1756 (CO) 1691 (CO); ^{1}H NMR 7.92 (1H, s, NH-COO-), 7.41 (5H, s, Ph), 7.21 (1H,s, NH-CO), 5.73 (1H, m, H_3), 5.60 (1H, m, H_2), 5.21 (2H, s, H_7), 3.03 (2H, d, J = 3.5 Hz H_4), 1.55 (3H, d J = 6.9 Hz, H_1); ^{13}C NMR 171.5 (C_6), 156.1 (C_5), 135.9 (C_8), 131.6 (C_2), 128.9 (C_9), 128.7 (C_{11}), 128.5 (C_{10}) 122.8 (C_3), 68.2 (C_7), 38.5 (C_4), 18.3 (C_1). M/Z (EI): 248 (3), 204 (1), 106 (32), 91 (57), 55 (60). Found C, 62.73, H, 6.52, N, 11.22, ($C_{13}H_{16}N_2O_3$ requires C, 62.89, H, 6.50, N, 11.28).

4-Benzyl-3-phenyl-[1,2,4]triazinan-6-one (239)



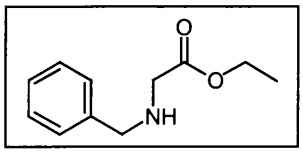
Benzylamino acetic acid hydrazide (0.10 g, 0.56 mmol) was dissolved in ethanol (3.0 mL) and then benzaldehyde (0.060 mL, 0.56 mmol) was added. The mixture was heated at reflux for 3 h and then cooled until a white precipitated was formed. Filtration gave **239** (0.14g, 94%) as white prisms: mp 92 °C; IR ν_{max} (cm^{-1}) (KBr) 3321 (NH) 3362 (NH), 3163 (Ar), 1676 (CO); ^{1}H NMR 8.84 (1H, s, H_4), 7.49 (5H, m, H_{11-14}), 7.28 (5H, m, H_{7-10}), 5.40 (1H, s, H_3), 3.87 (1H, d, J = 13 Hz H_2), 3.64 (1H, d J = 15 Hz, H_6) 3.49 (1H, d, J = 13 Hz H_2), 3.25 (1H, d J = 15 Hz, H_6), 1.63 (1H, s, H_5); ^{13}C NMR 168.4 (C_1), 137.6 (C_{11}), 134.8 (C_7), 130.8 (C_{12}), 129.7 (C_8), 129.0 (C_9; C_{13}) 128.8 (C_{10}; C_{14}), 83.3 (C_3), 56.8 (C_2), 54.9 (C_6). M/Z (EI): 266 (M-1; 3%), 225 (45), 91 (75), 55 (70).

Benzylamino acetic acid hydrazide (240)[196]



N-Benzylglycine ethyl ester (0.2 g, 1.0 mmol) and hydrazine hydrate (0.06 mL, 1.0 mmol) were dissolved in ethanol (2.0 mL) and heated at reflux for 8 h. Ethanol was then evaporated under reduced pressure. The residue was dissolved in toluene and the latter evaporated to remove unreacted hydrazine. The residue was recrystallised from diethyl ether to give **240** (0.2 g, 44%) as white needles: mp 81-84 °C (lit[196] mp 82-85 °C). ^{1}H NMR 8.18 (1H, s, H_4), 7.35 (5H, m, H_{7-10}), 3.80 (2H, s, H_2), 3.40 (2H, s, H_6); ^{13}C NMR 172.1 (C_1), 139.5 (C_7), 129.0 (C_8), 128.5 (C_9) 127.8 (C_{10}) 54.3 (C_2), 51.4 (C_6).

_N_-Benzylglycine ethyl ester (243)



To a solution of glycine ethyl ester (1.0 g, 7.2 mmol), in anhydrous ethanol (35 mL) were successively added benzaldehyde (0.73 mL, 7.2 mmol) and triethylamine (2.0 mL, 14.4 mmol). The solution was stirred at 20 °C until t.l.c. showed the absence of glycine ethyl ester (2 h). Sodium borohydride (1.3 g, 35 mmol) was then added in portions to the reaction mixture cooled to –5 °C, which was vigorously stirred for 3.5 h. The reaction was quenched with water (50 mL) and the ethanol was evaporated under reduced pressure. The aqueous solution was extracted with ethyl acetate (3 x 40 mL), the combined organic layers were then dried over Na_2SO_4 and concentrated under reduced pressure. The residue oil was finally purified by column chromatography (silica gel, 3:7 methanol:chloroform) to give **243** (0.97 g, 71%) as white microprisms: mp 123 °C; ^{1}H NMR 7.35 (5H, m, Ph), 4.17 (2H, q, J = 6 Hz $C\underline{H}_2CH_3$), 3.81 (2H, s, CH_2Ph), 3.41 (2H, s, CH_2), 2.03 (1H, s, NH), 124 (3H, t, J = 6 Hz, CH_3); ^{13}C NMR 172.4 (CO), 139.6 (C_i), 128.6 (C_m), 128.2 (C_p), 126.4 (C_o), 60.7 ($\underline{C}H_2CH_3$), 53.3 (CH_2Ph), 50.1 (CH_2), 14.2 (CH_3).

4.7 References

(179) Fernandes, R. A.; Yamamoto, Y. *J.Org.Chem.* **2004**, *69*, 735.

(180) Tellgren, R.; Andejlkovich, K. *J.Coord.Chem.* **2003**, *56*, 611.

(181) Natic, M.; Tesic, Z.; Andejlkovich, K. *Syn.React.Inorg.Metal* **2004**, *34*, 101.

(182) El-Sekily, M. A.; Elba, M. E.; Fouad, F. S. *J.Indian.Chem.Soc.* **2000**, *77*, 168.

(183) Okitsu, O.; Oyamada, H.; Furita, T.; Kobayashi, S. *Heterocycles* **2000**, *52*, 1143.

(184) Manabe, K.; Oyamada, H.; Sugita, K.; Kobayasky, S. *J.Org.Chem.* **1999**, *64*, 8054.

(185) Shen, Y.; Friestad, G. K. *J.Org.Chem.* **2002**, *67*, 6236.

(186) Patient, L.; Berry, M. B.; Coles, S. J.; Hursthouse, M. B.; Kilburn, J. D. *Chem.Commun.* **2003**, 2552.

(187) Kobayashi, S.; Ogawa, C.; Konishi, H.; Sugiura, M. *J. Am.Chem.Soc.* **2003**, *125*, 6610.

(188) Hamada, T.; Manabe, K.; Kobayasky, S. *Angew.Chem., Int.Ed.Engl.* **2003**, *42*, 3927.

(189) England, W. B.; Kovacic, P.; Hanrah, S. M.; Jones, M. B. *J.Org.Chem.* **1980**, *45*, 2057.

(190) Ragnarsson, U. *Chem.Soc.Rev.* **2001**, *30*, 205.

(191) Kim, Y. H.; Choi, J. Y. *Tetrahedron Lett.* **1996**, *37*, 5543.

(192) Viret, J.; Gabard, J.; Collet, A. *Tetrahedron lett.* **1987**, *43*, 891.

(193) Thompson, S. K.; Halbert, S.; Desjalais, R. L.; Tomaszek, T. A.; Levy, M. A.; Tew, G. D. *Bioorg.Med.Chem.* **1999**, *7*, 599.

(194) Tsai, J. H.; Waldman, A. S.; Nowich, J. S. *Bioorg.Med.Chem.* **1999**, *7*, 29-38.

(195) Ross, W. J.; Jamieson, W. B. *J. Med.Chem.* **1975**, *18*, 158.

(196) Massarani, E.; Nardi, D.; Tajana, A.; Degen, L. *J. Med.Chem.* **1971**, *14*, 633.

(197) Arion, D.; Parniak, M. A.; Fletcher, R. S.; Abrams, M. E.; Sluis-Cremer, N. *J. Biol.Chem.* **2002**, *277*, 1370.

(198) Nassar, N.; Horn, G.; Herrmann, C.; Scherer, A.; McCormick, F.; Wittnghofer, A. *Nature* **1995**, *375*, 554.

(199) Roberts, J. C.; Pallai, P. V.; Rebek, J. J. *Tetrahedron Lett.* **1995**, *36*, 691.

(200) Boumendjel, A.; Roberts, J. C.; Pallai, H. E.; Rebek, J. J. P. V. *J.Org.Chem.* **1996**, *61*, 4434.

(201) Smith III, A. B.; Keenan, T. P.; Holcomb, R. C.; Sprengler, P. A.; Guzman, M. C.; Wood, J. L.; Carrol, P. J. *J. Am.Chem.Soc.* **1993**, *114*, 10672.

(202) Zutshi, R.; Fransiskovich, J.; Schultz, M.; Schweitzer, B.; Bishop, P.; Wilson, M. *J. Am.Chem.Soc.* **1997**, *119*, 4841.

(203) Somers, W. S.; Phillips, S. E. V. *Nature* **1992**, *359*, 387.

(204) Verbeek, M. M.; Ruiter, D. J.; de Waal, R. M. W. *Biol.Chem.* **1997**, *378*, 937.

(205) Selkoe, D. J. *J.Peptide Protein Res.* **1994**, *53*, 438.

(206) Lansbury, P. T. *Acc.Chem.Res.* **1996**, *29*, 317.

(207) Perutz, M. F.; Johonson, T.; Suzuki, M.; Finch, J. T. *Proc.Natl.Acad.Sci.USA* **1994**, *91*, 5355.

(208) Stott, K.; Blackburn, J. M.; Butler, P. J. G.; Perutz, M. *Proc.Natl.Acad.Sci.USA* **1995**, *92*, 6509.

(209) Wu, E. S. C.; Kover, A.; Loch III, J. T.; Rosenberg, P.; Semus, S. F.; Verhoest, P. K.; Machulskis, A. C.; Blosser, J. C. *Bioorg.Med.Chem.Lett.* **1996**, *6*, 2525.

(210) Kodata, I.; Park, J. Y.; Yamamoto, Y. *J. Chem. Soc., Chem.Commun.* **1996**, 841.

(211) Denmark, S. E.; Weber, T.; Piotrowski, D. W. *J.Am.Chem.Soc.* **1987**, *109*, 2224.

(212) Bulugahapitiya, P.; Landais, Y.; Parra-Lapado, L.; Weber, V. *J.Org.Chem.* **1997**, *62*, 1637.

(213) Fields, L.; Reynolds, D. D.; Miller, J. B. *J.Org.Chem.* **1965**, *30*, 248.

(214) Boyer, J. H.; Chang, M. S. *J.Am.Chem.Soc.* **1960**, 2220.

(215) Korotkikh N.I *J.Org.Chem.USSR EN* **1979**, 860.