The Zav'yalov Pyrrole Synthesis Revisited: Some Derivatives of 3-Hydroxy- and 3-Amino- Pyrroles

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Abstract

The Zav'yalov Pyrrole Synthesis Revisited: Some Derivatives of 3-Hydroxy- and 3-Amino-pyrroles

Georgina Kate Armitage

The objective of this study was to investigate the acylative-cyclisation-decarboxylation reactions of enamino acids derived from 1,3-difunctional compounds. Remarkably little is known regarding the generality of these variants of the Zav'yalov pyrrole synthesis, despite their considerable scope for the synthesis of functionalised pyrroles.

The cyclisation of diethyl 2-(1-carboxyalkylaminomethylene)malonates provided access to a range of 5-(un)substituted-4-acetoxypyrrole-3-carboxylates. However, in some instances the corresponding 4-ethoxypyrrole-3-carboxylates also accounted for up to 20% of the reaction product. 1-Acetyl-4-ethoxy-5-ethylpyrrole-3-carboxylate was characterised by X-ray crystallography. Some of the (aminomethylene)malonates from bifunctional α-amino acids provided anomalous products. For example, the glutamine-derived enamino malonate gave a 5-acetylpyrrolidin-2-one *via* a Dakin-West-type reaction. The asparagine-enamino malonate cyclised to 4-acetoxy-1-acetyl-5-cyanomethylpyrrole-3-carboxylate probably *via* an isosuccinimide intermediate. Several mechanisms for the formation of the pyrrole products have been discussed. A ^{13}C-labelling experiment confirmed that the carboxyl function in the starting material is not incorporated in the product. Evidence for the involvement of a 1,3-oxazolium-5-olate (münchnone) accrued from cyclisation of diethyl 2-(1-carboxymethylaminomethylene)malonate with Ac_2O in the presence of dimethyl acetylenedicarboxylate which provided a novel 1-alkenylpyrrole, characterised by X-ray crystallography. An alternative pathway supervenes in the Zav'yalov reaction when α,α-disubstitution of the amino acid prevents münchnone and thus pyrrole formation to afford an *N*-alkenyloxazolidin-5-one.

Novel ethyl 4-(di)acetamido-5-(un)substituted-pyrrole-3-carboxylates and the corresponding 3-carbonitriles have been obtained in good yields *via* the cyclisation of ethyl 2-(1-carboxyalkylaminomethylene)cyanoacetates and (1-carboxyalkylaminomethylene)malononitriles respectively. Evidence for a different cyclisation pathway, in the former, involving intramolecular acylation of the enaminonitrile moiety was observed. Thus, ethyl (2*R**,3*S**)-1-acetyl-3-cyano-2,4-diacetoxy-5-methyl-2,3-dihydropyrrole-3-carboxylate was characterised by X-ray crystallography.

A wide range of novel 2-alkanoyl- and 2-aroyl-3-(1-carboxyalkylamino)acrylonitriles has been obtained *via* aminomethylenation of β-ketonitriles. The products from their cyclisations (Ac_2O-NEt_3) were largely independent of the nature of the acyl group but determined by the substituent in the α-amino acid moiety. The 3-(1-carboxy-1-phenylmethylamino)acrylonitriles provided mixtures of 3-acyl-4-(di)acetamido-5-phenylpyrroles in which the 4-acetamido- derivatives predominated. Contrasting behaviour was displayed by the 3-(1-carboxyalkylamino)acrylonitriles derived from alanine, 2-aminobutyric acid and valine in which the cyclisation followed an unexpected course, *via* enaminone acylation, to the novel 4-acetoxy-1-acetyl-5-alkylpyrrole-3-carbonitriles in high yields. The acylative cyclisation of the 2-acyl-3-(1-carboxymethylamino)acrylonitriles furnished mixtures of pyrroles. In two cases, 3-acetamido-6-aryl-5-cyanopyran-2-ones, generated by a unique cyclisation pathway were isolated. The structure of the 6-phenyl- derivative was confirmed by unambiguous synthesis. The synthesis and acylative cyclisation of (*Z*)-2-benzoyl-3-(1-carboxyalkylamino)crotononitriles was investigated. Whereas the 3-(1-carboxyethylamino)-derivative provided 4-acetoxy-1-acetyl-2,5-dimethylpyrrole-3-carbonitrile exclusively, the 3-(1-carboxy-1-phenylmethylamino)crotononitrile afforded a mixture of pyrroles. A remarkable minor component was characterised as 4-acetoxy-1-benzoyl-2-methyl-5-phenylpyrrole-3-carbonitrile, the result of sequential [1,5]-benzoyl migrations of a 3*H*-pyrrole intermediate.

The acylative cyclisation of 3-(1-carboxyalkylamino)-2-tosylacrylonitriles provides access to hitherto unknown 3-diacetamido-4-tosyl- and 3-acetamido-4-tosylpyrroles. Cyclisation of 2-(1-carboxyalkylaminomethylene)dibenzoylmethanes offers an excellent, complementary approach to access 5-(un)substituted-3-benzoyl-4-phenylpyrroles, to the existing tosylmethyl isocyanide-based protocols.

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Guide to the Referencing System

The referencing system employed in this thesis is that devised by Katritzky and utilised in Comprehensive Heterocyclic Chemistry [84CHEC-I(1)5]. This system is used in place of numerical references and allows the reader to extract the reference directly from the text. The references are given in the format (NNLLNN) where the initial numbers denote the year in which the citation was published, the letters indicate the journal, book or patent from which the citation has originated and the final numbers refer to the page number. For journals which publish more than one volume per year, the volume number is given in parantheses after the journal code. Less common journals are assigned the code MI.

Abbreviation	Journal/Book/Patent Title
ACIE	Angewandte Chemie, International Edition
AHC	Advances in Heterocyclic Chemistry
ARK	Arkivoc
B	Biochemistry
BSF	Bulletin de la Societe Chimique de France
CB	Chemische Berichte
CC	Chemical Communications
CCC	Collection of Czech Chemical Communications
CEJ	Chemistry, A European Journal
CHE	Chemistry of Heterocyclic Compounds
CHEC	Comprehensive Heterocyclic Chemistry
CJC	Canadian Journal of Chemistry
CPB	Chemical and Pharmaceutical Bulletin
CRV	Chemical Reviews
CSR	Chemical Society Reviews
EJOC	European Journal of Organic Chemistry
EJP	European Journal of Pharmacology
H	Heterocycles
HC	Chemistry of Heterocyclic Compounds (Weissberger-Taylor Series, Wiley-Interscience
HCA	Helvetica Chimica Acta
IC	Inorganic Chemistry
JA	Journal of the American Chemical Society
JCS	Journal of the Chemical Society
JCS(P1)	Journal of the Chemical Society, Perkin Transactions 1
JHC	Journal of Heterocyclic Chemistry
JMC	Journal of Medicinal Chemistry
JPH	Japanese Patent (Kokai Tokkyo Koho)
JOC	Journal of Organic Chemistry
JPR	Journal für Praktische Chemie
JPS	Journal of Pharmaceutical Sciences
LOC	Letters in Organic Chemistry
MD	Molecular Diversity
MHC	Modern Heterocyclic Chemistry
MI	Miscellaneous, Book or Journal
MOL	Molecules
MRR	Medicinal Research Reviews
NJC	New Journal of Chemistry
NPR	Natural Product Reports
NRM	Nature Reviews Microbiology
OBC	Organic and Biomolecular Chemistry
OL	Organic Letters
OPPI	Organic Preparations and Procedures International
OPRD	Organic Process Research and Development
OR	Organic Reactions
OS	Organic Syntheses

P	Polyhedron
RC	Roczniki Chemii
RCB	Russian Chemical Bulletin
RSC(A)	Royal Society of Chemistry Advances
S	Synthesis
SAA	Spectrochimica Acta Part A
SC	Synthetic Communications
SL	Synlett
T	Tetrahedron
TH	Thesis
THC	Topics in Heterocyclic Chemistry
TL	Tetrahedron Letters
USP	United States Patent
WO	World Application, Patent Cooperation Treaty
YZ	Yakugaku Zasshi

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Abbreviations

Abbreviation	Meaning
δ	Chemical Shift (ppm)
Δ	Heat
Ac	Acetyl
An	4-Methoxyphenyl (*p*-Anisyl)
APCI	Atmospheric-Pressure Chemical Ionisation
app.	Apparent
Aq.	Aqueous
Ar	Aryl
Boc	*tert*-Butoxycarbonyl
BOP	1*H*-Benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate
b.p.	Boiling Point
br.	Broad
cm^{-1}	Wavenumbers
COSY	Correlated Spectroscopy
d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
dd	Doublet of Doublets
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
DMAD	Dimethyl acetylenedicarboxylate
DMF	*N*,*N*-Dimethylformamide
DMFDMA	*N*,*N*-Dimethylformamide Dimethyl Acetal
DMSO	Dimethyl sulfoxide
DP	4-Dimethylaminophenyl
dt	Doublet of Triplets
Equiv.	Equivalents
ESI	Electrospray Ionisation
FT-IR	Fourier Transform Infrared
FVP	Flash Vacuum Pyrolysis
HMBC	Heteroatom Multiple Bond Coherence Spectroscopy
HRMS	High Resolution Mass Spectrometry
HSQC	Heteroatom Single Quantum Coherence Spectroscopy
Hünig's Base	Diisopropylethylamine
J	Coupling Constant (Hz)
m	Multiplet
m.p.	Melting Point
NMP	*N*-Methylpyrrolidin-2-one
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
NSI	Nanospray Ionisation
PNP	4-Nitrophenyl
ppm	parts per million

q	Quartet
rt	Room Temperature
s	Singlet
sep.	Septet
sex.	Sextet
t	Triplet
TBDMS	*tert*-Butyldimethylsilyl
TFAA	Trifluoroacetic anhydride
TLC	Thin Layer Chromatography
TosMIC	(*p*-Toluenesulfonylmethyl) isocyanide
Ts	*p*-Toluenesulfonyl

Chapter 1

Introduction

Chapter 1 Introduction

1.1 Structure and Historical Significance

The first discovery of pyrrole by Runge in 1834; a compound obtained through distillation of coal tar was observed to turn the wood splinters it was applied to red, upon the application of acid, was named pyrrole [11MHC269]. The first pure sample of pyrrole was obtained from distillation of bone oil by Anderson in 1857 [1857MI571] and the structure subsequently determined by Baeyer and Emmerling in 1870 to be a five-membered heterocycle containing nitrogen [Figure 1.1a), 11MHC269]. Pyrrole is a colourless oil which darkens when exposed to air or light [13MI18]. Some physical and chemical properties of pyrrole are given in Table 1.1.

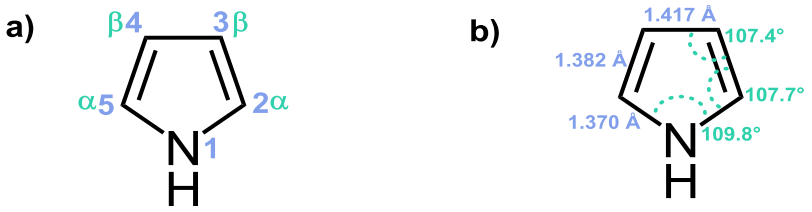


Figure 1.1 Structure of pyrrole with a) atom labels; and b) important bond lengths and angles.

Table 1.1 Physical properties of pyrrole.

Physical Data	Value	Reference
Boiling point	130 °C	11MHC269
Melting point	–23 °C	11MHC269
pK_a	17.5 (in water) 23.0 (in DMSO)	85MI126
^{1}H NMR ($CDCl_3$)	δ 6.68 ppm (H-2/H-5) δ 6.22 ppm (H-3/H-4)	13MI18
^{13}C NMR ($CDCl_3$)	δ 118.2 ppm (C-2/C-5) δ 109.2 ppm (C-3/C-4)	13MI18
^{14}N NMR (Neat)	235 ppm	84CHEC-I(4)89
Bird's Unified Aromaticity Index, I_A	85[a]	92T355
Bond Lengths and Angles	Figure 1.1b)	03MI86

[a]where the I_A for benzene = 100, thiophene = 81.5 and furan = 53.

The resonance structures for pyrrole are shown in Figure 1.2. Resonance leads to partial negative charge on the carbon atoms and a partial positive charge on nitrogen. This mesomeric effect is

more significant than the competing inductive effect towards nitrogen and therefore the negative portion of the dipole is directed away from nitrogen [Figure 1.2, 10MI316].

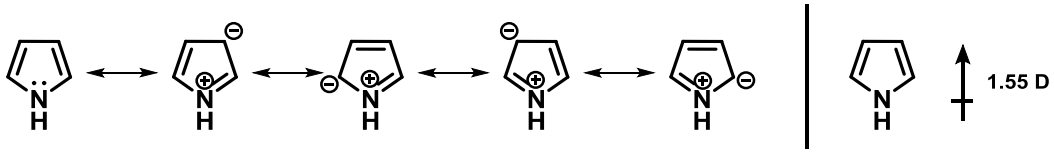


Figure 1.2 Resonance structures and dipole moment.

Pyrrole is planar and has five overlapping p-orbitals from the four sp^2-hydridised carbons and an sp^2 nitrogen which includes the lone pair of electrons, these are delocalised around the ring making the system aromatic (Figure 1.3). The aromaticity is reflected in the bond lengths [Figure 1.1b)], the N–C2, N–C5 and C3–C4 bonds are shorter than expected for single bonds: 1.475 Å (N–C) and 1.53 (C–C) and C2=C3 and C4=C5 are longer than a typical C=C double bond (1.316 Å). Due to the contribution of the lone pair, each of the atoms in the system has an electron density of >1 making pyrrole π-electron excessive [03MI86].

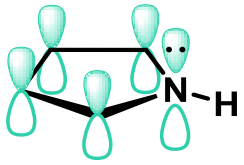
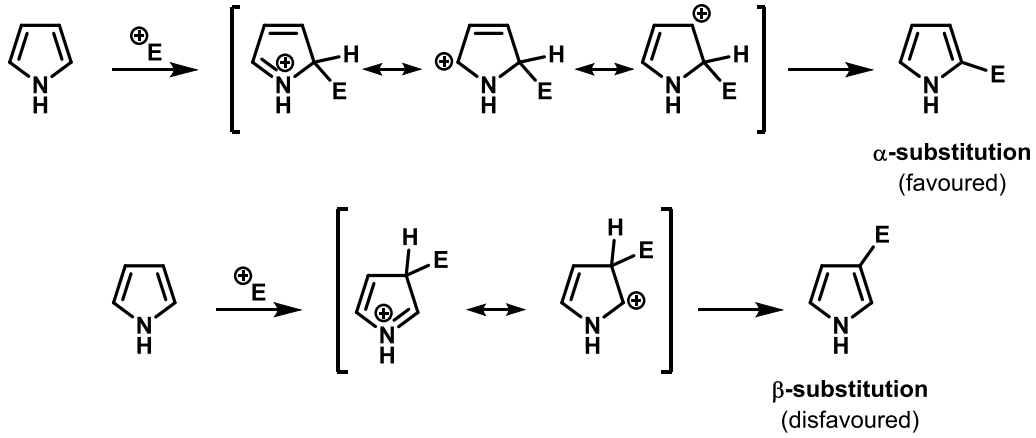


Figure 1.3 p-Orbital overlap in pyrrole.

The π-excessive nature of the pyrrole ring confer upon it strong susceptibility towards S_EAr reactions under mild conditions. The relative ease with which the ring can be deprotonated is an important facet allowing, by appropriate choice of reagents and conditions substitutions as either N-1 or C-2 to be accomplished. A brief overview of the reactivity of the pyrrole ring is provided in the following section.

1.2 Reactivity of Pyrrole

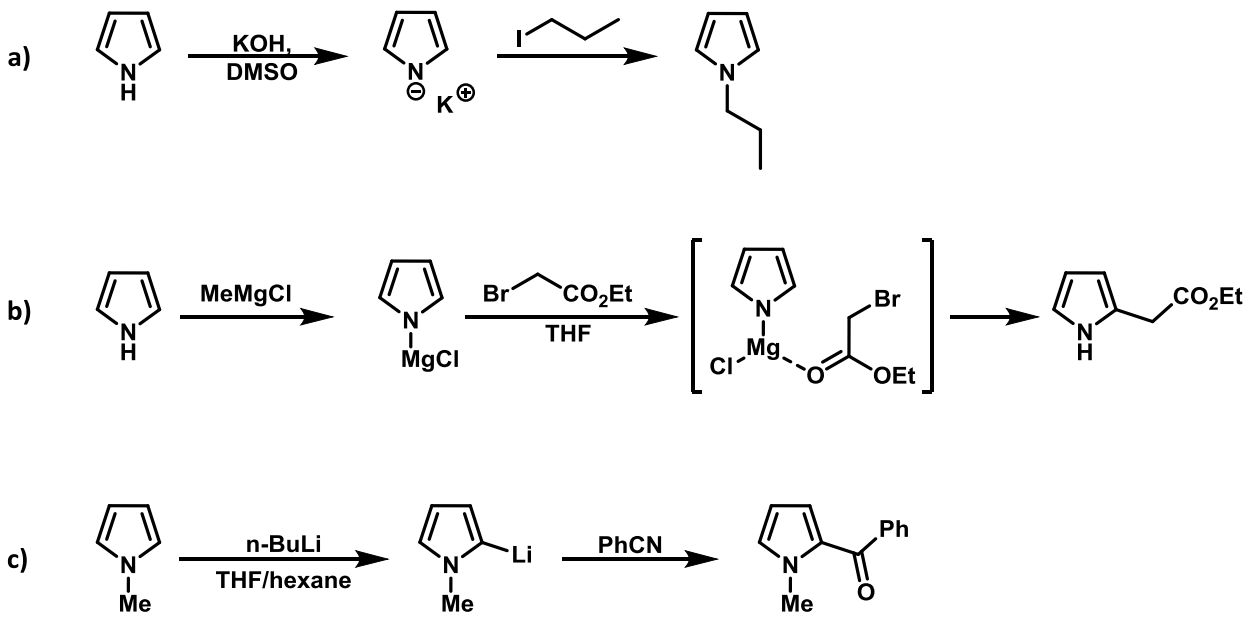
Due to the electron rich nature of the pyrrole ring, it readily undergoes electrophilic substitution, resulting in mainly, 2-substituted pyrroles. Attack occurs more readily at the α-position due to the stabilisation of the intermediate σ-complexes, delocalisation is maintained more in the reaction at the 2-position than at the 3-position [Scheme 1.1, 10MI316].



Scheme 1.1

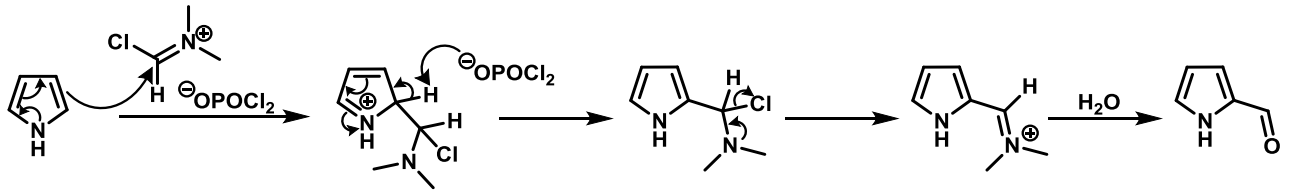
If a bulky protecting group, such as triisopropylsilyl (TIPS), is placed on nitrogen, the 2-position is blocked from attack and substitution at the 3-position is preferred, the use of electron withdrawing groups on either nitrogen or the C2-position also encourages β-substitution [11MHC296]. The use of acids leads to rapid polymerisation of pyrrole [11MI18]. Electrophilic substitution does not take place on nitrogen due to a resultant loss of resonance and a localised positive charge on nitrogen being unfavourable [10MI316].

To effect substitution at the nitrogen atom, it is necessary to deprotonate prior to electrophilic trapping. Deprotonation can be achieved using sodium, sodium hydride, potassium, alkali metal hydroxides, butyllithium or with a Grignard reagent. For example, the potassium salt of the pyrrolyl anion reacts with 1-iodoalkanes to afford *N*-alkylpyrroles [Scheme 1.2a), 73JCS(P1)499, 85MI126, 03MI86]. When lithium or magnesium salts are used, however, electrophilic attack occurs on carbon [Scheme 1.2b), 96CHEC-II(2)39, 11MHC296] although the outcome is dependent upon the conditions used and in some instances mixtures of *N*- and *C*- substitution products are obtained. It is also possible to metallate at the C2-carbon if the nitrogen is already substituted, in this case, electrophilic trapping will occur at the 2-position of the ring [Scheme 1.2c), 82SC231].



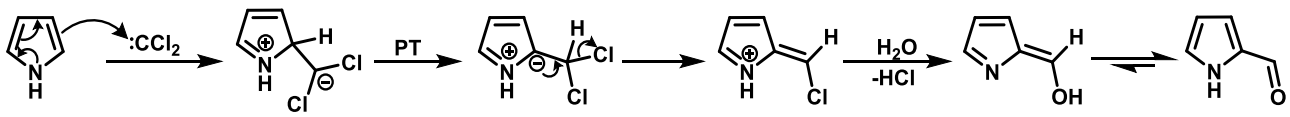
Scheme 1.2

The Vilsmeier-Haack reaction introduces an aldehyde function to the 2-position of electron rich heterocycles. The Vilsmeier reagent is a chloroiminium salt formed *in situ* from DMF and phosphorous oxychloride and with pyrrole, the reaction proceeds *via* an iminium ion which is then hydrolysed to the product [Scheme 1.3, 11MI18].



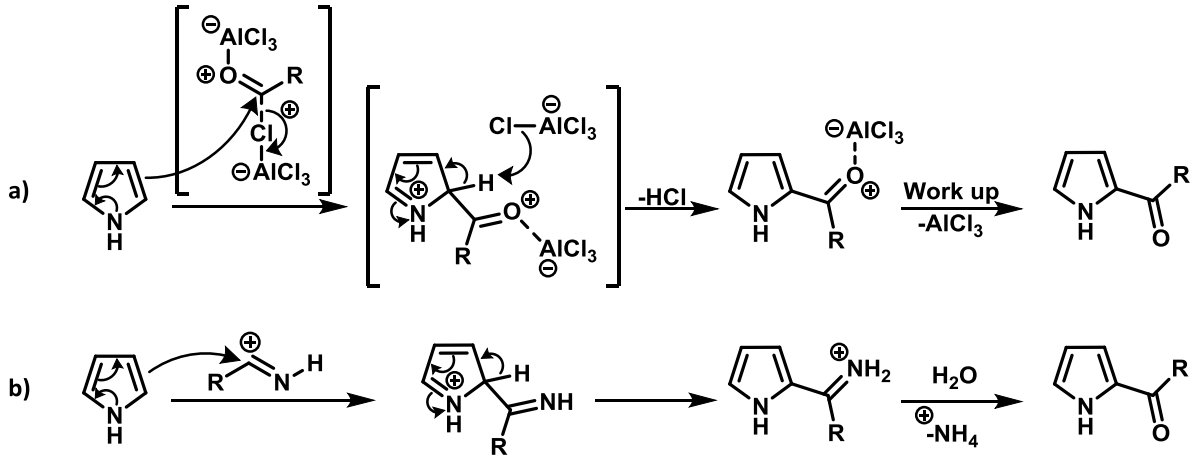
Scheme 1.3

Alternatively pyrrole can be formylated using the Reimer-Tiemann reaction. A dichlorocarbene is formed from chloroform in sodium hydroxide solution, initially the pyrrole ring undergoes an electrophilic substitution at the α-position and is further hydrolysed to produce the 2-formylpyrrole [Scheme 1.4, 85MI126, 03MI86].



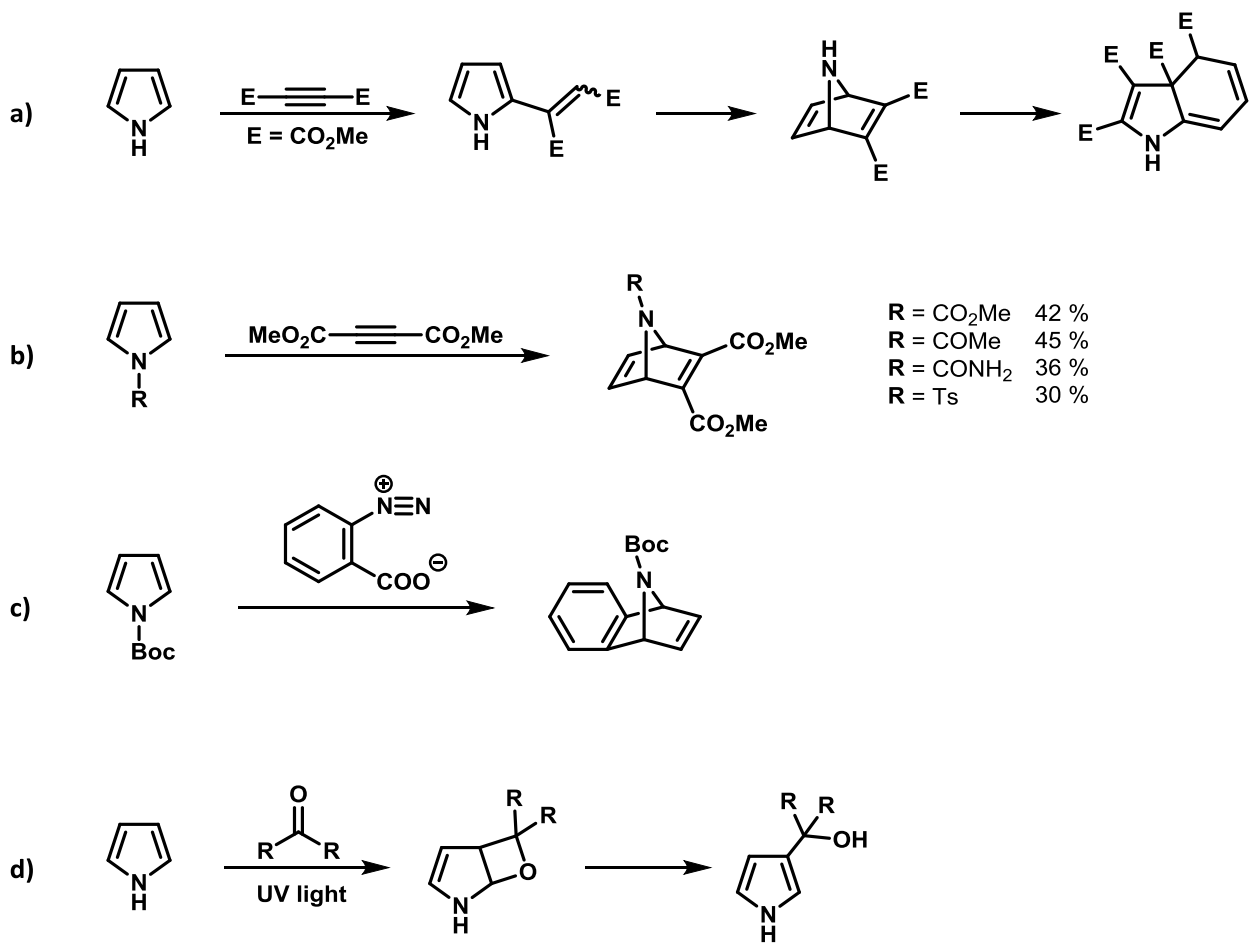
Scheme 1.4

Pyrroles are readily acylated [Scheme 1.5]. The Friedel-Crafts acylation reaction begins with coordination of a Lewis acid (e.g. aluminium chloride) to an acylating agent (e.g. an acyl chloride) followed by ionisation from another equivalent of the Lewis acid [Scheme 1.5a)]. The complex then reacts with pyrrole to form an aromatic ketone after hydrolysis. The use of an electron withdrawing group at nitrogen, such as a phenylsulfonyl group, directs the reaction to the β-position [03MI86]. The Houben-Hoesch acylation reaction involves the reaction of an iminium ion, formed by the reaction of a nitrile with HCl, with pyrrole, the reaction proceeds *via* an iminium species which is subsequently hydrolysed to afford the acyl pyrrole [Scheme 1.5b), 03MI86].



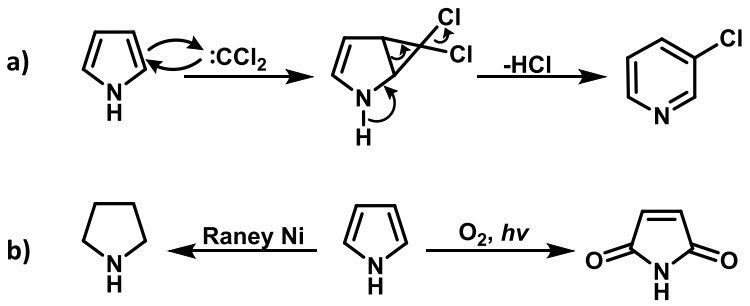
Scheme 1.5

Pyrrole is not a good diene and therefore does not undergo Diels-Alder reactions as readily as furan, and attempts to do so, generally result in the Michael addition product, which can react further to afford a complex mixture of products [Scheme 1.6a), 80JOC4573, 96CRV1179]. Introduction of an electron withdrawing group on the nitrogen, enhances reactivity significantly and the [4+2] cycloadduct is obtained; however, the major products are still the Michael addition products [Scheme 1.6b), 61MI3116, 96CRV1179]. When *N*-Boc pyrrole is reacted with benzyne, generated *in situ* from anthranilic acid and isoamyl nitrite, the cycloadduct is formed in 63% yield [Scheme 1.6c), 02OL3465]. Reaction with dialkylketones in the presence of UV light results in a [2+2]-cycloaddition reaction the Paterno-Büchi reaction [Scheme 1.6d)]. This fused ring system undergoes a cycloreversion reaction resulting in a 3° alcohol at the β-position of the pyrrole ring [85MI126].



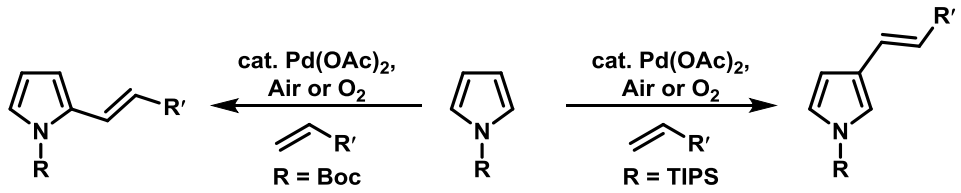
Scheme 1.6

[2+1]-Cycloaddition reactions can occur under the conditions of the Reimer-Tiemann reaction [Scheme 1.4] especially when weak bases are used to generate the carbene. The carbene cycloadds to the pyrrole and then the ring is expanded to afford a 3-chloropyridine, accompanied by the loss of HCl [Scheme 1.7a), 03MI86]. Other reactions which involve transformation of the ring include reduction of the pyrrole ring to pyrrolidine and oxidation under photo-oxidative conditions to maleimide [Scheme 1.7b), 84CHEC-I(4)201].



Scheme 1.7

C-H Activation allows new functionality to be introduced in to heterocycles; with the use of transition metal catalysts new C-C bonds can be installed in a quick and simple manner without the requirement for multiple reaction steps. Directing groups can be utilised to ensure the regioselectivity of the reaction which proceeds *via* electrophilic palladation of the pyrrole ring. Due to many C-H activation methods using acidic and oxidative conditions, they are not as widely used with pyrroles as with other heterocycles [Scheme 1.8, 06JA2528, 10ARK(i)247].

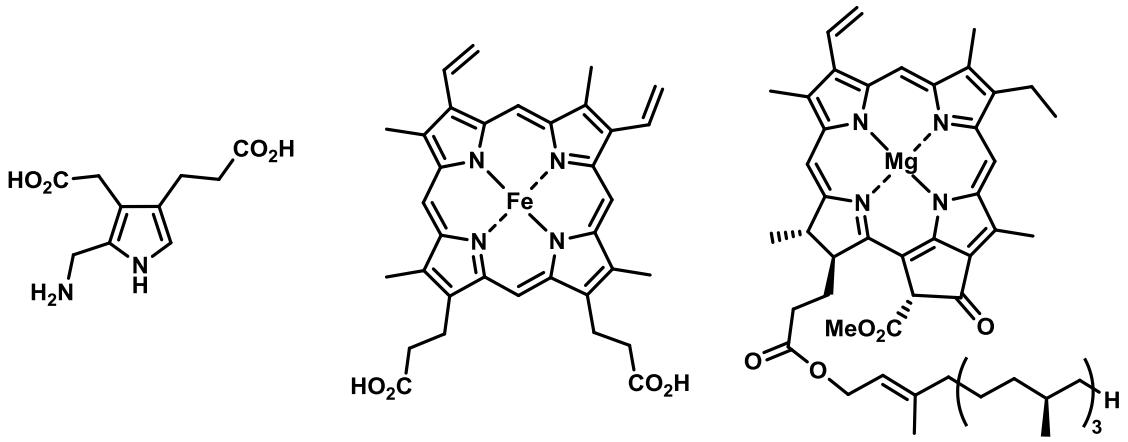


R′ = CO_2Bn, $CO_2{}^nBu$, COEt, SO_2Me, $PO(OEt)_2$, 4-$MeO_2CC_6H_4$, CN

Scheme 1.8

1.3 Importance of Pyrroles and Natural Occurrence

Pyrroles, amongst other heterocycles, are present in a number of naturally occurring molecules and are vital to our existence; porphobilinogen **1.1** (Figure 1.4) is a simple pyrrole found in the urine of patients with acute porphyria [53B1176], is the precursor to tetrapyrrole-containing molecules (porphyrins) such as haems (haem B **1.2**), chlorophylls (chlorophyll a **1.3**) and vitamin B_{12} [96JCS(P1)2633]. Haem B is vital for human existence and is responsible for oxygen transport around the body [00NPR507]. Chlorophyll a is found in all plants and is responsible for mediating photosynthesis [00NPR507].

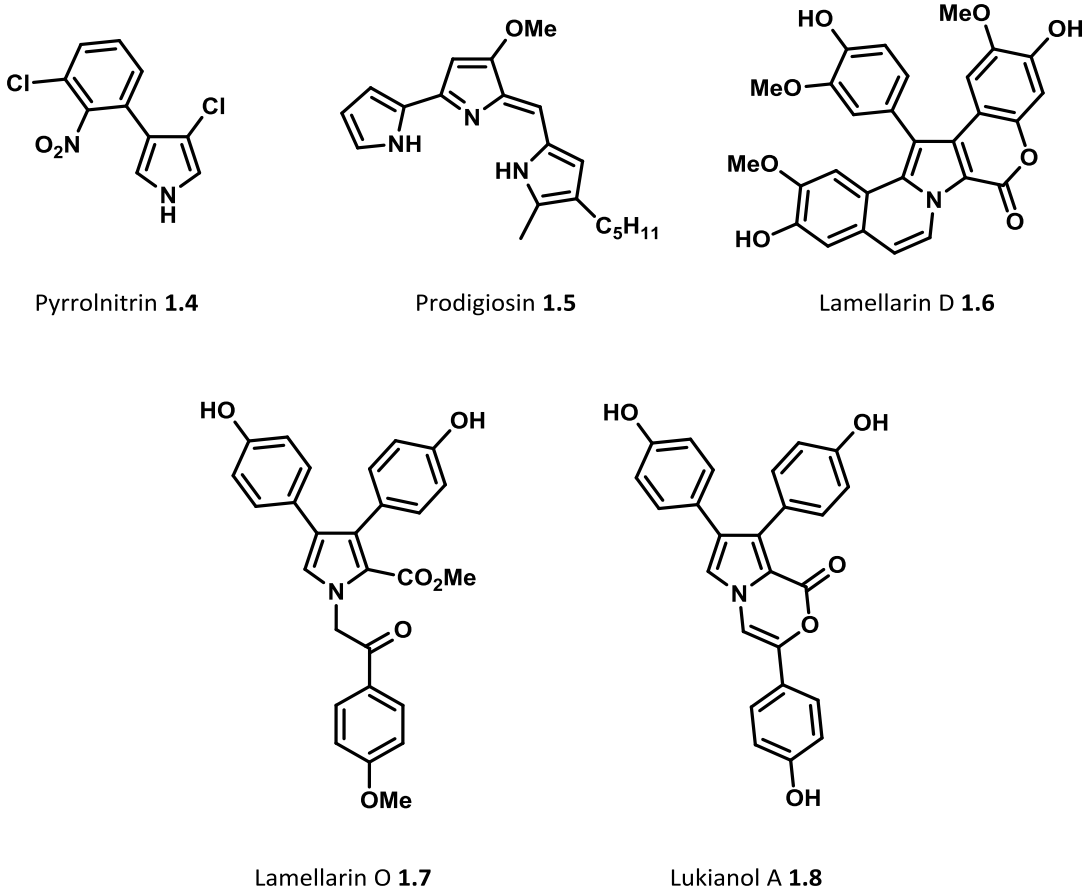


Porphobilinogen **1.1** Haem B **1.2** Chlorophyll a **1.3**

Figure 1.4 Naturally occurring pyrroles porphobilinogen **1.1**, haem B **1.2** and chlorophyll-a **1.3** [00NPR507].

Further examples of pyrrole-containing natural products are shown in Figure 1.5, these pyrroles have an interesting and diverse range of bioactive properties [10NPR1801, 13OPPI171]. Pyrrolnitrin **1.4** is a secondary metabolite found in various strains of bacteria and is an antifungal antibiotic [97AEM2147, 13OPPI171]. Prodigiosin **1.5** is a tripyrrole produced by a number of microorganisms and is known to have potent cytotoxicity against cancers such as breast cancer [03MI1447] and neuroblastoma [07EJP111]. Prodigiosin **1.5** is also an effective immunosuppressant [06NRM887]. The synthesis and properties of prodigiosin alkaloids have been reviewed [15RSC10899] lamellarins (e.g. D **1.6** and O **1.7**) and lukianols (A **1.8**) have been isolated from various marine invertebrates and sponges [06T7213]. Lamellarins are a group of over 50 pyrrole alkaloids which are structurally divided into three categories – type Ia (partially saturated), type Ib (unsaturated) and type II (simple pyrroles) [14MI6142]. Lamellarin D **1.6** (type Ib) has the most potent cytotoxicity of the lamellarin alkaloids [14MI6142], and is effective against prostate cancer and leukaemia [05MI165], whilst lamellarin A **1.7** (type II) is not cytotoxic but has antibiotic

properties; both have the ability to reverse multidrug resistance [06T7213]. Lukianol A **1.8** is a structurally similar compound to the lamellarins which is affective against epidermoid carcinoma and leukaemia [14MI6142].

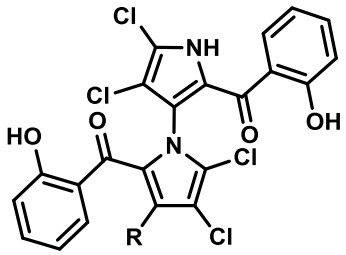


Pyrrolnitrin **1.4** Prodigiosin **1.5** Lamellarin D **1.6**

Lamellarin O **1.7** Lukianol A **1.8**

Figure 1.5 Natural pyrrole containing compounds [06T7213, 13OPPI171].

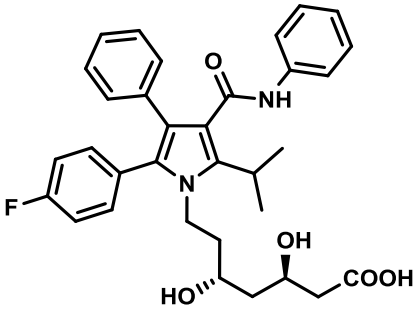
Marinopyrroles are 1,3'-bipyrroles recently isolated from extracts of bacteria found in marine sediment. Marinopyrrole A **1.9** and marinopyrrole B **1.10** (Figure 1.6) have been reported to be active against methicillin-resistant *Staphylococcus aureus* (MRSA) [14CSR4633]. Since the discovery of pyrroles able to overcome the serious problem of drug resistant bacteria, their synthesis has gained increasing interest and the chemistry of marinopyrroles has been reviewed [13T5067, 16MRR169].



Marinopyrrole A **1.9 R** = H
Marinopyrrole B **1.10 R** = Br

Figure 1.6 Marinopyrroles A and B (**1.9** and **1.10** respectively).

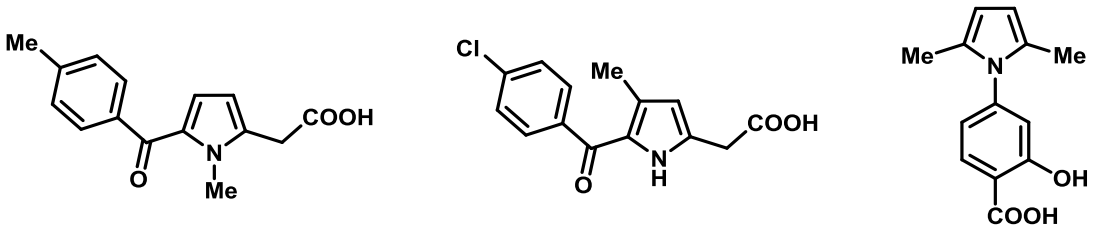
As well as natural products, synthetic pyrroles have great value in the pharmaceutical sector, particularly atorvastatin **1.11**, the best-selling drug to date (Figure 1.7). Atorvastatin is effective in lowering blood cholesterol levels by inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase [08CHEC-III(4)353, 14CSR4633].



Atorvastatin **1.11**

Figure 1.7 Synthetic pyrrole atorvastatin **1.11**.

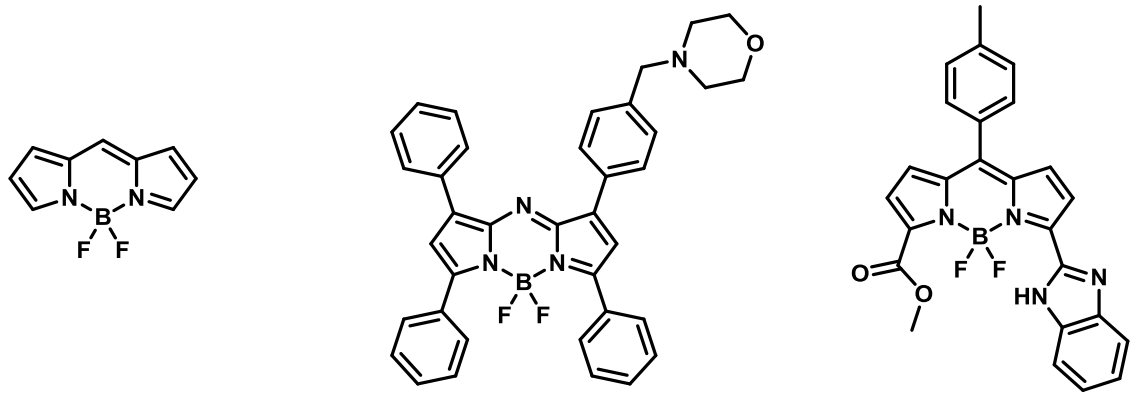
Further examples of synthetic pyrroles with bioactive properties include tolmetin (**1.12**) and zomepirac (**1.13**), these pyrrole-2-carboxylic acid derivatives are non-steroidal anti-inflammatory agents effective in the treatment of rheumatoid arthritis [Figure 1.8, 14CSR4633, 15RSC15233]. The synthetic 1-arylpyrrole **1.14** has shown promise as a HIV-type 1 inhibitor [Figure 1.8, 04AAC4349, 08CHEC-III(4)353]. The synthesis of pyrrole-containing scaffolds in pharmacologically active compounds has been reviewed [15EJM176, 15RSC15233]. In addition to their pharmaceutical activity, pyrroles have a wide range of other applications [15RSC15233].



1.12 **1.13** **1.14**

Figure 1.8 Synthetic pyrroles with bioactive properties

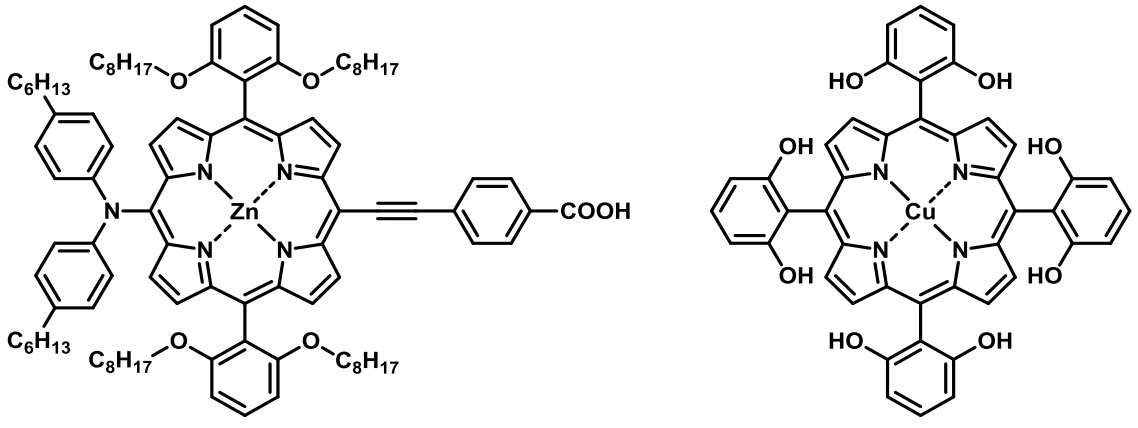
BODIPY dyes are a class of compounds with a boron-dipyrromethene core (**1.15**, Figure 1.9), BODIPY dyes are highly fluorescent compounds with high quantum yields [07CR4891]. BODIPY dyes can be chemically tuned to emit in the near-IR region, this coupled with their stability in physiological conditions makes them ideal for real-time cell imaging. Their characteristics mean they have the potential for a wide range of applications, for example, as pH sensors (**1.16**, Figure 1.9). Aza-BODIPY **1.16** has its fluorescence quenched by electron donor, morpholine, by photoinduced electron transfer (PET). When the pH of the environment is low, the morpholine moiety is protonated which subsequently switches the fluorescence back on by inhibition of the PET process, making the molecule useful as a pH sensor in biological systems allowing for detection of abnormal cell pH and has been proven successful *in vitro* for imaging in HeLa cell lines [14OBC3774]. BODIPY dyes can also be useful as metal ion detectors. BODIPY **1.17** selectively captures Hg(II) through binding at the benzimidazole moiety which consequently has a hypsochromic shift in the emission spectrum coupled with an increase in fluorescence quantum yield, this is also a result of PET inhibition. The compound has been shown to successfully detect submicromolar quantities of Hg(II) in human breast adenocarcinoma cells both *in vitro* and *in vivo* [13IC11136, 14OBC3774].



1.15 **1.16** **1.17**

Figure 1.9 BODIPY dyes.

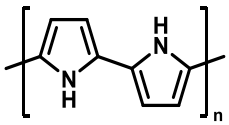
Porphyrins such as chlorophyll (**1.3**, Figure 1.1) with the ability to convert light to chemical energy have inspired a collection of porphyrin dyes for use in dye-sensitised solar cells. Efficient porphyrin dyes are more desirable than ruthenium complexes as they are more cost effective and environmentally safer, the disadvantage of using porphyrin dyes is that they generally have lower power conversion efficiency than ruthenium complexes. Porphyrin dye **1.18** (Figure 1.10) when used in conjunction with a cobalt electrolyte is the first to have a greater power conversion efficiency than the most efficient ruthenium dyes and can absorb light up to 700 nm [11SCI(334)629, 13CSR291]. A further use for porphyrins is as heterogeneous catalysts; the copper-porphyrin **1.19** (Figure 1.10) has the ability to selectively reduce CO_2 to hydrocarbons with high catalytic activity, thus showing promise for conversion of emissions back to fuels [16JA8076].



1.18 **1.19**

Figure 1.10 Porphyrins for use in porphyrin-sensitised solar cells (**1.18**) and catalysis (**1.19**).

Chemical or electrochemical polymerisation of pyrrole results in polypyrrole (**1.20**, Figure 1.11), which, due to its conjugation, makes it a good conducting polymer [01RFP125, 06JRSI741, 16JSSE839]. Polypyrroles are attractive due to their simple synthesis, environmental stability and the scope to tune their properties [01RFP125, 16JSSE839]. Their properties make them ideal candidates in a wide variety of applications, for example, as biosensors, gas sensors, wires, rechargeable batteries, liquid crystals and for pharmaceutical drug release [01MI990, 01RFP125, 06JRSI741, 16JSSE839].



1.20

Figure 1.11 Polypyrrole.

As a result of their natural occurrence, and their wide scope as pharmaceuticals and as building blocks in materials and polymer chemistry, pyrroles continue to attract intense academic and industrial interest.

1.4 Pyrrole Syntheses

The syntheses of pyrrole rings has been widely studied and numerous reviews have been published to summarise the vast number of publications on the multiple methods of pyrrole synthesis. Detailed reviews of the reactivity, structure and syntheses of pyrroles can be found in the major reference work *Comprehensive Heterocyclic Chemistry* [synthesis: 84CHEC-I(4)89, 96CHEC-II(2)119, 08CHEC-III(3)269; structure: 84CHEC-I(4)155; reactivity: 96CHEC-II(2)39; applications: 08CHEC-III(4)353] and the treatise *Modern Heterocyclic Chemistry I–III* [11MHC269]. In addition, extensive coverage of all aspects of pyrrole chemistry is provided by the earlier monographs by Gossauer [74MI1], Jones and Bean [77MI1] and two volumes in the Weissberger–Taylor series *The Chemistry of Heterocyclic Compounds* [90HC(48-1)1, 92HC(49-2)1]. A recent book by Trofimov *et al.* provides coverage of mainly Russian work on pyrrole chemistry [14MI1]. Pyrrole chemistry has been reviewed annually since 1989 in *Progress in Heterocyclic Chemistry* published by Elsevier. Pyrrole syntheses have been reviewed based on their starting materials or catalysts [synthesis from active methylenes 16RSC37039, *N*-propargylamines 16RSC18619, alcohols 17CCR(331)37, α-imino Rh complexes 16CEJ17910 and syntheses mediated by Cu, Ag and Au catalysis 16OBC7136] and their reaction types [01OPPI411, 13OPPI171]. The use of multicomponent reactions in the synthesis of pyrroles has been reviewed thoroughly [10CSR4402, 14CSR4633, 15ACR2822].

1.4.1 De Novo Ring Syntheses

Rather than refer to pyrrole syntheses by a name reaction, R. J. Sundberg developed a classification system which indicates the number of bonds formed in the synthesis followed by the location of the new bond(s) (Figure 1.12) [96CHEC-II(2)119]. Whilst the classification is useful, it is dependent upon the definition of the starting material [08CHEC-III(3)269]. In the following summary only the most important and useful syntheses are discussed.

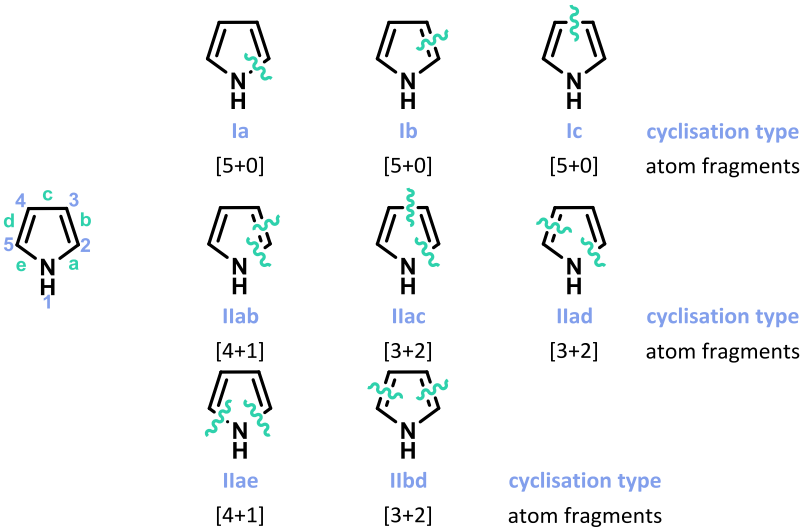
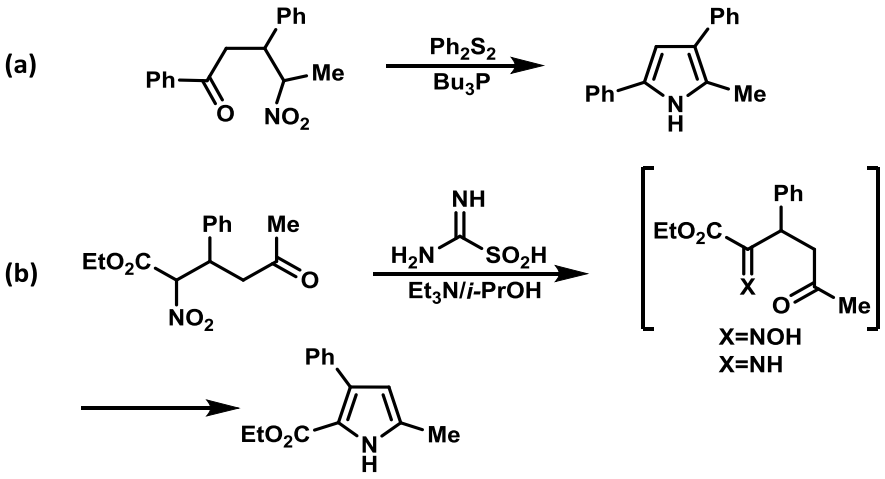


Figure 1.12 Sundberg's classification of pyrroles.

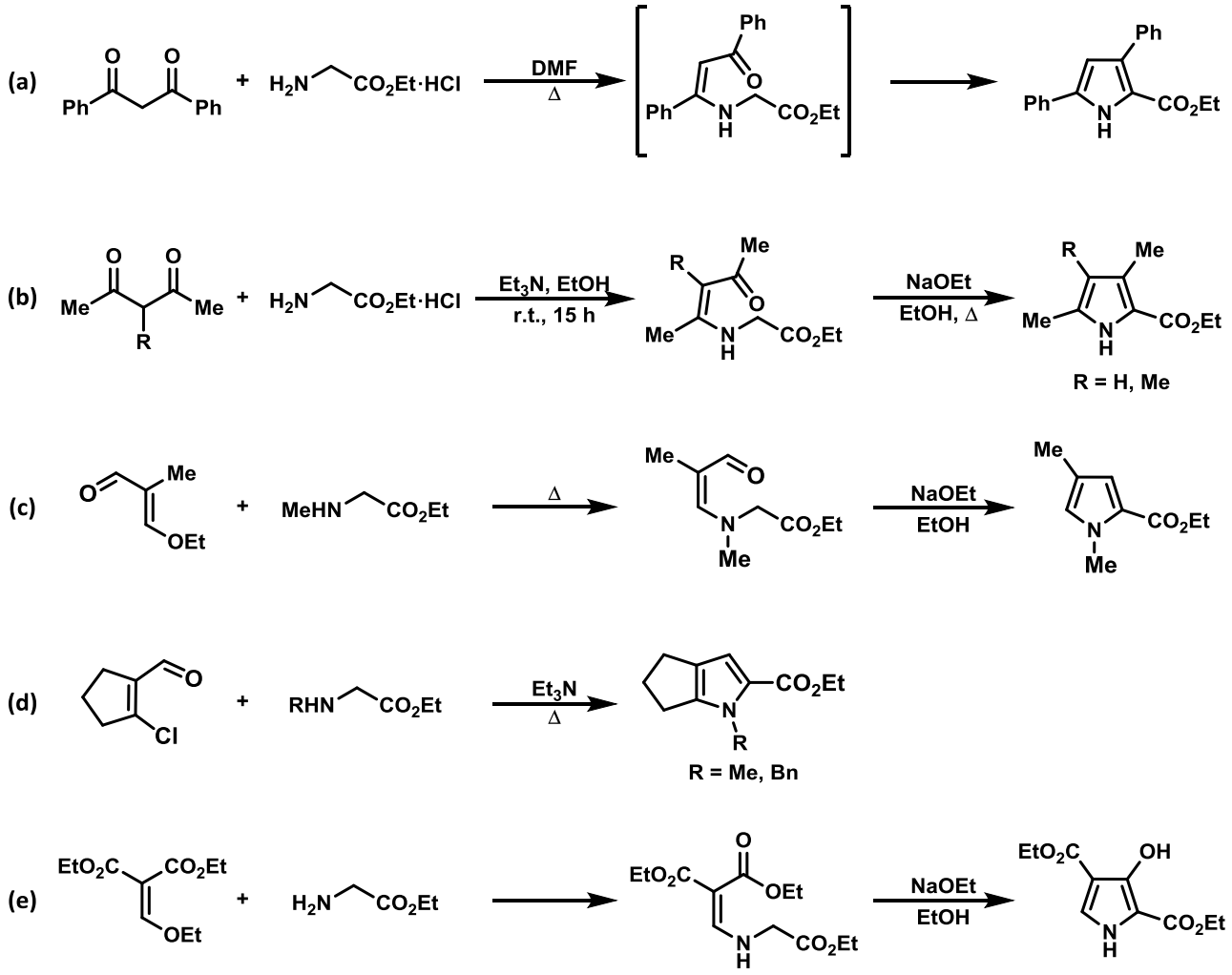
Scheme 1.9 shows two syntheses that involve an intramolecular [5+0] reaction and are categorised as type Ia cyclisations. Scheme 1.9a) shows the cyclisation of a γ-nitroketone by reduction with tributylphosphine and diphenyl disulfide. The reaction proceeds *via* an imine intermediate and cyclodehydration to provide the pyrrole in good yield (90 %) [84TL3707]. Scheme 1.9b) follows a similar pathway involving either an oxime (X = NOH) or imine (X = NH) intermediate from the reduction of a γ-nitroketone with formamidinesulfinic acid with yields of 45–89 % [95TL9469].



Scheme 1.9

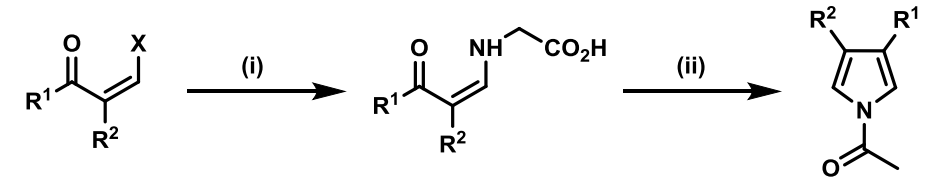
Glycine esters and their hydrochloride salts have been used to generate the precursors for [5+0] type Ib cyclisations (Scheme 1.10). Scheme 1.10a) shows the condensation reaction of ethyl glycinate hydrochloride with a 1,3-diketone to afford an enaminone intermediate which

undergoes cyclisation to the 2,3,5-trisubstituted pyrrole in good yields [82S157]. Another example using ethyl glycinate hydrochloride is shown in Scheme 1.10b), the intermediate enaminone can be isolated and cyclised by treatment with base [90S389]. In a related approach 3-ethoxymethacrolein reacts with α-aminoacetates to generate the corresponding enamino aldehydes. Cyclisation to the pyrrole is accomplished by heating with base [Scheme 1.10c), 89S337]. 2-Chlorocyclopentene-1-carboxaldehyde has been reported to afford the pyrrole directly upon heating with ethyl sarcosinate or ethyl *N*-benzylglycinate, although no experimental details were reported [Scheme 1.10d), 85TL1839]. In a similar manner the glycine ester has been used to synthesise an aminomethylenemalonate which was cyclised under basic conditions in a Dieckmann-type condensation reaction [Scheme 1.10e), 78CPB2224]. All of these methods are similar to the Zav'yalov synthesis which will be discussed in more detail subsequently.



Scheme 1.10

The Zav'yalov pyrrole synthesis facilitates the synthesis of 3,4-disubstituted pyrroles *via* the cyclisation of enamino acids accessible from condensation of α-amino acids with 1,3-dicarbonyls (Scheme 1.11) [73RCB(22)2505, 02JCS(P1)2799]. This simple synthesis has remained under-exploited.

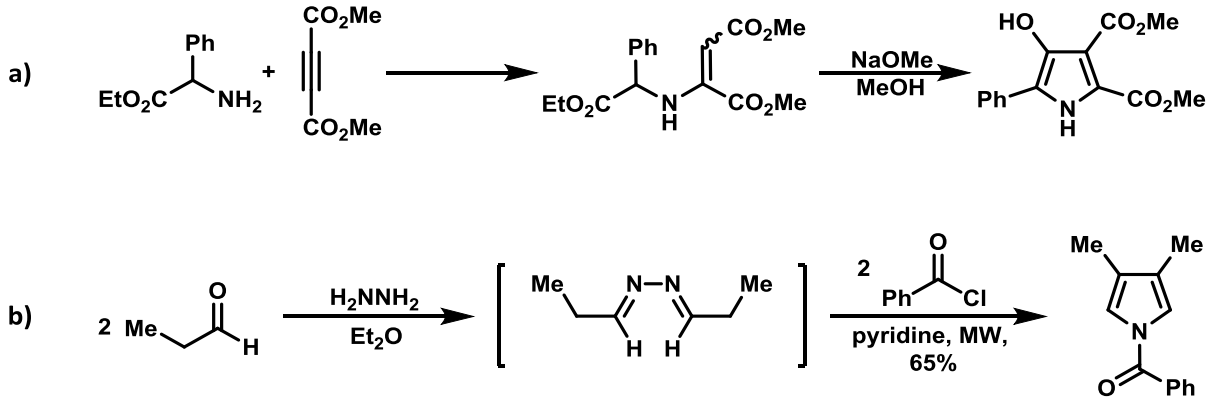


X = NMe_2, OH, OR

Reagents: (i) α-amino acid, NaOAc, aq. EtOH; (ii) Ac_2O, anhyd. NaOAc.

Scheme 1.11

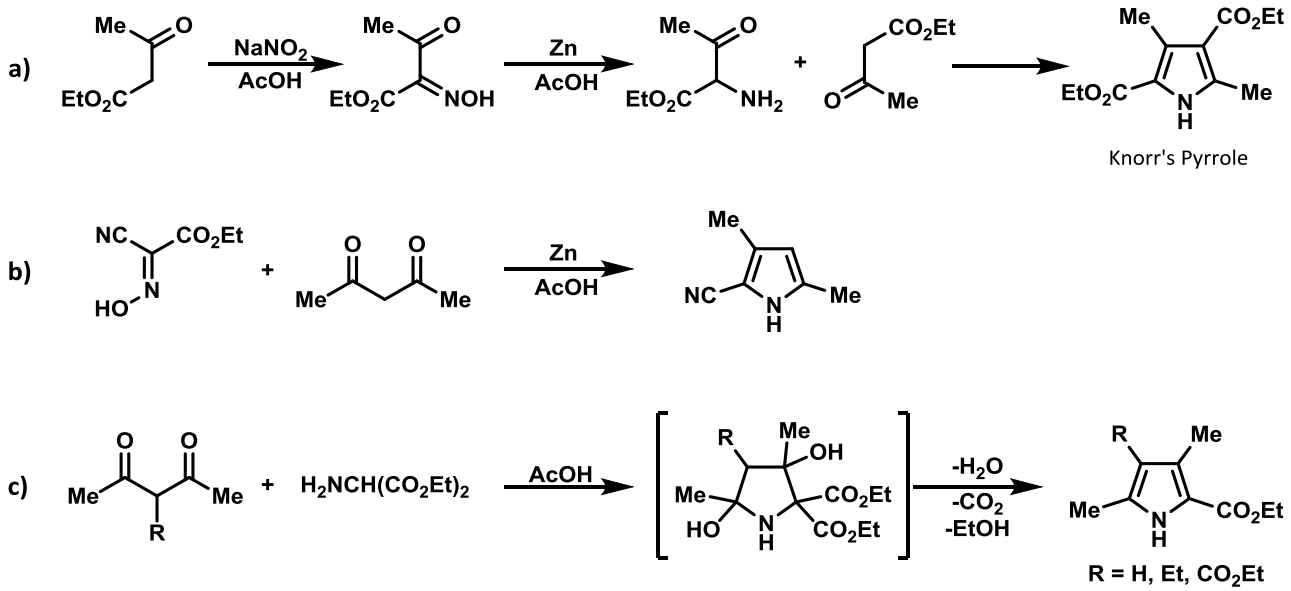
α-Amino acid esters react with DMAD to produce enamines; the enamines can then be cyclised in the presence of sodium methoxide to generate a pyrrole in good yield [Scheme 1.12a)] [94SC1887]. The reaction can either be categorised as a [3+2] type IIac cyclisation based on the starting materials or a [5+0] type Ic reaction based on the intermediate enamino-diester. Similarly, the Piloty-Robinson pyrrole synthesis can be classed as a [5+0] type Ic reaction based on the intermediate [Scheme 1.12b)]. In the first of two steps, hydrazine is added to an aldehyde (2 equiv.) to produce a symmetrical azine. In the final step, the azine is acylated with an aroyl chloride (2 equiv.) resulting in tautomerism, [3,3]-sigmatropic rearrangement and cyclisation to produce a 3,4-disubstituted pyrrole [07JOC3941].



Scheme 1.12

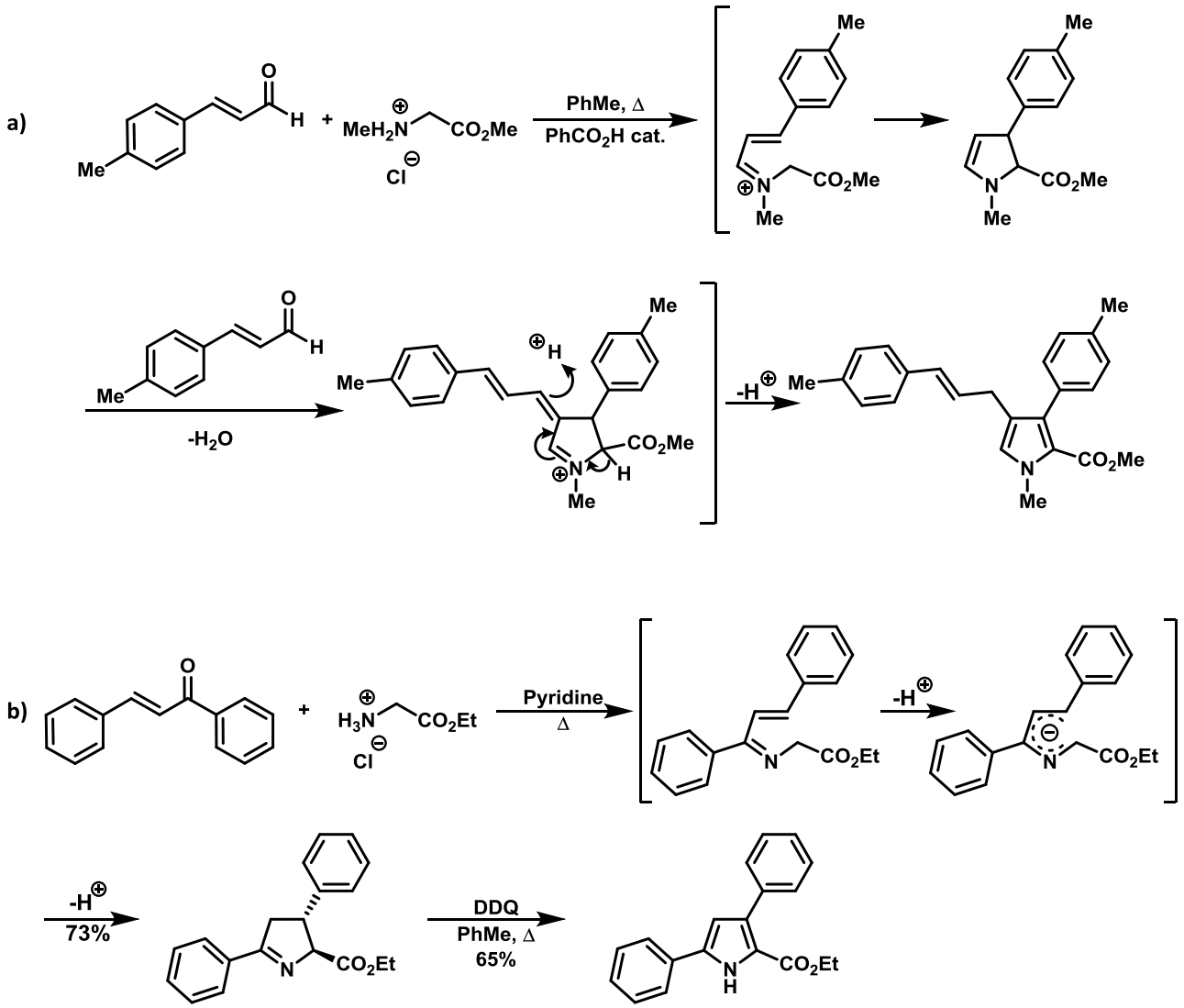
The most important example of the [3+2] reactions is provided by the Knorr pyrrole synthesis, a type IIac cyclisation (Scheme 1.13). The synthesis involves the condensation of a 1,3-dicarbonyl and an α-amino ketone derived from the *in situ* formation and reduction of an isonitroso ketone

thus preventing self-condensation of the α-amino ketone [05MI244]. The sequence in Scheme 1.13a) illustrates the formation of Knorr's pyrrole from ethyl acetoacetate [43OSC(2)202]. The reaction is capable of considerable variation. Scheme 1.13b) illustrates the formation of a pyrrole-2-carbonitrile from reduction of ethyl (isonitroso)cyanoacetate in the presence of acetylacetone; the reaction proceeds with dealkoxylcarbonylation [99S46]. Early work by Kleinspehn [55JA1546], later optimised [85JOC5598, 87JOC3986], demonstrated the formation of pyrrole-2-carboxylic esters from the condensation of diethyl aminomalonate with 1,3-diketones [Scheme 1.13c)].



Scheme 1.13

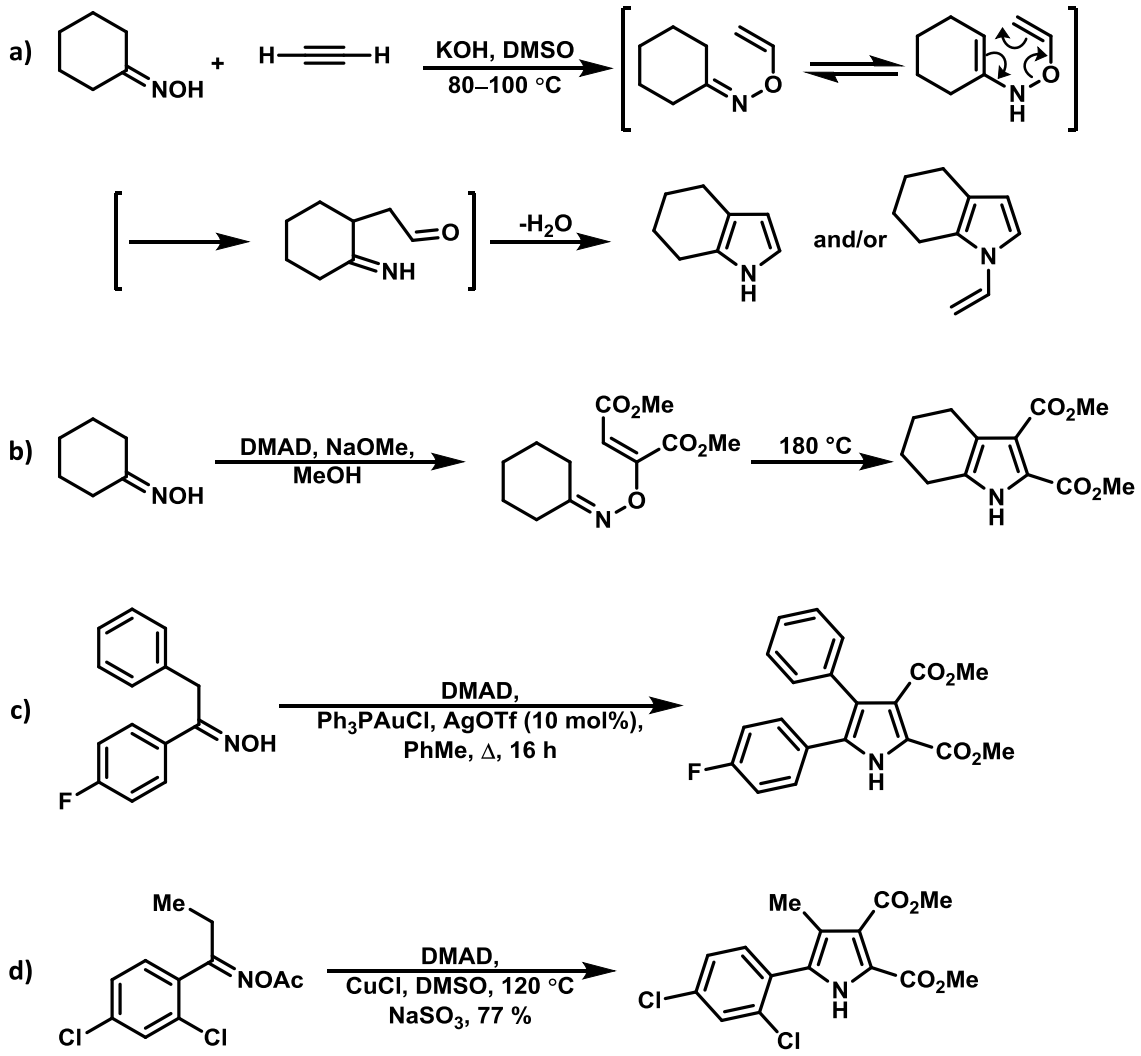
α,β-Unsaturated aldehydes and ketones provide useful and novel entries to pyrroles. Zu *et al.* described the acid-catalysed formation of 4-cinnamylpyrrole-2-carboxylates from the condensation of cinnamaldehydes with glycine esters [Scheme 1.14a), 14OL3580]. In a similar vein, the condensation of ethyl glycinate hydrochloride with chalcones proceeds readily in pyridine to afford high yields of 4,5-dihydro-3*H*-pyrroles which result from initial imine formation and an anionic 6π-electrocyclisation. Dehydrogenation to the pyrrole can be accomplished by treatment with DDQ in toluene. The sequence is compatible with a variety of chalcone derivatives. Unsymmetrically substituted derivatives with electronically dissimilar rings react regiospecifically [Scheme 1.14b), 14JOC11750].



Scheme 1.14

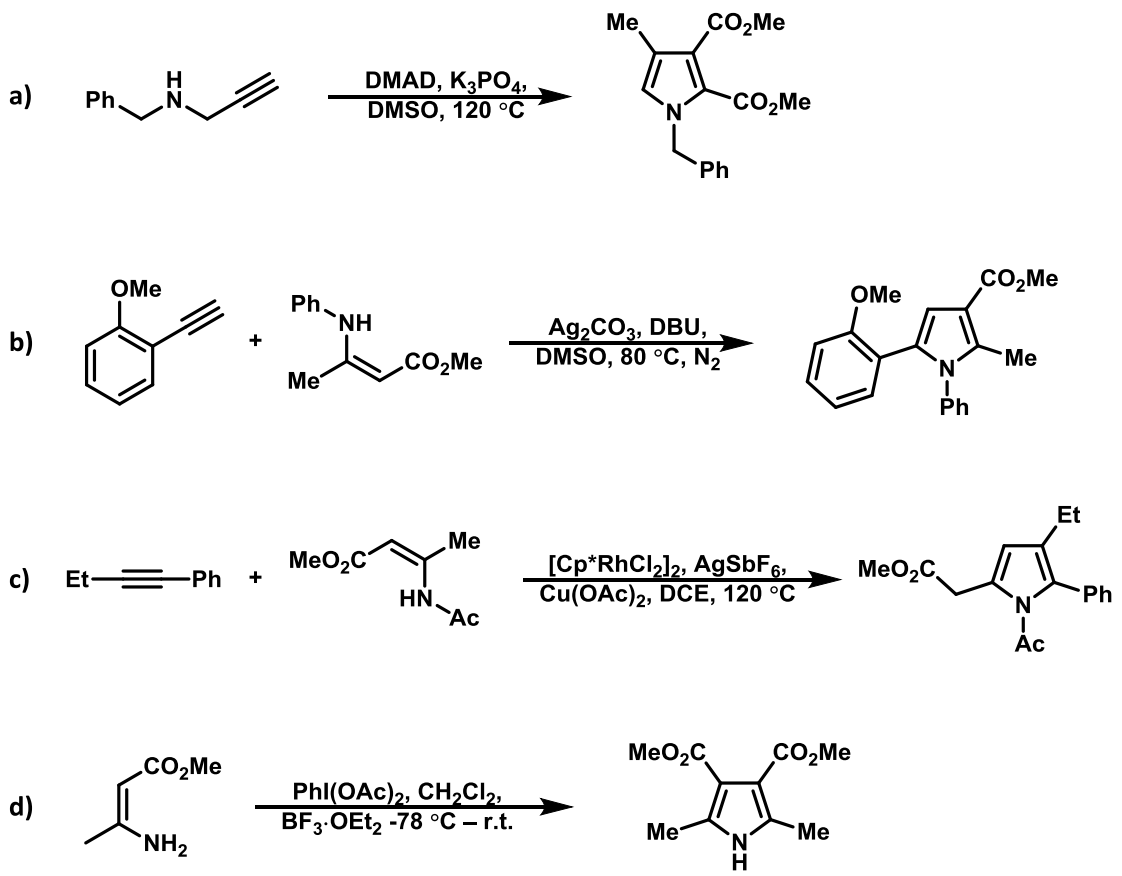
An example of a type IIac reaction is the Trofimov synthesis which can produce 2,3-unsubstituted pyrroles with a cyclic moiety fused at the 4,5-positions [Scheme 1.15a)]. This cyclisation involves the reaction of a ketoxime and an alkyne under strongly basic conditions. The intermediate *O*-vinyloxime undergoes isomerisation to an enamine from which a [3,3]-sigmatropic shift generates an imine aldehyde that cyclises to the product. The product can be tuned by conditions to either be the *NH*- or the *N*-vinylpyrrole [Scheme 1.15a), 10MI316, 15T124]. Sheradsky reported the thermal rearrangement of *O*-vinylketoximes derived from DMAD afforded pyrrole-2,3-dicarboxylates in moderate yield [Scheme 1.15b), 70TL25]. More recently it has been demonstrated that *O*-vinylation of ketoximes and their subsequent conversion to pyrroles is smoothly promoted by a cationic Au(I) complex [Scheme 1.15c), 13JOC920]. Ketoxime *O*-acetates

afford high yields of the corresponding pyrrole-2,3-diesters when treated with DMAD in the presence of Cu(I) under aerobic conditions [Scheme 1.15d), 13CC9597].



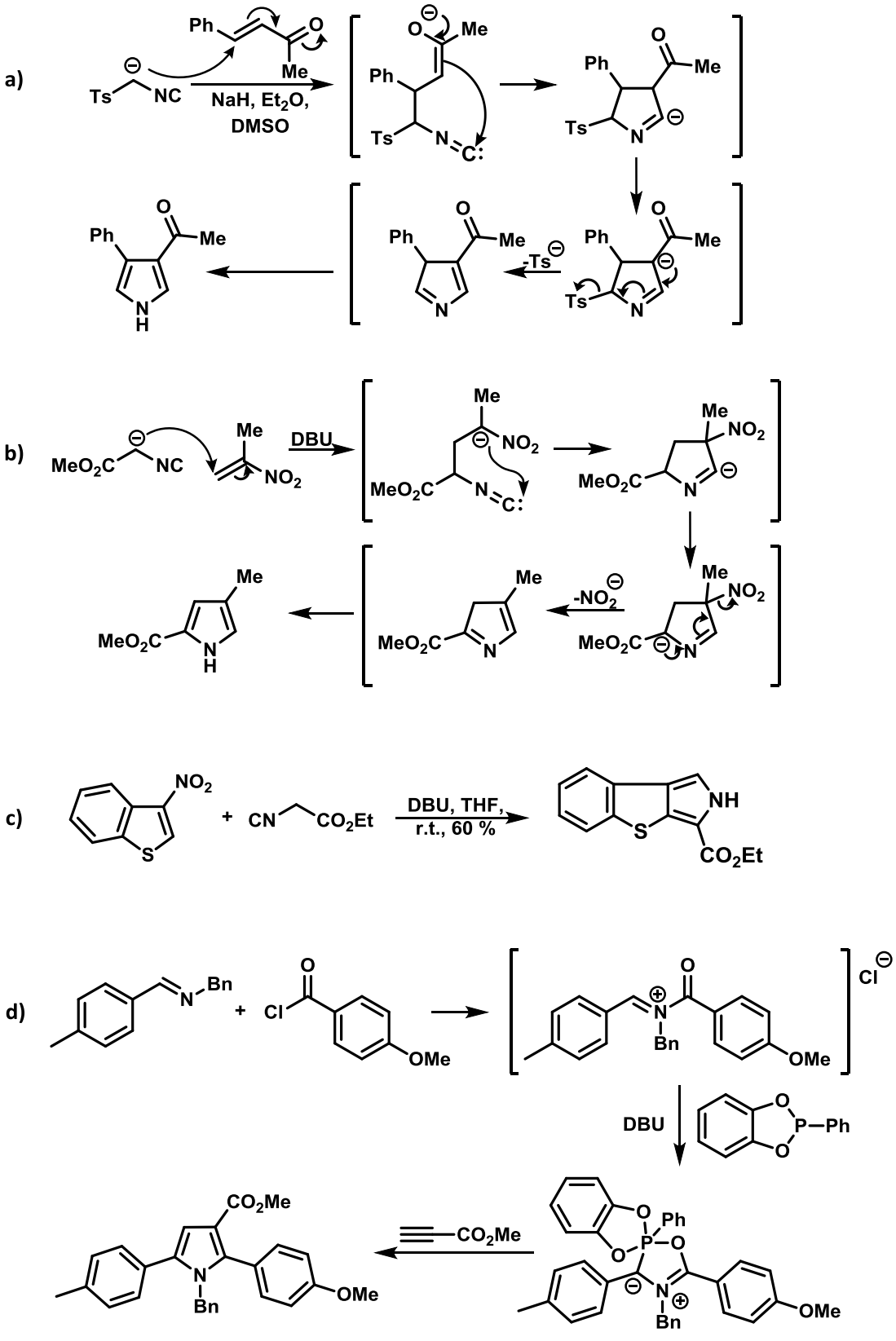
Scheme 1.15

Tetrasubstituted pyrroles can be synthesised from the reaction of a propargylamine and an alkyne in the presence of base. The reaction proceeds *via* a Michael addition followed by cyclisation in a [3+2] IIac type reaction [Scheme 1.16a), 15EJOC3164]. 1,2,3,5-Tetrasubstituted pyrroles can be constructed from the silver-mediated cross-coupling and cyclisation of terminal alkynes and β-enamino esters in good yield [Scheme 1.16b), 13CC7549]. Pyrroles can be synthesised in a [3+2] IIac manner by rhodium(III) catalysed C-H activation of an enamine and subsequent coupling to an unactivated alkyne to afford the pyrrole regioselectively [Scheme 1.16c), 10JA9585]. Enamine esters undergo homocoupling in the presence of (diacetoxyiodo)benzene and $BF_3{\cdot}OEt_2$ to produce symmetrical substituted pyrroles [Scheme 1.16d), 09SL2529].



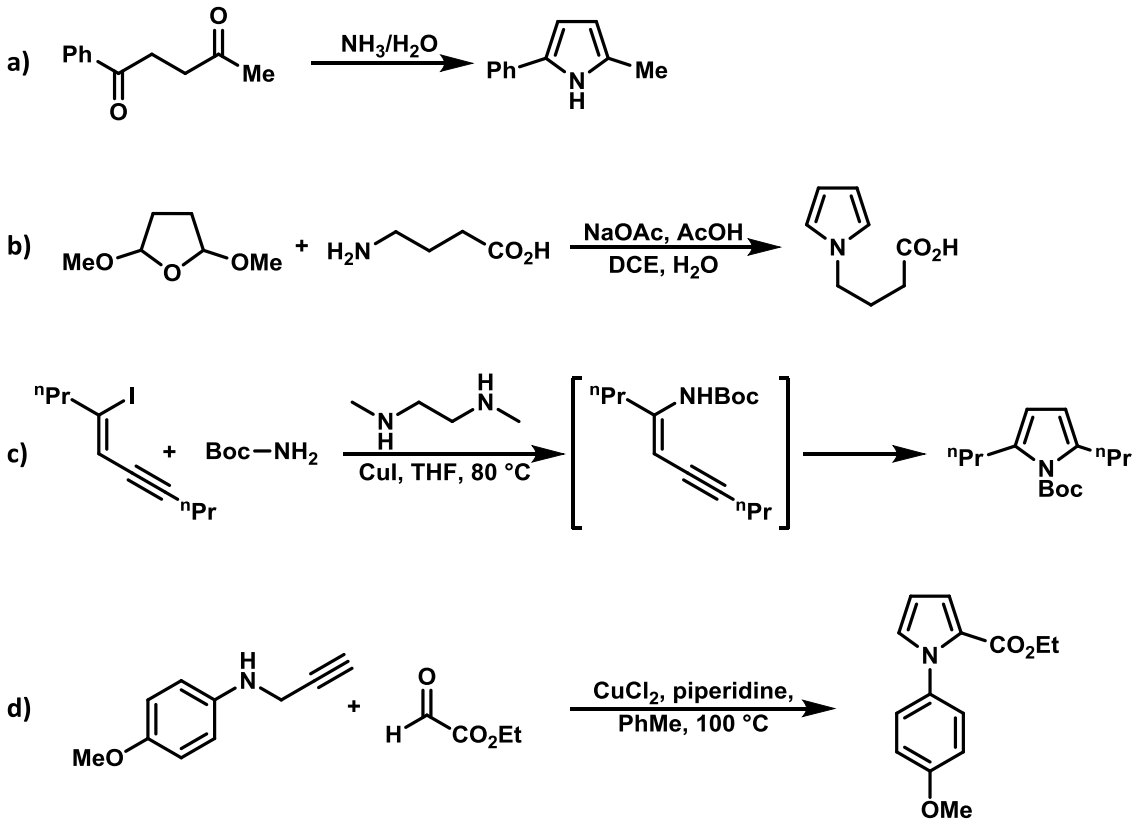
Scheme 1.16

The reaction of tosylmethyl isocyanide (TosMIC) with α,β-unsaturated ketones, esters or nitriles under basic conditions is known as the van Leusen synthesis. The reaction proceeds *via* a Michael-type addition and forms bonds in the b and d positions making it a formal [3+2] type IIbd cyclisation [Scheme 1.17a), 72TL5337]. In a similar manner, the Barton-Zard reaction uses an α-isocyanoacetate compound which reacts with an α,β-unsaturated nitroalkene under basic conditions to give the pyrrole following elimination of nitrite [Scheme 1.17b), 90T7587]. The reaction is also applicable to nitroarenes and provides a means to access fused pyrroles [Scheme 1.17c), 96JCS(P1)417]. Reviews of the synthesis of pyrroles from isocyanides are available [01OR(57)417 and 17CSR1295; 15RSC52769 TosMIC and 12MI385 TosMIC and α-isocyanoacetates]. A further example of a [3+2] IIbd type reaction uses a Wittig-type phosphite derived from catechol which reacts with an iminium species, formed from an aryl imine and an acid chloride, to afford a mesoionic species that subsequently undergoes a 1,3-dipolar cycloaddition to afford the 1,2,3,5-tetrasubstituted pyrrole in very good yield (88%) [Scheme 1.17d), 07JA12366, 12MI123].



Scheme 1.17

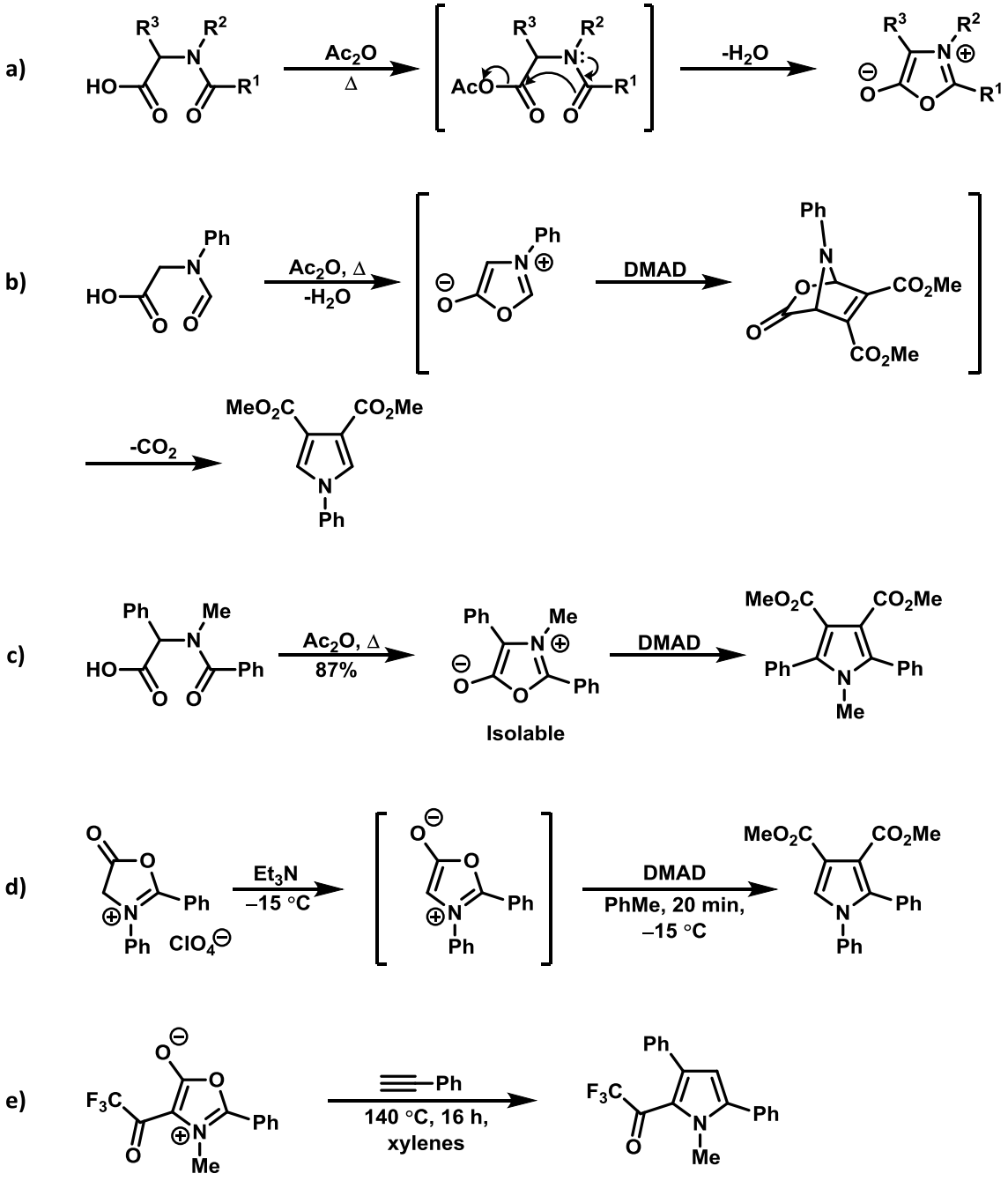
The Paal-Knorr synthesis has been comprehensively reviewed [14AHC(111)95] and is one of the most well-known and simplest methods for pyrrole synthesis and involves the reaction of a 1,4-dicarbonyl compound with ammonia or a primary amine. The reaction can be categorised as a [4+1] IIae type cyclisation and is accompanied by loss of water [Scheme 1.18a), 05MI328]. A variation of the Paal-Knorr synthesis is the Clauson-Kaas reaction. 2,5-Dimethoxytetrahydrofuran behaves in a similar manner to the 1,4-dicarbonyl compound, and as such is a source of succindialdehyde, to produce an *N*-substituted pyrrole in excellent yield [Scheme 1.18b), 06TL799, 09JOC3160]. Another example of a [4+1] IIae type cyclisation is the copper-catalysed C-N coupling reaction of a haloenyne and *t*-butyl carbamate followed by a hydroamidation reaction to afford 2,5-substituted pyrroles in good yield [Scheme 1.18c), 06ACIE7079]. Copper(II) chloride catalyses the [4+1] IIab type cyclisation from ethyl glyoxylate and a propargylamine to afford 1,2-substituted pyrroles [Scheme 1.18d), 17TL63].



Scheme 1.18

1.4.2 Synthesis *via* Ring Transformation

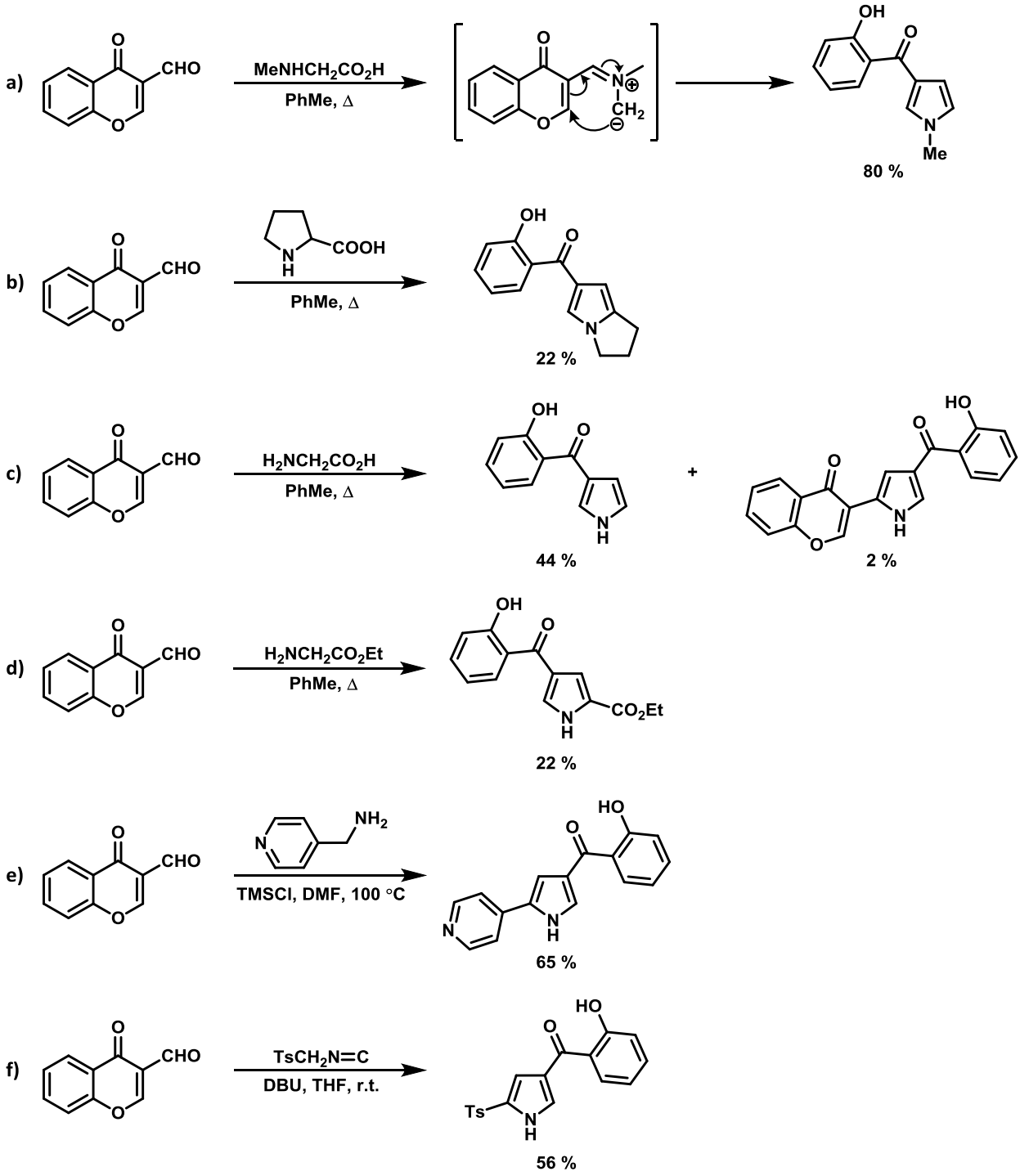
Pyrroles can also be synthesised from other heterocycles. 1,3-Oxazolium-5-olates (münchnones) represent an important group of mesionic heterocycles that have been intensively studied since they were first characterised by Huisgen in 1964, extensive reviews of münchnone chemistry are available [86HC(45)731, 03HC(60)473]. Münchnones can be obtained by the cyclodehydration of *N*-acyl α-amino acids [Scheme 1.19a)] and are effectively masked azomethine ylide equivalents. Unless fully substituted (R^1, R^2 and $R^3 \neq H$) the compounds are not isolable but can be generated and trapped with a 1,3-dipolarophile *in situ* [Scheme 1.19b) and c)] With an alkynyl ester the 1,3-dipolar cycloaddition is followed by a cycloreversion and loss of CO_2 to afford pyrroles in good yield [70CB2611]. 2,3-Disubstituted münchnones can be conveniently generated *in situ* by deprotonation of 3-substituted oxazolium salts at low temperatures and show high reactivity towards DMAD [Scheme 1.19d), 95MI5]. Münchnones generated by a cyclodehydration-acylation sequence of *N*-benzoylsarcosine with trifluoroacetic anhydride can be isolated and react with terminal alkynes to afford a 1,2,3,5-tetrasubstituted pyrrole regioselectively [Scheme 1.19e), 16EJOC2789]. A regioselective 1,3-dipolar cycloaddition of a complex münchnone has been employed in the synthesis of atorvastatin [15TL3208].



Scheme 1.19

3-(2-Hydroxybenzoyl)pyrroles are obtained from the condensation reaction of 3-formylchromone with α-amino acids [Scheme 1.20a–c), 85JCS(P1)1747]. A 1,5-dipolar cyclisation of an *in situ* generated azomethine ylide has been invoked to rationalise formation of the products [07T910]. In a similar vein pyrrole-2-carboxylic esters can be generated from ethyl glycinate [Scheme 1.20d), 85JCS(P1)1747] together with complex pyridine derivatives. With (aminomethyl)heteroarenes, under trimethylsilyl chloride catalysis 5-heteroarylpyrroles can be

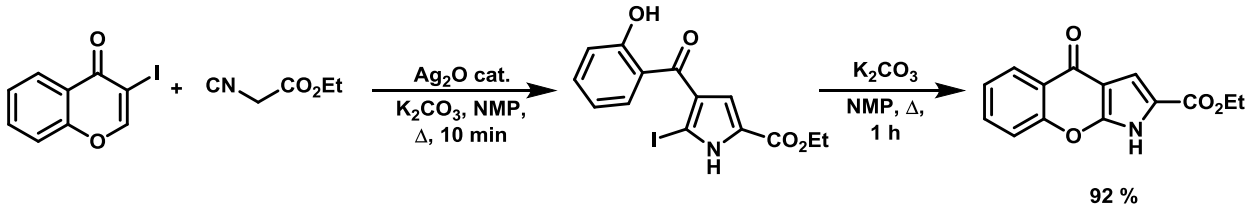
obtained in good yields [Scheme 1.20e), 08T5933]. 2-Tosylpyrroles are obtained *via* conjugate addition of the TosMIC anion to 3-formylchromone [Scheme 1.20f), 07T7828].



Scheme 1.20

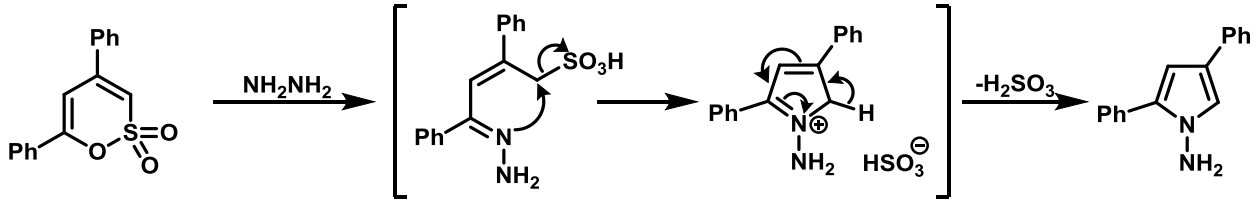
In the presence of Ag_2O and base, ethyl isocyanoacetate undergoes a complex series of reactions initiated *via* conjungate addition of an isocyanide-Ag(I) complex to 3-iodochromone and culminating in the formation of a 5-iodopyrrole-2-carboxylate. Prolonged heating of the latter with

K_2CO_3 results in cyclisation to the benzopyrano[2,3-*b*]pyrrole system, the key structural motif of the pyralomicin antibiotics [15OL5590, Scheme 1.21].



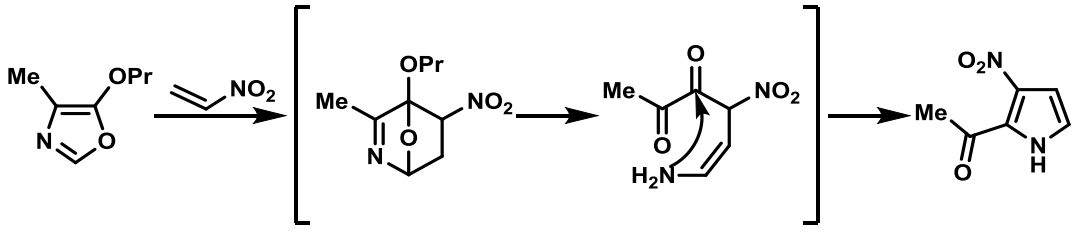
Scheme 1.21

4,6-Diphenyl-1,2-oxathiin 2,2-dioxide, available in high yield from the reaction of phenylacetylene with SO_3-dioxane complex, undergoes nucleophilic addition of hydrazine to C-6 with concomitant ring cleavage followed by cyclisation with elimination of H_2SO_3 to give 1-amino-2,4-diphenylpyrrole [Scheme 1.22, 16ARK(iii)15].



Scheme 1.22

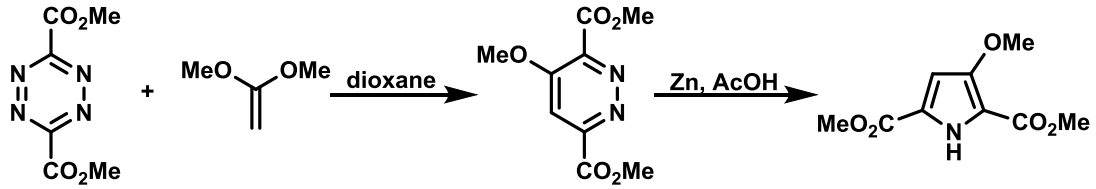
Oxazoles form cyclic adducts when reacted with dienophiles. In most cases the reaction leads to formation of a pyridine ring, however, in the reaction of nitroethylene with an oxazole, the breaking of both the C=N and C–O bonds produces an amino diketone which cyclises further creating a nitropyrrole (Scheme 1.23); this approach and other routes to pyrroles from oxazoles have been reviewed [12CHE59].



Scheme 1.23

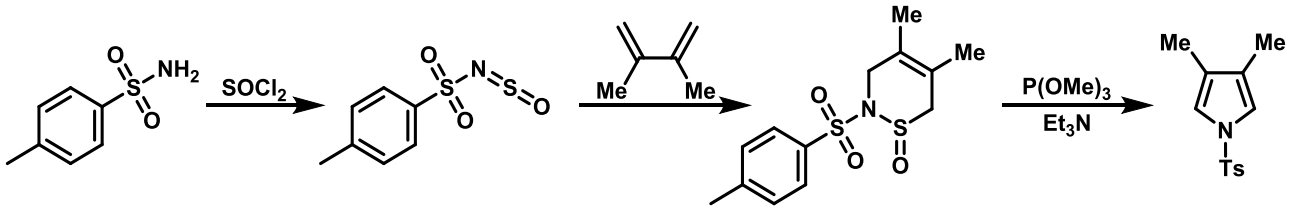
Pyrroles can also be formed from 1,2,4,5-tetrazines, initially the tetrazine undergoes an inverse electron-demand Diels-Alder reaction with an electron rich dienophile to give, following a retro-

Diels-Alder elimination of N_2, a pyridazine. The latter is then reduced to produce the pyrrole in good yield (Scheme 1.24) [84JOC4405].



Scheme 1.24

1,2-Thiazine 1-oxides, available from the [4+2]-cycloaddition of *N*-sulfinylsulfonamides with 1,3-dienes, undergo a ring contraction and desulfurisation upon treatment with trimethyl phosphite and base to afford *N*-sulfonylpyrroles (Scheme 1.25) [94SC175, 04TL7553].

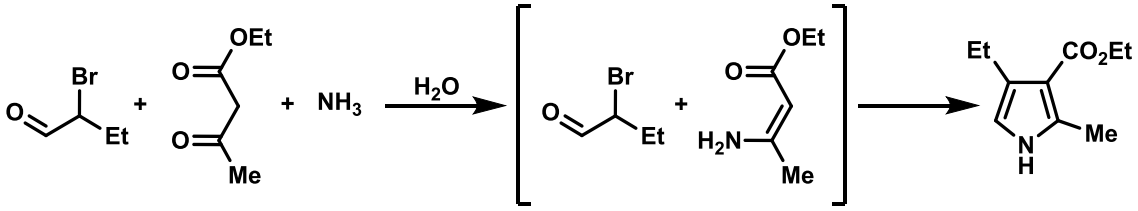


Scheme 1.25

1.4.3 Pyrroles from Multicomponent Reactions (MCRs)

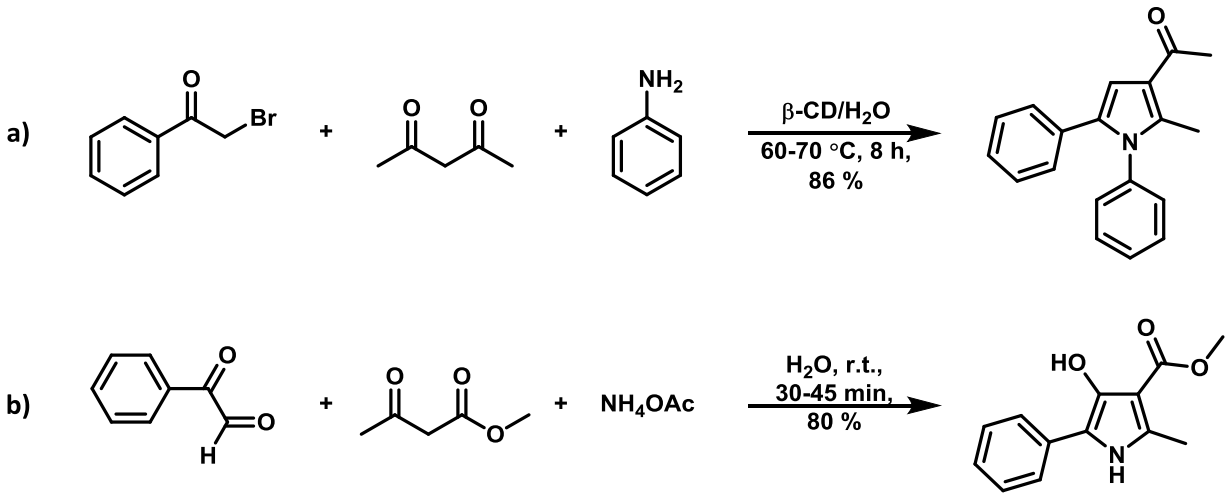
Multicomponent reactions (MCRs) are defined as those that use three or more simple starting materials to access a single reaction product whilst retaining the majority of the components/atoms of the reactants. Multicomponent reactions can be used to access complex heterocycles which may require difficult or lengthy syntheses to otherwise obtain [04EJOC4957, 16ACS236]. Further advantages of MCRs are: reduced step counts, which are highly time consuming and result in lower yields from purification of intermediates and a reduction in the amount of solvents and other materials making this a green chemistry technique [09HCA2118]. The use of MCRs for the synthesis of pyrroles has been reviewed [10CSR4402, 14CSR4633]. The following schemes provide a brief overview of some of these reactions.

Whilst the Hantzsch synthesis of pyrroles could be categorised as a [3+2] type IIac reaction (Scheme 1.15), it is perhaps more appropriately classed as a MCR (Scheme 1.26). Typically, an enamino carbonyl compound is generated from ammonia and a β-ketoester. The α-halo carbonyl compound subsequently reacts with the enamine to afford the pyrrole in moderate yield [70CJC1689].



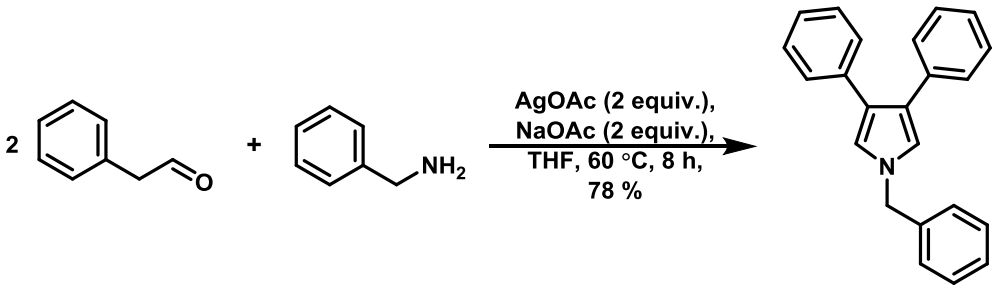
Scheme 1.26

MCRs can be used to access highly substituted pyrroles, for example, 1,2,3,5-tetrasubstituted pyrroles have been obtained using the supramolecular catalyst β-cyclodextrin in the reaction of 2-bromoacetophenone, acetylacetone and substituted anilines [Scheme 1.27a)]. The role of the catalyst is to hold the 2-bromoacetophenone in the cavity and activate it through hydrogen bonding ready for reaction with the diketone followed by the aniline [09HCA2118]. 2,3,4,5-Tetrasubstituted pyrroles can be constructed from glyoxal derivatives, β-dicarbonyls and ammonium acetate. The reaction proceeds *via* an aldol addition followed by a Paal-Knorr type cyclocondensation reaction [Scheme 1.27b), 08JOC2090, 09HCA2118, 10CSR4402].



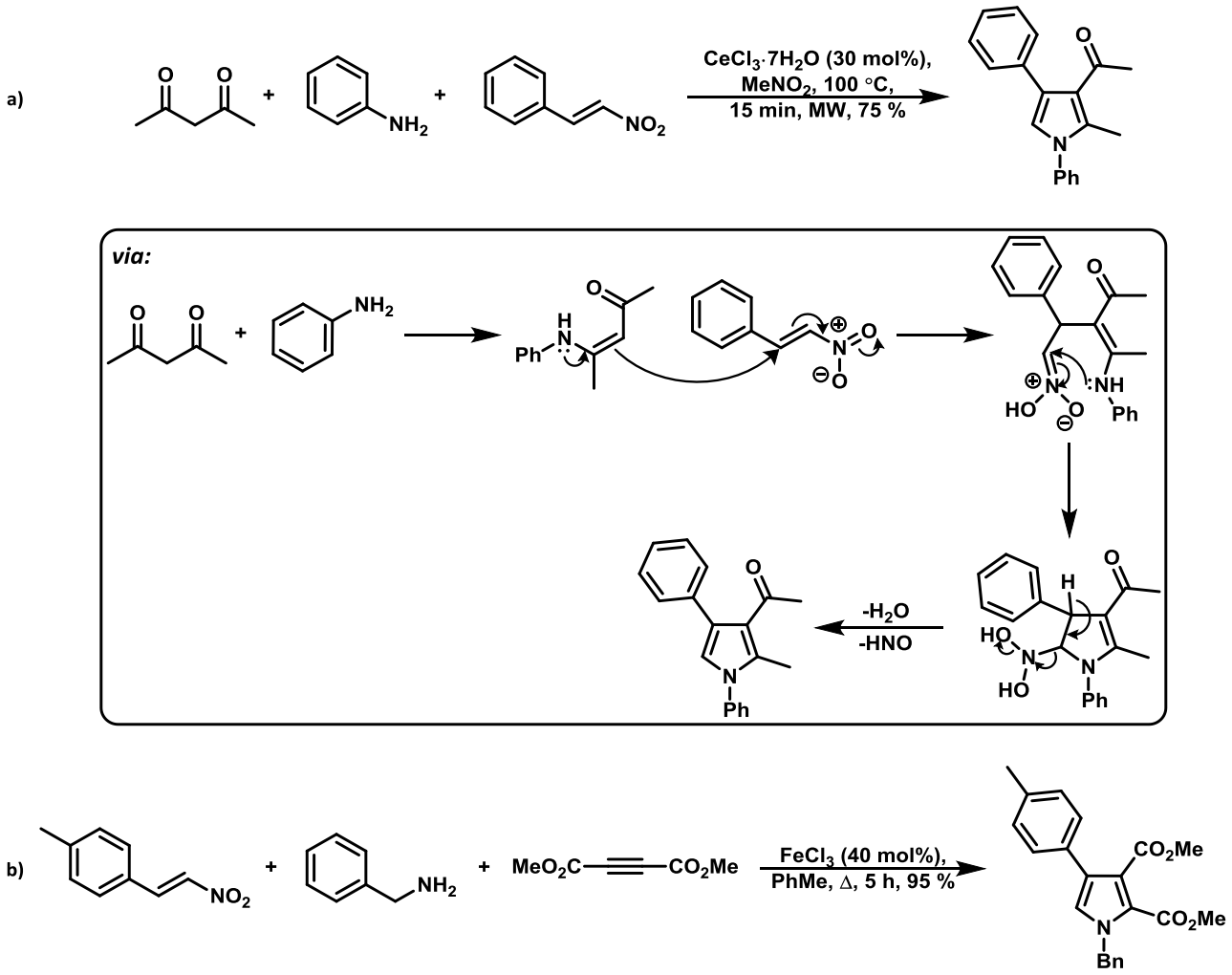
Scheme 1.27

3,4-Disubstituted (2,5-unsubstituted) pyrroles can be synthesised through MCRs from an amine and two equivalents of an aldehyde in the presence of silver acetate (Scheme 1.28). Silver acetate is necessary for oxidative homodimerisation of the formed imines and the reaction proceeds in a similar manner to that of the Piloty-Robinson pyrrole synthesis [10OL4066, 14CSR4633]. The reaction of benzylamine with 2 equivalents of phenylacetaldehyde can also be carried out in solvent-free, ball milling conditions in the presence of manganese(III) acetate [17TL674].



Scheme 1.28

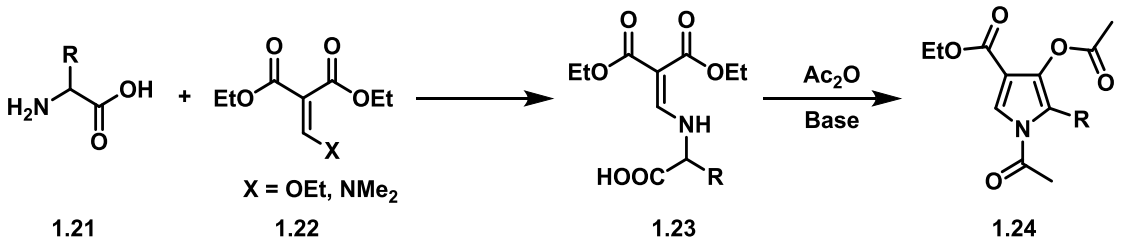
β-Enaminocarbonyls, formed *in situ* from 1,3-dicarbonyls and amines, react with nitroalkenes in the presence of cerium(III) chloride to form 1,2,3,4-tetrasubstituted pyrroles in good yield. The nitro group stabilises the intermediate formed in the reaction and is easily lost as hyponitrous acid [Scheme 1.29a), 13T9076, 14CSR4633]. Tetrasubstituted pyrroles can also be synthesised in excellent yield from nitroalkenes and amines with dialkyl acetylenedicarboxylates in the presence of iron(III) chloride [Scheme 1.29b), 11T5415, 14CSR4633], the reaction proceeds *via* the same mechanism as Scheme 1.29a).


a)
$CeCl_3 \cdot 7H_2O$ (30 mol%),
$MeNO_2$, 100 °C,
15 min, MW, 75 %
via:
-H_2O
-HNO
b)
$FeCl_3$ (40 mol%),
PhMe, Δ, 5 h, 95 %

Scheme 1.29

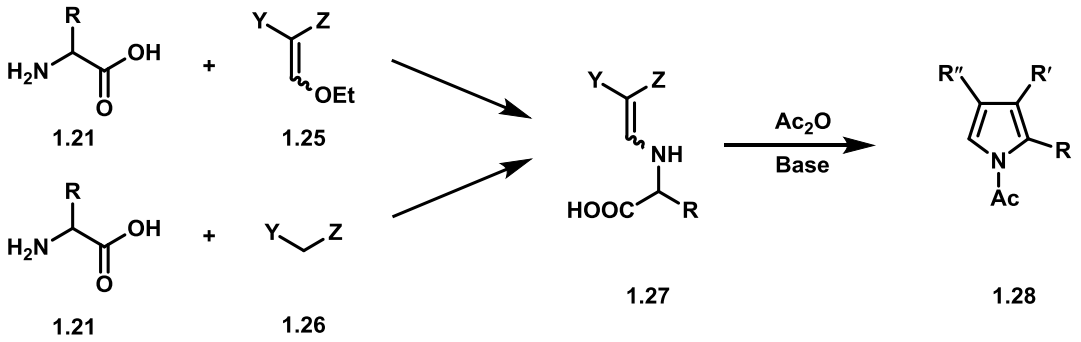
1.5 Aims of the Project

The objective of this research project is to build upon previous studies [02JCS(P1)2799] and exploit the Zav'yalov reaction to access a wide range of pyrroles with a view to generating new building blocks for the synthesis of both natural products and novel materials. Initial work will focus on the synthesis of 4-acetoxypyrrole-3-carboxylates and modification of the functional group in the 5-position of the pyrrole **1.24**. Compounds of the latter type can be obtained by variation of the α-amino acid starting materials **1.21** (Scheme 1.30).



Scheme 1.30

Once an array of ethyl 4-acetoxy-1-acetyl-5-substituted-1*H*-pyrrole-3-carboxylates **1.24** has been synthesised, the functionality at the 3- and 4-positions of the ring can be modified (Scheme 1.31). By substituting the malonate **1.22** for ethyl (ethoxymethylene)cyanoacetate (**1.25**, Y = CO_2Et, Z = CN), (ethoxymethylene)malononitrile (**1.25**, Y = Z = CN) or starting with β-ketoacetonitrile derivatives (**1.26**, Y = COR, Z = CN) a series of enamino acids **1.27** can be synthesised. The acylative cyclisations of the latter derivatives will be investigated.



Scheme 1.31

It is planned to assess the applicability of this approach for the synthesis of halogenated pyrroles and naturally occurring 1,3'-bipyrroles.

Chapter 2

3-Alkoxy-, 3-Acyloxy- and 3-Hydroxypyrrole Derivatives

Chapter 2 3-Alkoxy-, 3-Acyloxy- and 3 Hydroxypyrrole Derivatives

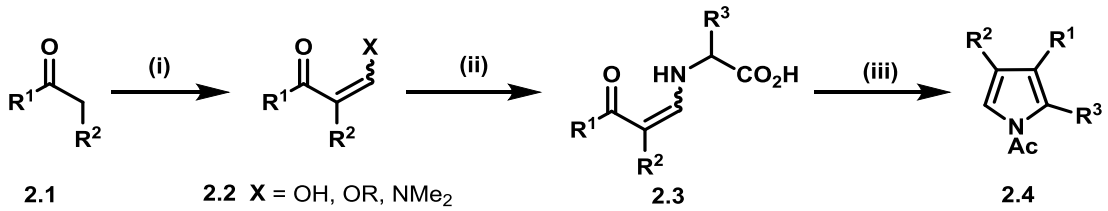
2.1 Synthesis of 3-Hydroxypyrrole Derivatives

2.1.1 Introduction

The high level of interest in pyrroles has consequently ensured that studies of their synthesis have been maintained over many years as will be evident by perusal of any current organic chemistry journal. Many pyrrole syntheses are known and since 1980 these have been reviewed in over 35 papers and monographs [see section 1.4 and 84CHEC-I(4)89, 96CHEC-II(2)119, 08CHEC-III(3)269, 01OPPI411, 11MHC269]. Despite the plethora of methods available to access the pyrrole ring it is surprising that compounds in which the C-2 and C-5 positions are unsubstituted remain relatively inaccessible and few general routes exist [13OPPI171]. Although the addition of activated methyl isocyanides (e.g. $TsCH_2NC$ or EtO_2CCH_2NC) to Michael acceptors affords high yields of pyrroles, introduction of an additional functionality is restricted by the availability of the appropriate isocyanide starting material [01OR417]. A related approach that involves conjugate addition to nitroalkenes (Barton-Zard reaction [90T7587]) also suffers from similar drawbacks.

In preliminary work [99CC289, 02JCS(P1)2799] our group investigated and extended a novel potentially extremely useful approach to 3,4-disubstituted (2,5-unsubstituted) pyrroles **2.4** based upon that reported by Zav'yalov *et al.* [73RCB(22)2505], in 1973 in which an intermediate enamino acid **2.3**, readily available from a ketone **2.1** *via* the 1,3-dicarbonyl compound **2.2** (X = OH or its equivalent X = OR, NMe_2) and an α-amino acid, undergoes cyclodehydration, decarboxylation and acylation when heated in acetic anhydride (Scheme 2.1).

Despite the obvious versatility and flexibility of this pyrrole synthesis it is indeed remarkable that little use of the original Zav'yalov chemistry has been reported [80JMC481, 82JHC1045, 82HCA1694, 91SC1971, 00T7267]. Not one of the major reviews on pyrrole chemistry alludes to it at all.

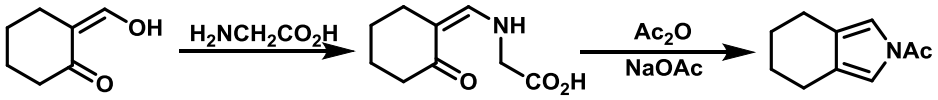


2.1 2.2 **X** = OH, OR, NMe_2 2.3 2.4

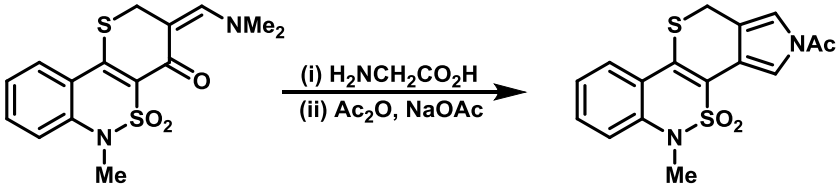
Conditions: (i) DMFDMA; (ii) α-amino acid, NaOAc, aq. EtOH; (iii) anhyd. NaOAc, Ac_2O.

Scheme 2.1

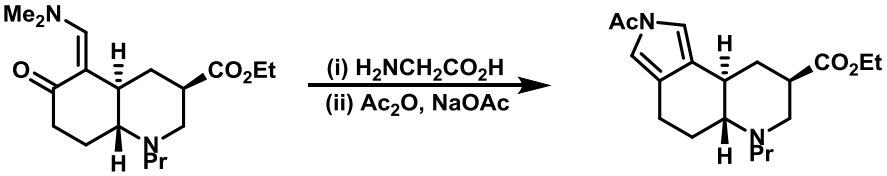
In work published so far, this reaction has been investigated not only with a wider range of α-amino acids than Zav'yalov's original work, but also with a select, rather limited series of 1,3-difunctional compounds, which include 1,3-keto esters, malonic esters and 1,3-diketones. In this way pyrrole-3-carboxylic esters, and 3-acetoxypyrrole-4-carboxylates were obtained; however, only two examples of this cyclisation onto an ester group were explored [02JCS(P1)2799]. The initial aim of the project was to investigate the scope and limitations of this approach in more detail, and to follow this with detailed studies of the cyclisation of enamino acids derived from a wider range of 1,3-bifunctional compounds. It is pertinent to note that of the few examples of the Zav'yalov procedure so far reported, the majority are concerned with the generation of fused-ring pyrroles from enamino acids derived from cyclic ketones. Examples of these are shown in Scheme 2.2.

a) 

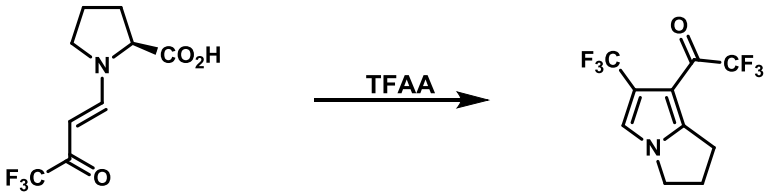
[73RCB(22)2505]

b) 

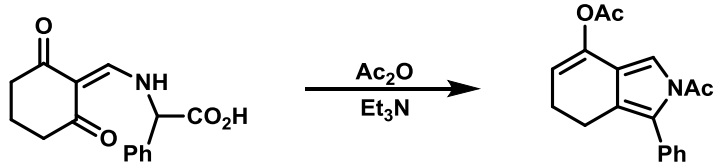
[82JHC1045]

c) 

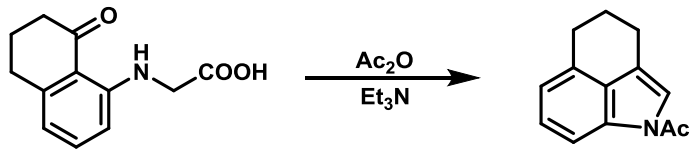
[80JMC481, 82HCA1694]

d) 

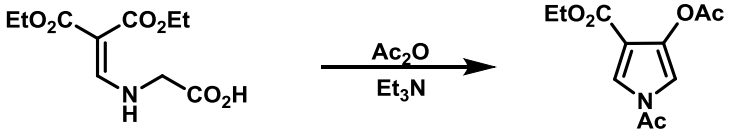
[00T7267]

e) 

[02JCS(P1)2799]

f) 

[06JA4946]

g) 

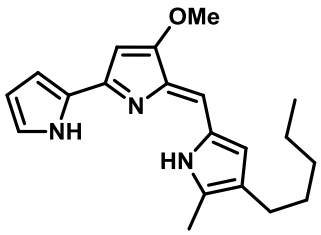
[02JCS(P1)2799]

Scheme 2.2

With the aim of developing the Zav'yalov synthesis of 1,3-bifunctional compounds, as illustrated in Scheme 2.2g), the initial work in the present project sought to prepare a range of enamino acids derived from alkylidene malonates. Two useful starting materials in this regard are diethyl (dimethylaminomethylene)malonate and the commercially available diethyl (ethoxymethylene)malonate (see section 2.2).

2.1.2 3-Alkoxy-, 3-Acyloxy- and 3-Hydroxypyrroles

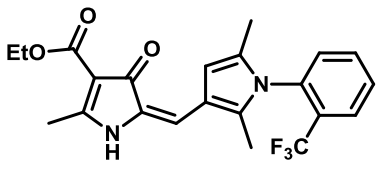
Many 3-hydroxypyrrole derivatives have been described in the literature, including the naturally occurring red pigment, prodigiosin **2.5**, which exhibits anticancer and antimalarial properties [Scheme 2.3, 15RSC10899].



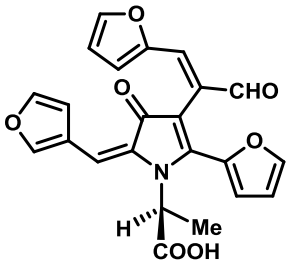
2.5

Scheme 2.3

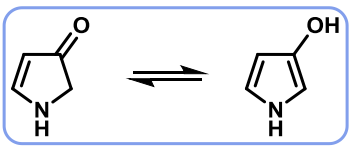
A synthetic bipyrrolemethine derivative, which also has antimalarial properties is **2.6** which contains a pyrrol-3-(2*H*)-one moiety [13JMC2975]. Pyrrol-3-(2*H*)-one **2.7** was isolated from a Maillard-type reaction of furan-2-carbaldehyde and L-alanine [Scheme 2.4, 97HCA1843]. Pyrrol-3-(2*H*)-ones can tautomerise to 3-hydroxypyrrole in polar aprotic solvents [Scheme 2.4, 92HC(49-2)352] and when unsubstituted at C-2 exist preferentially as the 3-hydroxypyrrole tautomer in solvents such as DMSO [09S2535]



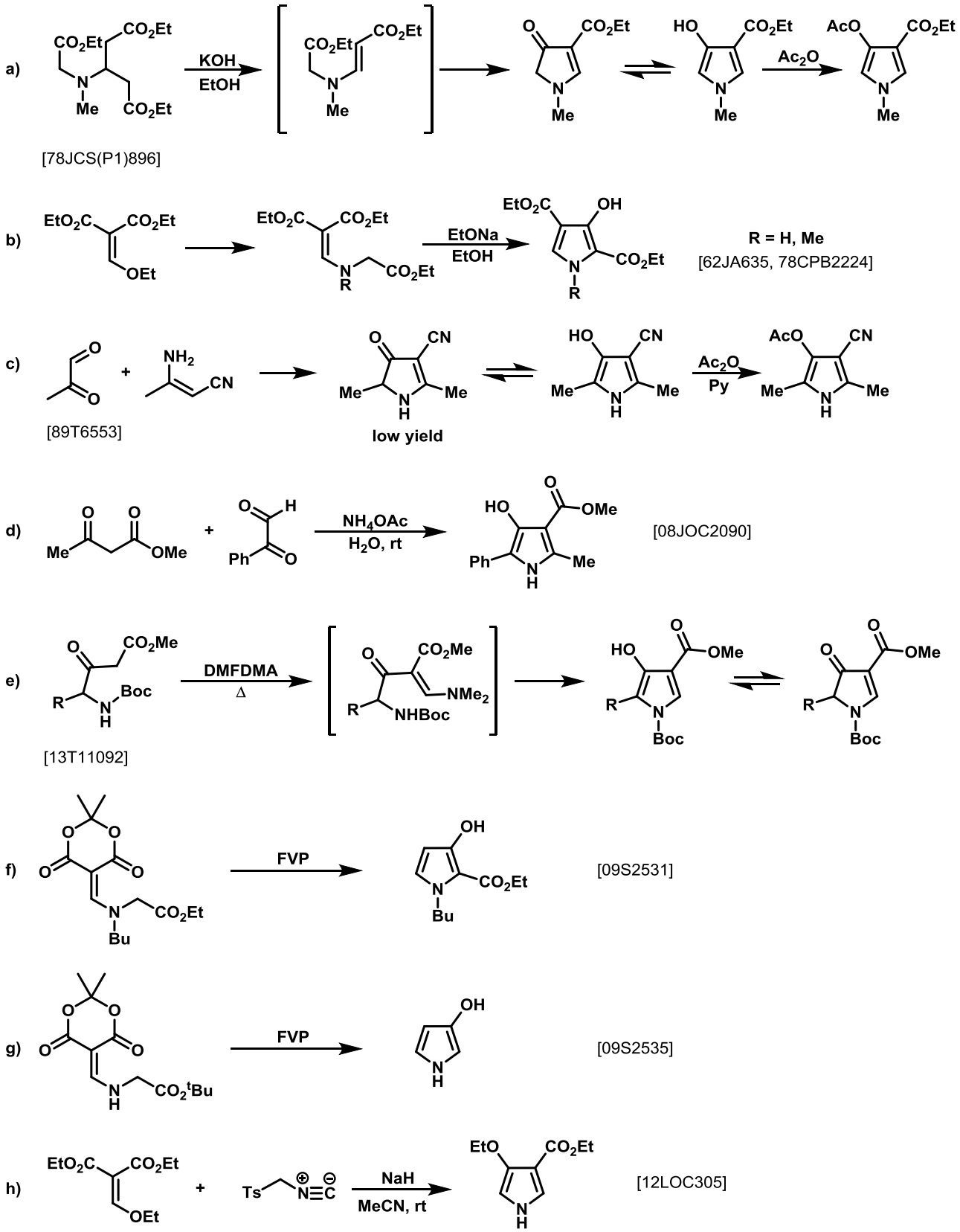
2.6



2.7



Scheme 2.4


a)
KOH
EtOH
Me
[78JCS(P1)896]
b)
EtONa
EtOH
R = H, Me
[62JA635, 78CPB2224]
c)
[89T6553]
low yield
d)
NH4OAc
H2O, rt
[08JOC2090]
e)
DMFDMA
Δ
[13T11092]
f)
FVP
[09S2531]
g)
FVP
[09S2535]
h)
NaH
MeCN, rt
[12LOC305]

Scheme 2.5

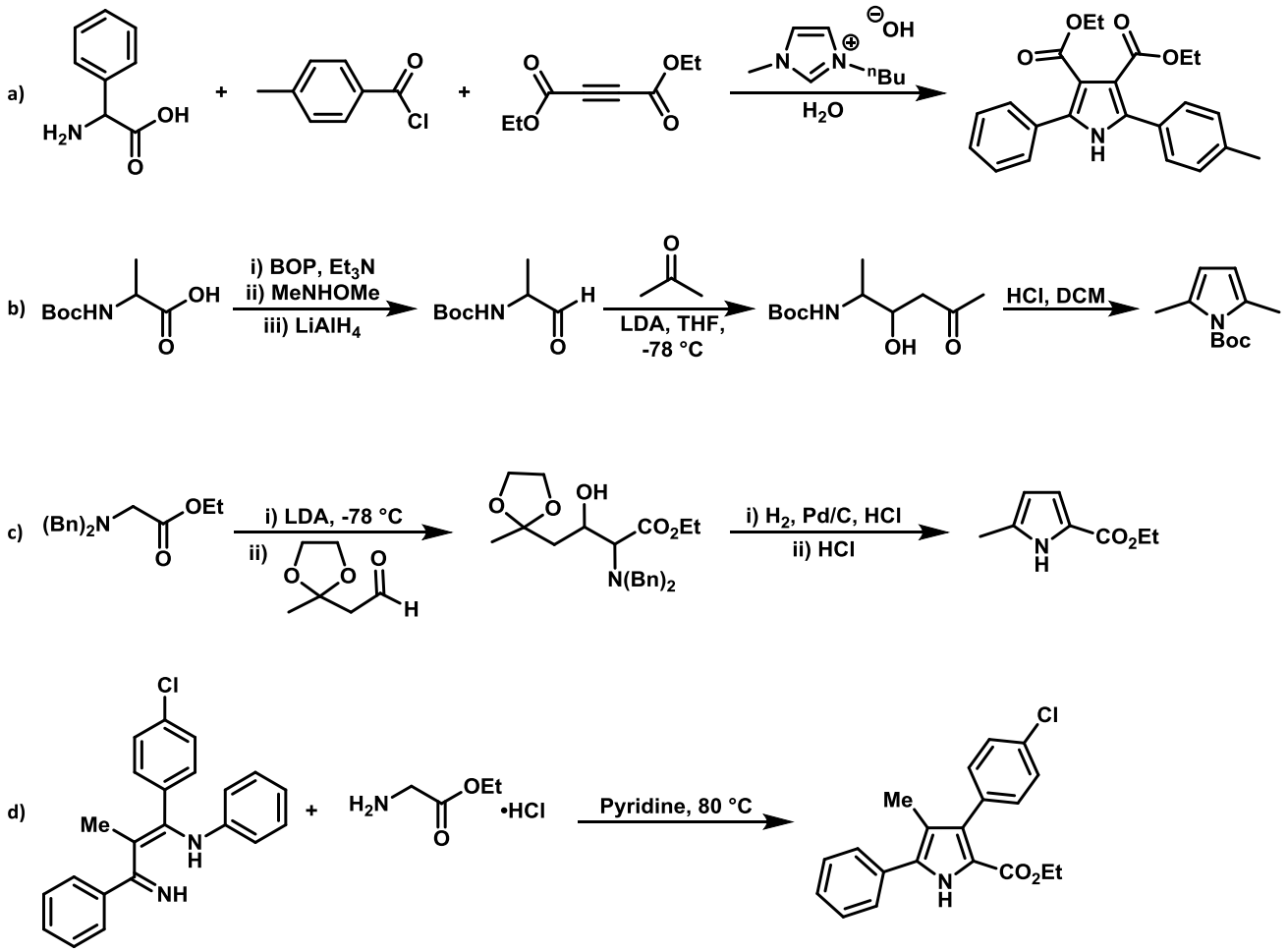
Most of the existing routes to 3-hydroxypyrrole derivatives above, afford compounds which are either heavily substituted, or employ starting materials that are difficult to access [e.g. Scheme 2.5a)]. The Dieckmann-type condensation Scheme 2.5b) affords pyrroles containing an ester substituent at C-2. The diester R = H was used as a starting material in an early total synthesis of prodigiosin [62JA635]. Scheme 2.5c) and Scheme 2.5d) illustrate routes to 2,4,5-trisubstituted pyrroles that employ condensation reactions of 1,2- and 1,3-dicarbonyl compounds respectively. An intramolecular conjugate addition-elimination sequence has been developed to provide access to *N*-Boc-3-hydroxypyrrole derivatives some of which exist as their pyrrol-3-(2*H*)-one tautomers [Scheme 2.5e)]. Ethyl 3-hydroxypyrrole-2-carboxylates have been obtained from Meldrum's acid derivatives [Scheme 2.5f)]. Whilst the parent compound 3-hydroxypyrrole [Scheme 2.5g)] is only accessible using flash vacuum pyrolysis. Noteworthy is the 3-ethoxypyrrole from diethyl (ethoxymethylene)malonate and TosMIC [Scheme 2.5h)].

2.1.3 The Use of α-Amino Acids in the Synthesis of Pyrroles

Figure 2.1 Structure of α-amino acids.

An essential group of starting materials for the Zav'yalov pyrrole synthesis are the α-amino acids. These compounds are cheap, readily available chiral molecules found in nature [15AHC(114)77]. They have a diverse range of functionality at the R group, which, for example, can include linear and branched alkyl chains, alcohols, thiols, (di)sulfides, carboxylic acids, aliphatic or (hetero)aromatic groups and amides (Figure 2.1) and have therefore become important precursors for the synthesis of alkyl- and aryl- heterocycles [95AHC(64)1]. Scheme 2.6 shows some examples of α-amino acids and their esters as starting materials for pyrroles (further examples are in Schemes 1.10, 1.11, 1.12, 1.14 and 1.20). The MCR of an α-amino acid with an acyl chloride and dialkyl acetylenedicarboxylate in an aqueous ionic liquid, [bmim]OH^-, medium proceeds with the formation of tetrasubsitituted pyrroles [Scheme 2.6a), 08SL897]. α-Amino aldehydes can be synthesised from their respective Boc-protected amino acids *via* formation of Weinreb amides, the aldehydes react with the lithium enolates of ketones to form aldol intermediates which subsequently cyclise under acidic conditions to produce 2,5-disubstituted *N*-Boc pyrroles [Scheme 2.6b), 96JOC4999]. Another example of the use of an enolate is shown in Scheme 2.6c), the lithium

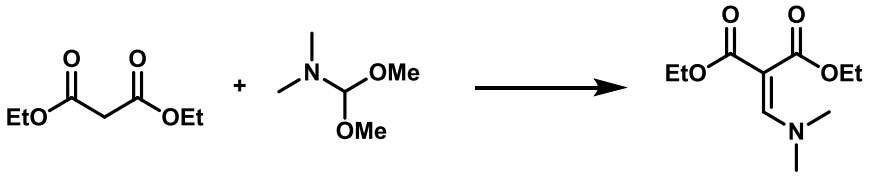
enolate of ethyl *N,N*-dibenzylglycinate reacts with β-ketoacetals, the intermediate, following debenzylation can be cyclised to afford pyrrole-2-carboxylates [89SC763]. Glycine ester hydrochloride initiates an exchange reaction with the imine of an azabutadiene. The resulting intermediate, upon deprotonation, undergoes an electrocyclisation to afford 3,5-diarylpyrrole-2-carboxylates [Scheme 2.6d), 82JOC1696].



Scheme 2.6

2.2 Synthesis of Pyrroles from (Aminomethylene)malonates

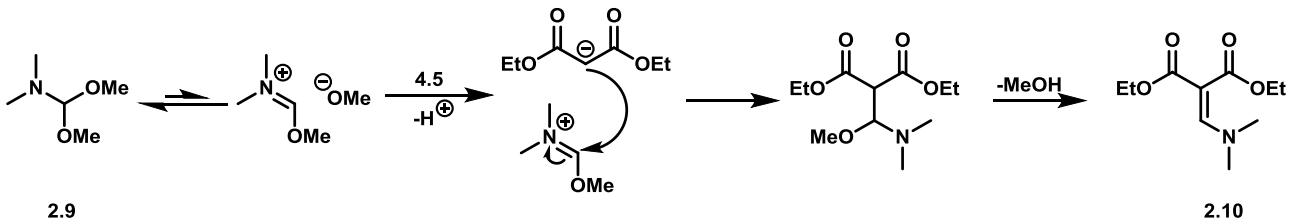
2.2.1 Synthesis of Diethyl (Dimethylaminomethylene)malonate



2.8 **2.9** **2.10**

Scheme 2.7

Diethyl (dimethylaminomethylene)malonate **2.10** was originally prepared following a literature procedure by Wasserman and Han (Scheme 2.7, 84TL3743): Thus, diethyl malonate **2.8** and *N,N*-dimethylformamide dimethyl acetal **2.9** were stirred at ambient temperature. After 6 hours the volatile material was removed *in vacuo* and the residue was subjected to Kügelrohr distillation. The final product impure based on the ^{1}H NMR spectrum and therefore modification to the procedure was necessary. The temperature was increased to reflux for the duration of the reaction and any remaining starting material was removed with an aqueous work-up (brine) and extraction with ethyl acetate, Kügelrohr distillation was used to further purify the product. The modified method provided a pure product in good yield (78 %). The ^{1}H NMR spectrum at +40 °C in $CDCl_3$ (Figure 2.2) displays four signals, a sharp singlet at δ 3 ppm represents the two interchanging *N*-methyl groups; as the temperature is decreased, the signal becomes broader (27 °C) and eventually coalesces (0 °C) before splitting into the two individual singlets (-10 °C). As the temperature is decreased further, the signals become sharper and more defined as the methyl groups are no longer interchangeable (-40 °C). Although known for many years [61CB2278], no spectroscopic data for **2.10** has ever been reported. The mechanism of formation of **2.10** involves initial attack of an iminium species derived from **2.9** (Scheme 2.8).



2.9 **2.10**

Scheme 2.8

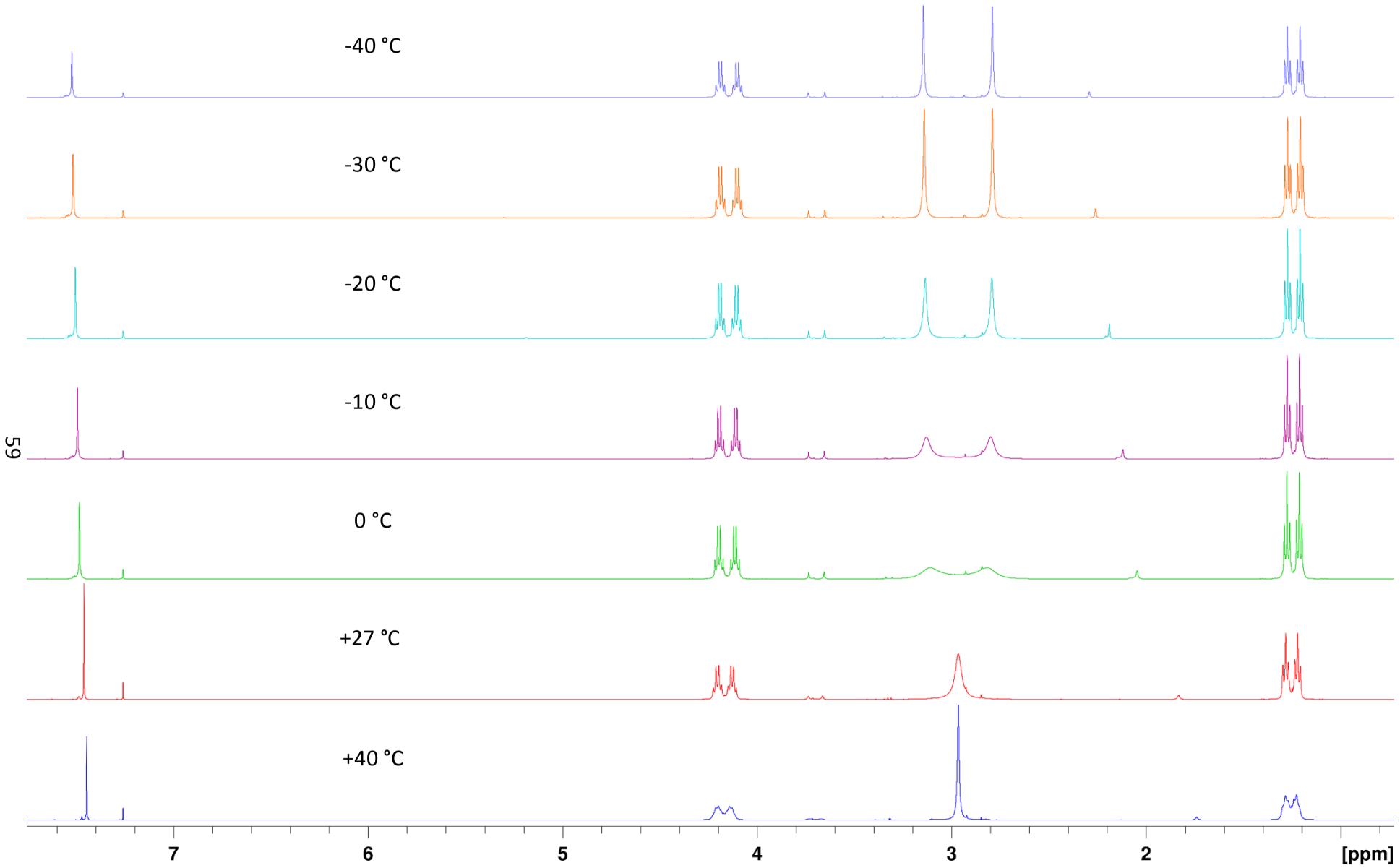


Figure 2.2 Variable temperature ^{1}H NMR spectra of diethyl (dimethylaminomethylene)malonate **2.10** (-40 – +40 °C, 500 MHz, $CDCl_3$).

Coalescence can also be observed in the ^{13}C NMR spectrum for the *N*-methyl signals of enamino ester **2.10**. At 27 °C the methyl signals are not visible [Figure 2.3b)] and can only be seen from their interaction on the 2D HSQC and HMBC spectra. When the temperature is raised to +40 °C, there is a broad signal at δ 43 ppm [Figure 2.3b)], the peaks fully resolve into two individual signals in the spectrum acquired at -40 °C with signals at δ 40 and 47 ppm [Figure 2.3b)].

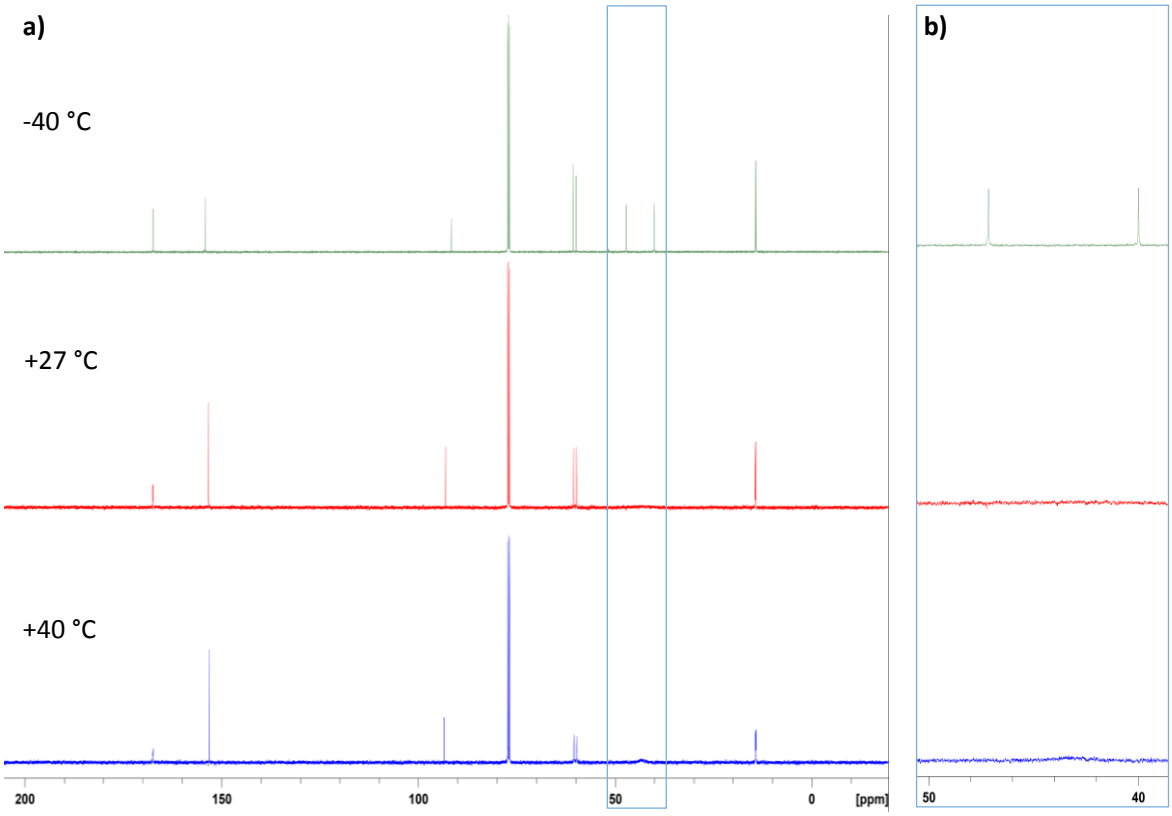
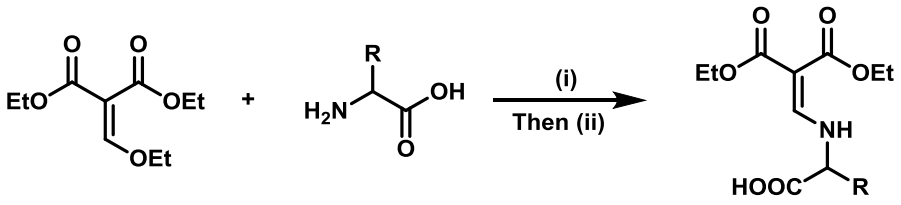


Figure 2.3 a) ^{13}C NMR Spectrum of **2.10** at various temperatures (-40 °C to +40 °C) and b) expansion of 40-50 ppm (125 MHz, $CDCl_3$).

2.2.2 Synthesis of Diethyl 2-(1-carboxyalkylaminomethylene)malonates

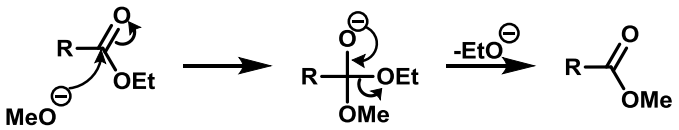


2.11 **2.12a–o** **2.13a–o**

Reagents: (i) KOH, EtOH, Δ; (ii) 2M HCl; **R** as described in Table 2.1

Scheme 2.9

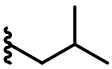
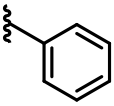
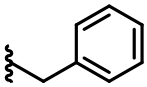
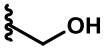
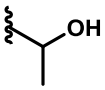
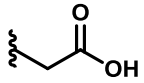
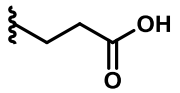
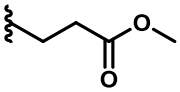
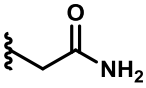
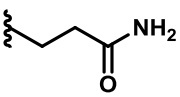
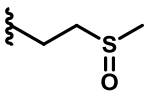
Most of the enamino acids **2.13a–o** required for this work were synthesised from the addition of commercially available diethyl (ethoxymethylene)malonate to the respective α-amino acid in ethanol using potassium hydroxide as the base, with stirring at reflux for a period of 1 hour (Scheme 2.9). The solvent was removed *in vacuo* and the residue dissolved in the minimum volume of water and acidified with 2M hydrochloric acid. The resulting oil was isolated *via* extraction with ethyl acetate. After drying, the solvent was removed to provide the product as a solid or in some cases, as an oil. This method is based on a literature procedure for the *N*-protection of amino acids as their *N*-[2,2-bis(ethoxycarbonyl)vinyl] derivatives [89S544]. The original authors employed methanol as the solvent - however, in the present work this was replaced with ethanol in order to circumvent any potential problems with transesterification [Scheme 2.10, 93CRV1449]. A further change was an increase in reaction time from 5 minutes to 10 minutes (Table 2.1 entries 1–6 and 14).



Scheme 2.10

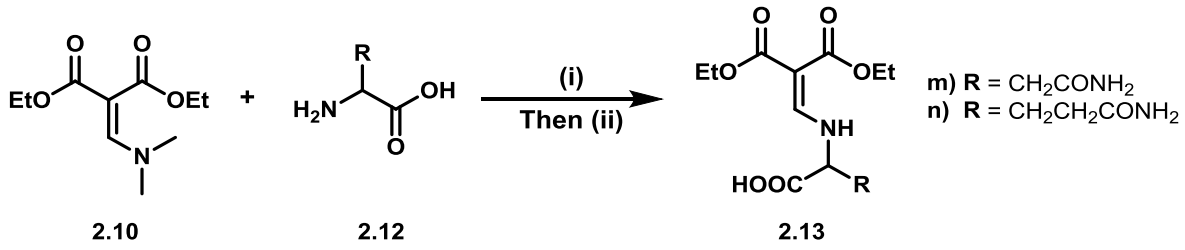
It was found that if the reaction mixture was refluxed for a period of 1 hour in place of stirring for 10 minutes at room temperature, the yields of products improved (Table 2.1 entries 2 and 6). Whilst some of the enamino acids **2.13** have been reported previously, only two were isolated and characterised by the original authors [Table 2.1 entries 1 and 10, 89S544]. The remainder of the compounds have been isolated and characterised for the first time.

Table 2.1 Yields of compound **2.13** from diethyl (ethoxymethylene)malonate.

Entry	Compound 2.13	R	10 mins r.t. Yield (%)[a]	1 h Reflux Yield (%)[a]
1	**2.13a**		88	-
2	**2.13b**		39	58[a] (75)[b]
3	**2.13c**		46	-
4	**2.13d**		28	-
5	**2.13e**		74	-
6	**2.13f**		17	93
7	**2.13g**		-	78
8	**2.13h**		-	67
9	**2.13i**		-	79
10	**2.13j**		-	66
11	**2.13k**		-	72
12	**2.13l**		-	0[c]
13	**2.13m**		-	-
14	**2.13n**		10	-
15	**2.13o**		-	55

[a]50 mmol scale; [b]Yield from large scale reaction (150 mmol); [c]after 24 h at reflux,

It was also found that increasing the scale of the reaction with, for example, DL-alanine **2.12b** further increased the product yield for compound **2.13b** from 58 % to 75 %, when carried out on three times the scale (Table 2.1 entry 2).



2.10 **2.12** **2.13**

Reagents: (i) $NaOAc{\cdot}3H_2O$, aq. EtOH, Δ; (ii) 2M HCl.

Scheme 2.11

The condensation of malonate **2.11** with L-glutamine **2.10n** provided only a low yield (10 %) of **2.13n** (Table 2.1 entry 14). Thus, an alternative approach was adopted to obtain enamino acids **2.13** derived from the amide-containing α-amino acids asparagine **2.12m** (R = CH_2CONH_2) and glutamine **2.12n** (R = $CH_2CH_2CONH_2$). Thus, **2.13m** and **2.13n** were prepared by transamination of diethyl (dimethylaminomethylene)malonate **2.10** in aqueous ethanol with sodium acetate trihydrate as the base [Scheme 2.11, 02JCS(P1)2799]. The reaction mixture was stirred for 4 hours at reflux and subjected to an aqueous workup. Whilst this method proved successful in accessing the enamino acids **2.13m** and **2.13n**, the yields were poor (10 % and 29 % respectively). The reaction conditions were modified further, the solvent and base were substituted for acetonitrile and triethylamine respectively (Scheme 2.12). L-Asparagine **2.9m** was dissolved in acetonitrile in the presence of triethylamine prior to the addition of diethyl (ethoxymethylene)malonate **2.10**, the reaction was carried out under reflux and continued until complete by TLC. The solvent was removed *in vacuo* and the residue, upon aqueous acidic workup, yielded **2.10** as an oil in 55 % yield. The ^{1}H NMR spectrum of compounds **2.10m** and **2.10n** showed two broad singlets for the amide NH_2 protons with approximately 0.5 ppm separation for apparently structurally equivalent protons (Figure 2.4). Non-equivalence of $CONH_2$ protons is occasionally observed. For example, the data reported by Yanada *et al.* for the spectrum of 2-(1-hexynyl)benzamide [14OS27].

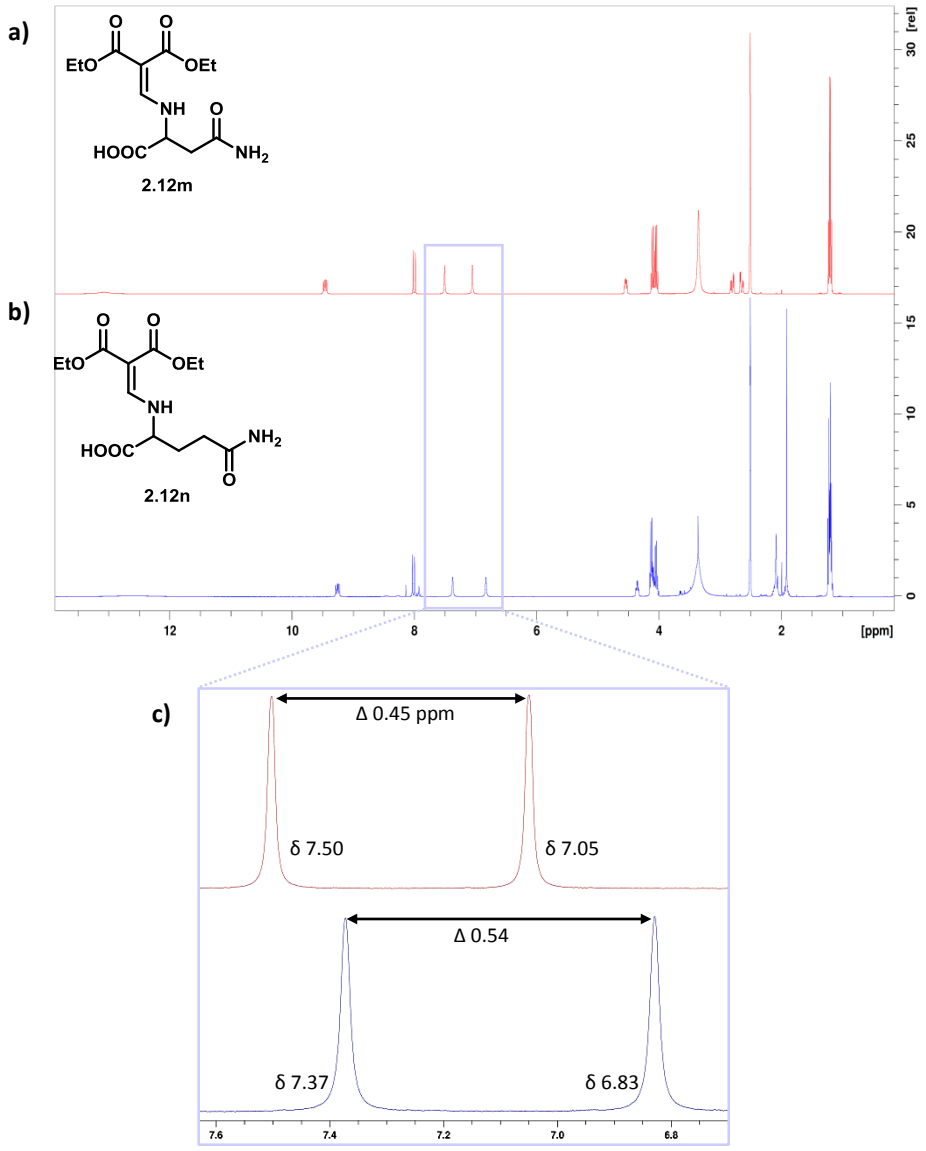
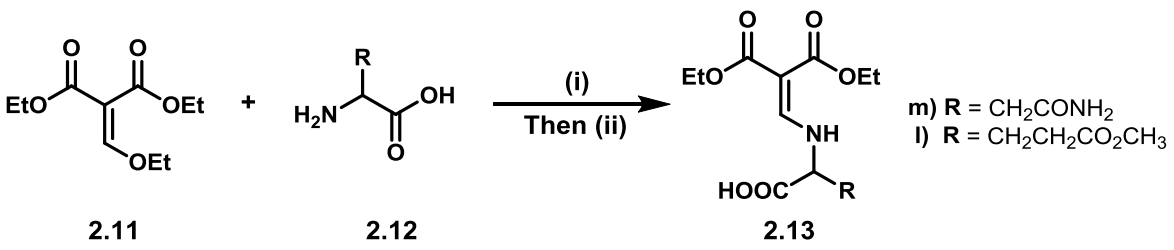


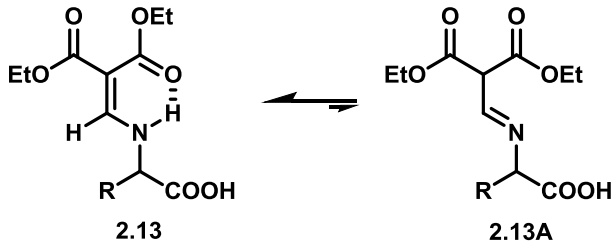
Figure 2.4 ^{1}H NMR spectra of a) **2.12m**, b) **2.12n** and c) Expansion of region δ 6.8–7.6 ppm (400 MHz, DMSO-d_6).



Reagents: (i) Et_3N, MeCN, Δ; (ii) 2M HCl.

Scheme 2.12

The enamino acid from L-glutamic acid 5-methyl ester **2.9l** was inaccessible using the original conditions (**2.11**, KOH, EtOH). It could however be synthesised when the reaction was conducted using the acetonitrile and triethylamine combination. The pure product **2.10l** was prepared in good yield (86 %, Scheme 2.12) using these modified conditions.



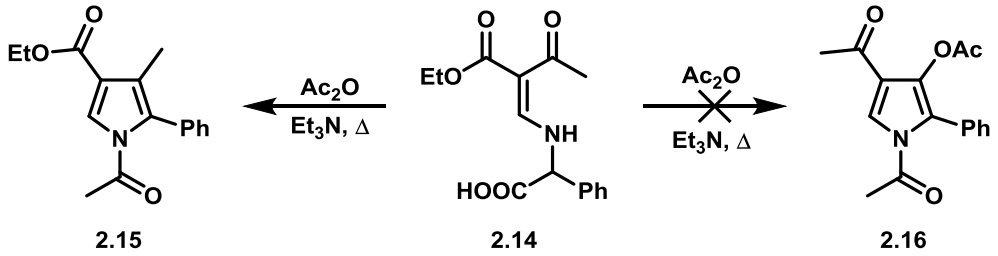
R as defined in Table 2.1

Figure 2.5 Prototropic tautomerisation of **2.13** to **2.13A**.

All the ^{1}H NMR spectra of **2.13a–o** exhibited a peak around δ 9 – 10 as a doublet of doublets due to the nature of the NH proton, the shift indicated the proton is deshielded by the virtue of intramolecular H-bonding to the ester carbonyl group. The magnitude of the larger *J* value (14 Hz) corresponds to coupling between the alkenic and NH protons and reflects their zig-zag arrangement which favours efficient coupling interactions [95MI100]. Coupling between the sp^{3}-methine proton and the NH is of smaller magnitude and was in the range of 7–9 Hz. These data are consistent with a preference for the enamine tautomer **2.13** over the less conjugated imine form **2.13A** (Figure 2.5).

2.2.3 Synthesis of Pyrroles: The Cyclisation of Diethyl 2-(1-Carboxyalkylaminomethylene)malonates

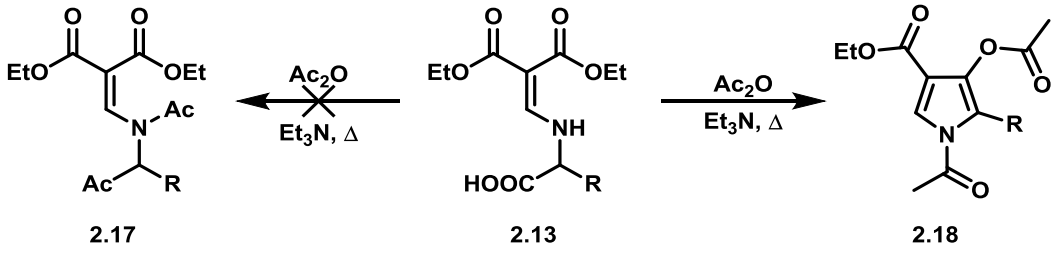
Earlier work by our research group [02JCS(P1)2799] had established that with enamino acids **2.14** derived from 1,3-keto esters, the acylative cyclodehydration-decarboxylation sequence under Zav'yalov conditions, proceeds with cyclisation onto the more reactive ketone carbonyl function. The example in Scheme 2.13 is illustrative, the pyrrole-3-carboxylic ester **2.15** was the sole product [02JCS(P1)2799]. The alternative pathway involving cyclisation onto the ester function to generate **2.16** was not observed.



2.15 **2.14** **2.16**

Scheme 2.13

However, when presented with an ester group as the only possible cyclisation terminus, the enamino acids **2.13** cyclise smoothly to give the 3-acetoxypyrroles **2.18**. The course of the reaction does not appear to be diverted and products such as **2.17** resulting from a Dakin-West reaction [88CSR91] were not observed.

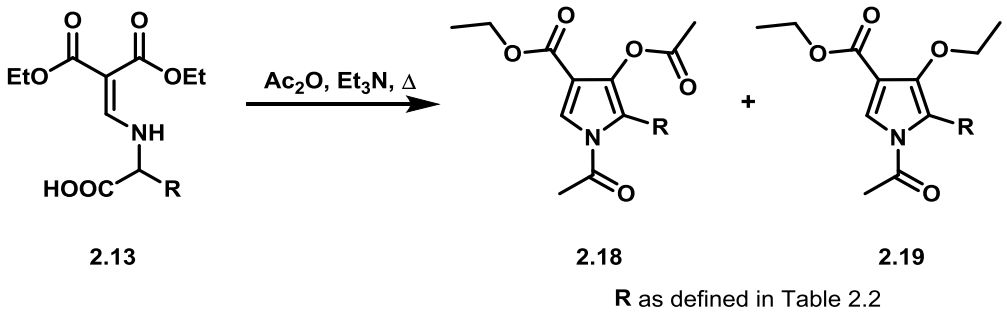


2.17 **2.13** **2.18**

Scheme 2.14

The formation of the 3-acetoxypyrrole **2.18** (R = H or Ph) represents a remarkable result as it provides simple direct access to these 3-hydroxypyrrole derivatives that lack additional functionality at the C-2 position. Existing routes to 3-hydroxy-, 3-acyloxy- and 3-alkoxy- pyrroles are outlined in Section 2.1.2.

The objective of the project was to explore the scope and outcome of the cyclisation of enamino malonates **2.13** with a wider range of R groups than examined initially. Based on previous results [02JCS(P1)2799, Scheme 2.14] the enamino acids **2.13** were each refluxed in acetic anhydride with triethylamine, the reaction was monitored by limewater bubbler until evolution of carbon dioxide ceased. The reaction mixture was cooled, hydrolysed and extracted with dichloromethane. The brown oil so obtained was purified by flash column chromatography. Cyclisation of the enamino acids **2.13a**, **2.13f** and **2.13g** proceeded straightforwardly and each afforded **2.18a**, **2.18f** and **2.18g** only (Table 2.2, entries 1, 6 and 7) in good to moderate yields. However, for other enamino acids (**2.13b, c, d, e, l**), the cyclisation also provided a second product. This additional compound could be isolated by careful flash chromatography (Table 2.2, entries 2–5 and 8). From ^{1}H NMR analysis of these compounds, the spectra were consistent with the ethoxypyrrole structure **2.19** (Scheme 2.15) which was also supported by HRMS data.

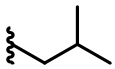
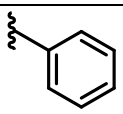
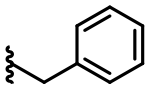
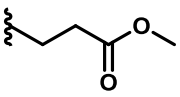


2.13 **2.18** **2.19**

R as defined in Table 2.2

Scheme 2.15

Table 2.2 Yields of pyrroles **2.18** and **2.19** derived from **2.13**.

Entry	R	Pyrrole 2.18	Yield (%)	Pyrrole 2.19	Yield (%)
1		**2.18a**	54	**2.19a**	-
2		**2.18b**	80	**2.19b**	20
3		**2.18c**	49	**2.19c**	10
4		**2.18d**	36	**2.19d**	4
5		**2.18e**	45	**2.19e**	12
6		**2.18f**	20	**2.19f**	-
7		**2.18g**	51	**2.19g**	-
8		**2.18l**	37	**2.19l**	7

Comparative ^{1}H NMR data for **2.18b** and **2.19b** are shown in Figure 2.6, the similarity of the shifts are apparent.

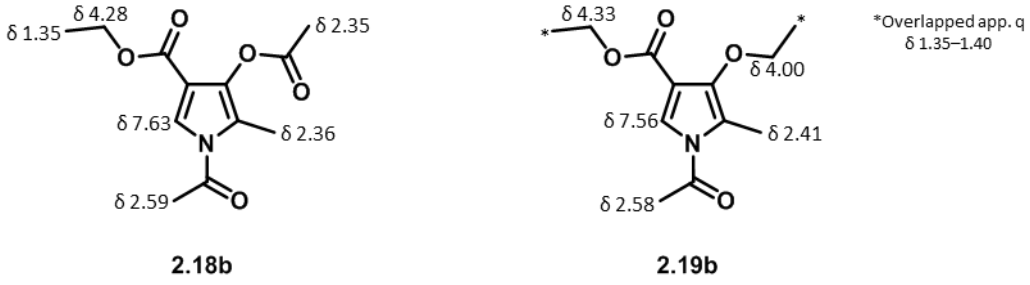
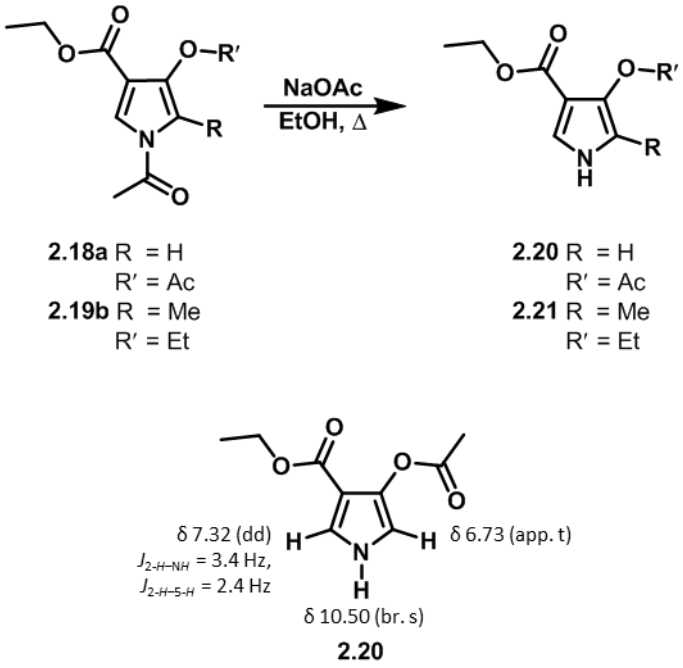


Figure 2.6 Compounds **2.18b** and **2.19b** and their ^{1}H NMR shifts.

Treatment of **2.19b** with NaOAc in hot EtOH [64CJC1524] for 1 hour effected cleavage of the *N*-acetyl group to give **2.21** as an oil in high yield (89 %). This *N*-unsubstituted compound exhibited an upfield shift of the C-5 methyl group that resonated at 2.16 ppm, whilst the 2-*H* proton was

shielded by 0.45 ppm and now appears at δ 7.11 as a doublet by virtue of coupling to the N-*H* proton for which $J_{2\text{-H–NH}}$ = 3.4 Hz [74MI84, 84CHEC-I(4)155]. The N-*H* proton gave rise to a broadened signal centred at 8.16 ppm. Similarly, hydrolysis of **2.18a** provided **2.20** which also exhibited an upfield shift of the 2-*H* proton, this signal was displayed as a doublet of doublets due to it coupling with both the N-*H* and 5-*H* protons (Scheme 2.16).

The NMR data of the hydrolysis product **2.21** taken in conjunction with that from **2.18a** provides support for the 3-ethoxypyrrole structure **2.19b**.



Scheme 2.16

The 3-ethoxypyrrole **2.18c** provided crystals suitable for X-ray crystallography from which the structure was definitively established. The X-ray crystal structure of **2.19c** is shown in Figure 2.7. The bond lengths and angles (Appendix 1) are unremarkable and comparable to those of other pyrroles reported in the literature [Table 2.3, 84CHEC-I(4)155]. Of note however, is the disposition of the *N*-acetyl group in which the bulky methyl unit is remote from the 5-ethyl moiety, presumably to minimise steric interactions.

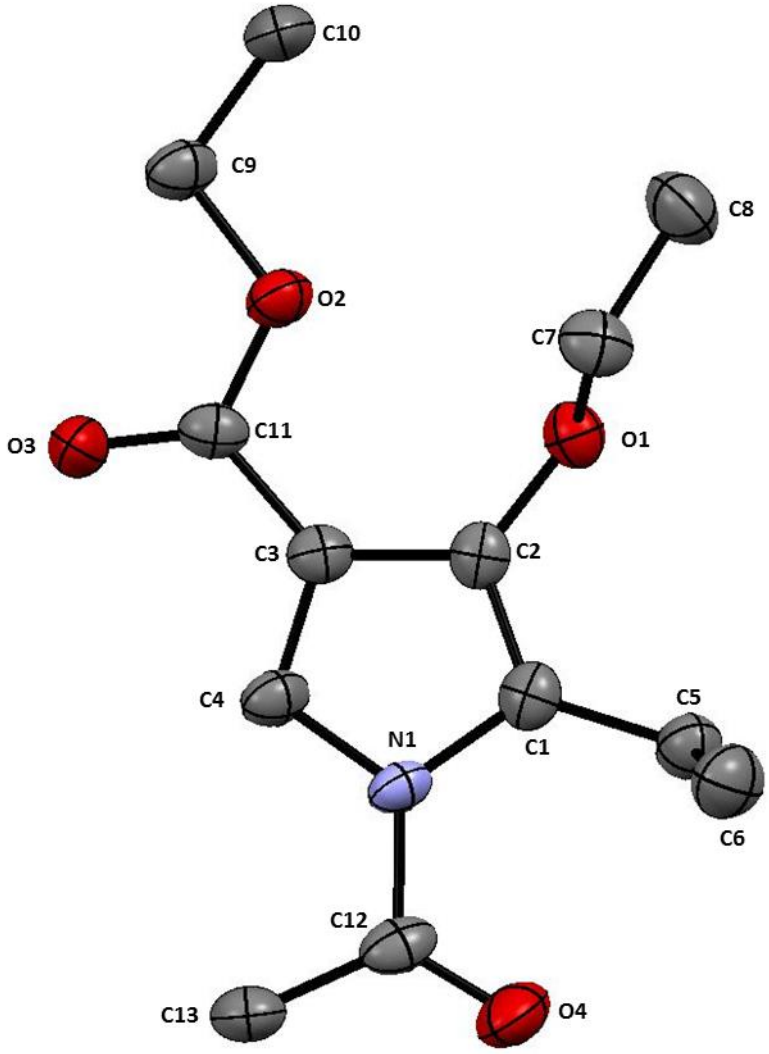


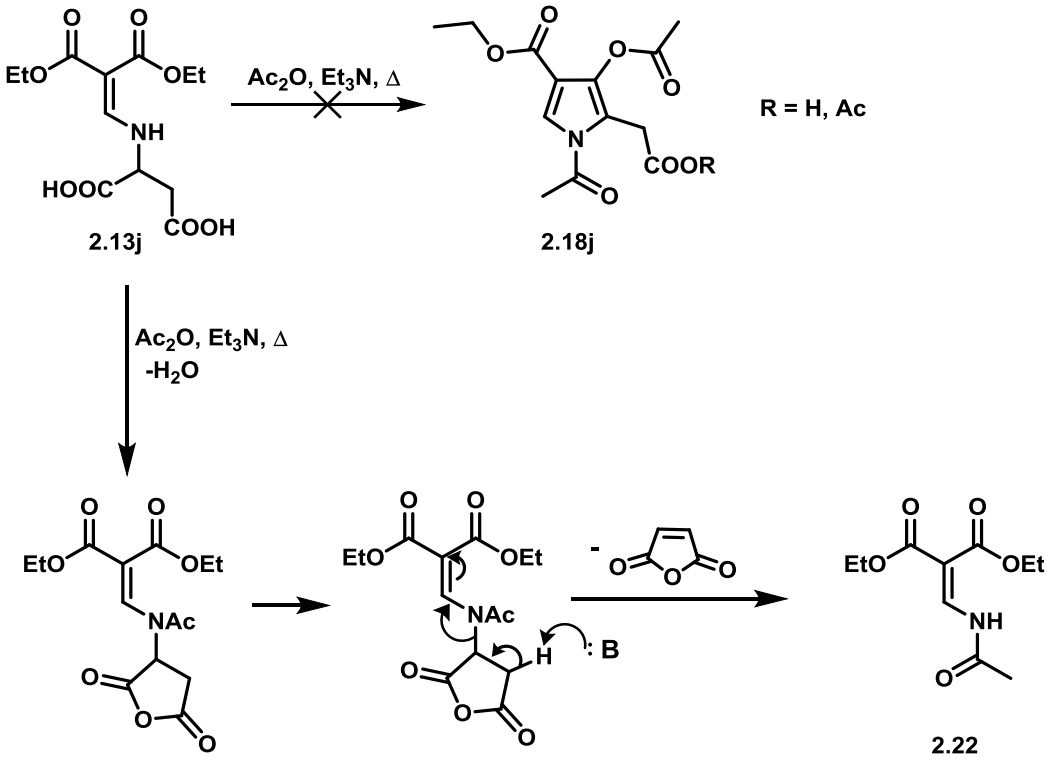
Figure 2.7 ORTEP plot of **2.19c**, hydrogens have been removed for clarity, ellipsoids are at 50 % probability.

Table 2.3 Selected bond lengths and angles for **2.19c**.

Atom 1	Atom 2	Length (Å)	Atom 1	Atom 2	Atom 3	Angle (°)
N1	C1	1.424	C1	N1	C4	109.05
N1	C4	1.379	N1	C1	C2	105.73
C1	C2	1.347	N1	C4	C3	106.60
C3	C4	1.363	C1	C2	C3	110.16
C2	C3	1.432	C2	C3	C4	106.45

Formation of the ethoxypyrroles **2.19** (Table 2.2) is a remarkable result and poses an interesting mechanistic question. Indeed, the pathway by which formation of the 4-acetoxypyrrole-3-carboxylate occurs remains to be resolved. The mechanisms are considered in Section 2.6.

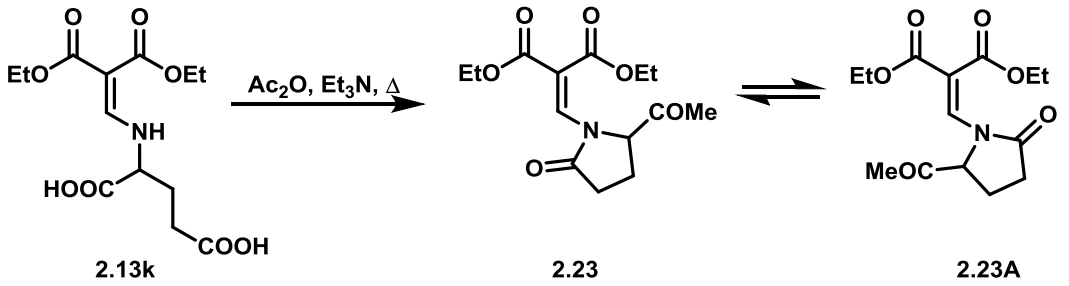
Cyclisation of a number of the enamino acids derived from functionalised α-amino acids gave a number of interesting products. Thus, attempted cyclisation of **2.13j** derived from aspartic acid did not provide the expected pyrrole **2.18j**; instead the only isolable product was diethyl (acetamidomethylene)malonate **2.22** obtained by flash chromatography. The identity of this material was confirmed by comparison with physical and spectroscopic data from the literature [76RC661]. Formation of the product is rationalised *via* cyclodehydration of the carboxyl groups producing a succinic anhydride which facilitates formation of **2.22** *via* a retro-Michael elimination of maleic anhydride. It is not known whether *N*-acetylation occurs prior to or following formation of the cyclic anhydride. It is also possible that *N*-acylation follows elimination of maleic anhydride (Scheme 2.17).



Scheme 2.17

There are remarkably few reports relating to **2.22** which has been previously prepared in good yield by high temperature condensation of diethyl (ethoxymethylene)malonate **2.11** with acetamide [76RC661].

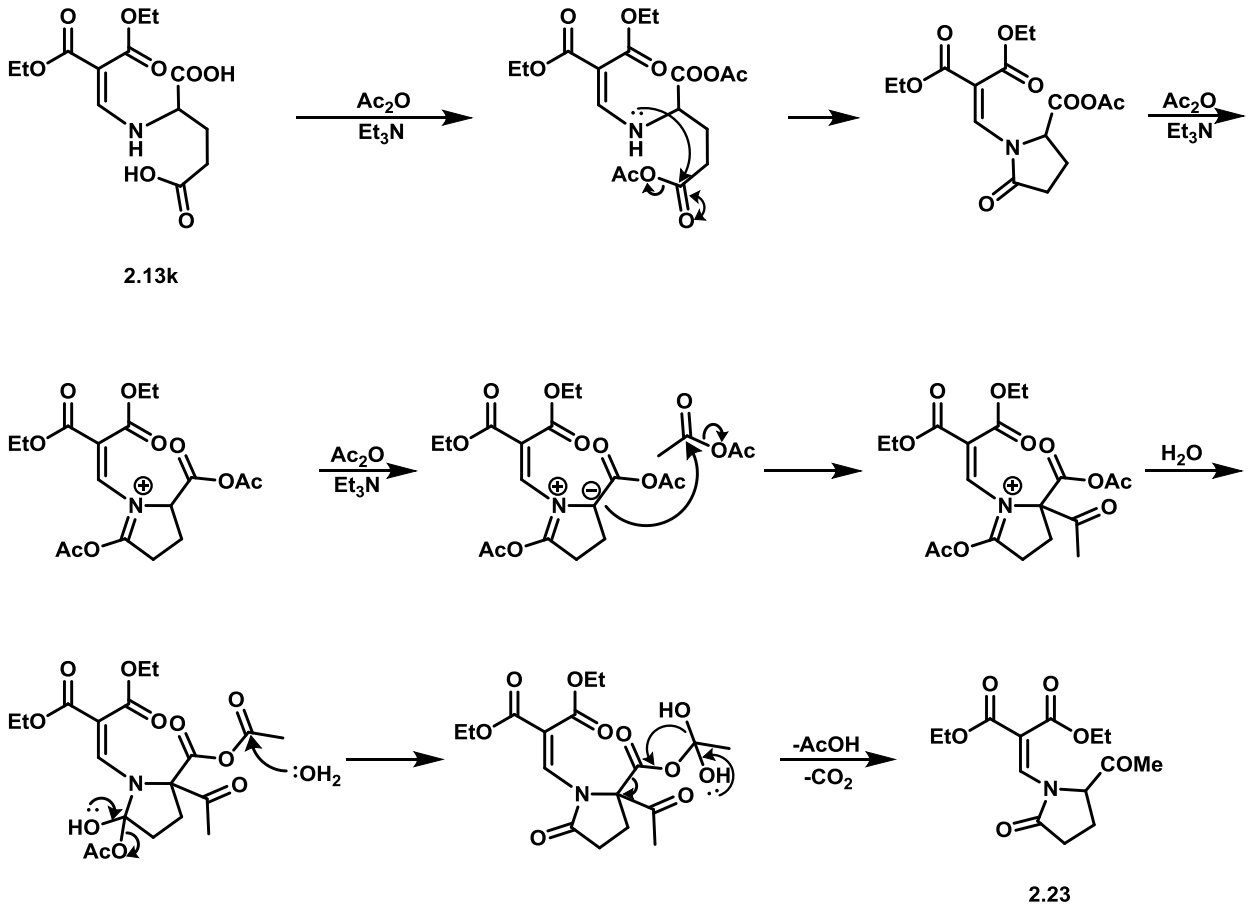
Cyclisation of the homologue of **2.13j**, enamino acid **2.13k**, derived from glutamic acid also gave anomalous results. None of the expected pyrroles were obtained. The only identifiable product was the 5-acetylpyrrolidin-2-one **2.23** formed in 18 % yield (Scheme 2.18).



2.13k 2.23 2.23A

Scheme 2.18

The ^{1}H NMR spectrum of this product revealed the presence of two rotamers (**2.23** and **2.23A**) in a 1:1 ratio, this was apparent by the complexity of the CH_2 signals at δ 2.35–2.66 and the pyrrolidine methine protons which gave rise to a multiplet resulting from superimposed double doublets in the region 4.88–4.91 ppm. The acetyl methyl groups were superimposed and resonated at δ 2.23. The formation of **2.23** does have a literature precedent; it has been previously shown that the Dakin-West reaction (conditions: Ac_2O, NaOAc) [88CSR91] of glutamic acid affords 5-acetylpyrrolidin-2-one [83JCS(P1)395]. A mechanism for the formation of **2.23** is presented in Scheme 2.19.

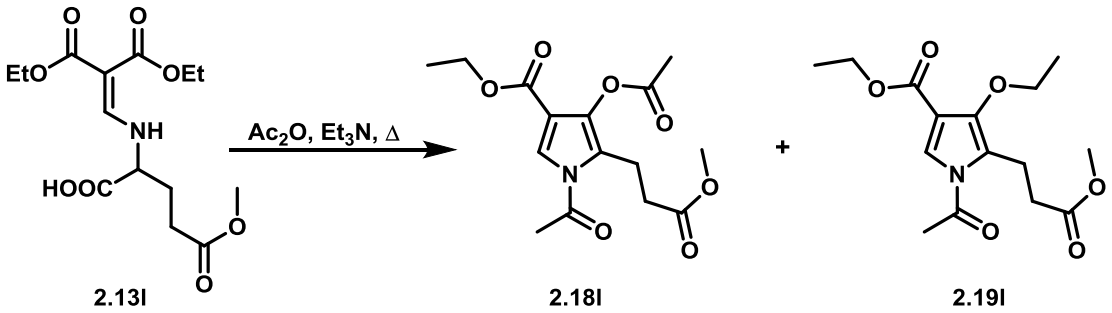


Scheme 2.19

Initially a mixed anhydride is formed which then cyclises to provide the pyrrolidinone ring, as shown. Further acylations occur as above, affording the product on aqueous work-up.

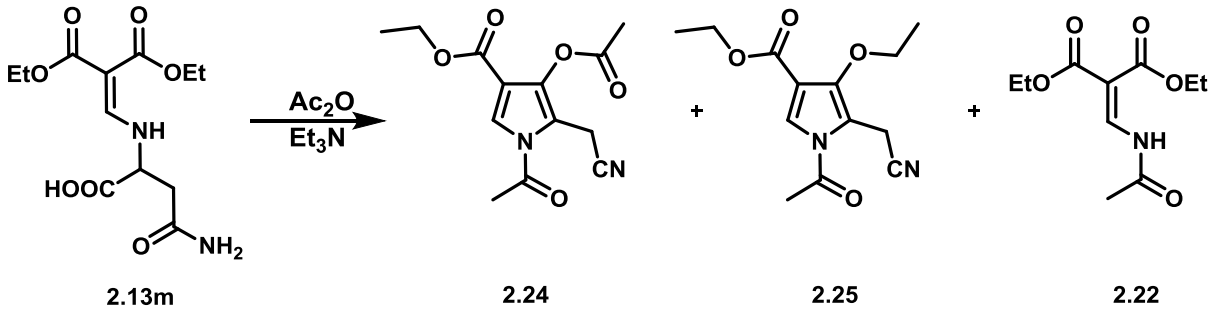
The two enamino acids containing hydroxyl groups, **2.13h** and **2.13i** from serine **2.12h** and threonine **2.12i** respectively, did not cyclise successfully and gave complex ^{1}H NMR spectra for which no distinct structures could be determined. In conjunction, when the TLC was run in 30 % EtOAc in hexane, the resulting plate was indistinct and no clear spot corresponding to a product could be seen.

In contrast, when the 5-methyl ester derivative of glutamic acid, **2.13r** was subjected to cyclisation, none of the Dakin-West product was obtained and the expected pyrrole **2.18r** was obtained in 37 % yield together with the corresponding 4-ethoxypyrrole **2.19r** in 7 % yield (Scheme 2.20).



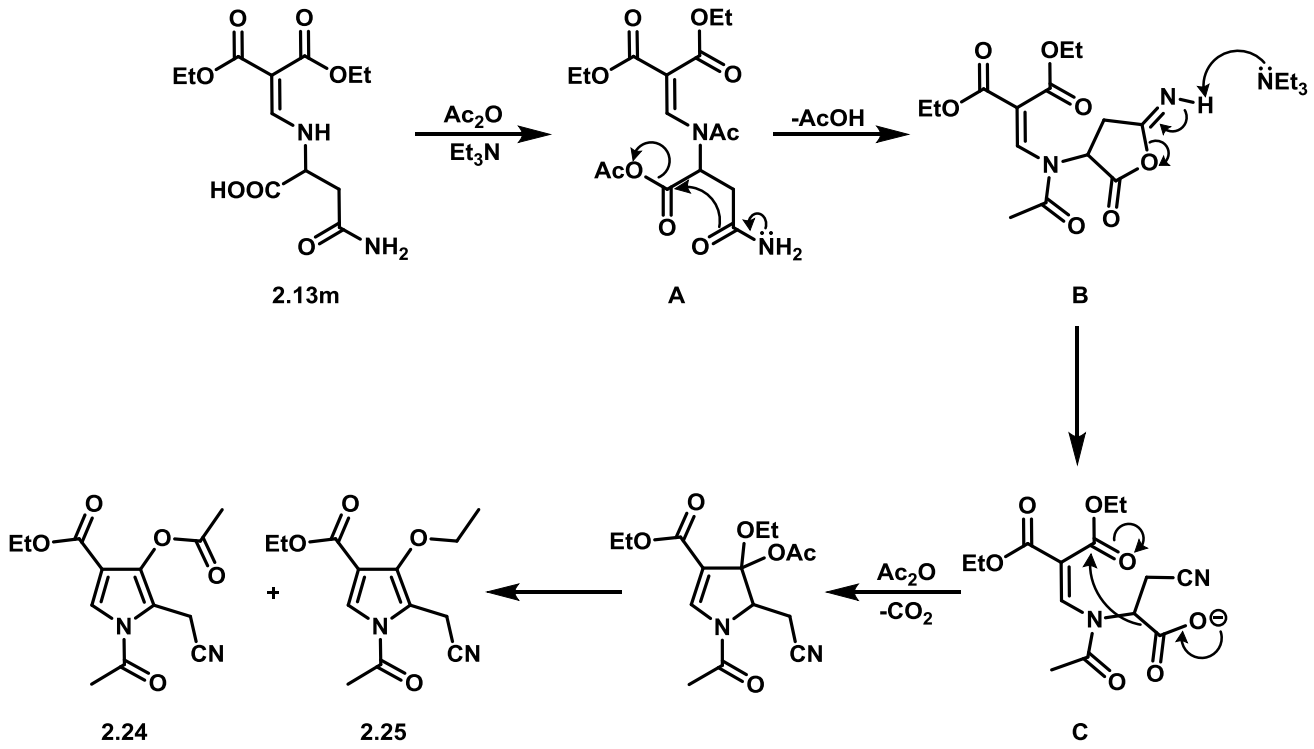
Scheme 2.20

The cyclisation of the asparagine derivative **2.13p**, also resulted in the formation of the diethyl (acetamidomethylene)malonate **2.22** (Scheme 2.17). However, in contrast to **2.13j**, the 4-acetoxy- and 4-ethoxypyrroles (**2.24** and **2.25** respectively) were also isolated; interestingly the amide groups had undergone dehydration to generate a nitrile function (Scheme 2.21).



Scheme 2.21

Formation of the nitrile may occur by direct acylative dehydration of an intermediate pyrroleacetamide. However dehydration of primary amides to nitriles mediated solely by acetic anhydride is not common [99MI1983]. It is possible therefore that the nitriles **2.24** and **2.25** are derived by a pathway analogous to that shown in Scheme 2.17. A possible reaction sequence is depicted in Scheme 2.22. Thus, acylation of **2.13p** affords the mixed anhydride **A** from which displacement of acetate is facilitated by the amide carbonyl function. Subsequent deprotonation of the cyclic imidate (isosuccinimide) **B** leads to the nitrile **C** which is predisposed to undergo cyclisation to the pyrrole ring with concomitant decarboxylation. The mechanism for the cyclisation is considered in more detail in section 2.6.



Scheme 2.22

The presence of the nitrile group was confirmed by the absence of the amide protons in the ^{1}H NMR spectrum and appearance of a signal at δ 115 in the ^{13}C NMR spectrum. Surprisingly, the IR spectrum did not exhibit the characteristic band $\nu_{C\equiv N}$ 2210–2260 cm^{-1}. Crystals of X-ray diffraction quality were grown and ultimately confirmed the structure of product **2.24** (Figure 2.8). The bond lengths and angles are comparable to those of **2.13c** and to values in the literature [Table 2.4, Appendix 2, 84CHEC(4)155], the oxygen atom of the *N*-acetyl group is again directed towards the cyanomethyl group.

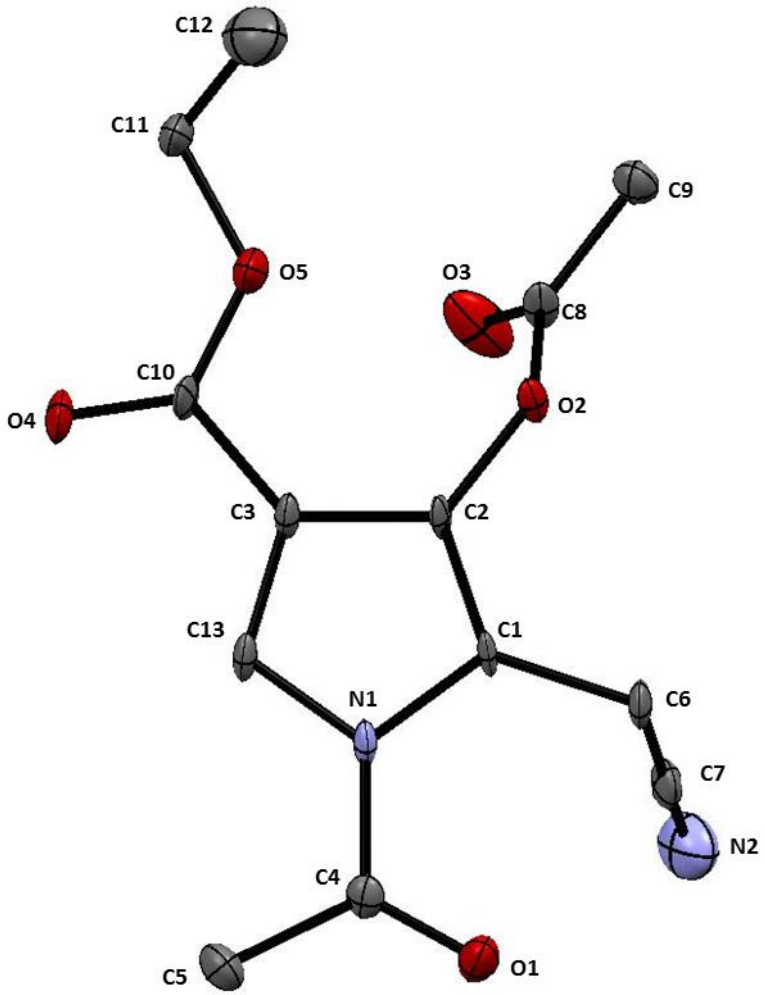
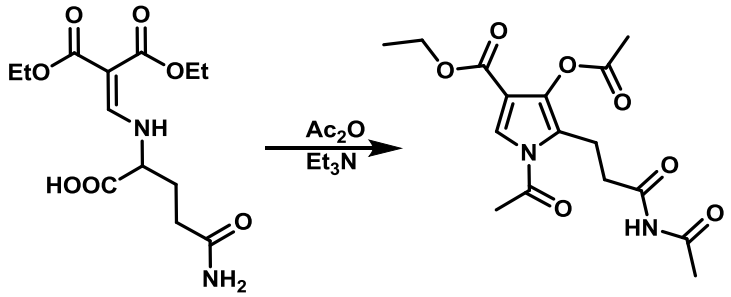


Figure 2.8 ORTEP plot of **2.24**, hydrogen atoms have been removed for clarity, ellipsoids at 50 % probability.

Table 2.4 Selected bond lengths and angles for **2.24**.

Atom 1	Atom 2	Length (Å)	Atom 1	Atom 2	Atom 3	Angle (°)
N1	C1	1.406	C1	N1	C13	108.42
N1	C13	1.383	N1	C1	C2	106.99
C1	C2	1.345	N1	C13	C3	108.94
C3	C13	1.365	C1	C2	C3	109.55
C2	C3	1.433	C2	C3	C13	106.09

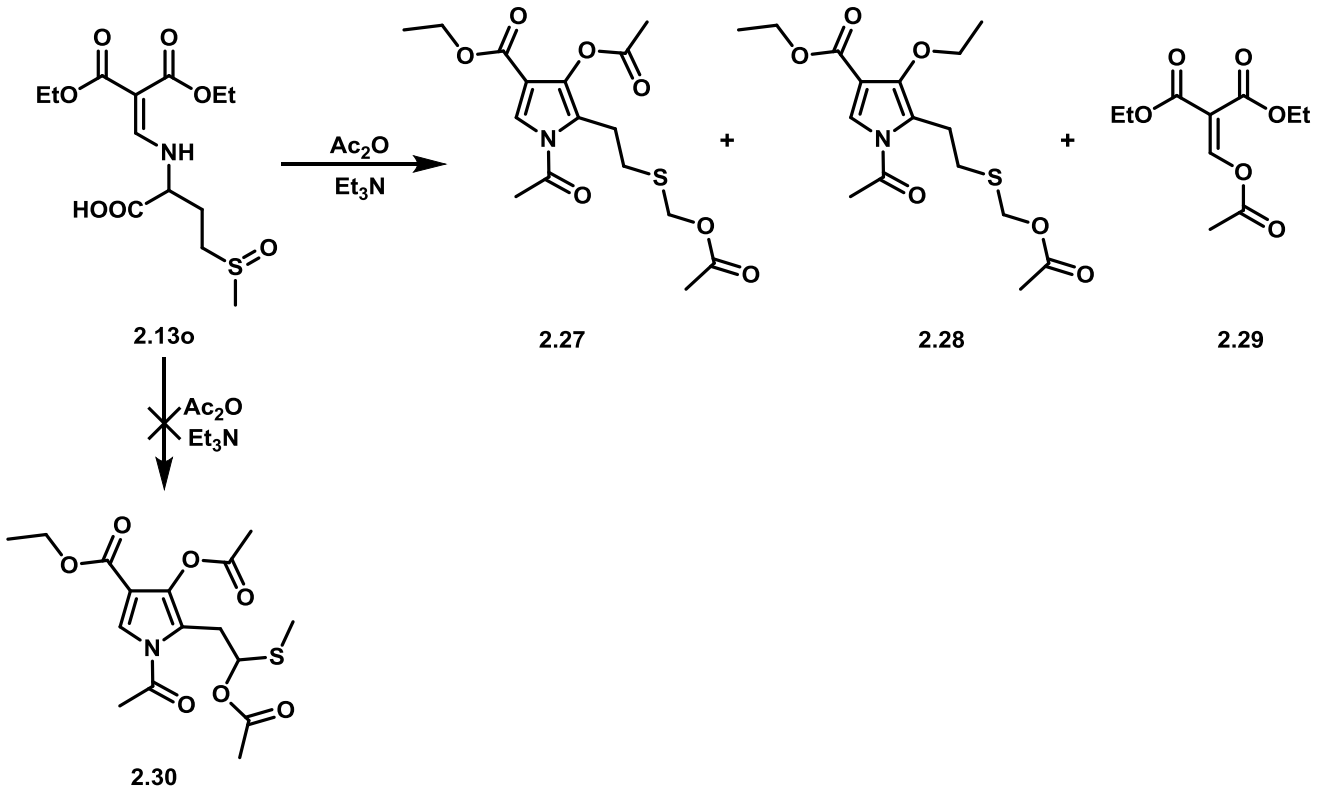
The homologue of **2.13m** from glutamine **2.13n**, when subjected to the usual cyclisation conditions (Ac_2O and Et_3N), gave a single pyrrole derivative **2.26** in which *N*-acylation of the amide side-chain had occurred (Scheme 2.23). This was apparent from the ^1H NMR spectrum that exhibited only one singlet for the N*H* proton rather than two and the signal had shifted downfield to δ 7.99 from δ 6.83 and 7.37 ppm. Furthermore, there was also a singlet at δ 2.35 integrating for 6H, for both the pyrrole and imido *N*-acetyl functions. The ^{13}C NMR spectrum displayed five carbonyl signals between 162 – 172 ppm.



2.13n **2.26**

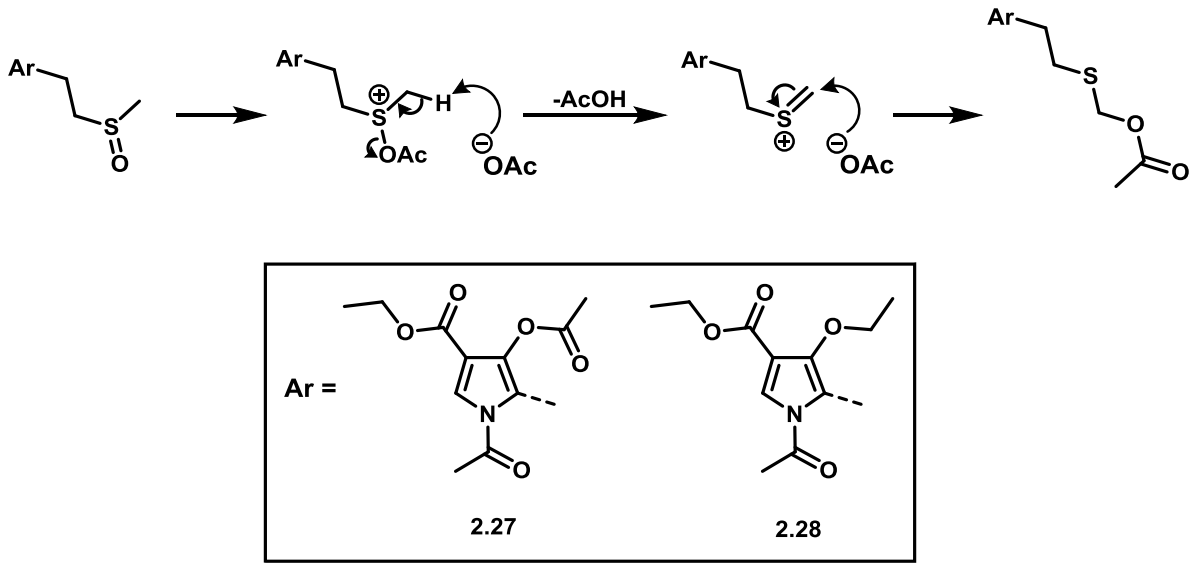
Scheme 2.23

Cyclisation of the enamino acid **2.13o** derived from methionine sulfoxide was of interest since the presence of the sulfoxide moiety might initiate other reaction pathways *via* intermediates derived from a Pummerer rearrangement. Thus when **2.13o** was treated with Ac_2O/Et_3N under the standard conditions, aqueous work-up and flash chromatography of the reaction product gave three compounds. The major compound (18 %) was shown to be the 4-acetoxypyrrole **2.27** together with the 4-ethoxypyrrole **2.28** (8 %) and diethyl (acetoxymethylene)malonate **2.29** (6 %) identified by comparison of its IR and ^1H NMR spectra with those of authentic material [88JOC5464, Scheme 2.24]. It was found that Pummerer rearrangement of the side chain occurred in a regiospecific manner to give a single acetoxy sulfide readily distinguished by a singlet at *ca.* 5.3 ppm for the O–CH_2–S functions. None of the isomeric pyrrole **2.30** was observed in this reaction.



Scheme 2.24

It is not known whether the Pummerer rearrangement [91OR157] precedes formation of the pyrrole ring. The mechanism for the formation of the products **2.27** and **2.28** can be rationalised as shown in Scheme 2.25.



Scheme 2.25

2.3 Condensation of Secondary Amino Acids with Diethyl (Ethoxymethylene)malonate

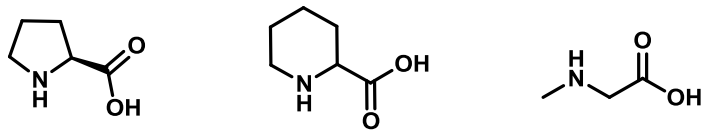
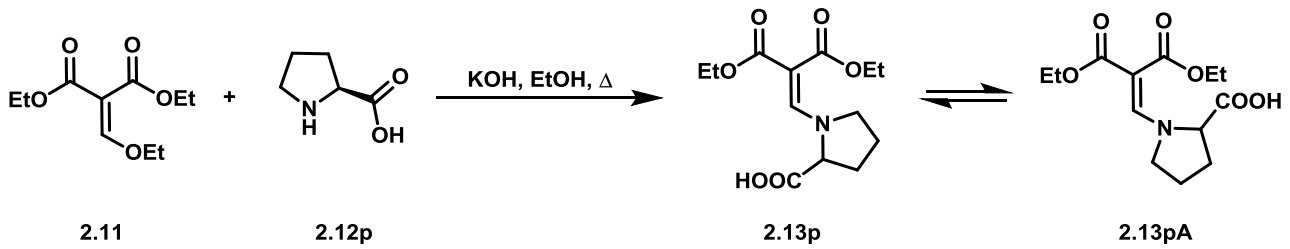


Figure 2.9 Secondary α-amino acids.

A small series of secondary α-amino acids was investigated in the Zav'yalov pyrrole synthesis. Cyclic secondary amino acids L-proline **2.13p** and DL-pipecolinic acid **2.13q** and the *N*-alkylated glycine, sarcosine **2.13r** are shown in Figure 2.9.



Scheme 2.26

Under the original reaction conditions (1 h at reflux, Scheme 2.9), L-proline **2.12p** (Scheme 2.26), furnished the known enamino acid **2.13p** [89S544] in 51 % yield. Analysis by ^{1}H NMR in $CDCl_3$ (Figure 2.10) showed that the product was present as a mixture of two rotamers (**2.13p** and **2.13pA**) in a ratio of 1:0.6 based on the integration of the singlets representing the methylene groups at δ 8.35 and δ 7.71 respectively. Mellor *et al*. [00T7267] observed comparable results in the ^{1}H NMR spectrum of (2*S*)-1-[(*E*)-4,4,4-trifluoro-3-oxo-1-butenyl]tetrahydro-1*H*-pyrrole-2-carboxylic acid.

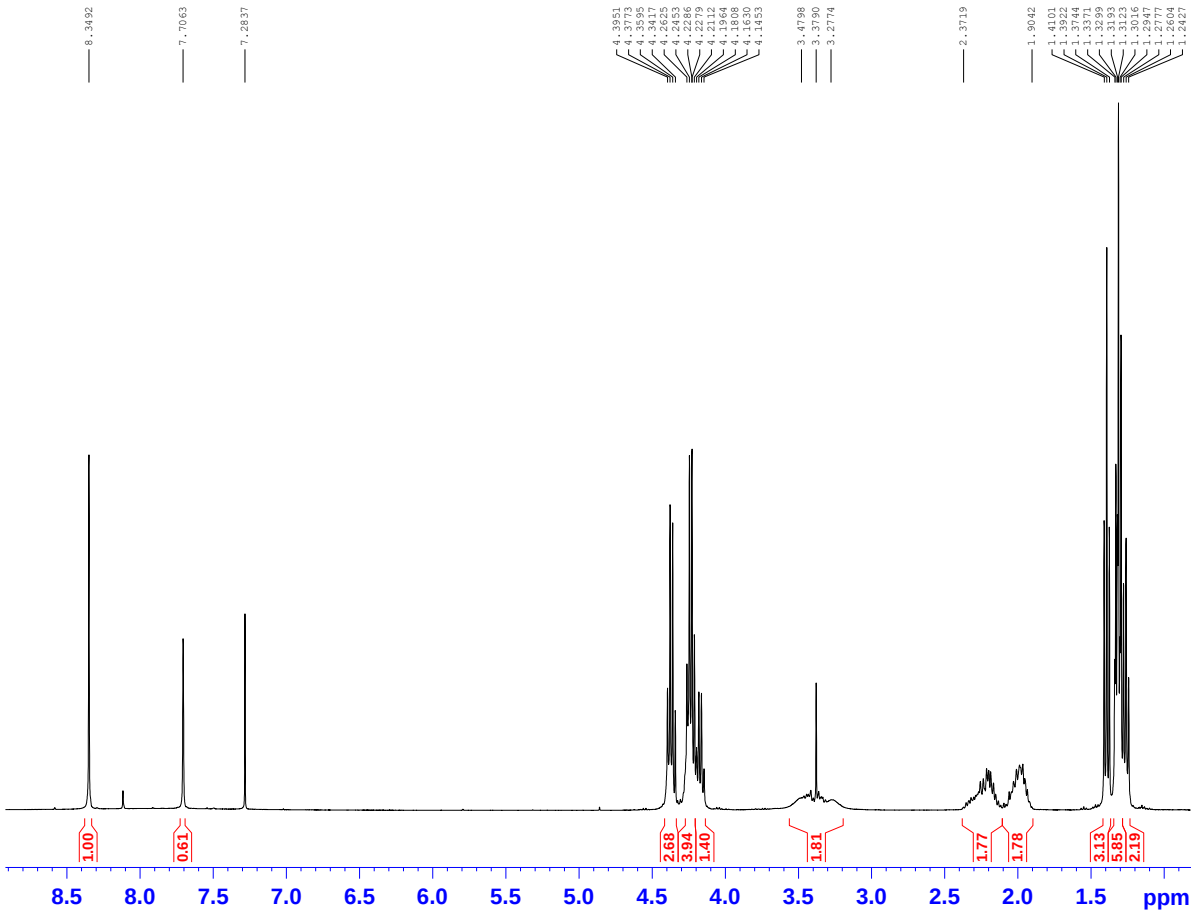
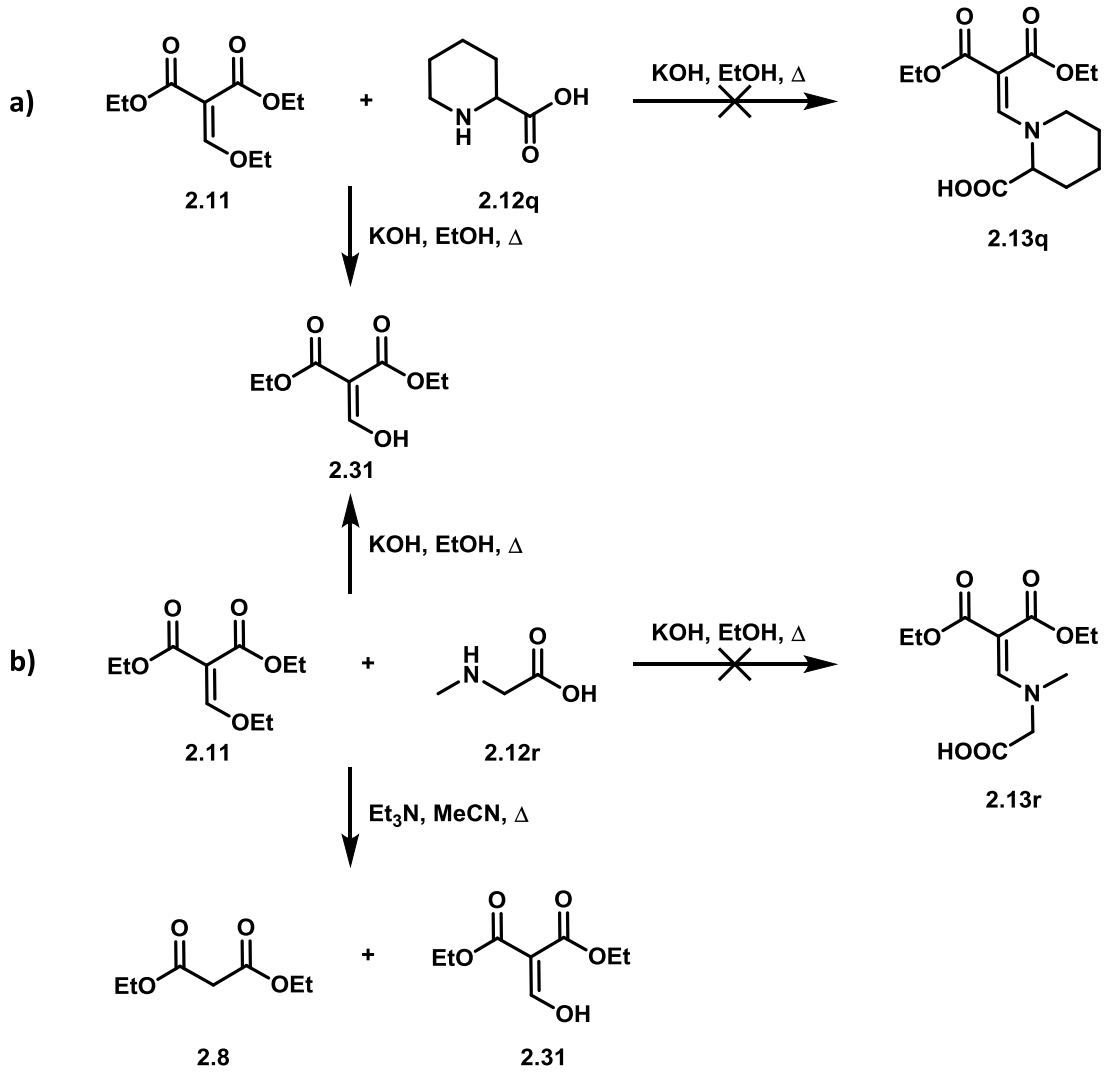


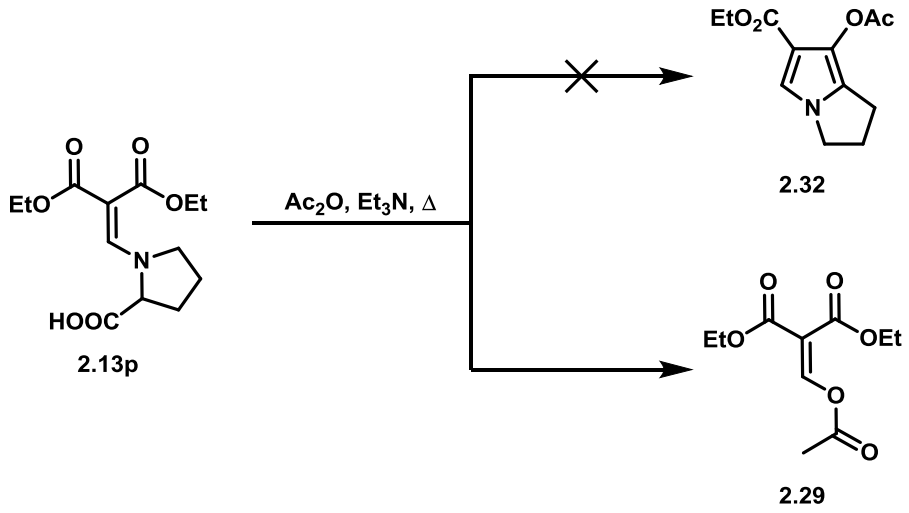
Figure 2.10 ^{1}H NMR Spectrum for **2.13p** (400 MHz, $CDCl_3$).

When the reaction of diethyl (ethoxymethylene)malonate with either DL-pipecolinic acid **2.12q** [Scheme 2.27a)] or sarcosine **2.12r** [Scheme 2.27b)] was carried out, neither amino acid provided the corresponding enamino acid **2.13**; instead both reactions provided diethyl 2-(hydroxymethylene)malonate **2.31** in 84 % and 87 % yields respectively derived from conjugate addition of hydroxide to **2.11**. The identity of **2.31** was confirmed by comparison of spectroscopic data with that in the literature [88JOC5464]. A further attempt was made to access **2.13r** from sarcosine using the conditions outlined in Scheme 2.12 that employed acetonitrile and triethylamine. Unfortunately, this approach also proved ineffective, providing instead, a mixture of diethyl 2-(hydroxymethylene)malonate **2.31** and diethyl malonate **2.8** [Scheme 2.27b)] in a ratio of 0.15:1 respectively based on ^{1}H NMR integrals of the mixtures.



Scheme 2.27

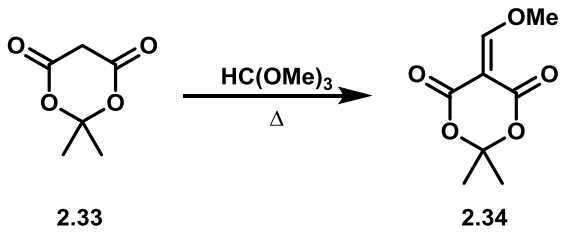
The only isolated product from the attempted cyclisation of the proline derived enamino acid **2.13m** was diethyl (acetoxymethylene)malonate **2.29** (40 % yield, Scheme 2.28), previously observed from the cyclisation of **2.13o** (Scheme 2.24). The absence of any pyrrole product may be due to steric hindrance from the pyrrolidine moiety, or more likely, through the strain associated with formation of the 5-5-fused ring system. However it is pertinent to note that Mellor *et al.* were able to effect cyclodehydration, decarboxylation and acylation of (*E*)-(4,4,4-trifluoro-3-oxobut-1-en-1-yl)-L-proline to 7-trifluoroacetyl-6-trifluoromethyl-2,3-dihydro-1*H*-pyrrolizine [Scheme 2.2d), 00T7267]. Presumably in this case the cyclisation is facilitated by the electrophilic trifluoroacetyl group.


EtO
O
O
OEt
N
HOOC
2.13p
Ac2O, Et3N, Δ
EtO2C
OAc
N
2.32
EtO
O
O
OEt
O
O
2.29

Scheme 2.28

2.4 Attempted Cyclisation of 5-(Carboxylalkylaminomethylene)-2,2-dimethyl-1,3-dioxane-3,5-diones

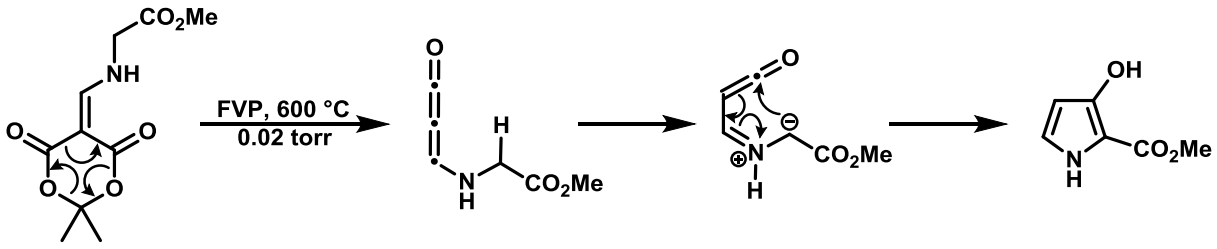
Meldrum's acid **2.33** (2,2-dimethyl-1,3-dioxane-3,5-dione) has been used as a starting material in the syntheses of heterocycles such as substituted phenanthrolines [02T9095], oxazinones [96T3136] and 3-hydroxypyrroles *via* flash vacuum pyrolysis [86JCS(P1)1465, 88JCS(P1)863]. As a cyclic analogue of a malonate and due to its usefulness in the synthesis of heterocycles [78CSR345, 91H(32)529, 09MD399], derivatives of Meldrum's acid were investigated as starting materials in the Zav'yalov pyrrole synthesis. Thus, 2,2-dimethyl-5-methoxymethylene-1,3-dioxane-4,6-dione **2.34** was synthesised according to a literature procedure [10NJC236]. Meldrum's acid **2.33** was stirred in trimethyl orthoformate at 50 °C for 3 hours and allowed to cool to room temperature to give after concentration *in vacuo* an oily orange solid (Scheme 2.29). The ^{1}H NMR spectrum of this material showed the presence of some unreacted Meldrum's acid which was removed by washing with Et_2O [04WO2004113303A1] to afford an orange solid in 60 % yield.



2.33 **2.34**

Scheme 2.29

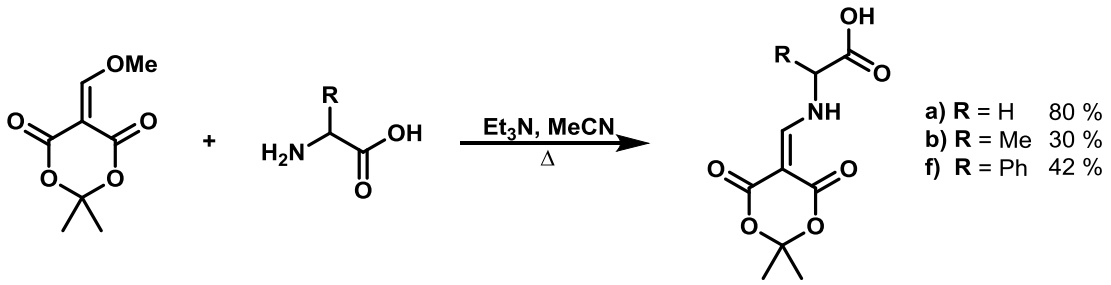
Methoxymethylene Meldrum's acid **2.34** was used to synthesise known enamino acids **2.37a** and **2.37b** from glycine (**2.13a**) and alanine (**2.13b**) and **2.37f** from phenylglycine **2.13f** [86YZ154]. Apart from elaboration to afford tripeptides, no chemistry of these compounds has been investigated. McNab *et al.* have shown that FVP of the enamino ester **2.35** affords methyl 3-hydroxypyrrole-2-carboxylate **2.36** *via* a methyleneketene intermediate [09S2531, Scheme 2.30].



2.35 **2.36**

Scheme 2.30

It has been found that methyleneketenes can be generated at substantially lower temperatures (~150 – 200 °C) [09MD399] which provided an additional impetus to investigate the behaviour of the enamino acids **2.37a, b** and **f** (Scheme 2.31). Methoxymethylene Meldrum's acid **2.34** and the appropriate amino acid **2.12** were stirred in acetonitrile at reflux under nitrogen in the presence of triethylamine as base (Scheme 2.31). The reaction was monitored by TLC and once complete (40 mins – 2.5 hours) the reaction mixture was allowed to cool and the solvent removed under reduced pressure. The residue was dissolved in water and acidified with 2M HCl and isolated *via* ethyl acetate. The enamino acids were isolated in poor to good yields (30 – 80 %).



2.34 **2.12** **2.37**

Scheme 2.31

The ^{1}H NMR spectra exhibited broad signals for the NH proton in all enamino acids (**2.37a, b** and **f**). In a similar manner to those observed for **2.13** (Figure 2.5), the proton is deshielded by intramolecular H-bonding, as shown by the shifts of 9.70 – 10.4 ppm (Figure 2.11). This feature is noticeable in the ^{13}C NMR spectra, the lactone carbonyls from the Meldrum's acid moiety are non-equivalent (δ 162.8 and δ 164.7).

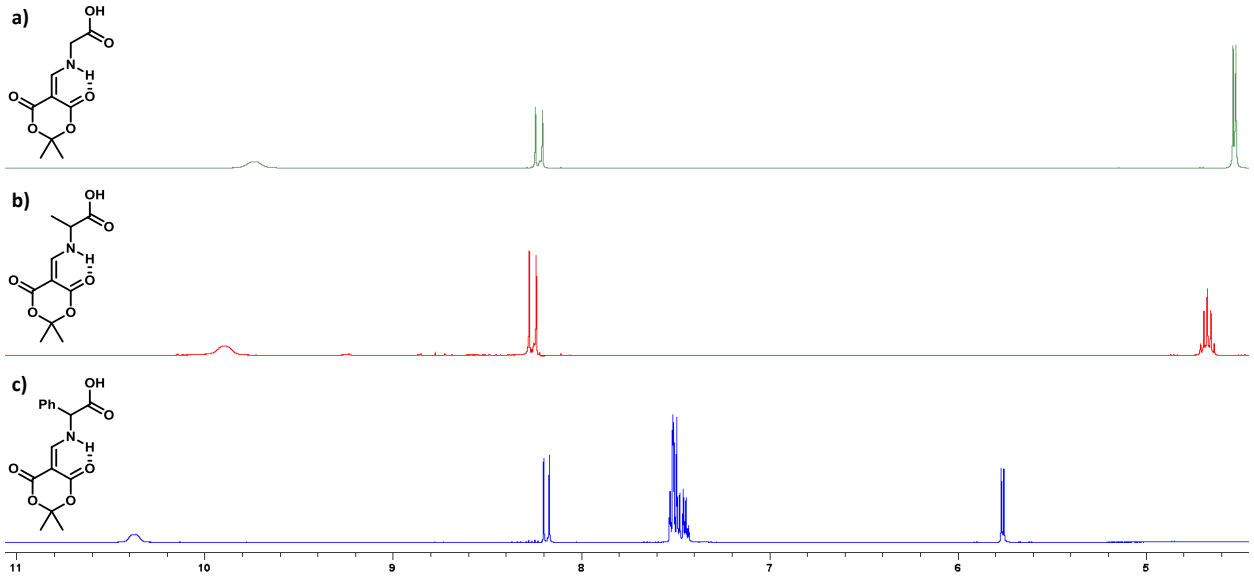
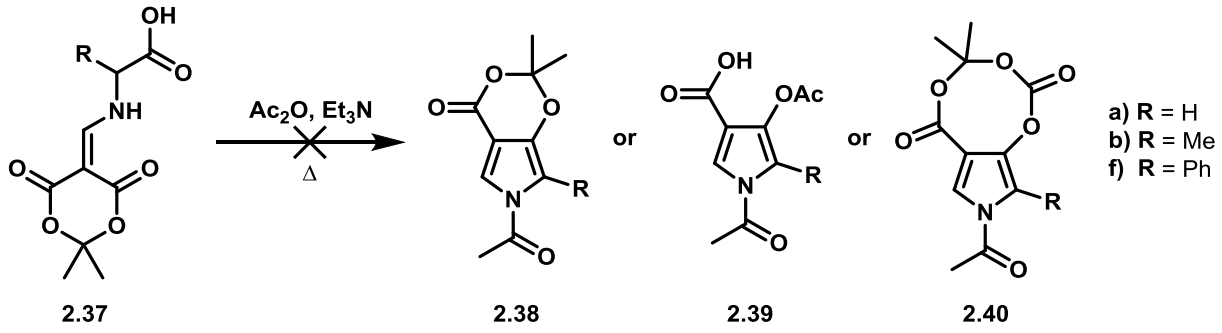


Figure 2.11 ^{1}H NMR [400 MHz, $(CD_3)_2CO$] of a) **2.37a,** b) **2.37b** and c) **2.37f**.

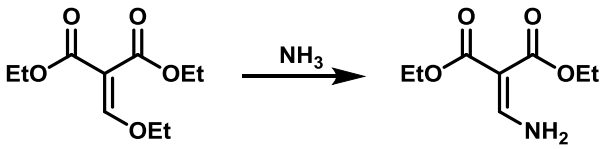
Cyclisation of the enamino acids **2.37a, b** and **f** could potentially provide bicycle **2.38** or pyrrole-3-carboxylic acid **2.39** upon elimination of CO_2. An alternative possibility would be the 1,3,5-trioxocine **2.40** derived by a ring expansion reaction, analogous to the formation of oxocino[2,3-*c*]pyrroles from the cyclisation of 2-[(1-carboxyalkylamino)methylene]cyclohexane-1,3-diones [02JCS(P1)2799]. When heated with Ac_2O-Et_3N all of the enamino acids **2.37a, b** and **f** reacted with vigorous CO_2 evolution. However, aqueous work-up followed by flash column chromatography provided none of the potential products, instead, the ^{1}H NMR spectra revealed in each case a complex mixture from which no product could be identified (Scheme 2.32).



Scheme 2.32

2.5 Attempted Petasis Reaction of Diethyl 2-(Aminomethylene)malonate

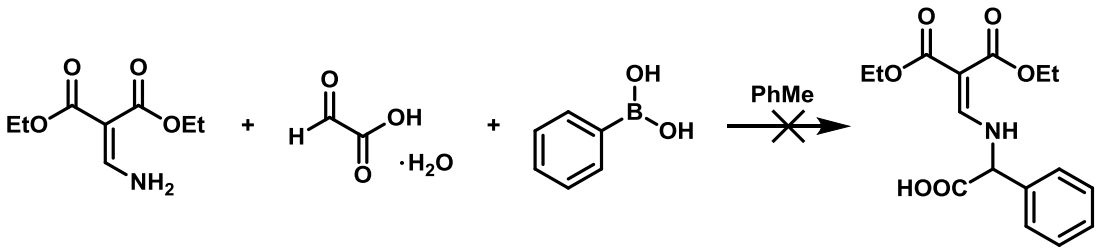
The Petasis reaction is a multicomponent reaction in which α-amino acids can be obtained from an amine, glyoxylic acid and a boronic acid or ester. In an attempt to introduce further functionality unavailable from traditional α-amino acids, diethyl 2-(aminomethylene)malonate **2.41** was synthesised. Following literature procedure [61JA4225] **2.41** was prepared from diethyl (ethoxymethylene)malonate **2.11** in 86 % yield.



2.11 **2.41**

Scheme 2.33

Diethyl 2-(aminomethylene)malonate **2.41** was added to glyoxylic acid monohydrate **2.42** and phenylboronic acid **2.43** in toluene. Unfortunately, from the reaction no product could be isolated or detected by ^{1}H NMR (Scheme 2.34). Presumably the low nucleophilicity of the amino group in **2.41** is responsible for the failure of this reaction. This disappointing outcome is in marked contrast to the behaviour of electron deficient aromatic amines which react readily [09TH319, 10CRV6169].

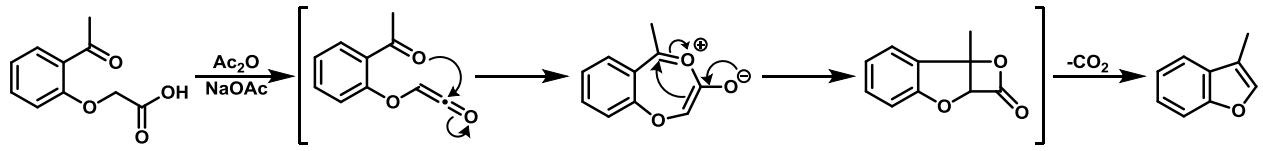


2.41 **2.42** **2.43** **2.13f**

Scheme 2.34

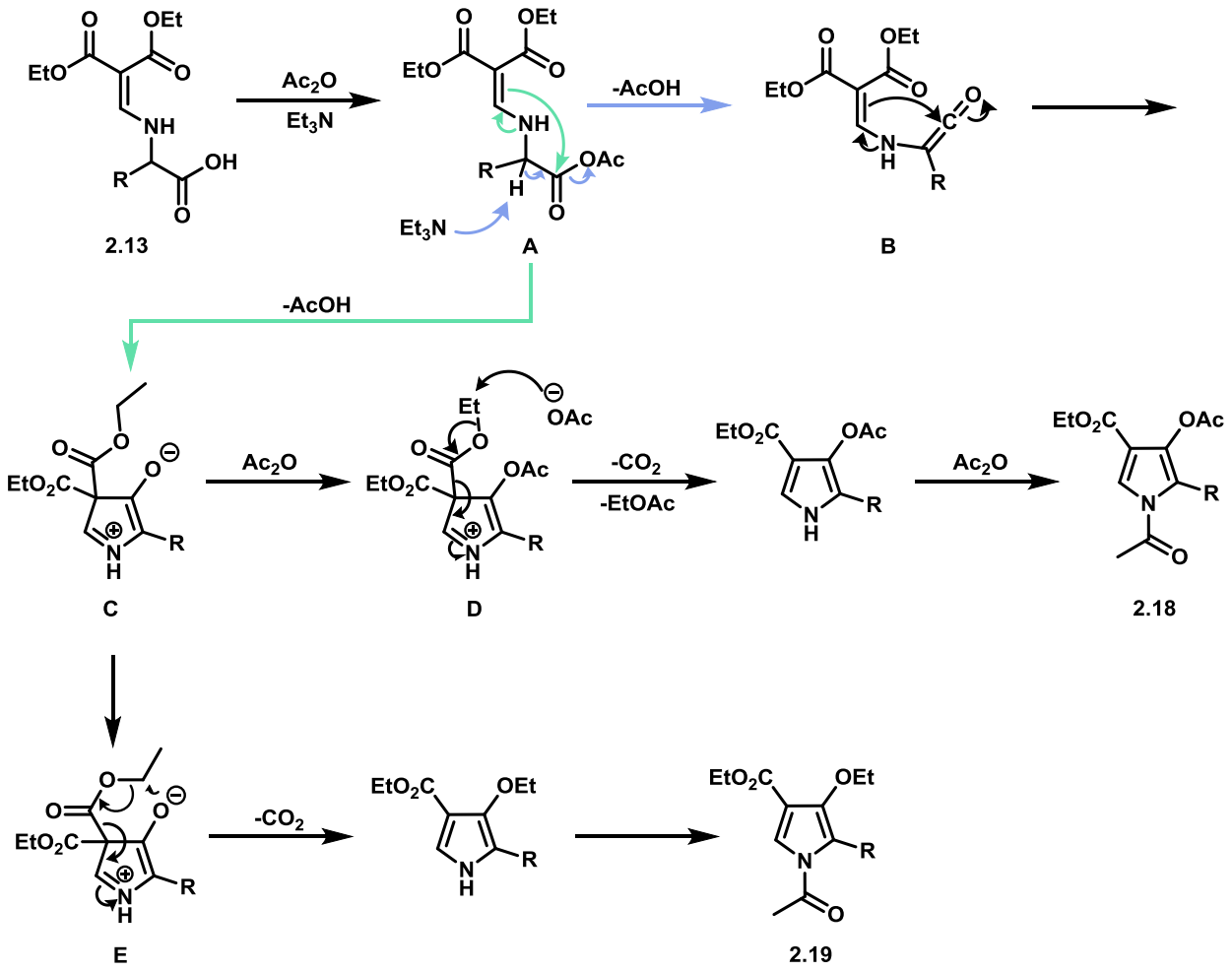
2.6 Mechanistic Studies of Pyrrole Ring Formation

It is well established [80MI223, 06MI1, 10OPRD579] that treatment of any substituted acetic acid, or indeed any *N*-protected α-amino acid with acetic anhydride in the presence of base results in the formation of a mixed anhydride which can undergo elimination to afford a ketene [94JOC7529]. The latter have been trapped as their [2+2] cycloadducts with a variety of alkenes leading to cyclobutanone derivatives [85JOC5177, 87JOC3457, 91JOC6118, 88JHC969]. Ketenes are highly susceptible to nucleophilic attack [06MI1] and are even attacked by the lone pair on a C=O function. For example, when heated with Ac_2O containing NaOAc, 2-acetylphenoxyacetic acid is smoothly cyclised to 3-methylbenzo[*b*]furan. The intermediacy of a 1,4-benzodioxepine, derived by nucleophilic attack of the ketone on a phenoxyketene has been proposed to account for the formation of the product (Scheme 2.35). *p*-Electron-donating substituents that increase the nucleophilicity of the ketone oxygen afford high yields of products [88JHC969].



Scheme 2.35

In view of these observations tentative mechanisms for the formation of the 4-acetoxypyrroles **2.18** and the 4-ethoxypyrroles **2.19** are shown below (Scheme 2.36).

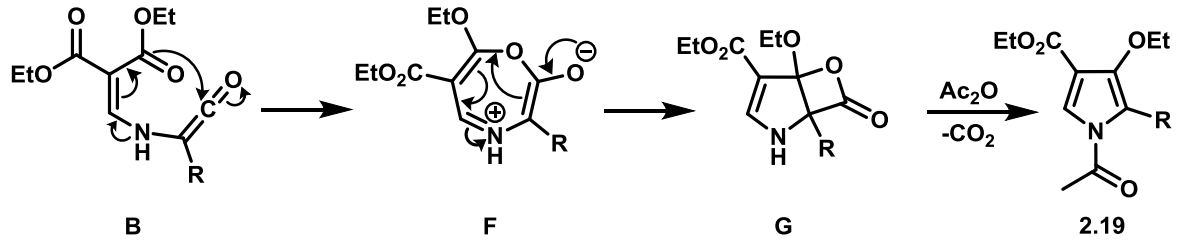


Scheme 2.36

Initially the enamino acid **2.13** is deprotonated by triethylamine and the carboxylate anion acylated by acetic anhydride to provide mixed anhydride **A**. From this point two reaction pathways are possible. Thus, deprotonation results in elimination of acetate to give the aminoketene derivative **B**. The latter cyclises as shown to provide the enolate **C** which undergoes further acylation to afford **D**. In the presence of acetate a Krapcho-type dealkoxycarbonylation ensues [07ARK(ii)1, 07ARK(ii)54] to afford, after *N*-acylation, the pyrrole **2.18**.

Alternatively, formation of the enolate **C** could also be derived by direct cyclisation onto the mixed anhydride **A** without invoking the participation of the ketene **B**. Trapping experiments to verify the intermediacy of the latter were carried out as part of further investigation of the mechanism and are outlined in section 2.6.4. Formation of the 4-ethoxypyrrole **2.19** is more difficult to rationalise, however direct transfer of an ethyl group *via* an S_Ni reaction (**E**) may be possible. There are however no literature procedures for an analogous pathway involving alkyl group transfer from an ester. An alternative route to **2.19** may involve the intervention of an oxazepine intermediate **F**.

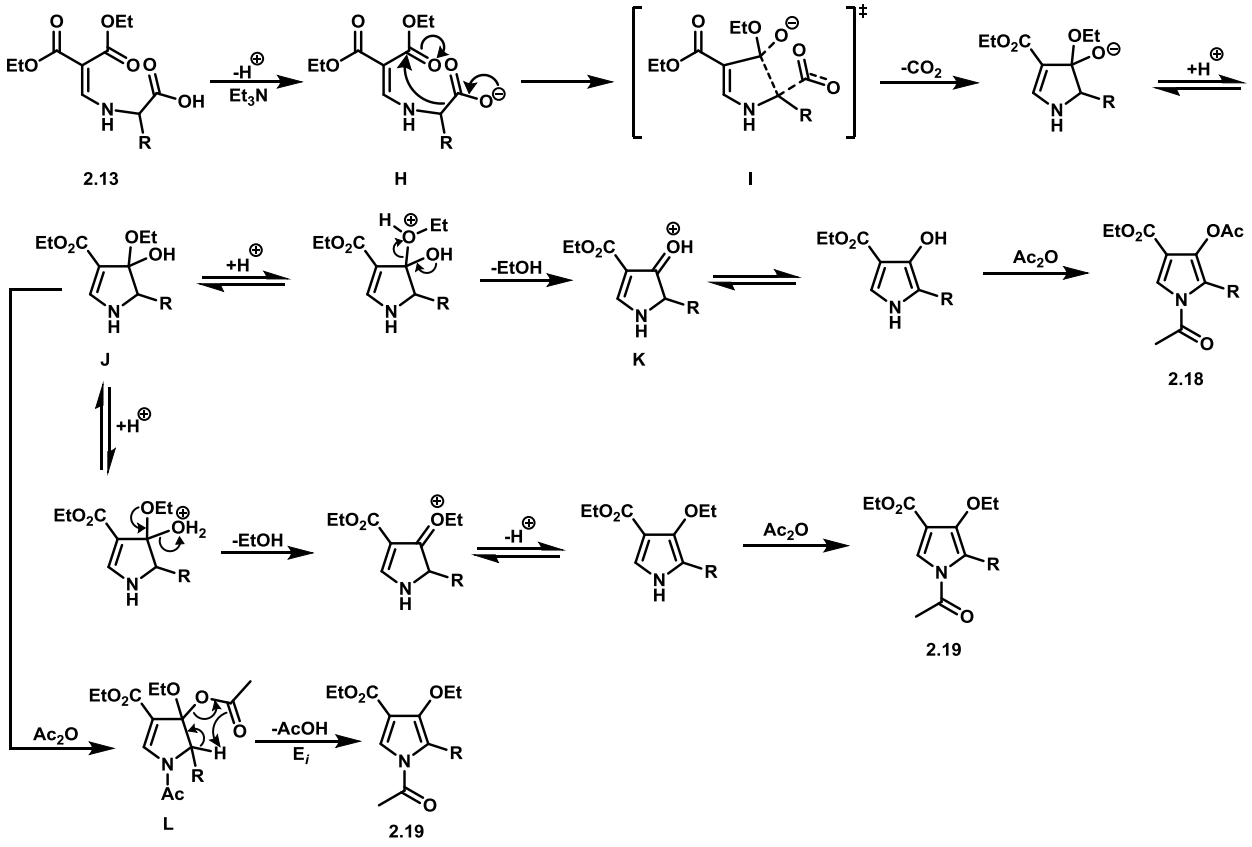
Thus, the ester carbonyl groups in **B**, which are electron rich by virtue of conjugation with the enamino- function, could intercept the ketene intermediate **B** as shown below (Scheme 2.37). Ring contraction of **F** [*cf.* Scheme 2.35, 88JHC969] would afford **G**, which, following cycloreversion of CO_2 provides ethoxypyrrole **2.19**.



Scheme 2.37

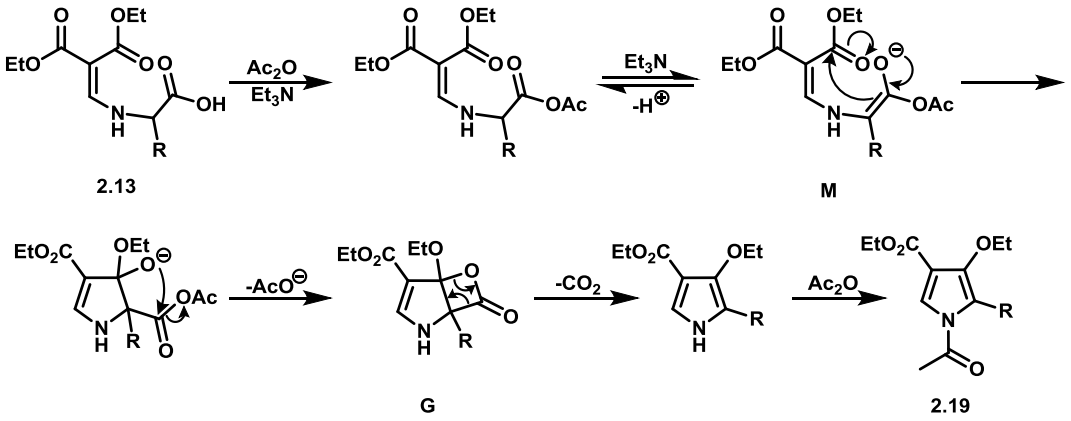
Attempts to intercept the oxazepine **F** (a 1,3-dipole) by addition of *N*-phenylmaleimide or dimethyl acetylenedicarboxylate (DMAD) were not successful. However, **2.13b** (R = Me) reacted with DMAD in the absence of base to afford an *N*-alkenylpyrrole (section 2.6.4).

The pathways outlined in Scheme 2.36 all involve formation of the pyrrole ring by nucleophilic attack of an enamine function onto an activated carbonyl group *i.e.* the pyrrole C-3 carbon is derived from the carboxyl group. The CO_2 evolved originates from one of the ester groups. In Scheme 2.37 3-ethoxypyrrole formation effectively involves expulsion of the side-chain carboxyl function. In a similar manner, pyrrole formation mediated *via* dercarboxylation of the amino acid side chain can be rationalised as shown in Scheme 2.38 and Scheme 2.39.



Scheme 2.38

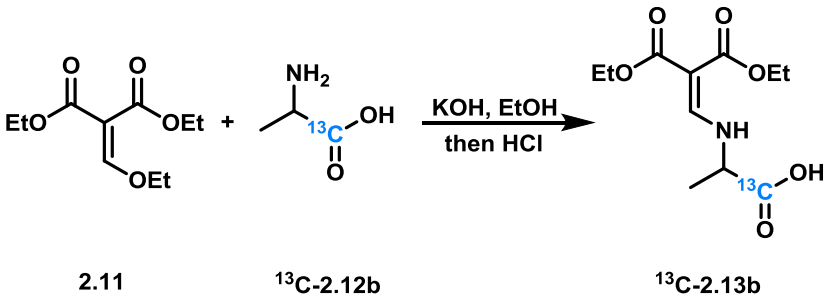
Cyclisation of the enamino malonate may be promoted by deprotonation to afford the carboxylate **H** (Scheme 2.38) which cyclises presumably *via* a transition state akin to **I**. Loss of CO_2 followed by protonation would generate the hemiketal **J**, then disposed towards loss of EtOH or H_2O. Protonation of the more basic alkoxy function will ensue leading to the hydroxypyrrole tautomer **K** *via* an E_1-type elimination, a process facilitated by electron release from the ring nitrogen. Acylation of **K** with Ac_2O will then afford the 3-acetoxypyrrole derivative **2.18**. Protonation of the hydroxyl group in **J** will, following dehydration and acylation, generate the 3-ethoxypyrrole **2.19**. The timing of the *N*- and *O*-acetylation reaction steps is uncertain so it is possible that the *O*-acetylketal **L** may be generated from **J**. The former is disposed towards an intramolecular (E_i) *syn*-elimination of AcOH to afford the 3-ethoxypyrrole **2.19**. An additional pathway to the ethoxypyrrole may be proposed by invoking of the enolate **M** from which decarboxylation of intermediate β-lactone **G** leads to the product (Scheme 2.39).



Scheme 2.39

Scheme 2.36, Scheme 2.37, Scheme 2.38 and Scheme 2.39 illustrate a number of potential pathways by which the 3-acetoxypyrroles **2.18** and 3-ethoxypyrroles **2.19** may be formed. It was therefore of interest to establish which of the foregoing reaction pathways operate. The pathways in Scheme 2.36 imply that the carboxyl group is retained in the pyrrole products. In Scheme 2.37 the carboxyl group is eliminated from the putative intermediate **G**. The failure to trap intermediate **F** with dipolarophiles indicated that this pathway was probably not operative. The choice remains between the pathways in Scheme 2.36 (carboxyl retained) and Scheme 2.38 and Scheme 2.39 (carboxyl eliminated), although it is recognised that more than one pathway may be involved. Further investigation of the mechanistic pathways was undertaken. A straightforward approach to establish the origin of the C-3 carbon was by isotopic labelling of the starting material, as outlined in the following section.

2.6.1 Synthesis of [3-Ethoxy-2-(ethoxycarbonyl)-3-oxoprop-1-en-1-yl]-DL-alanine-1-^{13}C



Scheme 2.40

The ^{13}C-labelled enamino acid **^{13}C-2.12b** was chosen as the most suitable substrate since it provided the highest yields of the pyrroles. Thus, labelled DL-alanine-1-^{13}C reacted straightforwardly with diethyl (ethoxymethylene)malonate **2.11** to afford **^{13}C-2.13b** in 61 % yield.

This reaction represents the first example of any chemistry using **^{13}C-2.12b**. The labelled carboxylic acid was readily characterised from its NMR spectrum and the intense carboxyl carbon can be clearly seen at δ 173.60 in the ^{13}C NMR spectrum (100 MHz, DMSO-d_6, Figure 2.12). The presence of a ^{13}C atom at the carboxyl carbon group results in spitting of some of the other signals. Thus, the tertiary carbon from the NH*C*HCOOH function appears as a doublet at δ 55.9 with $^{1}J_{C–C}$ = 58.3 Hz. The methylidene carbon resonates at δ 158.8 and also gives rise to a doublet by virtue of long range coupling to the carbonyl carbon for which $^{3}J_{C–C}$ = 2.0 Hz. The absence of $^{2}J_{C=O–CH_3}$ is noteworthy and the alanine methyl signal resonates as a singlet at δ 19.4. This absence of $^{2}J_{^{13}C–^{13}C}$ compared to $^{3}J_{^{13}C–^{13}C}$ has been occasionally noted [88MI468]. In the ^{1}H NMR spectrum of **^{13}C-2.13b** the alanine methyl signal at δ 1.42 is split into a doublet of doublets ($^{2}J_{C–H}$ = 4.4 Hz, $^{3}J_{CH–Me}$ = 7.1 Hz) whilst the alanine methine proton resonated at δ 4.42 as an apparent sextet (Figure 2.12).

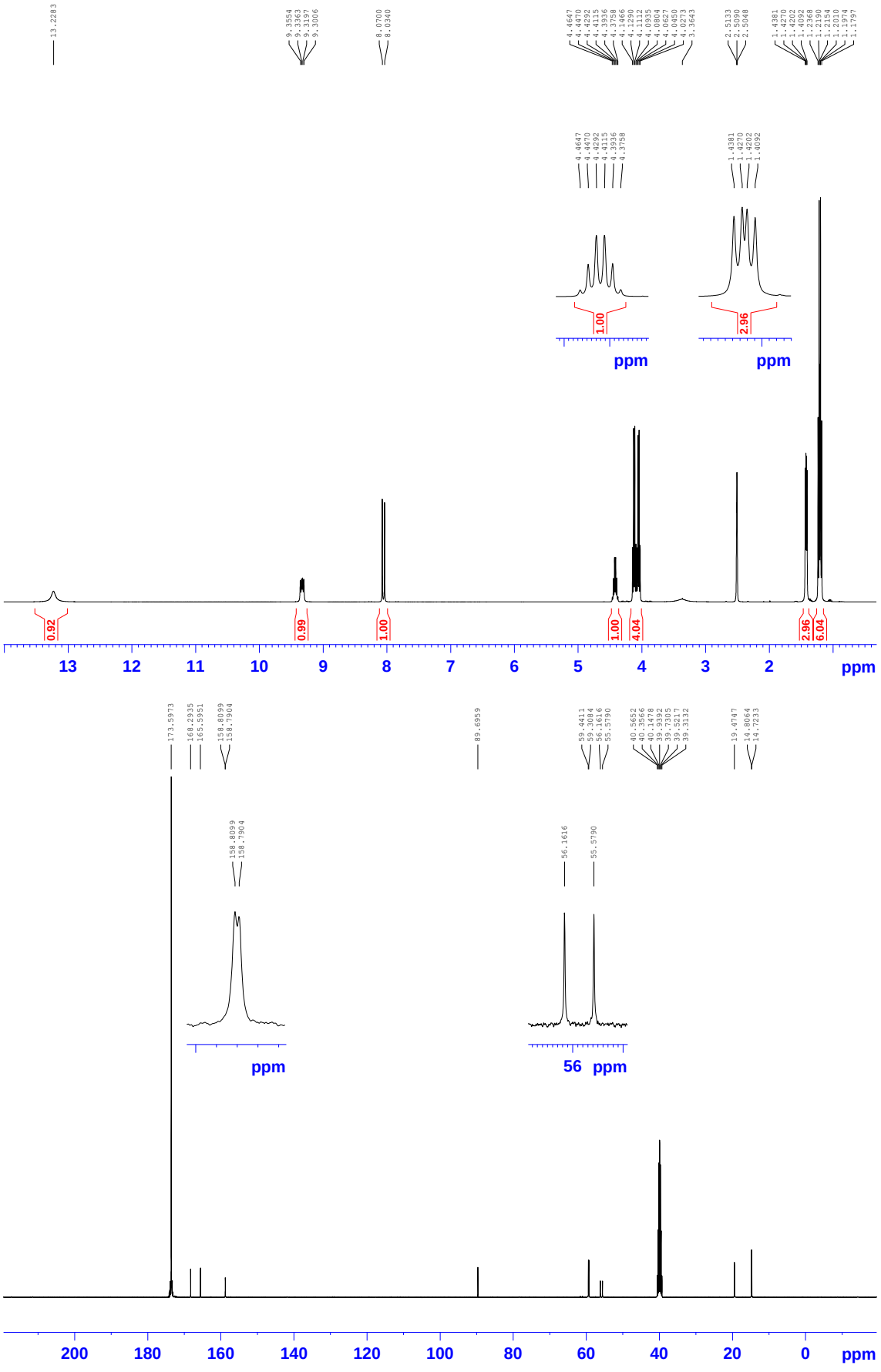
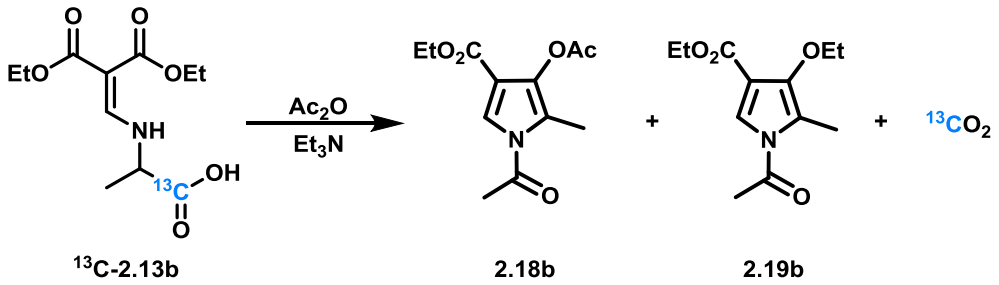


Figure 2.12a) ^{1}H (400 MHz) and b) ^{13}C NMR (100 MHz) spectra of **^{13}C-2.13b** (DMSO-d_6).

Cyclisation of labelled enamino acid **^{13}C-2.13b** in acetic anhydride and triethylamine afforded ethoxypyrrole **2.19b** and acetoxypyrrole **2.18b** in 8 % and 67 % yield, respectively following aqueous work-up and flash chromatography (Scheme 2.41). The ^{13}C NMR spectra of the two products showed an absence of the ^{13}C-labelled atom, which therefore established that it is lost as CO_2 and is not incorporated into the pyrrole ring. These findings therefore exclude any of the pathways indicated in Scheme 2.36.



Scheme 2.41

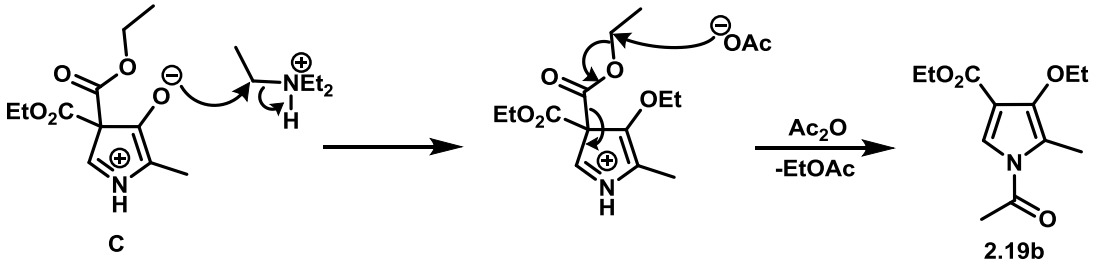
2.6.2 Effect of Base on the Cyclisation of Diethyl 2-(1-Carboxyethylaminomethylene)malonate, 2.13b

Some studies of the influence of the nature of the reaction medium upon the distribution of products have been undertaken in order to shed some light upon the pathways which may operate. From these studies some interesting facts emerge (Table 2.5). In the absence triethylamine the direct heating of **2.13b** in acetic anhydride provided the acetoxypyrrole **2.18b** as the only isolable product, however, the reaction time had to be extended to 1 hour (Table 2.5, entry 1). A similar result was obtained when the reaction was conducted in the presence of sodium acetate (Table 2.5, entry 2).

Table 2.5 Studies on the effect of base on the cyclisation of **2.13b**

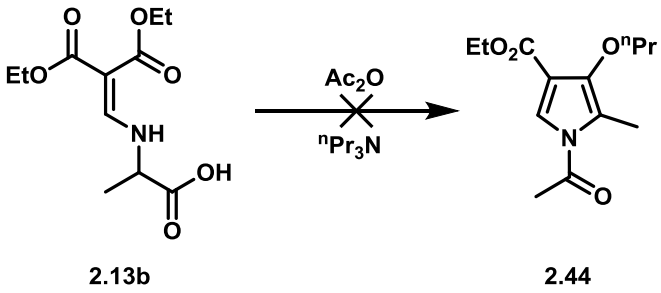
Entry	Conditions	Yield 2.18b (%)	Yield 2.19b (%)
1	Ac_2O, heat	61	-
2	Ac_2O, NaOAc (7 equiv.), heat	68	-
3	**Ac_2O, Et_3N (7 equiv.), heat (original conditions)**	**80**	**20**
4	Ac_2O, Et_3N (14 equiv.), heat	57	16
5	Ac_2O, $^{i}Pr_2NEt$ (7 equiv.), heat	64	2
6	Ac_2O, $^{n}Pr_3N$ (7 equiv.), heat	52	4
7	Ac_2O, Et_3N (7 equiv.), ambient temperature	56	11

Increasing the amount of triethylamine provided both **2.18b** and **2.19b**, yielding a similar amount of **2.19b**, but reducing that of **2.18b** (Table 2.5 entry 4). With the stronger amine Hünig's base ($^{i}Pr_2NEt$) both acetoxy- and ethoxy- pyrroles were formed, however the yield of the latter was diminished (Table 2.5, entry 5). The yield of **2.19b** was also diminished in the presence of tripropylamine (Table 2.5, entry 6). Conducting the reaction under the standard conditions (Ac_2O/Et_3N) at ambient temperature gave **2.18b** and **2.19b** with the yields both reduced when compared to the higher temperature reaction (Table 2.5, entry 7). The reduced temperature also necessitated an increase in reaction time. Because the yield of the ethoxypyrrole **2.19b** diminished when the reaction was conducted in the presence of Hünig's base it was thought that formation of the ethoxypyrrole may result from alkyl-transfer from the amine (or rather the trialkylammonium salt under the reaction conditions) to the enolate **C** *via* an S_N2 reaction as shown below (Scheme 2.42).



Scheme 2.42

Some evidence that this process probably does not occur accrued from the reaction of **2.13b** with acetic anhydride and tripropylamine which would be expected to afford the 4-propoxypyrrole-3-carboxylate **2.44** as one of the products (Scheme 2.43).

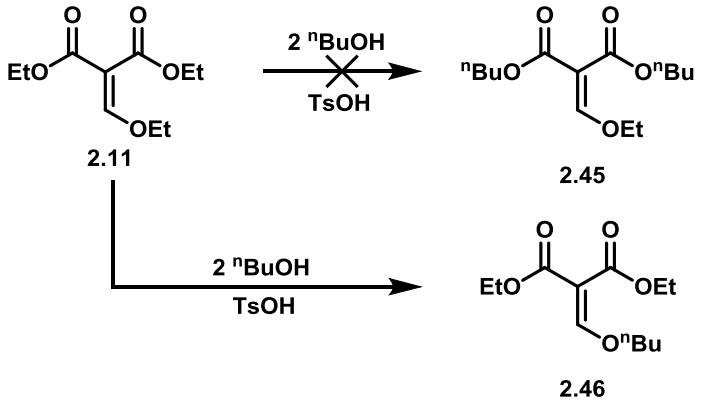


Scheme 2.43

However, despite numerous attempts none of the pyrrole **2.44** was detected, however both the acetoxy- **2.18b** (52 %) and ethoxypyrrole **2.19b** (4 %) were the only isolable products.

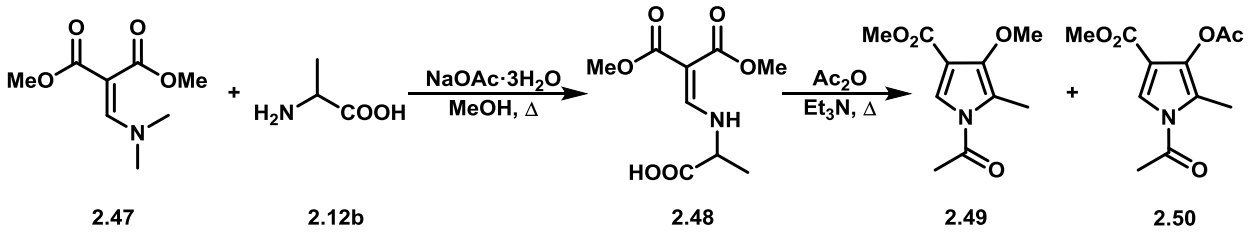
2.6.3 Cyclisation of Other Dialkyl 2-(1-carboxylalkylaminomethylene)malonates

The synthesis of some other dialkyl 2-(ethoxymethylene)malonates was investigated in order to explore the influence of the ester group upon the cyclisation and establish the ease with which other 3-alkoxypyrroles could be generated. Thus, the preparation of dibutyl 2-(ethoxymethylene)malonate **2.45** was attempted *via* a transesterification reaction of diethyl (ethoxymethylene)malonate **2.11** with *n*-butanol following a patent procedure [85USP4503074]. The malonate was heated to reflux in butanol with a catalytic amount of *p*-toluenesulfonic acid and the mixture distilled to remove ethanol. The product was further purified by Kügelrohr distillation. The resulting oil was characterised and identified as the undesired product, diethyl 2-(butoxymethylene)malonate **2.46** (Scheme 2.44), therefore obtaining a different product to that assigned in the literature (**2.45**).



Scheme 2.44

Due to the failure of the transesterification reaction, experiments to explore the formation of 4-methoxypyrroles **2.49** from the enamino acid **2.48** were undertaken (Scheme 2.45). Dimethyl (dimethylaminomethylene)malonate **2.47** was prepared analogously to diethyl (dimethylaminomethylene)malonate **2.10** (Scheme 2.7) from dimethyl malonate and DMFDMA in good yield (76 %). Dimethyl (dimethylaminomethylene)malonate **2.47** was added to alanine **2.12b** and sodium acetate trihydrate in methanol, and the reaction mixture stirred at reflux for 4 hours. The solvent was then removed *in vacuo* and the residue dissolved in water and acidified. The product was isolated *via* extraction into in ethyl acetate. The enamino acid was obtained as a yellow oil in 60 % yield.



Scheme 2.45

Purification by flash column chromatography following the cyclisation of **2.48** under standard conditions (Ac_2O, Et_3N) provided in the first fraction a very small amount of the methoxypyrrole **2.49** (3 % yield), the second and final fraction was identified as pure acetoxypyrrole **2.50** in good yield (67 %). The ^1H NMR spectra of pyrroles **2.49** and **2.50** are very simple. Figure 2.13a) shows the methoxypyrrole **2.49** with the C-2 methyl and *N*-acetyl signals at δ 2.40 and 2.56 ppm respectively, and the ester methyl and the methoxy methyl absorptions at δ 3.79 and 3.85 ppm respectively. The 3-acetoxypyrrole **2.50** displays three singlets for the acetoxy (δ 2.34), methyl (δ 2.35) and *N*-acetyl (δ 2.58) functions and a singlet at δ 3.81 for the ester methyl group [Figure 2.13b)]. The pyrrole protons exhibited singlets at δ 7.55 for **2.49** and at δ 7.62 for **2.50**. The pyrroles could also be distinguished by their ^{13}C NMR and IR spectra, for the latter these were of course closely similar to **2.18b**.

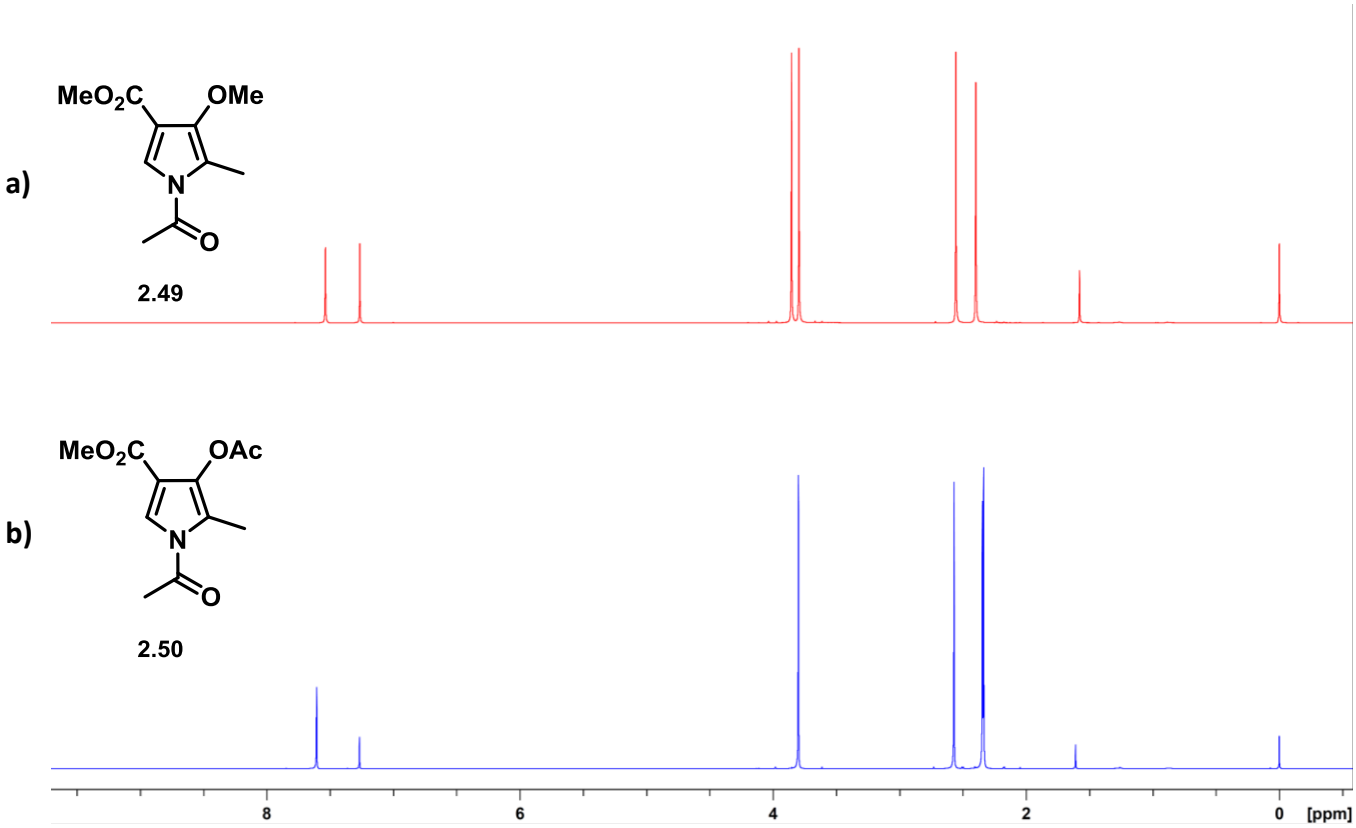
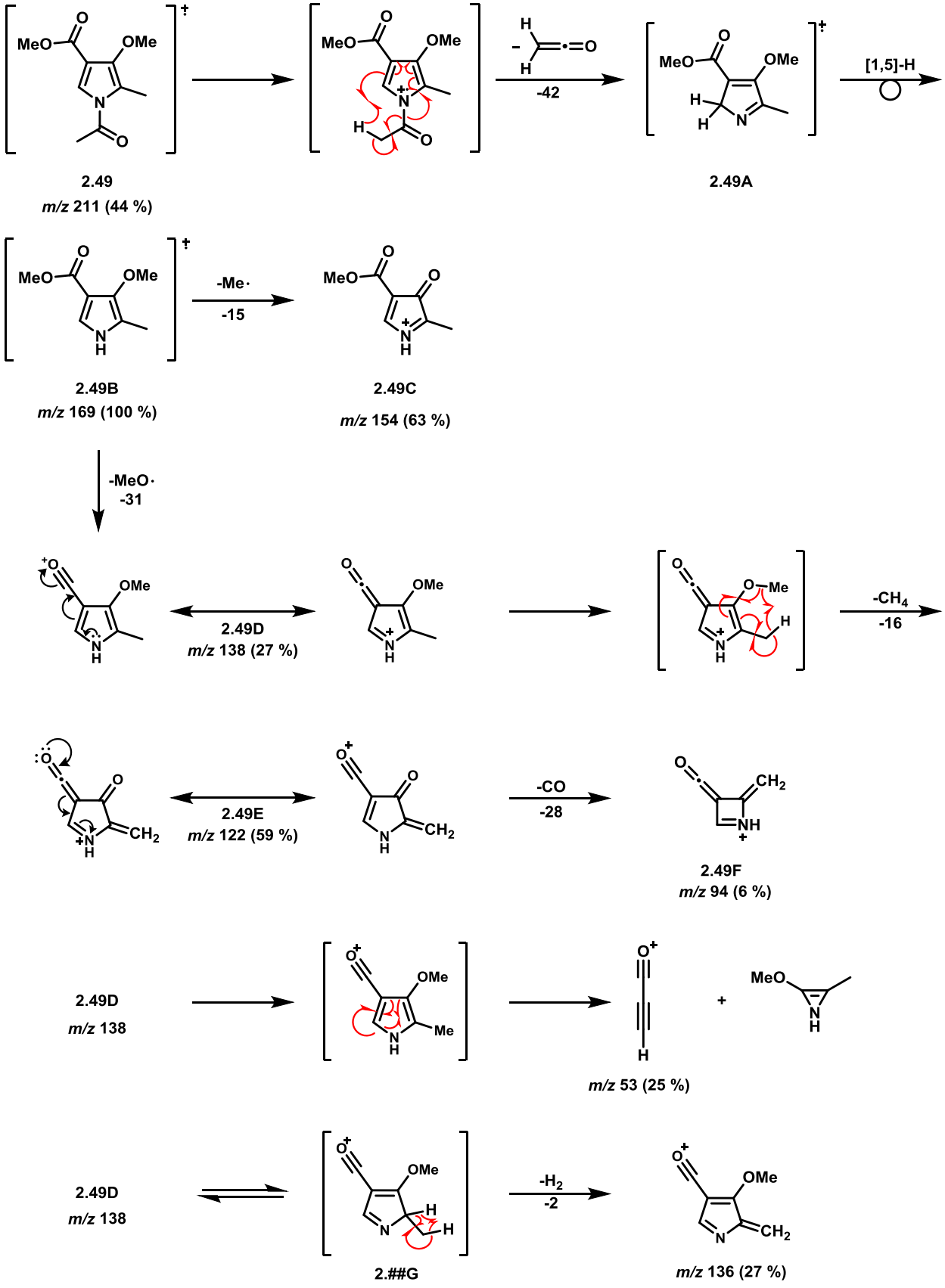


Figure 2.13 ^{1}H NMR spectra of a) **2.49** and b) **2.50** (400 MHz, $CDCl_3$).

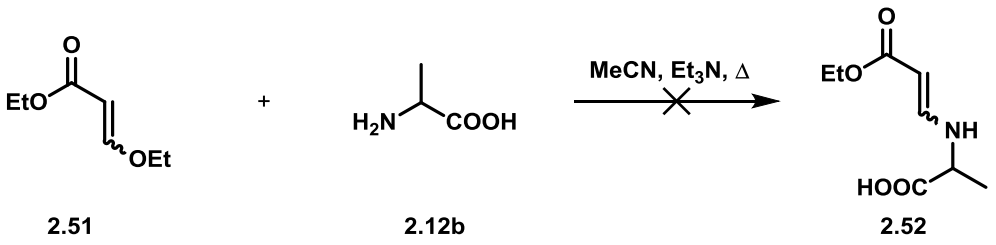
The constitution of **2.49** was confirmed from the electron impact mass spectral (EI-MS) fragmentation pattern. Although the structures of the ions derived from **2.49** shown in Scheme 2.46 have not been definitively established, the fragmentation modes can be rationalised based on extensive literature precedents for the EI-MS fragmentation of substituted pyrroles for which reviews are available [85MI533, 90HC(48-1)61]. The methoxypyrrole **2.49** gives rise to an intense molecular ion at *m/z* 211 from which the base peak corresponding to the *N*-deacylpyrrole **2.49B** (*m/z* 169) is derived. It is proposed that the latter arises *via* elimination of ketene and transfer of H to the pyrrole ring to give the 2H-pyrrole radical cation **2.49A** which may rearrange to **2.49B** from which loss of Me• occurs to generate **2.49C**. The ion **2.49B** can also expel a methoxyl radical to afford **2.49D** from which **2.49E** (*m/z* 122) results by elimination of CH_4. Expulsion of CO from the latter affords **2.49F** (*m/z* 94). Two additional fragmentation modes of **2.49D** can be envisaged providing the ion at *m/z* 53 (25 %) and a neutral azirine species. Related processes resulting in fracture of the pyrrole ring have a literature precedent [85MI533, 90HC(48-1)61]. Loss of H_2 from **2.49D** to give the peak at *m/z* 136 can be rationalised by invoking prototropy and elimination *via* **2.49G** (Scheme 2.46).


2.49
m/z 211 (44 %)
-42
2.49A
[1,5]-H
2.49B
m/z 169 (100 %)
-Me·
-15
2.49C
m/z 154 (63 %)
-MeO·
-31
2.49D
m/z 138 (27 %)
-CH4
-16
2.49E
m/z 122 (59 %)
-CO
-28
2.49F
m/z 94 (6 %)
2.49D
m/z 138
m/z 53 (25 %)
2.49D
m/z 138
-H2
-2
2.##G
m/z 136 (27 %)

Scheme 2.46

Due to the presence of the 3-methoxypyrrole from the cyclisation of **2.48**, the alkoxy moiety must be derived from the ester group.

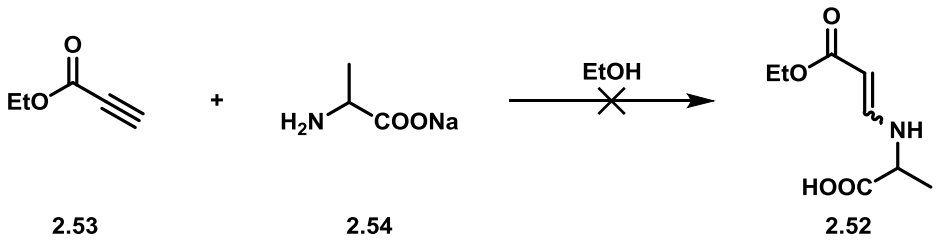
In addition to investigating the behaviour of other dialkyl malonates, many attempts were undertaken to access a monoester derivative **2.52** of the enamino acid **2.13b**; the objective here was to investigate whether ring closure would occur onto the ester function or by acylation at the β-position of the enaminone. Initially, ethyl 3-ethoxyacrylate **2.51** was used as a substrate in an attempt to access the monoester **2.52**. When **2.51** was reacted with alanine in acetonitrile in the presence of triethylamine and refluxed for 3 days, the reaction only provided unreacted ethyl 3-ethoxyacrylate **2.51** as a mixture of the *E*- and *Z*-isomers (Scheme 2.47).



2.51 **2.12b** **2.52**

Scheme 2.47

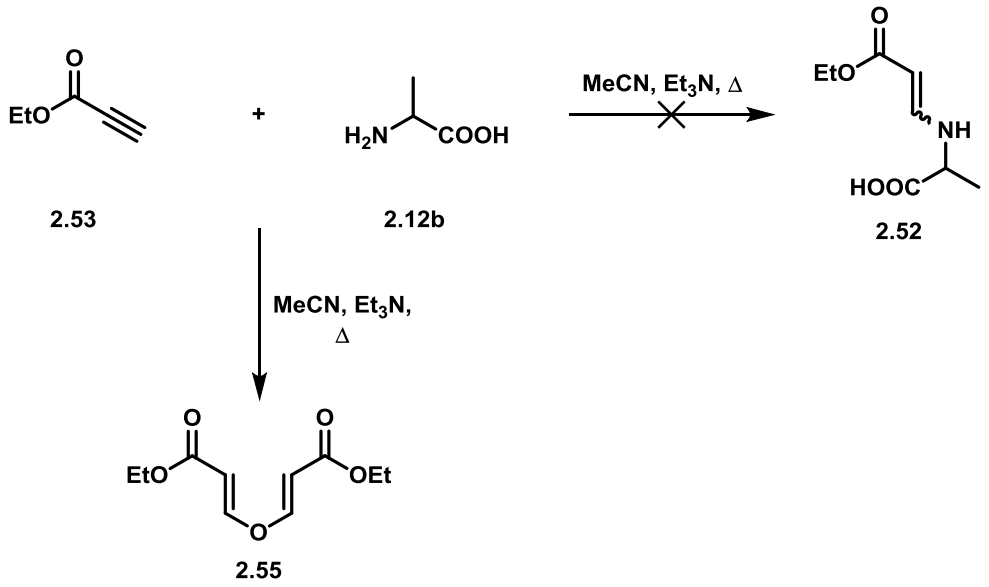
In an attempt to access **2.52** the ethoxyacrylate **2.51** was replaced with ethyl propiolate **2.53**, a highly reactive Michael acceptor. Reaction with the sodium salt of alanine **2.54** (made *in situ* from ethanolic sodium ethoxide) provided a complex reaction product. The ^{1}H NMR spectrum of this material revealed that none of the enamino acid **2.52** had been formed (Scheme 2.48).



2.53 **2.54** **2.52**

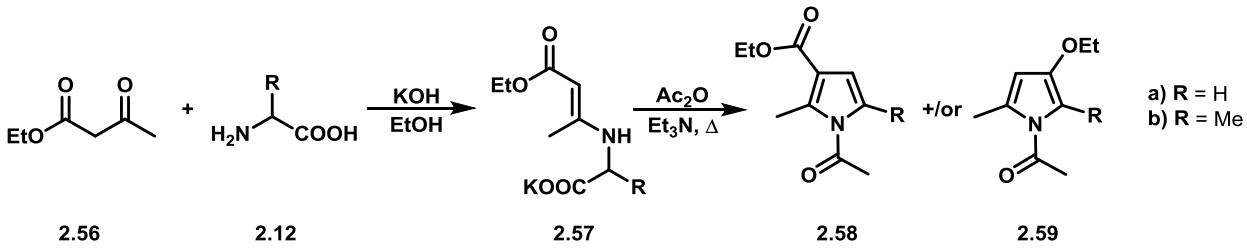
Scheme 2.48

The synthesis of **2.52** was attempted from ethyl propiolate again under different conditions (triethylamine and acetonitrile). However, the reaction afforded (2*E*,2′*E*)-diethyl 3,3′-oxydiacrylate **2.55** as the only isolable product (Scheme 2.49). The latter can be synthesised from ethyl propiolate and triethylamine when a small amount of water is present *via* ethyl β-hydroxyacrylate which reacts with another molecule of ethyl propiolate to afford **2.55** [74CJC3569].



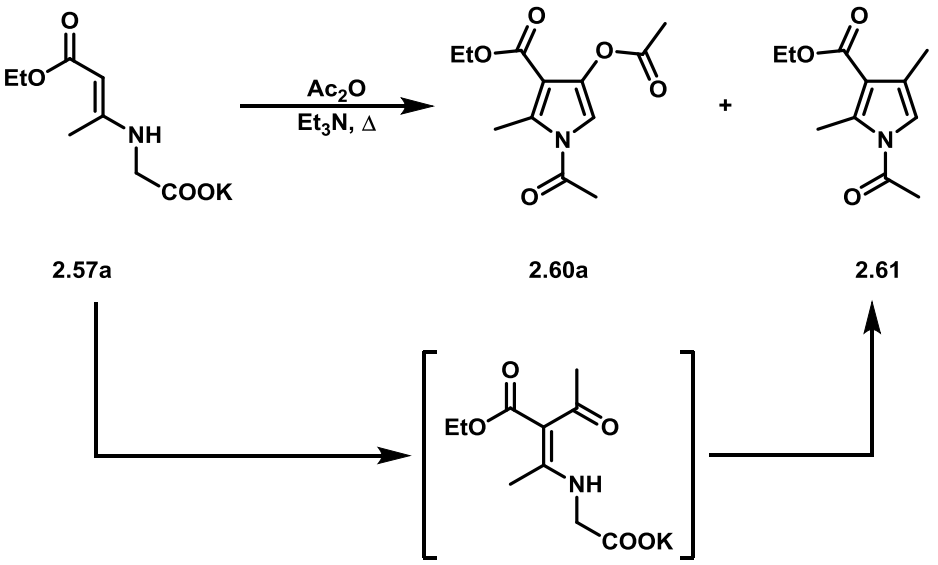
Scheme 2.49

As enamino acid **2.52** could not be accessed, Dane salts were synthesised from ethyl acetoacetate **2.56** and glycine and alanine **2.12a** and **2.12b** [Scheme 2.50, 65CB789].



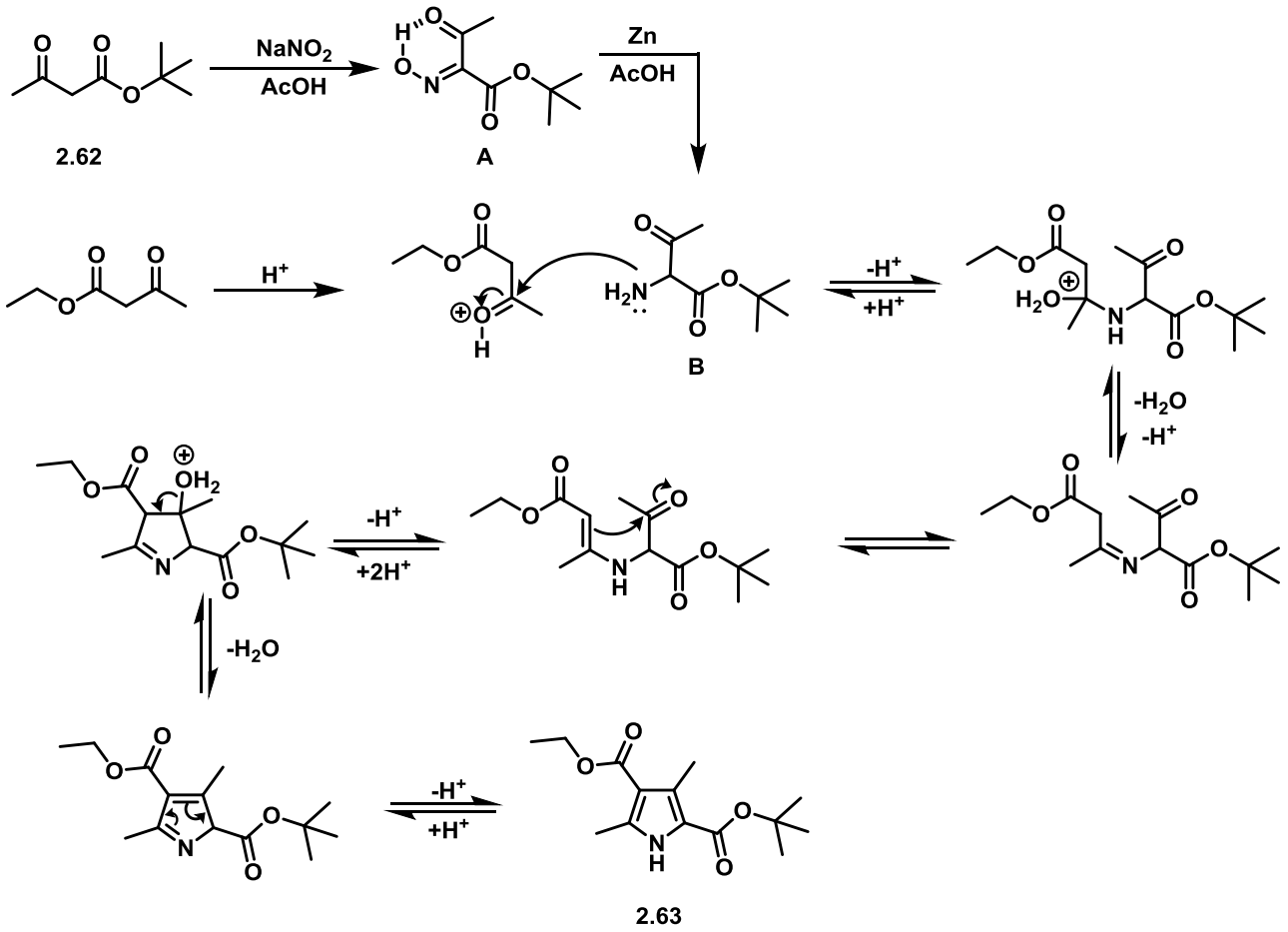
Scheme 2.50

The Dane salts **2.57a** and **2.57b**, from glycine and DL-alanine respectively, were synthesised in good to excellent yields (98 % and 74 % respectively). Attempts were made to access the free acid by gently acidifying with one equivalent of acetic acid, which, unfortunately only resulted in hydrolysis to ethyl acetoacetate **2.56**. However, it was found that cyclisation could still be initiated from the potassium salts (**2.57**) in acetic anhydride producing pyrroles **2.60a** and **2.60b**, the 3-acetoxy derivatives of **2.58**. However, the yields of the pyrrole products were poor (<10 %). None of the ethoxypyrrole **2.59** was observed. The cyclisation of **2.57a** also produced a second reaction product, **2.61**. The presence of this pyrrole signifies an acylation at the carbon β- to the amino function prior to the cyclisation resulting in incorporation of a methyl group at the C-4 position of the ring (Scheme 2.51).



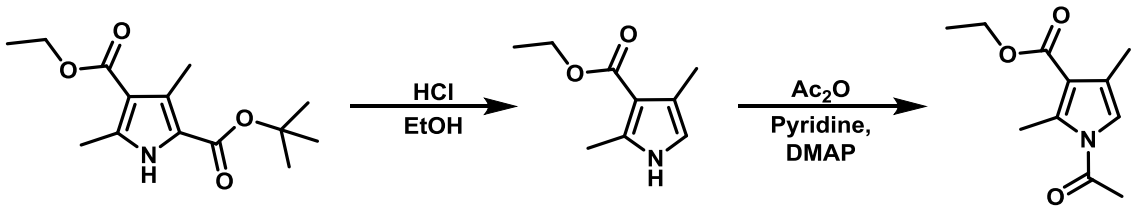
Scheme 2.51

Formation of **2.60a** can only result from cyclisation of the mixed anhydride (or the derived aminoketene) generated from **2.57** onto the β-carbon of the enamino ester. Clearly, further work is required to optimise the yields of pyrroles from this reaction. Compound **2.61** appears to be a novel compound and to verify its constitution an unambiguous synthesis *via N*-acylation of the known ethyl 2,4-dimethylpyrrole-3-carboxylate **2.64** [Scheme 2.52, 09JA8578] was performed. Initially, tetrasubstituted pyrrole **2.63** was synthesised *via* a Knorr pyrrole synthesis from *tert*-butyl acetoacetate **2.62**; reduction of the isonitroso compound **A,** formed *in situ* by slow addition of sodium nitrite, provides the corresponding amine. The amine **B** readily underwent a condensation reaction with ethyl acetoacetate and subsequent cyclisation to provide pyrrole **2.63** in 46 % yield [Scheme 2.52, 11WO2011119777].



Scheme 2.52

The *tert*-butyl ester function was removed by the addition of concentrated hydrochloric acid to a stirred solution of pyrrole **2.63** in hot ethanol. The resulting trisubstituted pyrrole **2.64** crystallised upon cooling following dilution with water (69 % yield, Scheme 2.53). The pyrrole was stirred at 60 °C in a 1:1 mixture of acetic anhydride and pyridine in the presence of a catalytic amount of DMAP for 4 days. The product was subjected to an aqueous work-up, extracted with ethyl acetate, dried and the solvent removed *in vacuo* to give a mixture of products. The *N*-acetylpyrrole was isolated from unreacted *NH*-pyrrole **2.64** by flash column chromatography to provide **2.61** [Scheme 2.53, 95AJC1491]. The ^{1}H and ^{13}C NMR spectra for the pyrrole from the cyclisation of **2.57a** and the sample prepared by acetylation of known pyrrole **2.64** were identical.



2.63 2.64 2.61

Scheme 2.53

2.6.4 The Acylative Cyclisation of Enamino Acid 2.13b; Trapping of Intermediates using Dimethyl Acetylenedicarboxylate (DMAD)

In an attempt to gain a better insight into the mechanism of the enamino acid cyclisation the acylative cyclisation of **2.13b** was reinvestigated and the cyclisation was conducted in the absence of any base, conditions that facilitate exclusive formation of the acetoxypyrrole **2.18b**. It was thought that the failure to intercept any ketene or dipolar species such as **F** (Scheme 2.37) may stem from competitive nucleophilic addition of the base to the dipolarophile.

Thus, **2.13b** was heated in neat acetic anhydride in the presence of DMAD (2.5 equiv.). The reaction proceeded rapidly with vigorous evolution of CO_2. Aqueous work-up provided a new compound that exhibited signals in the ^{1}H NMR spectrum for two non-equivalent ethyl ester groups [δ 1.13 and 1.39 ($CH_2C\mathit{H}_3$) and δ 4.17 and 4.38 ($C\mathit{H}_2CH_3$)], a singlet for two methyls (δ 2.32), a single signal for two methoxy groups (methyl ester) at δ 3.85 and an alkene or aromatic proton signal at δ 7.59. The ^{13}C NMR spectrum revealed two equivalent methyl groups (δ 11.6), non-equivalent ethyl esters [δ 13.7 and 14.1 ($CO_2CH_2\mathit{C}H_3$), δ 62.3 and 62.6 ($CO_2\mathit{C}H_2CH_3$) and δ 162.2 and 162.4 ($\mathit{C}O_2CH_2CH_3$)] and two equivalent methyl esters [δ 51.6 ($CO_2\mathit{C}H_3$), and δ 165.4 ($\mathit{C}O_2CH_3$)]. There is a *C*H signal for an alkenic carbon at δ 137.2 and a quaternary carbon at δ 130.9. Furthermore, there are two other signals for quaternary carbons at 114.1 and 134.0 ppm for two carbons each. The ^{1}H and ^{13}C NMR data together are entirely consistent with *N*-alkenylpyrrole **2.65**. The structure of this compound was verified by X-ray crystallography (Figure 2.14, Appendix 3).

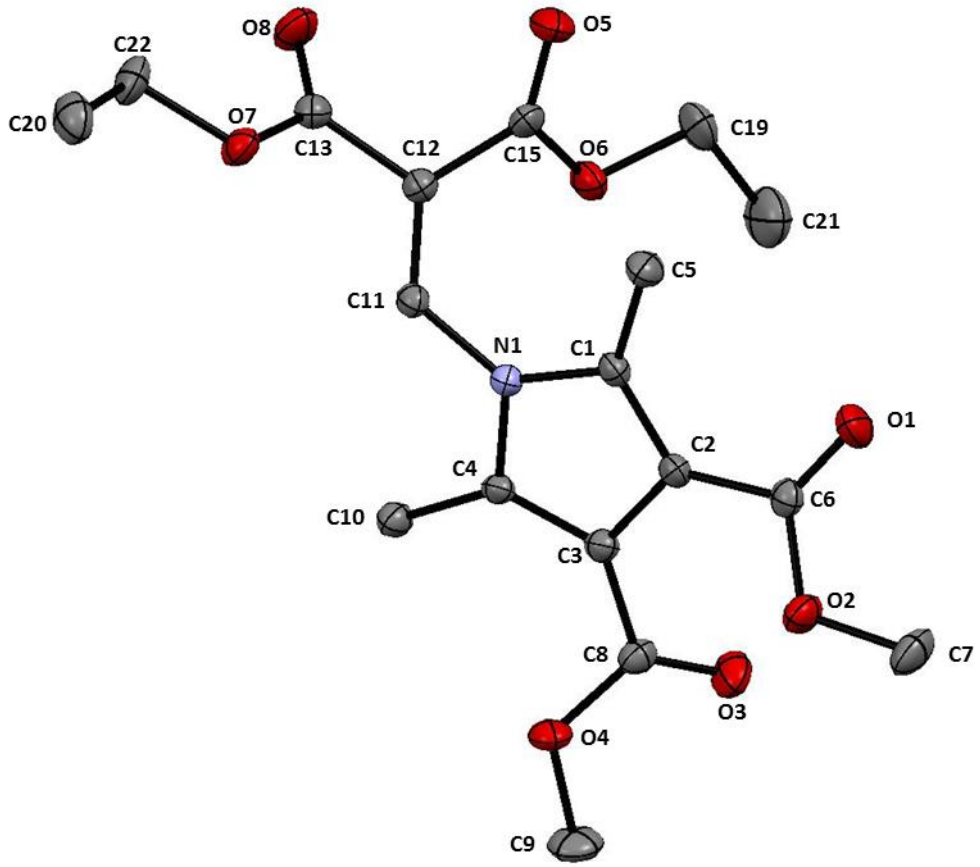
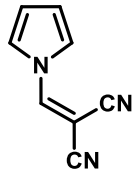


Figure 2.14 ORTEP plot of **2.65**, hydrogen atoms have been removed for clarity, ellipsoids at 50 % probability.

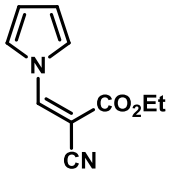
Table 2.6 Selected bond lengths and angles for **2.65**.

Atom 1	Atom 2	Length (Å)	Atom 1	Atom 2	Atom 3	Angle (°)
N1	C1	1.388	C1	N1	C4	109.97
N1	C4	1.392	N1	C1	C2	106.98
C1	C2	1.365	N1	C4	C3	107.14
C3	C4	1.362	C1	C2	C3	108.06
C2	C3	1.437	C2	C3	C5	107.84

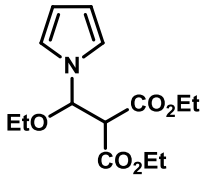
No derivatives of **2.65** have been described previously, the closest examples are represented by **2.66** and **2.67** obtained by reaction of pyrrolylpotassium with $EtOCH=C(CN)_2$ and $EtOCH=C(CN)CO_2Et$ respectively. Under the same conditions diethyl (ethoxymethylene)malonate **2.11** provided **2.68** as the only product [82CB714].



2.66

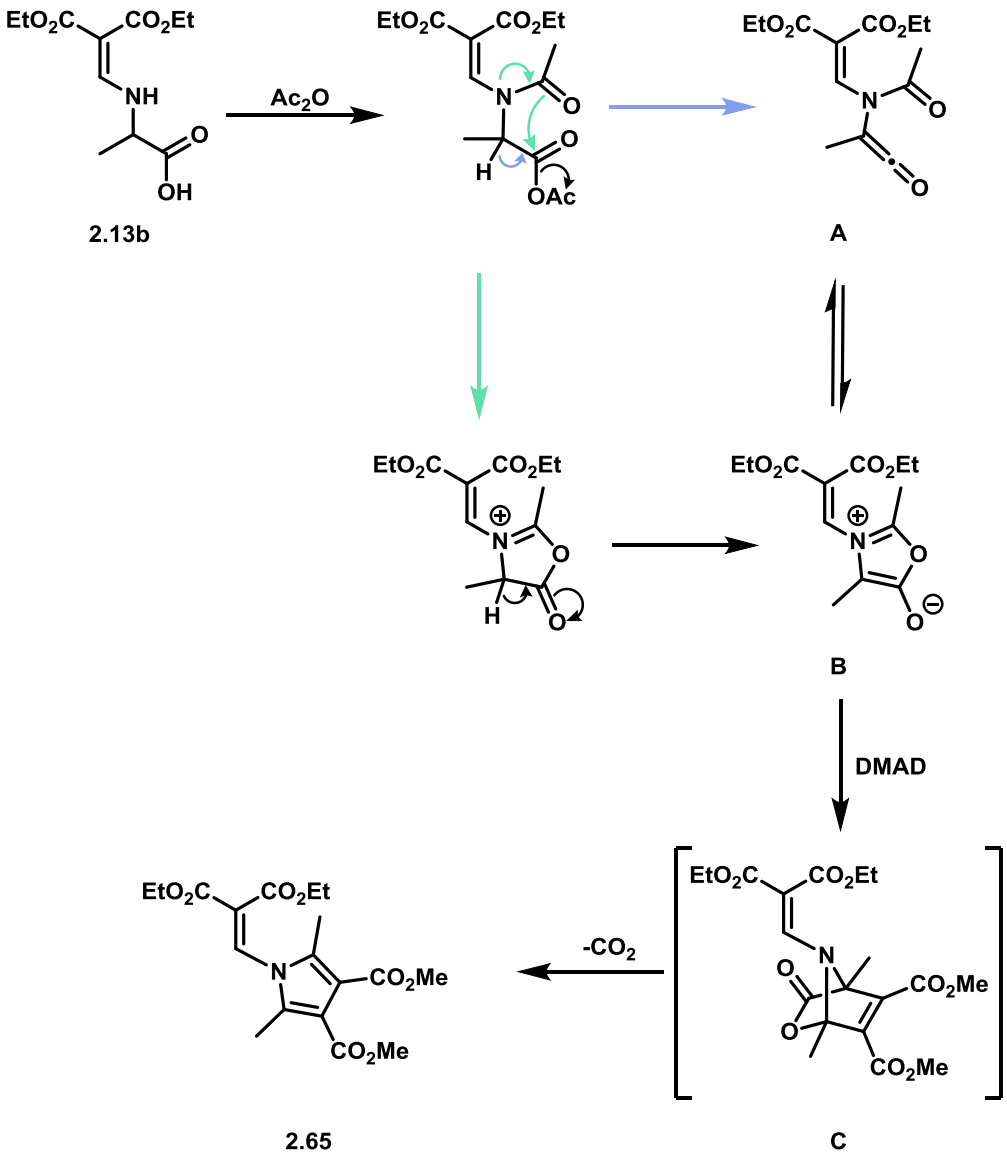


2.67



2.68

The formation of **2.65** can be rationalised by formation of an *N*-acylated mixed anhydride from **2.13b** which can either undergo elimination to give a ketene **A** which then undergoes cyclisation to a mesoionic münchnone system (1,3-oxazolium-5-olate) **B**. The latter may also arise by displacement of acetate by the amide carbonyl [86HC(45)731, Scheme 2.54]. Once generated **B** will undergo a 1,3-dipolar cycloaddition with DMAD followed by a facile cycloreversion of CO_2 to afford pyrrole **2.65** (52 % yield) as the only characterisable product.

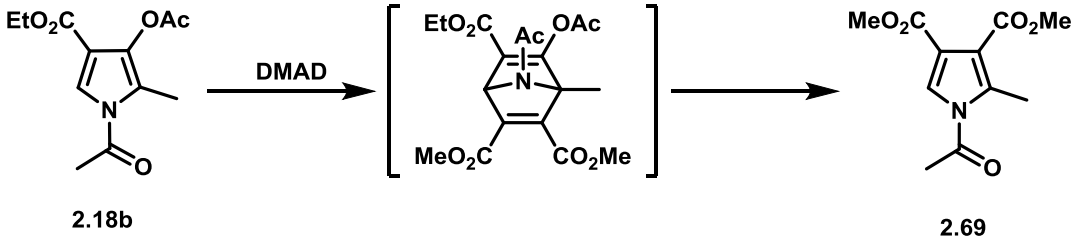


Scheme 2.54

These results provide evidence for the involvement of a münchnone intermediate in the cyclisation of **2.13b** to pyrroles **2.18b** and **2.19b** and thus do not preclude participation of a ketene intermediate. It should be noted that *N*-acylketene-münchnone valence tautomerism has been observed previously [88TL2027], however, no vinylogous examples have been reported.

Evidence that the formation of the *N*-vinylpyrrole **2.65** did not involve in any way the 3-acetoxypyrrole **2.18b** was gathered by subjecting the latter to the trapping conditions; to prevent any interaction between Ac_2O and the pyrrole ring, the solvent was substituted for xylenes due to the similarities in boiling point. When DMAD was heated with the pyrrole (**2.18b**) the latter underwent a [4+2] cycloaddition – [4+2] cycloreversion sequence with the elimination of ethyl 3-acetoxypropiolate (not isolated, not reported) affording pyrrole diester **2.69** (57 %, Scheme 2.55).

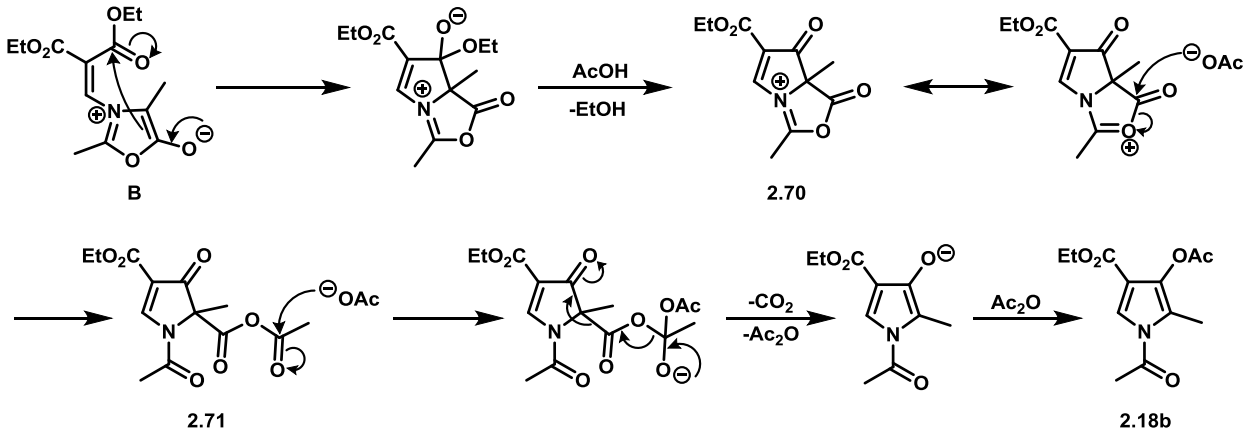
The latter has been obtained previously [*via* 3-acetyl-2-methyl-1,3-oxazolium-5-olate, generated *in situ* from MeCOCl and 5-(TBDMS-O)-2-methyloxazole, and DMAD] in lower yield but no characterisation data was reported [88TL2027].



2.18b **2.69**

Scheme 2.55

Formation of the *N*-vinylpyrrole **2.65** definitively established involvement of a münchnone intermediate and in the absence of DMAD, the reaction of **2.13b** with acetic anhydride provides **2.18b** as the only isolable product. This finding suggests a further reaction pathway for the formation of the acetoxypyrrole **2.18b** as well as the other acetoxypyrroles, as outlined in Scheme 2.56.



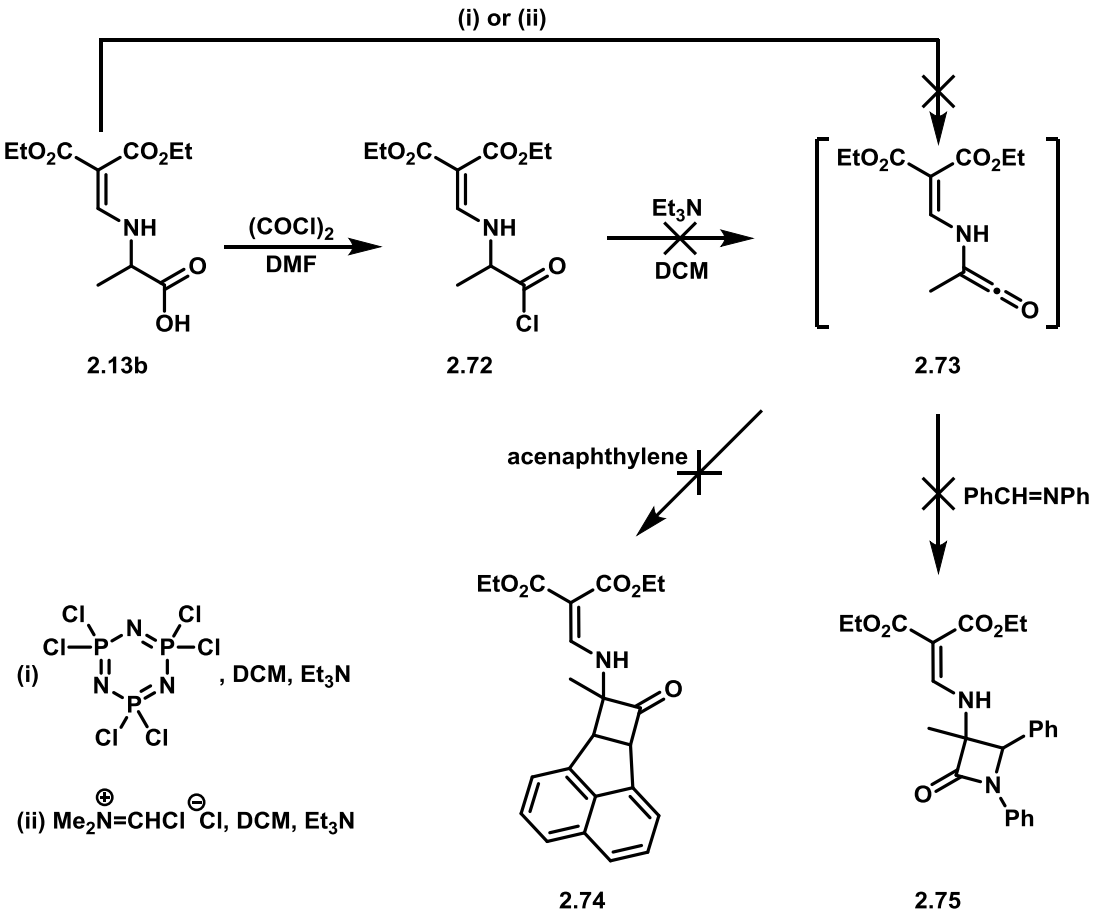
B **2.70** **2.71** **2.18b**

Scheme 2.56

Nucleophilic attack by C-4 of the münchnone ring on the pendant ester function could lead to the bicyclic intermediate **2.70** following elimination of EtOH. In this species, the lactone carbonyl will be susceptible to addition of acetate to afford the mixed anhydride **2.71** from which expulsion of CO_2 ensues, as shown, followed by *O*-acylation to afford the pyrrole product **2.18b**. It is pertinent to note that the pathway outlined above also provides a rationale to explain why no ^{13}C label would be retained in the product.

2.6.5 Attempted Ketene Generation from Diethyl 2-(1-carboxyethylaminomethylene)malonate

Following the successful trapping of the münchnone intermediate, the synthesis of the (aminomethylene) ketene intermediate was attempted from **2.13b**. The enamino acid chloride **2.72** was synthesised following a procedure for the preparation of *N*-(trifluoroacetyl)-α-amino acid chlorides [$CF_3CONHCH(R)COCl$] [84JOC4107]. The enamino acid was stirred under nitrogen in anhydrous DCM at 0 °C. To the solution was added a catalytic amount of DMF whilst oxalyl chloride was added dropwise. The solvent was removed under reduced pressure and the carboxylic acid proton was absent in the ^1H NMR spectrum. The crude acyl chloride **2.72** was dissolved in anhydrous DCM under nitrogen and cooled to 0 °C, triethylamine was added and the reaction allowed to warm room temperature and stirred for a further 4 hours. After aqueous work-up, the solvent was removed. The ^1H NMR spectrum was complex and no distinct structure could be determined (Scheme 2.57). The aminoketene **2.73** would be anticipated to be highly unstable so the base treatment of the acid chloride was performed in the presence of the ketene trap acenaphthylene, which is known to generate fused cyclobutanones from a [2+2]-cycloaddition [84JCS(P1)1465]. The reaction did not provide any product **2.74** and acenaphthylene was recovered unchanged. Attempts to generate ketene **2.73** directly dehydration of **2.13b** using either phosphonitrilic chloride [13T6620] or with the Vilsmeier reagent [09T2927] in the presence of benzylideneaniline failed to generate any of the β-lactam **2.75** (Scheme 2.57). No further attempts to dehydrate **2.13b** were undertaken.

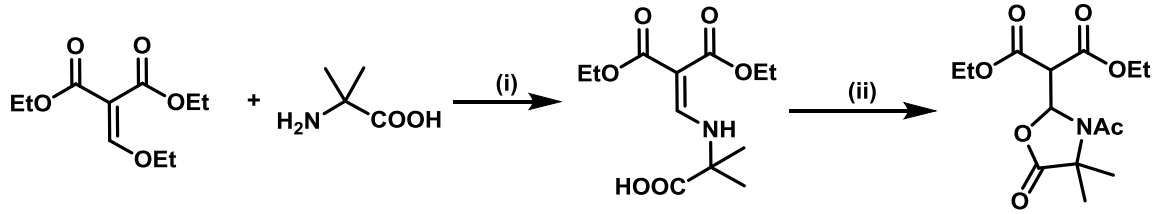


Scheme 2.57

2.6.6 Attempted Cyclisation of Diethyl 2-[(1-carboxy-1-methyl)ethylaminomethylene]malonate

A further mechanistic question is the importance of the presence of an α-proton in the amino acid and consequently the enamino acid **2.13** in initiating the cyclisation step. Therefore, to investigate this aspect, 2-aminoisobutyric acid **2.76** was utilised to synthesise enamino acid **2.77** in 80 % yield (Scheme 2.58). When **2.77** was subject to the usual cyclisation conditions (Ac_2O, Et_3N) a new, non-aromatic product was obtained. The product was characterised as the novel oxazolidine **2.78**. Thus, the ^{1}H NMR spectrum exhibited overlapping signals for each of the ethyl esters [δ 1.26–1.33 (2 × $CO_2CH_2CH_3$) and δ 4.17–4.30 (2 × $CO_2CH_2CH_3$)] and two singlets for the geminal dimethyl groups at δ 1.65 and 1.73. The *N*-acetyl methyl signal was exhibited as a singlet at δ 2.20 and the two methine groups were each displayed as a doublet at δ 4.47 and δ 6.30 for the C*H*$(CO_2Et)_2$ and OC*H*N protons respectively (J = 2.7 Hz). The ^{13}C NMR displayed a single peak for the two methyl groups at δ 14.0 and the adjacent carbon resonated at 58.5 ppm. The non-equivalent ethyl ester groups exhibited signals at δ 22.9 and 24.6 ($CO_2CH_2CH_3$), δ 61.8 and 62.2 ($CO_2CH_2CH_3$) and 165.5 and 165.8 ppm for the two carbonyls. The *N*-acetyl group gave a signal at δ 26.7 for the methyl

and 169.3 ppm for the carbonyl group; the two methine carbons exhibited signals at δ 86.0 for the ring *C*H and δ 53.5 for the carbon adjacent to the two ester groups. The lactone carbonyl resonated at 174.6 ppm. The IR band for the lactone carbonyl absorbed at 1803 cm^{-1}.

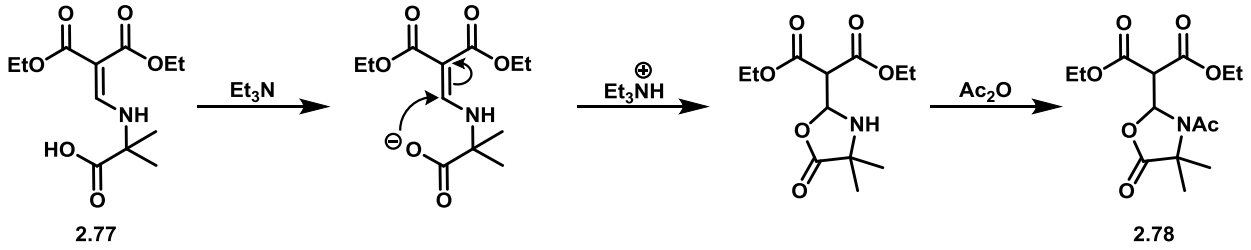


2.11 **2.76** **2.77** **2.78**

Reagents: (i) KOH, EtOH, Δ, then 2M HCl; (ii) Ac_2O, Et_3N, Δ.

Scheme 2.58

Formation of **2.78** can be rationalised simply as an intramolecular conjugate addition of the carboxylate anion to the highly activated Michael acceptor in a 5-*exo*-*trig* ring closure [76CC734]. Acylation completes the sequence (Scheme 2.59).



2.77 **2.78**

Scheme 2.59

The requirement for an α-proton in the enamino acids **2.13** is thus established. Indeed the Dakin-West reaction (which involves a münchnone intermediate) does not operate when two substituents are present at the α-position [88CSR91].

2.7 Summary

Some of the main features from this work are summarised below.

From the diethyl 2-(1-carboxyalkylaminomethylene)malonates acylative cyclodehydration and decarboxylation occur upon treatment with Ac_2O, Ac_2O-NaOAc or Ac_2O-Et_3N to provide 3-acetoxypyrroles in moderate yields. The latter reagent pairing providing varying amounts of the corresponding 3-ethoxypyrroles. ^{13}C Labelling revealed that β-acylation of the enaminone function in **2.13** does not occur thereby excluding the pathways outlined in Scheme 2.36. Distinction between the mechanisms outlined in Scheme 2.38 and Scheme 2.39 has not proved possible, though both have some similar features. The involvement of a münchnone intermediate in these reactions has been demonstrated by trapping with DMAD to give the *N*-alkenylpyrrole **2.65** and it may be that the reaction follows the course depicted in Scheme 2.56. Further trapping experiments of the münchnone intermediates are merited.

As yet the differing outcomes from the cyclisations using Ac_2O and Ac_2O-Et_3N (the latter affords up to 20 % of the 3-ethoxypyrrole) remain unclear.

The enamino acids **2.13j** and **2.13k** derived from aspartic acid and glutamic acid respectively exhibited differing behaviour compared to compounds containing a monofunctional amino acid residue. The former provided diethyl acetamidomalonate as the sole product, whilst the latter afforded the *N*-alkenylpyrrolidin-2-one derivative **2.23**; the participation of five-membered intermediates accounts for formation of the pyrrole-2-acetonitrile derivatives **2.24** and **2.25** from treatment of the asparagine **2.13m**.

Both the 3-ethoxy- and 3-acetoxypyrrole were obtained when the enamino malonate **2.13o** from methionine sulfoxide was treated with Ac_2O-Et_3N.

A novel cyclisation leading to an oxazolidin-5-one *via* a conjugate addition has been obtained from cyclisation of the aminoisobutyric acid **2.77** in which formation of a münchnone intermediate is prevented.

Chapter 3

3-Aminopyrrole Derivatives

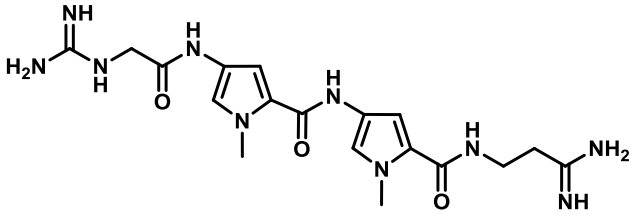
Chapter 3 3-Aminopyrrole Derivatives

3.1 Synthesis of 3-Aminopyrrole Derivatives

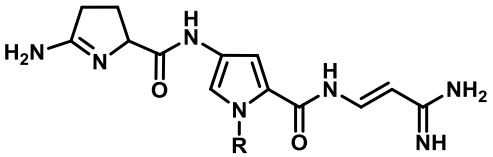
3.1.1 Introduction

Examples of all three aminopyrrole derivatives are known and an extensive review of the synthesis and properties of these compounds is available [92HC(49-2)299]. A SciFinder search revealed 180 references using the search term "1-aminopyrroles" (1926–2017), 1414 references to "2-aminopyrroles" (1904–2017) and 1694 publications relating to 3-aminopyrrole derivatives from 1923–2017. Although there are a larger number of references to the latter compounds, there are significantly fewer routes available for their synthesis compared to the 2-amino- counterparts.

3-Aminopyrroles have been found in nature (as a class of pyrrole-amidine antiviral antibiotics), represented by congocidine (from *Streptomyces netropsis*) **3.1** and kikumycins A **3.2** and B **3.3** from *S. phaeochromogenes* [Figure 3.1, 67BSF4348, 72TL1873, 78CPB3080], and are extremely useful building blocks in the synthesis of bioactive compounds [04T2267].



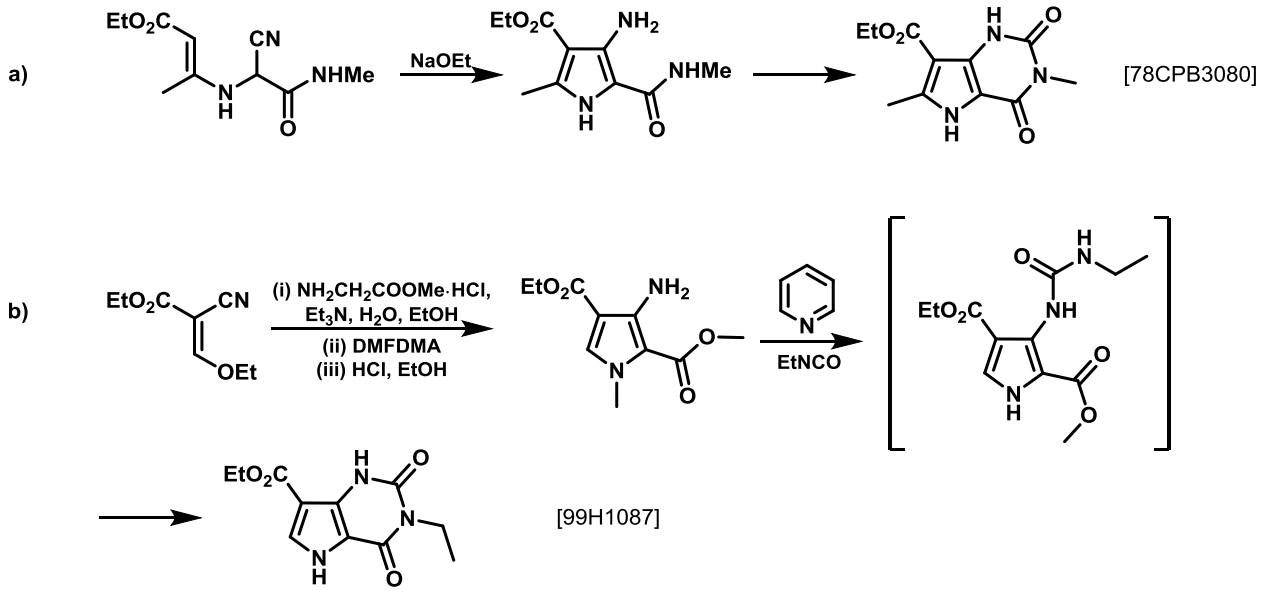
3.1



3.2 R = H
3.3 R = Me

Figure 3.1 Pyrrole-amidine antiviral antibiotics, congocidine **3.1** and kikumycins A **3.2** and B **3.3**.

The primary reason for the synthesis of 3-aminopyrroles is to construct pyrrolo[3,2-*d*]pyrimidines (9-deazapurines) and pyrrolo[3,4-*d*]pyrimidines. Pyrrolo[3,2-*d*]pyrimidines are closely related to purines, which are of biological significance and are abundant in nature [78JCS(P1)483]. The syntheses and uses of 3-aminopyrroles are illustrated below (Scheme 3.1). Scheme 3.1a) – c) concern pyrrolo[3,2-*d*]pyrimidines and all use enamines as precursors to the 4-aminopyrrole-3-carboxylate [Scheme 3.1a)], 3-aminopyrrole-2,4-dicarboxylate [Scheme 3.1b)] and 3-aminopyrrole-2-carboxylate [Scheme 3.1c)]. Scheme 3.1d) begins in a similar manner and employs a Thorpe-type cyclisation; the aminopyrrole is then converted to an iminophosphorane and undergoes an aza-Wittig reaction before further cyclisation to the pyrrolo[3,4-*d*]pyrimidine [13ARK(iii)199].



Scheme 3.1

Relatively few 3-aminopyrroles have been described. In general the majority of synthetic routes provide compounds possessing an electron-withdrawing group at C-2. Further consideration of the

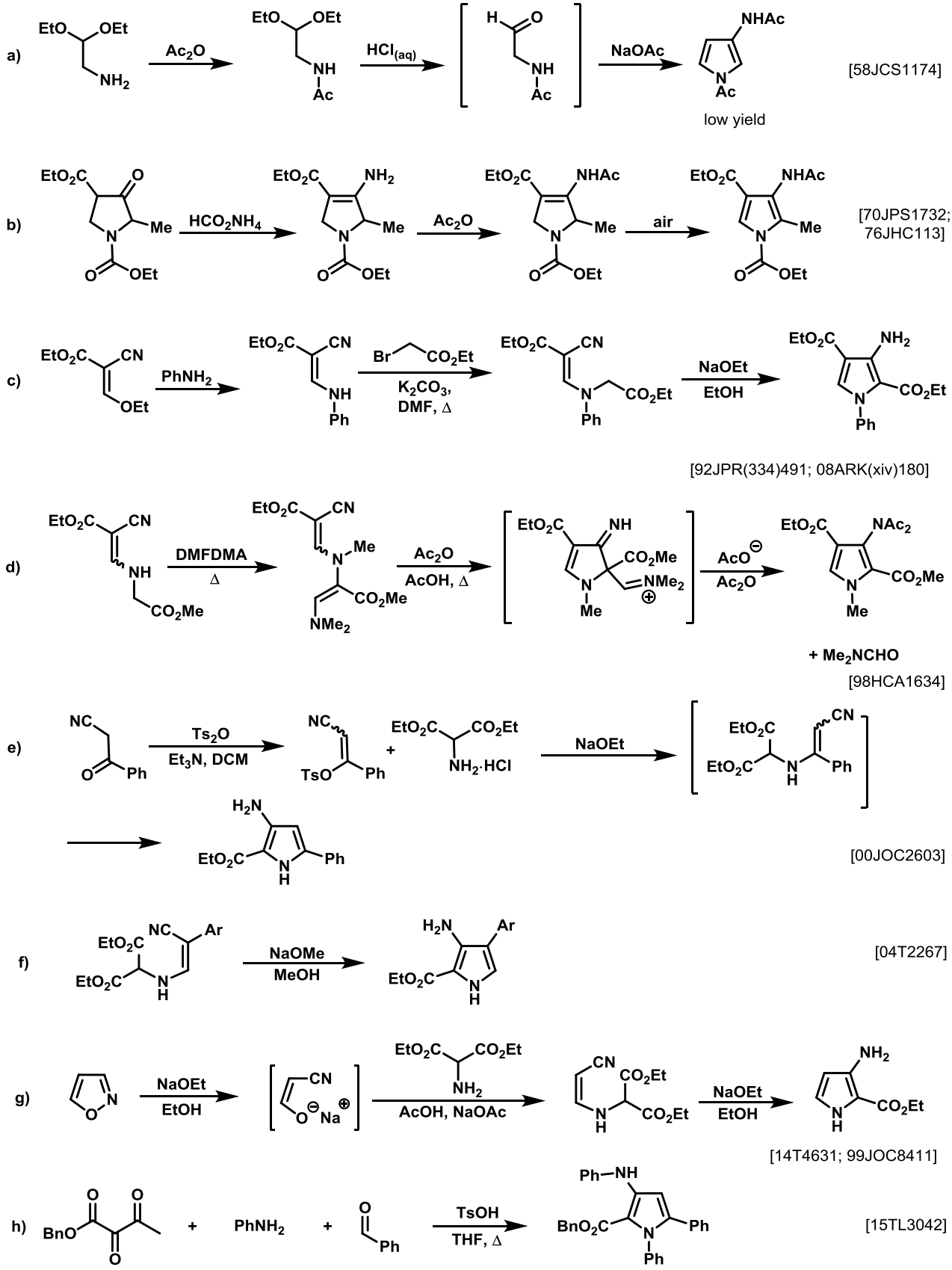
various approaches is appropriate and the most important pathways are outlined in Scheme 3.2. The first 3-aminopyrrole derivative described was 3-acetamido-1-acetylpyrrole, obtained in low yield from the self-condensation of acetamidoacetaldehyde, generated *in-situ* by hydrolysis of the diethyl acetal [Scheme 3.2a)].

A multistep sequence involving the amination of an *N*-acylpyrrolidin-3-one, acetylation and aerial oxidation provided a low yielding route to ethyl 4-acetamido-1-ethoxycarbonyl-5-methylpyrrole-3-carboxylate. The cumbersome preparation of the pyrrolidin-3-one further detracts from this approach [Scheme 3.2b); 70JPS1732; 76JHC113].

A Thorpe-type reaction provides access to a tri-substituted 3-aminopyrrole from an enamino ester and thence to the fused pyrimidinedione [Scheme 3.1a); 78CPB3080]. Numerous variations of Thorpe-type condensations involving enamino nitriles have been reported as depicted in Scheme 3.1b)–d) and Scheme 3.2 c) and d). In a variation of this approach enol esters or ethers derived from β-cyano ketones condense with diethyl aminomalonate under basic conditions to afford ethyl 3-aminopyrrole-2-carboxylates. Variation of the β-cyano carbonyl compounds permits products having a substituent at C-4 or C-5 to be obtained [Scheme 3.2e)].

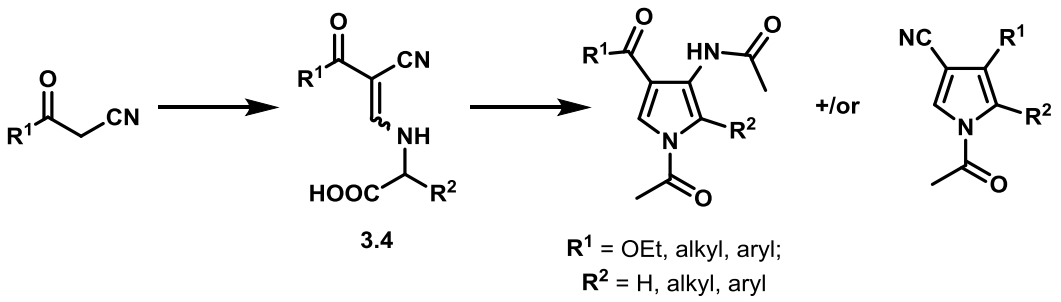
Methylenation of arylacetonitriles can be readily accomplished *via* treatment with HCO_2Et-NaOEt, to provide 3-aminopyrroles possessing an aryl substituent at C-4 [Scheme 3.2f)]. The highly unstable cyanoacetaldehyde, generated by base-mediated ring cleavage of isoxazole, has been condensed *in situ* with diethyl aminomalonate to afford an enaminonitrile that can be cyclised to give ethyl 3-aminopyrrole-2-carboxylate [Scheme 3.2g)].

A three-component condensation between an α,β-diketo ester and aromatic amines and aldehydes proceeds under acidic conditions to afford 3-aminopyrrole-2-carboxylates [Scheme 3.2h)]. An enamino intermediate derived by the attack of $PhNH_2$ on the β-carbonyl group has been invoked to rationalise the outcome of this reaction [15TL3042].


a)
Ac2O
HCl(aq)
NaOAc
low yield
[58JCS1174]
b)
HCO2NH4
Ac2O
air
[70JPS1732; 76JHC113]
c)
PhNH2
K2CO3, DMF, Δ
NaOEt
EtOH
[92JPR(334)491; 08ARK(xiv)180]
d)
DMFDMA
Δ
Ac2O
AcOH, Δ
AcO⊖
Ac2O
+ Me2NCHO
[98HCA1634]
e)
Ts2O
Et3N, DCM
NaOEt
[00JOC2603]
f)
NaOMe
MeOH
[04T2267]
g)
NaOEt
EtOH
AcOH, NaOAc
NaOEt
EtOH
[14T4631; 99JOC8411]
h)
PhNH2
TsOH
THF, Δ
[15TL3042]

Scheme 3.2

Following the application of the Zav'yalov pyrrole synthesis to a wide range of enamino acids, it was of interest to explore the scope of the reaction by investigating the outcome of the acetylative cyclisations of enamino acids derived from a range of β-cyanocarbonyl compounds **3.4** as shown in Scheme 3.3. These enaminones possess two potential cyclisation termini and could afford either 3-acetamidopyrroles or pyrrole-3-carbonitriles or, indeed other products.



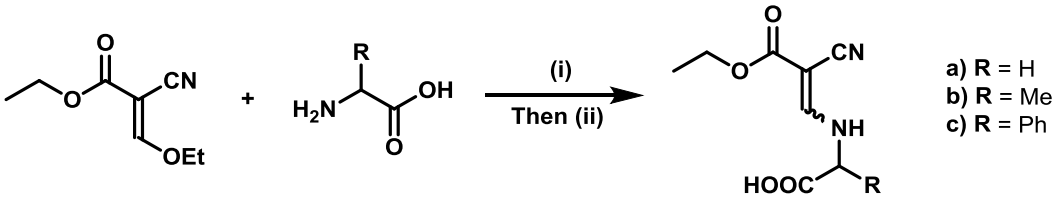
Scheme 3.3

It is apparent from Scheme 3.1 and Scheme 3.2 that the majority of routes to 3-aminopyrroles afford compounds possessing an ester or nitrile function in the α (C-2) position. The Zav'yalov approach has the advantage in obviating the need for functional group manipulation to obtain the 2,5-unsubstituted derivatives. Moreover, substituents can be introduced into the C-5 position by appropriate choice of α-amino acid derivative.

3.2 Synthesis of Pyrroles from (Aminomethylene)cyanoacetates

The initial work required access to enamino acids derived from ethyl cyanoacetate i.e. **3.4** (R = OEt). To this end the commercially available ethyl (*E*)-(ethoxymethylene)cyanoacetate was selected as the starting material.

3.2.1 Synthesis of Ethyl 2-(1-carboxyalkylaminomethylene)cyanoacetates



3.5 **3.6** **3.7**

Reagents: (i) KOH, EtOH, Δ; (ii) 2M HCl.

Scheme 3.4

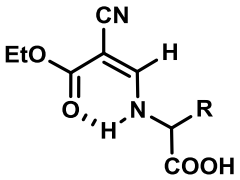
The enamino acids **3.7** derived from ethyl (ethoxymethylene)cyanoacetate **3.5** were prepared analogously to the majority of enamino acids **2.13** described previously (Scheme 2.9, Scheme 3.4). Thus, the commercially available cyanoacetate **3.5** was added to an α-amino acid and potassium hydroxide in ethanol, and the mixture refluxed with stirring for 1 hour. The solvent was removed *in vacuo* and the residue diluted with water prior to acidification with dilute hydrochloric acid (2M). The product was then isolated *via* extraction into ethyl acetate. Glycine, DL-alanine and DL-phenylglycine were chosen as the initial amino acid condensation partners because of their potential to afford interesting products. All of the enamino acids **3.7a–c** are unknown in the literature and were synthesised in moderate to very good yields (Table 3.1). With an increase in scale of the reaction (from 50 to 100 mmol) glycine gave an increased yield from 46 % to 88 % (Table 3.1, entry 1).

Table 3.1 Yields of compound **3.7**.

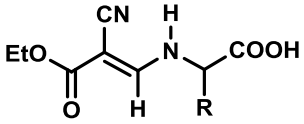
Entry	Compound	R	Yield	Ratio *E/Z* isomers
1	**3.7a**	H	46 % (88 %)[a]	0.7 : 1
2	**3.7b**	CH_3	63 %	0.7 : 1
3	**3.7c**	Ph	81 %	0.4 : 1

[a]2 × scale

The three enamino acids **3.7a–c** were, as expected, obtained as a mixture of the *E*- and *Z*- isomers (Scheme 3.5, Table 3.1), the ratios of which are based on the relative integrals of the alkenyl proton (Figure 3.2).



(*Z*)-3.7



(*E*)-3.7

a) R = H
b) R = Me
c) R = Ph

Scheme 3.5

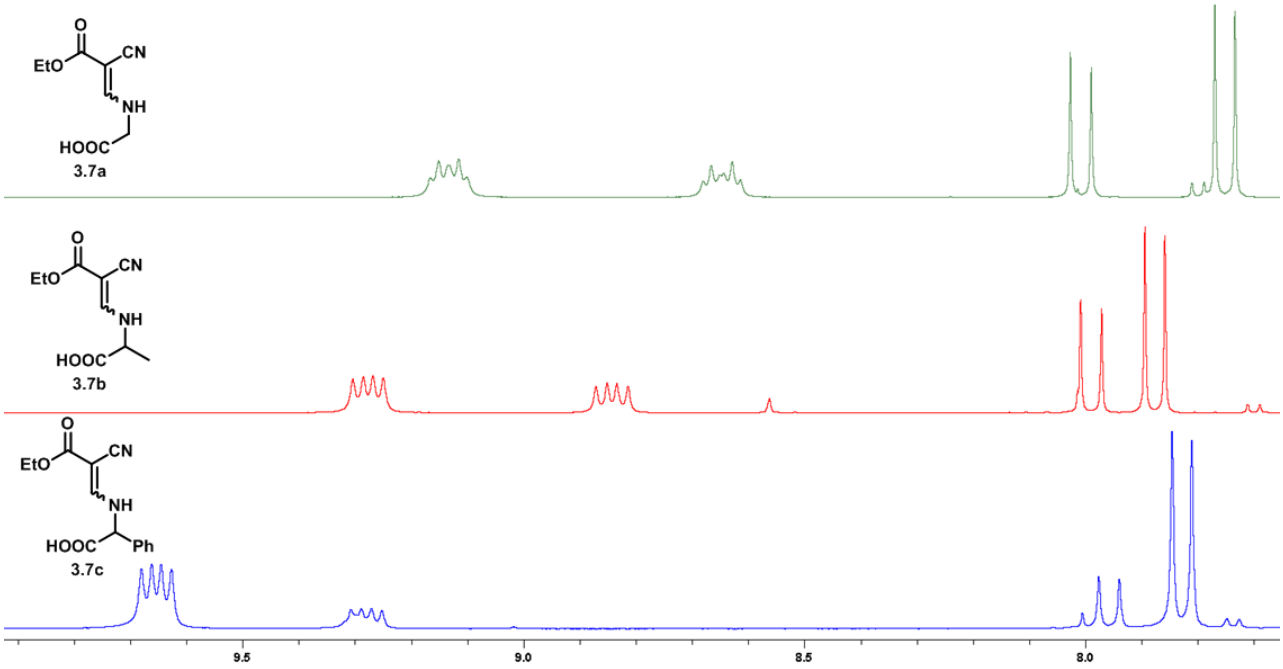
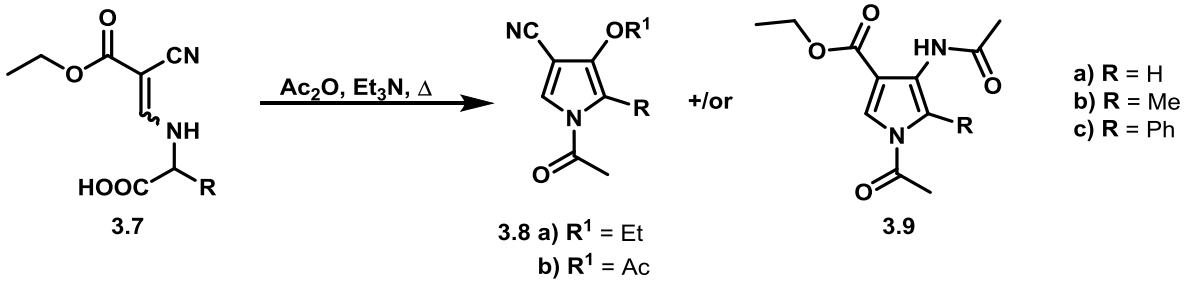


Figure 3.2 ^{1}H NMR [400 MHz, DMSO-d_6] of (*E*)- and (*Z*)- Isomers of **3.7a–c**.

Distinction between the (*Z*)- and (*E)*-isomers of **3.7a–c** (Scheme 3.5) was readily accomplished from the ^{1}H NMR spectra of the mixture (Figure 3.2). In the (*Z*)-isomer, intramolecular hydrogen bonding of the N-H function with the ester carbonyl group provides a six-membered chelate and will result in substantial deshielding of the N-H proton signal. However, in the (*E*)-isomer, in which no such intramolecular hydrogen bonding is possible, the N-H function will resonate at a higher field position. In the three enamino acids **3.7a–c** the N-H protons in the (*Z*)-isomers were deshielded by *ca.* 0.4 ppm compared to those of the (*E*)-isomers. Interestingly, in the latter isomers the alkene proton signal was always more deshielded than those in the (*Z*)-isomer, a

reflection of its proximity to the anisotropic ester carbonyl group. With **3.7a–c** to hand, their acylative cyclisation reactions under the standard conditions (Ac_2O, Et_3N) were explored. The results are described in the following section.

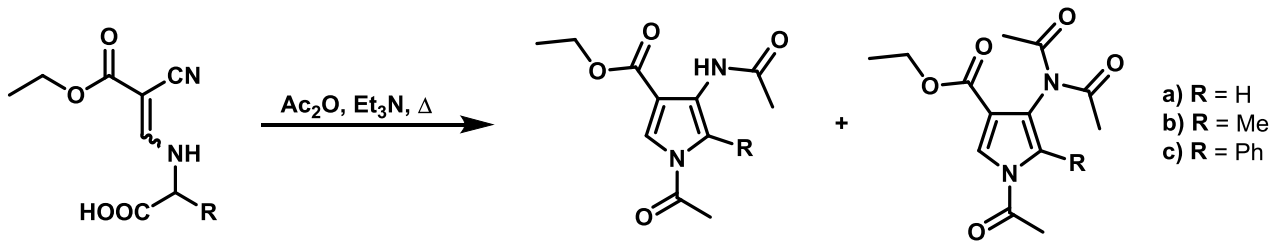
3.2.2 Cyclisation of Ethyl 2-(1-carboxyalkylaminomethylene)cyanoacetates



3.7 **3.8 a)** R^1 = Et **b)** R^1 = Ac **3.9**

Scheme 3.6

When subjected to the cyclisation conditions, acetic anhydride and base at reflux, the cyano esters **3.7a–c** could generate either the cyano- **3.8** or the amidopyrroles **3.9** or, perhaps, a mixture of both (Scheme 3.6). Thus when **3.7a–c** were heated in acetic anhydride and triethylamine, the reactions proceeded quickly with rapid evolution of CO_2. The reaction mixtures were hydrolysed prior to extraction with dichloromethane. The residue from the organic extracts was purified by flash column chromatography. The products from **3.7a–c** were identified as the novel amido- **3.9a–c** and the imidopyrroles **3.10b** and **c** (Scheme 3.7) in varying ratios.



3.7 **3.9** **3.10**

Scheme 3.7

Table 3.2 Yields of amidopyrroles **3.9** and imidopyrroles **3.10.**

Entry	R in 3.7	Pyrrole 3.9	Yield (%)	Pyrrole 3.10	Yield (%)
1	H	**3.9a**	43	**3.10a**	-
2	Me	**3.9b**	40	**3.10b**	6
3	Ph	**3.9c**	41	**3.10c**	23

The imidopyrrole **3.10** is a consequence of acetylation of the pyrrole **3.9**. For example, the cyclisation of **3.7b** was conducted in the absence of Et_3N to reduce the speed of reaction (Table 2.5) and when stopped after 15 minutes, only the amidopyrrole **3.9b** was obtained in low yield (22 %). When the reaction was repeated and stirred for 1 hour at reflux the sole product was imidopyrrole **3.10b** in good yield (64 %).

From the cyclisation of **3.7a**, the novel 3-amidopyrrole **3.9a** was obtained in moderate yield (43 %, 10 mmol). When the reaction was repeated on a larger scale (100 mmol) a trace amount of a mixture containing **3.8a** (0.4 %) was also isolated. The ^{1}H NMR spectrum (Figure 3.3) showed the presence of a very small amount of the acetoxypyrrole **3.8b** (ratio 1:0.08 based on integration). The shifts of the ethyl signals δ 1.33 and δ 4.00 in **3.8a** are comparable to known compounds 4-ethoxy-1*H*-pyrrole-3-carbonitrile (δ 1.41 and 3.97) [12LOC305] and 4-ethoxy-1'*H*-[1,3'-bipyrrole]-3,4'dicarbonitrile (δ 1.35 and δ 3.97) [12TL446]. The ^{13}C NMR shifts of the nitrile and the C-3 carbon are also comparable δ 113.9 (lit. 115.7 [12LOC305] and lit. 115.0 ppm [12TL446]) and δ 90.1 (lit. 83.8 [12LOC305] and lit. 91.9 ppm [12TL446]), respectively. On the larger scale (100 mmol), the yield of **3.9a** was improved to 56 %.

Plausible mechanisms for the formation of the products will be discussed subsequently.

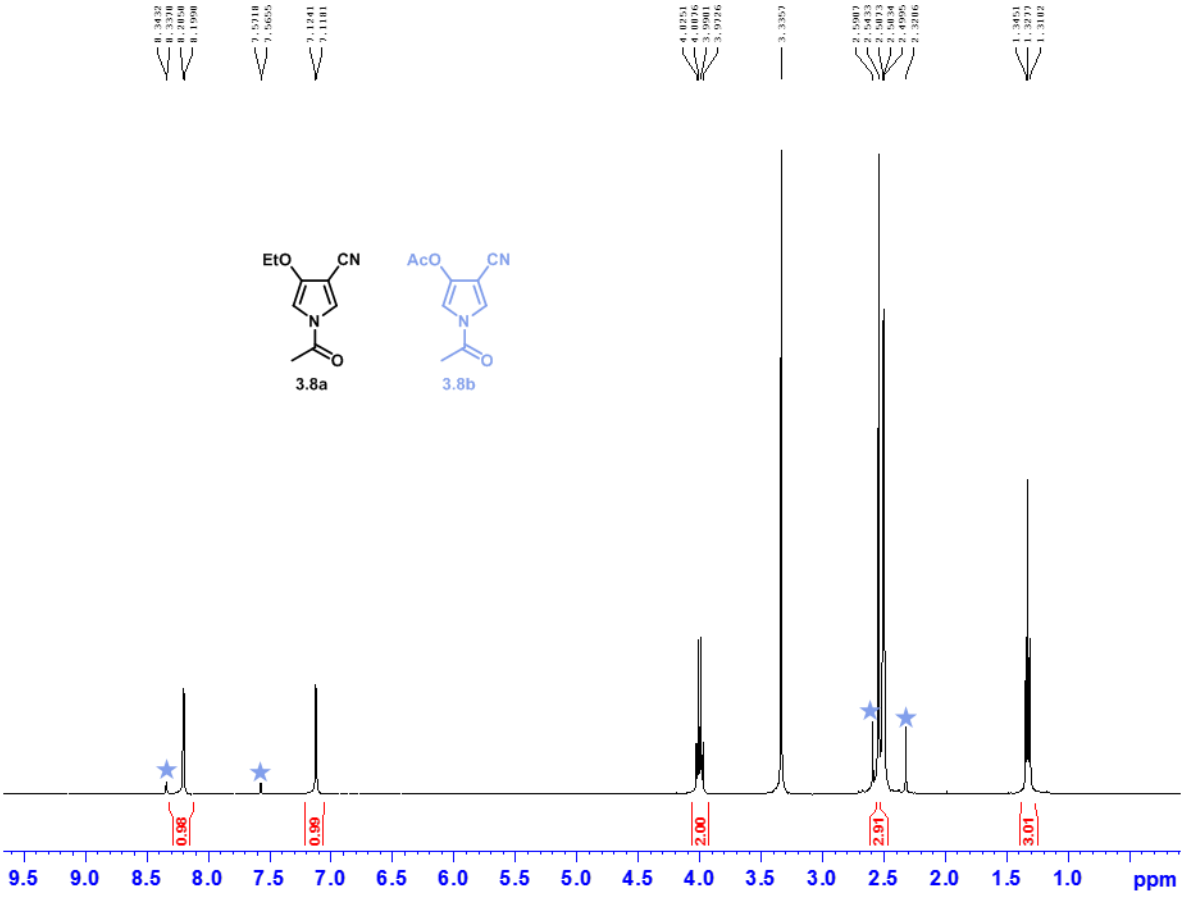


Figure 3.3 ^{1}H NMR Spectrum [400 MHz, $(CD_3)_2SO$] of pyrrole-3-carbonitriles **3.8a** and **3.8b.**

The reaction of **3.7b** with acetic anhydride and triethylamine gave three products (TLC) separable by flash column chromatography. The first product to elute from the column (30 % EtOAc in hexane) gave a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) which exhibited four methyl environments (δ 2.17 – 2.28), a methine proton (δ 6.87) and an ethoxycarbonyl group. This product was finally identified by X-ray crystallography (Figure 3.4) as 2,3-dihydropyrrole **3.11** in 3 % yield. The bond lengths and angles (Table 3.3, Appendix 4) are comparable to substituted 2,3-dihydropyrroles in the literature [11OL3806]. Continued elution of the column (30 % EtOAc in hexane) provided a small amount of **3.10b** (6 %) followed by 3-amidopyrrole **3.9b** (40 %).

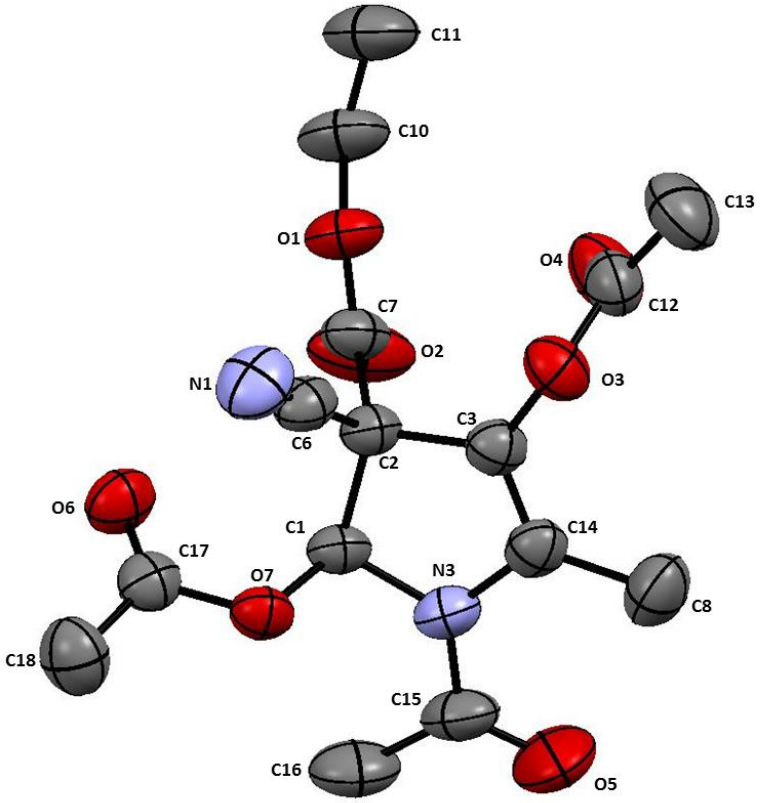
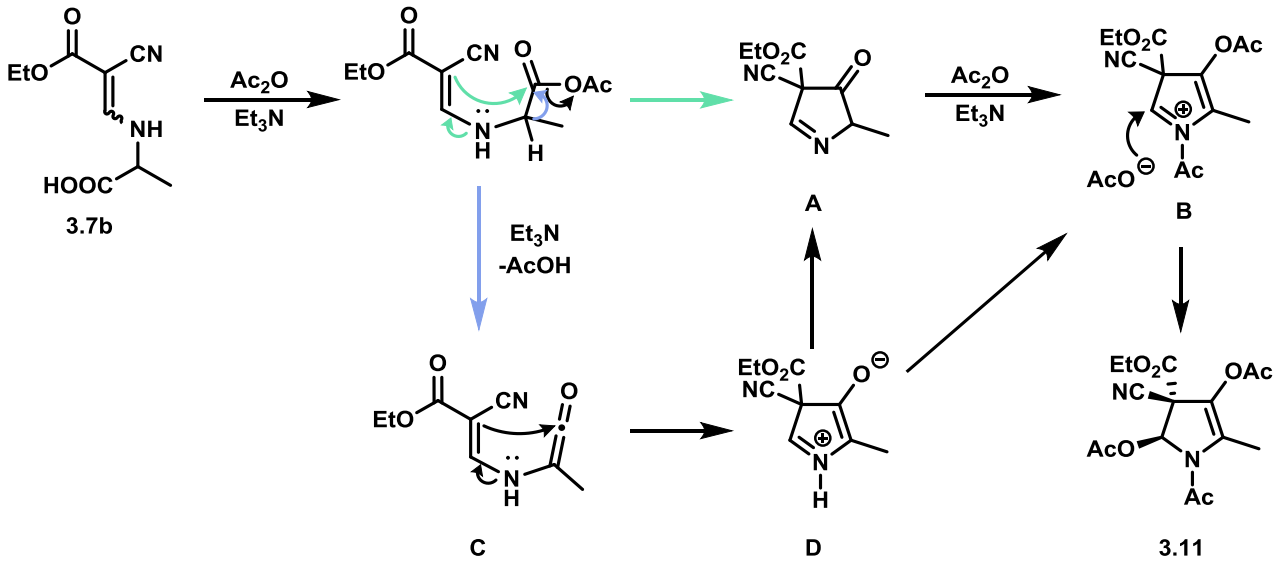


Figure 3.4 ORTEP plot of 2,3-dihydropyrrole **3.11**, hydrogens have been removed for clarity, ellipsoids are at 50 % probability.

Table 3.3 Selected bond lengths and angles for **3.11**.

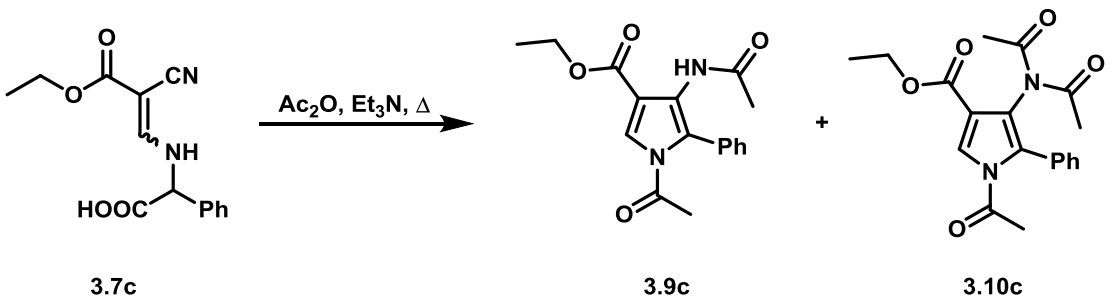
Atom 1	Atom 2	Length (Å)	Atom 1	Atom 2	Atom 3	Angle (°)
N3	C1	1.454	C1	N3	C14	110.25
N3	C14	1.416	N3	C1	C2	105.18
C1	C2	1.564	N3	C14	C3	109.92
C2	C3	1.508	C1	C2	C3	101.19
C3	C14	1.322	C2	C3	C14	113.17

The 2,3-dihydropyrrole **3.11** was obtained as a single diastereoisomer for which the relative stereochemistry (2*R**,3*S**) was established. The mechanism for its formation is proposed below (Scheme 3.8).



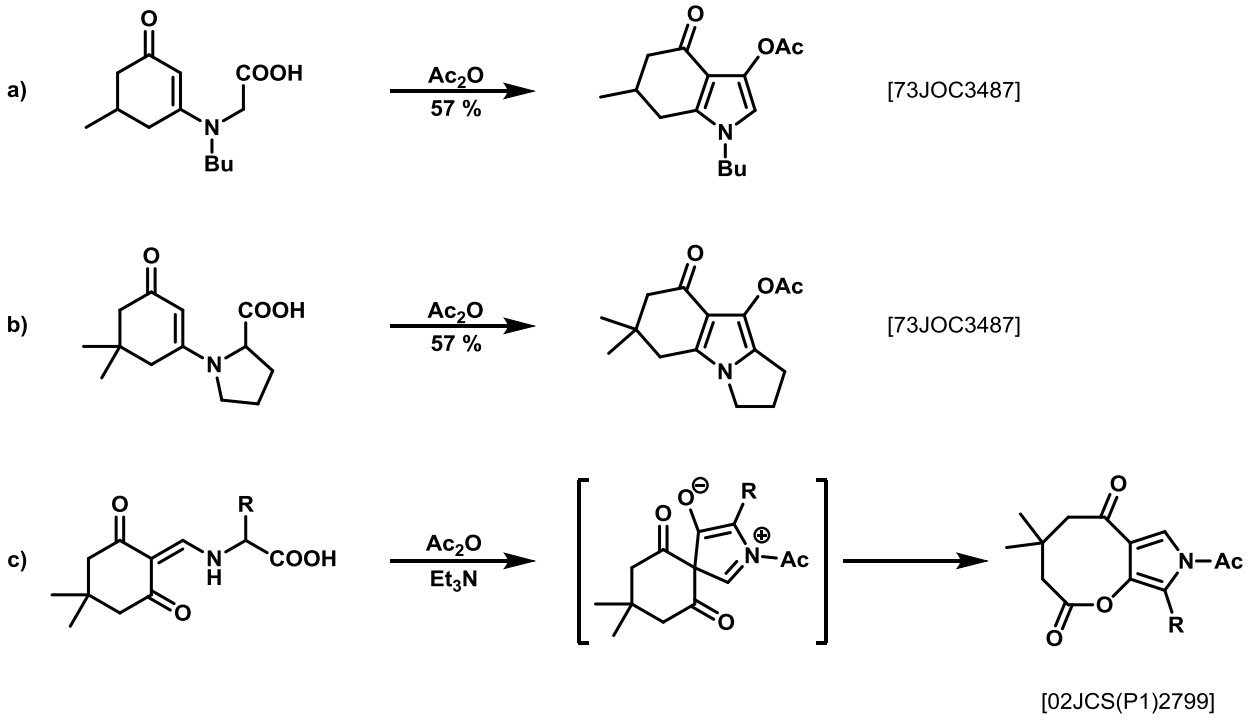
Scheme 3.8

Triethylamine deprotonates the acid and the carboxylate anion is acetylated by the acetic anhydride resulting in the mixed anhydride. Subsequent ring closure onto the anhydride carbonyl group is facilitated by electron release from the enamine moiety (nitrogen) and the elimination of acetic acid thereby providing the 2,4-dihydro-3*H*-pyrrol-3-one **A**. Further acetylation affords the pyrrolium ion **B**, in which the iminium moiety will be susceptible to attack by acetate. Addition of the latter proceeds in a diastereoselective manner with addition to the least hindered face of the iminium function i.e. *syn* to the least sterically demanding nitrile group. An alternative pathway to **3.11** can be envisaged to proceed *via* elimination from the mixed anhydride to provide the enamino ketene **C** which then cyclises to **D** from which intermediates **A** and **B** could be derived. X-ray crystallography established that the 2-acetoxy- and C-3 ester groups in **3.11** possess a *trans*-disposition i.e. (2*R**,3*S**). By contrast, cyclisation of the enamino acid **3.7c**, derived from phenylglycine **3.6c**, provided only the amido- **3.9c** and imidopyrroles **3.10c** (Scheme 3.9).



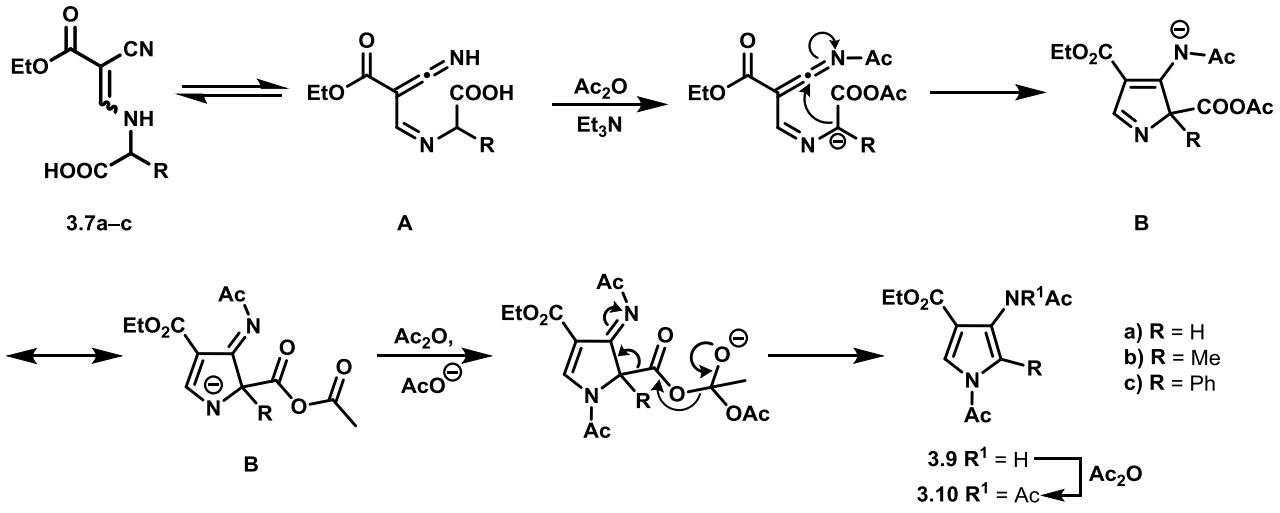
Scheme 3.9

Pyrrole formation *via* acylative β-cyclisation onto an enamine as depicted in Scheme 3.8 does have some literature precedents. Franck *et al.* reported the cyclisation of enaminones derived from cyclohexane-1,3-diones Scheme 3.10a) and Scheme 3.10b) which was exploited by Edstrom for the synthesis of a range of 3-acetoxytetrahydroindoles [94JOC2473, 95SL49] and pyrrolo[2,3-*d*]pyrimidindiones [93JOC403]. The cyclisation of an exocyclic enaminodione which affords an oxocino[2,3-*c*]pyrrole *via* a spiro-linked 3*H*-pyrrole provides another example [Scheme 3.10c)]



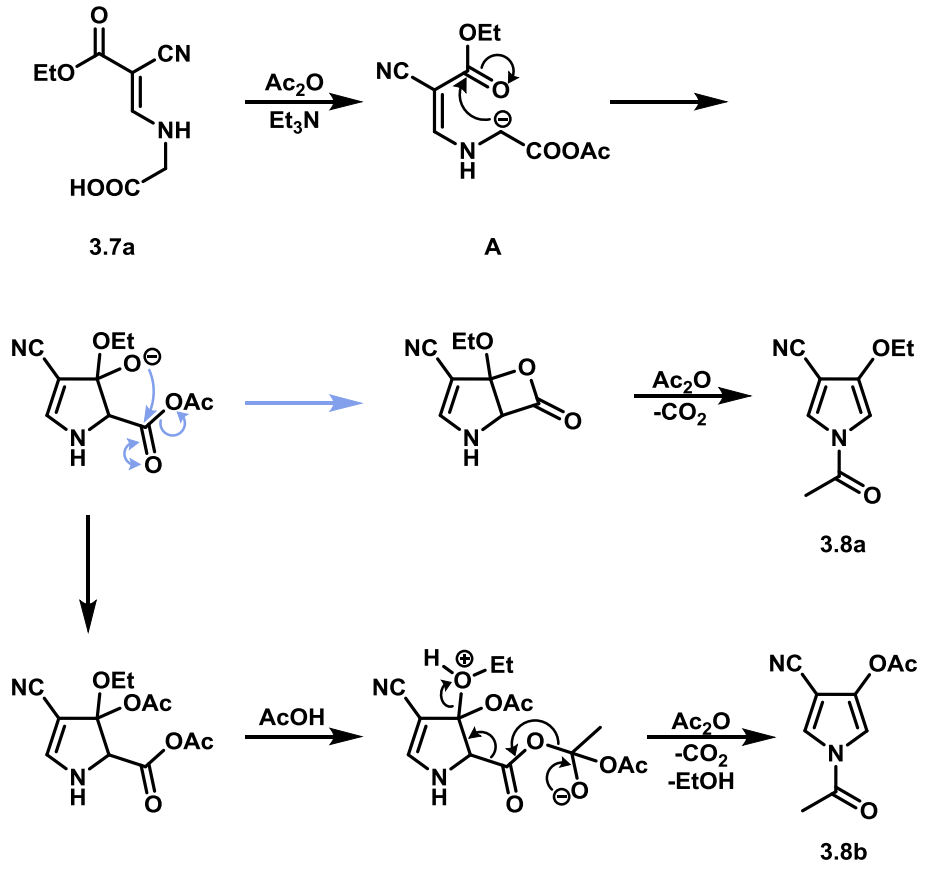
Scheme 3.10

Formation of the pyrroles **3.9** and **3.10** can be rationalised as shown in Scheme 3.11 which also indicates a possible pathway for the isomerism of the diastereomeric enamino acids for **3.7a–c** *via* prototropy to the minor ketenimine tautomer **A** (*cf*. p. 158) which following further acylation affords the stabilised anion **B**. Acetylation and concomitant hydrolysis of the mixed anhydride generates **3.9** and **3.10**. A related pathway is outlined in Scheme 3.53 and Scheme 3.54 for the cyclisation of enamino acids from β-ketonitriles.



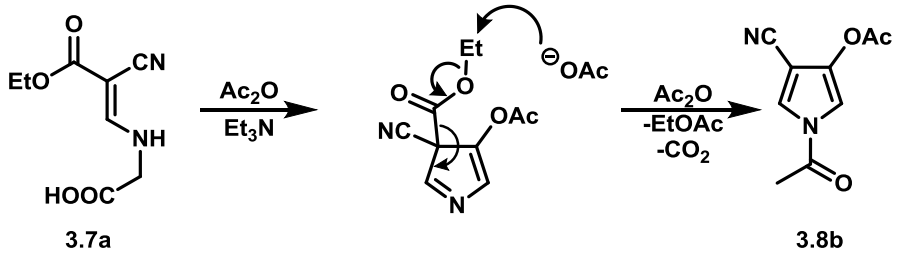
Scheme 3.11

Formation of minor products **3.8a** and **3.8b** can be rationalised by cyclisation of the enolate **A** from the mixed anhydride derived from **3.7a** (Scheme 3.12). This pathway is akin to those shown in Schemes 2.38 and 2.39.



Scheme 3.12

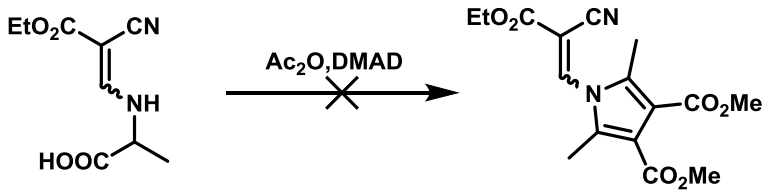
However, formation of **3.8b** may also proceed *via* a 3*H*-pyrrole (*cf.* Scheme 3.8). A Krapcho dealkoxycarbonylation would then lead to the product (Scheme 3.13).



3.7a 3.8b

Scheme 3.13

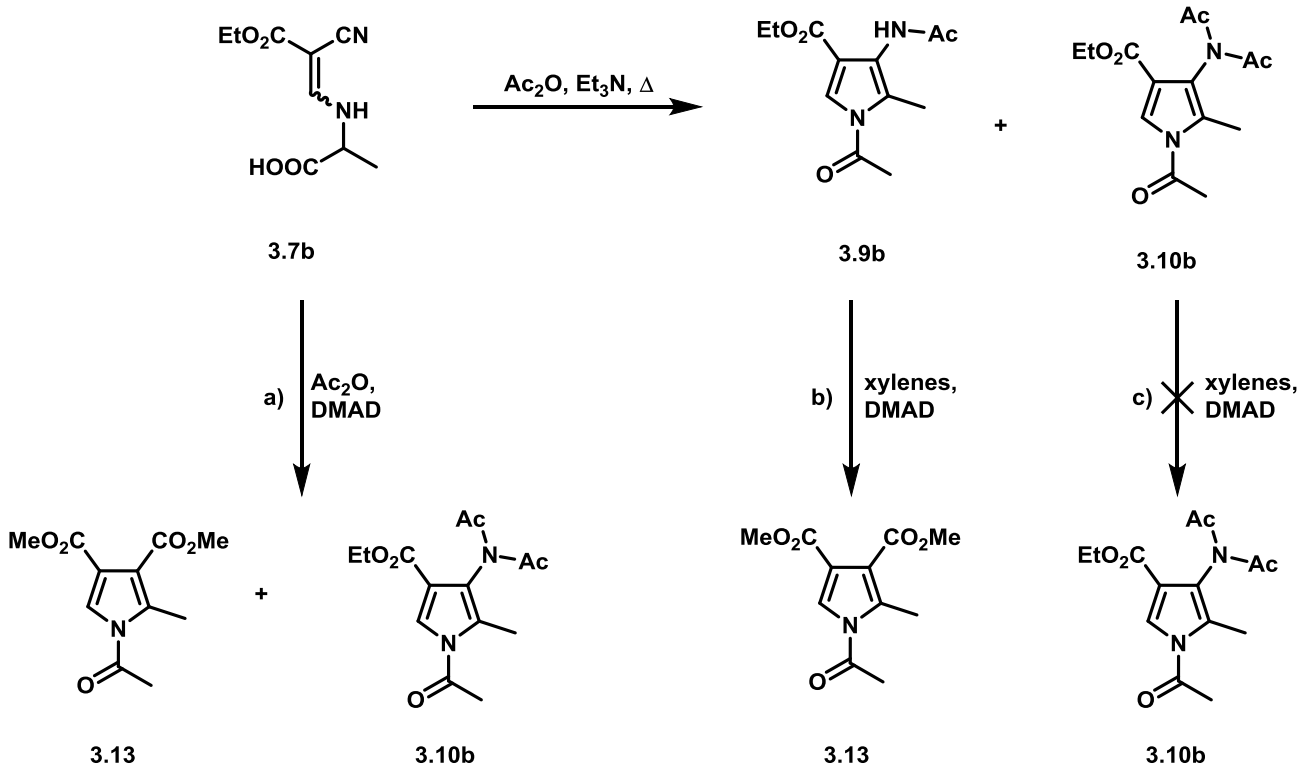
The trapping conditions used in section 2.6.4, Schemes 2.54 and 2.55 were applied to the cyclisation of cyanoester **3.7b** in an attempt to produce the analogous pyrrole **3.12** (Scheme 3.14). However, when **3.7b** was heated with DMAD (2.5 equiv.) in Ac_2O the reaction provided a mixture of **3.13** (16 %) and **3.10b** (50 %), thus indicating that the cyclisation to the 3-amidopyrrole and 3-imidopyrroles proceeds more rapidly than münchnone formation (*cf*. Scheme 2.56) and implicating the pathway in Scheme 3.11 [Scheme 3.15a)].



3.7b 3.12

Scheme 3.14

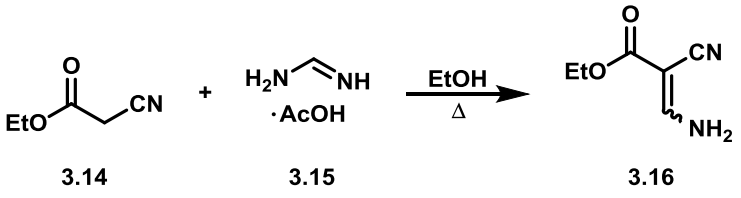
DMAD selectively undergoes the [4+2] cycloaddition – [4+2] cycloreversion sequence with **3.9b** to generate the same pyrrole (**3.13**) as that from **2.18b**. The reaction with DMAD in xylene was then applied to the 3-amidopyrrole **3.9b** (path b) and the 3-imidopyrrole **3.10b** (path c) separately. No reaction was observed between DMAD and **3.10b** whereas the expected pyrrole **3.13** from **3.9b** was isolated in low yield (25 % yield). The failure of **3.10b** to react with DMAD presumably stems from its decreased electron density.



Scheme 3.15

3.2.3 Attempted Synthesis of Ethyl{2-[(aryl)carboxymethylamino]methylene}cyanoacetates

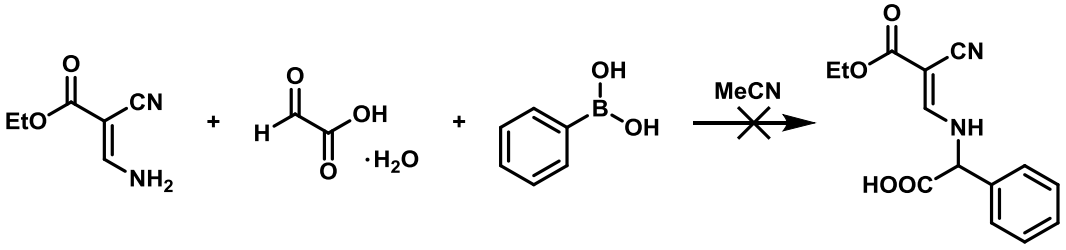
In order to extend the range of enamino acids **3.7** available for the synthesis of pyrroles it was or interest to apply the Petasis reaction (see section 2.5) to readily available ethyl (aminomethylene)cyanoacetate **3.16** since it was hoped that a wider range of enamino acids would be accessible by this means. Thus ethyl (aminomethylene)cyanoacetate **3.16** was synthesised by direct aminomethylenation of ethyl 2-cyanoacetate **3.14** with formamidine acetate **3.15** (Scheme 3.16). The reaction was carried out following literature procedure [60JA3138] and afforded **3.16** in 56 % yield as a mixture of *E*- and *Z*-isomers.



Scheme 3.16

The Petasis reaction was attempted with the enaminonitrile **3.16**, glyoxylic acid **3.17** and phenylboronic acid **3.18** in acetonitrile. Unfortunately no product **3.19** could be isolated or

detected by ^{1}H NMR (Scheme 3.17). Presumably the diminished nucleophilicity of the amino group in **3.16** was responsible for this lack of reactivity; in contrast electron deficient aromatic amines react readily [09TH319, 10CRV6169].



3.16 **3.17** **3.18** **3.19**

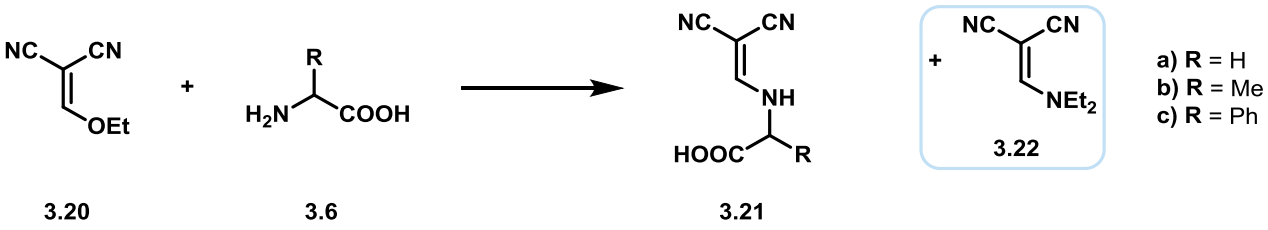
Scheme 3.17

3.3 Synthesis of Pyrroles from (Aminomethylene)malononitriles

The acylative cyclisation of enaminomalononitriles was investigated to ascertain whether they could provide access to 4-acetamidopyrrole-3-carbonitriles of which few examples are known.

3.3.1 Synthesis of 2-(1-Carboxyalkylaminomethylene)malononitriles

The novel enamino acids **3.21a–c** were synthesised from commercially available (ethoxymethylene)malononitrile **3.20** (Scheme 3.18). Initially, the synthesis was attempted using just the malononitrile **3.20** and an α-amino acid **3.6** in ethanol. The reaction mixture was stirred at reflux for 50 minutes and allowed to cool to room temperature, the ethanol was removed under reduced pressure and the residue dissolved in water. The product was isolated *via* extraction with ethyl acetate and the resulting oil triturated with diethyl ether; the precipitate was removed and the filtrate concentrated *in vacuo* to afford the product as an orange oil which later solidified. The yield of **3.21a** from glycine **3.6a** was poor and the ^{1}H NMR spectrum showed impurities (Table 3.4, entry 1). In an attempt to improve the yield, glycine **3.6a** was treated with triethylamine in acetonitrile prior to the addition of (ethoxymethylene)malononitrile **3.20**. The reaction mixture was stirred at reflux under nitrogen for 2.5 hours and allowed to cool to room temperature. The solvent was removed under reduced pressure and the brown residue was dissolved in water and extracted with ethyl acetate to afford a brown oil. The ^{1}H NMR spectrum showed the presence of product and another compound which was identified as 2-[(diethylamino)methylene]malononitrile **3.22** (Scheme 3.18), available by reaction of (ethoxymethylene)malononitrile **3.20** with diethylamine at 0 °C [07SC417], the spectral data was in agreement with literature values [72JCS(P2)1823]. Although unexpected, formation of the enaminomalononitrile **3.22** can be rationalised by a conjugate addition-elimination sequence of Et_3N to (ethoxymethylene)malononitrile **3.20** followed by S_N2 displacement from the triethylammonium function, by EtOH. Acidification of the aqueous phase with dilute HCl (2M) and subsequent extraction with ethyl acetate provided the pure product as an orange solid (52 % yield, Table 3.4, entry 2). Finally the enamine **3.21a** was accessed *via* reaction of glycine **3.6a** with (ethoxymethylene)malononitrile **3.20** in ethanol in the presence of potassium hydroxide. The reaction mixture was stirred at reflux for 1 hour and allowed to cool to room temperature, the solvent was removed under reduced pressure and the residue dissolved in water prior to acidification with dilute HCl (2M). The product was isolated *via* extraction with ethyl acetate and the solvent removed to afford the pure product in very good yield (83 %, Table 3.4, entry 3).



Reagents and Conditions outlined in Table 3.4.

Scheme 3.18

Table 3.4 Reaction conditions for the synthesis of [(carboxylmethylamino)methylene]malononitrile **3.21a**.

Entry	Conditions	Ratio of reactants 3.6a:3.20	Yield (%)
1	EtOH, Δ	1:1	38[a]
2	MeCN, Et_3N (1.5 equiv.), Δ	1:1	52
3	EtOH, KOH (1.05 equiv.), Δ	1:1.5	83

[a]Impure

This method (Table 3.4, entry 3) was used to synthesise the enamino acids **3.21** from alanine **3.6b** and phenylglycine **3.6c** (Table 3.5, entries 2 and 3 respectively).

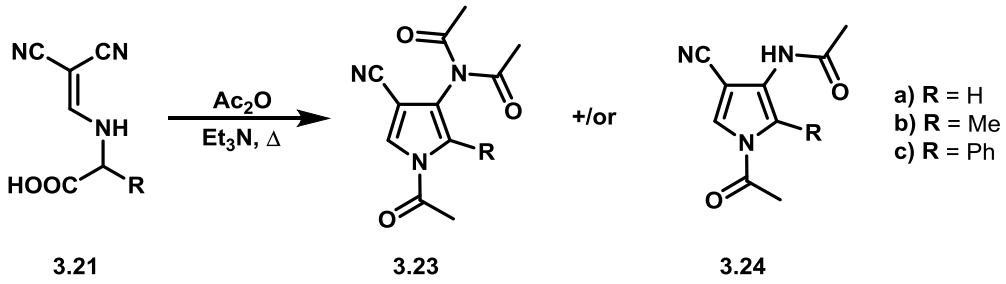
Table 3.5 Yields for the synthesis of [(carboxylmethylamino)methylene]malononitriles **3.21a–c.**

Entry	R	Compound 3.21	Yield (%)
1	H	**3.21a**	83
2	Me	**3.21b**	68[a]
3	Ph	**3.21c**	87

[a]after recrystallisation from EtOAc/hexane

3.3.2 Cyclisations of 2-(1-Carboxyalkylaminomethylene)malononitriles

Cyclisations of the enamino acids **3.21** derived from (ethoxymethylene)malononitrile **3.20** were expected to give either the imido- (**3.23**) or amidopyrrole (**3.24**) or a mixture of the two (Scheme 3.19). Thus, cyclisation of **3.21a** from glycine and **3.21c** from phenylglycine provided only imidopyrroles **3.23a** and **3.23c** respectively (Table 3.6, entries 1 and 3). Running the cyclisation reaction of **3.21a** without base (Et_3N) provided the pyrrole **3.23a** in only 1 % yield.



3.21 3.23 3.24

Scheme 3.19

Table 3.6 Yields for cyclisation reactions of 2-(1-carboxyalkylaminomethylene)malononitriles **3.21a–c**.

Entry	R	Pyrrole 3.23	Yield (%)
1	H	**3.23a**	15
2	Me	**3.23b**	49
3	Ph	**3.23c**	52

Cyclisation of **3.21b** from alanine, however provided two pyrrole products, initially, the imidopyrrole **3.23b** (Table 3.6, entry 2) was isolated by flash column chromatography followed by another pyrrole product. The ^{1}H NMR data of the latter displayed the absence of one of the acetyl methyl singlets and instead had a broad singlet at δ 8.99. The pyrrole proton has an upfield shift with respect to **3.23b** [Figure 3.5a)] from δ 7.65 to δ 7.12 and appears as a doublet ($J_{1,2}$ = 3.3 Hz) instead of a singlet, indicating that the product obtained is the *NH*-imidopyrrole **3.25** (Figure 3.5).

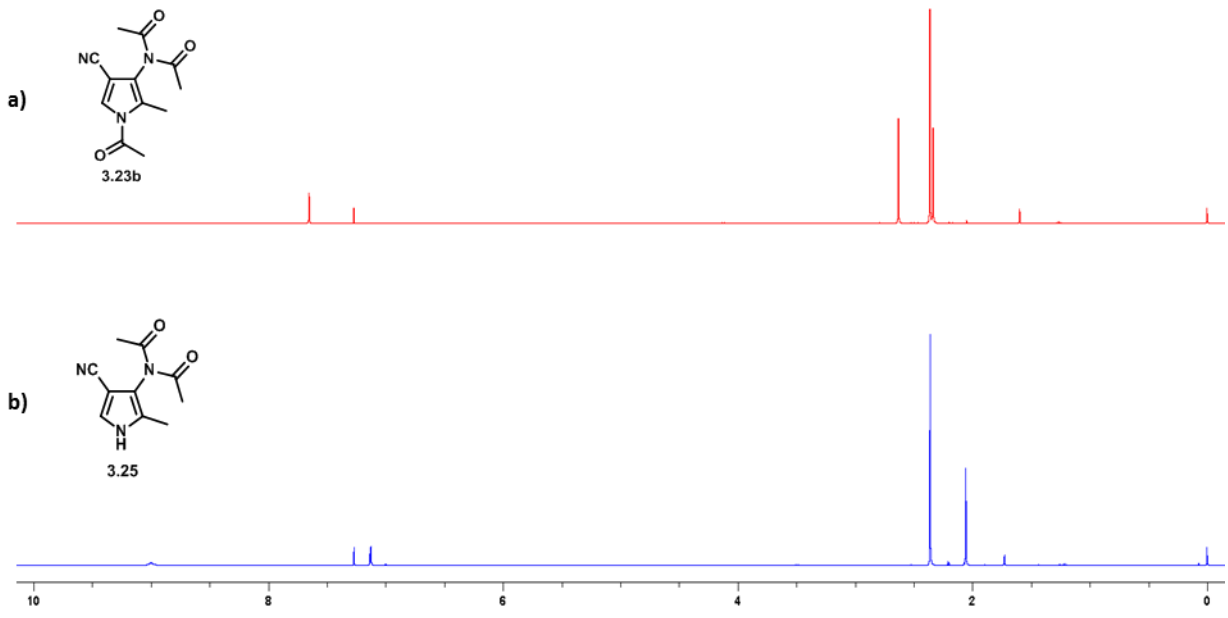
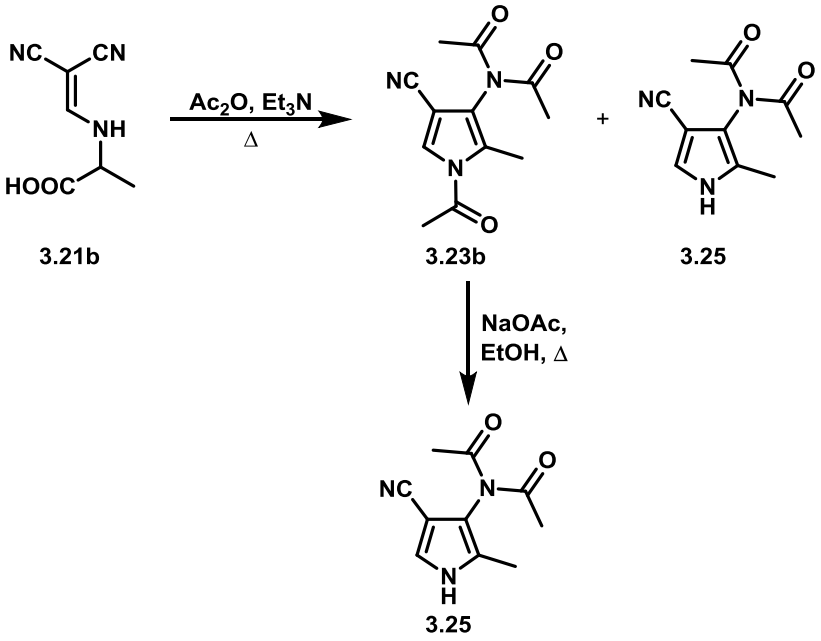


Figure 3.5 ^{1}H NMR Spectra of imidopyrroes a) **3.23b** and b) **3.25** (400 MHz, $CDCl_3$).

The structure of the product was confirmed by selective removal of the pyrrole *N*-acetyl group from **3.23b** (Scheme 3.20). Thus, the latter was refluxed in ethanol containing sodium acetate for 3 hours to afford, after aqueous work-up, the pure pyrrole **3.25** (Scheme 3.20). The physical and spectral data confirmed the structure of the pyrrole observed from the cyclisation of **3.23b**.

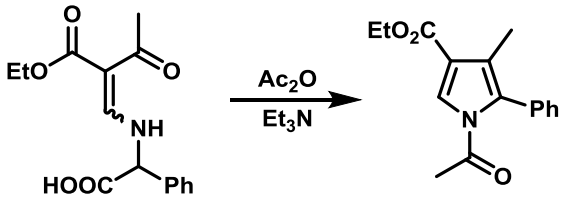


Scheme 3.20

Thus, cyclisations of the enaminonitriles provided the expected pyrrole-3-carbonitriles **3.23a–c** although the amino function had been bis-acetylated.

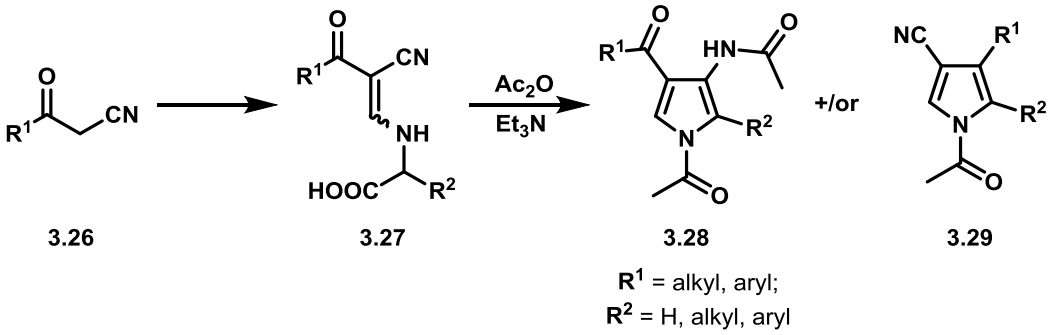
3.4 Synthesis of Pyrroles from 2-(Aminomethylene)-1,3-ketonitriles

Cyclisation of enaminonitriles derived from ethyl cyanoacetate proceeds onto the nitrile function, in preference to the ester group. Previous studies had shown that enamino acids derived from β-ketoesters cyclise exclusively onto the more reactive ketone carbonyl group (Scheme 3.21) [02JCS(P1)2799].



Scheme 3.21

In light of this and the results outlined in section 3.1.3 it was of interest to extend investigations to the synthesis and acylative cyclisations of novel enamino acids **3.27** derived from β-ketonitriles **3.26** since these substrates could afford either 4-acetamido-3-pyrrolyl ketones **3.28** and/or pyrrole-3-carbonitriles **3.29** (Scheme 3.22).



3.26 **3.27** **3.28** **3.29**

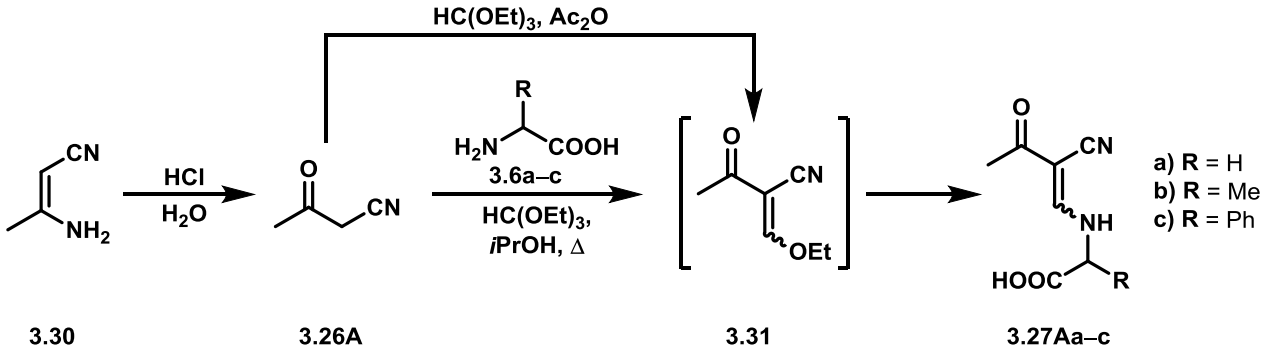
R^1 = alkyl, aryl;
R^2 = H, alkyl, aryl

Scheme 3.22

3.4.1 Synthesis of 2-Alkoyl- and 2-Aroyl-3-(1-carboxyalkylamino)acrylonitriles

Next, a series of β-ketonitriles was investigated for the synthesis and subsequent cyclisation of enamino acids. Initially, cyanoacetone **3.27** was synthesised by hydrolysis of commercially available 3-aminocrotononitrile **3.30**, following a literature procedure [Scheme 3.23, 09OPPI515]. Concentrated hydrochloric acid was added dropwise to a slurry of 3-aminocrotononitrile in water in an ice-water bath over a 1 hour period. Upon completion, the reaction mixture was heated to 80 °C and stirred for 2 hours before cooling to room temperature. Ethyl acetate was added to the reaction mixture which was then filtered through celite. The biphasic filtrate was separated and the product extracted from the aqueous phase with ethyl acetate, the organic extracts provided

the unstable cyanoacetone **3.26A** (80 %) as a brown oil which was used immediately to synthesise enamino acids **3.27Aa–c** (Scheme 3.23). Treatment of crude cyanoacetone with triethyl orthoformate in isopropanol in the presence of α-amino acids **3.6a–c** provided the enamino acids **3.27Aa–c** directly in moderate yields. This procedure, which involves *in situ* formation of (ethoxymethylene)cyanoacetone **3.31**, was found to be most convenient. The latter has been reported from the reaction of cyanoacetone with triethyl orthoformate in the presence of Ac_2O [90CCC1038]. However, attempts to obtain **3.31** by this procedure failed to provide a tractable product (Scheme 3.23).



Scheme 3.23

The route outlined in Scheme 3.23 for the synthesis of enamino acids **3.27Aa–c** using $HC(OEt)_3$ in isopropanol was developed from that reported for the aminomethylenation of other enolisable 1,3-dicarbonyl compounds; more specifically the condensation of 4-hydroxycoumarins with α-amino acids and $HC(OEt)_3$ to afford *N*-(methylene-4-oxocoumarinyl)amino acids [92JHC1817]. This one-pot sequence was found to be highly suitable for the preparation of many of the enaminones in the present work. Under protic conditions, $HC(OEt)_3$ is readily ionised to afford the diethoxycarbenium ion ($EtOCH{=}OEt^+$) its similarity to DMFDMA (Scheme 2.7) for methylenations is thus apparent. Cyanoacetone **3.26A** was dissolved in isopropanol and the appropriate α-amino acid (**3.6a–c**) was added along with excess triethyl orthoformate. The reaction mixture was stirred at reflux overnight and allowed to cool to room temperature. The volatile components were removed under reduced pressure and the residue was dissolved in DCM, the product was extracted into saturated sodium bicarbonate solution, acidified (2 M HCl) and the product isolated with ethyl acetate to afford the pure enamino acids **3.27Aa–c** (Scheme 3.23, Table 3.7). The enamino acids **3.27Aa–c** were each isolated as a mixture of their *E*- and *Z*- isomers (Scheme 3.24) which was apparent from their ^1H NMR spectra, from the signals resulting from the NH and alkenyl

protons. The signals for the *Z*-isomer were displayed between 10.33–11.07 ppm and 7.71–7.84 ppm for the amine and alkene protons respectively. The signal for the amine proton appeared as a doublet of triplets for **3.27Aa** when R = H (Table 3.7, entry 1) and a doublet of doublets for **3.27Ab** and **3.27Ac** [R = methyl (Table 3.7, entry 2) and R = phenyl (Table 3.7, entry 3)]. The amine protons have an upfield shift in the *E*-isomer ranging from 8.72–9.40 ppm and the alkenyl protons have a small downfield shift with respect to the *Z*-isomer and resonated between 8.06 and 8.09 ppm (Table 3.7). In the *E*-isomers the amine proton appeared as broad singlets for **3.27Aa–c** (Table 3.7, entries 1–3) due to the proton being more able to exchange than in the *Z*-isomer in which it is stabilised by intramolecular hydrogen bonding. The nitrile group can be seen as a strong, sharp band in the IR spectra at 2204–2208 cm^{-1} and in the ^{13}C NMR spectra at 118 ppm for the *E*-isomers and 121 ppm for the *Z*-isomers of **3.27Aa–c**.

Scheme 3.24

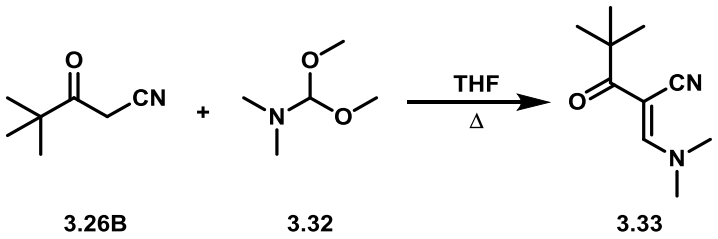
Table 3.7 ^{1}H NMR data for enamino acids **3.27Aa–c** derived from cyanoacetone **3.26**.

Entry	R	Compound 3.27A	Yield (%)	Ratio *E/Z*-isomers	^{1}H NMR shifts N*H* [400 MHz, $(CD_3)_2SO$]	^{1}H NMR shifts =C*H* [400 MHz, $(CD_3)_2SO$]
1	H	**3.27Aa**	42	0.6 : 1	8.72 [br. s, (*E*)] 10.33 [dt, (*Z*)][a]	8.09 [d, (*E*)][b] 7.71 [d, (*Z*)][c]
2	Me	**3.27Ab**	40	0.6 : 1	8.93 [br. s, (*E*)] 10.62 [dd, (*Z*)][a]	8.07 [d, (*E*)][b] 7.84 [d, (*Z*)][c]
3	Ph	**3.27Ac**	58	0.4 : 1	9.40 [br. s, (*E*)] 11.07 [dd, (*Z*)][a]	8.06 [d, (*E*)][b] 7.80 [d, (*Z*)][c]

[a] *J* = 6.0–7.7 Hz, 13.5–13.9 Hz; [b] *J* = 14.6–14.9 Hz; [c] *J* = 13.5–13.9 Hz

Following the synthesis of enamino acids from cyanoacetone, the commercially available 4,4-dimethyl-3-oxopentanenitrile **3.26B** was used to investigate the outcome of the cyclisation of enamino acids **3.6a–c** containing a more sterically demanding group. The enamino nitrile **3.33** is a known compound and was synthesised following a literature method to give a single *E*-isomer of the product [10JOC4288]; compound **3.33** has been used in the synthesis of trisubstituted

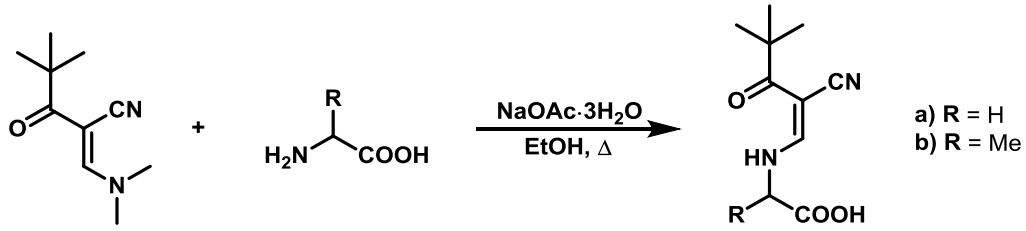
pyrazoles [17P206]. 4,4-Dimethyl-3-oxopentanenitrile **3.26B** was dissolved in dry THF and DMFDMA **3.32** was added in one portion, the reaction mixture was stirred under nitrogen at room temperature overnight. The solvent was removed *in vacuo* to afford **3.33** as a yellow solid which was recrystallised (82 % yield, Scheme 3.25). The ^{1}H and ^{13}C NMR spectra were identical to those described in the literature [10JOC4288].



3.26B **3.32** **3.33**

Scheme 3.25

The synthesis of **3.27Ba–b** was initially attempted following the method used for the synthesis of enamino acids **2.13m** and **2.13n** derived from asparagine **2.12m** and glutamine **2.12n** and diethyl (dimethylaminomethylene)malonate **2.10** (Scheme 2.8, Scheme 3.26). Sodium acetate trihydrate and the amino acids **3.6** (glycine **3.6a** and alanine **3.6b**) were added to 2-[(dimethylamino)methylene]-4,4-dimethyl-3-oxopentanenitrile **3.33** in ethanol. The reaction mixture was stirred for 3 hours at reflux and the solvent was removed *in vacuo*. The residue was dissolved in water and acidified (2 M HCl), the product was isolated *via* extraction with ethyl acetate to afford an oil. The ^{1}H NMR spectra showed the products derived from both glycine **3.6a** and alanine **3.6b** as single *Z*-isomers, however, a significant number of impurities were also present.

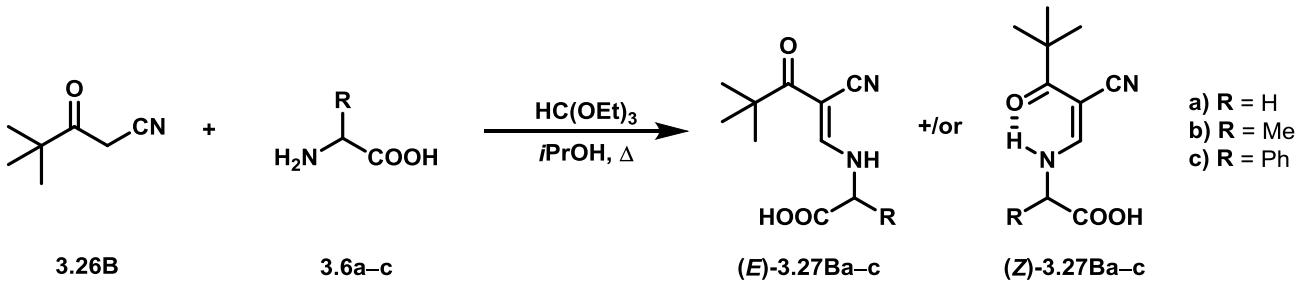


3.33 **3.6a–b** **3.27Ba–b**

Scheme 3.26

In order to circumvent these difficulties the one-pot orthoformate procedure used for the synthesis of enamino acids from cyanoacetone **3.26A** was employed (Scheme 3.23, Scheme 3.27). The reactions, monitored by TLC, were stirred at reflux for 4–36 hours. The enamino acids **3.27Ba–**

c were obtained as oils which solidified upon standing, recrystallisation from ethyl acetate and hexane provided the clean products albeit in low yield (Table 3.8, entries 1–3). The ^{1}H and ^{13}C NMR spectra of **3.27Ba** showed the *Z*-isomer as the sole product (Table 3.8, entry 1). However for **3.27Bb** and **3.27Bc** the ratio of *E*/*Z*-isomers was much smaller than the analogous compounds **3.27Aa–c** from cyanoacetone **3.26A** due to the steric interation of the *tert*-butyl group with the adjacent nitrile group (Table 3.8, entries 2 and 3). In contrast to compounds **3.27Aa–c**, the signals for NH protons in the ^{1}H NMR spectra are well defined for the *E*-isomers of **3.27Bb** and **3.27Bc** and are displayed as a doublet of doublets at δ 10.77 and 9.23 ppm respectively (*J* = 6.8, 15.0 Hz). All enamino acids **3.27Ba–c** showed the loss of CO_2 in the HRMS spectra.

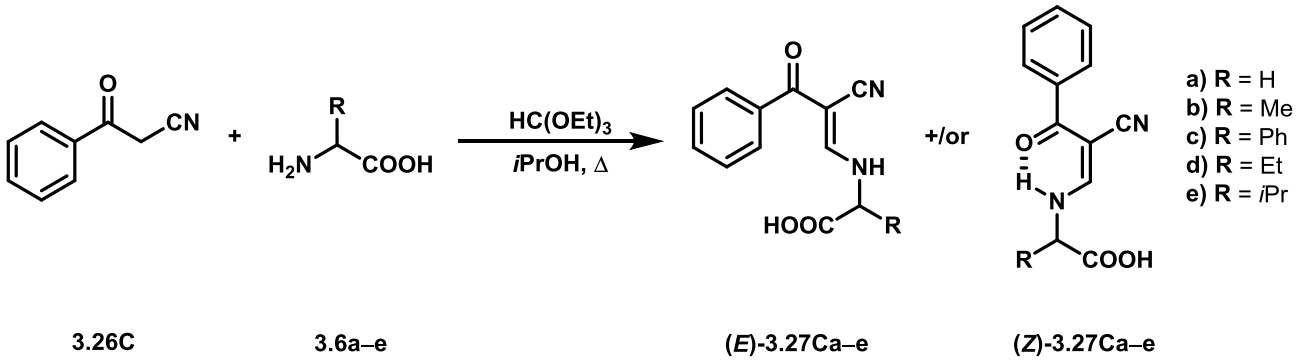


Scheme 3.27

Table 3.8 Yields for 3-(1-carboxyalkylamino)-2-pivaloylacrylonitriles **3.27Ba–c**.

Entry	R	Compound 3.27B	Yield (%)	Ratio *E*/*Z*-isomers
1	H	**3.27Ba**	22	0 : 1
2	Me	**3.27Bb**	53	0.3 : 1
3	Ph	**3.27Bc**	50	0.2 : 1

Commercially available benzoylacetonitrile was employed to introduce an aryl ketone moiety into the enamino acids (Scheme 3.28). Beginning with the usual α-amino acids **3.6a–c** the orthoformate method was used (Scheme 3.28), the yields from these reactions were good (70–75 %, Table 3.9, entries 1–3). Due to the ease of synthesis, good yields and availability of benzoylacetonitrile **3.26C**, two additional α-amino acid examples were investigated, 2-aminobutyric acid **3.6d** (R = Et) and valine **3.6e** (R = *i*Pr), both worked well in the reaction with yields of 68% and 78 %, respectively (Table 3.9, entries 4–5). When R was a larger or more bulky group, the ratio of *E*/*Z*-isomers was smaller [Figure 3.6c) and e), Table 3.9, entries 3 and 5].



3.26C **3.6a–e** **(*E*)-3.27Ca–e** **(*Z*)-3.27Ca–e**

Scheme 3.28

Table 3.9 Yields of 3-(1-carboxyalkylamino)-2-benzoylacrylonitriles **3.27Ca–c**.

Entry	R	Compound 3.27C	Yield (%)	Ratio *E/Z*-isomers
1	H	**3.27Ca**	70	0.8 : 1
2	Me	**3.27Cb**	71	0.7 : 1
3	Ph	**3.27Cc**	75	0.4 : 1
4	Et	**3.27Cd**	65	0.6 : 1
5	*i*Pr	**3.27Ce**	78	0.3 : 1

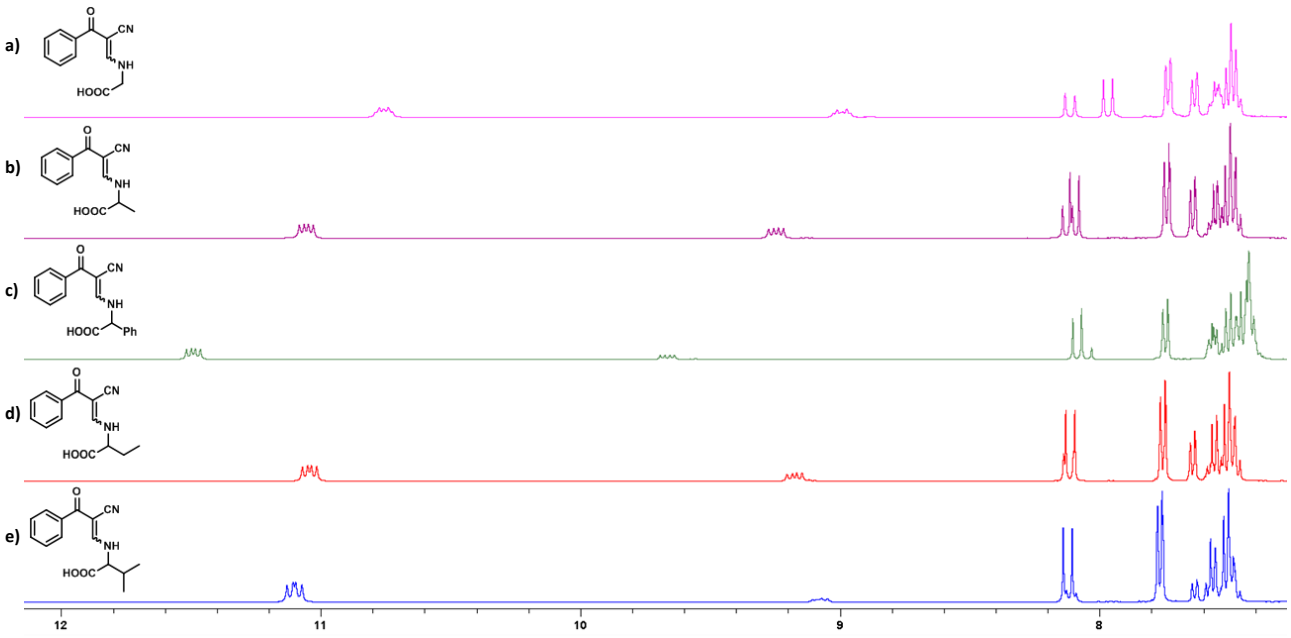
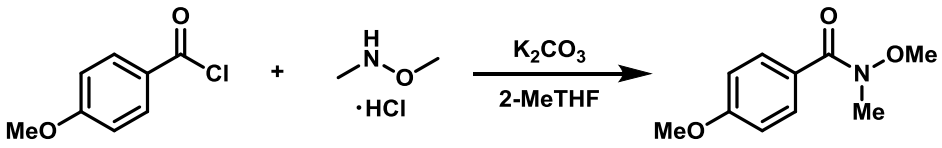


Figure 3.6 ^{1}H NMR spectra [400 MHz, DMSO-d_6] of 2-(1-carboxyalkylamino)-2-benzoylacrylonitriles a) **3.27Ca**, b) **3.27Cb,** c) **3.27Cc**, d) **3.27Cd and** e) **3.27Ce**.

With the enamino acids **3.27Ca–c** from benzoylacetonitrile **3.26C** to hand, the synthesis of an aryl derivative containing an electron donating group was attempted. Thus, the anisyl derivative, 4-

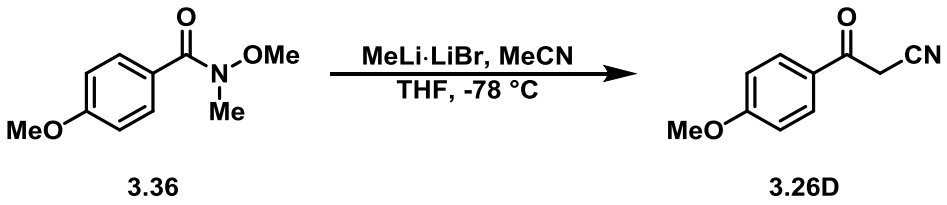
methoxybenzoylacetonitrile **3.26D**, was synthesised; a number of procedures for its preparation have been reported. Initially, synthesis of the Weinreb amide **3.36** was undertaken following a literature procedure [Scheme 3.29, 13RSC(A)10158]. *N,O*-Dimethylhydroxylamine hydrochloride **3.35** was added to 4-methoxybenzoyl chloride **3.34** in 2-methyltetrahydrofuran, the reaction mixture was cooled to 0 °C and aqueous potassium carbonate was added in 2 portions. The mixture was then stirred at room temperature for 1 hour and subjected to aqueous work-up to afford the Weinreb amide **3.36** as an oil in excellent yield (93 %). The spectroscopic data was in agreement with the literature [13RSC(A)10158].



3.34 **3.35** **3.36**

Scheme 3.29

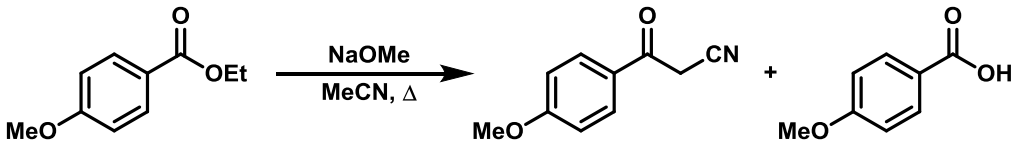
With the Weinreb amide **3.36** now available it could be transformed to the desired β-ketonitrile *via* cyanomethylation [Scheme 3.30, 15OBC1969]. Methyllithium-lithium bromide complex was added dropwise to acetonitrile in THF at -78 °C and the mixture stirred for 30 min before a solution of Weinreb amide **3.36** in THF was added over 5 min. After stirring for a further 1.5 h at -78 °C the reaction mixture was quenched with saturated aqueous ammonium chloride and allowed to warm to room temperature. Upon the addition of diethyl ether to extract the product, a white precipitate began to form in the aqueous phase. The solid was removed by filtration and identified as 4-methoxybenzoylacetonitrile **3.26D** in 60 % yield. In an attempt to increase the yield and improve the ease of isolation of the product, the reaction was repeated and modified. After 1.5 h stirring the reaction mixture was first allowed to warm to room temperature and then quenched with 1 M HCl and ethyl acetate was used in place of diethyl ether. However, once the extraction was complete and the solvent removed, the product required purification by flash column chromatography and as a consequence, was obtained in a greatly diminished yield.



3.36 3.26D

Scheme 3.30

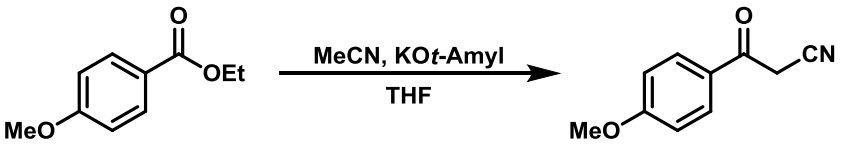
In order to have more straightforward access to 4-methoxybenzoylacetonitrile **3.26D** a Claisen-type condensation used for the synthesis of a small range of similar compounds including benzoylacetonitrile [Scheme 3.31, 12MOL9683] was investigated. Sodium methoxide and ethyl 4-methoxybenzoate **3.37** were stirred in acetonitrile at reflux for 2 days until the starting material was absent by TLC. The reaction mixture was allowed to cool to room temperature and the resulting solid collected by filtration and washed with diethyl ether and hexane. The solid was dissolved in water, acidified with dilute HCl and the product was extracted with ethyl acetate. The residue obtained upon removal of the solvent was purified by flash column chromatography to afford initially **3.26D** (33 % yield) followed by 4-methoxybenzoic acid **3.38** as the major product (36 % yield, Scheme 3.31).



3.37 3.26D (33 %) 3.38 (36 %)

Scheme 3.31

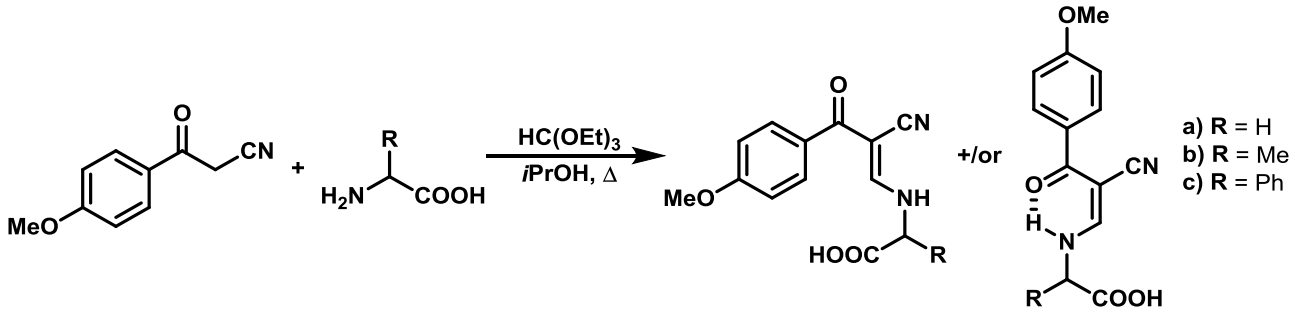
Because of these disappointing results a modification of this approach which used potassium *tert*-pentyloxide, a powerful, toluene soluble, non-nucleophilic base and a stoichiometric amount of acetonitrile to synthesise 4-methoxybenzoylacetonitrile **3.26D** [Scheme 3.32, 11ACIE8979]. Potassium *tert*-pentyloxide (1.7 M in PhMe) was added dropwise to a stirring solution of acetonitrile in anhydrous tetrahydrofuran at room temperature. Ethyl 4-methoxybenzoate **3.37** was added dropwise and the mixture stirred for a further 24 hours. Following acidification (dilute HCl) and work-up the residue was subjected to purification by flash column chromatography. 4-Methoxybenzoylacetonitrile **3.26D** was isolated in very good yield (88 %). In contrast to the literature method [11ACIE8979] the molar equivalents of the ester **3.37** and base were reduced to 1.1 and 2.5 equiv. from 4 and 3 equiv. respectively with no diminution in yield.



3.37 3.26D

Scheme 3.32

Enamino acids **3.27Da–c** were synthesised from 4-methoxybenzoylacetonitrile **3.26D** and amino acids **3.6a–c** using the triethyl orthoformate procedure [Scheme 3.33, 92JHC1817]. The reactions worked well giving yields of 69–79 % (Table 3.10, entries 1–3). The ratio of *E*/*Z*-isomers was comparable to the enamino acids **3.27Ca–c** from benzoylacetonitrile (Table 3.10, entries 1–3).



3.26D 3.6a–c (*E*)-3.27Da–c (*Z*)-3.27Da–c

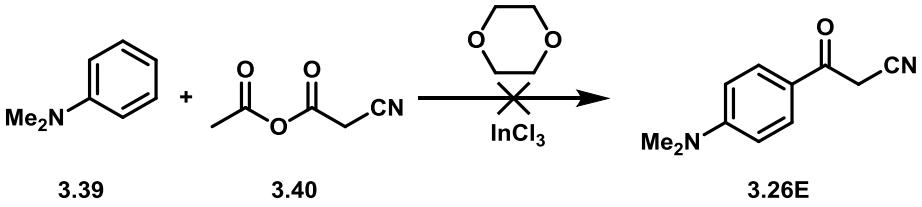
Scheme 3.33

Table 3.10 Yields of 3-(1-carboxyalkylamino)-2-(4-methoxybenzoyl)acrylonitriles **3.27Da–c**.

Entry	R	Compound 3.27D	Yield (%)	Ratio *E*/*Z*-isomers
1	H	**3.27Da**	79	0.7 : 1
2	Me	**3.27Db**	71	0.6 : 1
3	Ph	**3.27Dc**	69	0.4 : 1

It was also of interest to obtain and arylacetonitrile containing a more powerful electron donating substituent. To this end the synthesis of 4-(dimethylamino)benzoylacetonitrile **3.26E** from *N,N*-dimethylaniline **3.39** was undertaken following the literature procedure [Scheme 3.34, 12MOL897]. Thus, $PhNMe_2$ **3.39** was added to a solution of acetic 2-cyanoacetic anhydride **3.40**, from acetic anhydride and cyanoacetic acid, in anhydrous 1,4-dioxane in the presence of a catalytic amount of indium trichloride. The reaction mixture was stirred at reflux under nitrogen

for 1 hour and poured onto water. The resulting solid was collected by filtration, washed with water and recrystallised from ethanol. Unfortunately, the ^{1}H NMR spectrum of this material was complicated and in contrast to the claims in the literature, no signals corresponding to the product were visible.

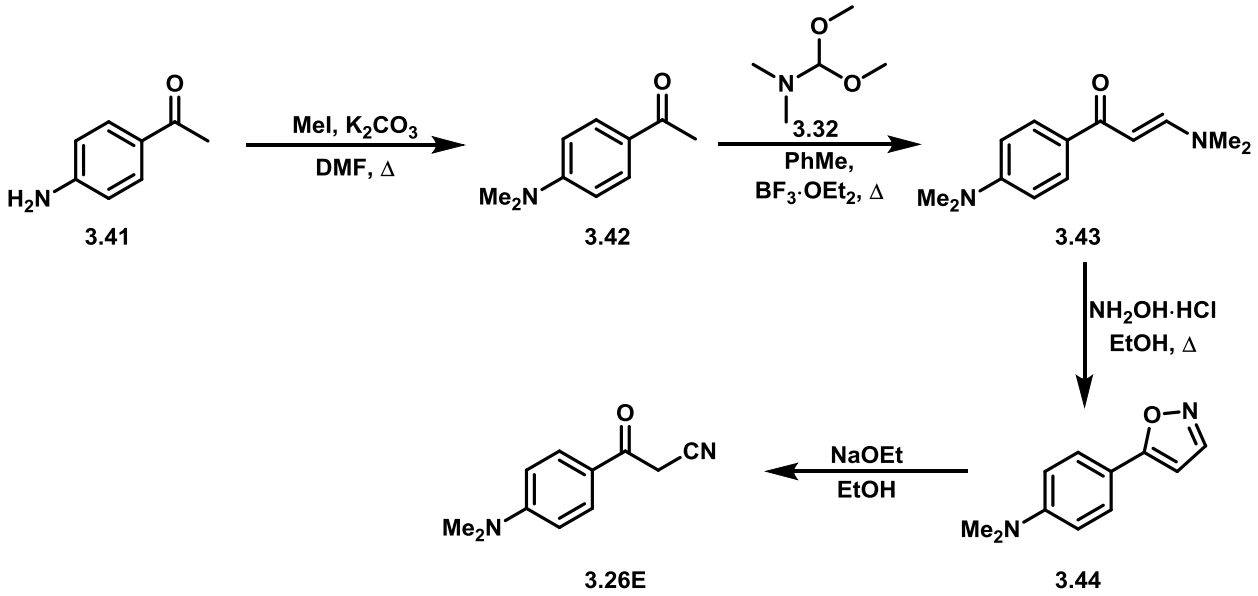


3.39 3.40 3.26E

Scheme 3.34

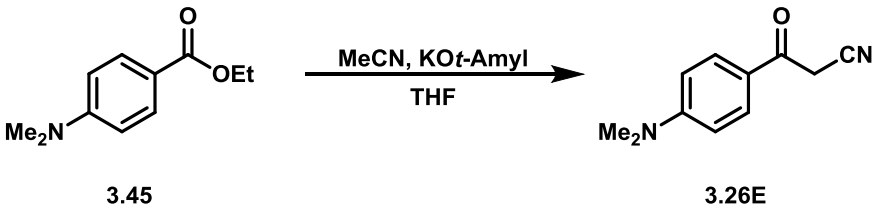
An alternative means to access **3.26E** was therefore implemented. As isoxazoles are known to undergo ring opening to β-ketonitriles in the presence of base (for a review see [80AHC(25)147]), this route was adopted. Initially, 4'-aminoacetophenone was methylated following the literature procedure [09T2079]. Iodomethane was added to 4'-aminoacetophenone **3.41** and potassium carbonate in DMF. The mixture was stirred for 1 day at 60 °C, allowed to cool to room temperature and quenched with ice-water. After drying and purification the clean product was obtained in low yield (27 %). Methylenation of 4'-(dimethylamino)acetophenone **3.42** was accomplished by prolonged heating with DMFDMA **3.32** in the presence of a catalytic amount of boron trifluoride diethyl etherate at reflux, following a general literature procedure reported by Martins *et al.* [08JHC879], in toluene for 30 days (2 further portions of DMFDMA **3.32** were added after 4 and 20 days). The solvent was removed under reduced pressure and the product washed with brine and hexane. The product was isolated from unreacted **3.42** by flash column chromatography to afford **3.43** in 41 % yield. Though **3.43** was not reported by Martins, it has been synthesised in a similar manner but in a much lower yield (18 %) [14WO2014089364A]. To synthesise the isoxazole **3.44** regioselectively, a literature protocol applicable to a range of other 5-aryl derivatives was adopted [08JHC879]. Thus, the enaminone **3.43** in ethanol and hydroxylamine hydrochloride was stirred overnight at reflux under nitrogen and allowed to cool to room temperature. The solvent was removed and the residue subjected to aqueous work-up to afford the novel isoxazole **3.44** in very good yield (81 %). The product was readily characterised from its ^{1}H NMR spectrum which exhibited the isoxazole ring protons as two doublets at δ 6.30 and δ 8.21 for 4-H and 3-H, respectively. The NMe_2 group resonated at 3.03 ppm, whilst the four most intense lines from the aryl group AA'BB' system appeared at δ 6.73 and δ 7.66 for the *meta*-

and *ortho*-protons, respectively. Ring opening of the isoxazole followed literature method for a similar system [08JOC1121] and simply involved treatment with ethanolic sodium ethoxide at room temperature overnight to afford 4-(dimethylamino)benzoylacetonitrile **3.26E** in 36 % yield. Though successful in providing the product the overall yield from 4′-aminoacetophenone **3.41** was very low (3 % over 4 steps).



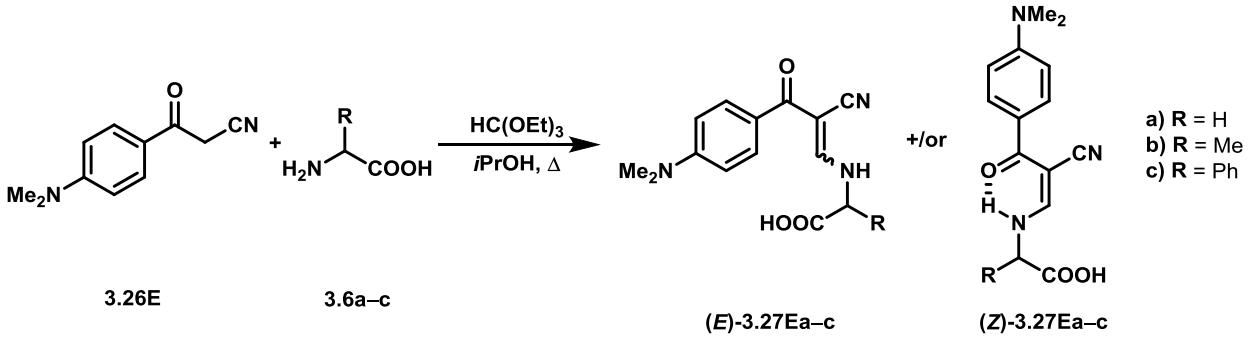
Scheme 3.35

Because of the success of the Claisen-type condensation of ethyl 4-methoxybenzoate with acetonitrile in the presence of potassium *tert*-pentyloxide (Scheme 3.32), this method was used for the synthesis of **3.26E** from ethyl 4-(dimethylamino)benzoate **3.45**. 4-(Dimethylamino)benzoylacetonitrile **3.26E** was isolated in excellent yield (94 %) [Scheme 3.36, 11ACIE8979] from this simple one-pot procedure.



Scheme 3.36

Enamino acids **3.27Ea–c** were prepared from **3.26E** following the standard orthoformate method in low to fair yields (27–55 %) [Scheme 3.37, Table 3.11, entries 1–3].

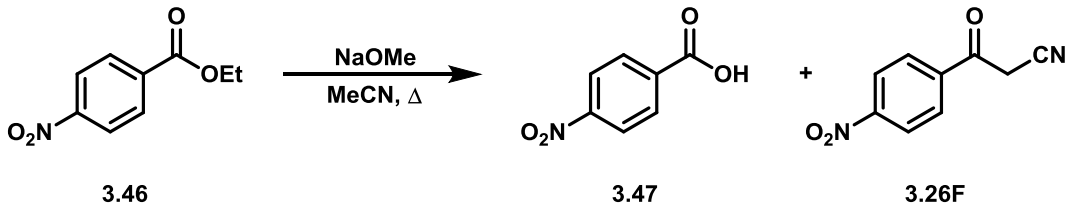


Scheme 3.37

Table 3.11 Yields of 3-(1-carboxyalkylamino)-2-(4-dimethylaminobenzoyl)acrylonitriles **3.27E**.

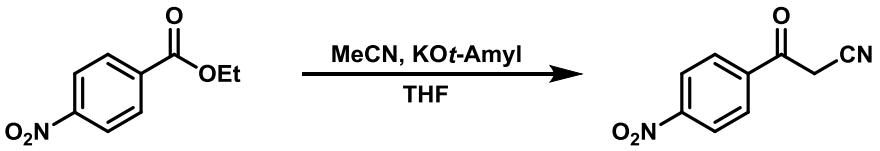
Entry	R	Compound 3.27E	Yield (%)	Ratio *E/Z*-isomers
1	H	**3.27Ea**	27	0.6 : 1
2	Me	**3.27Eb**	29	0.6 : 1
3	Ph	**3.27Ec**	55	0.3 : 1

With enamino acids derived from both electron neutral and electron-rich aroylacetonitriles attention was focussed on derivatives containing an electron withdrawing group. Thus, the synthesis of **3.26F** was attempted using ethyl 4-nitrobenzoate **3.46** and MeCN with sodium methoxide [Scheme 3.31, 12MOL9683]. The reaction was monitored by TLC and refluxed for a period of 48 hours. Upon the completion of the reaction the product was purified by flash column chromatography to afford a mixture of 4-nitrobenzoic acid **3.47** and the desired β-ketonitrile **3.26E** in a 0.5:1 ratio by ^{1}H NMR spectroscopy [Scheme 3.38].



Scheme 3.38

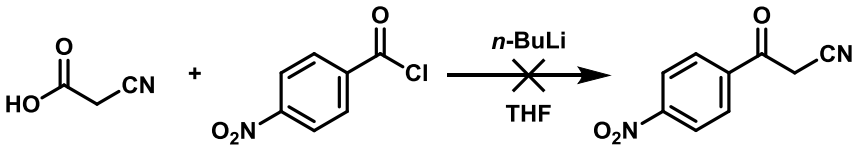
When NaOMe was replaced with potassium *tert*-pentyloxide for the synthesis of 4-nitrobenzoylacetonitrile **3.26E** [Scheme 3.39, 11ACIE8979] the yield of product was very low (10 %) and the product was difficult to purify (still impure by ^{1}H NMR after flash column chromatography and recrystallisation).



3.46 **3.26F**

Scheme 3.39

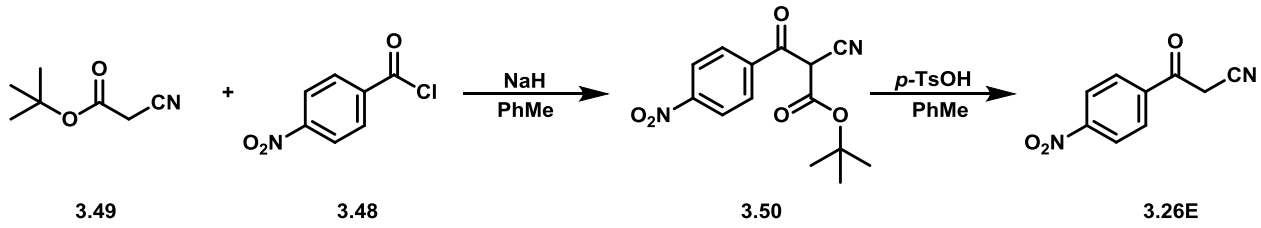
A similar literature method, using potassium *tert*-butoxide has been described in the literature as "unsuccessful" for the synthesis of 4-nitrobenzoylacetonitrile **3.26E** [99JMC3629]. Therefore an alternative literature method for the synthesis of **3.26E** *via* acylation of the dianion of $NCCH_2CO_2H$ was investigated. *n*-Butyllithium solution was added to cyanoacetic acid in anhydrous tetrahydrofuran at -78 °C. The reaction was allowed to warm to 0 °C and stirred for 30 minutes before recooling to -78 °C. A solution of 4-nitrobenzoyl chloride **3.48** in THF was slowly added and the mixture stirred for 1 hour and then allowed to warm to room temperature. The reaction was gradually acidified and the product was isolated with DCM and the residue purified by flash column chromatography. Unfortunately, the ^{1}H NMR spectrum of the solid was complex and none of the product could be identified [Scheme 3.40, 99JMC3629].



3.48 **3.26E**

Scheme 3.40

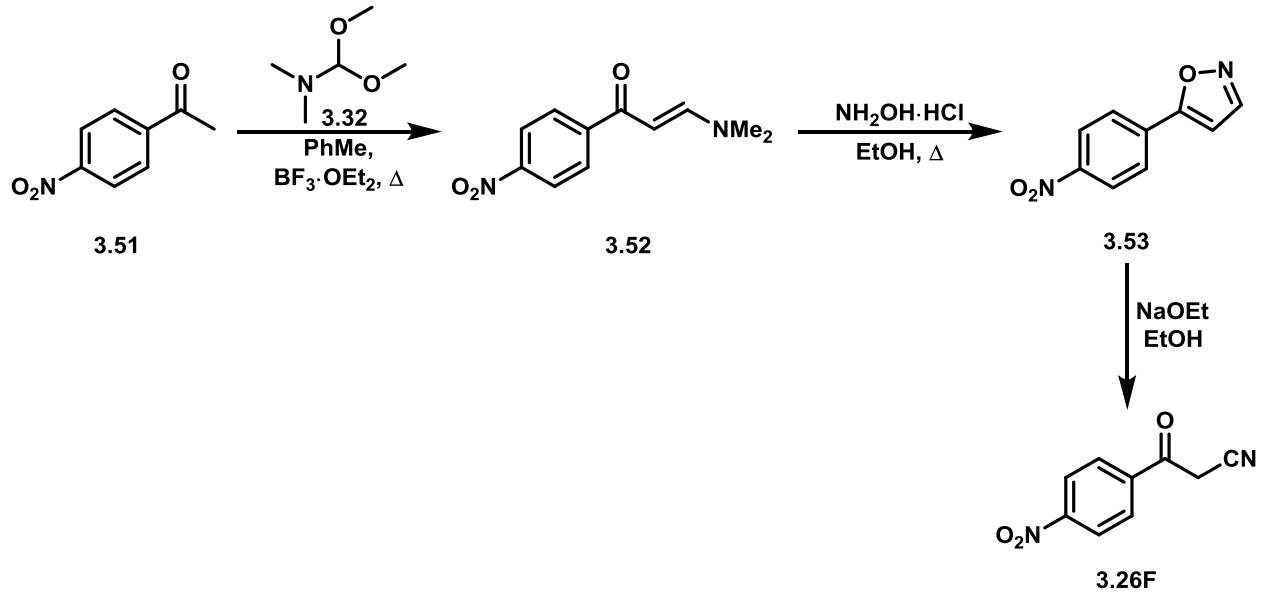
It has been reported that aroylacetonitriles and other β-ketonitriles can be obtained by *C*-acylation of the enolate from *tert*-butyl cyanoacetate **3.49** [Scheme 3.41, 97S337]. Conversion to the β-ketonitrile is accomplished by the protolytic elimination of isobutene and CO_2. Thus, the reaction provided the β-ketoester **3.50** that was stirred with TsOH in toluene overnight. Flash column chromatography provided the product but in exceedingly low yield (4 %).



3.49 3.48 3.50 3.26E

Scheme 3.41

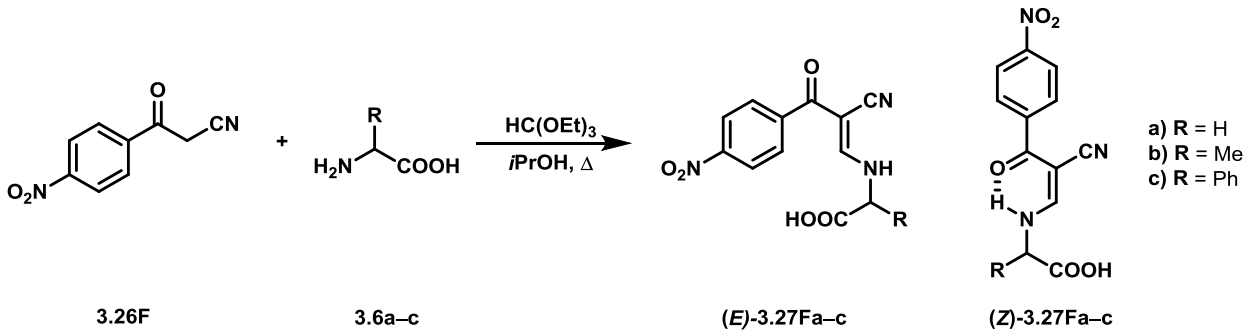
However, when the procedure described for the synthesis of 4-(dimethylamino)benzoylacetonitrile **3.26E** *via* the isoxazole [Scheme 3.35] was applied to 4′-nitroacetophenone **3.51**, 4-nitrobenzoylacetonitrile could be efficiently synthesised in 41 % yield over 3 steps [Scheme 3.42, 08JOC1121, 08JHC879]. The yields for the syntheses of enaminone **3.52** and isoxazole **3.53** were 92 % and 75 %, respectively, which are comparable with those in the literature [08JHC879].



3.51 3.52 3.53 3.26F

Scheme 3.42

Enamino acids **3.27Fa–c** from 4-nitrobenzoylacetonitrile **3.26E** were prepared in 24–49 % yields using the orthoformate methylenation reaction (Scheme 3.43, Table 3.12, entries 1–3). The enamino acid from glycine had an *E*/*Z*-ratio of 0.8:1 (Table 3.12, entry 1), in contrast enamino acids **3.27Fb** and **3.27Fc** only exhibited the *Z*-stereochemistry by ^{1}H NMR (Table 3.12, entries 2 and 3). The reason for the differing stereochemical preferences of these as well as many of the other enamino acids are unclear.



Scheme 3.43

Table 3.12 Yields of 3-(1-carboxyalkylamino)-2-(4-nitrobenzoyl)acrylonitriles **3.27F**.

Entry	R	Compound 3.27F	Yield (%)	Ratio *E/Z*-isomers
1	H	**3.27Fa**	24	0.8 : 1
2	Me	**3.27Fb**	33	0 : 1
3	Ph	**3.27Fc**	49	0 : 1

The electron withdrawing effect of the nitro group and electron donating effect of the methoxy group in these aroyl enamino acids are evident in the ^{1}H NMR spectra (Figure 3.7). Figure 3.7a)–c) show the spectra of **3.27Fa**, **3.27Ca** and **3.27Da**, respectively, the *meta*-protons are indicated with stars and show the large difference in chemical shifts. Figure 3.7a) shows a shift of 8.30–8.35 ppm which is 0.9 ppm further downfield than that in the benzoylacetonitrile derivative **3.27Ca** (δ 7.45–7.58) due to the deshielding effects of the nitro moiety [Figure 3.7b)]. The equivalent protons in **3.27Da** have an upfield shift of 0.4 ppm due to the shielding effects of the methoxy group with respect to **3.27Ca** [Figure 3.7c)]. The same pattern is exhibited by the NH protons, but not to the same extent, the NH protons in **3.27Fa** and **3.27Da** are shifted 0.3 ppm downfield and 0.1 ppm upfield respectively in the *E*-isomers and 0.03 ppm downfield and 0.05 ppm upfield respectively in the *Z*-isomers (Figure 3.7).

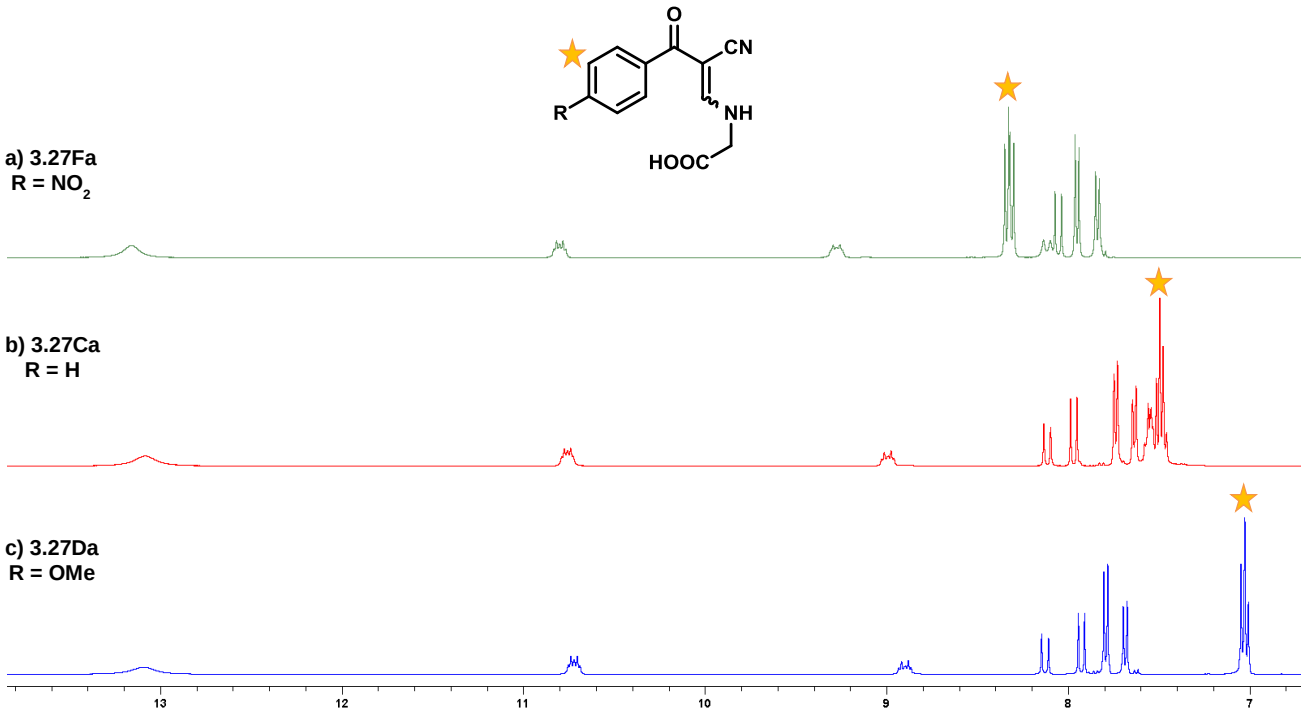
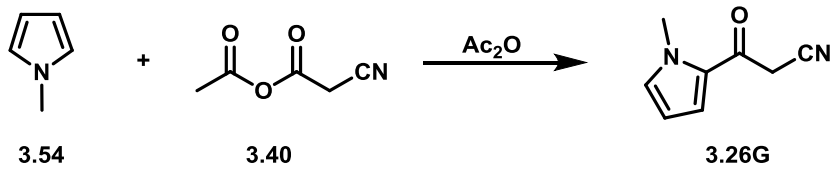


Figure 3.7 ^{1}H NMR spectra (400 MHz, $CDCl_3$) of 2-aroyl-3-(carboxymethylamino)acrylonitriles a) **3.27Fa** (R = NO_2), b) **3.27Ca** (R = H) and c) **3.27Da** (OMe).

It was of interest to obtain a heteroaroylacetonitrile derivative and 2-cyanoacetyl-1-methylpyrrole **3.26G** was an attractive substrate because of the π-excessive nature of the pyrrole ring. Furthermore, the direact cyanoacetylation of pyrroles can be readily accomplished using *in situ* generated acetic 2-cyanoacetic anhydride **3.40** as described by Bergman *et al.* [04S2760]. Thus, cyanoacetic acid and *N*-methylpyrrole **3.54** were heated in acetic anhydride for 45 minutes, the mixture was allowed to cool to room temperature before pouring onto ice. The resulting precipitate was washed with hexane to afford the product in excellent yield (94 %). All the spectroscopic and physical data were in perfect agreement with the literature with the exception of the IR spectrum in which the nitrile absorption was absent in the sample prepared in the present work [04S2760, Scheme 3.44].

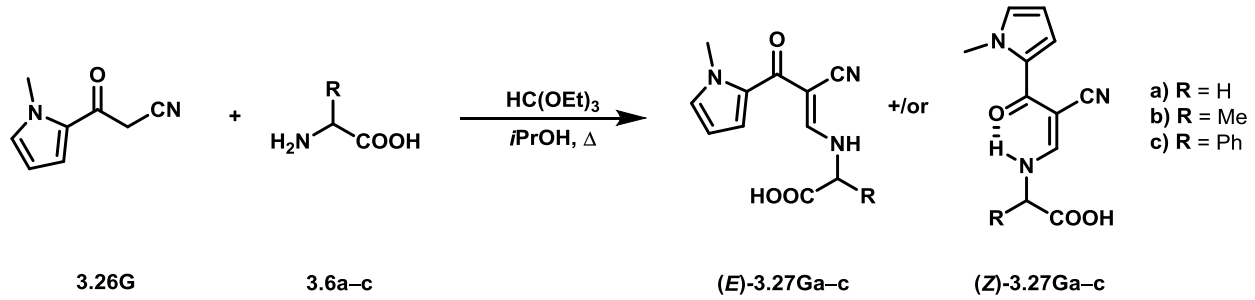


3.54 3.40 3.26G

Scheme 3.44

The β-ketonitrile derivative **3.26G** was used in the reaction with α-amino acids **3.6a–c** and triethyl orthoformate in isopropanol. The products were isolated in fair yields (49–66 %, Table 3.13,

entries 1–3). The nitrile band was visible in the IR spectra for all of the enamino acids at 2190–2217 cm^{-1}. Interestingly, all enamino acids **3.27Ga–c** showed fragmentation in the ES-MS spectra with a loss of *m/z* 81, correlating to an *N*-methylpyrrole fragment.



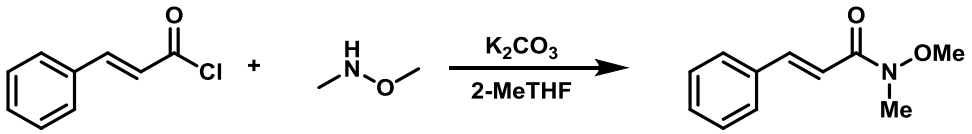
3.26G **3.6a–c** (*E*)-**3.27Ga–c** (*Z*)-**3.27Ga–c**

Scheme 3.45

Table 3.13 Yields of 3-(1-carboxyalkylaminomethylene)-2-(1-methyl-2-pyrrolyl)acrylonitriles **3.27G**.

Entry	R	Compound 3.27G	Yield (%)	Ratio *E/Z*-isomers
1	H	**3.27Ga**	52	0.7 : 1
2	Me	**3.27Gb**	49	0.6 : 1
3	Ph	**3.27Gc**	66	0.4 : 1

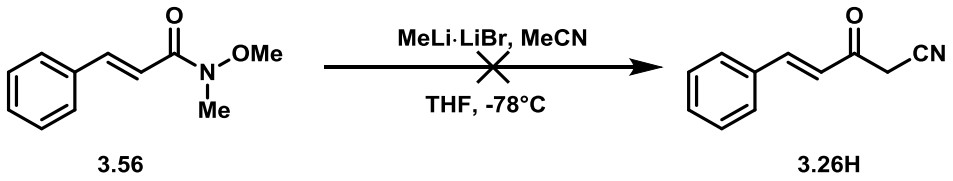
An attempt was made to synthesise the cinnamoyl derivative **3.26H** a vinylogue of benzoylacetonitrile *via* a Weinreb amide following the method used in Scheme 3.29. The Weinreb amide **3.56** from cinnamoyl chloride **3.55** was synthesised in very good yield (83 %) [13RSC(A)10158, Scheme 3.46].



3.55 **3.56**

Scheme 3.46

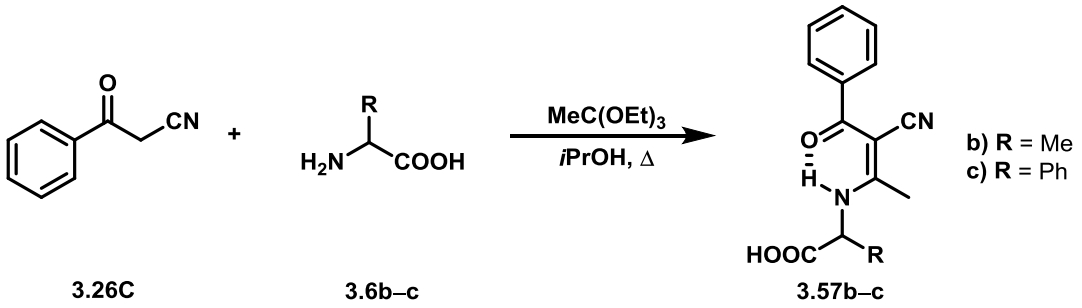
However, in a similar manner to the cyanomethylation of **3.36** (Scheme 3.30) the synthesis of 3-oxo-5-phenylpent-4-enenitrile **3.26H** was unsuccessful providing material with a complex ^{1}H NMR spectrum from which no product could be identified [15OBC1969, Scheme 3.47]. Repetition of the reaction gave identical results and no further effort was devoted to the preparation of cinnamoylacetonitrile **3.26H**.



3.56 3.26H

Scheme 3.47

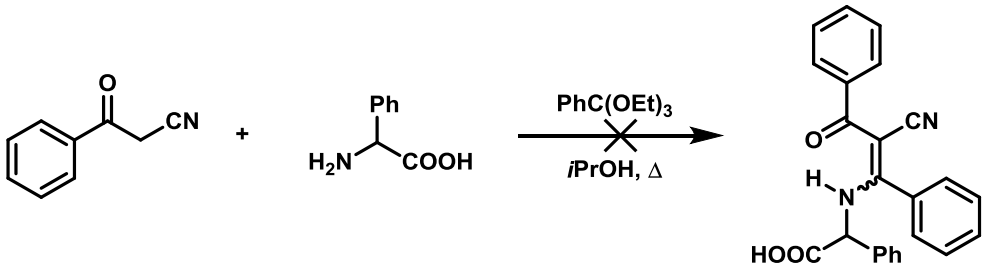
All of the enamino acids derived from the β-ketonitriles were, so far, derived by methylenation with $HC(OEt)_3$ and nucleophilic substitution with the requisite α-amino acid. It was also of value to explore the ethylidenation and benzylidenation of the β-ketonitrile. To this end triethyl orthoformate was reaplaced with triethyl orthoacetate and triethyl orthobenzoate, respectively, in the condensation with benzoylacetonitrile. Introduction of new functionality at the alkene in the enamino acid has the potential for the synthesis of pentasubstituted pyrroles. The α-amino acids used in the condensation were alanine **3.6b** and phenylglycine **3.6c**. Reaction of **3.26C** with triethyl orthoacetate and the α-amino acids **3.6** provided the enamino acids **3.57b** and **3.57c** as the single *Z*-isomers in low yields, 29 % and 17 %, respectively (Scheme 3.48).



3.26C 3.6b–c 3.57b–c

Scheme 3.48

Unfortunately, when the reaction of **3.26C** was conducted using triethyl orthobenzoate and phenylglycine **3.6c**, no product **3.58c** could be isolated or detected by ^1H NMR spectroscopy, this could potentially be due to a combination of adverse steric factors as well as the diminished reactivity of the highly resonance stabilised phenyldiethoxycarbenium $[PhC(OEt)_2^+]$ ion towards the enolisable β-ketonitrile (Scheme 3.49).

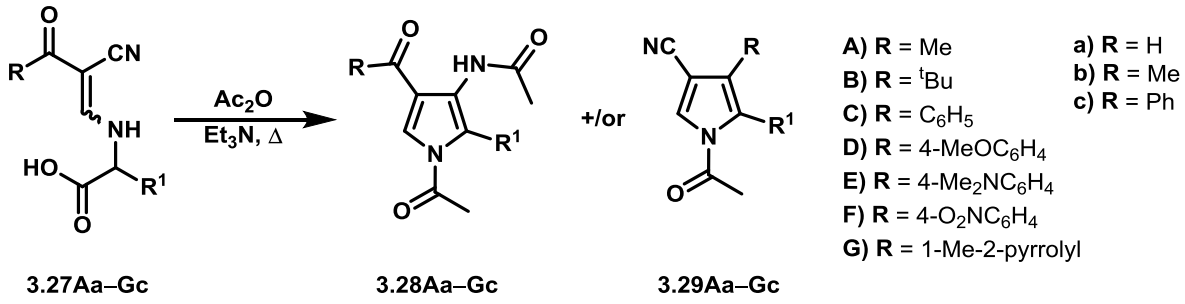


3.26C 3.6c 3.58c

Scheme 3.49

3.4.2 Cyclisations of 2-Alkanoyl- and 2-Aroyl-3-(1-carboxyalkylamino)acrylonitriles

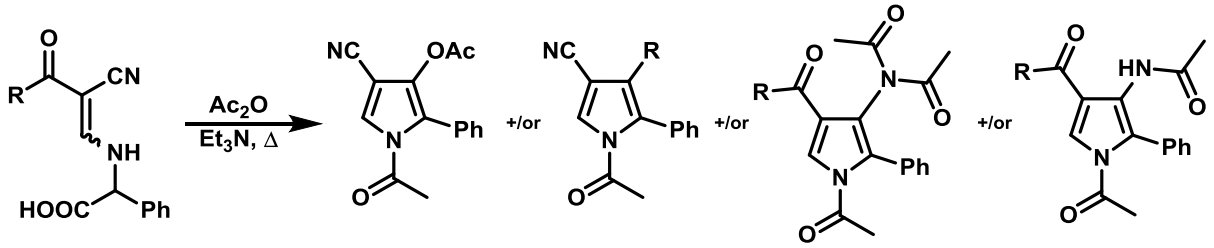
With a range of enamino acids derived from β-ketonitriles having varying steric and electronic properties available, their acylative cyclisation manifolds under Zav'yalov conditions were investigated. Substituent effects on the distribution of pyrrole products were explored. There are a number of ways in which the enamino acids **3.27Aa–Gc** could cyclise, the expected pyrrole products are shown in Scheme 3.50 which are a result of cyclisation onto the nitrile function, **3.28Aa–Gc** or onto the ketone carbonyl **3.29Aa–Gc**. Interestingly, the outcome of the cyclisation reactions was dictated by the nature of the R^1 group and varying the electronic and steric properties of the R group had little effect on the outcome of the reaction.



Scheme 3.50

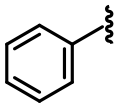
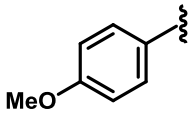
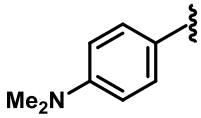
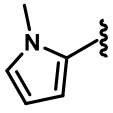
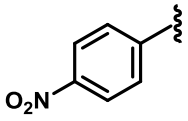
When the enamino acids **3.27Ac–Gc** derived from phenylglycine **3.6c** (R = Ph) were cyclised the pyrrole products from each cyclisation were the result of cyclisation onto the nitrile, resulting in imido- and amido- pyrroles **3.59Ac–Gc** and **3.28AcGc** respectively (Scheme 3.51, Table 3.14, entries 1–7). All of the compounds in Table 3.14 are novel and have not been described previously.

Table 3.14 Yields and distribution of products from the cyclisation of cyanoenamino acids **3.27Ac–G** from phenylglycine **3.6c**.

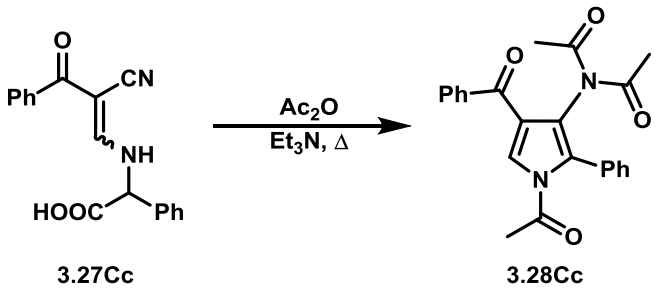


3.27Ac–Gc | 3.60c | 3.29Ac–Gc | 3.59Ac–Gc | 3.28Ac–Gc

Scheme 3.51

Entry	3.27Ac–Gc R =	3.60c	3.29Ac–Gc	3.59Ac–Gc	3.28Ac–Gc
1	 3.27Ac			33 %	22 %
2	 3.27Bc			18 %	63 %
3	 3.27Cc			19 %	61 %
4	 3.27Dc			25 %	51 %
5	 3.27Ec			41 %	31 %
6	 3.27Gc			32 %	39 %
7	 3.27Fc	13 %	8 %	17 %	19 %

The combined yields from the cyclisation reactions were good with the majority being above 70 % (lowest yield 55 %, Table 3.14, entry 1). To ensure the imidopyrrole was a result of acetylation of the amidopyrrole, the reaction of **3.27Cc** from benzoylacetonitrile **3.26C** was carried out with a reflux period of 2 hours, rather than the usual reaction time of 15–30 minutes (until the evolution of CO_2 had ceased). The sole product from the prolonged reaction was the imidopyrrole **3.59Cc** in good yield (79 %, Scheme 3.52), comparable to combined yield of the imido- **3.59Cc** and amidopyrroles **3.28Cc** from the short reaction time (Table 3.14, entry 3, Scheme 3.52). The cyclisation of **3.27Fc** from 4-nitrobenzoylacetonitrile provided an array of products isolated by flash column chromatography (Table 3.14, entry 7). Initially, acetoxypyrrole **3.60c**, which is a result of hydrolytic cleavage of the aroyl group, *vide infra*, was isolated in 13 % yield, followed by 3-cyanopyrrole **3.29Fc**; finally, the imido- **3.59Fc** and amidopyrroles **3.28Fc** were isolated and account for the majority of the reaction products.



3.27Cc **3.28Cc**

Scheme 3.52

All of the novel products (**3.59 Ac–Gc**, **3.28Ac–Gc**, **3.29Gc** and **3.60c**) were characterised by their IR, ^{1}H and ^{13}C NMR spectra, 2D NMR experiments (COSY, NOESY, HSQC and HMBC) and their mass spectra. Figure 3.8 shows the ^{1}H NMR spectra of pyrroles formed in the cyclisation of **3.27Ec** (Table 3.14, entry 5). In Figure 3.8a) the singlets at δ 2.19 (3H) and 2.27 (6H) are *N*-acetyl signals assigned to the N-1 acetyl and the diacetamido function respectively, in Figure 3.8b), the analogous signals at δ 1.94 and 2.12, with integrations of 3H correspond to the acetamido- methyl protons and the pyrrole N-1 acetyl group respectively. Interestingly, the signals for the phenyl group are displayed as two multiplets in the spectrum of **3.59Ec** [Figure 3.8a)] but as a singlet in the spectrum of **3.28Ec** [Figure 3.8b)]. The pyrrole proton 5-H has a small but significant upfield shift in **3.28Ec** with respect to **3.59Ec** for which Δδ = 0.13 ppm. The signal for the amido N*H* proton overlaps with the *ortho*-protons of the 4-dimethylaminophenyl group at δ 7.90–7.92.

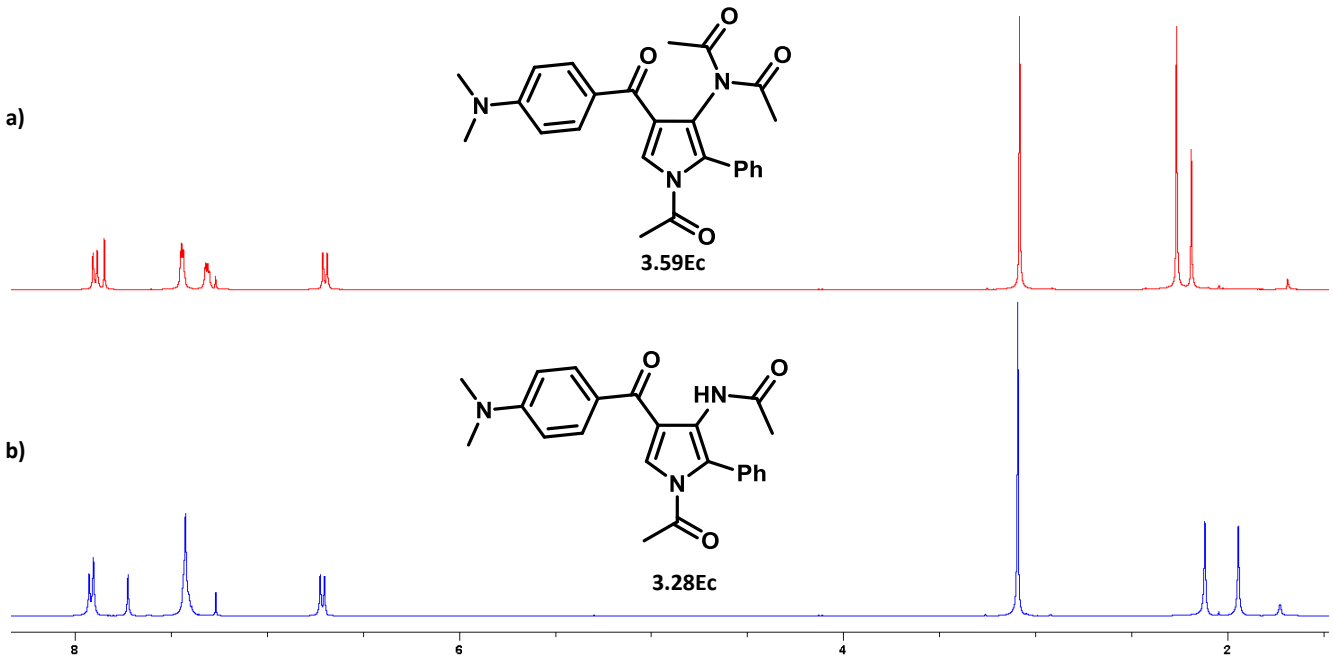


Figure 3.8 ^{1}H NMR spectra (400 MHz, $CDCl_3$) of 3-(4-dimethylaminobenzoyl)pyrroles a) **3.59Ec** and b) **3.28Ec**.

The ESI mass spectra for pyrroles **3.28Ac–Gc** and **3.59Ac–Gc** show fragmentation with small peaks showing the loss of the acetyl groups. The only exception are the pyrroles from the cyclisations of **3.27Dc** and **3.27Ec**. An example is given in Figure 3.9; the mass spectrum of **3.59Fc** shows both the $[M+H]^+$ and the $[M+Na]^+$ ions at *m/z* 434.1347 and 456.1166 respectively. A loss corresponding to an acetyl group, from $[M+H]^+$, eliminated as a ketene ($H_2C=C=O$) fragment (M+H – 42) can be seen with the peak *m/z* at 392.1241 and subsequent losses can be seen at *m/z* 350.1135 and 308.1028 (Figure 3.9).

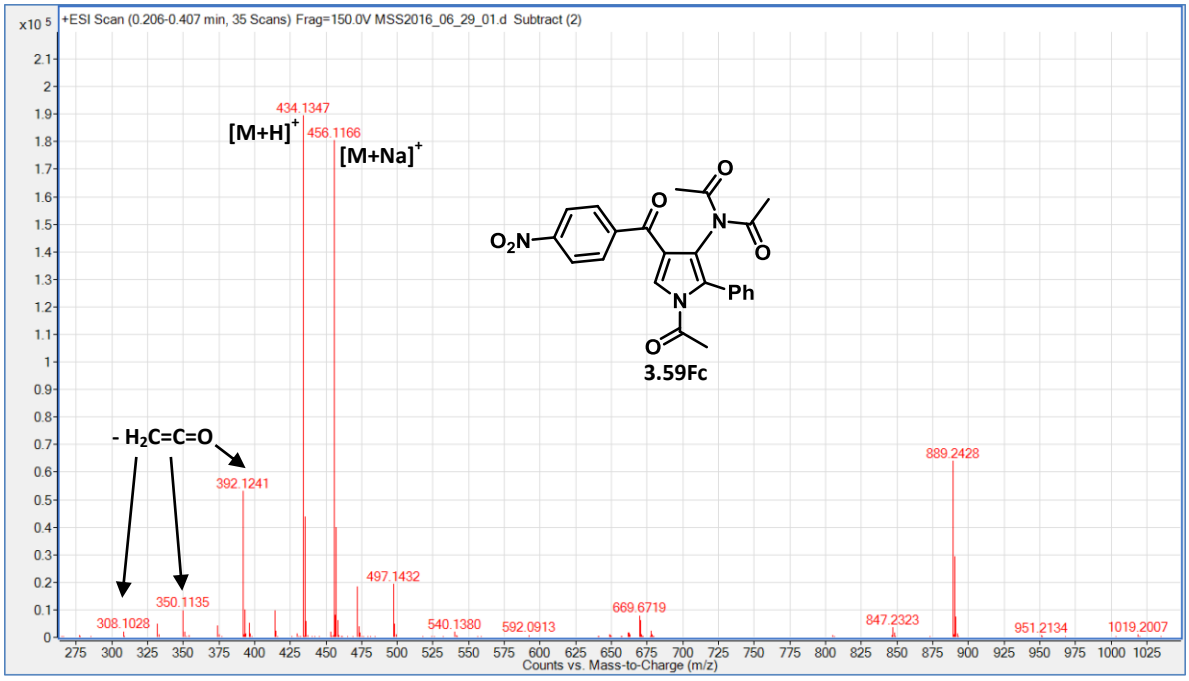
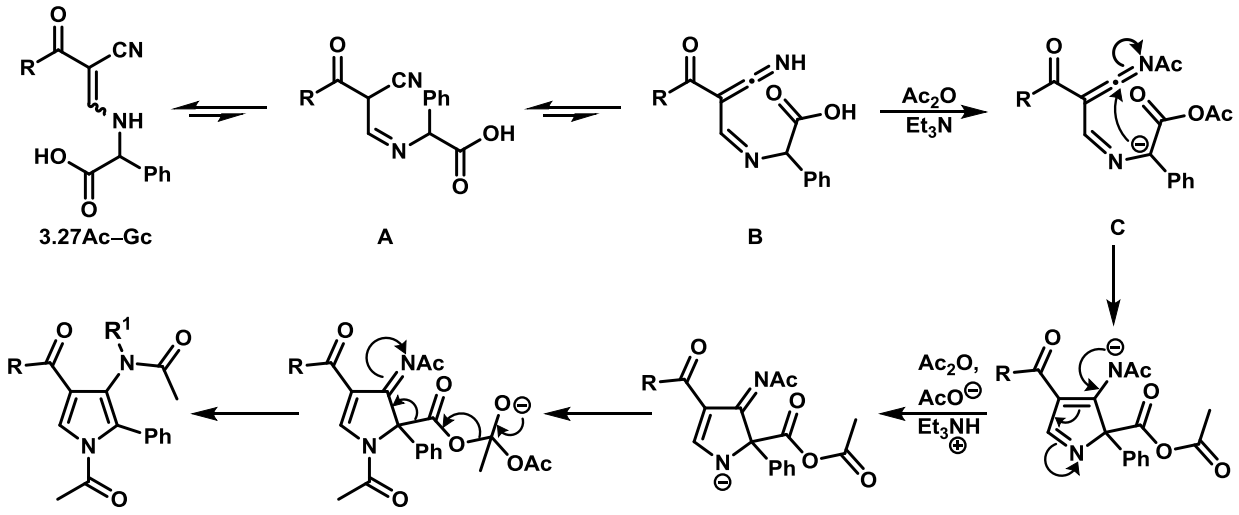


Figure 3.9 ESI-HRMS spectrum of the 3-(4-nitrobenzoyl)pyrrole **3.59Fc**.

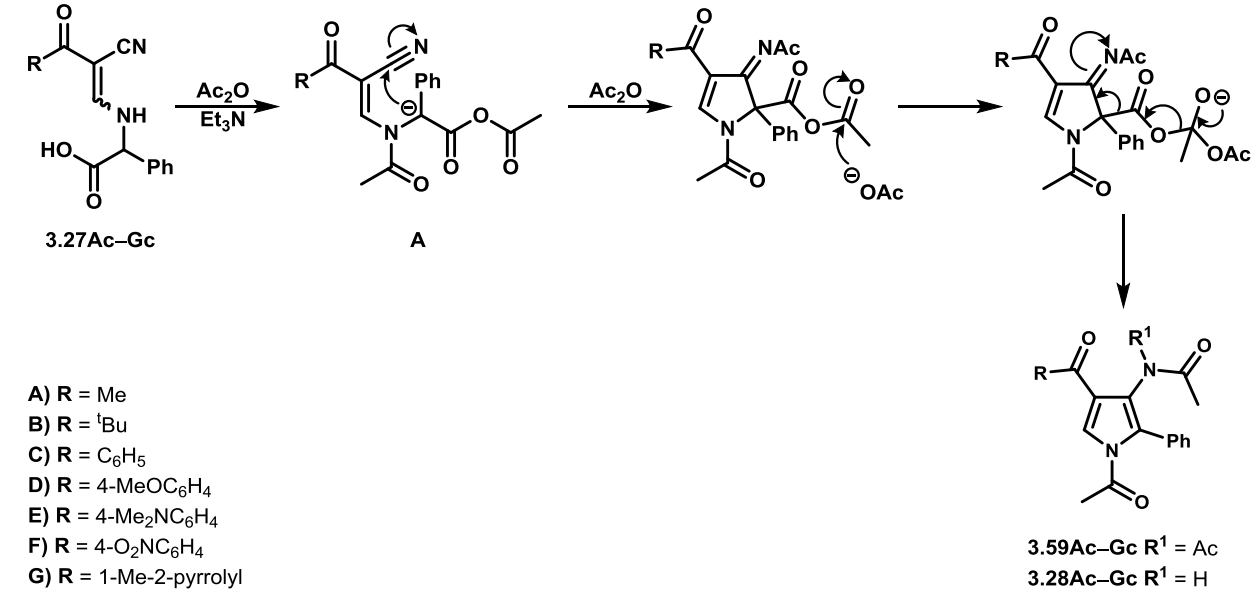
Possible mechanisms for the formation of **3.59** and **3.28** are outlined in Scheme 3.53 and Scheme 3.54 and both have similarities to that outlined in Scheme 3.13. Scheme 3.53 provides a pathway to account for the isomerisation of the *Z*-enamino acid **3.27** to facilitate cyclisation. Thus, tautomerism of the enaminonitrile **3.27** provides the enolisable nitrile **A** from which the ketenimine tautomer **B** (or its anion) may result. The involvement of ketenimine tautomers from enaminonitriles has been noted [10SAA367, 12CSR5687, 13CRV7287]. Subsequent acetylation of **B** at nitrogen and of the carboxylic acid affords an anion of the mixed anhydride **C** from which cyclisation can occur. Addition of the acetate facilitates cleavage of the anhydride side chain and further *N*-acylation can now proceed.



A) R = Me, **B) R** = ^{t}Bu, **C) R** = C_6H_5, **D) R** = 4-$MeOC_6H_4$, **E) R** = 4-$Me_2NC_6H_4$, **F) R** =4-$O_2NC_6H_4$, **G) R** = 1-Me-2-pyrrolyl

Scheme 3.53

In Scheme 3.54 the *E*-isomer of the enaminonitrile is acetylated to give the mixed anhydride **A**, the enolate of which cyclises onto the nitrile function. Subsequent steps are as shown in Scheme 3.54.

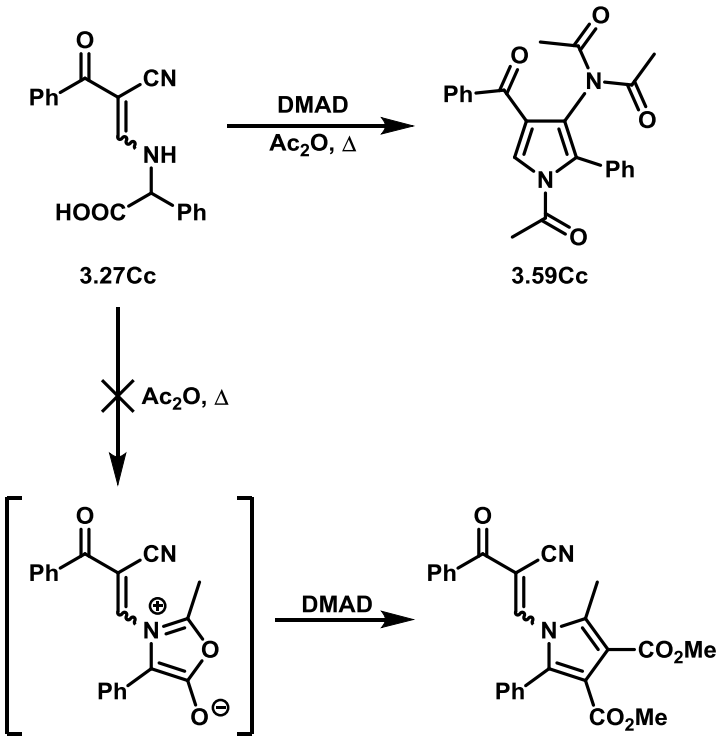


A) R = Me
B) R = ^{t}Bu
C) R = C_6H_5
D) R = 4-$MeOC_6H_4$
E) R = 4-$Me_2NC_6H_4$
F) R = 4-$O_2NC_6H_4$
G) R = 1-Me-2-pyrrolyl

Scheme 3.54

To further investigate the mechanism, the cyclisation reaction of **3.27Cc** was carried out in the presence of DMAD (Scheme 3.55). The reaction provided only pyrrole **3.59Cc** (57 % yield) indicating that the cyclisation either occurred too quickly for the intermediates to be trapped or

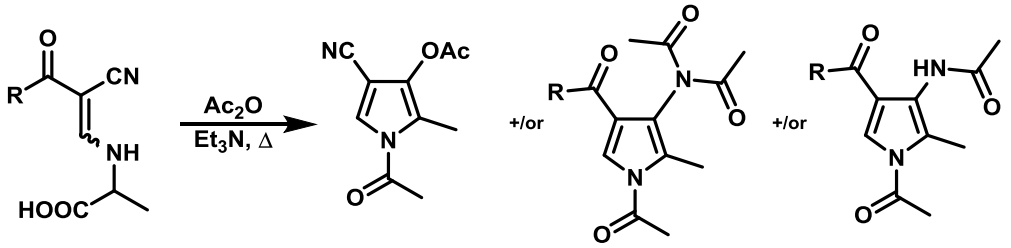
that no münchnone or ketene was formed in the reaction (Scheme 3.15). This outcome resembles that for **3.7b** (Scheme 3.13).



Scheme 3.55

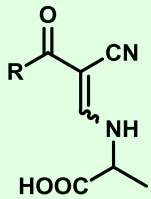
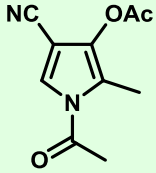
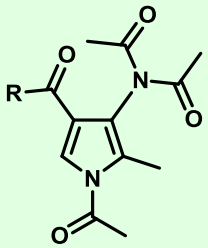
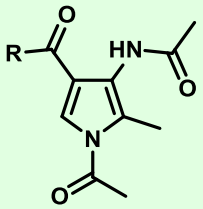
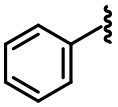
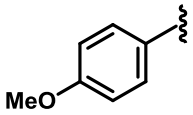
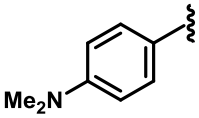
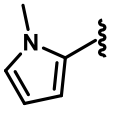
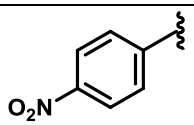
In complete contrast to the phenylglycine analogues **3.27Ac–Gc**, cyclisation of enamino acids derived from alanine **3.27Ab–Gb** generally provided only one pyrrole product, 4-acetoxy-1-acetyl-5-methylpyrrole-3-carbonitrile **3.60b** (Table 3.15, entries 1, 3, 4 and 7). This outcome was completely unanticipated; the carbonyl functionalities had been replaced by an acetoxy group at C-3 (Table 3.15, entries 1–7). When only a single pyrrole was formed (TLC) the products did not require flash column chromatography, instead recrystallisation was sufficient for their purification. The yields from the single product reactions were 49–79 % (Table 3.15, entries 1, 3, 4 and 7). A small amount of imidopyrrole was isolated from the cyclisation of **3.27Eb** (Table 3.15, entry 5), whilst the cyclisations of **3.27Bb** and **3.27Gb** provided both imido- and amidopyrroles (Table 3.15, entries 2 and 6) as the major products.

Table 3.15 Yields and distribution of products from the cyclisation of enamino acids **3.27Ab–Gb** from alanine **3.6b**.

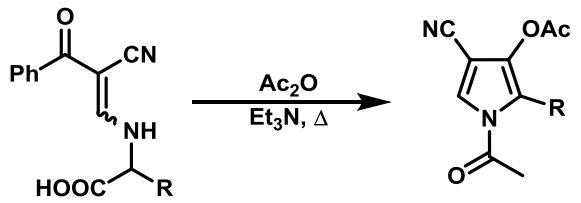


3.27Ab–Gb **3.60b** **3.59Ab–Gb** **3.28Ab–Gb**

Scheme 3.56

Entry	 **3.27Ab–Gb** R =	 **3.60b**	 **3.59Ab–Gb**	 **3.28Ab–Gb**
1	 **3.27Ab**	61 %		
2	 **3.27Bb**	26 %	10 %	19 %
3	 **3.27Cb**	75 %		
4	 **3.27Db**	79 %		
5	 **3.27Eb**	42 %	1 %	
6	 **3.27Gb**	26 %	12 %	19 %
7	 **3.27Fb**	49 %		

Cyclisation of the enamino acids **3.27Cd** and **3.27Ce** from benzoylacetonitrile and 2-aminoisobutyric acid **3.6d** and valine **3.6e** respectively, only afforded the novel acetoxypyrroles in good yields (Scheme 3.57). As only one product had been formed in the reaction, flash column chromatography was unnecessary and the pyrroles were purified simply by recrystallisation from ethyl acetate and hexane.



3.27Cd R = Et
3.27Ce R = *i*Pr

3.60d 63 %
3.60e 71 %

Scheme 3.57

The ^{1}H NMR spectrum of 4-acetoxy-1-acetyl-5-methylpyrrole-3-carbonitrile **3.60b** is very simple (Figure 3.10) and was assigned in combination with 2D NMR such as HSQC and HMBC, to distinguish between the C-5 methyl and OCOMe signals. For example, the HMBC spectrum revealed that the C-5 methyl signal has a cross-peak with the C-3 ring carbon (δ 93.4), whilst the acetyl methyl signal only exhibited a cross-peak with the adjacent carbonyl (δ 168.3). Thus, the most upfield signal at δ 2.33 corresponds to the C-5 methyl group. The adjacent acetoxy methyl group resonates at δ 2.34, the *N*-acetyl signal is displayed at 2.58 ppm. The pyrrole 2-H proton absorbs at 7.50 ppm (Figure 3.10). The ^{13}C NMR spectrum exhibited the *N*-acetyl carbonyl group at δ 168.2 a very similar shift to the acetoxy carbonyl function (δ 168.3). The signal for the nitrile carbon resonated at δ 112.5 whilst the signal at δ 93.4 correlates to the adjacent *ipso*-carbon (C-3). High field signals have been observed previously for *ipso*-carbon signals in pyrrole-3-carbonitriles [89T6553, 08EJOC2288, 12LOC305, 12TL446]. The IR spectrum exhibited a band for ν_{CN} at 2233 cm^{-1}, whilst the ester and *N*-carbonyl absorptions appeared at 1745 and 1760 cm^{-1}, respectively.

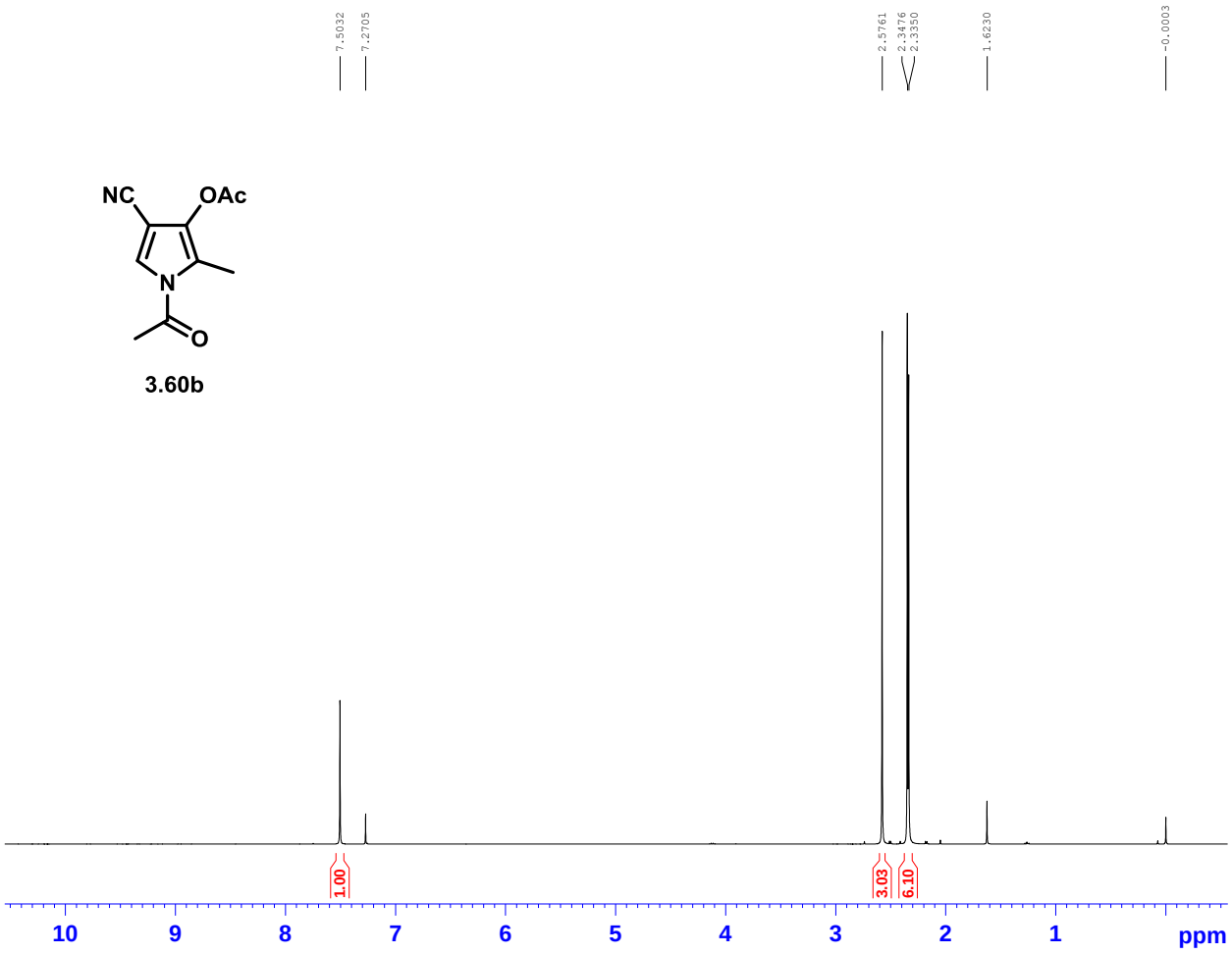
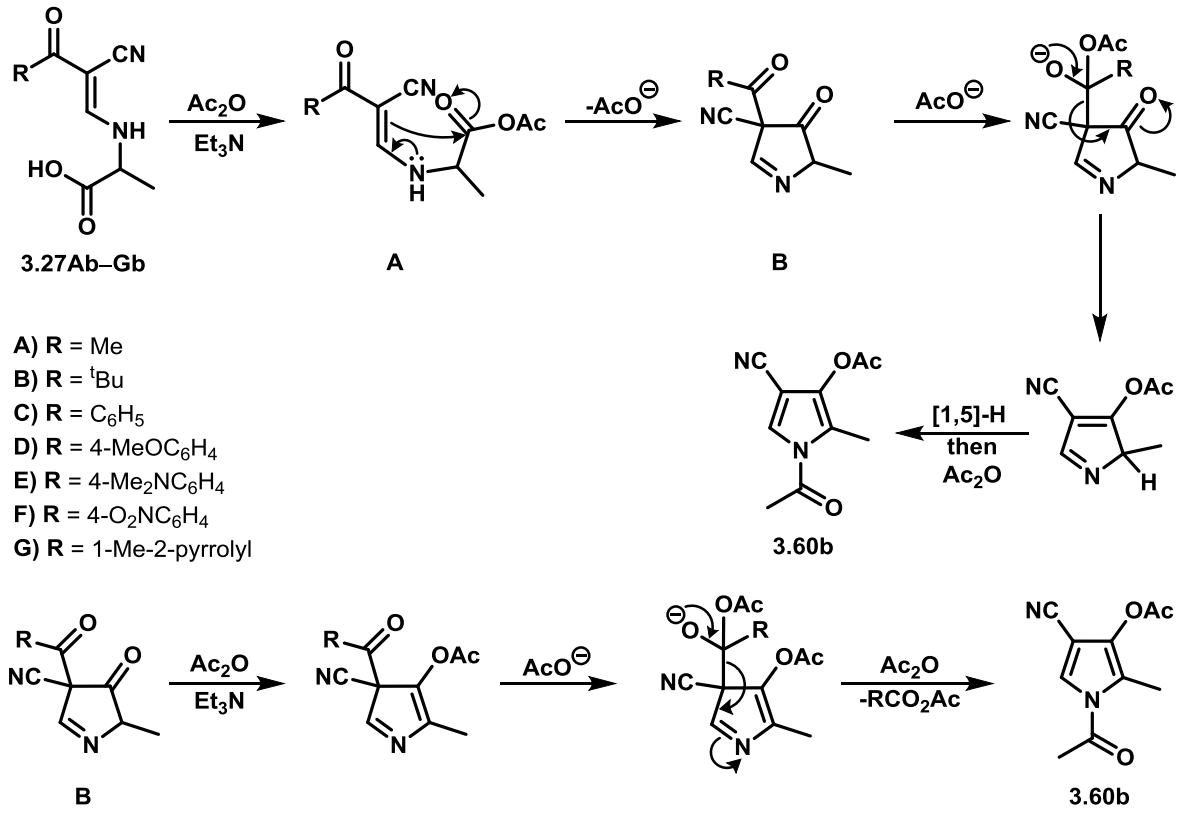


Figure 3.10 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 4-acetoxy-1-acetyl-5-methylpyrrole-3-carbonitrile **3.60b**.

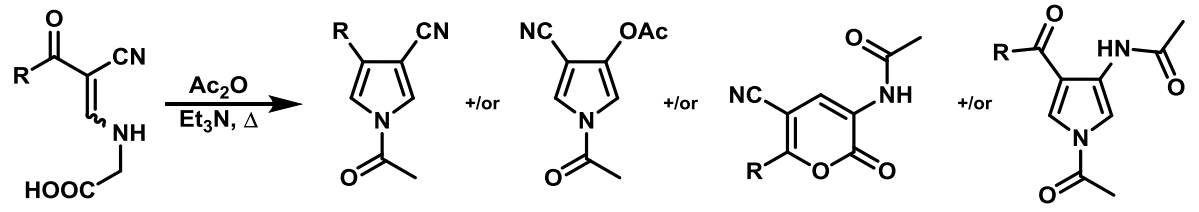
The proposed mechanism for the formation of the 4-acetoxypyrrole-3-carbonitrile **3.60b** is shown in Scheme 3.58. It is likely that the sequence is initiated by formation of a mixed anhydride **A**, the carbonyl function β- to the amino groups is activated to nucleophilic attack by the enamine as shown leading to intermediate **B**. Non-enolisable 1,3-dicarbonyl compounds are susceptible to cleavage under basic conditions [13MI723]; attack by acetate results in the formation of a stabilised enolate which leads to the product *via* an acylation-prototropy-acylation sequence. Alternatively, *O*-acetylation of **B** may afford a 3*H*-pyrrole through which an analogous series of transformations may occur. A precedent for β-acylation of the enamine to form the pyrrole ring is provided by the formation of the 2,3-dihydropyrrole **3.11** (Scheme 3.8) and by the acylative cyclisations in Scheme 3.10.



Scheme 3.58

Formation of the 4-acetoxy-1-acetyl-5-alkylpyrrole-3-carbonitriles **3.60e** and **3.60f** from 2-aminobutyric acid and valine will of course follow an identical pathway. In contrast, the cyclisation reactions of the glycine-derived enamino acids **3.27Aa–Ga** were much less predictable and a greater diversity of products were formed (Scheme 3.59, Table 3.16, entries 1–7). Thus, each reaction afforded an array of pyrrole products including those already seen from the cyclisations of **3.27Ac–Gc** and **3.27Ab–Gb**. Surprisingly, the cyclisation of enamino acids from benzoylacetonitrile and 4-methoxybenzoylacetonitrile also provided another product (Table 3.16, entries 3 and 4).

Table 3.16 Yields and distribution of products from the cyclisation of enamino acids **3.27Aa–Ga** from glycine **3.6a**.



3.27Aa–Ga **3.29Aa–Ga** **3.60a** **3.61C–D** **3.28Aa–Ga**

Scheme 3.59

Entry	R =	3.29Aa–Ga	3.60a	3.61C–D	3.28Aa–Ga
1	3.27Aa		23 %		12 %
2	3.27Ba	13 %			34 %
3	3.27Ca	4 %	23 %	2 %	11 %
4	3.27Da	10 %	10 %	13 %	
5	3.27Ea	8 %			26 %
6	3.27Ga	19 %			34 %
7	3.27Fa		46 %		

A product previously unobserved from any of these acylative ring closures was isolated from the cyclisations of **3.27Ca** and **3.27Da**, with this product, a pyran-2-one derivative, being the major component from the cyclisation of **3.27Da** (Table 3.16, entry 4). The ^{1}H NMR spectrum showed the presence of an acetyl group at δ 2.25, a phenyl group for **3.61C** [δ 7.52–7.60 for the *meta*- and *para*-protons and δ 8.00–8.02 for the *ortho*-protons, Figure 3.11a)] and the anisyl protons for **3.61D** [δ 3.90 for the methoxy protons, a doublet at δ 7.18 for the *meta*-protons and a doublet at δ 7.89 for the *ortho*-protons, Figure 3.11b)]. A broad singlet is visible in both spectra at δ 7.97 in **3.61C** and at δ 7.87 in **3.61D**, due to an N*H* proton. A singlet can be seen at around 8.45 ppm in both **3.61C** and **3.61D**, this is shifted substantially downfield with respect to the pyrrole protons at the 2- and 5- positions, and due to its multiplicity and absence of another proton, the product cannot be a pyrrole. The ^{13}C NMR spectra of **3.61C** and **3.61D** both showed the presence of a nitrile at δ 123.6 ($CDCl_3$) and δ 123.5 (DMSO-d_6), respectively. Signals for the *N*-acetyl carbonyl in **3.61C** and **3.61D** are displayed at δ 169.4 ($CDCl_3$) and δ 171.1, respectively, ring carbonyl signals are apparent at δ 160.9 (**3.61C**, $CDCl_3$) and δ 161.3 (**3.61D**, DMSO-d_6). The IR spectra of **3.61C** and **3.61D** have bands at 1717 cm^{-1} and 1712 cm^{-1} which is indicative of a potential α,β-unsaturated ester. From the ^{1}H and ^{13}C NMR and IR spectra it was proposed that these products were pyran-2-ones (Scheme 3.59).

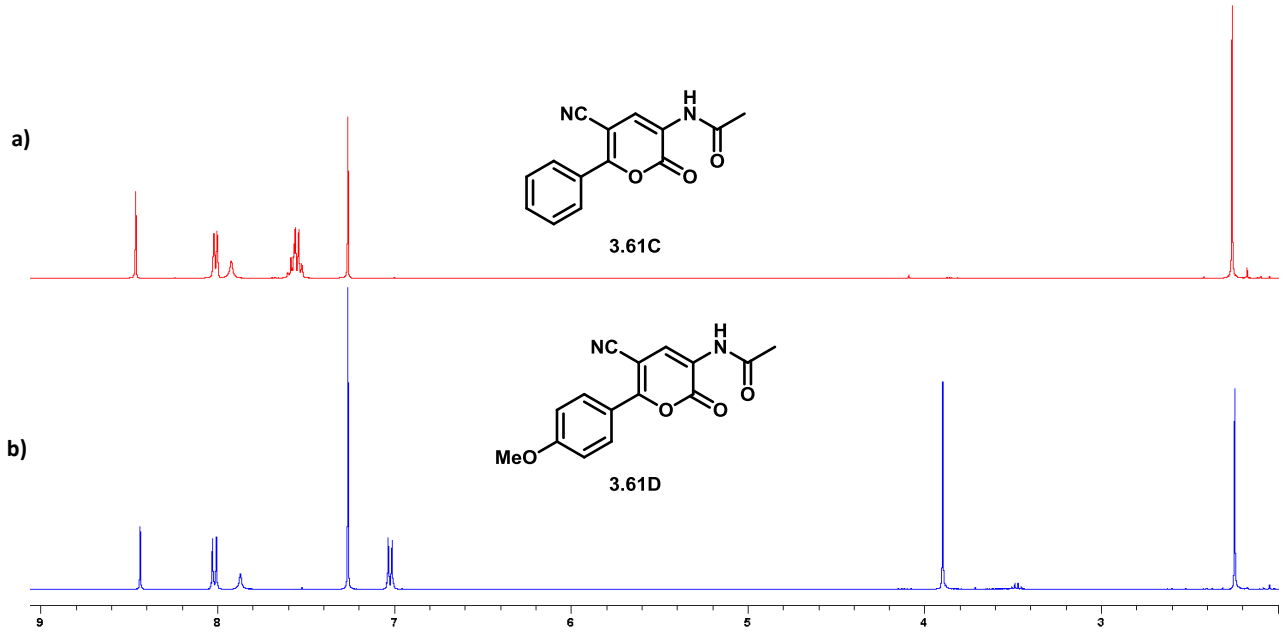
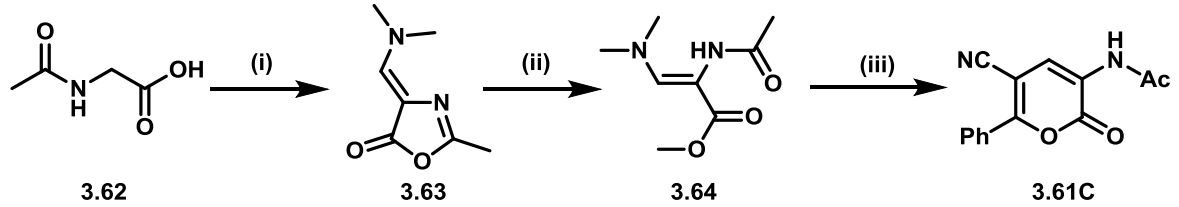


Figure 3.11 ^{1}H NMR spectra (400 MHz, $CDCl_3$) of 3-acetamidopyran-2-ones a) **3.61C** and b) **3.61D**.

To definitively determine the structures of **3.61C** and **3.61D** (Table 3.16, entries 3 and 4), pyranone

3.61C was synthesised unambiguously from *N*-acetylglycine **3.62** [97JHC247, Scheme 3.60] which upon treatment with the Vilsmeier reagent ($Me_2N{=}CHCl^+PO_2Cl_2^-$), generated *in situ* by addition of $POCl_3$ to a solution of **3.62** in DMF, is cyclised and aminomethylenated in a single operation to give (*Z*)-4-(dimethylaminomethylene)-2-methyloxazolin-5(4*H*)-one **3.63**. The product was obtained in 24 % yield when the reaction was performed as described in the literature [97JHC247] (40 °C for 1 hour). However, when the heating period was extended to 3 hours and the reaction quenched with aqueous ammonia, the oxazolone **3.63** was obtained as pale orange crystals (from EtOH) in greatly improved yield (50 %). The oxazolone **3.63** was subjected to methanolysis in the presence of K_2CO_3 as described by Stanovnik *et al.* [97JHC247] to give the enamino ester **3.64** as an oil which crystallised upon trituration with Et_2O. Recrystallisation from $CHCl_3$–Et_2O provided the ester **3.64** as colourless crystals. The ^1H NMR spectrum showed a mixture of the *E*- and *Z*-isomers in a 1:0.3 ratio. The isomers were not assigned spectroscopically in the literature. From the ^1H–^1H COSY spectrum, it can be seen that the minor isomer is the *Z*-isomer due to a cross-peak as a result of the W-coupling interaction between the N*H* proton and the alkenyl proton (Figure 3.12). There is no such interaction between these protons in the major *E*-isomer and therefore no cross-peak.



Reagents and Conditions: (i) DMF, $POCl_3$, 40 °C, 3 h; (ii) K_2CO_3, MeOH, Δ, 30 m; (iii) $PhCOCH_2CN$ (**3.26C**), AcOH, Δ, 2 h.

Scheme 3.60

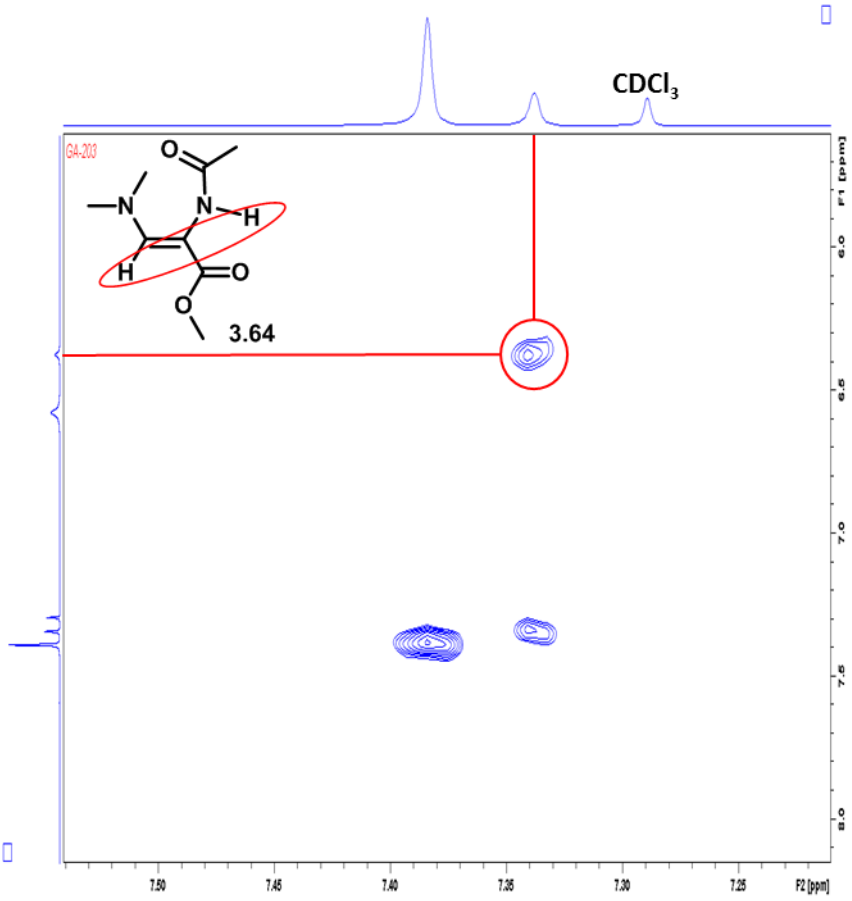
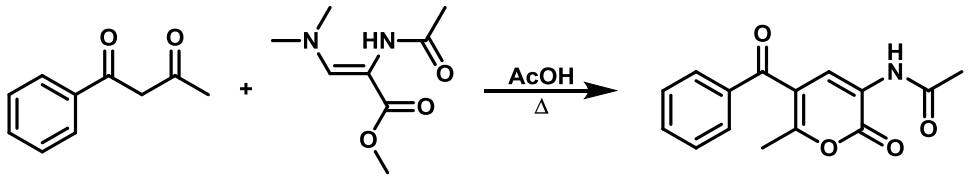


Figure 3.12 $^{1}H–^{1}H$ COSY 2D NMR spectrum (400 MHz, $CDCl_3$) of aminoacrylate **3.64**.

Stanovnik *et al.* described the reaction of the 3-(dimethylamino)propenoate **3.64** with a wide range of 1,3-dicarbonyl compounds [97JHC247, 04CRV2433] for the synthesis of 3-acetamidopyran-2-ones. For example, benzoylacetone reacted to provide **3.65** in good yield (Scheme 3.61).

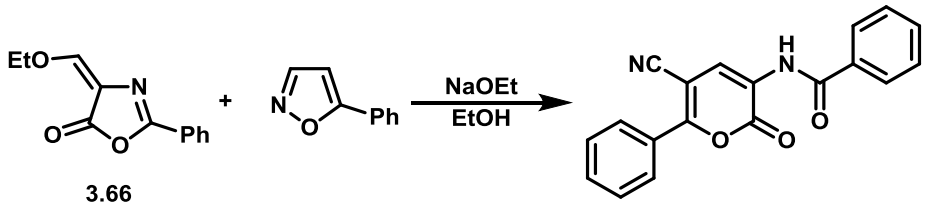


3.64 **3.65**

Scheme 3.61

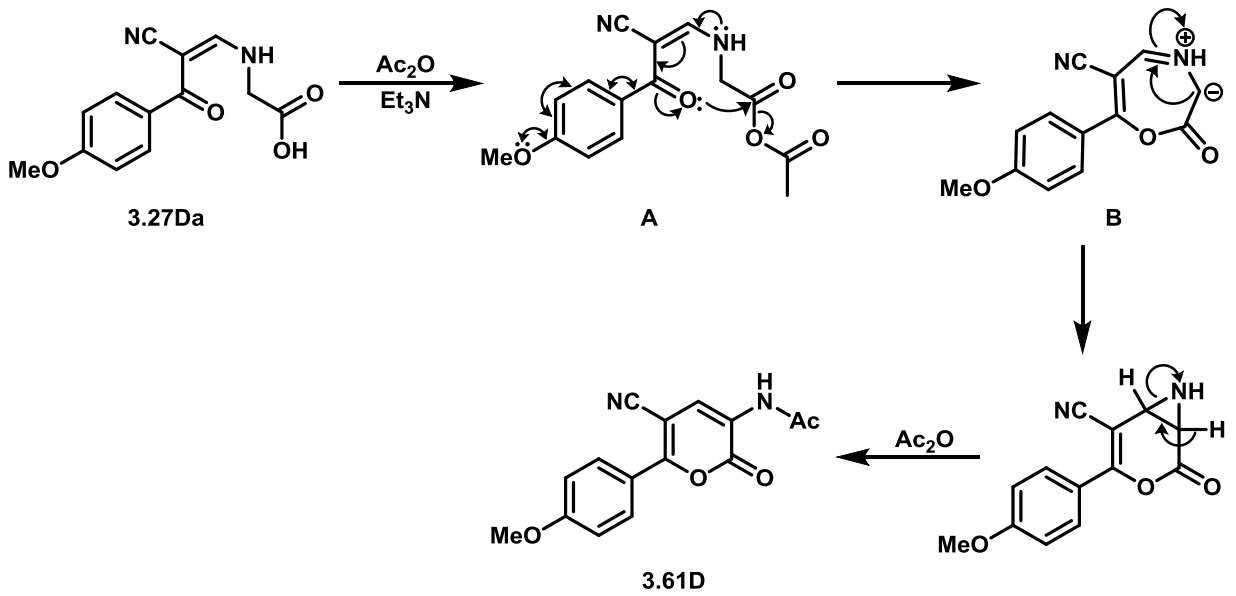
In a similar manner benzoylacetonitrile reacted with **3.64** in refluxing AcOH. The reaction was complete within 2 hours (TLC). The reaction mixture was quenched with water and the product isolated *via* extraction with EtOAc. The novel pyran-2-one **3.61C** was obtained in 96 % yield. The physical and spectroscopic data were in perfect agreement with the pyran-2-one isolated from the

cyclisation reaction. The closest example to **3.61C** in the literature has a benzamido function in place of the 3-acetamido group, the characteristic pyranone ring proton in this compound has a shift of 8.66 ppm ($CDCl_3$) [68CPB1576] and was prepared by reaction of $PhCOCH_2CN$, generated *in situ* from 5-phenylisoxazole with the oxazolone **3.66** (Scheme 3.62).



Scheme 3.62

The formation of **3.61C** and **3.61D** can be rationalised by the mechanism in Scheme 3.63. Electron release from the (+M) methoxy group may explain why the pyranone was the major product from the cyclisation of **3.27Da**, whilst the cyclisation of benzoyl derivative **3.27Ca** only provided a small amount of the pyranone. The pyranone product was not observed from the alanine and phenylglycine derived enamino acids as both protons α to the amine are necessary for the reaction to proceed.

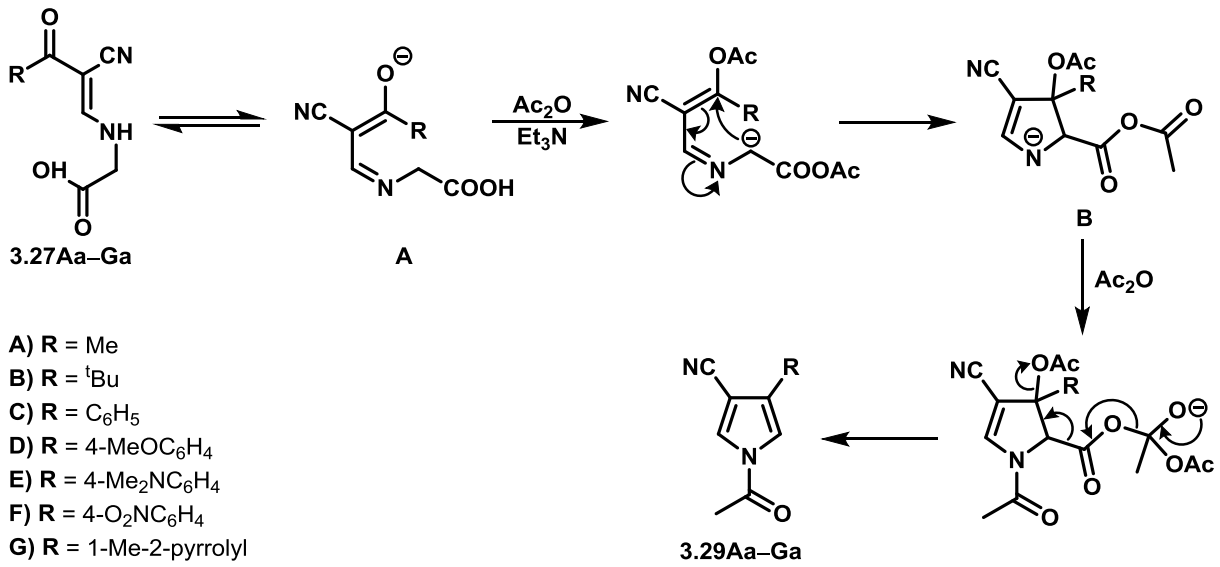


Scheme 3.63

It is proposed that cyclisation to the pyranone is initiated by nucleophilic attack of the electron rich C=O function of the enaminone moiety on the mixed anhydride **A** to give a 1,4-oxazepin-2-one intermediate, which undergoes a 1,3-dipolar cyclisation *via* **B** to provide the product **3.61D** *via* an

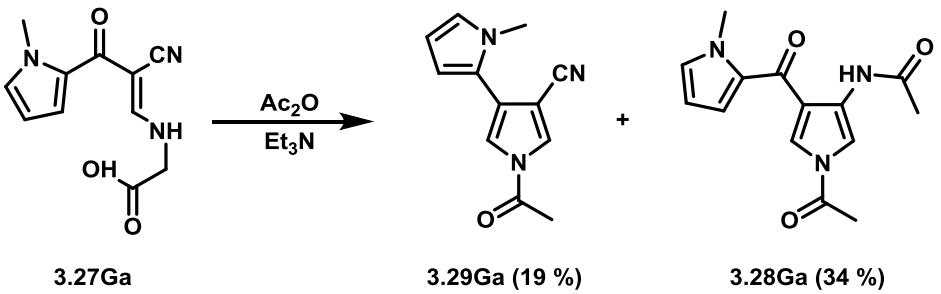
aziridine (or its *N*-acetyl derivative) intermediate. There do not appear to be any literature precedents for such a pathway. This reaction merits further investigation.

The formation of **3.29Aa–Ga**, a derivative of which was also isolated from the cyclisation of **3.27Ac–Gc** (Table 3.14, entry 7), is proposed by the mechanism in Scheme 3.64. Tautomerism provides the enolate **A** which is acetylated and the resulting anion undergoes an electrocyclisation to provide the 5-membered ring **B**. The anhydride side chain is solvolysed and cleaves to Ac_2O and CO_2. The acetoxy group is eliminated to afford pyrrole **3.29Aa–Ga** (Scheme 3.64). An alternative pathway analogous to that in Scheme 3.54 is also possible.



Scheme 3.64

By this mechanism, cyclisation of the enamino acid from *N*-methylpyrrole **3.27Ga** provided a novel 2,3′-bipyrrole as the minor product (19 % yield, Scheme 3.65, Table 3.16, entry 6).



Scheme 3.65

The ^{1}H NMR spectrum displays two doublets for the pyrrole protons centred at δ 7.80 and δ 7.32 for 2′-*H* and 5′-*H* respectively, the coupling constant is 2.0 Hz, consistent with typical $J_{2,5}$ values of

1.9 Hz in pyrroles [89MI1429]. The protons of the *N*-methylpyrrole moiety resonate at 6.20, 6.50 and 6.73 ppm for the 4-*H*, 3-*H* and 5-*H* protons, respectively. The 5-*H* proton appears as an apparent triplet, whereas, the 3-*H* and 4-*H* protons both appeared as double doublets. The coupling constants for this pyrrole unit are also consistent with the literature data, with a $J_{4,5}$ value of 2.8 Hz (lit. 2.7 Hz), $J_{3,4}$ = 3.7 Hz (lit. 3.3 Hz) and a $J_{3,5}$ value of 1.7 Hz (lit. 1.4 Hz) (Figure 3.13, all literature values from [89MI1429]).

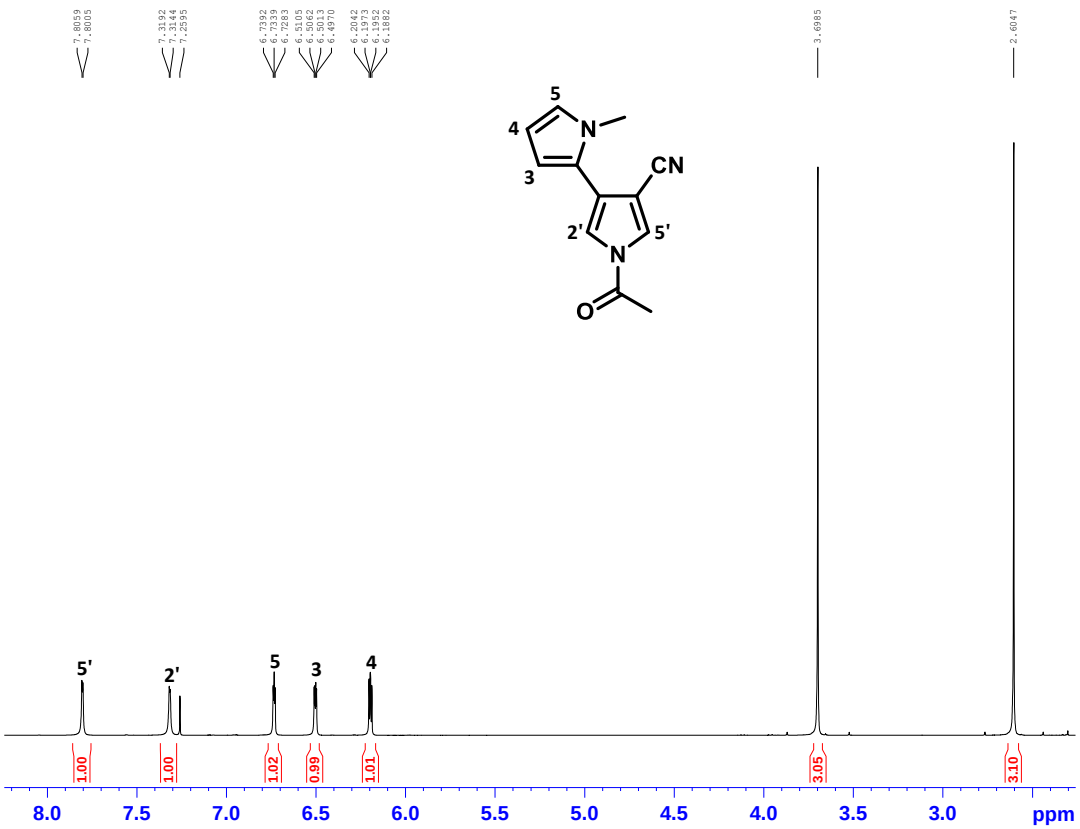
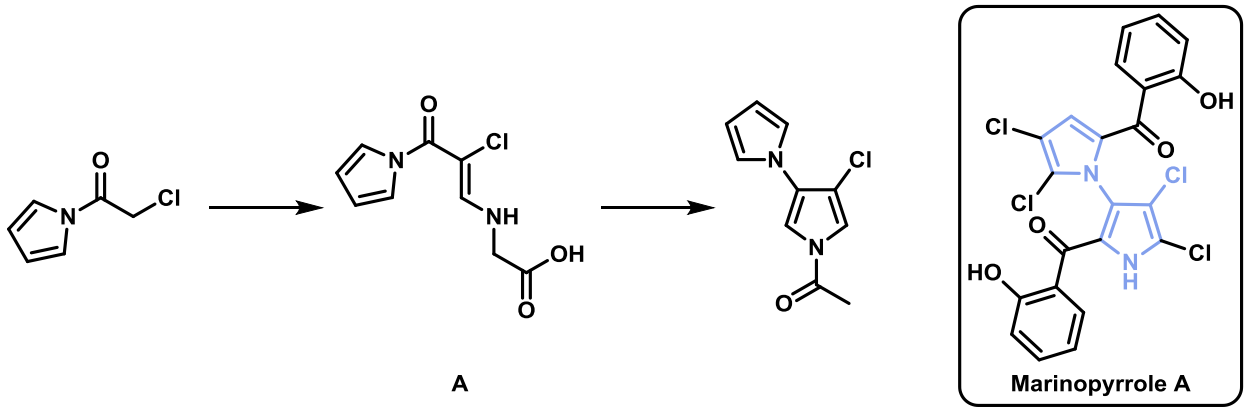


Figure 3.13 ^{1}H NMR spectrum of 2,3′-bipyrrole **3.29Ga** (400 MHz, $CDCl_3$).

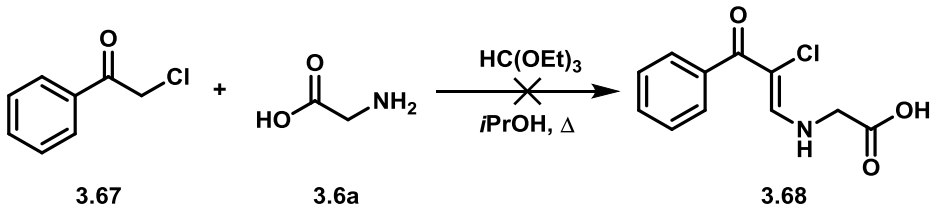
Formation of **3.29Ga** albeit in modest yield is an interesting result and provides a new route to 2,3′-bipyrroles. Indeed this result provided the impetus to utilise the Zav'yalov reaction as a new route to marinopyrrole-like structures (Scheme 3.66). There are surprisingly few general routes to 2,3′-bipyrroles and compounds sparsely substituted are the most difficult to access. The regiospecific, oxidative homocoupling of 1-benzylpyrrole to 1,1′-dibenzyl-2,3′-bipyrrole with $PhI(OOCCF_3)_2$ and $BF_3{\cdot}OEt_2$ in DCM provides an example [07S2913]. The marinopyrroles represent a group of 1,3′-bipyrroles, isolated from marine sediment which exhibit activity against MRSA. The

compounds, which exist as homochiral atropisomers have attracted much interest from the synthetic community and a review of marinopyrrole chemistry is available [13T5067].



Scheme 3.66

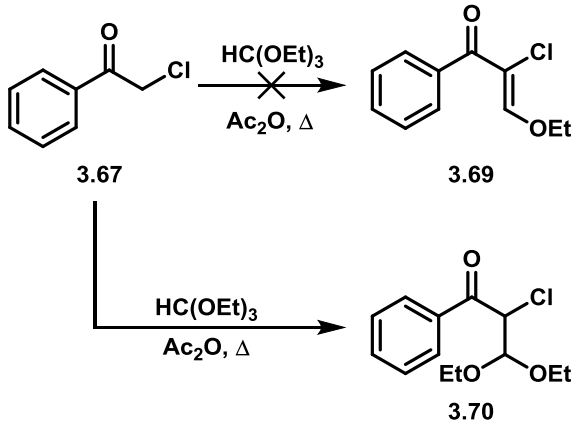
A key intermediate to construct the 3-chloro-1,3′-bipyrrole core is the *N*-acylpyrrole **A**. However, in order to assess the feasibility of obtaining 3-chloropyrroles *via* the Zav'yalov approach, a simpler enamino acid was selected. Thus, a number of attempts were made to synthesise enamino acid **3.68** from 2-chloroacetophenone **3.67**. Initially, 2-chloroacetophenone and glycine were subjected to treatment with triethyl orthoformate in isopropanol (Scheme 3.67). Unfortunately, despite a number of attempts, **3.68** could not be obtained and only a small amount of an oily product was obtained from the reaction. The ^{1}H NMR spectrum was complicated and no product was detected.



Scheme 3.67

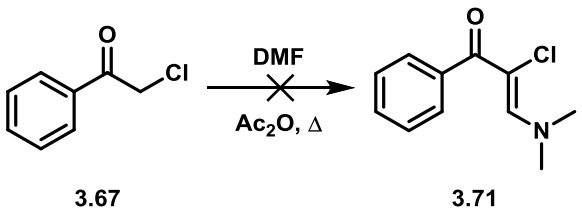
Because the one-pot procedure was unsuccessful, a step-wise approach was employed, in which synthesis of ethoxymethylene intermediate **3.69** was attempted (Scheme 3.68). Following a literature procedure, 2-chloroacetophenone was stirred with triethyl orthoformate in acetic anhydride for 50 hours at reflux. Following aqueous work-up the resulting oil was purified by flash column chromatography and two fractions were separated [10SL1963]. The initial fraction was identified as 2-chloro-3,3-diethoxy-1-phenylpropan-1-one **3.70** (15 % yield) from its ^{1}H NMR spectrum, the final fraction was starting material (73 % recovered) (Scheme 3.68). A detailed

experimental method was not provided in Langer's report [10SL1963] and despite numerous attempts the preparation of **3.69** could not be reproduced.



Scheme 3.68

An attempt was made to access the enaminone **3.71** and further react this with glycine **3.6a.** Following the literature method outlined in [99S2103] (DMF, Ac_2O, Δ) for the aminomethylenation of 1,3-dicarbonyls including 1,3-dimethylbarbituric acid and Meldrum's acid, only starting material was returned (Scheme 3.69). 2-Chloroacetophenone **3.67** and DMF were stirred in hot acetic anhydride for 2 hours before hydrolysis of the acetic anhydride. The product was extracted with ethyl acetate, washed with water and dried. Removal of the solvent under reduced pressure provided only unchanged 2-chloroacetophenone **3.67**.



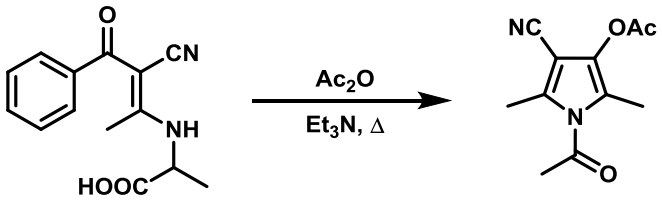
Scheme 3.69

As neither Langer's compound **3.69** nor the enaminone **3.71** from 2-chloroacetophenone **3.67** could be obtained, no further work towards the synthesis of chloroenaminones was undertaken.

3.4.3 Cyclisation of (*Z*)-[2-Benzoyl-3-(1-carboxyalkylamino)crotononitriles

Cyclisation of the enamino acid **3.57b** derived from $PhCOCH_2CN$, triethyl orthoacetate and alanine **3.6b** provided, as expected the pentasubsitituted acetoxypyrrole **3.72** as the sole product in 59 %

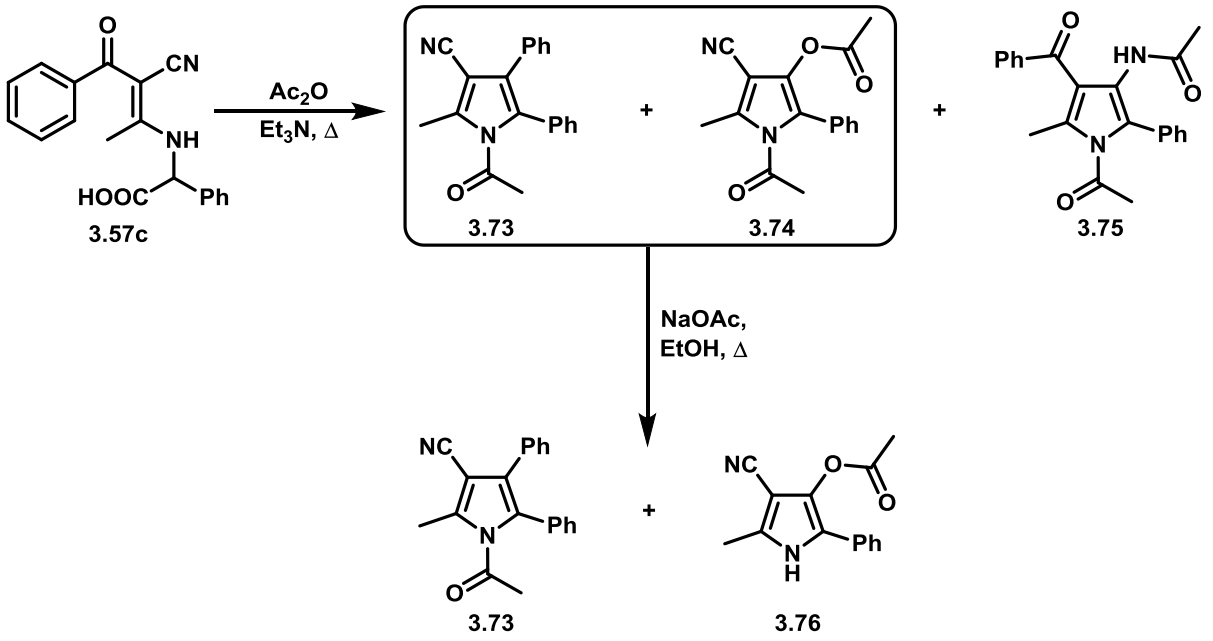
yield after flash column chromatography (Scheme 3.70). The *N*-unsubstituted pyrrole is known in the literature and was obtained by the acetylation of the corresponding 3-hydroxypyrrole, accessible in low yield from pyruvic aldehyde and 3-aminocrotononitrile [89T6553]. The ^{1}H NMR spectrum of 1-acetyl-4-cyano-2,5-dimethyl-1*H*-pyrrol-3-yl acetate **3.72** was simple and was assigned in combination with 2D NMR (HSQC and HMBC), to distinguish between the four methyl signals. The signal from the *N*-acetyl protons was seen at δ 2.61 whilst the acetoxy methyl group appeared at δ 2.33. The two ring methyl groups are distinguished by a cross-peak in the HMBC spectrum between the 5-C*H*$_3$ (δ 2.52) and the nitrile in the ^{13}C spectrum (δ 113.9) and the 2-C*H*$_3$ was displayed at δ 2.21. The ^{13}C spectrum exhibited signals at δ 27.6 (*C*H$_3$) and 171.7 (*C*=O) for the acetamido group and at δ 20.5 (*C*H$_3$) and 169.0 (*C*=O) for the acetoxy group. The two ring-methyl carbons resonated at 11.8 and 15.6 for the 2-*C*H$_3$ and 5-*C*H$_3$ groups, respectively.



3.57b **3.72**

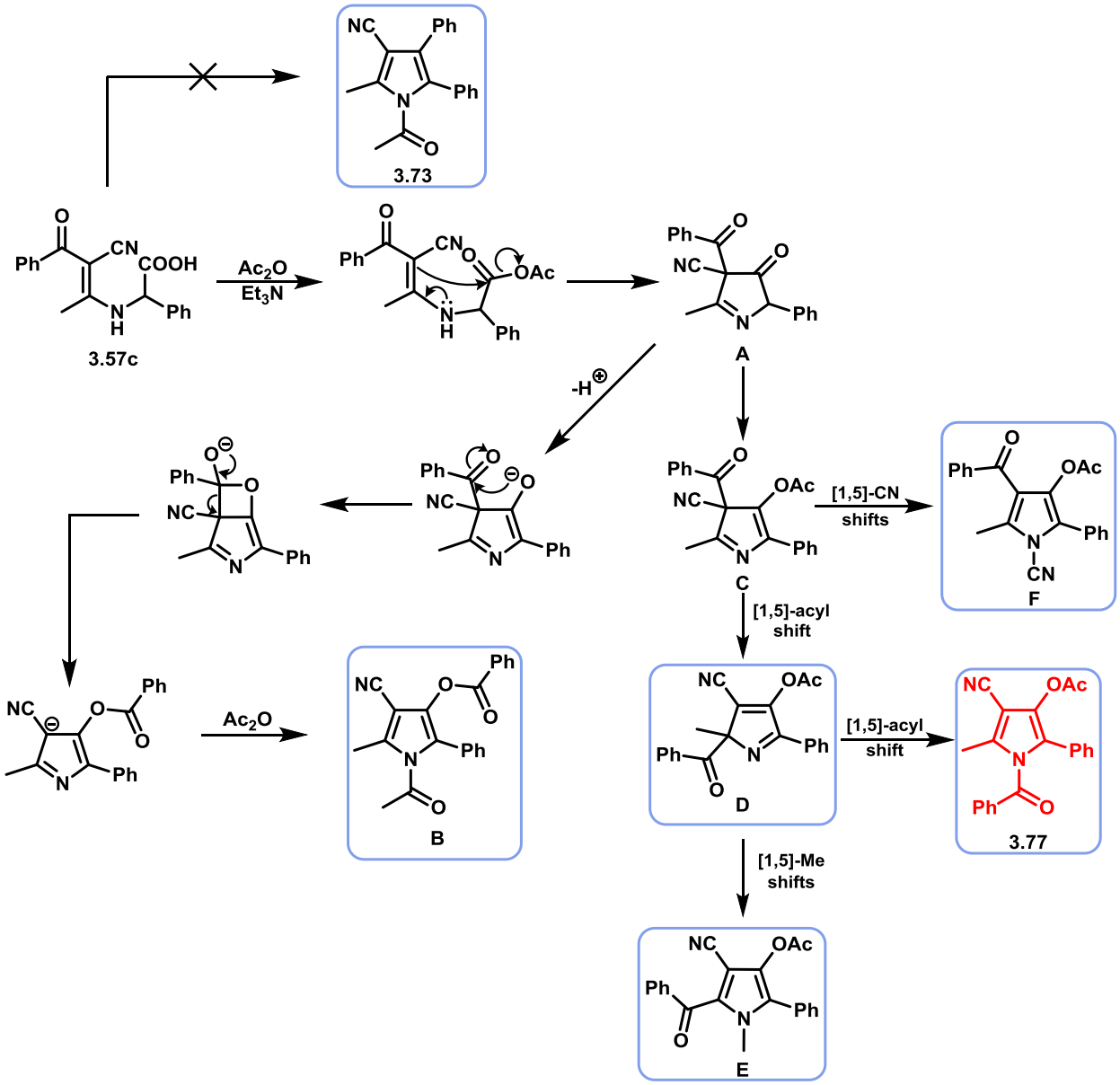
Scheme 3.70

Cyclisation of the related enamino acid **3.57c** from phenylglycine **3.6c**, however, provided a range of products including two inseparable pyrroles to which structures **3.73** and **3.74** were assigned and easily isolable **3.75** (5 %). Separation of **3.73** and **3.74** was only possible by removal of the *N*-acetyl group from pyrrole **3.74** and exploiting the difference in polarity between *N*-deacylpyrrole **3.76** (23 % yield) and the putative compound **3.73** (11 % yield). The latter posed an intriguing question; if the structure was correct, why had it not been deacetylated upon treatment with NaOAc in EtOH?



Scheme 3.71

Although the ^{1}H NMR spectrum of **3.73** was consistent with the structure, the ^{13}C NMR spectrum revealed the presence of 17 non-equivalent carbons. Structure **3.73**, if correct, would exhibit only 16 signals. HRMS confirmed the constitution as $C_{21}H_{16}N_2O_3$ (*m/z* 345.1234 for $[M+H]^+$) and the spectrum exhibited a prominent fragment at *m/z* 105, characteristic of a Ph-C≡O$^+$ ion. Clearly re-evaluation of structure **3.73** was necessary. Consideration of the possible cyclisation pathways of the enamino acid **3.57c** reveal a number of possible products (Scheme 3.72). Enamine acylation by a mixed anhydride would afford the pyrrol-3-one **A** from which rearrangement to the 3-benzoyloxypyrrole **B** is possible. Acylation of **A** to afford the 3*H*-pyrrole **C** is possible, indeed precedents for this exist (*cf.* Scheme 3.8, Scheme 3.13). The non-aromatic system **C** could rearrange *via* the 2*H*-pyrrole **D** to afford the *N*-benzoylpyrrole **3.77** or the *N*-methylpyrrole **E**. Alternatively, migration of the nitrile group in **C** could afford **F**. The IR, ^{1}H and ^{13}C NMR data as well as 2D NMR experiments readily exclude **B** which did not have the expected IR band at ν_{max} ~1720 cm^{-1} for a phenyl ester [76JCS(P1)794], there was also the absence of any interaction between the methyl and acetyl groups in the NOESY spectrum. The absence of a carbonyl signal in the ^{13}C NMR spectrum at around 190 ppm excludes structures **C**, **D**, **E** and **F**. Only the benzoylpyrrole **3.77** remains; and the spectroscopic data provide compelling evidence in its favour. The presence of an *N*-benzoyl, rather than an *N*-acetyl group in the product accounts for the "greater than expected" stability towards NaOAc in EtOH.



Scheme 3.72

The ^{1}H NMR spectrum of **3.77** [Figure 3.14a)] clearly shows the presence of two distinct phenyl groups one of which appears as a multiplet, the remaining signals give rise to three distinct peaks in the ratio 2:1:2 and have similar chemical shifts to 1-benzoylpyrrole {δ_H ($CDCl_3$) 7.67, 7.53, 7.42 [00JHC15]} itself. Two methyl signals at δ 2.25 and 2.48 correspond to the acetoxy methyl and 2-C methyl groups respectively. The ^{13}C spectrum revealed two carbonyl signals at δ 168.7 and 169.0 [Figure 3.12b)] corresponding to the *N*-acyl and ester functions respectively ($\delta_{C=O}$ 1-benzoylpyrrole = 167.3 ppm [00JHC15]). Characteristic signals for the 3-C carbon at δ 91.9 and the nitrile group (δ 113.3) were also apparent.

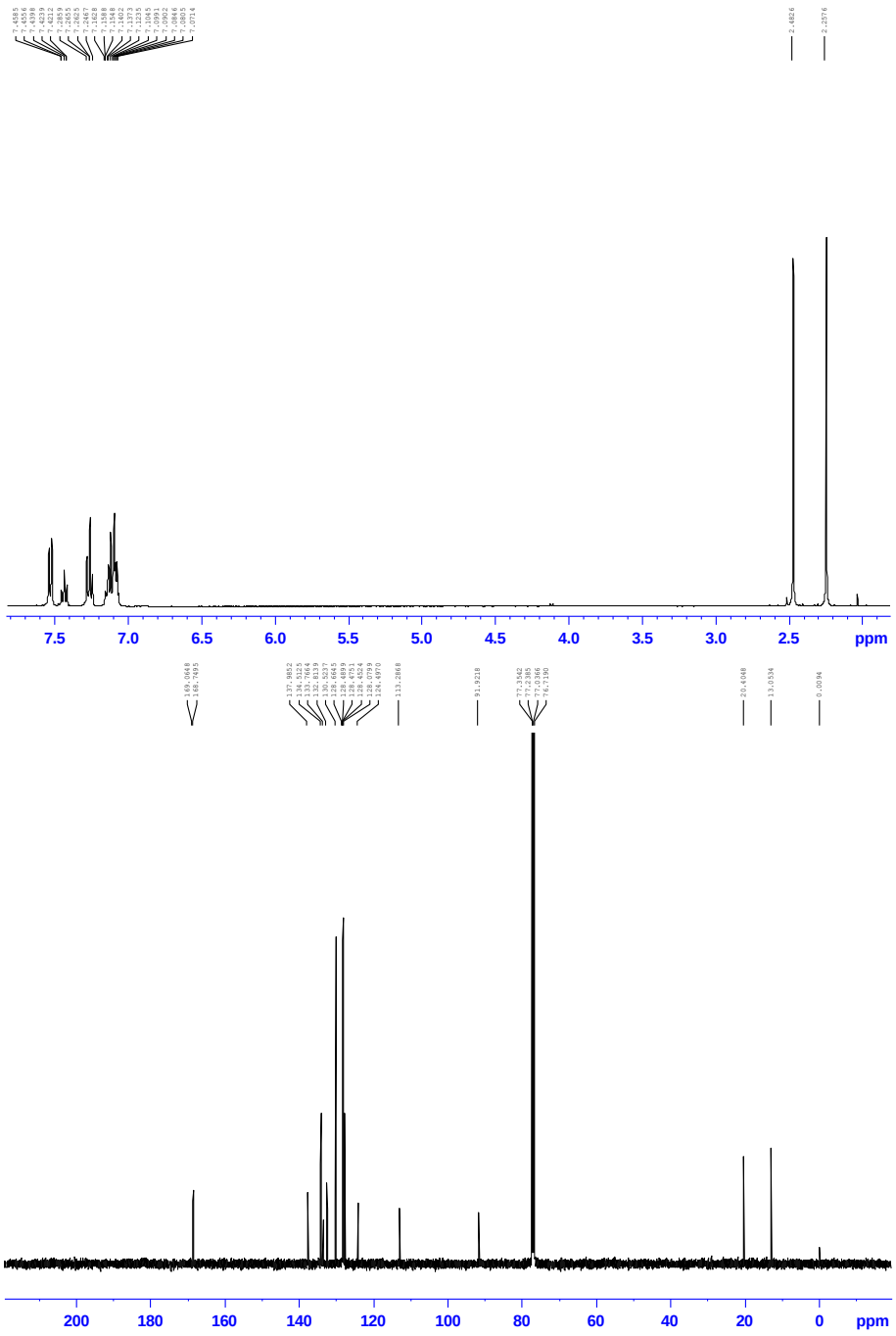


Figure 3.14 NMR spectra of the 1-benzoylpyrrole **3.77** a) ^{1}H (400 MHz, $CDCl_3$) and b) ^{13}C (100 MHz, $CDCl_3$).

The NOESY spectrum (Figure 3.15) revealed a cross-peak corresponding to interaction between the 2-C methyl group and the *ortho*-protons of the benzoyl group. The IR spectrum exhibits bands at 2225, 1776 and 1710 cm^{-1} corresponding to the nitrile, ester carbonyl and *N*-acyl vibrations. The nitrile and ester absorptions within this range have been observed for other compounds obtained in the present work, but also for those reported in the literature [89T6553].

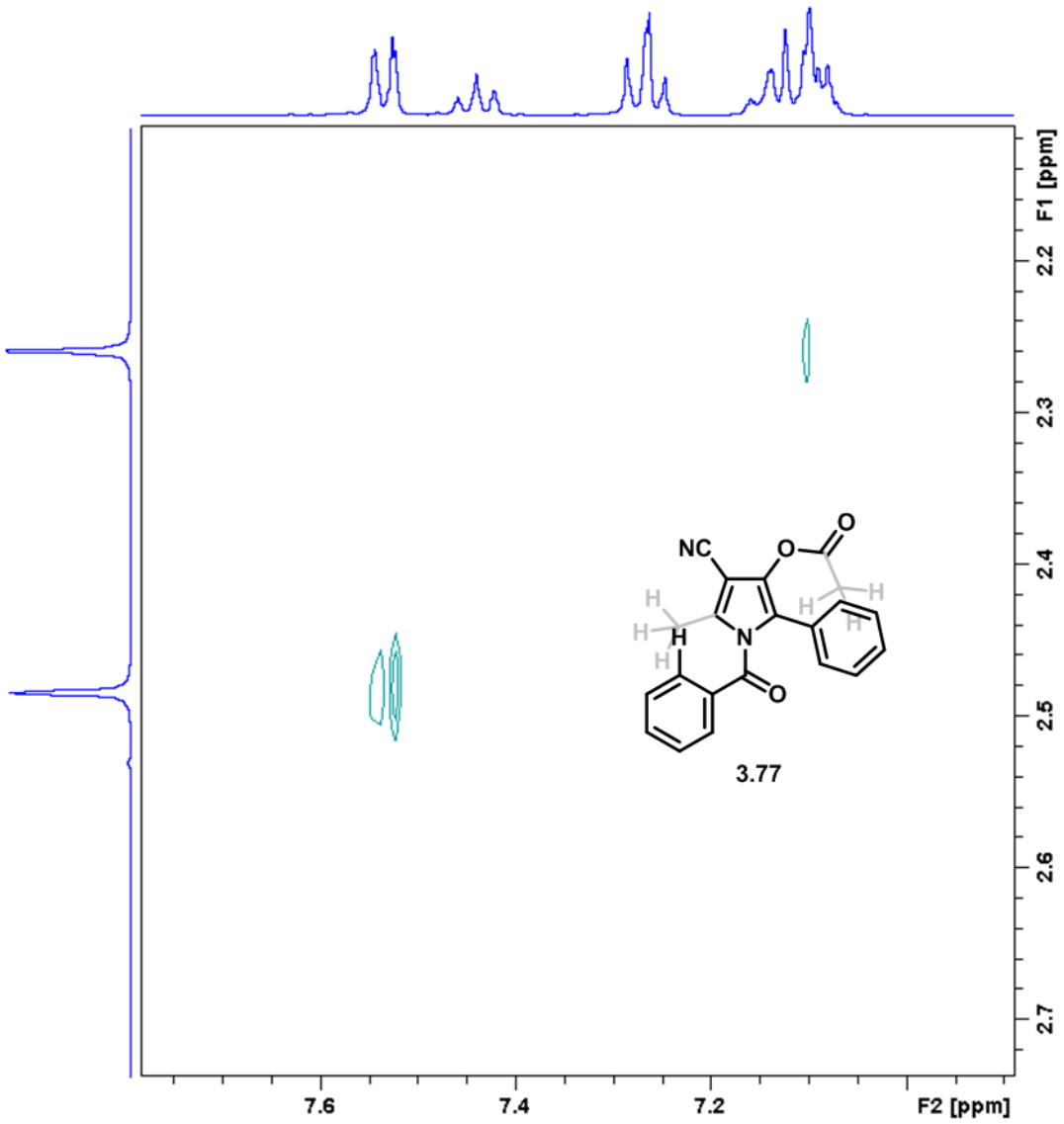
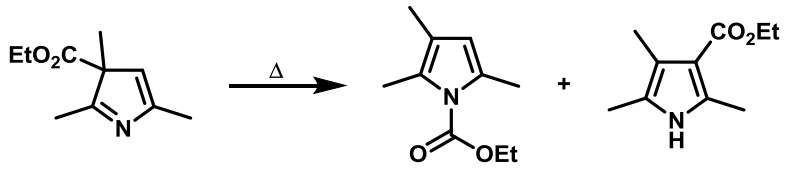


Figure 3.15 NOESY spectrum of the 1-benzoylpyrrole **3.77**.

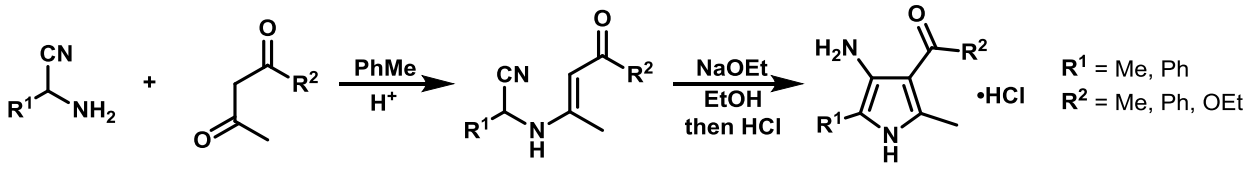
Formation of the *N*-benzoylpyrrole is rationalised by invoking the the formation of the 3*H*-pyrrole **C** which then undergoes two consecutive 1,5-acyl migrations to provide, presumably *via* the 2*H*-pyrrole **D**, the product **3.77**. 1,5-Acyl group migrations have been documented for 3*H*-pyrroles. Thus, Chiu and Sammes observed when **3.78** was heated, with or without solvent, the *N*-ethoxycarbonylpyrrole **3.79** was obtained together with 1*H*-pyrrole **3.80** [Scheme 3.73, 90T3439]. 1,5-Acyl group migration is known in heterocycles and 1,5-benzoyl migration has been documented in indoles [11JA4702, 16JA487] and ester migration has been documented in pyrazoles [14HCA808].



3.78 3.79 3.80

Scheme 3.73

The preceding reactions have shown that the Zav'yalov reaction provides a useful means to access 3-acyl-4-(di)acetamidopyrroles from the cyclisation of 2-acyl-3-(1-carboxy-1-phenylmethylaminomethylene)acrylonitriles (Scheme 3.50). It is pertinent to note that the only examples in the literature relate to the preparation and base-mediated cyclisation of 3-[(α-cyanoalkyl)amino]propenones to provide 3-acyl-4-amino-2-phenylpyrroles. This approach is more limited in scope [Scheme 3.74, 80USP4198502, 80USP4212806] to that described in the present work.



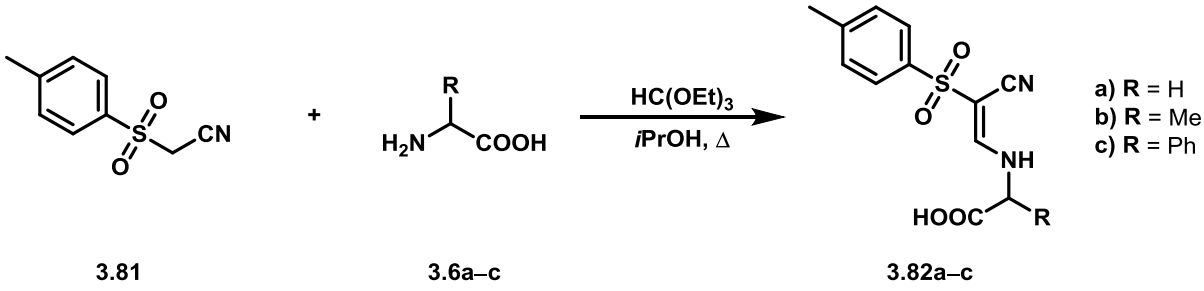
Scheme 3.74

3.5 Synthesis of Pyrroles from 2-(Aminomethylene)tosylacetonitriles

In order to gain an insight into the substituent effects that control the outcome from the acylative cyclisations of aroylacetonitrile derivatives it was of interest to explore the reactivity of enaminonitriles containing a sulfonyl function.

3.5.1 Synthesis of 3-(1-Carboxyalkylamino)-2-tosylacrylonitriles

Thus, commercially available (*p*-toluenesulfonyl)acetonitrile **3.81** was condensed with triethyl orthoformate and α-amino acids **3.6a–c** (Scheme 3.75). The products **3.82a–c** were obtained as single isomers and the ^{1}H NMR spectra (DMSO-d_6) revealed the signals for the tosyl group at δ 2.39 (Me) and around 7.4 and 7.7 ppm for the *meta*- and *ortho*-protons respectively. The alkenyl proton appeared as a doublet at 7.99 ppm and the N*H* was displayed as a doublet of triplets in **3.82a** (δ 8.95, *J* = 5.8, 14.6 Hz), and as double doublets in **3.82b** (δ 9.13, *J* = 8.0, 14.5 Hz) and **3.82c** (δ 9.71, *J* = 7.8, 14.2 Hz).



3.81 **3.6a–c** **3.82a–c**

Scheme 3.75

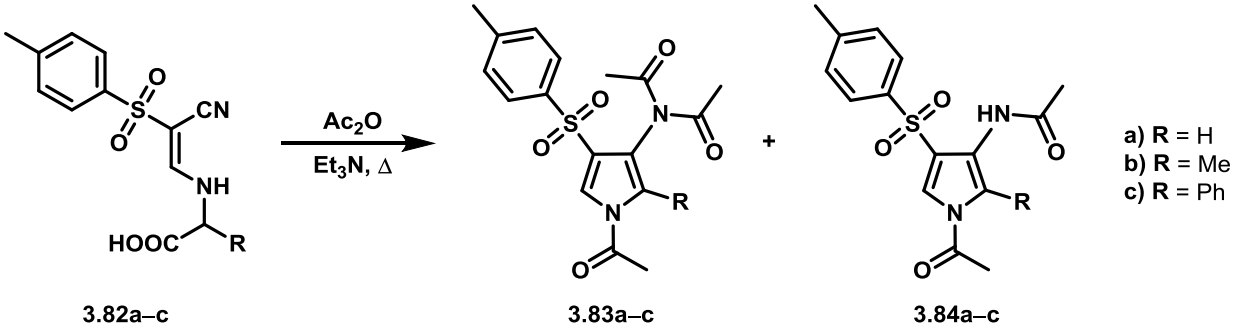
Table 3.17 Yields for the synthesis of 2-tosylacrylonitriles **3.82a–c**.

Entry	R	Compound 3.82	Yield (%)
1	H	**3.82a**	10
2	Me	**3.82b**	18
3	Ph	**3.82c**	8

Though the yields from these reactions were low (8–18 %), due to poor solubility of sulfone **3.81**, there was sufficient material to investigate their cyclisations to pyrrole derivatives (Scheme 3.76).

3.5.2 Cyclisation of 3-(1-Carboxyalkylamino)-2-tosylacrylonitriles

Cyclisation of the sulfonyl enamino nitriles (**3.82a–c**) provided both the imido- and acetamidopyrroles **3.83** and **3.84**, except in the case of **3.82a** which only furnished the acetamidopyrrole **3.84a** (Scheme 3.76, Table 3.18, entries 1–3) as the only identifiable products.



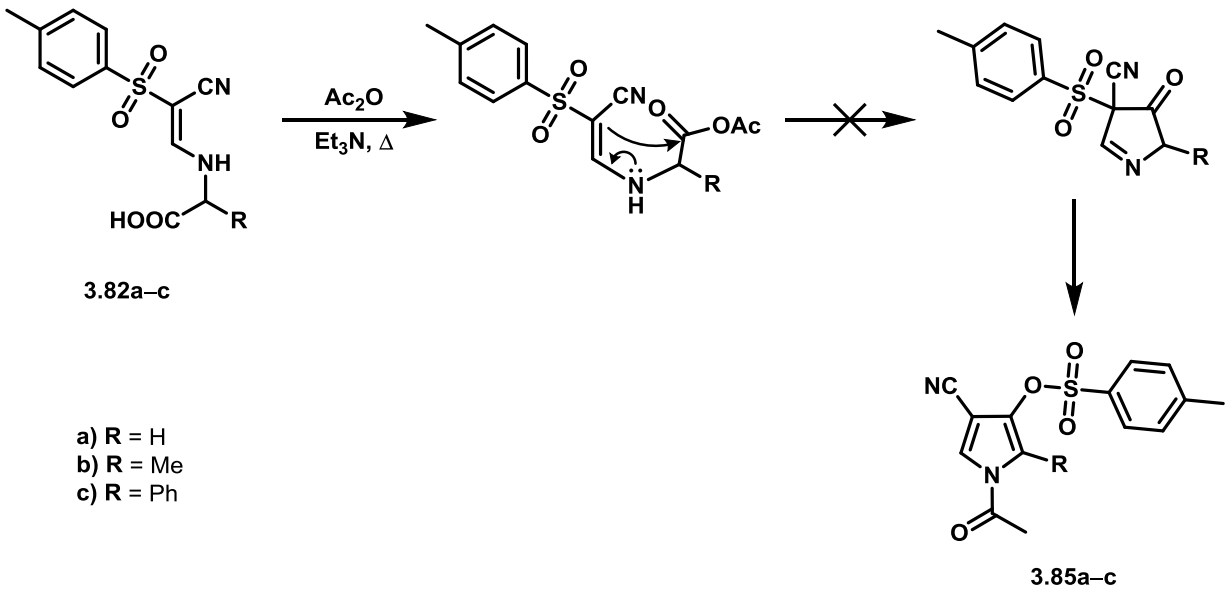
3.82a–c **3.83a–c** **3.84a–c**

Scheme 3.76

Table 3.18 Yields from the cyclisations of the 2-tosylacrylonitriles **3.82a–c**.

Entry	R	Pyrrole 3.83	Yield (%)	Pyrrole 3.84	Yield (%)
1	H	**3.83a**	-	**3.84a**	15
2	Me	**3.83b**	28	**3.84b**	30
3	Ph	**3.83c**	17	**3.84c**	19

The starting materials and pyrroles all had IR bands at around 1340–1320 cm^{-1} and 1150–1140 cm^{-1} characteristic of an S=O stretch in a sulfonyl group. The mass spectra of **3.83b** and **3.83c** both showed fragmentation with losses of all three acetyl groups and of both acetyl groups in **3.84b–c**, respectively. The ^{1}H NMR spectra of **3.83b** and **3.83c** revealed signals at δ 2.21 and 2.13 for the imido methyl groups, respectively, and at δ 2.65 and 2.24 for the *N*-acetyl methyl signals. The tosyl groups resonated at δ 2.43 (CH_3), 7.30 (*meta*-*H*) and around 7.70 for the *ortho*-protons. The 5-*H* pyrrole protons resonated at δ 7.83 in **3.83b** and 8.12 ppm in **3.83c**. The ^{1}H NMR spectra of **3.84a–c** exhibited signals for the acetamido groups at δ 2.22 (CH_3) and 8.61 (N*H*COCH_3) in **3.84a**, 2.11 (CH_3) and 7.14 ppm (N*H*COCH_3) in **3.84b** and δ 1.93 (CH_3) and 6.74 (N*H*COCH_3) in **3.84c**. The tosyl group signals appeared at δ 2.42 for the methyls and δ 7.30 for the *meta*-protons in **3.84a** and **3.84b** (the signal overlaps with the phenyl protons in **3.84c**), the *ortho*-protons are displayed at around 7.80 ppm. The pyrrole protons appear as doublets in **3.84a** [δ 7.75 (5-*H*) and 7.92 (2-*H*), *J* = 2.6 Hz] and as singlets in **3.84b** (δ 7.66) and **3.84c** (δ 8.00). Although the yields of the pyrroles **3.83b–c** and **3.84a–c** are only modest, the acylative cyclisation of the 3-[(1-carboxyalkylamino)methylene]-2-tosylacrylonitriles **3.82a–c** failed to provide any other identifiable product. Especially noteworthy was the absence of any compound (**3.85a–c**) derived by the acylation of the β-position of the enamine function (Scheme 3.77), a pathway observed for the 3-amino-2-benzoylacrylonitriles (Table 3.14–Table 3.16).



Scheme 3.77

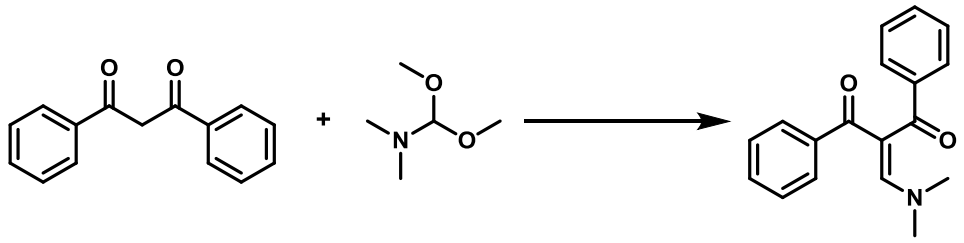
Clearly subtle electronic factors are responsible for controlling the outcome of these cyclisations. Whilst this modified Zav'yalov reaction affords only moderate yields of the 3-amido-4-tolsylpyrroles **3.84a–c** it represents the only means to access these novel pyrrole derivatives. Future work is, however, necessary to optimise the yields.

3.6 Synthesis of Pyrroles from 2-(Aminomethylene)dibenzoylmethanes

Because of the surprising outcomes from the cyclisations of the 2-acyl-3-aminoacrylonitriles (Table 3.14–Table 3.16) as well as the behaviour of the 3-amino-2-tosylacrylonitriles, it was of interest to explore the outcome from a substrate in which the nitrile group in the enamino acids had been replaced by an acyl group.

3.6.1 Synthesis of 2-(1-Carboxyalkylaminomethylene)dibenzoylmethanes

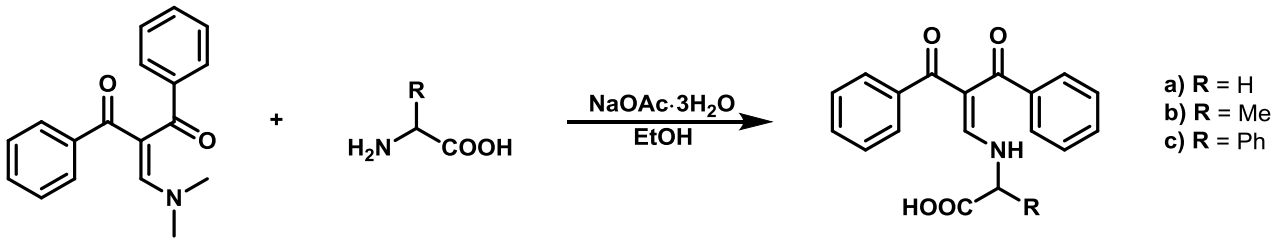
Dibenzoylmethane was employed as a starting material to investigate whether the cyclisation would provide an additional aromatic substituent on the pyrrole ring, or an acetoxypyrrole due to hydrolytic elimination of benzoic acid. Dibenzoylmethane **3.86** was stirred at reflux in DMFDMA for 30 hours, aqueous workup afforded the enaminedione **3.87** after recrystallisation in 49 % yield (Scheme 3.78). The material obtained had identical physical and spectroscopic properties to that described in the literature [05OPPI223].



3.86 **3.32** **3.87**

Scheme 3.78

From the enamindione **3.87** and α-amino acids **3.6a–c** in EtOH containing NaOAc·3H_2O, the enamino acids **3.88a–c** were obtained in fair yields (50–57 %, Scheme 3.79, Table 3.19, entries 1–3).



3.87 **3.6a–c** **3.88a–c**

Scheme 3.79

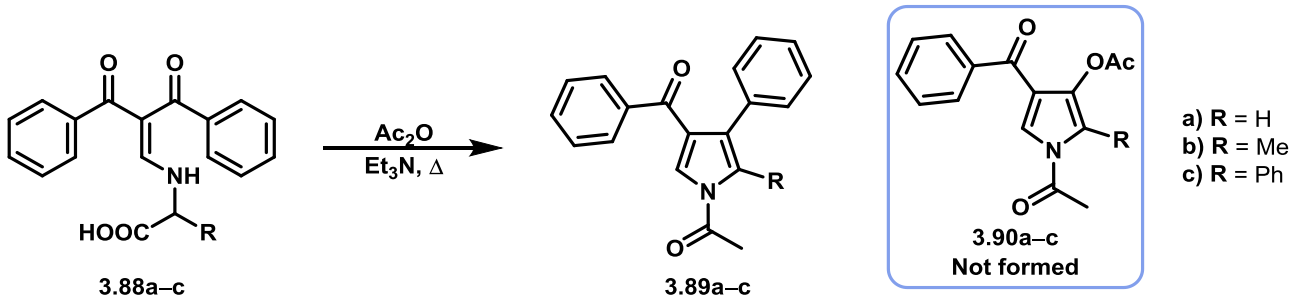
Table 3.19 Yields of (aminomethylene)dibenzoylmethanes **3.88a–c**.

Entry	R	Compound 3.88	Yield (%)
1	H	**3.88a**	54
2	Me	**3.88b**	50
3	Ph	**3.88c**	57

Compound **3.88a** (Table 3.19, entry 1) has been obtained previously, although no physical or spectroscopic data were reported [95JPH07157466A].

3.6.2 Cyclisation of 2-(1-Carboxyalkylaminomethylene)dibenzoylmethanes

When cyclised under the Zav'yalov conditions, **3.88a–c** each provided a single pyrrole **3.89 a–c** in good yields (66–82 %, Scheme 3.80, Table 3.20, entries 1–3). None of the acetoxypyrrole was observed from the reaction, indicating that a β-acylation of the enamine to form **3.90** was not favoured.



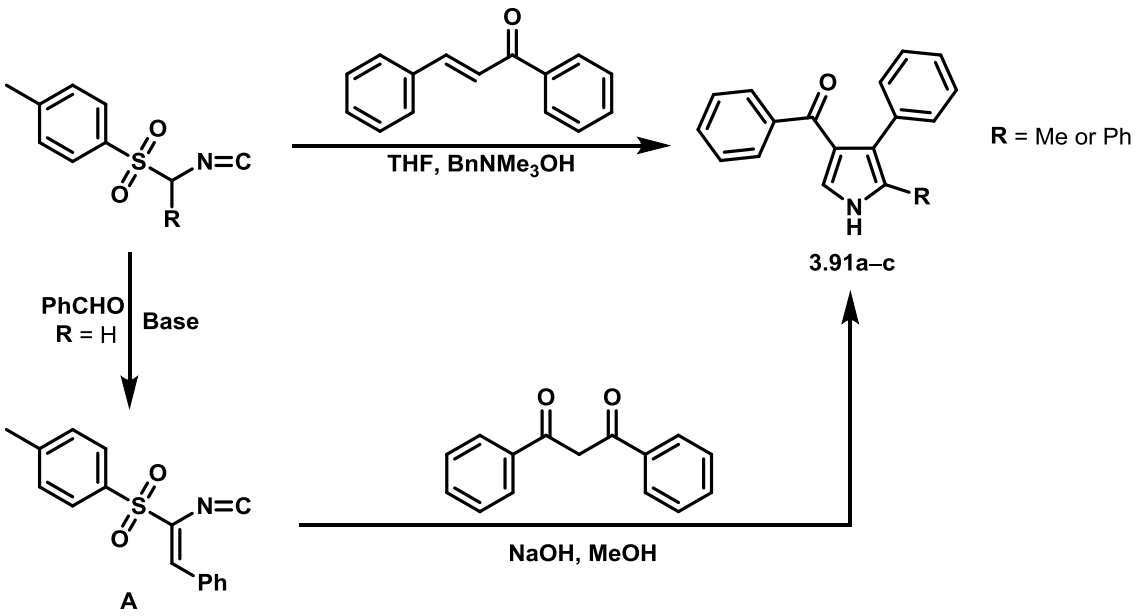
Scheme 3.80

Table 3.20 Yields from the cyclisation of 2-(1-carboxyalkylaminomethylene)dibenzoylmethanes **3.88a–c**.

Entry	R	Pyrrole 3.89	Yield (%)
1	H	**3.89a**	66
2	Me	**3.89b**	75
3	Ph	**3.89c**	82

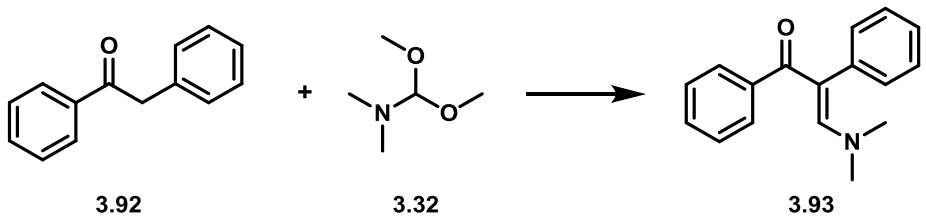
Although pyrrole **3.89a** has been obtained previously by Hamamoto [95JPH07157466A] *via* the same method as described in this thesis, no characterisation data was reported. Only a very limited number of enaminediones from amino acids have been subjected to Zav'yalov cyclisations. The only examples comprise the limited examples described by Hamamoto and our own group [02JCS(P1)2799].

It is pertinent to note that the *N*-deacetyl derivatives of **3.89a–c** have all been obtained *via* TosMIC anion addition to chalcone (Scheme 3.81). Because TosMIC itself is commercially available, the preparation of the parent compound **3.91a** is straightforward [72TL5337, 92JOC2245]. The latter is also accessible *via* conjugate addition of the anion of dibenzoylmethane to the isocyanoalkene **A** [Scheme 3.81, 92JOC2245]. The Zav'yalov approach for the synthesis of **3.89b** and **3.89c** or, rather their *N*-deacyl derivatives **3.91b–c** [77H72] has considerable advantages since α-alkyl or α-aryl TosMIC derivatives are less accessible.



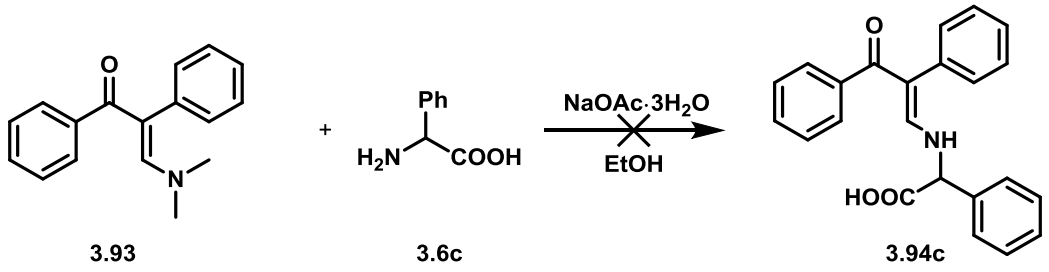
Scheme 3.81

Based on the results from the cyclisations of the dibenzoylmethane derivatives **3.88a–c**, it was of interest to investigate the use of deoxybenzoin **3.92** as a starting material. This would provide, from the cyclisation of the enamino acid from phenylglycine **3.6c**, a 2,3,4-triphenylpyrrole. Following initially the same reaction pathway as for dibenzoylmethane. In this way the enaminone **3.93** was synthesised in 82 % yield (Scheme 3.82). The physical and spectral data were in good agreement with the literature [85JOC3573].



Scheme 3.82

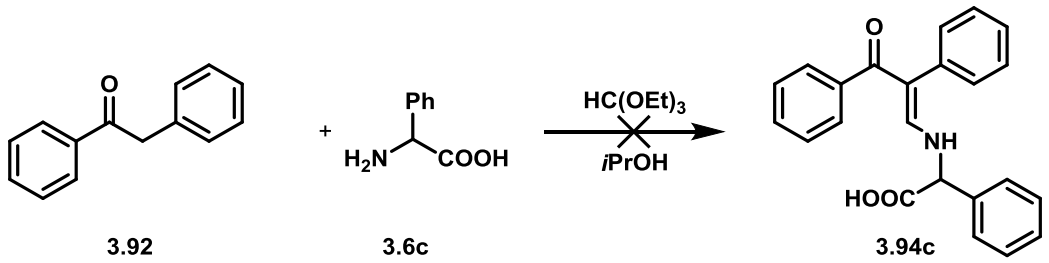
When the transamination of **3.93** was attempted using phenylglycine in ethanol containing sodium acetate trihydrate, the reaction failed to provide the desired product **3.94c** (Scheme 3.83). Unfortunately, the reaction resulted in hydrolytic deaminomethylenation and the only isolable product was shown by ^{1}H NMR to be deoxybenzoin **3.92**.



3.93 **3.6c** **3.94c**

Scheme 3.83

A further attempt was made to access **3.94c** using the one-pot procedure with triethyl orthoformate (Scheme 3.84). No reaction occurred and only deoxybenzoin **3.92** was isolated from the reaction mixture.



3.92 **3.6c** **3.94c**

Scheme 3.84

3.7 Summary

Some of the main features of the work described in this chapter are highlighted below.

The acylative cyclodehydration of ethyl 2-(1-carboxyalkylaminomethylene)cyanoacetates **3.7a–c** proceeds in a regiospecific manner to give ethyl 4-acetamido-1-acetyl-5-(un)substitutedpyrrole-3-carboxylates **3.9a–c**, in an admixture with the corresponding 4-diacetamido derivatives. Cyclisation of the 2-(1-carboxymethylaminomethylene)cyanoacetic ester also furnished a small amount of a mixture containing a 4-acetoxy- and 4-ethoxy-1-acetylpyrrole-3-carbonitriles, in which the ethoxypyrrole predominated. Interestingly, the cyclisation of ethyl 2-(1-carboxyethylaminomethylene)cyanoacetate **3.7b** provided in addition to the (di)acetamidopyrrole-3-carboxylate a small amount of ethyl (2*R**,3*S**)-1-acetyl-3-cyano-2,4-diacetoxy-5-methyl-2,3-dihydropyrrole-3-carboxylate **3.11**, the product of β-acylation of the enaminonitrile. Attempts to generate and intercept, with DMAD, a münchnone intermediate akin to that from the related malonate failed to provide any of the expected *N*-alkenylpyrrole **3.12**. It was found that the initially formed 4-acetamido-1-acetyl-5-methylpyrrole-3-carboxylate **3.9b** acted as an efficient Diels-Alder diene towards DMAD.

The cyclisation reactions of 2-(1-carboxyalkylaminomethylene)malononitriles **3.21** proceeded in an analogous manner to those described above to furnish the 4-(di)acetamidopyrrole-3-carbonitriles **3.23a–c**.

Cyclisations of the 2-alkanoyl- and 2-aroyl-3-(1-carboxyalkylamino)acrylonitriles **3.27Aa–Gc**, prepared *via* methylenation of β-ketonitriles **3.26**, furnished a variety of products upon treatment with Ac_2O-Et_3N. Thus, derivatives of the 3-(1-carboxy-1-phenylmethylamino)acrylonitriles **3.27Ac–Gc** gave mixtures of 1-acetyl-3-acyl-4-(di)acetamido-5-phenylpyrroles in high overall yields. In complete contrast, the latter compounds were the minor products from the acylative cyclisation of the 3-(1-carboxyethylamino)acrylonitriles **3.27Ab–Gb**. In this case the major product was the novel 4-acetoxy-1-acetyl-5-methylpyrrole-3-carbonitrile **3.60b**, obtained in up to 79 % yield. In a similar manner, the related 5-ethyl- and 5-isopropylpyrrole-3-carbonitriles were accessible in high yields *via* 2-aminoisobutyric acid **3.6d** and valine **3.6e**, respectively.

The greatest diversity of products was obtained from the acylative cyclisation of the 2-acyl-3-(1-carboxymethylamino)acrylonitriles **3.27Aa–Ga**. In two cases the cyclisation afforded small

amounts of 3-acetamido-6-aryl-5-cyanopyran-2-ones **3.61** (**C** Ar = Ph, **D** Ar = 4-$MeOC_6H_4$). The structure of one of these (**3.61C**) was confirmed by unambiguous synthesis.

Pyrrole products obtained from **3.27Aa–Ga** included 1-acetyl-4-alkyl- and 1-acetyl-4-aryl-pyrrole-3-carbonitriles, 4-acetoxy-1-acetylpyrrole-3-carbonitrile and 1-acetyl-4-alkanoyl- and 4-aroyl-3-acetamidopyrroles. A novel 2,3′-bipyrrole-4-carbonitrile was obtained from one of these cyclistations.

Cyclisation of the 2-benzoyl-3-(1-carboxyalkylamino)crotononitriles, prepared *via* $PhCOCH_2CN$ and $MeC(OEt)_3$, have been investigated. Thus, the 3-(1-carboxyethylamino)acrylonitrile **3.57b** cyclised efficiently to provide 4-acetoxy-1-acetyl-2,5-dimethylpyrrole-3-carbonitrile **3.72**. However, the 3-(1-carboxy-1-phenylmethylamino)acrylonitrile **3.57c** provided in addition to the expected acetoxypyrrole-3-carbonitrile **3.76** and the 4-acetamido-1-acetyl-3-benzoyl-2-methyl-5-phenylpyrrole **3.75** a novel, unexpected compound, albeit in low yield that was characterised as the 1-benzoylpyrrole-3-carbonitrile **3.77**.

1-Acetyl-2-(un)substituted-3-(di)acetamido-4-tosylpyrroles have been obtained *via* acylative cyclisation of 3-(1-carboxyalkylamino)-2-tosylacrylonitriles. These reactions proceeded entirely as expected. In like manner, the cyclisation of 2-(1-carboxyalkylmethylene)dibenzoylmethyanes proceded by cyclisation onto a ketone carbonyl function. No products resulting from ketone hydrolysis *via* β-acylation of the enaminedione were observed.

Mechanisms to rationalise formation of the products have been proposed.

Chapter 4

Experimental

Chapter 4 Experimental

4.1 Equipment and Reagents

Unless otherwise stated, reagents were used as supplied. Reagents were purchased from Alfa Aesar, Fluorochem, and Sigma Aldrich. DL-Alanine-1-^{13}C was obtained from Cambridge Isotope Laboratories Inc. (Goss Scientific Ltd).

NMR spectra were recorded on a Bruker Avance 400 spectrometer (^{1}H 400 MHz and ^{13}C 100 MHz) or a Bruker Avance 500 spectrometer (^{1}H 500 MHz and ^{13}C 125 MHz). Coupling constants are given in Hz.

Accurate mass measurements were obtained from the EPSRC National Mass Spectrometry Service Centre at the Swansea University and the IPOS Mass Spectrometry Service at the University of Huddersfield. Single crystal studies were recorded on a Bruker D8 Venture diffractometer with Dual IμS Microfocus Sources using Mo and/or Cu radiation. The temperature of data collection was 100K.

Melting points were determined in capillary tubes, using a Stuart SMP10 melting point apparatus, and are uncorrected. Distillations were performed using a bulb-to-bulb (Kügelrohr) apparatus (Büchi GKR-50 glass tube oven). All the boiling points quoted relate to the oven temperature at which the distillation commenced. FT-IR spectra were recorded on a Nicolet 380 Spectrum Spotlight system, equipped with a diamond probe ATR attachment (neat sample). TLC was performed on Merck TLC Aluminium sheets, silica gel 60 F_{254} using a range of eluent systems of differing polarity. Flash column chromatographic separations were performed on Aldrich, 35–70μ, 60A silica gel or Fluorochem 40–63μ, 60A silica gel, according to the literature procedure [78JOC2923].

4.2 Chapter 2 Experimental

4.2.1 Synthesis of Diethyl 2-(1-carboxyalkylaminomethylene)malonates (2-{[3-ethoxy-2-(ethoxycarbonyl)-3-oxoprop-1-en-1-yl]amino} acids)

Diethyl (dimethylaminomethylene)malonate, 2.10 A mixture of diethyl malonate (12.01 g, 75 mmol) and *N,N*–dimethylformamide dimethyl acetal (25 mL, 188 mmol, 2.5 equiv.) was stirred

under nitrogen at reflux. After 6 hours the mixture was allowed to cool to room temperature, before the addition of brine (50 mL) and extraction with EtOAc (4 × 20 mL). The organic layer was washed with brine (50 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue was purified by Kügelrohr distillation {b.p. 145 °C, 1.6 × 10^{-2} mbar (lit. b.p. not given [84TL3743])} to afford a pale yellow oil (12.59 g, 78 %). ν_{max} 2979, 1601, 1198, 1058 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.29 (6H, br. s, 2 × CH_2CH_3), 3.00 [6H, s, $N(CH_3)_2$], 4.21 (4H, d, *J* = 7.9Hz, 2 × CH_2CH_3), 7.50 [1H, s, $CCHN(CH_3)_2$]. δ_C (100 MHz, $CDCl_3$) 14.3, 14.4, 59.8, 60.6, 93.0, 153.4, 167.4, 167.5, 167.8.

General methods for the synthesis of 2-{[3-ethoxy-2-(ethoxycarbonyl)-3-oxoprop-1-en-1-yl]amino} acids:

Method A The α-amino acid (50 mmol) was added to KOH (85 %, 3.96 g, 60 mmol, 1.2 equiv.) in EtOH (70 mL), before the addition of diethyl (ethoxymethylene)malonate (10.81 g, 50 mmol, 1 equiv.). The reaction mixture was stirred for 10 minutes at room temperature and the solvent was removed under reduced pressure. The residue was dissolved in water and acidified with dil. HCl (2 M, aq.) before extraction with EtOAc (3 × 50 mL). The organic portion was washed with water (100 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure.

Method B Identical in all respects to method A except that the 10 minute reaction time at room temperature was replaced with a reflux period of 1 h.

Method C To a solution of diethyl (dimethylaminomethylene)malonate, **2.10** (5.38 g, 25 mmol) in EtOH (60 mL), was added the α-amino acid (30 mmol, 1.2 equiv.) and sodium acetate trihydrate (4.08 g, 30 mmol, 1.2 equiv.) dissolved in the minimum amount of aq. EtOH (50 %). The solution was stirred for 4 h at reflux before the volume was reduced. The product was precipitated with 60 mL ice-water and the solution acidified with dil. HCl (2 M, aq.). The precipitate was collected by vacuum filtration and washed with water.

Method D To the α-amino acid (50 mmol) and triethylamine (8.5 mL, 60 mmol, 1.2 equiv.) dissolved in MeCN (60 mL) was added diethyl (ethoxymethylene)malonate (10.81 g, 50 mmol, 1 equiv.). The mixture was stirred at reflux under nitrogen until the reaction was complete by TLC and allowed to cool to room temperature. The solvent was removed under reduced pressure and the residue was dissolved in water and acidified with dil. HCl (2 M, aq.). The resulting precipitate was collected by vacuum filtration and washed with water.

2-{[3-Ethoxy-2-(ethoxycarbonyl)-3-oxoprop-1-en-1-yl]amino}acetic acid, 2.13a From glycine (Method A: 3.75 g; Method C: 2.25 g) as an off white crystalline solid (Method A: 10.83 g, 88 %; Method C: 2.68 g, 44 %). m.p. 134 – 137 °C {lit. m.p. 138 – 140 °C [02JCS(P1)2799], 145 – 147 °C [89S544]}. ν_{max} 3312, 2988, 2937, 1708, 1676, 1619, 1205, 800 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.31 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 1.36 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 4.16 (2H, d, *J* = 6.0 Hz, NCH_2COOH), 4.20 – 4.29 (4H, m, 2 × CH_2CH_3), 5.92 (1H, br. s, COO*H*), 8.00 (1H, d, *J* = 14.0 Hz, CC*H*NH), 9.32 (1H, m, N*H*). δ_C (100 MHz, $CDCl_3$) 14.2, 14.3, 49.6, 60.3 (2 × C), 91.4, 160.4, 167.0, 169.0, 171.6.

2-{[3-Ethoxy-2-(ethoxycarbonyl)-3-oxoprop-1-en-1-yl]amino}propanoic acid, 2.13b From DL-alanine [Method A: 4.44 g; Method B: 4.44 g; Method B (3 × Scale): 13.38 g] as a yellow crystalline solid recrystallised from EtOAc and hexane (Method A: 5.07 g, 39 %; Method B: 7.49 g, 58 %; Method B (3 × scale): 29.27 g, 75 %). m.p. 97 – 100 °C. ν_{max} 3269, 2978, 2939, 2899, 1720, 1674, 1630, 1593, 1225, 796 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.31 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 1.36 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 1.62 (3H, d, *J* = 7.2 Hz, $CHCH_3$), 4.15 – 4.30 (5H, m, 2 × CH_2CH_3, NHC*H*COOH), 7.15 (1H, br. s, COO*H*), 8.03 (1H, d, *J* = 14.0 Hz, CC*H*NH), 9.45 (1H, dd, *J* = 7.9, 14.0 Hz, N*H*). δ_C (100 MHz, $CDCl_3$) 14.3, 14.4, 19.1, 56.4, 60.2 (2 × C), 91.2, 158.5, 166.9, 168.9, 174.8. HRMS (NSI) found $[M+H]^+$ = 260.1129 $C_{11}H_{18}NO_6$ requires $[M+H]^+$ = 260.1129.

2-{[3-Ethoxy-2-(ethoxycarbonyl)-3-oxoprop-1-en-1-yl]amino}butanoic acid, 2.13c From DL-2-aminobutyric acid (Method A: 5.15 g) as a yellow crystalline solid recrystallised from EtOAc and hexane (6.28 g, 46 %). m.p. 93 – 96 °C. ν_{max} 3259, 2975, 2936, 1722, 1674, 1630, 1593, 1226, 793 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.05 (3H, t, *J* = 7.4 Hz, $CHCH_2CH_3$), 1.31 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 1.37 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 1.89 – 2.08 (2H, m, $CHCH_2CH_3$), 4.00 – 4.05 (1H, m, NHC*H*COOH), 4.22 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 4.28 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 7.99 (1H, d, *J* = 14.0 Hz, CC*H*NH), 9.44 (1H, dd, *J* = 8.6, 13.9 Hz, N*H*). δ_C (100 MHz, $CDCl_3$) 9.6, 14.3, 14.4, 26.6, 60.2 (2 × C), 62.5, 91.2, 158.9, 166.8, 168.9, 174.5. HRMS (NSI) found $[M+H]^+$ = 274.1286 $C_{12}H_{20}NO_6$ requires $[M+H]^+$ = 274.1285.

2-{[3-Ethoxy-2-(ethoxycarbonyl)-3-oxoprop-1-en-1-yl]amino}-3-methylbutanoic acid, 2.13d From DL-valine (Method A: 5.87 g) as a yellow crystalline solid recrystallised from EtOAc and hexane (3.95 g, 28 %). m.p. 110 – 112 °C. ν_{max} 2962, 2911, 1738, 1644, 1598, 1259, 1225, 1209, 1090 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.01 [3H, d, *J* = 6.8 Hz, $CH(CH_3)_2$], 1.05 [3H, d, *J* = 6.8 Hz, $CH(CH_3)_2$], 1.31 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 1.36 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 2.28 – 2.36 [1H, m , $CH(CH_3)_2$], 3.88 (1H, dd, *J* = 4.9, 9.4 Hz, NHC*H*COOH), 4.21 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 4.28 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 7.95 (1H,

d, *J* = 13.9 Hz, CC*H*NH), 9.48 (1H, dd, *J* = 9.6, 13.7 Hz, N*H*). δ_C (100 MHz, $CDCl_3$) 14.3, 14.4, 17.2, 19.1, 31.8, 60.2 (2 × C), 67.5, 91.1, 159.3, 166.7, 168.9, 174.4. HRMS (NSI) found $[M+H]^+$ = 288.1442 $C_{13}H_{22}NO_6$ requires $[M+H]^+$ = 288.1442.

2-{[3-Ethoxy-2-(ethoxycarbonyl)-3-oxoprop-1-en-1-yl]amino}-4-methylpentanoic acid, 2.13e From L-leucine (Method A: 6.56 g) as a yellow oil (11.13 g, 74 %). ν_{max} 2958, 2872, 1739, 1656, 1605, 1220, 1071, 800 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 0.83 – 0.90 [1H, m, C*H*$(CH_3)_2$], 0.96 [6H, dd, *J* = 6.2, 8.1 Hz, CH(C*H*$_3)_2$], 1.29 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 1.34 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 1.75 – 1.80 [2H, m, C*H*$_2$CH$(CH_3)_2$], 4.03 – 4.09 (1H, m, NHC*H*COOH), 4.18 – 4.27 (4H, m, 2 × C*H*$_2$CH$_3$), 7.98 (1H, d, *J* = 14.0 Hz, CC*H*NH), 8.59 (1H, br. s, COO*H*), 9.33 (1H, dd, *J* = 8.8, 14.0 Hz, N*H*). δ_C (100 MHz, $CDCl_3$) 14.3, 14.4, 21.4, 22.8, 24.5, 41.7, 60.1, 60.2 (2 × C), 91.1, 159.0, 166.8, 169.0, 174.9. HRMS (NSI) found $[M+H]^+$ = 302.1596 $C_{14}H_{24}NO_6$ requires $[M+H]^+$ = 302.1598.

2-{[3-Ethoxy-2-(ethoxycarbonyl)-3-oxoprop-1-en-1-yl]amino}-2-phenylacetic acid, 2.13f From DL-2-phenylglycine as a yellow oil [Method A: 2.72 g, 17 %; Method A (0.5 × scale, DCM extraction): 6.33 g, 79 %; Method B (0.37 × scale): 5.51 g, 93 %]. ν_{max} 2981, 1736, 1656, 1599, 1219, 1171, 1065 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.23 – 1.26 (3H, m, CH_2CH_3), 1.30 – 1.33 (3H, m , CH_2CH_3), 4.15 (2H, q, *J* = 7.1 Hz, C*H*$_2$CH$_3$), 4.23 (2H, q, *J* = 7.1 Hz, C*H*$_2$CH$_3$), 5.17 (1H, d, *J* = 6.8 Hz, NHC*H*COOH), 7.41 (5H, s, Ar-*H*), 7.61 (1H, br. s, COO*H*), 7.96 (1H, d, *J* = 14.1 Hz, CC*H*NH), 9.94 (1H, dd, *J* = 6.8, 14.1 Hz, N*H*). δ_C (100 MHz, $CDCl_3$) 14.2, 14.3, 60.2, 60.3, 64.2, 91.9, 127.3 (2 × C), 129.2, 129.3 (2 × C), 135.6, 158.2, 166.7, 168.7, 172.4.

2-{[3-Ethoxy-2-(ethoxycarbonyl)-3-oxoprop-1-en-1-yl]amino}-3-phenylpropanoic acid, 2.13g From DL-phenylalanine (Method B: 8.25 g) as a yellow oil (13.07 g, 78 %). ν_{max} 2983, 1742, 1652, 1607, 1221, 1076 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.24 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 1.33 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 3.07 (1H, dd, *J* = 8.8, 13.9 Hz, CHC*H*$_a$H$_b$Ph), 3.33 (1H, dd, *J* = 4.4, 13.9 Hz, CHCH$_a$*H*$_b$Ph), 4.11 – 4.18 (2H, m, C*H*$_2$CH$_3$), 4.22 – 4.28 (3H, m, C*H*$_2$CH$_3$, NHC*H*COOH), 6.79 (1H, br. s, COO*H*), 7.19 (2H, d, *J* = 7.1 Hz, *o*-Ar-*H*), 7.26 – 7.34 (3H, m*, *m*-Ar-*H*, *p*-Ar-*H*), 7.65 (1H, d, *J* = 14.0 Hz, CC*H*NH), 9.41 (1H, dd, *J* = 8.8, 13.9 Hz, N*H*). δ_C (100 MHz, $CDCl_3$) 14.2, 14.3, 39.8, 60.1, 60.2, 62.9, 90.9, 127.5, 128.9 (2 × C), 129.5 (2 × C), 135.1, 158.8, 166.7, 168.7, 173.1. HRMS (NSI) found $[M-H]^-$ = 334.1293 $C_{17}H_{20}NO_6$ requires $[M-H]^-$ = 334.1296.

* Overlaps with residual $CHCl_3$

2-{[3-Ethoxy-2-(ethoxycarbonyl)-3-oxoprop-1-en-1-yl]amino}-3-hydroxypropanoic acid, 2.13h From DL-serine (Method B: 9.17 g) in water (20 mL) as a yellow solid recrystallised from EtOAc and hexane (9.17 g, 67 %). m.p. 125 – 127 °C. ν_{max} 3238, 2981, 2902, 2552, 1733, 1663, 1604, 1235, 1075, 799 cm^{-1}. δ_H [400 MHz, $(CD_3)_2CO$] 1.23 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 1.28 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 4.00 – 4.13 (4H, m, CH_2CH_3, $CHCH_2OH$), 4.18 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 4.43 – 4.47 (1H, m, NHCHCOOH), 8.14 (1H, d, *J* = 14.3 Hz, CCHNH), 9.59 (1H, m, NH). δ_C [100 MHz, $(CD_3)_2CO$] 13.8, 13.9, 58.8, 58.9, 62.8, 63.1, 90.5, 159.2, 165.4, 168.3, 170.3. HRMS (NSI) found $[M-H]^-$ = 274.0932 $C_{11}H_{16}NO_7$ requires $[M-H]^-$ = 274.0932.

2-{[3-Ethoxy-2-(ethoxycarbonyl)-3-oxoprop-1-en-1-yl]amino}-3-hydroxybutanoic acid, 2.13i From L-threonine (Method B: 5.96 g) as a yellow oil (11.49 g, 79 %). ν_{max} 3454, 2981, 1729, 1655, 1601, 1222, 1074 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.25 – 1.35 [9H, m, 2 × CH_2CH_3, $CH(CH_3)OH$], 3.95 (1H, dd, *J* = 2.8, 9.2 Hz, NHCHCOOH), 4.17 – 4.26 (4H, m, 2 × CH_2CH_3), 4.41 – 4.46 [1H, qd, *J* = 2.8, 6.3 Hz, $CH(CH_3)OH$], 5.47 [2H, br. s, COOH, $CH(CH_3)OH$], 7.99 (1H, d, *J* = 14.2 Hz, CCHNH), 9.41 (1H, dd, *J* = 9.3, 14.1 Hz, NH). δ_C (100 MHz, $CDCl_3$) 14.1, 14.2, 14.3, 19.5, 60.2 (2 × C), 67.9, 91.1, 160.0, 166.9, 168.9, 172.3. HRMS (NSI) found $[M+H]^+$ = 290.1235 $C_{12}H_{20}NO_7$ requires $[M+H]^+$ = 290.1234.

2-{[3-Ethoxy-2-(ethoxycarbonyl)-3-oxoprop-1-en-1-yl]amino}succinic acid, 2.13j From L-aspartic acid (Method B: 6.67 g) in water (40 mL) using 2.4 equiv. KOH (7.92 g, 120 mmol) as a pale pink solid (10.06 g, 66 %). m.p. 157 – 158 °C [lit. m.p. 172 – 174 °C (89S544)]. ν_{max} 2984, 2943, 1741, 1727, 1646, 1596, 1087, 1071 cm^{-1}. δ_H [400 MHz, $(CD_3)_2SO$] 1.20 (6H, app. q, 2 × CH_2CH_3), 2.85 (1H, dd, *J* = 4.4, 17.4 Hz, CH_aH_bCOOH), 2.92 (1H, dd, *J* = 5.5, 17.4 Hz, CH_aH_bCOOH), 4.03 – 4.13 (4H, m, 2 × CH_2CH_3), 4.58 – 4.63 (1H, m, NHCHCOOH), 8.05 (1H, d, *J* = 14.2 Hz, CCHNH), 9.41 (1H, dd, *J* = 9.1, 14.2 Hz, NH), 12.74 (2H, br. s, 2 × COOH). δ_C [100 MHz, $(CD_3)_2SO$] 14.7, 14.8, 37.2, 57.9, 59.3, 59.4, 89.7, 160.1, 165.6, 168.1, 172.1, 172.5. HRMS (NSI) found $[M-H]^-$ = 302.0876 $C_{12}H_{17}NO_8$ requires $[M-H]^-$ = 302.0881.

2-{[3-Ethoxy-2-(ethoxycarbonyl)-3-oxoprop-1-en-1-yl]amino}pentanedioic acid, 2.13k From L-glutamic acid (Method B: 7.37 g) in water (30 mL) using 2.4 equiv. KOH (7.92 g, 120 mmol) as a yellow oil (11.42 g, 72 %). ν_{max} 2982, 1771, 1655, 1604, 1221, 1074, 800 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.25 – 1.34 (6H, m, 2 × CH_2CH_3), 2.11 – 2.22 (1H, m, $CHCH_aH_bCH_2$), 2.29 – 2.37 (1H, m, $CHCH_aH_bCH_2$), 2.52 (2H, t, *J* = 6.7 Hz, CH_2CH_2COOH), 4.17 – 4.26 (5H, m, 2 × CH_2CH_3, NHCHCOOH), 8.03 (1H, d, *J* = 14.0 Hz, CCHNH), 9.41 (1H, dd, *J* = 8.9, 13.8 Hz, NH), 10.82 (2H, br. s, 2 × COOH). δ_C

(100 MHz, $CDCl_3$) 14.0, 14.3, 28.0, 29.4, 60.3, 60.5, 91.5, 159.2, 167.1, 167.2, 168.9, 173.9, 177.2. HRMS (NSI) found $[M-H]^-$ = 316.1030 $C_{13}H_{18}NO_8$ requires $[M-H]^-$ = 316.1038.

2-{[3-Ethoxy-2-(ethoxycarbonyl)-3-oxoprop-1-en-1-yl]amino}-5-methoxy-5-oxopentanoic acid, 2.13l From L-glutamic acid 5-methyl ester (Method D: 8.08 g), acidification produced an oil which was therefore extracted with EtOAc (3 × 50 mL), washed with water and dried (Na_2SO_4). The solvent was removed under reduced pressure and the product was obtained as a yellow oil (14.26 g, 86 %). ν_{max} 2981, 1733, 1655, 1603, 1219, 1168, 1069 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.25 – 1.35 (6H, m, 2 × CH_2CH_3), 2.11 – 2.20 (1H, m, $CHCH_aH_bCH_2$), 2.28 – 2.37 (1H, m, $CHCH_aH_bCH_2$), 2.47 (2H, t, *J* = 7.2 Hz, $CH_2CO_2CH_3$), 3.69 (3H, s, CO_2CH_3), 4.17 – 4.27 (5H, m, 2 × CH_2CH_3, NHCHCOOH), 7.98 (1H, d, *J* = 13.9 Hz, 8.75 (1H, br. s, COOH), 9.37 (1H, dd, *J* = 8.8, 13.9 Hz, NH). δ_C (100 MHz, $CDCl_3$) 14.3, 14.4, 28.2, 29.5, 52.0, 60.2, 60.6, 91.5, 91.6, 158.9, 166.6, 168.8, 172.7, 173.1. HRMS (NSI) found $[M+H]^+$ = 332.1337 $C_{14}H_{22}NO_8$ requires $[M+H]^+$ 332.1340.

4-Amino-2-{[3-ethoxy-2-(ethoxycarbonyl)-3-oxoprop-1-en-1-yl]amino}-4-oxobutanoic acid, 2.13m From L-asparagine (Method C: 7.93 g; Method D: 6.61 g) as a white solid (Method C: 1.46 g, 10 %; Method D: 8.32 g, 55 %). m.p. 154 – 156 °C. ν_{max} 3418, 3254, 3083, 2984, 1719, 1681, 1658, 1643, 1580, 1205 cm^{-1}. δ_H [400 MHz, $(CD_3)_2SO$] 1.16 – 1.23 (6H, app. q, 2 × CH_2CH_3), 2.65 (1H, dd, *J* = 4.1, 16.5 Hz, $CH_aH_bCONH_2$), 2.80 (1H, dd, *J* = 5.8, 16.5 Hz, $CH_aH_bCONH_2$), 4.02 – 4.13 (4H, m, 2 × CH_2CH_3), 4.52 – 4.57 (1H, m, NHCHCOOH), 7.05 (1H, br. s, $CONH_aH_b$), 7.50 (1H, br. s, $CONH_aH_b$), 8.00 (1H, d, *J* = 14.4 Hz, CCHNH), 9.46 (1H, dd, *J* = 9.0, 14.4 Hz, NH), 13.08 (1H, br. s, COOH). δ_C [100 MHz, $(CD_3)_2SO$] 14.8, 14.9, 37.8, 58.2, 59.3 (2 × C), 89.4, 159.9, 165.7, 168.0, 171.7, 172.5. HRMS (NSI) found $[M-H]^-$ = 301.1038 $C_{12}H_{17}N_2O_7$ requires $[M-H]^-$ = 301.1041.

5-Amino-2-{[3-ethoxy-2-(ethoxycarbonyl)-3-oxoprop-1-en-1-yl]amino}-5-oxopentanoic acid, 2.13n From L-glutamine (Method A: 7.32 g; Method C: 4.39 g) as a white solid (Method A: 1.63 g, 10 %; Method C: 2.29 g, 29 %). m.p. 74 – 80 °C. ν_{max} 3237, 2983, 1715, 1667, 1602, 1212, 1075, 802 cm^{-1}. δ_H [400 MHz, $(CD_3)_2SO$] 1.18 – 1.24 (6H, m, 2 × CH_2CH_3), 1.91 – 2.12 (4H, m, CH_2CH_2), 4.00 – 4.15 (4H, m, 2 × CH_2CH_3), 4.35 (1H, td, *J* = 3.8, 8.3 Hz, NHCHCOOH), 6.83 (1H, s, $CONH_aH_b$), 7.37 (1H, s, $CONH_aH_b$), 8.01 (1H, d, *J* = 14.3 Hz, CCHNH), 9.25 (1H, dd, *J* = 8.5, 14.3 Hz, NH), 12.69 (1H, br. s, COOH). δ_C (100 MHz, $(CD_3)_2CO$) 13.5, 13.8, 30.3, 58.8, 59.0, 60.7, 90.3, 158.4, 161.7, 165.4, 172.2, 173.6. HRMS (NSI) found $[M+H]^+$ = 317.1343 $C_{13}H_{21}N_2O_7$ requires $[M+H]^+$ = 317.1343.

2-{[3-Ethoxy-2-(ethoxycarbonyl)-3-oxoprop-1-en-1-yl]amino}-4-(methylsulfinyl)butanoic acid, 2.13o From DL-methionine sulfoxide [Method B (0.3 × scale): 2.50 g] as a yellow oil (2.74 g, 55 %). ν_{max} 2981, 1651, 1600, 1253, 1216 cm^{-1}. The ^1H NMR spectrum (400 MHz, $CDCl_3$) showed the presence of two diastereoisomers (1:0.9) based on the integrals at δ 2.71 (3H, s, SOC*H*$_3$, *major isomer*) and δ 2.77 (3H, s, SOC*H*$_3$, *minor isomer*). δ_H (400 MHz, $CDCl_3$) 1.27 – 1.40 (6H × 2, m, 4 × CH_2CH_3), 2.29 – 2.54 (2H × 2, m, 2 × CH_2CH_2SO), 2.71 (3H, s, SOC*H*$_3$, *major*), 2.77 (3H, s, SOC*H*$_3$, *minor*), 2.80 – 2.90 (1H × 2, m, 2 × CH_aH_bSO), 2.94 – 3.04 (1H × 2, m, 2 × CH_aH_bSO), 4.15 – 4.39 (5H × 2, m, 4 × CH_2CH_3, 2 × NHC*H*COOH), 7.61 (1H, br. s, COO*H*, *major*), 7.74 (1H, br. s, COO*H*, *minor*), 7.99 (1H, d, *J* = 14.0 Hz, CC*H*NH, *minor*), 8.00 (1H, d, *J* = 13.9 Hz, CC*H*NH, *major*), 9.40 – 9.48 (1H × 2, m, 2 × N*H*). δ_C (100 MHz, $CDCl_3$) 14.3, 14.4, 26.9, 27.0, 37.7 (2 × C), 48.1, 48.7, 59.5, 60.1 (2 × C), 60.2, 61.8, 92.0, 92.1, 158.2, 158.5, 166.2, 166.4, 168.8, 171.5, 174.8. HRMS (NSI) found $[M-H]^-$ = 334.0963 $C_{13}H_{20}NO_7S$ requires $[M-H]^-$ = 334.0966.

4.2.2 Synthesis of Pyrroles: Cyclisation of Diethyl 2-(1-carboxyalkylaminomethylene)malonate (2-{[3-ethoxy-2-(ethoxycarbonyl)-3-oxoprop-1-en-1-yl]amino} acids)

General method for the cyclisation of 2-{[3-ethoxy-2-(ethoxycarbonyl)-3-oxoprop-1-en-1-yl]amino} acids

The 2-{[3-ethoxy-2-(ethoxycarbonyl)-3-oxoprop-1-en-1-yl]amino} acid (10 mmol) was dissolved in acetic anhydride (30 mL) prior to the addition of triethylamine (10 mL, 7 equiv.). The mixture was refluxed until the emission of CO_2 was complete (limewater bubbler) and allowed to cool to room temperature. The brown solution was poured into water (400 mL), stirred for 1 h and extracted with DCM (5 × 50 mL). The organic layer was washed with water (2 × 100 mL), aq. $NaHCO_3$ (5 × 50 mL) and water (100 mL). The dried (Na_2SO_4) solvent was removed under reduced pressure and the products were isolated by flash column chromatography.

The following compounds were synthesised by the above method.

Ethyl 4-acetoxy-1-acetyl-1*H*-pyrrole-3-carboxylate, 2.18a From **2.13a** (2.45 g) as white needles after flash column chromatography [25 % EtOAc in hexane] (1.30 g, 54 %). m.p. 77 – 79 °C (lit. b.p. 220 °C at 0.1 mm Hg [02JCS(P1)2799]). ν_{max} 3155, 3134, 2985, 1758, 1723, 1698, 1195 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.36 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 2.34 (3H, s, COC*H*$_3$), 2.58 (3H, s, NCOC*H*$_3$), 4.30 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 7.29 (1H, s, 5-*H*), 7.82 (1H, s, 2-*H*). δ_C (100 MHz, $CDCl_3$) 14.3, 20.7, 21.7,

60.4, 110.3, 113.4, 122.7, 138.4, 162.2, 167.0, 168.9. Selective removal of the *N*-acetyl group was achieved by the addition of **2.18a** (0.60 g) to sodium acetate (0.60 g) in EtOH (30 mL) prior to refluxing for 25 minutes. The solvent was removed under reduced pressure and the residue dissolved in water, extracted with Et_2O (5 × 50 mL) and washed with water. The organic layer was dried and the solvent removed under reduced pressure to yield *ethyl 4-acetoxy-1*H-*pyrrole-3-carboxylate* (**2.20**) as a brown oil which solidified (0.44 g, 89 %). ν_{max} 3270, 3134, 2981, 2906, 1766, 1673, 1207 cm^{-1}. δ_H [400 MHz, $(CD_3)_2CO$] 1.28 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 2.21 (3H, s, $OCOCH_3$), 4.18 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 6.73 – 6.74 (1H, app. t, 5-*H*), 7.32 (1H, dd, *J* = 2.4, 3.5 Hz, 2-*H*), 10.50 (1H, br. s, N*H*). δ_C (100 MHz, $CDCl_3$) 14.4, 20.8, 59.8, 108.2, 109.6, 122.5, 136.4, 163.5, 169.8. HRMS (NSI) found $[M+H]^+$ = 198.0759 $C_9H_{12}NO_4$ requires $[M+H]^+$ = 198.0761.

Ethyl 4-acetoxy-1-acetyl-5-methyl-1*H*-pyrrole-3-carboxylate, 2.18b From **2.13b** (2.59 g); flash column chromatography [25 % EtOAc in hexane] provided initially e*thyl 1-acetyl-4-ethoxy-5-methyl-1*H-*pyrrole-3-carboxylate* (**2.19b**) as white needles (0.49 g, 20 %). m.p. 67 – 69 °C. ν_{max} 3130, 2980, 2870, 1719, 1698, 1605, 1540, 1277, 1195, 1030 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.35 – 1.40 (6H, app. q, $CO_2CH_2CH_3$, OCH_2CH_3), 2.41 (3H, s, CH_3), 2.58 (3H, s, $NCOCH_3$), 4.00 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 4.33 (2H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 7.56 (1H, s, 2-*H*). δ_C (100 MHz, $CDCl_3$) 11.3, 14.4, 15.3, 23.4, 60.3, 70.6, 113.0, 112.8 (2 × C), 143.6, 163.1, 169.2. HRMS (NSI) found $[M+H]^+$ = 240.1230 $C_{12}H_{18}NO_4$ requires $[M+H]^+$ = 240.1230. Further elution afforded the **title compound** as white needles (2.03 g, 80 %). m.p. 98 – 100 °C. ν_{max} 3133, 2985, 2926, 1755, 1719, 1702, 1208, 1192 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.35 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 2.35 (3H, s, $OCOCH_3$), 2.36 (3H, s, CH_3), 2.59 (3H, s, $NCOCH_3$), 4.28 (2H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 7.63 (1H, s, 2-*H*). δ_C (100 MHz, $CDCl_3$) 11.3, 14.3, 20.5, 23.4, 60.4, 112.3, 122.8, 123.3, 135.3, 162.3, 169.1, 169.4. HRMS (NSI) found $[M+H]^+$ = 254.1024 $C_{12}H_{16}NO_5$ requires $[M+H]^+$ = 254.1023. Selective removal of the *N*-acetyl group was achieved by the addition of **2.19b** (0.46 g) to sodium acetate (0.60 g) in EtOH (30 mL) prior to refluxing for 60 minutes. The solvent was removed under reduced pressure and the residue dissolved in water, extracted with Et_2O (5 × 50 mL) and washed with water. The organic layer was dried and the solvent removed under reduced pressure to yield *ethyl 4-ethoxy-5-methyl-1*H-*pyrrole-3-carboxylate* (**2.21**) as an orange oil which turned purple on standing (0.30 g, 79 %). ν_{max} 3309, 2978, 1681, 1150, 1108, 1030 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.34 (6H, td, *J* = 3.6, 7.0 Hz, $CO_2CH_2CH_3$, OCH_2CH_3), 2.16 (3H, s, CH_3), 4.01 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 4.28 (2H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 7.11 (1H, d, *J* = 3.4 Hz, 2-*H*), 8.16 (1H, br. s, N*H*). δ_C (100 MHz, $CDCl_3$) 9.4, 14.4, 15.4,

59.5, 70.5, 108.7, 118.0, 120.1, 141.0, 164.3. HRMS (APCI) found $[M+H]^+$ = 198.1123 $C_{10}H_{16}NO_3$ requires $[M+H]^+$ = 198.1125.

Ethyl 4-acetoxy-1-acetyl-5-ethyl-1*H*-pyrrole-3-carboxylate, 2.18c From **2.13c** (2.73 g); flash column chromatography [25 % EtOAc in hexane] provided initially *ethyl 1-acetyl-4-ethoxy-5-ethyl-1*H-*pyrrole-3-carboxylate* (**2.19c**) as a white solid (0.26 g, 10 %). m.p. 80 – 81 °C. ν_{max} 3142, 2981, 2929, 2871, 1716, 1700, 1265, 1184 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.15 (3H, t, *J* = 7.3 Hz, CH_2CH_3), 1.38 (6H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$, OCH_2CH_3), 2.58 (3H, s, $NCOCH_3$), 2.89 (2H, q, *J* = 7.3 Hz, CH_2CH_3), 4.00 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 4.33 (2H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 7.54 (1H, s, 2-*H*). δ_C (100 MHz, $CDCl_3$) 14.3 (2 × C), 15.4, 18.0, 23.5, 60.2, 70.9, 112.8, 123.3, 129.0, 143.3, 163.1, 168.8. HRMS (NSI) found $[M+H]^+$ = 254.1387 $C_{13}H_{20}NO_4$ requires $[M+H]^+$ = 254.1387. Further elution afforded the **title compound** as a white solid (1.30 g, 49 %). m.p. 107 – 109 °C. ν_{max} 3134, 2976, 2937, 1765, 1738, 1699, 1274, 1180 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.15 (3H, t, *J* = 7.3 Hz, CH_2CH_3), 1.34 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 2.35 (3H, s, $OCOCH_3$), 2.60 (3H, s $NCOCH_3$), 2.82 (2H, q, *J* = 7.3 Hz, CH_2CH_3), 4.28 (2H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 7.62 (1H, s, 2-*H*). δ_C (100 MHz, $CDCl_3$) 13.6, 14.3, 18.3, 20.5, 23.5, 60.4, 122.2, 123.2, 129.2, 134.9, 162.3, 168.7, 169.6. HRMS (NSI) found $[M+H]^+$ = 268.1179 $C_{13}H_{18}NO_5$ requires $[M+H]^+$ = 268.1179.

Ethyl 4-acetoxy-1-acetyl-5-isopropyl-1*H*-pyrrole-3-carboxylate, 2.18d From **2.13d** (2.88 g); flash column chromatography [25 % EtOAc in hexane] provided initially *ethyl 1-acetyl-4-ethoxy-5-isopropyl-1*H-*pyrrole-3-carboxylate* (**2.19d**) as a yellow oil (0.11 g, 4 %). δ_H (400 MHz, $CDCl_3$) 1.32 [6H, d, *J* = 7.0 Hz, $CH(CH_3)_2$], 1.37 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 1.40 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 2.59 (3H, s, $NCOCH_3$), 3.74 [1H, sep, *J* = 7.0 Hz, $CH(CH_3)_2$], 3.98 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 4.32 (2H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 7.54 (1H, s, 2-*H*). δ_C (100 MHz, $CDCl_3$) 14.3, 15.4, 21.3 (2 × C), 24.1, 25.6, 70.8, 112.8, 123.9, 132.2, 144.0, 163.0, 169.1. Further elution afforded the **title compound** as an orange solid (1.02 g, 36 %). m.p. 79 – 81 °C. ν_{max} 3149, 2977, 2932, 1763, 1737, 1698, 1261, 1197, 1182 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.27 [6H, d, *J* = 7.0 Hz, $CH(CH_3)_2$], 1.34 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 2.34 (3H, s, $OCOCH_3$), 2.61 (3H, s, $NCOCH_3$), 3.79 (1H, sep, *J* = 7.0 Hz, $CH(CH_3)_2$), 4.28 (2H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 7.61 (1H, s, 2-*H*). δ_C (100 MHz, $CDCl_3$) 14.3, 20.7, 21.0 (2 × C), 24.1, 25.9, 60.3, 112.2, 123.6, 132.6, 135.3, 162.3, 169.1, 169.6. HRMS (NSI) found $[M+H]^+$ = 282.1336 $C_{14}H_{20}NO_5$ requires $[M+H]^+$ = 282.1336.

Ethyl 4-acetoxy-1-acetyl-5-isobutyl-1*H*-pyrrole-3-carboxylate, 2.18e From **2.13e** (3.10 g); flash column chromatography [25 % EtOAc in hexane] gave initially *ethyl 1-acetyl-4-ethoxy-5-isobutyl-*

*1*H-*pyrrole-3-carboxylate* **2.19e** as a yellow oil (0.33 g, 12 %). ν_{max} 2957, 2870, 1714, 1249, 1179, 1131 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 0.89 [6H, d, *J* = 6.6 Hz, $CH(CH_3)_2$], 1.37 (6H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$, OCH_2CH_3), 1.85 [1H, sep, *J* = 6.6 Hz, $CH(CH_3)_2$], 2.57 (3H, s, $NCOCH_3$), 2.71 [2H, d, *J* = 7.0 Hz, $CH_2CH(CH_3)_2$], 4.00 (2H,q, *J* = 7.0 Hz, OCH_2CH_3), 4.30 – 4.35 (2H, m, $CO_2CH_2CH_3$), 7.55 (1H, s, 2-*H*). δ_C (100 MHz, $CDCl_3$) 14.3, 15.5, 22.4 (2 × C), 23.6, 28.1, 33.4, 60.2, 70.5, 112.7, 123.5, 126.5, 144.6, 163.1, 168.9. HRMS (NSI) found $[M+H]^+$ = 282.1703 $C_{15}H_{24}NO_4$ requires $[M+H]^+$ = 282.1700. Further elution provided the **title compound** as a white solid (1.33 g, 45 %). m.p. 67 °C. ν_{max} 3133, 2957, 2870, 1759, 1708, 1266, 1202, 1182 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 0.91 [6H, d, *J* = 6.6 Hz, $CH(CH_3)_2$], 1.35 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 1.89 [1H, sep, *J* = 6.7 Hz, $CH(CH_3)_2$], 2.34 (3H, s, $OCOCH_3$), 2.60 (3H, s, $NCOCH_3$), 2.65 [2H, d, *J* = 7.0 Hz, $CH_2CH(CH_3)_2$], 4.29 (2H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 7.63 (1H, s, 2-*H*). δ_C (100 MHz, $CDCl_3$) 14.3, 20.6, 22.3 (2 × C), 23.6, 28.1, 33.6, 60.4, 112.2, 123.4, 126.9, 136.2, 162.4, 168.8, 169.4. HRMS (NSI) found $[M+H]^+$ = 296.1492 $C_{15}H_{22}NO_5$ requires $[M+H]^+$ = 296.1492.

Ethyl 4-acetoxy-1-acetyl-5-phenyl-1*H*-pyrrole-3-carboxylate, 2.18f From **2.13f** (2.18 g); flash column chromatography [25 % EtOAc in hexane] provided the **title compound** as a white solid (0.43 g, 20 %). m.p. 120 – 122 °C {lit. m.p. 122 – 124 °C [02JCS(P1)2799]}. ν_{max} 3142, 1768, 1742, 1702, 1591, 1275, 1232, 1193 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.36 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 2.20 (3H, s, $OCOCH_3$), 2.30 (3H, s, $NCOCH_3$), 4.31 (2H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 7.31 – 7.34 (2H, m, *o*-Ar-*H*), 7.41 - 7.45 (3H, m, *m*-Ar-*H*, *p*-Ar-H), 7.94 (1H, s, 2-*H*). δ_C (100 MHz, $CDCl_3$) 14.3, 20.5, 24.6, 60.4, 112.2, 124.0, 125.3, 128.4 (2 × C), 128.8, 129.4, 129.9 (2 × C), 136.3, 162.3, 168.4, 169.6.

Ethyl 4-acetoxy-1-acetyl-5-benzyl-1*H*-pyrrole-3-carboxylate, 2.18g From **2.13g** (3.34 g); flash column chromatography [30 % EtOAc in hexane] afforded the **title compound** as a yellow oil which solidified (1.68 g, 51 %). m.p. 73 – 78 °C. ν_{max} 2981, 1759, 1737, 1705, 1194, 1171, 1149 cm^{-1}. δ_H [400 MHz, $(CD_3)_2CO$] 1.31 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 2.27 (3H, s, $OCOCH_3$), 2.61 (3H, s, $NCOCH_3$), 4.18 (2H, s, CH_2Ph), 4.25 (2H, q, *J* =7.1 Hz, $CO_2CH_2CH_3$), 7.14 – 7.17 (3H, m, *m*-Ar-*H*, *p*-Ar-*H*), 7.22 – 7.27 (2H, m, *o*-Ar-*H*), 7.87 (1H, s, 2-*H*). δ_C [100 MHz, $(CD_3)_2CO$] 13.7, 19.7, 22.5, 29.8, 59.8, 111.7, 124.5, 124.6, 125.9, 128.0 (2 × C), 128.3 (2 × C), 136.7, 139.1, 161.8, 168.8, 169.1. HRMS (NSI) found $[M+H]^+$ = 330.1336 $C_{18}H_{20}NO_5$ requires $[M+H]^+$ = 330.1336.

Attempted preparation of 2-[3-Acetoxy-1-acetyl-4-(ethoxycarbonyl)-1*H*-pyrrol-2-yl]acetic acid, 2.18j From **2.13j** (3.02 g); flash column chromatography [30 % EtOAc in hexane] gave *diethyl 2-(acetamidomethylene)malonate* **2.22** as a yellow solid (1.11 g, 48 %). m.p. 53 – 55 °C (lit. m.p. 48.5

– 49.0 °C [03H161], 54.5 °C [76RC661], 52 – 53.5 °C [64JMC68]). ν_{max} 3282, 3085, 2982, 1720, 1662, 1593, 1223, 1189, 1077, 799 cm^{-1}. δ_H [400 MHz, $(CD_3)_2SO$] 1.22 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 1.25 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 2.21 (3H, s, $NCOCH_3$), 4.15 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 4.23 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 8.19 (1H, d, *J* = 12.4 Hz, CCHNH), 10.58 (1H, d, *J* = 12.4 Hz, NH). δ_C [100 MHz, $(CD_3)_2SO$]14.4, 14.6, 23.7, 60.9, 61.1, 102.9, 142.7, 164.7, 165.4, 170.0. HRMS (NSI) found $[M+Na]^+$ = 252.0839 $C_{10}H_{15}NNaO_5$ requires $[M+Na]^+$ = 252.0842.

Attempted preparation of 3-[3-acetoxy-1-acetyl-4-(ethoxycarbonyl)-1*H*-pyrrol-2-yl]propanoic acid, 2.18k From **2.13k** (3.17 g); flash column chromatography [50 % EtOAc in hexane] provided *diethyl 2-[(2-acetyl-5-oxopyrrolidin-1-yl)methylene]malonate* **2.23** as a brown oil (0.53 g, 18 %). ν_{max} 2983, 1702, 1624, 1180, 1062 cm^{-1}. The ^1H NMR spectrum (400 MHz, $CDCl_3$) was complicated by the presence of two rotamers (1:1) and the presence of an impurity with a signal at δ 2.04 – 2.11 (1H, m) which also affected the integrations of several signals. δ_H (400 MHz, $CDCl_3$) 1.29 – 1.35 (7H, m, 2 × CH_2CH_3), 2.04 – 2.11 (1H, m, impurity), 2.23 (3H, s, $COCH_3$), 2.35 – 2.66 (5H, m, CH_2CH_2), 4.13 – 4.39 (5H, m, 2 × CH_2CH_3), 4.88 – 4.91 (1H, m, $CHCOCH_3$), 8.21 (1H, s, CCHN). δ_C (100 MHz, $CDCl_3$) 14.0, 14.2, 22.1, 25.6, 28.1, 61.3, 61.8, 64.7, 107.6, 135.1, 165.0, 165.9, 174.6, 202.9. HRMS (APCI) found $[M+H]^+$ = 298.1283 $C_{14}H_{20}NO_6$ requires $[M+H]^+$ = 298.1285.

Ethyl 4-acetoxy-1-acetyl-5-(3-methoxy-3-oxopropyl)-1*H*-pyrrole-3-carboxylate, 2.18l From **2.13l** (3.36 g); flash column chromatography [30 % EtOAc in hexane] provided initially *ethyl 1-acetyl-4-ethoxy-5-(3-methoxy-3-oxopropyl)-1*H*-pyrrole-3-carboxylate* (**2.19l**) as a yellow solid (0.21 g, 7 %). m.p. 86 – 89 °C. ν_{max} 3141, 2984, 2874, 1716, 1701, 1599, 1262, 1032 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.38 (6H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$, OCH_2CH_3), 2.57 – 2.61 (5H, m, $NCOCH_3$, CH_2CH_2CO), 3.17 – 3.21 (2H, m, CH_2CH_2CO), 3.70 (3H, s, CO_2CH_3), 4.00 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 4.33 (2H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 7.56 (1H, s, 2-*H*). δ_C (100 MHz, $CDCl_3$) 14.4, 15.4, 20.3, 23.4, 33.7, 51.6, 60.4, 71.0, 113.0, 123.8, 125.0, 144.4, 162.9, 169.0, 173.3. HRMS (NSI) found $[M+H]^+$ = 312.1439 $C_{15}H_{22}NO_6$ requires $[M+H]^+$ = 312.1442. Further elution afforded the **title compound** as a yellow solid (1.20 g, 37 %). m.p. 115 – 116 °C. ν_{max} 3160, 2981, 1751, 1731, 1712, 1190, 1173, 1158 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.33 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 2.35 (3H, s, $OCOCH_3$), 2.57 – 2.61 (5H, m, $NCOCH_3$, CH_2CH_2CO), 3.10 – 3.14 (2H, m, CH_2CH_2CO), 3.67 (3H, s, CO_2CH_3), 4.27 (2H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 7.63 (1H, s, 2-*H*). δ_C (100 MHz, $CDCl_3$) 14.3, 20.4, 20.6, 23.4, 33.0, 51.7, 60.5, 112.5, 123.7, 125.5, 136.0, 162.1, 168.9, 169.5, 173.1. HRMS (NSI) found $[M+H]^+$ = 326.1233 $C_{15}H_{20}NO_7$ requires $[M+H]^+$ = 326.1234.

Attempted preparation of ethyl 4-acetoxy-1-acetyl-5-(2-amino-2-oxoethyl)-1*H*-pyrrole-3-carboxylate From **2.13m** (6.05 g, 20 mmol); flash column chromatography [30 % EtOAc in hexane] provided initially *diethyl 2-(acetamidomethylene)malonate* (**2.22**) as a yellow crystalline solid (0.50 g, 11 %). ν_{max} 3282, 3085, 2988, 2944, 1719, 1664, 1593, 1222, 1191, 1078, 799 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.33 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 1.38 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 2.26 (3H, s, $NHCOCH_3$), 4.26 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 4.33 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 8.53 (1H, d, *J* = 12.0 Hz, CCHNH), 10.91 (1H, br. d, *J* = 9.8 Hz, NH). Further elution gave *ethyl 1-acetyl-5-cyano-4-ethoxy-1*H*-pyrrole-3-carboxylate* (**2.25**) as an orange solid (0.10 g, 3 %). δ_H (400 MHz, $CDCl_3$) 1.39 (6H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$, OCH_2CH_3), 2.63 (3H, s, $NCOCH_3$), 3.98 (2H, s, CH_2CN), 4.11 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 4.34 (2h, q, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 7.65 (1H, s, 2-*H*). δ_C (100 MHz, $CDCl_3$) 14.3, 14.6, 15.3, 22.8, 60.7, 71.2, 113.1, 114.3, 116.6, 124.8, 145.9, 162.2, 168.9. HRMS (APCI) found $[M+H]^+$ = 265.1181 $C_{13}H_{17}N_2O_4$ requires $[M+H]^+$ = 265.1183. Finally *ethyl 4-acetoxy-1-acetyl-5-cyano-1*H*-pyrrole-3-carboxylate* (**2.24**) was obtained as pale orange crystals (0.88 g, 16 %). m.p. 157 – 160 °C. ν_{max} 3130, 2941, 1769, 1738, 1693, 1182 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.36 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 2.38 (3H, s, $OCOCH_3$), 2.65 (3H, s, $NCOCH_3$), 3.95 (2H, s, CH_2CN), 4.30 (2H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 7.72 (1H, s, 2-*H*). δ_C (100 MHz, $CDCl_3$) 14.3, 15.0, 20.5, 22.9, 60.8, 112.9, 114.7, 115.5, 124.5, 137.7, 161.5, 168.8, 168.9. HRMS (NSI) found $[M+NH_4]^+$ = 296.1240 $C_{13}H_{18}N_3O_5$ requires $[M+NH_4]^+$ = 296.1241.

Attempted preparation of ethyl 4-acetoxy-1-acetyl-5-(3-amino-3-oxopropyl)-1*H*-pyrrole-3-carboxylate From **2.13n** (1.91 g, 6.04 mmol); flash column chromatography [10 % MeOH in DCM] provided *ethyl 5-(3-acetamido-3-oxopropyl)-4-acetoxy-1-acetyl-1*H*-pyrrole-3-carboxylate* (**2.26**) as an orange solid (0.08 g, 4 %). m.p. 187 – 191 °C. ν_{max} 3134, 2985, 1766, 1737, 1689, 1261, 1198, 1146, 1024 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.35 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 2.35 (6H, s, $OCOCH_3$, $CONHCOCH_3$), 2.62 (3H, s, $NCOCH_3$), 2.74 – 2.78 (2H, m, CH_2CH_2CO), 3.13 – 3.16 (2H, m, CH_2CH_2CO), 4.29 (2H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 7.65 (1H, s, 2-*H*), 7.99 (1H, br. s, CONHCO). δ_C (100 MHz, $CDCl_3$) 14.3, 20.0, 20.5, 23.4, 25.1, 36.4, 60.5, 112.6, 123.8, 125.1, 136.2, 162.1, 169.2, 169.5, 172.2 (2 × C). HRMS (NSI) found $[M+H]^+$ = 353.1346 $C_{16}H_{21}N_2O_7$ requires $[M+H]^+$ = 353.1343.

Ethyl 4-acetoxy-5-{2-[(acetoxymethyl)thio]ethyl}-1-acetyl-1*H*-pyrrole-3-carboxylate, 2.27 From **2.13o** (2.41 g, 7.19 mmol); flash column chromatography [25 % EtOAc in hexane] provided initially *diethyl (acetoxymethylene)malonate* **2.29** as a yellow oil (lit. b.p. 105 – 107 °C at 0.09 mm Hg [88JOC5464]) (0.10 g, 6 %). ν_{max} 2984, 1786, 1720, 1655, 1124, 1074 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.28

– 1.35 (6H, m, 2 × CH_2CH_3), 2.26 (3H, s, $OCOCH_3$), 4.26 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 4.33 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 8.38 (1H, s, CCHO). Further elution afforded *ethyl 5-{2-[(acetoxymethyl)thio]ethyl}-1-acetyl-4-ethoxy-1*H*-pyrrole-3-carboxylate* **2.28** as a yellow oil (0.20 g, 8 %). δ_H (400 MHz, $CDCl_3$) 1.37 – 1.42 (6H, m, $CO_2CH_2CH_3$, OCH_2CH_3), 2.11 (3H, s, CH_2OCOCH_3), 2.59 (3H, s, $NCOCH_3$), 2.84 – 2.88 (2H, m, CH_2CH_2S), 3.18 – 3.22 (2H, m, CH_2CH_2S), 4.04 (2H, q, *J* = 7.0 Hz, $COCH_2CH_3$), 4.33 (2H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 5.22 (2H, s, SCH_2O), 7.57 (1H, s, 2-*H*). δ_C (100 MHz, $CDCl_3$) 14.4, 15.4, 21.2, 23.4, 25.6, 31.2, 60.4, 66.4, 71.0, 113.0, 123.9, 124.5, 144.9, 162.8, 169.1, 170.7. HRMS (APCI) found $[M+NH_4]^+$ = 375.1580 $C_{16}H_{27}N_2O_6S$ requires $[M+NH_4]^+$ = 375.1584. The final fraction provided the **title compound** as white needles (0.47 g, 18 %). m.p. 83 – 84 °C. ν_{max} 3131, 2987, 2941, 1760, 1739, 1703, 1272, 1199, 1147 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.35 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 2.11 (3H, s, CH_2OCOCH_3), 2.36 (3H, s, $OCOCH_3$), 2.62 (3H, s, $NCOCH_3$), 2.84 – 2.88 (2H, m , CH_2CH_2S), 3.12 – 3.15 (2H, m, CH_2CH_2S), 4.29 (2H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 5.29 (2H, s, SCH_2O), 7.64 (1H, s, 2-*H*). δ_C (100 MHz, $CDCl_3$) 14.3, 20.6, 21.1, 23.4, 25.9, 30.7, 60.5, 66.4, 112.5, 123.7, 125.1, 136.4, 162.1, 169.0, 169.4, 170.7. HRMS (NSI) found $[M+Na]^+$ = 394.0926 $C_{16}N_{21}NNaO_7S$ requires $[M+Na]^+$ = 394.0931.

4.2.3 Condensation of Secondary Amino Acids with Diethyl (ethoxycarbonylmethylene)malonate

1-[3-Ethoxy-2-(ethoxycarbonyl)-3-oxoprop-1-en-1-yl]pyrrolidine-2-carboxylic acid, 2.13p From L-proline (Method B: 5.96 g) as a yellow oil (7.26 g, 51 %). ν_{max} 2981, 1731, 1700, 1647, 1591, 1198, 1148, 1074 cm^{-1}. The ^1H NMR spectrum (400 MHz, $CDCl_3$) showed a mixture of rotamers (1:0.6) based on the integrals at δ 7.71 (1H, s, CCHN, *minor isomer*) and δ 8.35 (1H, s, CCHN, *major isomer*). δ_H 1.26 – 1.41 (6H × 2, m, 4 × CH_2CH_3), 1.95 – 2.35 (4H × 2, m, 2 × CH_2CH_2), 3.28 – 3.46 (2H × 2, br. m, 2 × NCH_2), 4.15 – 4.40 (5H × 2, m, 2 × CH_2CH_3, 2 × NCHCOOH), 7.71 (1H, s, CCHN, *minor*), 8.35 (1H, s, CCHN, *major*), 13.40 (v. br. s, COOH). HRMS (NSI) found $[M+H]^+$ = 286.1284 $C_{13}H_{20}NO_6$ requires $[M+H]^+$ = 286.1285.

Attempted preparation of 1-[3-ethoxy-2-(ethoxycarbonyl)-3-oxoprop-1-en-1-yl]piperidine-2-carboxylic acid, 2.13q From DL-pipecolinic acid (Method B: 6.47 g) to give *diethyl 2-(hydroxymethylene)malonate* **2.31** (7.89 g, 84 %) as an orange oil [lit. colourless oil (88JOC5464)]. ν_{max} 2984, 1732, 1645, 1418, 1191, 1076 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.31 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 1.39 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 4.23 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 4.37 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 8.27 (1H, br. d, *J* = 8.0 Hz, CCHOH), 13.32 (1H, br. d, *J* = 13.3 Hz, CHOH). δ_C (100 MHz, $CDCl_3$) 14.0, 14.2, 60.4, 61.8, 100.8, 163.6, 171.1, 174.8.

Attempted preparation of 2-{[3-ethoxy-2-(ethoxycarbonyl)-3-oxoprop-1-en-1-yl](methyl)amino}acetic acid, 2.13r From sarcosine (Method B: 4.45 g; Method D: 4.45 g) to give *diethyl 2-(hydroxymethylene)malonate* **2.31** (Method B: 8.15 g, 87 %) as an orange oil [lit. colourless oil (88JOC5464)] and a mixture of *diethyl malonate* **2.8** and *diethyl 2-(hydroxymethylene)malonate* **2.31** [Method D: 2.98 g, (1:0.15) based on the integrals of the ^{1}H NMR spectrum (400 MHz, $CDCl_3$) at δ 3.38 (2H, s, COC*H*$_2$CO, *major*) and δ 4.36 (2H, q, *J* = 7.1 Hz, C*H*$_2$CH$_3$, *minor*)]. δ_H (400 MHz, $CDCl_3$) *diethyl 2-(hydroxymethylene)malonate* 1.30 (3H, t, *J* = 7.1 Hz, CH$_2$C*H*$_3$), 1.38 (3H, t, *J* = 7.1 Hz, CH$_2$C*H*$_3$), 4.22 (2H, q, *J* = 7.1 Hz, C*H*$_2$CH$_3$), 4.36 (2H, q, *J* = 7.1 Hz, C*H*$_2$CH$_3$), 8.34 (1H, s, CC*H*OH), 13.37 (1H, br. s, O*H*). δ_H (400 MHz, $CDCl_3$) *diethyl malonate* 1.30 (6H, t, *J* = 7.1 Hz, 2 × CH$_2$C*H*$_3$), 3.38 (2H, s, COC*H*$_2$CO), 4.23 (4H, q, *J* = 7.1 Hz, 2 × C*H*$_2$CH$_3$).

Attempted synthesis of ethyl 7-acetoxy-2,3-dihydro-1H-pyrrolizine-6-carboxylate From **2.13p** (2.86 g); flash column chromatography [25 % EtOAc in hexane] provided *diethyl (acetoxymethylene)malonate* **2.29** as a colourless oil (0.85 g, 37 %). Physical and spectroscopic data identical to **2.29** from the cyclisation of **2.13o**.

4.2.4 Aminomethylenation Reactions of Meldrum's Acid (2,2-dimethyl-1,3-dioxane-3,5-dione)

5-(Methoxymethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione, 2.34 2,2-Dimethyl-1,3-dioxane-3,5-dione (28.83 g, 200 mmol) was heated to 50 °C in trimethyl orthoformate (240 mL, 2.19 mol, 11 equiv.) for 3 hours before cooling to room temperature. The reaction mixture was then concentrated under reduced pressure to yield a wet orange solid which was washed with Et_2O and filtered by suction to yield 22.45 g orange solid (60.3 %). m.p. 83 °C (decomp.). ν_{max} 2991, 2960, 1748, 1716, 1593, 1198, 1024 cm^{-1}. δ_H [400 MHz, $(CD_3)_2CO$] 1.68 [6H, s, C(C*H*$_3$)$_2$], 4.35 (3H, s, OC*H*$_3$), 8.24 (1H, s, CC*H*). δ_C [100 MHz, $(CD_3)CO$] 26.4 (2 × C), 65.6, 96.3, 103.7, 157.7, 162.7, 176.1.

General method for the synthesis of 2-{[(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methyl]amino} acids

To the α-amino acid (20 mmol) and triethylamine (3.3 mL, 23.7 mmol, 1.2 equiv.) dissolved in MeCN (25 mL) was added 5-(methoxymethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione **2.34** (3.72 g, 20 mmol, 1 equiv.). The mixture was stirred at reflux under nitrogen until the reaction was complete by TLC and allowed to cool to room temperature. The solvent was removed under reduced pressure and the residue was dissolved in water and acidified with dil. HCl (2 M, aq.). The

product was extracted with EtOAc (3 × 75 mL) and the combined organic portions washed with water (50 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure.

2-{[(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methyl]amino}acetic acid, 2.37a From glycine (1.50 g) as a red/brown solid (3.68 g, 80 %). m.p. 163–165 °C (lit. m.p. 190.5–191 °C [86YZ154]). ν_{max} 3278, 3009, 1734, 1703, 1651, 1627, 1197, 821 cm^{-1}. δ_H [400 MHz, $(CD_3)_2CO$] 1.65 [6H, s, $C(CH_3)_2$], 4.55 (2H, d, *J* = 4.8 Hz, $NHCH_2COOH$), 8.24 (1H, d, *J* = 11.8 Hz, CC*H*), 9.73 (1H, br. s, N*H*), 11.40 (1H, br. s, COO*H*). δ_C [100 MHz, $(CD_3)_2CO$] 26.0 (2 × C), 49.6, 85.1, 103.6, 160.9, 162.9, 164.6, 169.3. HRMS (NSI) found $[M+H]^+$ = 230.0657 $C_9H_{12}NO_6$ requires $[M+H]^+$ = 230.0659.

2-{[(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methyl]amino}propanoic acid, 2.37b From alanine (1.78 g) as a red solid recrystallised from EtOAc/hexane (1.44 g, 30 %). m.p. 175–176 °C (lit. m.p. 171 °C [86YZ154]). ν_{max} 3269, 2997, 1720, 1685, 1607, 1205, 804 cm^{-1}. δ_H [400 MHz, $(CD_3)_2CO$] 1.63 [6H, s, $C(CH_3)_2$], 1.67 (3H, d, *J* = 7.2 Hz, $CHCH_3$), 4.67 (1H, app. quin, NHC*H*COOH), 8.26 (1H, d, *J* = 14.8 Hz, CC*H*), 9.89 (1H, br. s, N*H*). δ_C [100 MHz, $(CD_3)_2CO$] 18.5, 26.0 (2 × C), 56.4, 85.1, 103.6, 158.9, 162.8, 164.7, 171.7. HRMS (NSI) found $[M+H]^+$ = 244.0813 $C_{10}H_{14}NO_6$ requires $[M+H]^+$ = 244.0816.

2-{[(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methyl]amino}-2-phenylacetic acid, 2.37f From phenylglycine (1.92 g, 12.7 mmol) as a red solid, recrystallised from EtOAc/hexane (1.61 g, 42 %). m.p. 178–179 °C. ν_{max} 3279, 3118, 1733, 1719, 1657, 1611, 1452, 1234, 650 cm^{-1}. δ_H [400 MHz, $(CD_3)_2CO$] 1.61 [3H, s, $C(CH_3)_a(CH_3)_b$], 1.63 [3H, s, $C(CH_3)_a(CH_3)_b$], 5.76 (1H, d, *J* = 5.4 Hz, NHC*H*COOH), 7.42–7.53 (5H, m, Ar-*H*), 8.18 (1H, d, *J* = 11.5 Hz, CC*H*), 10.37 (1H, br. d, N*H*). δ_C [100 MHz, $(CD_3)_2CO$] 26.1 (2 × C), 63.6, 85.8, 103.9, 237.6 (2 × C), 129.2, 129.4 (2 × C), 136.4, 158.5, 162.7, 164.7, 169.9. HRMS (NSI) found $[M+H]^+$ = 306.0968 $C_{15}H_{16}NO_6$ requires $[M+H]^+$ = 306.0972.

4.2.5 Attempted Petasis Reaction of Diethyl 2-(aminomethyene)malonate

Diethyl 2-(aminomethylene)malonate, 2.41 Prepared following the literature procedure [61JA4225]. Diethyl (ethoxymethylene)malonate (37.84 g, 175 mmol) was added to conc. ammonia (8 M, 90 mL, 9.25 equiv.) at 0 °C and the reaction mixture was stirred until crystals formed. The ammonia solution was decanted and to the solid was added ice-water (100 mL). The product was extracted with DCM (3 × 75 mL), washed with water (100 mL), dried (Na_2SO_4) and the solvent removed *in vacuo* to afford the **title compound** as a pale yellow solid (28.28 g, 86 %). m.p. 53 – 56 °C (lit. m.p. 64 – 65.5 °C [61JA4225]). ν_{max} 3383, 3233, 2982, 1674, 1643, 1273, 1054, 669

cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 1.35 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 4.19 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 4.26 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 5.84 (1H, br. s, NH_aH_b), 8.12 (1H, dd, *J* = 8.5, 15.4 Hz, CCHN), 8.70 (1H, br. s, NH_aH_b). δ_C (100 MHz, $CDCl_3$) 14.4 (2 × C), 59.8, 59.9, 92.3, 157.8, 166.0, 168.7.

Attempted preparation of 2-{[3-ethoxy-2-(ethoxycarbonyl)-3-oxoprop-1-en-1-yl]amino}-2-phenylacetic acid, 2.13f

Benzeneboronic acid (1.22 g, 10 mmol) was added to diethyl 2-(aminomethylene)malonate **2.41** (1.87 g, 10 mmol, 1 equiv.) and glyoxylic acid monohydrate (0.91 g, 10 mmol, 1 equiv.) in toluene (30 mL) and the reaction mixture stirred at reflux for 10 days (TLC). The reaction was allowed to cool and the solvent removed under reduced pressure. To the residue was added water and the product extracted with EtOAc (3 × 50 mL). The combined organic portions were washed with water (50 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure to afford an oily brown solid (1.93 g). The ^{1}H NMR spectrum was complex and no structure could be determined.

4.2.6 Mechanistic Studies of Pyrrole Ring Formation

[3-Ethoxy-2-(ethoxycarbonyl)-3-oxoprop-1-en-1-yl]-DL-alanine-1-^{13}C, ^{13}C-2.13b

DL-Alanine-1-^{13}C (1.00 g, 11.2 mmol) was added to KOH (85 %, 0.89 g, 13.5 mmol, 1.2 equiv.) in EtOH (30 mL), before the addition of diethyl (ethoxymethylene)malonate (2.43 g, 11.2 mmol, 1 equiv.). The reaction mixture was stirred for 1 hour at reflux, cooled to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in water and acidified with dil. HCl (2 M, aq.) before extraction with EtOAc (3 × 50 mL). The organic portion was washed with water (100 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure to afford **^{13}C-2.13b** as a colourless solid that was recrystallised from EtOAc/hexane (1.77 g, 61 %). m.p. 99 – 100 °C. ν_{max} 3269, 2978, 2939, 2899, 1678, 1630, 1593, 1227, 796 cm^{-1}. δ_H [400 MHz, $(CD_3)_2SO$] 1.20–1.24 (6H, m, 2 × CH_2CH_3), 1.42 (3H, dd, *J* = 4.4, 7.1 Hz, $CHCH_3$), 4.05 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 4.12 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 4.46–4.38 (1H, app. sex., NHCHCOOH), 8.05 (1H, d, *J* = 14.4 Hz, CCHNH), 9.33 (1H, dd, *J* = 7.6, 14.4 Hz, NH), 13.23 (1H, br. s, COOH). δ_C [100 MHz, $(CD_3)SO$] 14.7, 14.8, 19.5, 55.9 (d, *J* = 56.3 Hz), 59.3, 59.4, 89.7, 158.8 (d, *J* = 2.0 Hz), 166.6, 168.3, 173.6. HRMS (ESI) found $[M+H]^+$ = 261.1208 $^{13}CC_{10}H_{18}NO_6$ requires $[M+H]^+$ = 261.1207

Attempted preparation of Dibutyl 2-(ethoxymethylene)malonate, 2.45 Following a literature procedure [85USP4503074]. To a solution of diethyl (ethoxymethylene)malonate (21.94 g, 100

mmol) in *n*-butanol (14.99 g, 200 mmol, 2 equiv.) was added a catalytic amount of *p*-toluenesulfonic acid (10 mg) and the mixture heated to reflux with stirring for 15 minutes. The mixture was then distilled to remove ethanol formed in the reaction; the product was further purified by Kügelrohr distillation {b.p. 170 °C, 4.0 × 10^{-1} mbar [lit. b.p. 143-145 °C at 1.6 mbar (85USP4503074)]} to afford *diethyl 2-(butoxymethylene)malonate* (**2.46**) as a colourless oil (21.77 g, 88 %). ν_{max} 2961, 2875, 1705, 1630, 1176, 1078 cm^{-1}. δ_H (500 MHz, $CDCl_3$) 0.96 (3H, t, *J* = 7.4 Hz, $CH_2CH_2CH_3$), 1.30 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 1.33 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 1.38 – 1.47 (2H, m, $CH_2CH_2CH_3$), 1.69 – 1.75 (2H, m, $CH_2CH_2CH_3$), 4.14 (2H, t, *J* = 6.6 Hz, OCH_2CH_2), 4.23 (2H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 4.29 (2H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 7.61 (1H, s, CCHOBu).

Dimethyl (dimethylaminomethylene)malonate, 2.47 A mixture of dimethyl malonate (9.83 g, 75 mmol) and *N,N*–dimethylformamide dimethyl acetal (25 mL, 188 mmol, 2.5 equiv.) was stirred under nitrogen at reflux. After 6 h the mixture was allowed to cool to room temperature, before the addition of brine (50 mL) and extraction with EtOAc (4 × 20 mL). The organic layer was washed with brine (50 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure. The resulting yellow oil slowly solidified and was recrystallised from EtOAc/hexane as a yellow crystalline solid (10.56 g, 76 %). m.p. 66 – 67 °C (lit. m.p. = 65 – 67 °C [69JA6683]) ν_{max} 2955, 1713, 1681, 1592, 1203, 1074 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 3.01 [6H, br. s, $N(CH_3)_2$], 3.72 (3H, s, CO_2CH_3), 3.79 (3H, s, CO_2CH_3), 7.57 [1H, s, CCHN$(CH_3)_2$]. δ_C (100 MHz, $CDCl_3$) 51.4 (2 × C), 51.7 (2 × C), 92.1, 154.2, 167.8. HRMS (NSI) found $[M+H]^+$ = 188.0914 $C_8H_{14}N_1O_4$ requires $[M+H]^+$ = 188.0917.

2-{[3-Methoxy-2-(methoxycarbonyl)-3-oxoprop-1-en-1-yl]amino}propanoic acid, 2.48 To a solution of dimethyl (dimethylaminomethylene)malonate **2.47** (4.70 g, 25 mmol) in MeOH (60 mL), was added DL-alanine (2.69 g, 30 mmol, 1.2 equiv.) and sodium acetate trihydrate (4.08 g, 30 mmol, 1.2 equiv.) dissolved in the minimum amount of water. The solution was stirred for 4 h at reflux before the volume was reduced. The resulting yellow oil was dissolved in ice-water (60 mL) and the solution acidified with dil. HCl (2M, aq.). The product was extracted with EtOAc (3 × 50 mL), washed with water, dried (Na_2SO_4) and the solvent removed under reduced pressure to yield a yellow oil (3.45 g, 59 %). ν_{max} 2954, 1716, 1662, 1606, 1223, 1140, 1081 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.60 (3H, d, *J* = 7.2 Hz, $CHCH_3$), 3.74 (3H, s, CO_2CH_3), 3.80 (3H, s, CO_2CH_3), 4.13 – 4.20 (1H, m, NCHCOOH), 8.05 (1H, d, *J* = 14.1 Hz, CCHN), 9.53 (1H, dd, *J* = 7.6, 14.1 Hz, NH), 9.83 (1H, br. s, COOH). δ_C (100 MHz, $CDCl_3$) 19.3, 51.4 (2 × C), 56.6, 90.5, 158.6, 166.7, 169.2, 175.5. HRMS (NSI) found $[M+H]^+$ = 232.0815 $C_9H_{14}NO_6$ requires $[M+H]^+$ = 232.0816.

Methyl 4-acetoxy-1-acetyl-5-methyl-1*H*-pyrrole-3-carboxylate, 2.50 2-{[3-Methoxy-2-(methoxycarbonyl)-3-oxoprop-1-en-1-yl]amino}propanoic acid, **2.48** (1.16 g, 5 mmol) was dissolved in acetic anhydride (30 mL) prior to the addition of triethylamine (10 mL). The mixture was refluxed until the emission of CO_2 was complete (limewater bubbler) and allowed to cool to room temperature. The brown solution was poured into water (400 mL), stirred for 1 h and extracted with DCM (5 × 50 mL). The organic layer was washed with water (2 × 100 mL), aq. $NaHCO_3$ (5 × 50 mL) and water (100 mL). The dried (Na_2SO_4) solvent was removed under reduced pressure and the products were isolated by flash column chromatography [20 % EtOAc in hexane]. Initial elution provided *methyl 1-acetyl-4-methoxy-5-methyl-1*H*-pyrrole-3-carboxylate* (**2.49**) as a yellow solid (0.03 g, 3 %). δ_H (400 MHz, $CDCl_3$) 2.41 (3H, s, C*H*$_3$), 2.56 (3H, s, NCOC*H*$_3$), 3.79 (3H, s, CO_2C*H*$_3$), 3.86 (3H, s, OC*H*$_3$), 7.55 (1H, s, 2-*H*). δ_C (100 MHz, $CDCl_3$) 11.1, 23.4, 51.5, 62.4, 112.3, 122.5, 122.8, 145.0, 163.4, 169.2. HRMS (ESI) found $[M+H]^+$ = 212.0918 $C_{10}H_{14}NO_4$ requires $[M+H]^+$ = 212.0917. Further elution provided the **title compound** as a white solid (0.80 g, 67 %). m.p. = 115 – 117 °C. ν_{max} 3161, 2980, 1769, 1735, 1708, 1181, 1123 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.34 (3H, s, OCOC*H*$_3$), 2.35 (3H, s, C*H*$_3$), 2.58 (3H, s, NCOC*H*$_3$), 3.81 (3H, s, CO_2C*H*$_3$), 7.62 (1H, s, 2-*H*). δ_C (100 MHz, $CDCl_3$) 11.3, 20.5, 23.3, 51.5, 111.8, 122.8, 123.3, 135.3, 162.7, 169.0, 169.5. HRMS (NSI) found $[M+H]^+$ = 240.0867 $C_{11}H_{14}NO_5$ requires $[M+H]^+$ = 240.0866.

Attempted synthesis of 2-[(3-ethoxy-3-oxoprop-1-en-1-yl)amino]propanoic acid, 2.52, from ethyl 3-ethoxyacrylate To DL-alanine (2.68 g, 30 mmol) in acetonitrile (45 mL) was added triethylamine (5 mL, 35.9 mmol, 1.2 equiv.) followed by ethyl 3-ethoxyacrylate (4.3 mL, 30 mmol, 1 equiv.), the reaction was stirred at reflux under nitrogen for 3 days. The reaction mixture was allowed to cool and the solvent removed under reduced pressure, the residue was dissolved in water and washed with EtOAc (3 × 20 mL), the aqueous phase was acidified (2M HCl) and the product extracted with EtOAc (3 × 20 mL). The organic portions were washed with water, dried (Na_2SO_4) and the solvent removed under reduced pressure to provide only ethyl 3-ethoxyacrylate.

Attempted synthesis of 2-[(3-ethoxy-3-oxoprop-1-en-1-yl)amino]propanoic acid, 2.52, from ethyl propiolate and sodium alaninate Sodium (1.22 g, 55 mmol, 1.1 equiv.) was dissolved in EtOH (80 mL) under nitrogen at room temperature prior to the addition of alanine (4.91 g, 55 mmol, 1.1 equiv.) followed by ethyl propiolate (5 mL, 49.3 mmol). The reaction mixture was stirred for 2.5 hours at room temperature under nitrogen, and the solvent removed under reduced pressure. The residue was dissolved in water, acidified (2M HCl) and extracted with EtOAc (3 × 75 mL). The

organic portions were washed with water, dried (Na_2SO_4) and the solvent removed under reduced pressure. The ^1H NMR spectrum was complex and no structure could be determined.

Attempted synthesis of 2-[(3-ethoxy-3-oxoprop-1-en-1-yl)amino]propanoic acid, 2.52, from ethyl propiolate and alanine To a solution of alanine (2.67 g, 30 mmol) and triethylamine (5 mL, 35.9 mmol, 1.2 equiv.) in acetonitrile (50 mL) was added ethyl propiolate (3 mL, 30 mmol, 1 equiv.). The reaction was stirred under nitrogen at room temperature for 2 days and the solvent removed under reduced pressure. The residue was dissolved in water, acidified (2M HCl) and extracted with DCM (3 × 50 mL). The organic portions were washed with water, dried (Na_2SO_4) and the solvent removed under reduced pressure to afford a brown solid which was purified by FCC [20 % EtOAc in hexane]. Elution provided *(2*E*,2'*E*)-diethyl 3,3'-oxydiacrylate* **2.55** as a colourless solid (0.41 g, 6 %). m.p. 109 – 111 °C (lit. m.p. 110 – 111 °C [72JCS(P1)904]). ν_{max} 3087, 2985, 2940, 1712, 1677, 1610, 1119, 1096, 847 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.29 (6H, t, *J* = 7.1 Hz, 2 × CH_2CH_3), 4.21 (4H, q, *J* = 7.1 Hz, 2 × CH_2CH_3), 5.65 (2H, d, *J* = 12.2 Hz, 2 × OC*H*CH), 7.58 (2H, d, *J* = 12.1 Hz, 2 × CHC*H*CO). δ_C (100 MHz, $CDCl_3$) 14.3 (2 × C), 60.5 (2 × C), 104.3 (2 × C), 157.3 (2 × C), 166.1 (2 × C).

Potassium (*E*)-2-[(4-ethoxy-4-oxobut-2-en-2-yl)amino]acetate, 2.57a To glycine (7.50 g, 0.1 mol) and potassium hydroxide (85 %, 6.60 g, 0.1 mol, 1 equiv.) in methanol (70 mL) was added ethyl acetoacetate (12.6 mL, 0.1 mol, 1 equiv.). The mixture was refluxed with stirring for 1 h and allowed to cool to room temperature at which point a precipitate formed. The solid was washed with cold methanol, diethyl ether and hexane and dried by suction to yield an off-white solid (22.10 g, 98 %). m.p. 176 – 177 °C. ν_{max} 3404, 3319, 2981, 2939, 1644, 1626, 1582, 779 cm^{-1}. δ_H [400 MHz, $(CD_3)_2SO$] 1.13 (3H, t, *J* = 7.0 Hz, CH_2CH_3), 1.82 (3H, s, CC*H*$_3$), 3.44* (1H, d, *J* = 8.5 Hz, C*H*$_a$H$_b$) 3.94 (2H, q, *J* = 7.0 Hz, C*H*$_2$CH$_3$), 4.24 (1H, d, *J* = 8.5 Hz, CH$_a$*H*$_b$), 8.82 (1H, br. s, N*H*). δ_C [100 MHz, $(CD_3)_2SO$] 15.2, 20.5, 47.7, 57.5, 80.0, 161.2, 169.3, 170.8. HRMS (NSI) found $[M\text{-}K]^-$ = 186.0773 $C_8H_{12}NO_4$ requires $[M\text{-}K]^-$ = 186.0772.

***** overlaps with residual H_2O in NMR solvent

Ethyl 4-acetoxy-1-acetyl-2-methyl-1*H*-pyrrole-3-carboxylate, 2.60a Potassium (*E*)-2-[(4-ethoxy-4-oxobut-2-en-2-yl)amino]acetate **2.57a** (2.25 g, 10 mmol) was dissolved in acetic anhydride (30 mL). The mixture was stirred at reflux until the emission of CO_2 was complete (limewater bubbler) and allowed to cool to room temperature. The solution was poured into water (400 mL), stirred for 1 h and extracted with DCM (5 × 50 mL). The organic layer was washed with water (2 × 100

mL), aq. $NaHCO_3$ (5 × 50 mL) and water (100 mL). The dried (Na_2SO_4) solvent was removed under reduced pressure and the products were isolated by flash column chromatography [20 % EtOAc in hexane]. Initial elution provided *ethyl 1-acetyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylate* (**2.61**) as an off-white solid (0.02 g, 1 %). m.p. 88 – 89 °C. ν_{max} 3149, 2986, 2926, 1732, 1693, 1231 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.36 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 2.18 (3H, s, 4-CH_3), 2.53 (3H, s, NCOCH_3), 2.79 (3H, s, 2-CH_3), 4.30 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 6.77 (1H, s, 5-*H*). δ_C (100 MHz, $CDCl_3$) 12.7, 14.3, 14.6, 24.7, 59.9, 117.1, 122.9, 139.6, 165.6, 169.4. Further elution provided the **title compound** as a yellow solid (0.10 g, 4 %). m.p. 98 – 100 °C. ν_{max} 3144, 2981, 1767, 1736, 1695, 1223, 1195 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.34 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 2.29 (3H, s, OCOCH_3), 2.54 (3H, s, NCOCH_3), 2.81 (3H, s, 2-CH_3), 4.27 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 6.96 (1H, s, 5-*H*). δ_C (100 MHz, $CDCl_3$) 14.3, 14.5, 20.8, 24.6, 60.2, 110.0, 110.7, 137.4, 138.4, 163.3, 169.2, 169.3. HRMS (ESI) found $[M+Na]^+$ = 276.0843 $C_{12}H_{15}NNaO_5$ requires $[M+Na]^+$ = 276.0842.

Potassium (*E*)-2-[(4-ethoxy-4-oxobut-2-en-2-yl)amino]propanoate, 2.57b To DL-alanine (8.92 g, 0.1 mol) and potassium hydroxide (85 %, 6.60 g, 0.1 mol, 1 equiv.) in methanol (70 mL) was added ethyl acetoacetate (12.6 mL, 0.1 mol, 1 equiv.). The mixture was stirred for 1 h at reflux and allowed to cool to room temperature at which a precipitate formed. The precipitate was washed with acetone and dried by suction to yield an off-white solid (17.56 g, 74 %). m.p. 125 - 127 °C. ν_{max} 3288, 2975, 2929, 1644, 1590, 1556, 1508, 1271, 1145 cm^{-1}. δ_H (400 MHz, CD_3OD) 1.23 (3H, t, *J* = 7.0 Hz, CH_2CH_3), 1.42 (3H, d, *J* = 6.9 Hz, $CHCH_3$), 1.94 (3H, s, CCH_3). 3.97 – 4.07 (3H, m, CH_2CH_3, $CHCH_3$), 4.40 (1H, s, CC*H*), 8.87 (1H, br. d, N*H*). δ_C (100 MHz, CD_3OD) 13.6, 18.1, 19.7, 53.6, 57.8, 80.8, 161.2, 170.6, 179.0. HRMS (NSI) found $[M-K]^-$ = 200.0929 $C_9H_{14}NO_4$ requires $[M-K]^-$ = 200.0928.

Ethyl 4-acetoxy-1-acetyl-2,5-dimethyl-1*H*-pyrrole-3-carboxylate, 2.60b Potassium (*E*)-2-[(4-ethoxy-4-oxobut-2-en-2-yl)amino]propanoate **2.57b** (2.39 g, 10 mmol) was dissolved in acetic anhydride (30 mL). The mixture was stirred at reflux until the emission of CO_2 was complete (limewater bubbler) and allowed to cool to room temperature. The solution was poured into water (400 mL), stirred for 1 h and extracted with DCM (5 × 50 mL). The organic layer was washed with water (2 × 100 mL), aq. $NaHCO_3$ (5 × 50 mL) and water (100 mL). The dried (Na_2SO_4) solvent was removed under reduced pressure and the products were isolated by flash column chromatography [20 % EtOAc in hexane]. Elution provided the **title compound** as a yellow solid (0.24 g, 9 %). ν_{max} 3339, 2981, 1701, 1200, 1130 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.32 (3H, t, *J* = 7.1 Hz,

CH_2CH_3), 2.21 (3H, s, 5-CH_3), 2.31 (3H, s, OCOCH_3), 2.58 (3H, s, NCOCH_3), 2.69 (3H, s, 2-CH_3), 4.25 (2H, q, *J* = 7.1 Hz, CH_2CH_3). δ_C (100 MHz, $CDCl_3$) 11.3, 14.3, 14.4, 20.6, 27.8, 60.0, 109.2, 119.2, 134.7, 135.1, 163.5, 169.6, 171.3. HRMS (ESI) found $[M+Na]^+$ = 290.0991 $C_{13}H_{17}NNaO_5$ requires $[M+Na]^+$ = 290.0999.

2-*tert*-Butyl-4-ethyl-3,5-dimethyl-1*H*-pyrrole-2,4-dicarboxylate, 2.63 To a stirring solution of *tert*-butyl acetoacetate (16.5 mL, 100 mmol) in acetic acid (20 mL) in an ice bath was added $NaNO_2$ (7.97 g, 116 mmol, 1.16 equiv.) in water (20 mL) dropwise over 2 hours, the temperature was maintained at < 10 °C. Upon completion of the addition, the reaction mixture was stirred overnight and allowed to warm to room temperature. A solution of ethyl acetoacetate (14.1 mL, 111 mmol, 1.11 equiv.) in acetic acid (50 mL) was heated to 60 °C and zinc powder (5 g) added. The nitroso ester solution was added dropwise alongside the addition of 20 g zinc powder (in 2.5 g portions) over a 40 min period. The reaction temperature was monitored and kept below 85 °C. The reaction was stirred for 1 hour at 60 °C before the addition of water (50 mL) and stirred for a further 1 hour. The reaction mixture was poured onto ice-water (300 mL) and stirred for 90 min in an ice-bath, the resulting white precipitate and zinc were filtered off and the product dissolved in hot EtOH/EtOAc (1:1). The hot mixture was filtered through celite and the solvent removed under reduced pressure, to the residue was added MeCN. The slurry was placed in the freezer overnight and the solid removed by vacuum filtration to afford the **title compound** as an off-white solid (12.32 g, 46 %). m.p. 131 – 134 °C (lit. m.p. 131 – 133 °C [09JA8578]). ν_{max} 3658, 3298, 2980, 2889, 1700, 1654, 1158, 1084, 778 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.36 (3H, t, *J* = 7.01 Hz, CH_2CH_3), 1.58 [6H, s, $C(CH_3)_3$], 2.51 (3H, s, 2-CH_3), 2.54 (3H, s, 4-CH_3), 4.29 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 9.19 (1H, br. s, N*H*). δ_C (100 MHz, $CDCl_3$) 12.0, 14.3, 14.4, 28.5 (3 × C), 59.4, 81.2, 113.4, 119.2, 130.0, 138.4, 161.3, 165.6. HRMS (NSI) found $[M+H]^+$ = 268.1543 $C_{14}H_{22}NO_4$ requires $[M+H]^+$ = 268.1543.

Ethyl 2,4-dimethyl-1*H*-pyrrole-3-carboxylate, 2.64 Concentrated HCl (9.1 mL) was added to a suspension of 2-(*tert*-butyl) 4-ethyl 3,5-dimethyl-1*H*-pyrrole-2,4-dicarboxylate **2.63** (6.52 g, 24.4 mmol) in EtOH (40 mL). The reaction mixture was stirred at 75 °C for 8.5 hours and diluted with 80 mL water. The reaction was left to stand overnight with cooling (ice-bath) and the resulting solid was filtered off and washed with hexane to afford the **title compound** as pink crystals (2.83 g, 69 %). m.p. 73 – 74 °C (lit. m.p. 72 – 74 °C [09JA8578]). ν_{max} 3645, 3300, 2980, 1660, 1263, 1090 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.35 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 2.24 (3H, d, *J* = 0.9 Hz, 4-CH_3), 2.49 (3H, s, 2-CH_3), 4.27 (2H, q, *J* = 7.1Hz, CH_2CH_3), 6.35 (1H, d, *J* = 0.9 Hz, 5-*H*), 8.03 (1H, br. s, N*H*). δ_C (100 MHz,

$CDCl_3$) 12.6, 14.1, 14.5, 59.1, 110.8, 114.2, 121.6, 135.9, 166.3. HRMS (NSI) found $[M+H]^+$ = 168.1017 $C_9H_{14}NO_2$ requires $[M+H]^+$ = 168.1019.

Ethyl 1-acetyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylate, 2.61 To a solution of ethyl 2,4-dimethyl-1*H*-pyrrole-3-carboxylate **2.64** (2.60 g, 24 mmol) in acetic anhydride (100 mL) and pyridine (100 mL) was added a catalytic amount of DMAP, the reaction was stirred at 60 °C for 2 days. The mixture was allowed to cool and diluted with water (200 mL) and the product extracted with EtOAc (3 × 200 mL). The organic portions were combined, washed with water (200 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure. The product was purified by flash column chromatography [20 % EtOAc in hexane] to afford the **title compound** as a yellow solid (1.50 g, 46 %). m.p. 88 – 89 °C. ν_{max} 3660, 3149, 2981, 2927, 1731, 1693, 1230 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.36 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 2.18 (3H, s, 4-CH_3), 2.53 (3H, s, NCOCH_3), 2.79 (3H, s, 2-CH_3), 4.30 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 6.77 (1H, s, 5-*H*). δ_C (100 MHz, $CDCl_3$) 12.7, 14.4, 14.6, 24.7, 59.9, 117.1, 117.7, 122.9, 139.6, 165.6, 169.4. HRMS (NSI) found $[M+H]^+$ = 210.1124 $C_{11}H_{16}NO_3$ requires $[M+H]^+$ = 210.1125. Further elution returned starting material **2.64** (0.47 g, 18 % recovered).

Dimethyl 1-[3-ethoxy-2-(ethoxycarbonyl)-3-oxoprop-1-en-1-yl]-2,5-dimethyl-1*H*-pyrrole-3,4-dicarboxylate, 2.65 To 2-{[3-ethoxy-2-(ethoxycarbonyl)-3-oxoprop-1-en-1-yl]amino}propanoic acid **2.13b** (2.61 g, 10 mmol) in acetic anhydride (30 mL) was added DMAD (3.1 mL, 25 mmol, 2.5 equiv.). The reaction mixture was stirred at reflux until the evolution of CO_2 ceased. The solvent was removed under reduced pressure and the product purified by flash column chromatography [25 % EtOAc in hexane]. The **title compound** was obtained as a yellow crystalline solid (2.00 g, 52 %). m.p. 100 - 102 °C. ν_{max} 2982, 1741, 1723, 1699, 1203, 1078 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.13 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 1.39 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 2.32 (6H, s, 2 × CH_3), 3.85 (6H, s, 2 × CO_2CH_3), 4.17 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 4.38 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 7.59 (1H, s, CC*H*). δ_C (100 MHz, $CDCl_3$) 11.6 (2 × C), 13.7, 14.1, 56.1 (2 × C), 62.3, 62.6, 114.1 (2 × C), 130.9, 134.0 (2 × C), 137.2, 162.2, 162.4, 165.4 (2 × C). HRMS (APCI) found $[M+H]^+$ = 382.1494 $C_{18}H_{24}NO_8$ $[M+H]^+$ = 382.1496.

Dimethyl 1-acetyl-2-methyl-1*H*-pyrrole-3,4-dicarboxylate, 2.69 To ethyl 4-acetoxy-1-acetyl-5-methyl-1*H*-pyrrole-3-carboxylate **2.18b** (2.53 g, 10 mmol) in xylenes (40 mL) was added DMAD (1.3 mL, 10.5 mmol, 1.05 equiv.). The reaction mixture was stirred at reflux until the evolution of CO_2 ceased. The solvent was removed under reduced pressure and the product purified by flash column chromatography [50 % EtOAc in hexane]. Initially, unreacted DMAD was recovered (0.15 g). Further elution provided the **title compound** as a yellow solid (1.37 g, 57 %). m.p. 100 - 103 °C.

ν_{max} 3619, 2955, 1731, 1709, 1186, 1086, 1053 cm^{-1}. δ_H (500 MHz, $CDCl_3$) 2.62 (3H, s, CH_3), 2.64 (3H, s, NCOCH_3), 3.85 (3H, s, CO_2CH_3), 3.89 (3H, s, CO_2CH_3), 7.59 (1H, s, CCH). δ_C (125 MHz, $CDCl_3$) 14.1, 24.3, 51.9, 52.1, 117.6 (2 × C), 124.6, 136.7, 163.4, 165.1, 169.1. HRMS (APCI) found $[M+H]^+$ = 240.0864 $C_{11}H_{14}NO_5$ $[M+H]^+$ = 240.0866.

2-{[3-Ethoxy-2-(ethoxycarbonyl)-3-oxoprop-1-en-1-yl]amino}-2-methylpropanoic acid, 2.77 From 2-aminoisobutyric acid (Method B: 5.16 g) as a yellow crystalline solid (10.93 g, 80 %). m.p. 89 – 93 °C. ν_{max} 2987, 2939, 1242, 1158, 807 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.30 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 1.34 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 1.63 [6H, s, $C(CH_3)_2$], 4.19 – 4.28 (4H, m, 2 × CH_2CH_3), 8.13 (1H, d, *J* = 14.4 Hz, CC*H*NH), 9.52 (1H, br. s, COO*H*), 9.85 (1H, d, *J* = 14.4 Hz, N*H*). δ_C (100 MHz, $CDCl_3$) 14.3, 14.4, 26.0 (2 × C), 59.0, 60.1, 60.2, 91.0, 156.1, 167.0, 169.0, 177.0. HRMS (NSI) found $[M+H]^+$ = 274.1287 $C_{12}H_{20}NO_6$ requires $[M+H]^+$ = 274.1285.

Attempted cyclisation of 2-{[3-ethoxy-2-(ethoxycarbonyl)-3-oxoprop-1-en-1-yl]amino}-2-methylpropanoic acid From **2.77** (2.73 g); flash column chromatography [gradient 1 % MeOH in DCM → 10 % MeOH in DCM] afforded *diethyl 2-(3-acetyl-4,4-dimethyl-5-oxooxazolidin-2-yl)malonate* **2.78** as a pale yellow oil (1.23 g, 39 %). ν_{max} 2982, 1803, 1729, 1653, 1228, 1091 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.26 – 1.33 (6H, m, 2 × CH_2CH_3), 1.65 [3H, s, $C(CH_3)_a(CH_3)_b$], 1.73 [3H, s, $C(CH_3)_a(CH_3)_b$], 2.20 (3H, s, NCOCH_3), 4.17 – 4.30 (4H, m, 2 × CH_2CH_3), 4.47 [1H, br. d, *J* = 2.7 Hz, CH(CO_2Et)$_2$], 6.30 (1H, d, *J* = 2.7 Hz, OC*H*N). δ_C (100 MHz, $CDCl_3$) 14.0 (2 × C), 22.9, 24.6, 26.7, 53.5, 58.5, 61.8, 62.2, 86.0, 165.5, 165.8, 169.3, 174.6. HRMS (NSI) found $[M+H]^+$ = 316.1391 $C_{14}H_{22}NO_7$ requires $[M+H]^+$ = 316.1391.

4.3 Chapter 3 Experimental

4.3.1 Synthesis of Ethyl 2-(1-carboxyalkylaminomethylene)cyanoactates (2-[(2-cyano-3-ethoxy-3-oxoprop-1-en-1-yl)amino] acids)

General Procedure for the synthesis of 2-[(2-cyano-3-ethoxy-3-oxoprop-1-en-1-yl)amino] acids

The α-amino acid (50 mmol) was added to KOH (85%, 3.96 g, 60 mmol, 1.2 equiv.) in EtOH (70 mL), before the addition of ethyl (*E*)-(ethoxymethylene)cyanoacetate (8.46 g, 50 mmol, 1 equiv.). The reaction mixture was stirred for 1 h at reflux and the solvent was removed under reduced pressure. The residue was dissolved in water and acidified with dil. HCl (2 M, aq.) before extraction

with EtOAc (3 × 50 mL). The organic extracts were washed with water (100 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure.

The following compounds were synthesised by the above method.

(*E/Z*)-2-[(2-Cyano-3-ethoxy-3-oxoprop-1-en-1-yl)amino]acetic acid, 3.7a From glycine (3.75 g; 2 × Scale: 7.50 g) as a pale yellow solid from EtOAc and hexane (4.51 g, 46 %; 2 × Scale: 17.53 g, 88 %). m.p. 143 – 146 °C. ν_{max} 3283, 2983, 2210, 1736, 1708, 1693, 1682, 1621, 1211 cm^{-1}. The ^1H NMR spectrum [400 MHz, $(CD_3)_2SO$] showed the presence of both the *E*- and *Z*- isomers in a 0.7:1 ratio based on the integrals at δ 7.75 (1H, d, *J* = 14.4 Hz, CC*H*N, *major*) and δ 8.01 (1H, d, *J* = 15 Hz, CC*H*N, *minor*). δ_H [400 MHz, $(CD_3)_2SO$] 1.16 – 1.24 (3H × 2, m, 2 × CH_2CH_3), 4.08 – 4.18 (2H × 4, m, 2 × CH_2CH_3, 2 × $NHCH_2COOH$), 7.75 (1H, d, *J* = 14.4 Hz, CC*H*N, *major*), 8.01 (1H, d, *J* = 15 Hz, CC*H*N, *minor*), 8.65 (1H, dt, *J* = 5.9, 15 Hz, N*H*, *minor*), 9.13 (1H, dt, *J* = 5.8, 14.4 Hz, N*H*, *major*), 13.02 (1H × 2, br. s, 2 × COO*H*) . δ_C [100 MHz, $(CD_3)_2SO$] 14.8, 14.9, 49.3, 49.8, 60.2, 60.3, 69.9, 70.9, 117.0, 119.4, 161.5, 161.6, 165.4, 166.8, 171.1, 171.4. HRMS (NSI) found $[M+H]^+$ = 199.0713 $C_8H_{11}N_2O_4$ requires $[M+H]^+$ = 199.0713.

(*E/Z*)-2-[(2-Cyano-3-ethoxy-3-oxoprop-1-en-1-yl)amino]propanoic acid, 3.7b From DL-alanine (4.45 g) as a pale yellow solid from EtOAc and hexane (6.69 g, 63 %). m.p. 104 – 107 °C. ν_{max} 2981, 2222, 1723, 1676, 1610, 1152, 1126 cm^{-1}. The ^1H NMR spectrum [400 MHz, $(CD_3)_2SO$] showed the presence of both the *E*- and *Z*- isomers in a 0.7:1 ratio based on the integrals at δ 7.88 (1H, d, *J* = 14.2 Hz, CC*H*N, *major*) and δ 7.99 (1H, d, *J* = 14.9 Hz, CC*H*N, *minor*). δ_H [400 MHz, $(CD_3)_2SO$] 1.18 – 1.24 (3H × 2, m, 2 × CH_2CH_3), 1.40 (3H, d, *J* = 7.2 Hz, $CHCH_3$, *minor*), 1.44 (3H, d, *J* = 7.2 Hz, $CHCH_3$, *major*), 4.08 – 4.18 (2H × 4, m, 2 × CH_2CH_3), 4.29 – 4.42 (1H × 2, m, 2 × NHC*H*COOH), 7.88 (1H, d, *J* = 14.2 Hz, CC*H*N, *major*), 7.99 (1H, d, *J* = 14.9 Hz, CC*H*N, *minor*), 8.84 (1H, dd, *J* = 8.0, 14.9 Hz, N*H*, *minor*), 9.28 (1H, dd, *J* = 7.4, 14.2 Hz, N*H*, *major*), 13.14 (1H × 2, br. s, 2 × COO*H*). δ_C [100 MHz, $(CD_3)_2SO$] 14.7, 14.9, 17.6, 19.0, 55.9, 56.9, 60.2 (2 × C), 70.1, 70.5, 117.1, 119.3, 165.6, 167.2, 173.2, 173.4. HRMS (NSI) found $[M+H]^+$ = 213.0871 $C_9H_{13}N_2O_4$ requires $[M+H]^+$ = 213.0870.

(*E/Z*)-2-[(2-Cyano-3-ethoxy-3-oxoprop-1-en-1-yl)amino]-2-phenylacetic acid, 3.7c From DL-2-phenylglycine (7.56 g) as a pale yellow solid (11.06 g, 81 %). m.p. 166 – 167 °C. ν_{max} 3222, 2979, 2225, 1723, 1685, 1615, 1218, 1188 cm^{-1}. The ^1H NMR spectrum [400 MHz, $(CD_3)_2SO$] showed the presence of both the *E*- and *Z*- isomers in a 0.4:1 ratio based on the integrals at δ 7.85 (1H, d, *J* = 14.0 Hz, CC*H*N, *major*) and δ 7.98 (1H, d, *J* = 14.6 Hz, CC*H*N, *minor*). δ_H [400 MHz, $(CD_3)_2SO$] 1.15 –

1.25 (3H × 2, m, 2 × CH_2CH_3), 4.00 – 4.21 (2H × 2, m, 2 × CH_2CH_3), 5.47 (1H, d, *J* = 7.4 Hz, NHC*H*COOH, *major*), 5.56 (1H, d, *J* = 7.4 Hz, NHC*H*COOH, *minor*), 7.35 – 7.47 (5H × 2, m, 2 × Ar-*H*), 7.85 (1H, d, *J* = 14.0 Hz, CC*H*N, *major*), 7.98 (1H, d, *J* = 14.6 Hz, CC*H*N, *minor*), 9.30 (1H, dd, *J* = 7.4, 14.6 Hz, N*H*, *minor*), 9.67 (1H, dd, *J* = 7.4, 14.0 Hz, N*H*, *major*). δ_C [100 MHz, $(CD_3)_2SO$] 14.7, 14.8, 60.3, 60.6, 63.5, 64.4, 71.2, 71.5, 116.7, 118.7, 126.7 (3 × C), 128.8, 128.9, 129.2 (2 × C), 129.4, 129.6 (2 × C), 136.8, 137.5, 159.1, 159.5, 165.4, 167.3, 171.2, 171.5. HRMS (NSI) found $[M+H]^+$ = 276.1029 $C_{14}H_{15}N_2O_4$ requires $[M+H]^+$ = 276.1026.

4.3.2 Synthesis of Pyrroles: Cyclisation of Ethyl 2-(1-carboxyalkylaminomethylene)cyanoactates (2-[(2-cyano-3-ethoxy-3-oxoprop-1-en-1-yl)amino] acids)

General method for the cyclisation of 2-[(2-cyano-3-ethoxy-3-oxoprop-1-en-1-yl)amino] acids

The 2-[(2-Cyano-3-ethoxy-3-oxoprop-1-en-1-yl)amino] acid (10 mmol) was dissolved in acetic anhydride (30 mL) prior to the addition of triethylamine (10 mL). The mixture was refluxed until the emission of CO_2 was complete (limewater bubbler) and allowed to cool to room temperature. The brown solution was poured into water (400 mL), stirred for 1 h and extracted with DCM (5 × 50 mL). The organic layer was washed with water (2 × 100 mL), aq. $NaHCO_3$ (5 × 50 mL) and water (100 mL). The dried (Na_2SO_4) solvent was removed under reduced pressure and the products were isolated by flash column chromatography.

The following compounds were synthesised by the above method.

Ethyl 4-acetamido-1-acetyl-1*H*-pyrrole-3-carboxylate, 3.9a From **3.7a** (1.98 g); flash column chromatography [30 % EtOAc in hexane] provided the **title compound** as a pale yellow solid (1.02 g, 43 %). m.p. 102 – 104 °C. ν_{max} 3357, 3192, 3157, 2981, 1732, 1696, 1674, 1204, 776 cm^{-1}. δ_H [400 MHz, $(CD_3)_2SO$] 1.32 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 2.12 (3H, s, NHCOCH_3), 2.61 (3H, s, NCOCH_3), 4.30 (2H,q, *J* = 7.1 Hz, CH_2CH_3), 7.83 (1H, d, *J* = 2.6 Hz, 2-*H*), 7.94 (1H, d, *J* = 2.6 Hz, 5-*H*), 9.20 (1H, br. s, N*H*COCH$_3$). δ_C [100 MHz, $(CD_3)_2SO$] 14.6, 22.4, 23.9, 60.8, 108.7, 110.0, 123.6, 125.8, 164.5, 168.1, 169.0. HRMS (NSI) found $[M+H]^+$ = 239.1025 $C_{11}H_{15}N_2O_4$ requires $[M+H]^+$ = 239.1026. Large scale reaction from **3.7a** (19.92 g, 100 mmol); flash column chromatography [30 % EtOAc in hexane] provided initially a mixture of *1-acetyl-4-ethoxy-1*H-*pyrrole-3-carbonitrile* (**3.8a**) and *1-acetyl-4-cyano-1*H-*pyrrol-3-yl acetate* (**3.8b**) in a 1:0.08 ratio as an orange solid (0.08 g). ν_{max} 3200, 3144, 2981, 2230, 1766, 1716, 1199, 629 cm^{-1}. δ_H [400 MHz, $(CD_3)_2SO$] 1.33 (3H, t, *J* = 7.0 Hz, CH_2CH_3,

3.8a), 2.32 (3H, s, OCOC*H*$_3$, **3.8b**), 2.54 (3H, s, NCOC*H*$_3$, **3.8a**), 2.59 (3H, s, NCOC*H*$_3$, **3.8b**), 4.00 (2H, q, *J* = 7.0 Hz, C*H*$_2$CH$_3$, **3.8a**), 7.12 (1H, d, *J* = 2.2 Hz, 5-*H*, **3.8a**), 7.57 (1H, d, *J* = 2.4 Hz, 2-*H*, **3.8b**), 8.21 (1H, d, *J* = 2.2 Hz, 2-*H*, **3.8a**), 8.34 (1H, d, *J* = 2.4 Hz, 5-*H*, **3.8b**). δ_C [100 MHz, (CD$_3$)$_2$SO, **3.8a**] 14.8, 22.1, 67.2, 90.1, 100.5, 113.2, 113.9, 127.2, 148.9, 168.2. Further elution provided the **title compound 3.9a** as a pale yellow solid (13.44 g, 56 %).

Ethyl 4-acetamido-1-acetyl-5-methyl-1*H*-pyrrole-3-carboxylate, 3.9b From **3.7b** (2.15 g); flash column chromatography [gradient 30 % EtOAc in hexane → 100 % EtOAc] provided initially *(2*R**,3*S**)-1-acetyl-3-cyano-3-(ethoxycarbonyl)-5-methyl-2,3-dihydro-1*H*-pyrrole-2,4-diyl diacetate* (**3.11**) as a clear colourless oil which crystallised on standing (0.09 g, 3 %). m.p. 89 – 90 °C. ν_{max} 2990, 1775, 1751, 1714, 1667, 1211, 1182 cm^{-1}. δ_H (400 MHz, CDCl$_3$) 1.32 (3H, t, *J* = 7.1 Hz, CH$_2$C*H*$_3$), 2.17 (3H, s, NCOC*H*$_3$), 2.19 (3H, s, CC*H*$_3$), 2.25 (3H, s, CHCOC*H*$_3$), 2.28 (3H, s, CCOC*H*$_3$), 4.29 (2H, q, *J* = 7.1 Hz, C*H*$_2$CH$_3$), 6.87 (1H, s, 2-*H*). δ_C (100 MHz, CDCl$_3$) 13.2, 13.7, 20.0, 20.7, 22.9, 56.4, 64.3, 83.6, 111.7, 125.2, 135.6, 162.9, 168.1, 168.3, 169.3. HRMS (NSI) found $[M+Na]^+$ = 361.1006 $C_{15}H_{18}N_2NaO_7$ $[M+Na]^+$ = 361.1006. Further elution provided *ethyl 1-acetyl-4-(*N*-acetylacetamido)-5-methyl-1*H*-pyrrole-3-carboxylate* (**3.10b**) as a yellow oil which solidified (0.18 g, 6 %). m.p. 76 – 78 °C. ν_{max} 3162, 2981, 1723, 1693, 1221, 1189 cm^{-1}. δ_H (400 MHz, CDCl$_3$) 1.30 (3H, t, *J* = 7.1 Hz, CH$_2$C*H*$_3$), 2.31 [6H, s, N(COC*H*$_3$)$_2$], 2.33 (3H, s, C*H*$_3$), 2.63 (3H, s, NCOC*H*$_3$), 4.25 (2H, q, *J* = 7.1 Hz, C*H*$_2$CH$_3$), 7.76 (1H, s, 2-*H*). δ_C (100 MHz, CDCl$_3$) 12.0, 14.2, 23.6, 26.2 (2 × C), 60.6, 115.0, 123.5, 124.8, 131.2, 162.4, 169.0, 172.9 (2 × C). HRMS (NSI) found $[M+H]^+$ = 295.1287 $C_{14}H_{19}N_2O_5$ requires $[M+H]^+$ = 295.1288. The final fractions provided the **title compound** as a fluffy white solid (1.01 g, 40 %). m.p. 183 – 185 °C. ν_{max} 3268, 3145, 2980, 1741, 1703, 1660, 1267, 1197 cm^{-1}. δ_H (400 MHz, CDCl$_3$) 1.36 (3H, t, *J* = 7.1 Hz, CH$_2$C*H*$_3$), 2.19 (3H, s, NHCOC*H*$_3$), 2.39 (3H, s, C*H*$_3$), 2.58 (3H, s, NCOC*H*$_3$), 4.29 (2H, q, *J* = 7.1 Hz, C*H*$_2$CH$_3$), 7.51 (1H, br. s, N*H*COCH$_3$), 7.59 (1H, s, 2-*S*). δ_C (100 MHz, CDCl$_3$) 14.0, 14.3, 23.6, 23.8, 60.4, 112.9, 121.6, 123.1, 127.6, 163.9, 168.7, 169.0. HRMS (NSI) found $[M+H]^+$ = 253.1184 $C_{12}H_{17}N_2O_4$ requires $[M+H]^+$ = 253.2283.

Ethyl 4-acetamido-1-acetyl-5-phenyl-1*H*-pyrrole-3-carboxylate, 3.9c From **3.7c** (2.74 g); flash column chromatography provided initially *ethyl 1-acetyl-4-(*N*-acetylacetamido)-5-phenyl-1*H*-pyrrole-3-carboxylate* (**3.10c**) as a pale orange solid (0.80 g, 23 %). m.p. 94 – 97 °C. ν_{max} 3138, 3061, 2989, 2924, 1743, 1701, 1203 cm^{-1}. δ_H [400 MHz, (CD$_3$)$_2$SO] 1.24 (3H, t, *J* = 7.1 Hz, CH$_2$C*H*$_3$), 2.10 [6H, s, N(COC*H*$_3$)$_2$], 2.57 (3H, s, NCOC*H*$_3$), 4.22 (2H, q, *J* = 7.1 Hz, C*H*$_2$CH$_3$), 7.21 – 7.23 (2H, m, *o*-Ar-

H), 7.38 – 7.40 (3H, m, *m*-Ar-*H*, *p*-Ar-*H*), 8.24 (1H, s, 2-*H*). δ_C [100 MHz, $(CD_3)_2SO$] 14.6, 24.4, 26.2 (2 × C), 60.5, 114.0, 124.5, 127.4, 128.6 (2 × C), 129.0, 129.4 (2 × C), 130.3, 132.1, 162.5, 169.5, 170.8, 172.9 (2 × C). HRMS (NSI) found $[M+H]^+$ = 357.1445 $C_{19}H_{21}N_2O_5$ requires $[M+H]^+$ = 357.1445. Further elution provided the **title compound** as an orange solid (1.29 g, 41 %). m.p. 140 – 141 °C. ν_{max} 2981, 1716, 1680, 1274, 1199, 1093 cm^{-1}. δ_H [400 MHz, $(CD_3)_2SO$] 1.26 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 1.84 (3H, s, $NHCOCH_3$), 2.55 (3H, s, $NCOCH_3$), 4.19 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 7.29 – 7.37 (5H, m, Ar-*H*), 8.02 (1H, s, 2-*H*), 9.10 (1H, br. s, $NHCOCH_3$). δ_C [100 MHz, $(CD_3)_2SO$] 14.7, 23.0, 24.4, 60.2, 115.7, 123.4, 126.3, 128.0, 128.1 (2 × C), 129.9 (2 × C), 130.7, 131.1, 162.6, 170.8. HRMS (NSI) found $[M+H]^+$ = 315.1339 $C_{17}H_{19}N_2O_5$ requires $[M+H]^+$ = 315.1339.

Attempted synthesis of dimethyl 1-(2-cyano-3-ethoxy-3-oxoprop-1-en-1-yl)-2,5-dimethyl-1*H*-pyrrole-3,4-dicarboxylate, 3.12 To 2-[(2-cyano-3-ethoxy-3-oxoprop-1-en-1-yl)amino]propanoic acid, **3.7b** (2.13 g, 10 mmol) in acetic anhydride (30 mL) was added DMAD (3.1 mL, 25 mmol, 2.5 equiv.). The reaction mixture was stirred at reflux until the evolution of CO_2 ceased. The solvent was removed under reduced pressure and the product purified by flash column chromatography [30 % EtOAc in hexane]. Unreacted DMAD was recovered initially (1.52 g). Further elution provided *dimethyl 1-acetyl-2-methyl-1*H-*pyrrole-3,4-dicarboxylate* (**3.13**) as a yellow solid (0.38 g, 16 %). ν_{max} 2955, 1726, 1712, 1224, 1088, 1076 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.60 (3H, s, CH_3), 2.62 (3H, s, $NCOCH_3$), 3.83 (3H, s, CO_2CH_3), 3.87 (3H, s, CO_2CH_3), 7.58 (1H, s, 5-*H*). δ_C (100 MHz, $CDCl_3$) 14.1, 24.3, 51.9, 52.1, 117.6 (2 × C), 124.6, 136.7, 163.4, 165.1, 169.1. Finally, *ethyl 1-acetyl-4-(*N-*acetylacetamido)-5-methyl-1*H-*pyrrole-3-carboxylate* (**3.10b**) was obtained as an orange oil which solidified on standing (1.39 g, 50 %) and was identical in all respects to that obtained previously.

Dimethyl 1-acetyl-2-methyl-1*H*-pyrrole-3,4-dicarboxylate, 3.13 (**2.69**) To ethyl 4-acetamido-1-acetyl-5-methyl-1*H*-pyrrole-3-carboxylate, **3.7b** (0.76 g, 3.01 mmol) in xylenes (40 mL) was added DMAD (0.4 mL, 3.16 mmol, 1.05 equiv.). The reaction mixture was stirred at reflux until the evolution of CO_2 ceased. The solvent was removed under reduced pressure and the product purified by flash column chromatography [30 % EtOAc in hexane]. Initially unreacted DMAD was recovered (0.28 g). Further elution provided the **title compound** as a yellow solid (0.18 g, 25 %). δ_H (400 MHz, $CDCl_3$) 2.60 (3H, s, CH_3), 2.62 (3H, s, $NCOCH_3$), 3.83 (3H, s, CO_2CH_3), 3.87 (3H, s, CO_2CH_3), 7.58 (1H, s, 5-*H*). IR and HRMS data as described for **2.69** (prepared from **2.18b**).

Ethyl (aminomethylene)cyanoacetate, 3.16 Prepared following a literature procedure [60JA3138]. Ethyl cyanoacetate (5.3 mL, 50 mmol) and formamidine acetate (10.41 g, 100 mmol, 2 equiv.)

were stirred in EtOH (120 mL) at reflux for 16 h. The reaction mixture was allowed to cool and the solvent removed. To the residue was added water and the product extracted with DCM (3 × 75 mL). The combined organic extracts were washed with water (100 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure to afford a white powder (3.92 g, 56 %). m.p. 136 – 139 °C (lit. m.p. 140.5 – 142.5 [60JA3138]). ν_{max} 3380, 3322, 3170, 2981, 2210, 1660, 1326, 1228, 708 cm^{-1}. δ_H (400 MHz, CD_3OD) 1.29 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 4.20 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 7.99 (1H, s, CC*H*N). The ^{13}C NMR spectrum showed the presence of both the *E*- and *Z*-isomers. δ_C (100 MHz, CD_3OD) 13.3 (2 × C), 59.8, 60.1, 70.5, 72.0, 115.5, 118.9, 158.5, 159.0, 166.3, 167.1.

Attempted preparation of (*E/Z*)-2-[(2-cyano-3-ethoxy-3-oxoprop-1-en-1-yl)amino]-2-phenylacetic acid, 3.19 Benzeneboronic acid (1.22 g, 10 mmol) was added to ethyl (aminomethylene)malonate **3.16** (1.39 g, 10 mmol, 1 equiv.) and glyoxylic acid monohydrate (0.91 g, 10 mmol, 1 equiv.) in MeCN (30 mL) and the reaction mixture stirred at reflux for 6 days (TLC). The reaction mixture was allowed to cool and the solvent removed under reduced pressure. To the residue was added water and the product extracted with EtOAc (3 × 50 mL). The combined organic portions were washed with water (50 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure to afford a yellow solid (3.17 g). Flash column chromatography provided a colourless solid (0.59 g). The ^1H NMR spectrum was complex and no definitive structure could be determined.

4.3.3 Synthesis of 2-(1-carboxyalkylaminomethylene)malononitriles (2-[(2,2)-dicyanovinyl)amino] acids)

Synthesis of 2-[(2,2)-dicyanovinyl)amino]acetic acid, 3.21a without base Glycine (2.25 g, 30 mmol) was added to (ethoxymethylene)malononitrile (3.66 g, 30 mmol, 1 equiv.) in EtOH (60 mL). The reaction was stirred for 50 min at reflux and allowed to cool to room temperature. The solvent was removed under reduced pressure and the residue was dissolved in water. The product was extracted with EtOAc (3 × 75 mL), washed with water, dried (Na_2SO_4) and the solvent removed under reduced pressure to afford an oil. To the oil was added ether, the resulting precipitate was filtered off and discarded. The solvent was removed *in vacuo* to afford the **title compound** as an orange solid (1.71 g, 38 %). Characterisation data is given in the following section.

Synthesis of 2-[(2,2)-dicyanovinyl)amino]acetic acid, 3.21a in MeCN with Et_3N (Ethoxymethylene)malononitrile (3.66 g, 30 mmol) was added to a solution of Et_3N (6.5 mL, 45 mmol, 1.5 equiv.) and glycine (2.25 g, 30 mmol, 1 equiv.) in MeCN (60 mL). The reaction was stirred under nitrogen for 2.5 hours at reflux and allowed to cool to room temperature. The solvent was removed under reduced pressure and the residue was dissolved in water and acidified (2M HCl). The product was extracted with EtOAc (3 × 75 mL), washed with water, dried (Na_2SO_4) and the solvent removed under reduced pressure to afford a mixture of the **title compound** and 2-[(diethylamino)methylene]malononitrile **3.22** (1.55 g). δ_H [400 MHz, $(CD_3)_2SO$] 1.18 [6H, t, *J* = 7.2 Hz, $N(CH_2CH_3)_2$, **3.22**], 3.10 [2H, q, *J* = 7.2 Hz, $N(CH_2CH_3)(CH_2CH_3)$, **3.22**], 3.11 [2H, q, *J* = 7.2 Hz, $N(CH_2CH_3)(CH_2CH_3)$, **3.22**], 4.02 (2H, d, *J* = 5.7 Hz, $NHCH_2COOH$, **3.21a**), 7.23 (1H, s, CC*H*, **3.22**), 7.91 (1H, d, *J* = 14.5 Hz, CC*H*, **3.21a**), 9.22 (1H, dt, *J* = 5.7, 14.5 Hz, N*H*, **3.21a**), 13.13 (1H, br. s, COO*H*, **3.21a**). The aqueous phase was further acidified (2M HCl) and the product extracted with EtOAc (3 × 75 mL). The organic phase was washed (H_2O), dried (Na_2SO_4) and the solvent removed *in vacuo* to afford the pure product **3.21a** as an orange solid (2.36 g, 52 %). Characterisation data is given in the following section.

General method for the synthesis of 2-[(2,2)-dicyanovinyl)amino] acids

(Ethoxymethylene)malononitrile (3.66 g, 30 mmol) was added to a solution of KOH (85 %, 2.08 g, 31.5 mmol, 1.05 equiv.) and the appropriate α-amino acid (45 mmol, 1.5 equiv.) in EtOH (60 mL). The reaction was stirred for 1 hour at reflux and allowed to cool to room temperature. The solvent was removed under reduced pressure and the residue was dissolved in water and acidified (2M HCl). The product was extracted with EtOAc (3 × 75 mL), washed with water, dried (Na_2SO_4) and the solvent removed under reduced pressure to afford the pure product.

2-[(2,2)-Dicyanovinyl)amino]acetic acid, 3.21a From glycine (3.38 g) as an orange solid (3.76 g, 83 %). m.p. 146 – 148 °C. ν_{max} 3189, 3084, 3036, 2237, 2220, 1755, 1634, 1202, 579 cm^{-1}. δ_H [400 MHz, $(CD_3)_2SO$] 4.01 (2H, d, *J* = 5.9 Hz, $NHCH_2COOH$), 7.91 (1H, d, *J* = 14.5 Hz, CC*H*), 9.22 (1H, dt, *J* = 5.9, 14.5 Hz, N*H*), 13.04 (1H, br. s, COO*H*). δ_C [100 MHz, $(CD_3)_2SO$] 47.8, 49.4, 114.9, 117.2, 164.0, 170.9. HRMS (NSI) found $[M–H]^-$ = 150.0308 $C_6H_4N_3O_2$ requires $[M–H]^-$ = 150.0309.

2-[(2,2)-Dicyanovinyl)amino]propanoic acid, 3.21b From DL-alanine (4.01 g) as an orange solid after recrystallisation from EtOAc/hexane (3.35 g, 68 %). m.p. 119 – 122 °C. ν_{max} 3655, 3235, 2982, 2210, 1728, 1651, 1144, 573 cm^{-1}. δ_H [400 MHz, $(CD_3)_2SO$] 1.40 (3H, d, *J* = 7.3 Hz, CH_3), 4.20–4.27

(1H, m, NHC*H*COOH), 7.93 (1H, d, *J* = 14.5 Hz, CC*H*), 9.37 (1H, dd, *J* = 7.8, 14.5 Hz, N*H*), 13.16 (1H, br. s, COO*H*). HRMS (NSI) found $[M–H]^–$ = 164.0465 $C_7H_6N_3O_2$ requires $[M–H]^–$ = 164.0465.

2-[(2,2)-Dicyanovinyl)amino]-2-phenylacetic acid, 3.21c From DL-2-phenylglycine (6.80 g) as an orange solid (5.95 g, 87 %). m.p. 160 – 162 °C. ν_{max} 3654, 3203, 2981, 2233, 2218, 1736, 1644, 1169, 697 cm^{-1}. δ_H [400 MHz, $(CD_3)_2SO$] 5.41 (1H, d, *J* = 7.9 Hz, NHC*H*COOH), 7.38–7.43 (5H, m, Ar-*H*), 7.94 (1H, d, *J* = 14.1 Hz, CC*H*), 9.98 (1H, dd, *J* = 7.9, 14.1 Hz, N*H*), 13.48 (1H, br. s, COO*H*). δ_C [100 MHz, $(CD_3)_2SO$] 48.3, 65. 3, 114.8, 117.4, 128.7 (2 × C), 129.0, 129.2 (2 × C), 136.5, 161.8, 171.1. HRMS (NSI) found $[M–H]^–$ = 226.0622 $C_{12}H_8N_3O_2$ requires $[M–H]^–$ = 226.0622.

4.3.4 Synthesis of Pyrroles: Cyclisation of 2-(1-carboxyalkylaminomethylene)malononitriles (2-[(2,2)-dicyanovinyl)amino] acids)

General method for the cyclisation of 2-[(2,2)-dicyanovinyl)amino] acids

The 2-[(2,2)-dicyanovinyl)amino] acid (10 mmol) was dissolved in acetic anhydride (30 mL) prior to the addition of triethylamine (10 mL). The mixture was refluxed until the emission of CO_2 was complete (limewater bubbler) and allowed to cool to room temperature. The brown solution was poured into water (400 mL), stirred for 1 h and extracted with DCM (5 × 50 mL). The organic layer was washed with water (2 × 100 mL), aq. $NaHCO_3$ (5 × 50 mL) and water (100 mL). The dried (Na_2SO_4) solvent was removed under reduced pressure and the products were isolated by flash column chromatography.

The following compounds were synthesised by the above method.

***N*-Acetyl-*N*-(1-acetyl-4-cyano-1*H*-pyrrol-3-yl)acetamide, 3.23a** From 2-[(2,2)-dicyanovinyl)amino]acetic acid **3.21a** (1.51 g) flash column chromatography [50 % EtOAc in hexane] provided the **title compound** as a brown oil (0.34 g, 15 %). ν_{max} 3149, 2927, 2233, 1712, 1366, 1199, 585 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.39 [6H, s, $N(COCH_3)_2$], 2.62 (3H, s, $NCOCH_3$), 7.34 (1H, d, *J* = 2.2 Hz, 2-*H*), 7.84 (1H, d, *J* = 2.2 Hz, 5-*H*). δ_C (100 MHz, $CDCl_3$) 21.8, 26.3 (2 × C), 98.8, 112.0, 118.5, 126.1, 127.3, 166.0, 172.0 (2 × C). HRMS (APCI) found $[M+H]^+$ = 234.0872 $C_{11}H_{12}N_3O_3$ requires $[M+H]^+$ = 234.0873.

***N*-Acetyl-*N*-(1-acetyl-4-cyano-2-methyl-1*H*-pyrrol-3-yl)acetamide, 3.23b** From 2-[(2,2)-dicyanovinyl)amino]propanoic acid **3.21b** (1.65 g) flash column chromatography [20 % EtOAc in

hexane] provided initially the **title compound** as a colourless crystalline solid (1.09 g, 49 %). m.p. 135–137 °C. ν_{max} 3151, 2979, 2929, 2230, 1742, 1713, 1223, 1195, 605 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.33 (3H, s, C*H*$_3$), 2.36 [6H, s, N(COC*H*$_3$)$_2$], 2.63 (3H, s, NCOC*H*$_3$), 7.65 (1H, s, 5-*H*). δ_C (100 MHz, $CDCl_3$) 12.3, 23.6, 36.1 (2 × C), 96.8, 112.4, 124.4, 126.1, 131.3, 168.1, 172.1 (2 × C). HRMS (NSI) found $[M+H]^+$ = 248.1027 $C_{12}H_{14}N_3O_3$ requires $[M+H]^+$ = 248.1030. Further elution provided N-*acetyl*-N-(*4-cyano-2-methyl-1*H-*pyrrol-3-yl)acetamide* **3.25** as a brown solid (0.07 g, 3 %). m.p. 98 – 101 °C. ν_{max} 3348, 3139, 2218, 1703, 1226, 1205, 590 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.05 (3H, s, C*H*$_3$), 2.36 [6H, s, N(COC*H*$_3$)$_2$], 7.12 (1H, d, *J* = 3.3 Hz, 5-*H*), 8.99 (1H, br. s, N*H*). δ_C (100 MHz, $CDCl_3$) 10.0, 26.2 (2 × C), 114.2, 120.8, 124.3, 126.8 (2 × C), 173.1 (2 × C). HRMS (NSI) found $[M+H]^+$ = 206.0922 $C_{10}H_{12}N_3O_2$ requires $[M+H]^+$ = 206.0924. Selective removal of the *N*-acetyl group was achieved by addition of the **title compound 3.23b** (0.40 g) to sodium acetate (0.58 g) in EtOH (30 mL) followed by refluxing for 3 h (monitored by TLC). The solvent was removed under reduced pressure and the brown residue was dissolved in water, extracted with Et_2O (3 × 50 mL) and washed with water. The organic layer was dried (Na_2SO_4) and the solvent removed under reduced pressure to afford N-*acetyl*-N-(*4-cyano-2-methyl-1*H-*pyrrol-3-yl)acetamide* as a white powder (0.05 g, 15 %). The physical and spectroscopic data were in agreement with that of **3.25**.

***N*-Acetyl-*N*-(1-acetyl-4-cyano-2-phenyl-1*H*-pyrrol-3-yl)acetamide, 3.23c** From 2-[(2,2)-Dicyanovinyl)amino]-2-phenylacetic acid **3.21c** (2.27 g) flash column chromatography [30 % EtOAc in hexane] provided the **title compound** as straw coloured needles after recrystallisation from EtOAc/hexane (1.30 g, 49 %). m.p. 167–170 °C. ν_{max} 3646, 3172, 2980, 2889, 2229, 1748, 1707, 1195, 596 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.21 (3H, s, NCOC*H*$_3$), 2.25 [6H, s, N(COC*H*$_3$)$_2$], 7.21–7.27 (2H, m, *o*-Ar-*H*), 7.43–7.51 (3H, m, *m*-Ar-*H*, *p*-Ar-*H*), 7.98 (1H, s, 5-*H*). δ_C (100 MHz, $CDCl_3$) 24.9, 26.0 (2 × C), 96.9, 112.3, 125.8, 127.1, 128.5, 129.2 (2 × C), 129.3 (2 × C), 130.2, 132.1, 167.6, 172.2 (2 × C). HRMS (NSI) found $[M+H]^+$ = 310.1187 $C_{17}H_{16}N_3O_3$ requires $[M+H]^+$ = 310.1186.

4.3.5 Synthesis of 2-(Aminomethylene)-1,3-Ketonitriles

General method for the synthesis of 2-[(2-cyano-3-oxoprop-1-en-1-yl)amino] acids

To a solution of the appropriate β-ketonitrile (1 equiv.) and the appropriate α-amino acid (1.05 equiv.) in isopropanol (80 mL) was added triethyl orthoformate (1.50 equiv.). The reaction mixture was refluxed under nitrogen until the starting material was absent by TLC. After cooling, the

solvent was removed under reduced pressure. The residue was dissolved in DCM and extracted into aq. $NaHCO_3$ (3 × 50 mL) and the aqueous extracts acidified with dil. HCl (2 M, aq.). The product was then extracted with EtOAc (3 × 50 mL), dried (Na_2SO_4) and the solvent removed *in vacuo* to yield the 2-[(2-cyano-3-oxoprop-1-en-1-yl)amino] acid. *If the product precipitated on addition of DCM it was filtered by suction, and the solid dissolved and acidified with dil. HCl (2 M, aq.) and extracted with EtOAc (3 × 50 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed* in vacuo*.*

Cyanoacetone, 3.26A To a slurry of 3-aminocrotononitrile (2.46 g, 30 mmol) in water (3 mL) was added conc. HCl (3 mL) dropwise and the temperature kept below 15 °C. After the addition, the reaction mixture was heated to 80 °C and stirred for 2 hours. The reaction mixture was allowed to cool to room temperature and EtOAc was added, the biphasic mixture was filtered through Celite. The product was extracted with EtOAc, the combined organic fractions were washed with brine, dried (Na_2SO_4) and the solvent removed *in vacuo* to afford a brown oil (2.00 g, 80 %) which was immediately used in the following reactions.

2-[(2-Cyano-3-methyl-3-oxoprop-1-en-1-yl)amino]acetic acid, 3.27Aa From cyanoacetone (2.00 g, 24 mmol) and glycine (1.89 g, 25 mmol) as a brown solid (1.70 g, 42 %). m.p. 200 – 201 °C. ν_{max} 3221, 2931, 2208, 1724, 1644, 1395, 1200 cm^{-1}. The ^1H NMR spectrum showed a mixture of the (*E*)- and (*Z*)- isomers in a 0.6:1 ratio determined by the signals at δ 8.09 (1H, d, *J* = 14.9 Hz, CC*H*, *minor*) and 7.71 (1H, d, *J* = 13.9 Hz, CC*H*, *major*). δ_H [400 MHz, $(CD_3)_2SO$] 2.13 (3H, s, CH_3, *minor*), 2.19 (3H, s, CH_3, *major*), 4.09 (2H, d, *J* = 5.9 Hz, NHCH_2COOH, *minor*), 4.13 (2H, d, *J* = 6.0 Hz, NHCH_2COOH, *major*), 7.71 (1H, d, *J* = 13.9 Hz, CC*H*, *major*), 8.09 (1H, d, *J* = 14.9 Hz, CC*H*, *minor*), 8.72 (1H, br. s, N*H*, *minor*), 10.33 (1H, dt, *J* = 6.0, 13.9 Hz, N*H*, *major*), 13.02 (2H, br. s, 2 × COO*H*). δ_C [100 MHz, $(CD_3)_2SO$] 26.8, 28.3, 49.5, 50.0, 81.2 (2 × C), 118.1, 121.4, 161.0, 161.2, 170.8, 171.2, 191.1, 195.1. HRMS (ESI) found $[M+Na]^+$ = 191.0429 $C_7H_8N_2NaO_3$ requires $[M+Na]^+$ = 191.0427.

2-[(2-Cyano-3-methyl-3-oxoprop-1-en-1-yl)amino]propanoic acid, 3.27Ab From cyanoacetone (2.00g, 24 mmol) and DL-alanine (2.24 g, 25 mmol) as a red oil which slowly solidified (1.70 g, 40 %). m.p. 130 – 133 °C. ν_{max} 3194, 2918, 2206, 1723, 1651, 1557, 1206 cm^{-1}. The ^1H NMR spectrum showed a mixture of the (*E*)- and (*Z*)- isomers in a 0.6:1 ratio determined by the signals at δ 8.07 (1H, d, *J* = 14.8 Hz, CC*H*, *minor*) and 7.84 (1H, d, *J* = 13.5 Hz, CC*H*, *major*). δ_H [400 MHz, $(CD_3)_2SO$] 1.40 – 1.45 (3H × 2, m, 2 × CH_3), 2.14 (3H, s, COCH_3, *minor*), 2.19 (3H,s, COCH_3, *major*), 4.30 – 4.42 (1H × 2, m, 2 × NHC*H*COOH), 7.84 (1H, d, *J* = 13.5 Hz, CC*H*, *major*), 8.07 (1H, d, *J* = 14.8 Hz, CC*H*,

minor), 8.93 (1H, br. s, N*H*, *minor*), 10.62 (1H, dd, *J* = 7.5, 13.5 Hz, N*H*, *major*), 13.17 (1H × 2, br. s, 2 × COO*H*). δ_C [100 MHz, $(CD_3)_2SO$] 17.7, 19.0, 56.2, 57.1, 81.4, 82.8, 118.2, 121.2, 159.3, 159.5, 172.9, 173.3, 191.2, 195.5. HRMS (ESI) found $[M+H]^+$ = 183.0766 $C_8H_{11}N_2NaO_3$ requires $[M+H]^+$ = 183.0764.

2-[(2-Cyano-3-methyl-3-oxoprop-1-en-1-yl)amino]-2-phenylacetic acid, 3.27Ac From cyanoacetone (2.00 g, 24 mmol) and DL-2-phenylglycine (3.80 g, 25 mmol) as a red foam (3.39 g, 58 %). ν_{max} 2204, 1731, 1645, 1582, 1211, 697 cm^{-1}. The ^1H NMR spectrum showed a mixture of the (*E*)- and (*Z*)- isomers in a 0.4:1 ratio determined by the signals at δ 8.06 (1H, d, *J* = 14.6 Hz, CC*H*, *minor*) and 7.80 (1H, d, *J* = 13.5 Hz, CC*H*, *major*). δ_H [400 MHz, $(CD_3)_2SO$] 2.11 (3H, s, CH_3, *minor*), 2.18 (3H, s, CH_3, *major*), 5.46 (1H, d, *J* = 7.7 Hz, NHC*H*COOH, *major*), 5.55 (1H, d, *J* = 7.6 Hz, NHC*H*COOH, *minor*), 7.32 – 7.42 (5H × 2, m, 2 × Ar-*H*), 7.80 (1H, d, *J* = 13.5 Hz, CC*H*, *major*), 8.06 (1H, d, *J* = 14.6 Hz, CC*H*, *minor*), 9.40 (1H, br. s, N*H*, *minor*), 11.07 (1H, dd, *J* = 7.7, 13.5 Hz, N*H*, *major*), 13.41 (1H × 2, br. s, 2 × COO*H*). δ_C [100 MHz, $(CD_3)_2SO$] 27.0, 28.4, 63.9, 64.8, 82.2, 83.2, 118.2, 120.8, 127.6 (2 × C), 128.8 (2 × C), 128.9, 129.2 (3 × C), 129.7 (2 × C), 136.8, 137.2, 158.8, 159.1, 171.0, 171.4, 191.3, 196.1. HRMS (ESI) found $[M+Na]^+$ = 267.0745 $C_{13}H_{12}N_2NaO_3$ requires $[M+Na]^+$ = 267.0740.

(*E*)-2-[(Dimethylamino)methylene]-4,4-dimethyl-3-oxopentanenitrile, 3.33 To 4,4-dimethyl-3-oxopentanenitrile (6.27 g, 50 mmol) in dry THF (50 mL) was added DMFDMA (8.6 mL, 65 mmol, 1.30 equiv.). The reaction mixture was stirred at room temperature for 18 hours. The solvent was removed under reduced pressure to afford a yellow crystalline solid from EtOAc/hexane (7.42 g, 82 %). m.p. 88 – 89 °C (lit. m.p. 48 – 49 °C (10JOC4288)]. ν_{max} 3024, 2959, 2933, 2874, 2190, 1644, 1586, 609 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.33 [9H, s, C(CH_3)$_3$], 3.24 (3H, s, NCH_3), 3.43 (3H, s, NCH_3), 7.92 (1H, s, CC*H*). δ_C (100 MHz, $CDCl_3$) 26.8 (3 × C), 38.8, 43.6, 48.3, 77.0, 121.3, 160.3, 200.2.

2-[(2-Cyano-3-*tert*-butyl-3-oxoprop-1-en-1-yl)amino]acetic acid, 3.27Ba From 4,4-dimethyl-3-oxopentanenitrile (3.76 g, 30 mmol) and glycine (2.37 g, 31.5 mmol) as a yellow oil which slowly solidified (1.40 g. 22 %). m.p. 99 – 101 °C. ν_{max} 3273, 2972, 2192, 1740, 1641, 1592, 1185 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.32 [9H, s, C(CH_3)$_3$], 4.15 (2H, d, *J* = 6.0 Hz, NHCH_2COOH), 7.33 (1H, d, *J* = 13.3 Hz, CC*H*), 7.47 (1H, br. s, COO*H*), 10.75 (1H, dt, *J* = 6.0, 13.3 Hz, N*H*). δ_C (100 MHz, $CDCl_3$) 26.4 (3 × C), 43.7, 49.7, 80.5, 120.9, 162.1, 171.0, 205.4. HRMS (NSI) found $[M-H]^-$ = 209.0932 $C_{10}H_{13}N_2O_3$ requires $[M-H]^-$ = 209.0932.

2-[(2-Cyano-3-*tert*-butyl-3-oxoprop-1-en-1-yl)amino]propanoic acid, 3.27Bb From 4,4-dimethyl-3-oxopentanenitrile (3.76 g, 30 mmol) and DL-alanine (2.81 g, 31.5 mmol) as an orange oil (3.58 g, 53 %). ν_{max} 2971, 2200, 1720, 1637, 1585 cm^{-1}. The ^1H NMR spectrum showed a mixture of the (*E*)- and (*Z*)- isomers in a 0.3:1 ratio determined by the signals at δ 8.15 (1H, d, *J* = 15.1 Hz, CC*H*, *minor*) and 7.84 (1H, d, *J* = 13.8 Hz, CC*H*, *major*). δ_H [400 MHz, $(CD_3)_2SO$] 1.21 [9H, s, C(CH_3)$_3$, *minor*], 1.23 [9H, s, C(CH_3)$_3$, *major*], 1.29 (3H, d, *J* = 7.2 Hz, CHCH_3, *minor*), 1.44 (3H, d, *J* = 7.2 Hz, CHCH_3, *major*), 4.30 – 4.45 (1H × 2, m, C*H*CH_3), 7.84 (1H, d, *J* = 13.7 Hz, CC*H*, *major*), 8.15 (1H, d, *J* = 15.1 Hz, CC*H*, *minor*), 10.77 (1H, dd, *J* = 7.6, 13.7 Hz, N*H*, *major*), 10.85 (1H, dd, *J* = 6.8, 15.0 Hz, N*H*, *minor*), 13.04 (1H × 2, br. s, COO*H*). δ_C [100 MHz, $(CD_3)_2SO$] 17.8, 19.2, 26.6 (3 × C), 26.9 (3 × C), 43.0, 43.3, 56.3, 57.0, 77.5, 77.7, 119.8, 122.2, 161.7, 161.8, 173.0, 173.3, 197.6, 202.9. HRMS (NSI) found $[M-H]^-$ = 223.1088 $C_{11}H_{14}N_2O_3$ requires $[M-H]^-$ = 223.1088.

2-[(2-Cyano-3-*tert*-butyl-3-oxoprop-1-en-1-yl)amino]-2-phenylacetic acid, 3.27Bc From 4,4-dimethyl-3-oxopentanenitrile (3.76 g, 30 mmol) and DL-2-phenylglycine (4.76 g) as a yellow solid (4.28 g, 50 %). m.p. 174 – 176 °C. ν_{max} 3684, 2980, 2890, 2199, 1741, 1636, 1376, 1174 cm^{-1}. The ^1H NMR spectrum showed a mixture of the (*E*)- and (*Z*)- isomers in a 0.2:1 ratio determined by the signals at δ 8.09 (1H, d, *J* = 15.0 Hz, CC*H*, *minor*) and 7.84 (1H, d, *J* = 13.5 Hz, CC*H*, *major*). δ_H [400 MHz, $(CD_3)_2SO$] 1.23 [9H × 2, s, 2 × C(CH_3)$_3$], 5.48 (1H, d, *J* = 7.7 Hz, NHC*H*COOH, *major*), 5.56 (1H, d, *J* = 6.8 Hz, NHC*H*COOH, *minor*), 7.35 – 7.47 (5H × 2, m, Ar-*H*), 7.84 (1H, d, *J* = 13.5 Hz, CC*H*, *major*), 8.09 (1H, d, *J* = 15.0 Hz, CC*H*, *minor*), 9.23 (1H, dd, *J* = 6.8, 15.0 Hz, N*H*, *minor*), 11.19 (1H, dd, *J* = 7.7, 13.5 Hz, N*H*, *major*), 13.75 (1H × 2, br. s, 2 × COO*H*). δ_C [100 MHz, $(CD_3)_2SO$] 26.6 (3 × C), 26.8 (3 × C), 43.1, 43.4, 64.0 (2 × C), 78.4, 78.5, 119.6, 121.7 (3 × C), 128.9 (2 × C), 129.0, 129.3 (3 × C), 129.7 (2 × C), 137.1, 137.2, 161.1, 161.6, 170.8, 171.1, 203.4, 204.4. HRMS (NSI) found $[M-H]^-$ = 285.1245 $C_{16}H_{16}N_2O_3$ requires $[M-H]^-$ = 285.1245.

2-[(2-Cyano-3-phenyl-3-oxoprop-1-en-1-yl)amino]acetic acid, 3.27Ca From benzoylacetonitrile (4.35 g, 30 mmol) and glycine (2.36 g, 31.5 mmol) as a yellow solid (4.80 g, 70 %). m.p. 176 – 178 °C. ν_{max} 2979, 2212, 1745, 1651, 1645, 1596, 1205, 777, 699 cm^{-1}. The ^1H NMR spectrum showed a mixture of the (*E*)- and (*Z*)- isomers in a 0.8:1 ratio determined by the signals at δ 7.97 (1H, d, *J* = 14.1 Hz, CC*H*, *major*) and 8.12 (1H, d, *J* = 15.0 Hz, CC*H*, *minor*). δ_H [400 MHz, $(CD_3)_2SO$] 4.15 (2H, d, *J* = 5.3 Hz, NHCH_2COOH, *minor*), 4.23 (2H, d, *J* = 6.0 Hz, NHCH_2COOH, *major*), 7.45 – 7.58 (3H × 2, m, 2 × *m*-Ar-*H*, 2 × *p*-Ar-*H*), 7.62 – 7.65 (2H, m, *o*-Ar-*H*, *minor*), 7.73 – 7.75 (2H, m, *o*-Ar-*H*, *major*), 7.97 (1H, d, *J* = 14.1 Hz, CC*H*, *major*), 8.12 (1H, d, *J* = 15.0 Hz, CC*H*, *minor*), 9.01 (1H, dt, *J* = 5.3, 15.0

Hz, N*H*, *minor*), 10.77 (1H, dd, *J* = 6.0, 14.1 Hz, N*H*, *major*), 13.10 (1H × 2, br. s, 2 × COO*H*). δ_C [100 MHz, $(CD_3)_2SO$] 49.6, 50.3, 79.7, 81.8, 118.4, 121.6, 127.8 (2 × C), 128.3 (2 × C), 128.7 (4 × C), 131.7, 131.9, 139.1, 139.2, 163.4 (2 × C), 170.7, 171.1, 188.5, 191.0. HRMS (ESI) found $[M+H]^+$ = 231.0759 $C_{12}H_{11}N_2O_3$ requires $[M+H]^+$ = 231.0764.

2-[(2-Cyano-3-phenyl-3-oxoprop-1-en-1-yl)amino]propanoic acid, 3.27Cb From benzoylacetonitrile (4.35 g, 30 mmol) and DL-alanine (2.82 g, 31.5 mmol) as a pale brown solid (5.22 g, 71 %). m.p. 159 - 161 °C. ν_{max} 2993, 2207, 1732, 1641, 1131, 710, 696 cm^{-1}. The ^1H NMR spectrum showed a mixture of the (*E*)- and (*Z*)- isomers in a 0.7:1 ratio determined by the signals at δ 1.43 (3H, d, *J* = 7.2 Hz, NCHCH_3, *minor*) and 1.51 (3H, d, *J* = 7.2 Hz, NCHCH_3, *major*). δ_H [400 MHz, $(CD_3)_2SO$] 1.43 (3H, d, *J* = 7.2 Hz, NCHCH_3, *minor*), 1.51 (3H, d, *J* = 7.2 Hz, NCHCH_3, *major*), 4.42 – 4.49 (1H × 2, m, 2 × NC*H*CH_3), 7.46 – 7.58 (3H × 2, m, 4 × *m*-Ar-*H*, 2 × *p*-Ar-*H*), 7.63 – 7.65 (2H, m, *o*-Ar-*H*, *minor*), 7.73 – 7.75 (2H, m, *o*-Ar-*H*, *major*), 8.10 (1H, d, *J* = 13.9 Hz, CC*H*, *major*), 8.12 (1H, d, *J* = 15.0 Hz, CC*H*, *minor*), 9.25 (1H, dd, *J* = 7.9, 15.0 Hz, N*H*, *minor*), 11.06 (1H, dd, *J* = 7.5, 13.9 Hz, N*H*, *major*), 13.29 (1H × 2, br. s, 2 × COO*H*). δ_C [100 MHz, $(CD_3)_2SO$] 17.6, 19.0, 56.5, 57.2, 79.8, 81.2, 118.5, 121.5, 127.9 (2 × C), 128.3 (2 × C), 128.7 (4 × C), 131.6, 131.9, 139.1, 139.2, 161.6, 161.7, 172.9, 173.2, 188.7, 191.3. HRMS (ESI) found $[M+H]^+$ = 245.0920 $C_{13}H_{13}N_2O_3$ requires $[M+H]^+$ = 245.0921

2-[(2-Cyano-3-phenyl-3-oxoprop-1-en-1-yl)amino]-2-phenylacetic acid, 3.27Cc From benzoylacetonitrile (4.35 g, 30 mmol) and DL-2-phenylglycine (4.78 g, 31.5 mmol) as a pink powder (6.90g, 75 %). m.p. 191 – 193 °C. ν_{max} 2980, 2214, 1737, 1634, 1376, 1208, 728, 630 cm^{-1}. The ^1H NMR spectrum showed a mixture of the (*E*)- and (*Z*)- isomers in a 0.4:1 ratio determined by the signals at δ 5.59 (1H, d, *J* = 7.7 Hz, NHC*H*COOH, *major*), 5.62 (1H, d, *J* = 7.0 Hz, NHC*H*COOH, *minor*). δ_H [400 MHz, $(CD_3)_2SO$] 5.59 (1H, d, *J* = 7.7 Hz, NHC*H*COOH, *major*), 5.62 (1H, d, *J* = 7.0 Hz, NHC*H*COOH, *minor*), 7.37 – 7.59 [18H, m, 2 × CH-Ar-*H*, 2 × *m*-Ar-*H*, 2 × *p*-Ar-*H*, *o*-Ar-*H* (*minor*)], 7.73 – 7.76 (2H, m, *o*-Ar-*H*, *major*), 8.03 – 8.10 (1H × 2, m, 2 × CC*H*), 9.67 (1H, dd, *J* = 7.0, 14.8 Hz, N*H*, *minor*), 11.49 (1H, dd, *J* = 7.7, 13.7 Hz, N*H*, *major*), 13.52 (1H × 2, br. s, 2 × COO*H*). δ_C [100 MHz, $(CD_3)_2SO$] 64.1, 64.5, 80.6, 82.0, 118.2, 121.1, 127.8 (2 × C), 127.9 (4 × C), 128.2, 128.7 (5 × C), 128.9, 129.1, 129.3, 129.4, 129.8 (2 × C), 131.7, 132.1, 136.2, 137.0, 138.8, 139.0, 160.8, 161.6, 170.9, 171.3, 188.7, 191.7. HRMS (ESI) found $[M+H]^+$ = 307.1076 $C_{18}H_{15}N_2O_3$ requires $[M+H]^+$ = 307.1077.

2-[(2-Cyano-3-phenyl-3-oxoprop-1-en-1-yl)amino]butanoic acid, 3.27Cd From benzoylacetonitrile (4.35 g, 30 mmol) and DL-2-aminobutyric acid (3.27 g, 31.5 mmol) as an orange solid (5.03 g, 65 %). m.p. 147 – 148 °C. ν_{max} 2966, 2207, 1716, 1640, 1392, 1284, 714 cm^{-1}. The ^1H NMR spectrum showed a mixture of the (*E*)- and (*Z*)- isomers in a 0.6:1 ratio determined by the signals at δ 4.27 (1H, ddd, *J* = 4.5, 8.3, 9.7 Hz, C*H*CH_2CH_3, *minor*) and 4.37 (1H, dt, *J* = 5.2, 7.9 Hz, C*H*CH_2CH_3, *major*). δ_H [400 MHz, $(CD_3)_2SO$] 0.87 – 0.92 (3H × 2, m, 2 × CH_2CH_3), 1.76 – 1.99 (2H × 2, m, 2 × CH_2CH_3), 4.27 (1H, ddd, *J* = 4.5, 8.3, 9.7 Hz, C*H*CH_2CH_3, *minor*), 4.37 (1H, dt, *J* = 5.2, 7.9 Hz, C*H*CH_2CH_3, *major*), 7.46 – 7.59 (3H × 2, m, 4 × *m*-Ar-*H*, 2 × *p*-Ar-*H*), 7.63 – 7.65 (1H × 2, m, 2 × *o*-Ar-*H*, *minor*), 7.74 – 7.77 (1H × 2, m, 2 × *o*-Ar-*H*, *major*), 8.11 (1H, d, *J* = 13.8 Hz, CC*H*, *major*), 8.12 (1H, d, *J* = 15.0 Hz, CC*H*, *minor*), 9.18 (1H, dd, *J* = 8.3, 15.0 Hz, N*H*, *minor*), 11.04 (1H, dd, *J* = 7.9, 13.8 Hz, N*H*, *major*), 13.28 (1H × 2, br. s, 2 × COO*H*). δ_C [100 MHz, $(CD_3)_2SO$] 9.6, 10.9, 24.5, 26.1, 62.1, 63.1, 80.0, 81.3, 118.5, 121.4, 127.9 (2 × C), 128.3, 128.7 (2 × C), 131.7, 132.0, 139.0, 139.2, 162.0, 162.1, 172.2, 172.7, 188.7, 191.5. HRMS (ESI) found $[M+H]^+$ = 259.1076 $C_{14}H_{15}N_2O_3$ requires $[M+H]^+$ = 259.1077.

2-[(2-Cyano-3-phenyl-3-oxoprop-1-en-1-yl)amino]-3-methylbutanoic acid, 3.27Ce From benzoylacetonitrile (4.35 g, 30 mmol) and DL-valine (3.69 g, 31.5 mmol) as a yellow solid (6.37 g, 78 %). m.p. 131 – 133 °C. ν_{max} 2970, 2212, 1736, 1638, 1592, 658 cm^{-1}. The ^1H NMR spectrum showed a mixture of the (*E*)- and (*Z*)- isomers in a 0.3:1 ratio determined by the signals at δ 4.11 (1H, app. t, NHC*H*COOH, *minor*) and 4.29 (1H, dd, *J* = 4.3, 9.4 Hz, NHC*H*COOH, *major*). δ_H [400 MHz, $(CD_3)_2SO$] 0.89 – 0.96 [6H × 2, m, 2 × $CH(CH_3)_2$], 2.18 – 2.29 [1H ×2, m, C*H*$(CH_3)_2$], 4.11 (1H, app. t, NHC*H*COOH, *minor*), 4.29 (1H, dd, *J* = 4.3, 9.4 Hz, NHC*H*COOH, *major*), 7.46 – 7.64 (8H, m, 2 × *m*-Ar-*H*, 2 × *p*-Ar-*H*, *o*-Ar-*H*, *minor*), 7.76 – 7.78 (2H, m, *o*-Ar-*H*, *major*), 8.11 (1H, d, *J* = 14.6 Hz, CC*H*, *minor*), 8.12 (1H, d, *J* = 14.3 Hz, CC*H*, *major*), 9.08 (1H, dd, *J* = 8.6, 14.6 Hz, N*H*, *minor*), 11.10 (1H, dd, *J* = 9.4, 14.3 Hz, N*H*, *major*), 13.13 (1H × 2, br. s, 2 × COO*H*). δ_C [100 MHz, $(CD_3)_2SO$] 17.3, 18.5, 19.0, 19.5, 30.5, 31.6, 55.4, 66.6, 67.1, 80.0, 118.3, 121.3, 128.0 (2 × C), 128.3 (2 × C), 128.7 (2 × C), 131.7 (2 × C), 132.1 (2 × C), 138.8, 139.1, 161.6, 162.6, 171.6, 172.1, 188.8, 191.8. HRMS (NSI) found $[M-H]^-$ = 271.1084 $C_{15}H_{15}N_2O_3$ requires $[M-H]^-$ = 271.1088.

***N*,4-Dimethoxy-*N*-methylbenzamide, 3.36** Prepared following the literature method [13RSC(A)10158]. To a stirring solution of 4-methoxybenzoyl chloride (8 mL, 59.3 mmol) in 2-MeTHF (100 mL) was added *N,O*-dimethylhydroxylamine hydrochloride (6.36 g, 65.2 mmol 1.1 equiv.) with cooling in an ice-MeOH bath. Once the temperature of the mixture reached 0 °C, a

solution of K_2CO_3 (18.07 g, 130.7 mmol, 2.2 equiv.) in water (100 mL) was added in two portions. The ice bath was removed and the mixture stirred at room temperature for 1 h prior to the addition of dil. HCl (1 M, 100 mL). The organic phase was separated, washed with water (100 mL), dried (Na_2SO_4) and the solved removed under reduced pressure to afford a yellow oil (10.71 g, 93 %). ν_{max} 2934, 2839, 1633, 1605, 1574, 1250, 1170, 839 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 3.36 (3H, s, NC*H*$_3$), 3.56 (3H, s, NOC*H*$_3$), 3.85 (3H, s, OC*H*$_3$), 6.90 (2H, d, *J* = 8.7 Hz, *m*-An-*H*), 7.73 (2H, d, *J*= 8.7 Hz, *o*-An-*H*). δ_C (100 MHz, $CDCl_3$) 33.9, 55.3, 60.9, 113.3 (2 × C), 126.0, 130.5 (2 × C), 161.5, 169.0.

Synthesis of 4-methoxybenzoylacetonitrile, 3.26D from 3.36 Prepared following a literature method [15OBC1696]. Acetonitrile (5.4 mL, 103.4 mmol, 4.5 equiv.) was stirred in dry THF (40 mL) and cooled to -78 °C. MeLi·LiBr (2.2 M in Et_2O, 42 mL, 92.2 mmol, 4 equiv.) was added dropwise over 30 min and the reaction mixture stirred at -78 °C for a further 30 min. *N*,4-Dimethoxy-*N*-methylbenzamide **3.36** (4.51 g, 23.1 mmol, 1 equiv.) in dry THF (40 mL) was added dropwise over 5 min and stirring at -78 °C continued for 1.5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL) and allowed to reach room temperature. Et_2O (50 mL) was added and the resulting precipitate was collected by filtration to yield the *title compound* as a white powder (2.43 g, 60 %). m.p. 131 – 132 °C (lit. m.p. 119 – 120 °C [15OBC1969], 132 – 133 °C [15JOC11138]). ν_{max} 3080, 2980, 2941, 1686, 1595, 1171, 847, 814 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 3.90 (3H, s, OC*H*$_3$), 4.03 (2H, s, C*H*$_2$CN), 6.96 – 7.00 (2H, m, *m*-Ar-*H*), 7.88 – 7.92 (2H, m, *o*-Ar-*H*). δ_C (100 MHz, $CDCl_3$) 29.0, 55.7, 114.1, 114.4 (2 × C), 127.3, 130.9 (2 × C), 164.8, 185.4. HRMS (NSI) found $[M+NH_4]^+$ = 193.0970 $C_{10}H_{13}N_2O_2$ requires $[M+NH_4]^+$ = 193.0972.

Synthesis of 4-methoxybenzoylacetonitrile, 3.26D using sodium methoxide Prepared following a literature method [12MOL9683]. Ethyl 4-methoxybenzoate (8.2 mL, 50 mmol) and sodium methoxide (4.59 g, 85 mmol, 1.7 equiv.) were stirred in MeCN (110 mL) at reflux for 48 h. The reaction was allowed to cool and the resulting solid filtered and washed with Et_2O (50 mL) and hexane (50 mL). The solid was dissolved in water (250 mL), acidified with dil. HCl (2 M) and extracted with EtOAc (3 × 250 mL). The combined organic extracts were washed with brine (250 mL), dried (Na_2SO_4) and the solvent removed *in vacuo*. The solid was purified by flash column chromatography [1 % MeOH in DCM → 10 % MeOH in DCM] which provided initially the **title compound** as an off-white solid (2.90 g, 33 %). Physical and spectroscopic data are in agreement with **3.26D** from **3.36**. Further elution provided 4-methoxybenzoic acid **3.38** as an orange solid (2.71 g, 36 %). m.p. 182 – 183 °C (lit. m.p. 181 – 183 °C [13T9335], 184 – 185 °C [17TL2512]). ν_{max}

2980, 2515, 1681, 1601, 1259, 842, 771 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 3.88 (3H, s, OCH_3), 6.95 (2H, d, *J* = 8.8 Hz, *m*-An-*H*), 8.07 (2H, d, *J* = 8.8 Hz). δ_C (100 MHz, $CDCl_3$) 55.5, 113.8 (2 × C), 121.6, 132.4 (2 × C), 164.0, 171.4.

Synthesis of 4-methoxybenzoylacetonitrile, 3.26D using potassium *tert*-pentyloxide Prepared following a literature method [11ACIE8979]. To a stirred solution of acetonitrile (2.6 mL, 50 mmol) in anhydrous THF (150 mL) was slowly added potassium *tert*-pentyloxide (1.7 M in toluene, 73.5 mL, 125 mmol, 2.5 equiv.) at room temperature. Ethyl 4-methoxybenzoate (9 mL, 55 mmol, 1.1 equiv.) was added dropwise and the reaction stirred under nitrogen for 24 hours prior to the addition of dil. HCl (1 M, aq) and EtOAc (100 mL). The layers were separated and the organic layer was washed with water (2 × 100 mL), saturated brine solution (2 × 100 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford an off-white solid. Flash column chromatography [30 % EtOAc in hexane] provided the **title compound** as colourless crystals (7.74 g, 88 %). Physical and spectroscopic data are in agreement with **3.26D** from **3.36**.

2-{[2-Cyano-3-(4-methoxyphenyl)-3-oxoprop-1-en-1-yl]amino}acetic acid, 3.27Da From 4-methoxybenzoylacetonitrile **3.26D** (5.26 g, 30 mmol) and glycine (2.36 g, 31.5 mmol) as a yellow solid (6.16 g, 79 %). m.p. 153 – 154 °C. ν_{max} 3210, 2980, 2205, 1715, 1640, 1602, 1377, 1222 cm^{-1}. The ^{1}H NMR spectrum showed a mixture of the (*E*)- and (*Z*)- isomers in a 0.7:1 ratio determined by the signals at δ 8.13 (1H, d, *J* = 15.1 Hz, CCH, *minor*) and 7.93 (1H, d, *J* = 14.0 Hz, CCH, *major*). δ_H [400 MHz, $(CD_3)_2SO$] 3.82 (3H, s, OCH_3, *minor*), 3.83 (3H, s, OCH_3, *major*), 4.15 (2H, d, *J* = 5.8 Hz, NHCH_2COOH, *minor*), 4.22 (2H, d, *J* = 6.0 Hz, NHCH_2COOH, *major*), 7.01 – 7.05 (2H × 2, m, *m*-An-*H*), 7.67 – 7.70 (2H, m, *o*-An-*H*, *minor*), 7.78 – 7.80 (2H, m, *o*-An-*H*, *major*), 7.93 (1H, d, *J* = 14.0 Hz, CC*H*, *major*), 8.13 (1H, d, *J* = 15.1 Hz, CC*H*, *minor*), 8.90 (1H, dt, *J* = 5.8, 15.1 Hz, N*H*, *minor*), 10.72 (1H, dt, *J* = 6.0, 14.0 Hz, N*H*, *major*), 13.10 (1H × 2, br s, 2 × COO*H*). δ_C [100 MHz, $(CD_3)_2SO$] 49.5, 50.2, 55.9 (2 × C), 79.2, 81.3, 113.9 (2 × C), 114.0 (2 × C), 118.7, 122.0, 130.1 (2 × C), 130.6 (2 × C), 131.4, 131.5, 162.2, 162.3, 163.3 (2 × C), 170.8, 171.2, 187.0, 189.6. HRMS (NSI) found $[M+H]^+$ = 261.0872 $C_{13}H_{13}N_2O_4$ requires $[M+H]^+$ = 261.0870.

2-{[2-Cyano-3-(4-methoxyphenyl)-3-oxoprop-1-en-1-yl]amino}propanoic acid, 3.27Db From 4-methoxybenzoylacetonitrile **3.26** (3.50 g, 20 mmol) and DL-alanine (1.87 g, 21 mmol) as a brown oil which was crystallised from DCM/hexane to afford a fine brown powder (3.87 g, 71 %). m.p. 138 – 140 °C. ν_{max} 2980, 2204, 1742, 1634, 1605, 1585, 1136, 846 cm^{-1}. The ^{1}H NMR spectrum showed a mixture of the (*E*)- and (*Z*)- isomers in a 0.6:1 ratio determined by the signals at δ 8.12

(1H, d, *J* = 15.0 Hz, CC*H*, *minor*) and 8.04 (1H, d, *J* = 13.8 Hz, CC*H*, *major*). δ_H [400 MHz, $(CD_3)_2SO$] 1.43 (3H, d, *J* = 7.2 Hz, CHCH_3, *minor*), 1.50 (3H, d, *J* = 7.2 Hz, CHCH_3, *major*), 3.82 (3H, s, OCH_3, *minor*), 3.83 (3H, s, OCH_3, *major*), 4.39 – 4.47 (1H × 2, m, 2 × C*H*CH_3), 7.00 – 7.05 (2H × 2, m, 2 × *m*-An-*H*), 7.67 – 7.70 (2H, m, *o*-An-*H*, *minor*), 7.78 – 7.80 (2H, m, *o*-Ar-*H*, *major*), 8.04 (1H, d, *J* = 13.8 Hz, CC*H*, *major*), 8.12 (1H, d, *J* = 15.0 Hz, CC*H*, *minor*), 9.11 (1H, dd, *J* = 7.9, 15.0 Hz, N*H*, *minor*), 11.01 (1H, dd, *J* = 7.6, 13.8 Hz, N*H*, *major*), 13.29 (1H × 2, br. s, 2 × COO*H*). δ_C [100 MHz, $(CD_3)_2SO$] 17.7, 19.1, 55.9 (2 × C), 56.4, 57.1, 79.4, 80.8, 113.9 (2 × C), 114.0 (2 × C), 118.9, 121.9, 130.1 (2 × C), 130.5 (2 × C), 131.4, 131.5, 161.5, 161.6, 162.2, 162.4, 172.9, 173.3, 187.1, 189.9. HRMS (NSI) found $[M-H]^-$ = 273.0881 $C_{14}H_{13}N_2O_4$ requires $[M-H]^-$ = 273.0881.

2-{[2-Cyano-3-(4-methoxyphenyl)-3-oxoprop-1-en-1-yl]amino}-2-phenylacetic acid, 3.27Dc From 4-methoxybenzoylacetonitrile **3.26D** (3.50 g, 20 mmol) and DL-2-phenylglycine (3.18 g, 21 mmol) as an orange solid (4.60 g, 69 %). m.p. 155 – 158 °C. ν_{max} 2980, 2211, 1743, 1719, 1635, 1600, 1248, 1166 cm^{-1}. The ^1H NMR spectrum showed a mixture of the (*E*)- and (*Z*)- isomers in a 0.4:1 ratio determined by the signals at δ 8.07 (1H, d, *J* = 14.8 Hz, CC*H*, *minor*) and 8.04 (1H, d, *J* = 13.5 Hz, CC*H*, *major*). δ_H [400 MHz, $(CD_3)_2SO$] 3.82 (3H, s, OCH_3, *minor*), 3.83 (3H, s, OCH_3, *major*), 5.57 (1H, d, *J* = 7.7 Hz, NHC*H*COOH, *major*), 5.61 (1H, d, *J* = 7.1 Hz, NHC*H*COOH, *minor*), 6.97 – 7.00 (2H, m, *m*-An-*H*, *minor*), 7.03 – 7.05 (2H, m, *m*-An-*H*, *major*), 7.38 – 7.49 (5H × 2, m, 2 × Ar-*H*), 7.61 – 7.64 (2H, m, *o*-An-*H*, *minor*), 7.80 – 7.82 (2H, m, *o*-An-*H*, *major*), 8.04 (1H, d, *J* = 13.5 Hz, CC*H*, *major*), 8.07 (1H, d, *J* = 14.8 Hz, CC*H*, *minor*), 9.53 (1H, dd, *J* = 7.1, 14.8 Hz, N*H*, *minor*), 11.48 (1H, dd, *J* = 7.7, 13.5 Hz, N*H*, *major*), 13.77 (1H × 2, br. s, 2 × COO*H*). δ_C [100 MHz, $(CD_3)_2SO$] 55.9 (2 × C), 64.1, 64.4, 80.1, 81.5, 113.9 (2 × C), 114.0 (2 × C), 118.6, 121.4, 127.2 (2 × C), 128.9, 129.0, 129.3 (4 × C), 129.7 (2 × C), 130.2 (2 × C), 130.5 (2 × C), 131.1, 131.2, 136.4, 137.2, 160.7, 161.5, 162.3, 162.5, 171.0, 171.4, 187.1, 190.2. HRMS (NSI) found $[M-COOH]^-$ = 291.1131 $C_{18}H_{15}N_2O_2$ requires $[M-COOH]^-$ = 291.1139.

Attempted synthesis of 4-(dimethylamino)benzoylacetonitrile, 3.26E from *N,N*-dimethylaniline Acetic anhydride (9.4 mL, 100 mmol) and cyanoacetic acid (8.50 g, 100 mmol, 1 equiv.) were stirred in anhydrous 1,4-dioxane (100 mL) at reflux for 15 min under N_2. The mixture was filtered and the filtrate allowed to cool to room temperature. To the filtrate was added anhydrous 1,4-dioxane (100 mL), *N,N*-dimethylaniline (12.7 mL, 100 mmol, 1 equiv.) and $InCl_3$ (1.27 g, 10 wt%) and the mixture stirred at reflux for 1 h under N_2. The reaction mixture was poured onto water

(100 mL) and the resulting solid filtered, washed with water and recrystallised from EtOH to afford a brown solid. No product could be detected by ^{1}H NMR of this material.

4'-Dimethylaminoacetophenone, 3.42 To 4'-aminoacetophenone (13.52 g, 100 mmol) in DMF (150 mL) was added K_2CO_3 (31.97 g, 230 mmol, 2.3 equiv.) and iodomethane (14.3 mL, 230 mmol, 2.3 equiv.) and the mixture stirred at 60 °C for 24 hours. The reaction mixture was allowed to cool and ice-water was added, the resulting solid was isolated by vacuum filtration and washed with hexane. The solid was dissolved in EtOAc and washed with water (2 × 100 mL). The organic portion was dried (Na_2SO_4) and the solvent removed *in vacuo* to afford a yellow solid (4.41 g, 27 %). (15DT15924) m.p. 106 – 107 °C. ν_{max} 2912, 1650, 1586, 1357, 1229, 818 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.51 (3H, s, COC*H*$_3$), 3.06 [6H, s, N(C*H*$_3$)$_2$], 6.63 – 6.67 (2H, m, *m*-DP-*H*), 7.86 – 7.89 (2H, m, *o*-DP-*H*).

1-[4-(Dimethylamino)phenyl]ethan-1-one, 3.43 To **3.42** (16.32 g, 100 mmol) in toluene (100 mL) was added DMFDMA (48 mL, 360 mmol, 3.6 equiv.) and $BF_3{\cdot}OEt_2$ (10 drops) and the reaction mixture stirred at reflux for 30 days. The reaction was allowed to cool to room temperature before the solvent was removed under reduced pressure. The resulting solid was washed with brine and hexane and purified by flash column chromatography [100 % EtOAc] to afford initially unreacted **3.42** (9.51 g, 58 mmol). Further elution provided the **title compound** as a brown solid (8.90 g, 41 %). m.p. 149 – 152 °C. ν_{max} 2897, 2802, 1645, 1592, 1565, 1527, 780 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.96 [6H, br. s, CHN(C*H*$_3$)$_2$], 3.01 [6H, s, DP-N(C*H*$_3$)$_2$], 5.73 [1H, d, *J* = 12.3 Hz, C*H*N(CH$_3$)$_2$], 6.64 (2H, d, *J* = 8.8 Hz, *m*-DP-*H*), 7.78 (1H, d, *J* = 12.3 Hz, COC*H*), 7.89 (2H, d, *J* = 8.8 Hz, *o*-DP-*H*). δ_C (100 MHz, $CDCl_3$) 37.2, 40.2 (2 × C), 43.3, 91.6, 110.8 (2 × C), 127.9, 129.5 (2 × C), 152.4, 153.5, 187.3. HRMS (ESI) found $[M+H]^+$ = 219.1497 $C_{13}H_{19}N_2O$ requires $[M+H]^+$ = 219.1492.

5-(4-Dimethylaminophenyl)isoxazole, 3.44 To **3.43** (8.60 g, 39 mmol) in EtOH (75 mL) was added hydroxylamine hydrochloride (5.56 g, 80 mmol, 2 equiv.) and the mixture was stirred at reflux for 17 hours under nitrogen. After cooling to rt the solvent removed under reduced pressure. The residue was dissolved in $CHCl_3$ and washed with water. The organic layer was dried (Na_2SO_4) and the solvent removed under reduced pressure to yield a brown solid (6.01 g, 81 %). m.p. 132 – 133 °C. ν_{max} 3087, 2904, 2808, 1609, 819, 780 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 3.03 [6H, s, N(C*H*$_3$)$_2$], 6.30 (1H, d, *J* = 1.7 Hz, 4-*H*), 6.73 (2H, d, *J* = 8.9 Hz, *m*-DP-*H*), 7.66 (2H, d, *J* = 8.9 Hz, *o*-DP-*H*), 8.21 (1H, d, *J* = 1.7 Hz, 3-*H*). δ_C (100 MHz, $CDCl_3$) 40.2 (2 × C), 95.8, 111.8 (2 × C), 115.3, 127.3 (2 × C), 150.8, 151.4, 170.2. HRMS (ESI) found $[M+H]^+$ = 189.1025 $C_{11}H_{13}N_2O$ requires $[M+H]^+$ = 189.1022.

4-(Dimethylamino)benzoylacetonitrile, 3.26E 5-(4-Dimethylaminophenyl)isoxazole **3.44** (6.65 g, 30 mmol) was added to a solution of NaOEt (2.07 g, 90 mmol, 3 equiv.) in EtOH and the mixture stirred under nitrogen at rt for 17 hours. Dil. HCl (0.5 M, 100 mL) was added and the product extracted with EtOAc (3 × 50 mL). The organic extracts were combined, washed with water (1 × 100 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure to afford an orange solid (2.01 g, 36 %). m.p. 160 – 163 °C [lit. m.p. 164 – 165 °C (09T9421)]. ν_{max} 2949, 2916, 1665, 1589, 1328, 1231, 821 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 3.09 [6H, s, N(CH_3)$_2$], 3.95 (2H, s, CH_2), 6.66 (2H, d, *J* = 9.1 Hz, *m*-DP-*H*), 7.80 (2H, d, *J* = 9.1 Hz, *o*-DP-*H*). δ_C (100 MHz, $CDCl_3$) 28.5, 40.0 (2 × C), 110.8 (2 × C), 114.8, 122.0, 130.9 (2 × C), 154.2, 184.4. HRMS (ESI) found $[M+Na]^+$ = 211.0841 $C_{11}H_{12}N_2NaO$ requires $[M+Na]^+$ = 211.0842.

Synthesis of 4-(dimethylamino)benzoylacetonitrile, 3.26E from ethyl 4-(dimethylamino)benzoate The reaction was conducted following literature method [11ACIE8979]. To a stirring solution of acetonitrile (2.6 mL, 50 mmol) in anhydrous THF (100 mL) was slowly added potassium *tert*-pentyloxide (1.7 M, 73.5 mL, 125 mmol, 2.5 equiv.) under nitrogen. A solution of ethyl 4-(dimethylamino)benzoate (10.63 g, 55 mmol, 1.1 equiv.) in anhydrous THF (50 mL) was then added dropwise and the mixture stirred for 24 hours at rt. To the reaction mixture was added dil. HCL (1 M, 120 mL), followed by EtOAc. The organic layer was isolated, washed with water (2 × 100 mL) and brine (2 × 100 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure to afford an orange solid (8.85 g, 94 %). Physical and spectroscopic data were in agreement with **3.26E** prepared from **3.44**.

2-({2-Cyano-3-[4-(dimethylamino)phenyl]-3-oxoprop-1-en-1-yl}amino)acetic acid, 3.27Ea From 4-(dimethylamino)benzoylacetonitrile **3.27E** (2.82 g, 15 mmol) and glycine (1.18 g, 16 mmol) as an orange solid from EtOAc/hexane (1.09 g, 27 %). m.p. 198 – 199 °C. ν_{max} 2980, 2193, 1734, 1644, 1603, 1207, 1165, 825, 781 cm^{-1}. The ^{1}H NMR spectrum showed a mixture of the (*E*)- and (*Z*)-isomers in a 0.6:1 ratio determined by the signals at δ 8.10 (1H, d, *J* = 14.9 Hz, CC*H*, *minor*) and 7.84 (1H, d, *J* = 13.8 Hz, CC*H*, *major*). δ_H [400 MHz, $(CD_3)_2SO$] 2.99 – 3.00 [6H × 2, m, 2 × N(CH_3)$_2$], 4.14 (2H, d, *J* = 5.9 Hz, NHCH_2COOH, *minor*), 4.19 (2H, d, *J* = 5.9 Hz, NHCH_2COOH, *major*), 6.72 – 6.75 (2H × 2, m, 2 × *m*-DP-*H*), 7.66 (2H, d, *J* = 8.9 Hz, *o*-DP-*H*, *minor*), 7.74 – 7.78 (2H, m, *o*-DP-*H*, *major*), 7.84 (1H, d, *J* = 13.8 Hz, CC*H*, *major*), 8.10 (1H, d, *J* = 14.9 Hz, CC*H*, *minor*), 8.69 (1H, dt, *J* = 5.9, 14.9 Hz, N*H*, *major*), 10.68 (1H, dt, *J* = 5.9, 13.8 Hz, N*H*, *minor*), 12.92 (1H × 2, br. s, 2 × COO*H*). δ_C [100 MHz, $(CD_3)_2SO$] 40.1* (2 × C), 40.2* (2 × C), 78.9, 80.8, 111.0 (4 × C), 117.4, 119.3, 122.5,

125.7, 125.8, 130.0 (2 × C), 130.5 (2 × C), 152.9, 153.5, 162.9 (2 × C), 168.0, 170.9, 171.4, 186.0, 188.8. HRMS (ESI) found $[M+H]^+$ = 274.1188 $C_{14}H_{16}N_3O_3$ requires $[M+H]^+$ = 274.1186.

*Overlaps with residual $(CH_3)_2SO$.

2-({2-Cyano-3-[4-(dimethylamino)phenyl]-3-oxoprop-1-en-1-yl}amino)propanoic acid, 3.27Eb From 4-(dimethylamino)benzoylacetonitrile **3.26E** (1.88 g, 10 mmol) and DL-alanine (0.94 g, 10.5 mmol) as a pale brown solid (0.84 g, 29 %). m.p. 140 – 142 °C. ν_{max} 3219, 3003, 2901, 2204, 1727, 1638, 1600, 1368, 1186, 789 cm^{-1}. The ^1H NMR spectrum showed a mixture of the (*E*)- and (*Z*)-isomers in a 0.6:1 ratio determined by the signals at δ 8.10 (1H, d, *J* = 14.9 Hz, CC*H*, *minor*) and 7.96 (1H, d, *J* = 13.6 Hz, CC*H*, *major*). δ_H [400 MHz, $(CD_3)_2SO$] 1.44 (3H, d, *J* = 7.2 Hz, CH_3, *minor*), 1.49 (3H, d, *J* = 7.2 Hz, CH_3, *major*), 3.00 [6H × 2, s, 2 × N(CH_3)$_2$], 4.38 – 4.45 (1H × 2, m, 2 × NHC*H*COOH), 6.71 – 6.74 (2H × 2, m, 2 × *m*-DP-*H*), 7.67 (2H, d, *J* = 8.8 Hz, *o*-DP-*H*, *minor*), 7.78 (2H, d, *J* = 8.8 Hz, *o*-DP-*H*, *major*), 7.96 (1H, d, *J* = 13.6 Hz, CC*H*, *major*), 8.10 (1H, d, *J* = 14.9 Hz, CC*H*, *minor*), 8.90 (1H, dd, *J* = 7.9, 14.9 Hz, N*H*, *minor*), 11.00 (1H, dd, *J* = 7.7, 13.6 Hz, N*H*, *major*), 13.27 (1H × 2, br. s, 2 × COO*H*). δ_C [100 MHz, $(CD_3)_2SO$] 17.8, 19.2, 40.1* (4 × C), 56.3, 56.9, 111.0 (4 × C), 119.4, 122.4, 125.7, 125.8, 130.0 (2 × C), 130.5 (2 × C), 152.9, 153.0, 161.1, 161.2, 173.1, 173.4, 186.1, 189.0. HRMS (ESI) found $[M+H]^+$ = 288.1348 $C_{15}H_{18}N_3O_3$ requires $[M+H]^+$ = 288.1343.

*Overlaps with residual $(CH_3)_2SO$.

2-({2-Cyano-3-[4-(dimethylamino)phenyl]-3-oxoprop-1-en-1-yl}amino)-2-phenylacetic acid, 3.27Ec From 4-(dimethylamino)benzoylacetonitrile **3.26E** (1.88 g, 10 mmol) and DL-2-phenylglycine (1.59 g, 10.5 mmol) as a yellow solid (1.95 g, 55 %). m.p. 161 – 162 °C. ν_{max} 2980, 1728, 1635, 1598, 1359, 1190, 1165, 767 cm^{-1}. The ^1H NMR spectrum showed a mixture of the (*E*)- and (*Z*)- isomers in a 0.3:1 ratio determined by the signals at δ 8.04 (1H, d, *J* = 14.8 Hz, CC*H*, *minor*) and 7.94 (1H, d, *J* = 13.4 Hz, CC*H*, *major*). δ_H [400 MHz, $(CD_3)_2SO$] 2.99 [6H, br. s, N(CH_3)$_2$, *minor*], 3.00 [6H, br. s, N(CH_3)$_2$, *major*], 5.53 (1H, d, *J* = 7.8 Hz, NHC*H*COOH, *major*), 5.59 (1H, d, *J* = 6.9 Hz, NHC*H*COOH, *minor*), 6.69 (2H, d, *J* = 8.9 Hz, *m*-DP-*H*, *minor*), 6.73 (2H, d, *J* = 9.0 Hz, *m*-DP-*H*, *major*), 7.39 – 7.48 (5H × 2, m, 2 × C$_6H_5$), 7.61 (2H, d, *J* = 8.9 Hz, *o*-DP-*H*, *minor*), 7.78 (2H, d, *J* = 9.0 Hz, *o*-DP-*H*, *major*), 7.94 (1H, d, *J* = 13.4 Hz, CC*H*, *major*), 8.04 (1H, d, *J* = 14.8 Hz, CC*H*, *minor*), 9.23 (1H, dd, *J* = 6.9, 14.8 Hz, N*H*, *minor*), 11.46 (1H, dd, *J* = 7.8, 13.4 Hz, N*H*, *major*), 13.71 (1H × 2, br. s, 2 × COO*H*). δ_C [100 MHz, $(CD_3)_2SO$] 40.7* (2 × C), 41.0* (2 × C), 64.0, 64.2, 79.7, 81.2, 111.0 (4 × C), 119.0, 121.9, 125.4 (2 × C), 127.7 (2 × C), 128.8 (2 × C), 129.0, 129.2, 129.3 (2 × C), 129.7 (2 × C), 130.1 (2 × C),

130.5 (2 × C), 136.7, 137.4, 153.0, 153.1, 160.3, 161.0, 171.1, 171.5, 185.9, 189.2. HRMS (ESI) found $[M+H]^+$ = 350.1509 $C_{20}H_{20}N_3O_3$ requires $[M+H]^+$ = 350.1499.

*Overlaps with residual $(CH_3)_2SO$.

Synthesis of 4-nitrobenzoylacetonitrile, 3.26F from ethyl 4-nitrobenzoate and potassium *tert*-pentyloxide The reaction was conducted following literature method [11ACIE8979]. To a stirring solution of acetonitrile (3.9 mL, 75 mmol) in anhydrous THF (150 mL) was slowly added potassium *tert*-pentyloxide (1.7 M, 110 mL, 187 mmol, 2.5 equiv.) under nitrogen. A solution of ethyl 4-nitrobenzoate (16.10 g, 82.5 mmol, 1.1 equiv.) in anhydrous THF (100 mL) was added dropwise, the mixture was stirred for 24 hours at rt. To the reaction mixture was added dil. HCL (1 M, 120 mL), followed by EtOAc. The organic layer was isolated, washed with water (2 × 100 mL) and brine (2 × 100 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure. The solid was purified by flash column chromatography to afford an orange solid (1.52 g, 10 %). m.p. 114 – 115 °C (lit. m.p. 122 – 123 °C [12MOL9683]). ν_{max} 2911, 1698, 1651, 1520, 1353, 853, 813 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 4.16 (2H, s, CH_2), 8.11 – 8.13 (2H, m, *o*-Ar-*H*), 8.38 – 8.40 (2H, m, *m*-Ar-*H*). δ_C (100 MHz, $CDCl_3$) 29.9, 112.8, 124.4 (2 × C), 129.6 (2 × C), 138.4, 151.2, 185.9. HRMS (APCI) found $[M-H]^-$ = 189.0313 $C_9H_5N_2O_3$ requires $[M-H]^-$ = 189.0306.

Synthesis of 4-nitrobenzoylacetonitrile, 3.26F from ethyl 4-nitrobenzoate and sodium methoxide The reaction was conducted following a literature method [12MOL9683]. Ethyl 4-nitrobenzoate (3.90 g, 20 mmol) and sodium methoxide (1.84 g, 34 mmol, 1.7 equiv.) were stirred in MeCN (60 mL) at reflux for 48 h. The reaction mixture was allowed to cool and the resulting solid filtered and washed with hexane (50 mL). The solid was dissolved in water (250 mL), acidified with dil. HCl (2 M) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (250 mL), dried (Na_2SO_4) and the solvent removed *in vacuo*. The solid was purified by flash column chromatography [30 % EtOAc in hexane] which provided a mixture of 4-nitrobenzoic acid and 4-nitrobenzoylacetonitrile (0.97 g).

Attempted synthesis of 4-nitrobenzoylacetonitrile, 3.26F from 4-nitrobenzoyl chloride and cyanoacetic acid The reaction was conducted following a literature method [99JMC3629]. Cyanoacetic acid (4.26 g, 50 mmol, 2 equiv.) was dissolved in anhydrous THF (100 mL) and cooled to -78 °C under nitrogen. *n*-BuLi (2.5 M in hexanes, 40 mL, 100 mmol, 4 equiv.) was added to the solution dropwise and the reaction allowed to reach 0 °C and stirred for 30 min. The mixture was

cooled to -78 °C and a solution of 4-nitrobenzoyl chloride (4.64 g, 25 mmol) in anhydrous THF (50 mL) was added dropwise. The reaction mixture was stirred for a further hour at -78 °C and allowed to warm to room temperature. The mixture was slowly acidified (2 M HCl) and the product extracted with DCM (2 × 75 mL). The organic portions were washed with aq. $NaHCO_3$, dried (Na_2SO_4) and the solvent removed under reduced pressure. The product was purified by flash column chromatography [30 % EtOAc in hexane]. The ^{1}H NMR was complex and no product could be identified.

Attempted Synthesis of 4-nitrobenzoylacetonitrile, 3.26F from 4-nitrobenzoyl chloride and *tert*-butyl cyanoacetate The reaction was conducted following a literature method [97S337]. NaH (60 % in oil, 2.80 g, 71 mmol) was suspended in anhydrous toluene (250 mL) and *tert*-butyl cyanoacetate (20.2 mL, 142 mmol, 2 equiv.) was added and the reaction mixture stirred under nitrogen until the evolution of H_2 ceased. To the suspension of the sodium salt was added 4-nitrobenzoyl chloride (13.15 g, 71 mmol, 1 equiv.) in anhydrous THF (50 mL) and the reaction mixture stirred for 16 h. Water (200 mL) was added and the organic solvent separated and washed with water (100 mL). The aqueous portions were combined and washed with Et_2O (100 mL). The aqueous layer was acidified (2 M HCl) and the product extracted with Et_2O (2 × 100 mL), washed with water (100 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure to afford tert-*butyl 2-cyano-3-(4-nitrophenyl)-3-oxopropanoate*. The intermediate was dissolved in anhydrous toluene (100 mL) and a catalytic amount of TsOH was added and the reaction mixture stirred at reflux overnight under nitrogen. The mixture was allowed to cool to room temperature and the solvent removed *in vacuo*. The product was purified by flash column chromatography [20 % EtOAc in hexane] to afford the **title compound** as a yellow solid (0.55 g, 4 %). Physical and spectroscopic data are identical to **3.26F** from ethyl 4-nitrobenzoate and KO*t*-pentyloxide.

3-(Dimethylamino)-1-(4-nitrophenyl)prop-2-en-1-one, 3.52 To 4'-nitroacetophenone (16.52 g, 100 mmol) in toluene (100 mL) was added DMFDMA (16 mL, 120 mmol, 1.2 equiv.) and $BF_3{\cdot}OEt_2$ (10 drops) and the reaction mixture stirred at reflux for 24 hours. The mixture was allowed to cool to room temperature before the solvent was removed under reduced pressure. The resulting solid was washed with hexane and collected by vacuum filtration affording a brown solid (20.33 g, 92 %). m.p. 147 – 149 °C (lit. m.p 139 – 141 °C [08JHC879]). ν_{max} 1633, 1602, 1513, 1322, 787, 712 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.98 (3H, s, NCH_3CH$_3$), 3.21 (3H, s, NCH$_3$CH_3), 5.68 (1H, d, *J* = 12.2 Hz, C*H*N),

7.87 (1H, d, *J* = 12.2 Hz, COC*H*), 8.01 – 8.03 (2H, m, *o*-PNP-*H*), 8.24 – 8.27 (2H, m, *m*-PNP-*H*). HRMS (ESI) found $[M+H]^+$ = 220.0842 $C_{11}H_{13}N_2O_3$ requires $[M+H]^+$ = 220.0848.

5-(4-Nitrophenyl)isoxazole, 3.53 To **3.52** (20.04 g, 91 mmol) in EtOH (150 mL) was added hydroxylamine hydrochloride (12.65 g, 182 mmol, 2 equiv.). The mixture was stirred at reflux for 1 hour and allowed to cool to room temperature. The solvent was removed under reduced pressure and the product dissolved in chloroform. The insoluble material was removed by filtration and the chloroform solution washed with water. The organic layer was dried (Na_2SO_4) and the solvent removed *in vacuo* to afford a pale yellow solid (12.98 g, 75 %). m.p. 174 – 176 °C (lit. m.p 163 – 165 °C [08JHC879]). ν_{max} 2911, 1650, 1576, 1514, 1354, 1230, 1067, 812 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 6.73 (1H, d, *J* = 1.8 Hz, 4-*H*), 7.97 – 8.00 (2H, m, *o*-Ar-*H*), 8.34 – 8.37 (2H, m, *m*-Ar-*H*), 8.38 (1H, d, *J* = 1.8 Hz, 3-*H*). δ_C (100 MHz, $CDCl_3$) 101.4, 124.5 (2 × C), 126.7 (2 × C), 132.6, 148.5, 151.1, 166.9. HRMS (ESI) found $[M+H]^+$ = 190.0376 $C_9H_7N_2O_3$ requires $[M+H]^+$ = 190.0378.

4-Nitrobenzoylacetonitrile, 3.54 Sodium (4.71 g, 205 mmol, 3 equiv.) was added to EtOH (300 mL) and stirred under nitrogen until effervescence had ceased. To the solution was added **3.53** (12.98 g, 68 mmol) and the mixture was stirred at room temperature for 17 hours under nitrogen. The solvent was removed under reduced pressure and the residue dissolved in water and acidified with dil. HCl (1 M). The product was extracted with EtOAc, the extracts washed with water, dried (Na_2SO_4) and the solvent removed under reduced pressure to provide an orange solid (7.60 g, 59 %). Physical and spectroscopic data are identical to **3.26F** from ethyl 4-nitrobenzoate and potassium *tert*-pentyloxide.

2-{[2-Cyano-3-(4-nitrophenyl)-3-oxoprop-1-en-1-yl]amino}acetic acid, 3.27Fa From 4-nitrobenzoylacetonitrile (1.90 g, 10 mmol) and glycine (0.80 g, 10.5 mmol) as an orange solid (0.67 g, 24 %). m.p. 177 – 179 °C. ν_{max} 3239, 2206, 1743, 1649, 1544, 1519, 1337, 1243, 721 cm^{-1}. The ^1H NMR spectrum showed a mixture of the (*E*)- and (*Z*)- isomers in a 0.8:1 ratio determined by the signals at δ 8.11 (1H, d, *J* = 15.2 Hz, CC*H*, *minor*) and 8.05 (1H, d, *J* = 14.2 Hz, CC*H*, *major*). δ_H [400 MHz, $(CD_3)_2SO$] 4.16 (2H, d, *J* = 5.9 Hz, NHCH_2COOH, *minor*), 4.25 (3H, d, *J* = 6.0 Hz, NHCH_2COOH, *major*), 7.82 – 7.84 (2H, m, *o*-Ar-*H*, *minor*), 7.94 – 7.96 (2H, m, *o*-Ar-*H*, *major*), 8.05 (1H, d, *J* = 14.2 Hz, CC*H*, *major*), 8.11 (1H, d, *J* = 15.2 Hz, CC*H*, *minor*), 8.30 – 8.35 (2H × 2, m, 2 × *m*-Ar-*H*), 9.27 (1H, dt, *J* = 6.0, 14.2 Hz, N*H*, *minor*), 10.80 (1H, dt, *J* = 5.9, 15.2 Hz, N*H*, *major*), 13.15 (1H × 2, br. s, 2 × COO*H*). δ_C [100 MHz, $(CD_3)_2SO$] 49.7, 50.5, 79.9, 117.7 (2 × C), 121.0, 124.0 (4 ×

C), 129.2 (2 × C), 129.5 (2 × C), 144.6, 144.9, 149.1, 149.2, 163.6, 163.7, 170.5, 170.9, 189.3 (2 × C). HRMS (ESI) found $[M+H]^+$ = 276.0616 $C_{12}H_{10}N_3O_5$ requires $[M+H]^+$ = 276.0615.

2-{[2-Cyano-3-(4-nitrophenyl)-3-oxoprop-1-en-1-yl]amino}propanoic acid, 3.27Fb From 4-nitrobenzoylacetonitrile (1.90 g, 10 mmol) and DL-alanine (0.94 g, 10.5 mmol) as a brown solid from EtOAc/hexane (0.94 g, 33 %). m.p. 183 – 185 °C. ν_{max} 2953, 2205, 1738, 1638, 1519, 1344, 852 cm^{-1}. ^1H NMR showed the presence of the (*Z*)-isomer. δ_H (400 MHz, $CDCl_3$) 1.71 (3H, d, *J* = 7.2 Hz, C*H*$_3$), 4.30 (1H, app quin, NHC*H*COOH), 6.64 (1H, br. s, COO*H*), 7.64 (1H, d, *J* = 13.6 Hz, CC*H*), 7.99 – 8.01 (2H, m, *o*-PNP-*H*), 8.29 – 8.32 (2H, m, *m*-PNP-*H*), 11.26 (1H, dd, *J* = 7.3, 13.6 Hz, N*H*). δ_C (100 MHz, $CDCl_3$) 18.9, 56.7, 81.9, 119.8, 123.6 (2 × C), 129.0 (2 × C), 143.2, 149.5, 160.3, 172.6, 190.2. HRMS (ESI) found $[M+H]^+$ = 290.0767 $C_{13}H_{12}N_3O_5$ requires $[M+H]^+$ = 290.0771.

2-{[2-Cyano-3-(4-nitrophenyl)-3-oxoprop-1-en-1-yl]amino}-2-phenylacetic acid, 3.27Fc From 4-nitrobenzoylacetonitrile (1.90 g, 10 mmol) and DL-2-phenylglycine (1.60 g, 10.5 mmol) as a brown oil which slowly solidified (1.71 g, 49 %). m.p. 80 – 82 °C. ν_{max} 3031, 2207, 1732, 1635, 1602, 1519, 1343, 697cm^{-1}. δ_H (400 MHz, $CDCl_3$) 5.01 (1H, br. s, COO*H*), 5.27 (1H, d, *J* = 5.6 Hz, NHC*H*COOH), 7.38 – 7.41 (2H, m, *o*-Ar-*H*), 7.46 – 7.49 (4H, m, *m*-Ar-*H*, *p*-Ar-*H*, CC*H*), 7.99 (2H, d, *J* = 8.8 Hz, *o*-PNP-*H*), 8.29 (2H, d, *J* = 8.8 Hz, *m*-PNP-*H*). δ_C (100 MHz, $CDCl_3$) 64.2, 82.4, 119.6, 123.6 (2 × C), 127.7 (2 × C), 129.1 (2 × C), 129.9 (2 × C), 130.2, 133.6, 143.0, 149.6, 160.2, 171.3, 190.3. HRMS (ESI) found $[M+H]^+$ = 352.0928 $C_{18}H_{14}N_3O_5$ requires $[M+H]^+$ = 352.0928.

3-(1-Methyl-1*H*-pyrrol-2-yl)-3-oxopropanenitrile, 3.26G *N*-Methylpyrrole (14.2 mL, 0.16 mol) was added to cyanoacetic acid (13.61 g, 0.16 mol, 1 equiv.) in acetic anhydride 80 mL and stirred at 75 °C for 45 minutes. The reaction mixture was allowed to cool before pouring onto ice. The resulting precipitate was isolated by vacuum filtration and washed with hexane to afford an off-white powder (22.41 g, 95 %). m.p. 104 – 106 °C (lit. m.p. 109 – 110 °C [08T11262, 16JHC1945], 110 °C [04S2760]). ν_{max} 3113, 2970, 1637, 760 cm^{-1}. δ_H [400 MHz, $(CD_3)_2SO$] 3.85 (3H, s, NC*H*$_3$), 4.43 (2H, s, C*H*$_2$CN), 6.18 (1H, dd, *J* = 2.5, 4.2 Hz, 4-*H*), 7.13 (1H, dd, *J* = 1.6, 4.2 Hz, 3-*H*), 7.25 (1H, m, 5-*H*). δ_C [100 MHz, $(CD_3)_2SO$] 29.7, 37.4, 109.0, 116.6, 121.7, 128.4, 133.8, 178.7. HRMS (NSI) found $[M+H]^+$ = 149.0705 $C_8H_9N_2O$ requires $[M+H]^+$ = 149.0709.

2-{[2-Cyano-3-(1-methyl-1*H*-pyrrol-2-yl)-3-oxoprop-1-en-1-yl]amino}acetic acid, 3.27Ga From 3-(1-methyl-1*H*-pyrrol-2-yl)-3-oxopropanenitrile (4.44 g, 30 mmol) and glycine (2.36 g, 31.5 mmol) as a brown oil which slowly solidified (3.62 g, 52 %). m.p. 147 – 149 °C. ν_{max} 2908, 2199, 1728, 1630,

1225, 745 cm^{-1}. The ^1H NMR spectrum showed a mixture of the (*E*)- and (*Z*)- isomers in a 0.7:1 ratio determined by the signals at δ 8.14 (1H, d, *J* = 14.9 Hz, CC*H*, *minor*) and 7.80 (1H, d, *J* = 13.8 Hz, CC*H*, *major*). δ_H [400 MHz, $(CD_3)_2SO$] 3.79 (3H, s, NCH_3, *minor*), 3.84 (3H, s, NCH_3, *major*), 4.13 (2H, d, *J* = 5.9 Hz, NHCH_2COOH, *minor*), 4.17 (2H, d, *J* = 6.1 Hz, NHCH_2COOH, *major*), 6.09 – 6.11 (1H × 2, m, 4-*H*), 6.97 (1H, dd, *J* = 1.5, 4.0 Hz, 3-*H*, *minor*), 7.06 – 7.07 (1H × 2, m, 5-*H*), 7.20 (1H, dd, *J* = 1.5, 4.1 Hz, 3-*H*, *major*), 7.80 (1H, d, *J* = 13.8 Hz, CC*H*, *major*), 8.14 (1H, d, *J* = 14.9 Hz, CC*H*, *minor*), 8.66 (1H, dt, *J* = 5.9, 14.9 Hz, N*H*, *minor*), 10.52 (1H, dt, *J* = 6.1, 13.8 Hz, *major*), 13.03 (1H × 2, br. s, 2 × COO*H*). HRMS (ESI) found $[M+H]^+$ = 234.0872 $C_{11}H_{12}N_3O_3$ requires $[M+H]^+$ = 234.0873.

2-{[2-Cyano-3-(1-methyl-1*H*-pyrrol-2-yl)-3-oxoprop-1-en-1-yl]amino}acetic acid, 3.27Gb From 3-(1-methyl-1*H*-pyrrol-2-yl)-3-oxopropanenitrile (4.44 g, 30 mmol) and DL-alanine (2.81 g, 31.5 mmol) as a brown solid (3.63 g, 49 %). m.p. 99 – 100 °C. ν_{max} 2982, 2190, 1733, 1630, 1391, 731 cm^{-1}. The ^1H NMR spectrum showed a mixture of the (*E*)- and (*Z*)- isomers in a 0.6:1 ratio determined by the signals at δ 8.14 (1H, d, *J* = 14.9 Hz, CC*H*, *minor*) and 7.80 (1H, d, *J* = 13.8 Hz, CC*H*, *major*). δ_H [400 MHz, $(CD_3)_2SO$] 1.43 (3H, d, *J* = 7.2 Hz, CH_3, *minor*), 1.47 (3H, d, *J* = 7.2 Hz, CH_3, *major*), 3.79 (3H, s, NCH_3, *minor*), 3.84 (3H, s, NCH_3, *major*), 4.34 – 4.44 (1H × 2, m, 2 × NHC*H*COOH), 6.10 – 6.12 (1H × 2, m, 2 × 4-*H*), 6.98 (1H, dd, *J* = 1.6, 4.0 Hz, 3-*H*, *minor*), 7.05 – 7.08 (1H × 2, m, 2 × 5-*H*), 7.21 (1H, dd, *J* = 1.6, 4.1 Hz, 3-*H*, *major*), 7.92 (1H, d, *J* = 13.7 Hz, CC*H*, *major*), 8.14 (1H, d, *J* = 15.0 Hz, CC*H*, *minor*), 8.87 (1H, dd, *J* = 7.8, 15.0, N*H*, *minor*), 10.78 (1H, dd, *J* = 7.7, 13.7 Hz, N*H*, *major*), 13.06 (1H × 2, br. s, 2 × COO*H*). δ_C [100 MHz, $(CD_3)_2SO$] 17.7, 19.2, 37.0, 37.6, 56.0, 56.9, 78.9, 80.7, 107.6, 107.7, 117.3, 117.5, 119.2, 122.3, 129.6, 129.7, 130.4, 131.0, 160.6, 161.0, 173.1, 173.4, 177.7, 180.7. HRMS (ESI) found $[M+H]^+$ = 248.1027 $C_{12}H_{14}N_3O_3$ requires $[M+H]^+$ = 248.1030.

2-{[2-Cyano-3-(1-methyl-1*H*-pyrrol-2-yl)-3-oxoprop-1-en-1-yl]amino}acetic acid, 3.27Gc From 3-(1-methyl-1*H*-pyrrol-2-yl)-3-oxopropanenitrile (4.44 g, 30 mmol) and DL-2-phenylglycine (4.76 g, 31.5 mmol) as a brown solid (6.12 g, 66 %). m.p. 159 – 162 °C. ν_{max} 2981, 2217, 1734, 1626, 1209, 726, 614 cm^{-1}. The ^1H NMR spectrum showed a mixture of the (*E*)- and (*Z*)- isomers in a 0.4:1 ratio determined by the signals at δ 8.07 (1H, d, *J* = 14.8 Hz, CC*H*, *minor*) and 7.90 (1H, d, *J* = 13.4 Hz, CC*H*, *major*). δ_H [400 MHz, $(CD_3)_2SO$] 3.75 (3H, s, NCH_3, *minor*), 3.84 (3H, s, NCH_3, *major*), 5.52 (1H, d, *J* = 7.7 Hz, NHC*H*COOH, *major*), 5.57 (1H, d, *J* = 6.9 Hz, NHC*H*COOH, *minor*), 6.07 (1H, dd, *J* = 2.6, 3.9 Hz, 4′-*H*, *minor*), 6.11 (1H, dd, *J* = 2.5, 4.1 Hz, 4′-*H*, *major*), 6.91 (1H, dd, *J* = 1.5, 3.9 Hz, 3′-*H*, *minor*), 7.04 (1H, app. t, 5′-*H*, *minor*), 7.10 (1H, app. t, 5′-*H*, *major*), 7.22 (1H, dd, *J* = 1.5, 4.1 Hz, 4′-

H, *major*), 7.38 – 7.48 (5H × 2, m, 2 × C_6H_5), 7.90 (1H, d, *J* = 13.4 Hz, CC*H*, *major*), 8.07 (1H, d, *J* = 14.8 Hz, CC*H*, *minor*), 9.19 (1H, dd, *J* = 6.9, 14.8 Hz, N*H*, *minor*), 11.21 (1H, dd, *J* = 7.7, 13.4 Hz, N*H*, *major*), 13.72 (1H × 2, br. s, 2 × COO*H*). δ_C [100 MHz, $(CD_3)_2SO$] 37.0, 37.7, 63.9, 64.1, 79.7, 81.6, 107.7, 107.9, 117.7 (2 × C), 118.9, 121.8, 127.7 (2 × C), 128.9 (2 × C), 129.0, 129.2, 129.3 (2 × C), 129.4, 129.5, 129.7 (2 × C), 130.6, 131.4, 136.6, 137.4, 159.8, 160.8, 171.2, 171.5, 177.4, 180.8. HRMS (ESI) found $[M+Na]^+$ = 332.1004 $C_{17}H_{15}N_3NaO_3$ requires $[M+Na]^+$ = 332.1006.

***N*-Methoxy-*N*-methylcinnamamide, 3.56** To a stirring solution of cinnamoyl chloride (10.00 g, 60.0 mmol) in 2-MeTHF (100 mL) was added *N,O*-dimethylhydroxylamine hydrochloride (6.36 g, 66.0 mmol 1.1 equiv.) and the mixture cooled in an ice-MeOH bath. Once the temperature reached 0 °C, a solution of K_2CO_3 (18.25 g, 132.1 mmol, 2.2 equiv.) in water (100 mL) was added in two portions. The ice bath was removed and the reaction mixture stirred at room temperature for 1 h prior to the addition of dil. HCl (1 M, 100 mL). The organic phase was separated, washed with water (100 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure to afford a pale yellow oil which solidified upon standing (9.56 g, 83 %). m.p. 35 – 36 °C (lit. m.p. 48 – 50 °C [13RSC(A)10158]). δ_H (400 MHz, $CDCl_3$) 3.31 (3H, s, NCH_3), 3.78 (3H, s, NOCH_3), 7.04 (2H, d, *J* = 15.8 Hz, C*H*Ph), 7.34 – 7.41 (3H, m, *m*-Ar-*H*, *p*-Ar-*H*), 7.55 – 7.59 (2H, m, *o*-Ar-*H*), 7.74 (2H, d, *J*= 15.8 Hz, COC*H*). δ_C (100 MHz, $CDCl_3$) 32.5, 61.9, 115.8, 128.1 (2 × C), 128.8 (2 × C), 129.9, 135.2, 143.5, 167.0.

Attempted synthesis of (*E*)-3-oxo-5-phenylpent-4-enenitrile, 3.26H from 3.56 The reaction was performed according to the literature method [15OBC1696]. Acetonitrile (4.2 mL, 80 mmol, 2 equiv.) was stirred in dry THF (40 mL) and cooled to -78 °C. MeLi·LiBr (2.2 M in Et_2O, 27 mL, 60 mmol, 1.5 equiv.) was added dropwise over 30 min and the mixture stirred at -78 °C for a further 30 min. *N*-Methoxy-*N*-methylcinnamamide **3.56** (7.65 g, 40 mmol, 1 equiv.) in dry THF (40 mL) was added dropwise over 5 min and stirring at -78 °C continued for 1.5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL) and allowed to reach room temperature. The product was extracted with Et_2O (2 × 100 mL). The combined organic portions were washed with brine (2 × 100 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure to afford an orange oil (5.62 g). None of the product was detected by ^1H NMR of the mixture.

General method for the synthesis of 2-[(3-cyano-4-oxo-4-phenylbut-2-en-2-yl)amino] acids

To a solution of benzoylacetonitrile (4.35 g, 30 mmol) and the appropriate α-amino acid (31.5 mmol, 1.05 equiv.) in isopropanol (80 mL) was added triethyl orthoacetate (8.5 mL, 45 mmol, 1.50 equiv.). The reaction mixture was refluxed under nitrogen until the starting material was absent by TLC. The reaction was allowed to cool and the solvent was removed under reduced pressure. The residue was dissolved in DCM and extracted into aqueous $NaHCO_3$ (3 × 50 mL) and the aqueous extracts acidified with dil. HCl (2 M, aq.). The product was then extracted with EtOAc (3 × 50 mL), dried (Na_2SO_4) and the solvent removed *in vacuo* to yield the **title compound**.

(*Z*)-2-[(3-Cyano-4-oxo-4-phenylbut-2-en-2-yl)amino]propanoic acid, 3.57b From DL-alanine (2.83 g) as a yellow solid (2.24 g, 29 %). m.p. 177 – 179 °C. ν_{max} 2980, 2889, 2201, 1745, 1613, 1581, 1284, 1210, 1140, 725 cm^{-1}. δ_H [400 MHz, $(CD_3)_2SO$] 1.50 (3H, d, *J* = 7.1 Hz, CHC*H*$_3$), 2.38 (3H, s, CC*H*$_3$), 4.65 – 4.73 (1H, m, NHC*H*COOH), 7.45 – 7.55 (3H, m, *m*-Ar-*H*, *p*-Ar-*H*), 7.67 – 7.69 (2H, m, *o*-Ar-*H*), 12.42 (1H, d, *J* = 7.8 Hz, N*H*), 13.57 (1H, br. s, COO*H*). δ_C [100 MHz, $(CD_3)_2SO$] 18.4, 19.3, 52.7, 81.8, 121.5, 127.9 (2 × C), 128.5 (2 × C), 131.4, 140.0, 172.0, 172.9, 191.7. HRMS (ESI) found $[M+H]^+$ = 259.1078 $C_{14}H_{15}N_2O_3$ requires $[M+H]^+$ = 259.1077

(*Z*)-2-[(3-Cyano-4-oxo-4-phenylbut-2-en-2-yl)amino]-2-phenylacetic acid, 3.57c From DL-2-phenylglycine (4.76 g, 31.5 mmol) as a yellow solid (1.62 g, 17 %). m.p. 205 – 207 °C. ν_{max} 2901, 2216, 1733, 1607, 1574, 1557, 723, 708 cm^{-1}. δ_H [400 MHz, $(CD_3)_2SO$] 2.23 (3H, s, C*H*$_3$), 5.79 (1H, d, *J* = 6.9 Hz, NHC*H*COOH), 7.39 – 7.56 (8H, m, CH-Ar-*H*, *m*-Ar-*H*, *p*-Ar-*H*), 7.71 (2H, d, *J* = 7.1 Hz, *o*-Ar-*H*), 12.92 (1H, d, *J* = 6.9 Hz, N*H*), 13.90 (1H, br. s, COO*H*). δ_C [100 MHz, $(CD_3)_2SO$] 19.0, 60.7, 82.4, 121.3, 127.5 (2 × C), 128.0 (2 × C), 128.5 (2 × C), 129.2, 129.7 (2 × C), 131.6, 137.0, 139.7, 170.9, 171.8, 191.8. HRMS (ESI) found $[M+H]^+$ = 321.1234 $C_{19}H_{17}N_2O_3$ $[M+H]^+$ = 321.1234.

4.3.6 Synthesis of Pyrroles: Cyclisation of 2-Alkanoyl- and 2-Aroyl-3-(1-carboxylalkylamino)acrylonitriles (2-[(2-Cyano-3-oxoprop-1-en-1-yl)amino] acids)

General method for the cyclisation of 2-[(2-cyano-3-oxoprop-1-en-1-yl)amino] acids

The 2-[(2-cyano-3-oxoprop-1-en-1-yl)amino] acid was dissolved in acetic anhydride (30 mL) prior to the addition of triethylamine (7 equiv.). The mixture was refluxed until the emission of CO_2 was complete (limewater bubbler) and allowed to cool to room temperature. The brown solution was poured into water (400 mL), stirred for 1 h and extracted with DCM (5 × 50 mL). The organic layer was washed with water (2 × 100 mL), aq. $NaHCO_3$ (5 × 50 mL) and water (100 mL). The dried (Na_2SO_4) solvent was removed under reduced pressure and the products were isolated by flash column chromatography or recrystallisation.

The following compounds were synthesised by the above method.

Cyclisation of 2-[(2-cyano-3-oxobut-1-en-1-yl)amino]-2-phenylacetic acid, 3.27Ac From **3.27Ac** (2.43 g, 10 mmol) flash column chromatography [30 % EtOAc in hexane → 100 % EtOAc] provided initially N-*acetyl*-N-*(1,4-diacetyl-2-phenyl-1*H-*pyrrol-3-yl)acetamide* **3.59Ac** as a brown solid (1.08 g, 33 %). m.p. 190 – 191 °C. ν_{max} 2981, 1742, 1707, 1662, 1237, 1199 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.16 (3H, s, NCOCH_3), 2.20 [6H, s, N(COCH_3)$_2$], 2.47 (3H, s, COCH_3), 7.24 – 7.27* (2H, m, *o*-Ar-*H*), 7.41 – 7.46 (3H, m, *m*-Ar-*H*, *p*-Ar-*H*), 8.10 (1H, s, 5-*H*). δ_C (100 MHz, $CDCl_3$) 25.3, 26.0 (2 × C), 27.7, 121.6, 124.5, 125.7, 129.1 (2 × C), 129.3, 129.5 (2 × C), 129.8, 132.8, 168.7, 173.1 (2 × C), 192.8. HRMS (ESI) found $[M+Na]^+$ = 349.1163 $C_{18}H_{18}N_2NaO_4$ requires $[M+Na]^+$ = 349.1159. Further elution provided N-*(1,4-diacetyl-2-phenyl-1*H-*pyrrol-3-yl)acetamide* **3.28Ac** as a pink solid (0.61 g, 22 %). m.p. 63 – 65 °C. ν_{max} 3236, 2980, 1737, 1661, 1371, 1201 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.00 (3H, s, NHCOCH_3), 2.10 (3H, s, NCOCH_3), 2.47 (3H, s, COCH_3), 7.35 – 7.42 (5H, m, Ar-*H*), 7.52 (1H, br. s, N*H*), 7.99 (1H, s, 5-*H*). δ_C (100 MHz, $CDCl_3$) 23.5, 25.4, 27.8, 121.0, 122.7, 124.8, 128.4 (2 × C), 129.7, 130.3 (3 × C), 131.3, 169.3, 169.6, 194.6. HRMS (ESI) found $[M+H]^+$ = 285.1237 $C_{16}H_{17}N_2O_3$ requires $[M+H]^+$ = 285.1234.

*Signal overlaps with residual $CHCl_3$.

Cyclisation of 2-[(2-cyano-4,4-dimethyl-3-oxopent-1-en-1-yl)amino]-2-phenylacetic acid, 3.27Bc From **3.27Bc** (2.86 g, 10 mmol) flash column chromatography [30 % EtOAc in hexane] provided

initially N-*acetyl*-N-*(1-acetyl-2-phenyl-4-pivaloyl-1*H-*pyrrol-3-yl)acetamide* **3.59Bc** as an orange oil which solidified on standing (0.67 g, 18 %). m.p. 130 – 131 °C. ν_{max} 2980, 2885, 1740, 1701, 1653, 1159, 956 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.35 [9H, s, C(C*H*$_3$)$_3$], 2.11 (3H, s, NCOC*H*$_3$), 2.20 [6H, s, N(COC*H*$_3$)$_2$], 7.24 – 7.27* (2H, m, *o*-Ar-*H*), 7.42-7.45 (3H, m, *m*-Ar-*H*, *p*-Ar-*H*), 8.10 (1H, s, 5-*H*). δ_C (100 MHz, $CDCl_3$) 25.5, 26.2 (2 × C), 27.9 (3 × C), 44.9, 118.8, 123.2, 126.4, 129.1 (2 × C), 129.5 (2 × C), 129.6, 129.8, 131.5, 169.0, 173.2 (2 × C), 202.1. HRMS (ESI) found $[M+H]^+$ = 368.1730 $C_{21}H_{25}N_2O_4$ requires $[M+H]^+$ = 368.1736. Further elution provided N-*(1-acetyl-2-phenyl-4-pivaloyl-1*H-*pyrrol-3-yl)acetamide* **3.28Bc** as a yellow solid (2.05 g, 63 %). m.p. 153 – 154 °C. ν_{max} 3252, 2980, 2928, 1717, 1682, 1663, 1170 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.36 [9H, s, C(C*H*$_3$)$_3$], 1.97 (3H, s, NHCOC*H*$_3$), 2.06 (3H, s, NCOC*H*$_3$), 7.37 – 7.44 (5H, m, Ar-*H*), 7.69 (1H, br. s, N*H*COCH$_3$), 7.99 (1H, s, 5-*H*). δ_C (100 MHz, $CDCl_3$) 23.6, 25.6 (2 × C), 28.1 (3 × C), 44.8, 118.0, 122.6, 124.2, 128.5 (2 × C), 128.9, 130.4 (2 × C), 169.2, 169.5 (2 × C), 204.4. HRMS (ESI) found $[M+H]^+$ = 326.1626 $C_{19}H_{22}N_2O_3$ requires $[M+H]^+$ = 326.1630.

*Signal overlaps with residual $CHCl_3$.

Cyclisation of 2-[(2-cyano-3-oxo-3-phenylprop-1-en-1-yl)amino]-2-phenylacetic acid, 3.27Cc From **3.27Cc** (3.07 g, 10 mmol) flash column chromatography [30 % EtOAc in hexane] provided initially N-*acetyl*-N-*(1-acetyl-4-benzoyl-2-phenyl-1*H-*pyrrol-3-yl)acetamide* **3.59Cc** as an orange oil which crystallised on standing (0.75 g, 19 %). m.p. 154 – 156 °C. ν_{max} 3131, 1743, 1705, 1642, 1204, 700, 667 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.17 (3H, s, NCOC*H*$_3$), 2.28 [3H, s, N(COC*H*$_3$)$_2$], 7.30 – 7.32 (2H, m, 2-*o*-Ar-*H*), 7.43 – 7.47 (3H, m, 2-*m*-Ar-*H*, 2-*p*-Ar-*H*), 7.49 – 7.52 (2H, m, 4-*m*-Ar-*H*), 7.59 – 7.63 (1H, m, 4-*p*-Ar-*H*), 7.87 (1H, s, 4-*o*-Ar-*H*), 7.90 (1H, s, 5-*H*). δ_C (100 MHz, $CDCl_3$) 25.3, 26.2 (2 × C), 120.8, 125.8, 126.6, 128.6 (2 × C), 129.1 (2 × C), 129.2 (2 × C), 129.4, 129.5 (2 × C), 129.8, 132.7, 132.8, 138.3, 168.7, 173.2 (2 × C), 189.9. HRMS (NSI) found $[M+H]^+$ = 389.1494 $C_{23}H_{21}N_2O_4$ requires $[M+H]^+$ = 389.1496. Further elution provided N-*(1-acetyl-4-benzoyl-2-phenyl-1*H-*pyrrol-3-yl)acetamide* **3.28Cc** as a yellow solid (1.61 g, 61 %). m.p. 147 – 149 °C. ν_{max} 3273, 3138, 1738, 1651, 1277, 1212, 713, 669 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.97 (3H, s, NHCOC*H*$_3$), 2.12 (3H, s, NCOC*H*$_3$), 7.43 (5H, s, 2-Ar-*H*), 7.49 – 7.53 (2H, m, 4-*m*-Ar-*H*), 7.59 – 7.63 (1H, m, 4-*p*-Ar-*H*), 7.66 (1H, br. s, N*H*COCH$_3$), 7.74 (1H, s, 5-*H*), 7.90 – 7.91 (2H, m, 4-*o*-Ar-*H*). δ_C (100 MHz, $CDCl_3$) 23.4, 25.3, 120.5, 123.7, 128.5, 128.6 (2 × C), 129.0, 129.3 (2 × C), 129.6, 130.3 (2 × C), 131.2, 132.7 (2 × C), 138.2 (2 × C), 169.2 (2 × C), 191.5. HRMS (NSI) found $[M+H]^+$ = 347.1389 $C_{21}H_{19}N_2O_3$ requires $[M+H]^+$ = 347.1390. (For crystallographic data see appendix 4).

From **3.27Cc** (1.55 g, 5 mmol) following the general cyclisation method except the reaction was stirred at reflux for 2 h. Flash column chromatography [30 % EtOAc in hexane] provided only N-*acetyl*-N-*(1-acetyl-4-benzoyl-2-phenyl-1*H-*pyrrol-3-yl)acetamide* **3.59Cc** as yellow needles from EtOAc/hexane (1.56 g, 79 %). The physical and spectroscopic data were in perfect agreement with those of **3.59Cc**.

Cyclisation of 2-{[2-cyano-3-(4-methoxyphenyl)-3-oxoprop-1-en-1-yl]amino}-2-phenylacetic acid, 3.27Dc From **3.27Dc** (3.36 g, 10 mmol) flash column chromatography [40 % EtOAc in hexane] provided initially N-*acetyl*-N-*(1-acetyl-4-(4-methoxybenzoyl)-2-phenyl-1*H-*pyrrol-3-yl)acetamide* **3.59Dc** as a pale orange powder (1.04 g, 25 %). m.p. 167 – 168 °C. ν_{max} 2981, 1723, 1698, 1227, 1204 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.18 (3H, s, NCOCH_3), 2.27 [6H, s, N(COCH_3)$_2$], 3.90 (3H, s, OCH_3), 6.98 – 7.00 (2H, m, *m*-An-*H*), 7.30 – 7.32 (2H, m, *o*-Ar-*H*), 7.45 – 7.47 (3H, m, *m*-Ar-*H*, *p*-Ar-*H*), 7.86 (1H, s, 5-*H*), 7.91 – 7.93 (2H, m, *o*-An-*H*). δ_C (100 MHz, $CDCl_3$) 25.3, 26.2 (2 × C), 55.6, 113.9 (2 × C), 121.1, 125.6, 126.0 (2 × C), 129.1 (2 × C), 129.5 (2 × C), 129.7, 131.0, 131.6 (2 × C), 132.5, 163.5, 168.8, 173.3 (2 × C), 188.4. HRMS (ESI) found $[M+H]^+$ = 419.1602 $C_{24}H_{23}N_2O_5$ requires $[M+H]^+$ = 419.1601. Further elution provided N-*[1-acetyl-4-(4-methoxybenzoyl)-2-phenyl-1*H-*pyrrol-3-yl]acetamide* **3.28Dc** as a pale yellow solid (1.91 g, 51 %). m.p. 166 – 167 °C. ν_{max} 3241, 3130, 2981, 1742, 1644, 1595, 1573, 1168 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.95 (3H, s, NHCOCH_3), 2.12 (3H, s, NCOCH_3), 3.90 (3H, s, OCH_3), 6.98 – 7.00 (2H, m, *m*-An-*H*), 7.42 (5H, s, Ar-*H*), 7.72 (1H, s, 5-*H*), 7.75 (1H, br. s, N*H*), 7.92 – 7.95 (2H, m, *o*-An-*H*). δ_C (100 MHz, $CDCl_3$) 23.4, 25.3, 55.6, 113.9 (2 × C), 120.8, 123.7, 124.8 (2 × C), 128.5 (2 × C), 128.9, 129.4, 130.3 (2 × C), 130.8, 131.3, 131.7 (2 × C), 163.5, 169.2, 190.0. HRMS (ESI) found $[M+Na]^+$ = 399.1310 $C_{22}H_{20}N_2NaO_4$ requires $[M+Na]^+$ = 399.1315.

Cyclisation of 2-({2-cyano-3-[4-(dimethylamino)phenyl]-3-oxoprop-1-en-1-yl}amino)-2-phenylacetic acid, 3.27Ec From **3.27Ec** (1.05 g, 3 mmol) flash column chromatography [50 % EtOAc in hexane → 100 % EtOAc] provided initially N-*acetyl*-N-*{1-acetyl-4-[4-(dimethylamino)benzoyl]-2-phenyl-1*H-*pyrrol-3-yl}acetamide* **3.59Ec** as a yellow crystalline solid (0.53 g, 41 %). m.p. 192 – 193 °C. ν_{max} 2980, 2908, 1722, 1698, 1351, 1235, 1207, 1183, 1151, 694 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.19 (3H, s, NCOCH_3), 2.27 [6H, s, N(COCH_3)$_2$], 3.08 [6H, s, N(CH_3)$_2$], 6.70 (2H, d, *J* = 8.9 Hz, *m*-DP-*H*), 7.30 – 7.32 (2H, m, *o*-Ar-*H*), 7.41 – 7.45 (3H, m, *m*-Ar-*H*, *p*-Ar-*H*), 7.85 (1H, s, 5-*H*), 7.89 (2H, d, *J* = 8.9 Hz, *o*-DP-*H*). δ_C (100 MHz, $CDCl_3$) 25.3, 26.3 (2 × C), 40.1 (2 × C), 110.8 (2 × C), 121.6, 124.7, 125.6, 126.2, 128.9 (2 × C), 129.5 (2 × C), 129.6, 129.8, 131.7 (2 × C), 132.2, 153.5, 168.9, 173.3 (2 ×

C), 187.6. HRMS (ESI) found $[M+Na]^+$ = 454.1745 $C_{25}H_{25}N_3NaO_4$ requires $[M+Na]^+$ = 454.1737. Further elution afforded N-*{1-acetyl-4-[4-(dimethylamino)benzoyl]-2-phenyl-1*H*-pyrrol-3-yl}acetamide* **3.28Ec** as a yellow solid (0.36 g, 31 %). m.p. 198 – 200 °C. ν_{max} 3323, 2981, 1732, 1681, 1591, 1368, 1182, 752, 691 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.94 (3H, s, NHCOCH_3), 2.12 (3H, s, NCOCH_3), 3.09 [6H, s, N(CH_3)$_2$], 6.71 (2H, d, *J* = 9.0 Hz, *m*-DP-*H*), 7.39 – 7.42 (5H, m, C_6H_5), 7.72 (1H, s, 5-*H*), 7.90 – 7.29 (3H, m, *o*-DP-*H*, N*H*). δ_C (100 MHz, $CDCl_3$) 23.4, 25.4, 40.1 (2 × C), 110.9 (2 × C), 121.0, 124.0, 124.1, 125.4, 128.4 (2 × C), 128.7, 129.1, 130.3 (2 × C), 131.7, 131.9 (2 × C), 153.6, 169.0, 169.4, 189.3. HRMS (ESI) found $[M+H]^+$ = 390.1821 $C_{23}H_{24}N_3O_3$ requires $[M+H]^+$ = 390.1812.

Cyclisation of 2-{[2-cyano-3-(1-methyl-1*H*-pyrrol-2-yl)-3-oxoprop-1-en-1-yl]amino}-2-phenylacetic acid, 3.27Gc From **3.27Gc** (3.04 g, 10 mmol) flash column chromatography [30 % EtOAc in hexane] provided initially N-*acetyl*-N-*(1-acetyl-4-(1-methyl-1*H*-pyrrole-2-carbonyl)-2-phenyl-1*H*-pyrrol-3-yl)acetamide* **3.59Gc** as a yellow solid (1.21 g, 32 %). m.p. 145 – 147 °C. ν_{max} 3104, 1745, 1702, 1607, 1530, 1200, 771 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.20 (3H, s, NCOCH_3), 2.26 [6H, s, N(COCH_3)$_2$], 3.95 (3H, s, NCH_3), 6.18 (1H, dd, *J* = 2.5, 4.0 Hz, 4'-*H*), 6.91 (1H, app. t, 5'-*H*), 7.00 (1H, dd, *J* = 1.5, 4.0 Hz, 3'-*H*), 7.29 – 7.31 (2H, m, *o*-Ar-*H*), 7.42 – 7.45 (3H, m, *m*-Ar-*H*, *p*-Ar-*H*), 7.93 (1H, s, 5-*H*). δ_C (100 MHz, $CDCl_3$) 25.2, 26.3 (2 × C), 37.2, 108.3, 121.4, 122.4, 124.3, 125.8, 128.9 (2 × C), 129.5 (2 × C), 129.6, 129.7, 130.9, 131.7, 132.1, 168.8, 173.2 (2 × C), 178.5. HRMS (ESI) found $[M+H]^+$ = 392.1606 $C_{22}H_{22}N_3O_4$ requires $[M+H]^+$ = 392.1605. Further elution provided N-*(1-acetyl-4-(1-methyl-1*H*-pyrrole-2-carbonyl)-2-phenyl-1*H*-pyrrol-3-yl)acetamide* **3.28Gc** as a yellow solid (1.33 g, 39 %). m.p. 198 – 200 °C. ν_{max} 3252, 3098, 1736, 1719, 1600, 1582, 1209, 741 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.95 (3H, s, NHCOCH_3), 2.14 (3H, s, NCOCH_3), 3.96 (3H, NCH_3), 6.18 (1H, dd, *J* = 2.5, 4.0 Hz, 4'-*H*), 6.91 (1H, app. t, 5'-*H*), 7.02 (1H, app. d, 3'-*H*), 7.41 (5H, s, Ar-*H*), 7.70 (1H, br. s, N*H*), 7.79 (1H, s, 5-*H*). δ_C (100 MHz, $CDCl_3$) 23.3, 25.2, 37.1, 108.5, 121.8, 122.1, 123.5, 123.7, 128.4 (2 × C), 128.7, 129.3, 130.2 (2 × C), 130.8, 131.5, 131.7, 169.1 (2 × C), 180.2. HRMS (ESI) found $[M+Na]^+$ = 372.1318 $C_{20}H_{19}N_3NaO_3$ requires $[M+Na]^+$ = 372.1319.

Cyclisation of 2-{[2-cyano-3-(4-nitrophenyl)-3-oxoprop-1-en-1-yl]amino}-2-phenylacetic acid, 3.27Fc From **3.27Fc** (0.70 g, 2 mmol) flash column chromatography [30 % EtOAc in hexane] provided initially *1-acetyl-4-cyano-2-phenyl-1*H*-pyrrol-3-yl acetate* **3.60c** as a green/brown solid (0.07 g, 13 %). m.p. 124 – 125 °C. ν_{max} 3167, 2233, 1749, 1587, 1340, 1188, 1141, 694 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.16 (3H, s, OCOCH_3), 2.21 (3H, s, NCOCH_3), 7.28 – 7.31 (2H, m, *o*-Ar-*H*), 7.43 – 7.46 (3H, m, *m*-Ar-*H*, *p*-Ar-*H*), 7.82 (1H, s, 5-*H*). δ_C (100 MHz, $CDCl_3$) 20.2, 24.8, 93.6, 112.3, 125.0, 125.3,

128.5, 128.8 (2 × C), 129.5, 130.0 (2 × C), 136.7, 167.7, 168.5. HRMS (ESI) found $[M+Na]^+$ = 291.0741 $C_{15}H_{12}N_2NaO_3$ requires $[M+Na]^+$ = 291.0740. Further elution provided *1-acetyl-4-(4-nitrophenyl)-2-phenyl-1*H*-pyrrole-3-carbonitrile* **3.29Fc** as a yellow solid (0.04 g, 8 %). m.p. 95 – 96 °C. ν_{max} 3296, 2231, 1741, 1598, 1520, 1345, 700 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.23 (3H, s, NCOC*H*$_3$), 7.24 – 7.27 (2H, m, *o*-Ar-*H*), 7.33 (2H, d, *J* = 8.6 Hz, *o*-PNP-*H*), 7.39 – 7.48 (3H, m, *m*-Ar-*H*, *p*-Ar-*H*), 8.03 (1H, s, 5-*H*), 8.10 (2H, d, *J* = 8.6 Hz, *m*-PNP-*H*). δ_C (100 MHz, $CDCl_3$) 21.1, 97.3, 114.3, 123.7 (2 × C), 125.9, 128.7, 129.1 (2 × C), 129.8, 129.9 (2 × C), 130.3, 130.7 (2 × C), 132.5, 137.9, 147.0, 167.9. HRMS (ESI) found $[M+H]^+$ = 332.1034 $C_{19}H_{14}N_3O_3$ requires $[M+H]^+$ = 332.1030. The following fraction provided N-*acetyl*-N-*[1-acetyl-4-(4-nitrobenzoyl)-2-phenyl-1*H*-pyrrol-3-yl]acetamide* **3.59Fc** as a brown oil which slowly solidified (0.15 g, 17 %). m.p. 155 – 157 °C. ν_{max} 3851, 3161, 2158, 1716, 1661, 1525, 1345, 1203, 710 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.16 (3H, s, NCOC*H*$_3$), 2.27 [6H, s, N(COC*H*$_3$)$_2$], 7.30 – 7.32 (2H, m, *o*-Ar-*H*), 7.46 – 7.52 (3H, m, *m*-Ar-*H*, *p*-Ar-*H*), 7.87 (1H, s, 5-*H*), 8.03 (2H, d, *J* = 8.7 Hz, *o*-PNP-*H*), 8.37 (2H, d, *J* = 8.7 Hz, *m*-Ar-*H*). δ_C (100 MHz, $CDCl_3$) 25.4, 26.2 (2 × C), 120.4, 123.9 (2 × C), 125.6, 126.9, 129.0, 129.2 (2 × C), 129.5 (2 × C), 130.0 (2 × C), 130.1, 133.2, 143.2, 150.1, 168.6, 173.0 (2 × C), 188.1. HRMS (ESI) found $[M+H]^+$ = 434.1347 $C_{23}H_{20}N_3O_6$ requires $[M+H]^+$ = 434.1347. Finally N-*[1-acetyl-4-(4-nitrobenzoyl)-2-phenyl-1*H*-pyrrol-3-yl]acetamide* **3.28Fc** was afforded as a brown oil which slowly solidified (0.15 g, 19 %). m.p. 188 – 189 °C. ν_{max} 3852, 3243, 2980, 1745, 1664, 1574, 1519, 1346, 1197, 702 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.98 (3H, s, NHCOC*H*$_3$), 2.12 (3H, s, NCOC*H*$_3$), 7.38 (1H, br. s, N*H*COCH$_3$), 7.40 – 7.42 (2H, m, *o*-Ar-*H*), 7.46 – 7.47 (3H, m, *m*-Ar-*H*, *p*-Ar-*H*), 7.72 (1H, s, 5-*H*), 8.05 (2H, d, *J* = 8.7 Hz, *o*-PNP-*H*), 8.36 (2H, d, *J* = 8.7 Hz, *m*-PNP-*H*. δ_C (100 MHz, $CDCl_3$) 23.4, 25.3, 120.3, 123.2, 123.8 (2 × C), 125.7, 128.7 (2 × C), 129.3, 129.9, 130.1 (2 × C), 130.2 (2 × C), 130.6, 143.2, 150.0, 169.0, 169.4, 189.3. HRMS (ESI) found $[M+H]^+$ = 392.1239 $C_{21}H_{18}N_3O_5$ requires $[M+H]^+$ = 392.1241.

Cyclisation of 2-[(2-cyano-3-oxobut-1-en-1-yl)amino]propanoic acid, 3.27Ab From **3.27Ab** (0.95 g, 5 mmol) flash column chromatography [30 % EtOAc in hexane] provided *1-acetyl-4-cyano-2-methyl-1*H*-pyrrol-3-yl acetate* **3.60b** as a pale yellow solid (0.65 g, 61 %). m.p. 119 – 122 °C. ν_{max} 3156, 2233, 1760, 1745, 1343, 1188, 1164 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.33 (3H, s, C*H*$_3$), 2.34 (3H, s, OCOC*H*$_3$), 2.58 (3H, s, NCOC*H*$_3$), 7.51 (1H, s, 5-*H*). δ_C (100 MHz, $CDCl_3$) 11.7, 20.3, 23.3, 93.4, 112.5, 123.2, 124.3, 135.7, 168.2, 168.3. HRMS (ESI) found $[M+K]^+$ = 245.0323 $C_{10}H_{10}KN_2O_3$ requires $[M+K]^+$ = 245.0323.

Cyclisation of 2-[(2-cyano-4,4-dimethyl-3-oxopent-1-en-1-yl)amino]propanoic acid, 3.27Bb From **3.27Bb** (2.16 g, 9.6 mmol) flash column chromatography [20 % EtOAc in hexane] provided initially *1-acetyl-4-cyano-2-methyl-1*H-*pyrrol-3-yl acetate* **3.60b** as an orange solid (0.52 g, 26 %). Physical and spectroscopic data in agreement with **3.60b** from **3.27Ab**. Further elution provided N-*acetyl*-N-*(1-acetyl-2-methyl-4-pivaloyl-1*H-*pyrrol-3-yl)acetamide* **3.59Bb** as an orange oil which solidified on standing (0.28 g, 10 %). m.p. 94 – 96 °C. ν_{max} 3159, 2970, 2930, 1734, 1709, 1681, 1641, 1230 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.30 [9H, s, C(C*H*$_3$)$_3$], 2.30 [6H, s, N(COC*H*$_3$)$_2$], 2.32 (3H, s, C*H*$_3$), 2.64 (3H, s, NCOC*H*$_3$), 7.66 (1H, s, 5-*H*). δ_C (100 MHz, $CDCl_3$) 11.8, 23.8, 26.1 (2 × C), 27.9 (3 × C), 44.8, 119.6, 121.7, 125.2, 130.4, 168.8, 173.2 (2 × C), 202.0. HRMS (NSI) found $[M+H]^+$ = 307.1653 $C_{16}H_{23}N_2O_4$ requires $[M+H]^+$ = 307.1652. The final compound to be eluted was N-*(1-acetyl-2-methyl-4-pivaloyl-1*H-*pyrrol-3-yl)acetamide* **3.28Bb** as a brown oil (0.49 g, 19 %). ν_{max} 3291, 2972, 2931, 1730, 1654, 1370, 1212 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.33 [9H, s, C(C*H*$_3$)$_3$], 2.17 (3H, s, C*H*$_3$), 2.35 (3H, s, NHCOC*H*$_3$), 2.60 (3H, NCOC*H*$_3$), 7.65 (1H, s, 5-*H*), 8.29 (1H, br. s, N*H*). δ_C (100 MHz, $CDCl_3$) 14.3, 23.8, 24.1, 28.3 (3 × C), 44.6, 117.1, 121.8, 123.3, 126.0, 168.5, 168.9, 204.4. HRMS (NSI) found $[M+H]^+$ = 265.1546 $C_{14}H_{21}N_2O_3$ requires $[M+H]^+$ = 265.1547.

Cyclisation of 2-[(2-cyano-3-oxo-3-phenylprop-1-en-1-yl)amino]propanoic acid, 3.27Cb From **3.27Cb** (2.44 g, 10 mmol) flash column chromatography [30 % EtOAc in hexane → 100 % EtOAc] provided *1-acetyl-4-cyano-2-methyl-1*H-*pyrrol-3-yl acetate* **3.60b** as a pale yellow solid (1.55 g, 75 %). Physical and spectroscopic data in agreement with **3.60b** from **3.27Ab**.

Cyclisation of 2-{[2-cyano-3-(4-methoxyphenyl)-3-oxoprop-1-en-1-yl]amino}propanoic acid, 3.27Db From **3.27Db** (2.74 g, 10 mmol), flash column chromatography [30 % EtOAc in hexane] provided *1-acetyl-4-cyano-2-methyl-1*H-*pyrrol-3-yl acetate* **3.60b** as off-white needles (1.62 g, 79 %). Physical and spectroscopic data in agreement with **3.60b** from **3.27Ab**.

Cyclisation of 2-({2-cyano-3-[4-(dimethylamino)phenyl]-3-oxoprop-1-en-1-yl}amino)propanoic acid, 3.27Eb From **3.27Eb** (0.57 g, 2 mmol) flash column chromatography [25 % EtOAc in hexane] afforded initially *1-acetyl-4-cyano-2-methyl-1*H-*pyrrol-3-yl acetate* **3.60b** as a pink solid (0.17 g, 42 %). Physical and spectroscopic data in agreement with **3.60b** from **3.27Ab**. Further elution provided N-*acetyl*-N-*{1-acetyl-4-[4-(dimethylamino)benzoyl]-2-methyl-1*H-*pyrrol-3-yl}acetamide* **3.59Eb** as an orange solid (0.01 g, 1 %). m.p. 177 – 180 °C. ν_{max} 2928, 1730, 1703, 1606, 1209, 1184, 1160, 593 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.36 [6H, s, N(COC*H*$_3$)$_2$], 2.38 (3H, s, C*H*$_3$), 2.60 (3H, s, NCOC*H*$_3$), 3.08 [6H, s, N(C*H*$_3$)$_2$], 6.68 (2H, d, *J* = 9.0 Hz, *m*-DP-*H*), 7.42 (1H, s, 5-*H*), 7.83 (2H, d, *J* =

9.0 Hz, *o*-DP-*H*). δ_C (100 MHz, $CDCl_3$) 12.0, 23.8, 26.3 (2 × C), 40.1 (2 × C), 110.8 (2 × C), 122.3, 123.4, 124.9, 125.6, 131.1, 131.6 (2 × C), 153.5, 169.1, 173.3 (2 × C), 187.6. HRMS (ESI) found $[M+H]^+$ = 370.1763 $C_{20}H_{24}N_3O_4$ requires $[M+H]^+$ = 370.1761.

Cyclisation of 2-{[2-cyano-3-(1-methyl-1*H*-pyrrol-2-yl)-3-oxoprop-1-en-1-yl]amino}propanoic acid, 3.27Gb From **3.27Gb** (2.50 g, 10 mmol) flash column chromatography [30 % EtOAc in hexane] provided initially *1-acetyl-4-cyano-2-methyl-1*H-*pyrrol-3-yl acetate* **3.60b** as colourless crystals (0.54 g, 26 %). The physical and spectroscopic data were in agreement with **3.60b** from **3.27Ab**. Further elution provided N-*acetyl*-N-*[1-acetyl-2-methyl-4-(1-methyl-1*H-*pyrrole-2-carbonyl)-1*H-*pyrrol-3-yl]acetamide* **3.59Gb** as an orange solid (0.39 g, 12 %). m.p. 149 – 150 °C. ν_{max} 3146, 2924, 1737, 1702, 1366, 1239, 1206 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.35 [6H, s, $N(COC\mathit{H}_3)_2$], 2.36 (3H, s, $NCOC\mathit{H}_3$), 3.93 (3H, s, $NC\mathit{H}_3$), 6.15 (1H, dd, *J* = 2.6, 3.8 Hz, 4′-*H*), 6.89 – 6.91 (2H, m, 3′-*H*, 5′-*H*), 7.52 (1H, s, 5-*H*). δ_C (100 MHz, $CDCl_3$) 11.9, 23.7, 26.3 (2 × C), 37.1, 108.3, 121.0, 123.0, 123.2, 124.5, 130.9, 131.1, 131.6, 169.1, 173.2 (2 × C), 178.6. HRMS (ESI) found $[M+Na]^+$ = 352.1268 $C_{17}H_{19}N_3NaO_4$ requires $[M+Na]^+$ = 352.1268. The final fraction afforded N-*[1-acetyl-2-methyl-4-(1-methyl-1*H-*pyrrole-2-carbonyl)-1*H-*pyrrol-3-yl]acetamide* **3.28Gb** as orange needles (0.55 g, 19 %). m.p. 183 – 184 °C. ν_{max} 3330, 3109, 2980, 2920, 1722, 1673, 653, 581 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.16 (3H, s, $NHCOC\mathit{H}_3$), 2.41 (3H, s, $C\mathit{H}_3$), 2.57 (3H, s, $NCOC\mathit{H}_3$), 3.96 (3H, s, $NC\mathit{H}_3$), 6.17 (1H, dd, *J* = 2.6, 3.8 Hz, 4′-*H*), 6.90 – 6.92 (2H, m, 3′-*H*, 5′-*H*), 7.44 (1H, s, 5-*H*), 8.13 (1H, br. s, N*H*). δ_C (100 MHz, $CDCl_3$) 14.2, 23.7, 24.0, 37.0, 108.5, 121.2, 121.3, 122.5, 122.8, 127.4, 130.8, 131.6, 168.5, 169.0, 180.5. HRMS (ESI) found $[M+Na]^+$ = 310.1165 $C_{15}H_{17}N_3NaO_3$ requires $[M+Na]^+$ = 310.1162.

Cyclisation of 2-{[2-cyano-3-(4-nitrophenyl)-3-oxoprop-1-en-1-yl]amino}propanoic acid, 3.27Fb From **3.27Fb** (0.60 g, 2 mmol) flash column chromatography [30 % EtOAc in hexane] provided *1-acetyl-4-cyano-2-methyl-1*H-*pyrrol-3-yl acetate* **3.60b** as a yellow solid (0.21 g, 49 %). The physical and spectroscopic data were in agreement with **3.60b** from **3.27Ab**.

Cyclisation of 2-[(2-cyano-3-oxo-3-phenylprop-1-en-1-yl)amino]butanoic acid, 3.27Cd From **3.27Cd** (2.57 g, 10 mmol); the brown solid was recrystallised from EtOAc/hexane to afford *1-acetyl-4-cyano-2-ethyl-1*H-*pyrrol-3-yl acetate* **3.60d** as red crystals (1.38 g, 63 %). m.p. 122 – 123 °C. ν_{max} 3145, 2979, 2881, 2232, 1763, 1750, 1187 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.25 (3H, t, *J* = 7.3 Hz, $CH_2C\mathit{H}_3$), 2.35 (3H, s, $OCOC\mathit{H}_3$), 2.59 (3H, s, $NCOC\mathit{H}_3$), 2.79 (2H, q, *J* = 7.3 Hz, $C\mathit{H}_2CH_3$), 7.50 (1H, s, 5-*H*). δ_C (100 MHz, $CDCl_3$) 13.2, 18.5, 20.3, 23.4, 93.4, 112.5, 124.7, 129.0, 135.3, 168.0, 168.6. HRMS (ESI) found $[M+NH_4]^+$ = 238.1187 $C_{11}H_{16}N_3O_3$ requires $[M+NH_4]^+$ = 238.1186.

Cyclisation of 2-[(2-cyano-3-oxo-3-phenylprop-1-en-1-yl)amino]-3-methylbutanoic acid, 3.27Ce From **3.27Ce** (2.72 g, 10 mmol); the orange oil solidified on standing and was recrystallised from EtOAc/hexane to afford *1-acetyl-4-cyano-2-isopropyl*-1H-*pyrrol-3-yl acetate* **3.60e** as fluffy yellow crystals (1.65 g, 71 %). m.p. 76 – 79°C. ν_{max} 3167, 2974, 2937, 2232, 1760, 1741, 1190, 619 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.24 [6H, d, *J* = 7.0 Hz, CH(C*H*$_3$)$_2$], 2.33 (3H, s, OCOC*H*$_3$), 2.59 (3H, s, NCOC*H*$_3$), 3.74 [1H, sep, *J* = 7.0 Hz, C*H*(CH$_3$)$_2$], 7.47 (1H, s, 5-*H*). δ_C (100 MHz, $CDCl_3$) 20.4, 20.8 (2 × C), 24.0, 26.0, 94.0, 112.4, 124.8, 132.4, 135.7, 168.3, 168.7. HRMS (NSI) found $[M+NH_4]^+$ = 252.1343 $C_{12}H_{18}N_3O_3$ requires $[M+NH_4]^+$ = 252.1343.

Cyclisation of 2-[(2-cyano-3-oxobut-1-en-1-yl)amino]acetic acid, 3.27Aa From **3.27Aa** (0.91 g, 5 mmol) flash column chromatography [30 % EtOAc in hexane] provided initially *1-acetyl-4-cyano-1*H-*pyrrol-3-yl acetate* **3.60a** as a yellow oil which solidified on standing (0.24 g, 23 %). m.p. 82 – 84 °C. ν_{max} 3151, 2980, 2232, 1776, 1724, 1363, 1199 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.34 (3H, s, OCOC*H*$_3$), 2.58 (3H, s, NCOC*H*$_3$), 7.51 (1H, d, *J* = 2.3 Hz, 2-*H*), 7.71 (1H, d, *J* = 2.3 Hz, 5-*H*). δ_C (100 MHz, $CDCl_3$) 20.7, 21.8, 93.1, 109.2, 112.2, 123.5, 138.7, 166.5, 167.2. HRMS (APCI) found $[M+NH_4]^+$ = 210.0872 $C_9H_{12}N_3O_3$ requires $[M+NH_4]^+$ = 210.0873. Further elution provided N-*(1,4-diacetyl-1*H-*pyrrol-3-yl)acetamide* **3.28Aa** as an orange solid (0.13 g, 12 %). m.p. 231 – 232 °C. ν_{max} 3349, 3205, 3120, 1719, 1672, 1651, 1250, 625 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.19 (3H, s, NHCOC*H*$_3$), 2.48 (3H, s, COC*H*$_3$), 2.59 (3H, s, NCOC*H*$_3$), 7.92 (2H, s, 2-*H*, 5-*H*), 9.69 (1H, br. s, N*H*). δ_C (100 MHz, $CDCl_3$) 22.4, 23.9, 27.4, 109.5, 117.9, 122.3, 126.4, 168.0, 168.2, 197.0. HRMS (ESI) found $[M+Na]^+$ = 231.0742 $C_{10}H_{12}N_2NaO_3$ requires $[M+Na]^+$ = 231.0740.

Cyclisation of 2-[(2-cyano-4,4-dimethyl-3-oxopent-1-en-1-yl)amino]acetic acid, 3.27Ba From **3.27Ba** (1.15 g, 5 mmol). Flash column chromatography [25 % EtOAc in hexane] provided initially *1-acetyl-4-(*t*-butyl)-1*H-*pyrrole-3-carbonitrile* **3.29Ba** as an orange oil (0.12 g, 13 %). ν_{max} 3146, 2970, 2871, 2227, 1732, 1246, 1206 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.36 [9H, s, C(C*H*$_3$)$_3$], 2.55 (3H, s, NCOC*H*$_3$), 7.06 (1H, s, 5-*H*), 7.74 (1H, s, 2-*H*). δ_C (100 MHz , $CDCl_3$) 22.1, 29.8 (3 × C), 31.3, 97.4, 114.9, 115.6, 128.0, 139.5, 166.6. HRMS (NSI) found $[M+NH_4]^+$ = 208.1445 $C_{11}H_{18}N_3O$ requires $[M+NH_4]^+$ = 208.1444 Further elution provided N-*(1-acetyl-4-pivaloyl-1*H-*pyrrol-3-yl)acetamide* **3.28Ba** as a yellow crystalline solid from EtOAc/hexane (0.42 g, 34 %). m.p. 109 – 112 °C. ν_{max} 3360, 3132, 2974, 2934, 1734, 1724, 1678, 1634, 1213, 588 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.37 [9H, s, C(C*H*$_3$)$_3$], 2.19 (3H, s, NHCOC*H*$_3$), 2.59 (3H, s, NCOC*H*$_3$), 7.97 (1H, d, *J* = 2.0 Hz, 2-*H*), 8.03 (1H, d, *J* = 2.0 Hz, 5-*H*), 10.08 (1H, br. s, N*H*COCH$_3$). δ_C (100 MHz, $CDCl_3$) 22.5, 24.1, 28.4 (3 × C), 44.9, 108.8,

113.7, 121.6, 128.0, 168.1, 168.2, 206.2. HRMS (NSI) found $[M+H]^+$ = 251.1391 $C_{13}H_{19}N_2O_3$ requires $[M+H]^+$ = 251.1390.

Cyclisation of 2-[(2-cyano-3-oxo-3-phenylprop-1-en-1-yl)amino]acetic acid, 3.27Ca From **3.27Ca** (2.33 g, 10 mmol). Flash column chromatography provided initially *1-acetyl-4-phenyl-1*H-*pyrrole-3-carbonitrile* **3.29Ca** as orange crystals (0.09 g, 4 %). m.p. 110 – 112 °C [lit. m.p. 112 – 114 °C (80USP4229465)]. ν_{max} 3134, 2223, 1727, 1366, 799, 692, 616 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.63 (3H, s, NCOC*H*$_3$), 7.35 – 7.39 (1H, m, *p*-Ar-*H*), 7.43 – 7.46 (2H, m, *m*-Ar-*H*), 7.50 (1H, d, *J* = 2.0 Hz, 5-*H*), 7.63 – 7.65 (2H, m, *o*-Ar-*H*), 7.85 (1H, d, *J* = 2.0 Hz, 2-*H*). δ_C (100 MHz, $CDCl_3$) 22.1, 97.7, 114.9, 116.5, 126.8 (2 × C), 127.7, 128.4, 129.1 (2 × C), 129.4, 131.0, 166.5. HRMS (NSI) found $[M+NH_4]^+$ = 228.1132 $C_{13}H_{14}N_3O$ requires $[M+NH_4]^+$ = 228.1131. Further elution provided *1-acetyl-4-cyano-1*H-*pyrrol-3-yl acetate* **3.60a** as an off-white powder (0.45 g, 23 %). The physical and spectroscopic data were in agreement with **3.60a** from **3.27Aa**. Subsequent elution provided N-*(5-cyano-2-oxo-6-phenyl-2*H-*pyran-3-yl)acetamide* **3.61C** as a brown powder (0.05 g, 2 %). m.p. 208 – 209 °C. ν_{max} 3355, 2980, 2232, 1717, 1693, 1518, 1369 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.26 (3H, s, NHCOC*H*$_3$), 7.52 (3H, m, *m*-Ar-*H*, *p*-Ar-*H*), 7.97 (1H, br. s, N*H*COCH$_3$), 8.01 (2H, d, *J* = 7.1 Hz, *o*-Ar-*H*), 8.46 (1H, s, 4-*H*). δ_C (100 MHz, $CDCl_3$) 24.6, 91.3, 115.8, 122.9, 123.6, 127.8 (2 × C), 129.2 (3 × C), 132.5, 157.1, 160.9, 169.4. HRMS (NSI) found $[M+H]^+$ = 255.0763 $C_{14}H_{11}N_2O_3$ requires $[M+H]^+$ = 255.0164. The final compound to be eluted was N-*(1-acetyl-4-benzoyl-1*H-*pyrrol-3-yl)acetamide* **3.28Ca** as a brown oil (0.30 g, 11 %). ν_{max} 3345, 2928, 1727, 1532, 1374, 1206, 1070, 672 cm^{-1}. δ_H 2.24 (3H, s, NHCOC*H*$_3$), 2.60 (3H, s, NCOC*H*$_3$), 7.50 – 7.54 (2H, m, *m*-Ar-*H*), 7.60 – 7.64 (1H, m, *p*-Ar-*H*), 7.77 – 7.79 (3H, m, *o*-Ar-*H*, 5-*H*), 8.02 (1H, d, *J* = 2.3 Hz, 2-*H*), 9.80 (1H, br. s, N*H*COCH$_3$). δ_C (100 MHz, $CDCl_3$) 22.5, 24.0, 109.7, 116.7, 124.3, 127.3, 128.6 (2 × C), 128.7 (2 × C), 132.5, 138.7, 168.0, 168.2, 193.8. HRMS (NSI) found $[M+H]^+$ = 271.1078 $C_{15}H_{15}N_2O_3$ requires $[M+H]^+$ = 271.1077.

Cyclisation of 2-{[2-cyano-3-(4-methoxyphenyl)-3-oxoprop-1-en-1-yl]amino}acetic acid, 3.27Da From **3.27Da** (2.60 g, 10 mmol) flash column chromatography [50 % DCM in hexane] provided initially *1-acetyl-4-(4-methoxyphenyl)-1*H-*pyrrole-3-carbonitrile* **3.29Da** as an orange solid (0.24 g, 10 %). m.p. 140 – 141 °C. ν_{max} 3132, 2980, 2226, 1729, 1249, 831 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.62 (3H, s, NCOC*H*$_3$), 3.85 (3H, s, OC*H*$_3$), 6.96 – 6.98 (2H, m, *m*-An-*H*), 7.42 (1H, d, *J* = 1.6 Hz, 5-*H*), 7.56 – 7.58 (2H, m, *o*-An-*H*), 7.83 (1H, d, *J* = 1.6 Hz, 2-*H*). δ_C (100 MHz, $CDCl_3$) 22.1, 55.4, 97.6, 114.5 (2 × C), 115.1, 115.7, 123.5, 127.6, 128.1 (2 × C), 129.2, 159.7, 166.5. HRMS (ESI) found $[M+NH_4]^+$ = 258.1234 $C_{14}H_{16}N_3O_2$ requires $[M+NH_4]^+$ = 258.1237. Further elution provided *1-acetyl-4-cyano-*

*1*H-*pyrrol-3-yl acetate* **3.60a** as a pink solid (0.19 g, 10 %). The physical and spectroscopic data were in agreement with **3.60a** from **3.27Aa**. The final fraction afforded N-*[5-cyano-6-(4-methoxyphenyl)-2-oxo-2*H-*pyran-3-yl]acetamide* **3.61D** as a yellow powder (0.38 g, 13 %). m.p. 245 – 247 °C. ν_{max} 3295, 2222, 1712, 1689, 1599, 1501, 1272 cm^{-1}. δ_H [400 MHz, $(CD_3)_2SO$] 2.17 (3H, s, NCOCH_3), 3.87 (3H, s, OCH_3), 7.18 (2H, d, *J* = 8.9 Hz, *m*-An-*H*), 7.89 (2H, d, *J* = 8.9 Hz, *o*-An-*H*), 8.25 (1H, s, 4-*H*), 10.04 (1H, s, N*H*$COCH_3$). δ_C [100 MHz, $(CD_3)_2SO$] 24.3, 56.1, 89.2, 115.1 (2 × C), 117.2, 122.2, 123.6, 124.1, 130.0 (2 × C), 156.7, 161.3, 162.7, 171.1. HRMS (NSI) found $[M+H]^+$ = 285.0872 $C_{15}H_{13}N_2O_4$ requires $[M+H]^+$ = 285.0870.

Cyclisation of 2-({2-cyano-3-[4-(dimethylamino)phenyl]-3-oxoprop-1-en-1-yl}amino)acetic acid, 3.27Ea From **3.27Ea** (0.54 g, 2 mmol) flash column chromatography [30 % EtOAc in hexane] provided initially *1-acetyl-4-[4-(dimethylamino)phenyl]-1*H-*pyrrole-3-carbonitrile* **3.29Ea** as a brown solid (0.04 g, 8 %). m.p. 198 – 199 °C. ν_{max} 3133, 2980, 2889, 2224, 1725, 1610, 1382, 1362, 811, 617 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.60 (3H, s, NCOCH_3), 3.00 [6H, s, N(CH_3)$_2$], 6.77 (2H, d, *J* = 8.6 Hz, *m*-DP-*H*), 7.38 (1H, br. s, 5-*H*), 7.54 (2H, d, *J* = 8.6 Hz, *o*-DP-*H*), 7.81 (1H, br. s, 2-*H*). δ_C (100 MHz, $CDCl_3$) 22.1, 40.4 (2 × C), 97.6, 112.6 (2 × C), 114.8, 115.4, 118.9, 127.5, 127.6 (2 × C), 129.7, 150.4, 166.6. HRMS (ESI) found $[M+H]^+$ = 254.1299 $C_{15}H_{16}N_3O$ requires $[M+H]^+$ = 254.1288. Further elution afforded N-*{1-acetyl-4-[4-(dimethylamino)benzoyl]-1*H-*pyrrol-3-yl}acetamide* **3.28Ea** as a yellow solid (0.16 g, 26 %). m.p. 196 – 198 °C. ν_{max} 3301, 3161, 2915, 1727, 1679, 1607, 1537, 1371, 1191, 769, 593 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.21 (3H, s, NHCOCH_3), 2.59 (3H, s, NCOCH_3), 3.09 [6H, s, N(CH_3)$_2$], 6.71 (2H, d, *J* = 8.9 Hz, *m*-DP-*H*), 7.81 – 7.83 (3H, m, *o*-DP-*H*, 5-*H*), 7.98 (1H, d, *J* = 2.0 Hz, 2-*H*), 9.87 (1H, br. s, N*H*). δ_C (100 MHz, $CDCl_3$) 22.5, 24.0, 40.1 (2 × C), 109.4, 110.9 (2 × C), 117.1, 122.8, 125.8, 127.5, 131.3 (2 × C), 153.5, 168.1 (2 × C), 191.2. HRMS (ESI) found $[M+Na]^+$ = 336.1331 $C_{17}H_{19}N_3NaO_3$ requires $[M+Na]^+$ = 336.1319.

Cyclisation of 2-{[2-cyano-3-(1-methyl-1*H*-pyrrol-2-yl)-3-oxoprop-1-en-1-yl]amino}acetic acid, 3.27Ga From **3.27Ga** (2.32 g, 10 mmol) flash column chromatography [30 % EtOAc in hexane] provided initially *1'-acetyl-1-methyl-1*H*,1'*H-*[2,3'-bipyrrole]-4'-carbonitrile* **3.29Ga** as an orange powder (0.40 g, 19 %). m.p. 114 – 116 °C. ν_{max} 3132, 2219, 1740, 713, 601 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.60 (3H, s, NCOCH_3), 3.70 (3H, s, NCH_3), 6.20 (1H, dd, *J* = 2.8, 3.7 Hz, 4-*H*), 6.50 (1H, dd, *J* = 1.7, 3.7 Hz, 3-*H*), 6.73 (1H, app. t, 5-*H*), 7.32 (1H, d, *J* = 2.0 Hz, 2′-*H*), 7.80 (1H, d, *J* = 2.0 Hz, 5′-*H*). δ_C (100 MHz, $CDCl_3$) 22.1, 35.2, 99.3, 108.2, 110.6, 114.7, 116.3, 121.3, 123.3, 124.6, 127.1, 166.5. HRMS (ESI) found $[M+H]^+$ = 214.0974 $C_{12}H_{12}N_3O$ requires $[M+H]^+$ = 214.0975. Further elution

provided N-*[1-acetyl-4-(1-methyl-1*H*-pyrrole-2-carbonyl)-1*H*-pyrrol-3-yl]acetamide* **3.28Ga** as a yellow powder (0.93 g, 34 %). m.p. 149 – 150 °C. ν_{max} 3347, 1721, 1682, 1618, 1369, 766, 581 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.21 (3H, s, NHCOCH_3), 2.59 (3H, s, NCOCH_3), 3.95 (3H, s, NCH_3), 6.19 (1H, dd, *J* = 2.5, 3.9 Hz, 4′-*H*), 6.93 – 6.96 (2H, m, 3′-*H*, 5′-*H*), 7.88 (1H, d, *J* = 2.2 Hz, 5-*H*), 7.97 (1H, d, *J* = 2.2 Hz, 2-*H*), 9.70 (1H, br. s, N*H*). δ_C (100 MHz, $CDCl_3$) 22.4, 24.0, 37.0, 108.6, 109.5, 117.8, 120.7, 122.1, 127.3, 130.6, 131.6, 168.0 (2 × C), 181.9. HRMS (ESI) found $[M+H]^+$ = 274.1185 $C_{14}H_{16}N_3O_3$ requires $[M+H]^+$ = 274.1186.

Cyclisation of 2-{[2-cyano-3-(4-nitrophenyl)-3-oxoprop-1-en-1-yl]amino}acetic acid, 3.27Fa From **3.27Fa** (0.28 g, 1 mmol) flash column chromatography [30 % EtOAc in hexane] provided *1-acetyl-4-cyano-1*H*-pyrrol-3-yl acetate* **3.60a** as a brown solid (0.09 g, 46 %). The physical and spectroscopic data were in agreement with **3.60a** from **3.27Aa**.

4-[(Dimethylamino)methylene]-2-methyloxazol-5(4*H*)-one, 3.63 Prepared following the literature procedure [97JHC247]. To *N*-acetylglycine (2.34 g, 20 mmol) was added $POCl_3$ (4.6 mL, 49 mmol, 2.5 equiv.) at 0 °C and stirred under nitrogen. To the reaction mixture was added DMF (3.8 mL, 49 mmol, 2.5 equiv.) dropwise and the reaction was heated to 40 °C for 3 h. The volatile components were removed under reduced pressure and to the resulting oil was added ice (40 g) and aqueous ammonia (25 %, 20 mL). The product was extracted with $CHCl_3$ (3 × 50 mL) and the combined organic extracts were washed with water (100 mL), brine (2 × 100 mL) and water (100 mL), dried (Na_2SO_4) and the solvent removed *in vacuo* to afford a brown solid which was recrystallised from EtOH to afford the **title compound** as pale orange crystals (1.55 g, 50 %). m.p. 151 – 152 °C (lit. m.p. 153 – 155 °C [97JHC247]). ν_{max} 2974, 2932, 1738, 1634, 1610, 858, 752 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.22 (3H, s, CH_3), 3.19 [3H, s, N(CH_3)(CH_3)], 3.47 [3H, s, N(CH_3)(CH_3)], 6.96 (1H, s, CC*H*). δ_C (100 MHz, $CDCl_3$) 15.0, 39.2, 46.4, 106.6, 142.3, 154.3, 170.8. HRMS (ESI) found $[M+H]^+$ = 155.0820 $C_7H_{11}N_2O_2$ requires $[M+H]^+$ = 155.0815.

Methyl 2-acetamido-3-(dimethylamino)acrylate, 3.64 Prepared following the literature procedure [97JHC247]. A mixture of **3.63** (0.75 g, 5 mmol) and K_2CO_3 (0.17 g, 1.25 mmol, 0.25 equiv.) was stirred in methanol (15 mL) at reflux for 30 min. The reaction was allowed to cool and the solvent removed under reduced pressure. The residue was diluted with water (50 mL) and the product extracted with $CHCl_3$ (5 × 30 mL). The combined organic portions were washed with water (50 mL), dried (Na_2SO_4) and the solvent removed *in vacuo* to afford a colourless oil which crystallised upon the application of Et_2O. The solid was recrystallised from $CHCl_3$/Et_2O to afford the **title compound**

as a colourless crystalline solid (0.28 g, 31 %). m.p. 99 – 101 (lit. m.p. 98 – 99 °C [97JHC247]). ν_{max} 3222, 2981, 1692, 1631, 1287, 1095 cm^{-1}. The ^1H NMR spectrum showed a mixture of the (*E*)- and (*Z*)- isomers in a 0.3:1 ratio determined by the signals at δ 7.34 (1H, s, CC*H minor*) and 7.38 (1H, s, CC*H*, *major*). δ_H (400 MHz, $CDCl_3$) 1.92 (3H, s, NHCOCH_3, *minor*), 2.09 (3H, s, NHCOCH_3, *major*), 3.02 [6H, s, N(CH_3)$_2$, *major*], 3.09 [6H, s, N(CH_3)$_2$, *minor*], 3.66 (3H, s, CO_2CH_3, *major*), 3.69 (3H, s, CO_2CH_3, *minor*), 6.37 (1H, br. s, N*H*, *minor*), 6.57 (1H, br. s, N*H*, *major*), 7.34 (1H, s, CC*H minor*), 7.38 (1H, s, CC*H*, *major*). δ_C (100 MHz, $CDCl_3$) 20.0, 23.1, 41.9 (4 × C), 51.2, 51.4, 93.9, 96.0, 146.6, 146.7, 168.0, 168.5, 171.7, 175.5. HRMS (ESI) found $[M+Na]^+$ = 209.0897 $C_8H_{14}N_2NaO_3$ requires $[M+Na]^+$ = 209.0897.

***N*-(5-Cyano-2-oxo-6-phenyl-2*H*-pyran-3-yl)acetamide, 3.61C** Prepared following the literature procedure [97JHC247]. A mixture of **3.64** (0.19 g, 1 mmol) and benzoylacetonitrile (0.15 g, 1 mmol, 1 equiv.) were stirred in AcOH (3 mL) for 2 h at reflux (TLC, 30 % EtOAc in hexane). The reaction was allowed to cool to room temperature and water (50 mL) was added and the product was extracted with EtOAc (3 × 25 mL). The combined organic portions were washed with water (25 mL), aq. $NaHCO_3$ (3 × 25 mL) and water (50 mL), dried (Na_2SO_4) and the solvent removed *in vacuo* to afford the pure product as a yellow solid (0.25 g, 96 %). Spectroscopic and physical data in agreement with that of **3.61C** from **3.27Ca**.

Attempted synthesis of (2-chloro-3-oxo-3-phenylprop-1-en-1-yl)glycine, 3.68 To a solution of 2-chloroacetophenone (4.64 g, 30 mmol) and glycine (2.36 g, 31.5 mmol, 1.05 equiv.) in isopropanol (80 mL) was added triethyl orthoformate (7.5 mL, 45 mmol, 1.50 equiv.). The reaction mixture was refluxed under nitrogen for 16 h. The mixture was allowed to cool and the solvent was removed under reduced pressure. The residue was dissolved in DCM and extracted into aq. $NaHCO_3$ (3 × 50 mL) and the aqueous extracts acidified with dil. HCl (2 M, aq.). The product was then extracted with EtOAc (3 × 50 mL), dried (Na_2SO_4) and the solvent removed *in vacuo* to obtain a brown solid (3.51 g). The ^1H NMR spectrum was complex but no signals corresponding to the product were presemt.

Attempted synthesis of 2-chloro-3-ethoxy-1-phenylprop-2-en-1-one, 3.69 2-Chloroacetophenone (7.73 g, 50 mmol) and triethyl orthoformate (25 mL, 150 mmol, 3 equiv.) were stirred at reflux in Ac_2O (14.2 mL) for 4 days. The reaction was cooled to room temperature, poured into water (400 mL) and stirred for 1 h. The product was extracted with EtOAc (3 × 50 mL), washed with water (100 mL) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue purified by flash

column chromatography (10 % EtOAc in hexane) to afford *2-chloro-3,3-diethoxy-1-phenylpropan-1-one* **3.70** as a yellow oil (1.97 g, 15 %). ν_{max} 2976, 2931, 1689, 1448, 1113, 1057, 689 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.05 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 1.31 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 3.55 (1H, dq, *J* = 7.0, 7.1 Hz, $OCH_aH_bCH_3$), 3.71–3.84 (3H, m, $OCH_aH_bCH_3$, OCH_2CH_3), 4.98 [1H, d, *J* = 7.9 Hz, $CH(OEt)_2$], 5.11 (1H, d, *J* = 7.9 Hz, CHCl), 7.49–7.51 (2H, m, *m*-Ar-*H*), 7.59–7.63 (1H, m, *p*-Ar-*H*), 7.97–8.00 (2H, m, *o*-Ar-*H*). δ_C (100 MHz, $CDCl_3$) 15.0, 15.3, 55.4, 63.7, 65.2, 102.9, 128.7 (2 × C), 128.9 (2 × C), 133.8, 135.3, 192.9.

Attempted synthesis of 2-chloro-3-(dimethylamino)-1-phenylprop-2-en-1-one, 3.71 2-Chloroacetophenone (7.74 g, 50 mmol) and DMF (6 mL, 77.5 mmol, 1.5 equiv.) were stirred at 90 °C in Ac_2O (25 mL) for 2 hours. The reaction was allowed to cool to room temperature and water was added. The product was extracted with EtOAc (3 × 50 mL), washed with water (100 mL) and brine (100 mL), dried (Na_2SO_4) and the solvent removed *in vacuo* to afford a colourless crystalline solid (7.12 g). The solid was identified as 2-chloroacetophenone by its ^1H NMR spectrum.

General method for the cyclisation of 2-[(3-cyano-4-oxo-4-phenylbut-2-en-2-yl)amino] acids

The 2-[(3-cyano-4-oxo-4-phenylbut-2-en-2-yl)amino] acid was dissolved in acetic anhydride (30 mL) prior to the addition of triethylamine (7 equiv.). The mixture was refluxed until the emission of CO_2 was complete (limewater bubbler) and allowed to cool to room temperature. The brown solution was poured into water (400 mL), stirred for 1 h and extracted with DCM (5 × 50 mL). The organic layer was washed with water (2 × 100 mL), aq. $NaHCO_3$ (5 × 50 mL) and water (100 mL). The dried (Na_2SO_4) solvent was removed under reduced pressure and the products were isolated by flash column chromatography.

The following compounds were synthesised by the above method.

Cyclisation of 2-[(3-cyano-4-oxo-4-phenylbut-2-en-2-yl)amino]propanoic acid, 3.57b From 2-[(3-cyano-4-oxo-4-phenylbut-2-en-2-yl)amino]propanoic acid **3.57b** (1.30 g, 5 mmol) flash column chromatography [30 % EtOAc in hexane] provided *1-acetyl-4-cyano-2,5-dimethyl-1H-pyrrol-3-yl acetate* **3.72** as an off-white solid (0.65 g, 59 %). m.p. 76 – 77 °C. ν_{max} 2980, 2884, 2223, 1781, 1744, 1166 cm^{-1}. δ_H [400 MHz, $(CD_3)_2SO$] 2.21 (3H, s, 2-CH_3), 2.33 (3H, s, $OCOCH_3$), 2.52 (3H, s, 5-CH_3), 2.61 (3H, s, $NCOCH_3$). δ_C [100 MHz, $(CD_3)_2SO$] 11.8, 15.6, 20.5, 27.6, 91.8, 113.9, 120.9,

133.6, 137.7, 169.0, 171.7. HRMS (ESI) found $[M+H]^+$ = 221.0921 $C_{11}H_{13}N_2O_3$ requires $[M+H]^+$ = 221.0921.

Cyclisation of 2-[(3-cyano-4-oxo-4-phenylbut-2-en-2-yl)amino]-2-phenylacetic acid, 3.57c From 2-[(3-cyano-4-oxo-4-phenylbut-2-en-2-yl)amino]-2-phenylacetic acid **3.57c** (1.59 g, 5 mmol) flash column chromatography [20% EtOAc in hexane] provided initially a mixture of *1-benzoyl-4-cyano-5-methyl-2-phenyl-1*H-*pyrrol-3-yl acetate* **3.77** and *1-acetyl-4-cyano-5-methyl-2-phenyl-1*H-*pyrrol-3-yl acetate* **3.74** as a yellow oil (0.73 g). Further elution provided N-*(1-acetyl-4-benzoyl-5-methyl-2-phenyl-1*H-*pyrrol-3-yl)acetamide* **3.75** as a brown solid (0.09 g, 5 %). m.p. 128 – 129 °C. ν_{max} 3266, 3055, 2928, 1728, 1651, 1645, 1259, 722 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.78 (3H, s, NCOCH_3), 1.99 (3H, s, NHCOCH_3), 2.27 (3H, s, 5-CH_3), 7.17 (1H, s, NHCOCH$_3$), 7.37 – 7.48 (7 H, m, 2-Ar-*H*, 4-*m*-Ar-*H*), 7.55 – 7.58 (1H, m, 4-*p*-Ar-*H*), 7.86 (2H, d, *J* = 7.1 Hz, 4-*o*-Ar-*H*). δ_C (100 MHz, $CDCl_3$) 14.6, 23.1, 28.3, 120.4, 121.0, 127.4, 128.5 (2 × C), 128.6, 129.0 (2 × C), 129.2 (2 × C), 129.5 (2 × C), 131.5, 132.7, 134.3, 139.1, 169.5, 172.8, 193.1. HRMS (ESI) found $[M+H]^+$ = 361.1548 $C_{22}H_{21}N_2O_3$ requires $[M+H]^+$ = 361.1547. The mixture of *1-benzoyl-4-cyano-5-methyl-2-phenyl-1*H-*pyrrol-3-yl acetate* **3.77** and *1-acetyl-4-cyano-5-methyl-2-phenyl-1*H-*pyrrol-3-yl acetate* **3.74** was dissolved in EtOH (30 mL) and sodium acetate was added (0.80 g), the mixture was stirred at reflux under nitrogen for 90 min. After cooling to room temperature the solvent was removed *in vacuo*. To the residue was added water and the product extracted with Et_2O (5 × 50 mL). The combined organic portions were washed with water (100 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure to afford an oil. Flash column chromatography [20 % EtOAc in hexane] provided initially *1-benzoyl-4-cyano-5-methyl-2-phenyl-1*H-*pyrrol-3-yl acetate* **3.77** as a yellow solid (0.18 g, 11 %). m.p. 111 – 113 °C. ν_{max} 2226, 1776, 1711, 1274, 1188, 711 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.26 (3H, s, OCOCH_3), 2.48 (3H, s, NCOCH_3), 7.07 – 7.16 (5H, m, 2-Ar-*H*), 7.25 – 7.29* (2H, m, 4-*m*-Ar-*H*), 7.42 – 7.46 (1H, m, 4-*p*-Ar-*H*), 7.52 – 7.55 (2H, m, 4-*o*-Ar-*H*). δ_C (100 MHz, $CDCl_3$) 13.1, 20.4, 91.9, 113.3, 124.5, 128.1, 128.5 (5 × C), 128.7 (2 × C), 130.5 (2 × C), 132.8, 133.8, 134.5, 138.0, 168.7, 169.1. HRMS (ESI) found M = 344.1164 $C_{21}H_{16}N_2O_3$ requires M = 344.1161. Further elution provided *4-cyano-5-methyl-2-phenyl-1*H-*pyrrol-3-yl acetate* **3.76** as a yellow solid (0.27 g, 23 %). m.p. 178 – 180 °C. ν_{max} 3375, 2222, 1747, 1196, 1184, 756, 692, 584 cm^{-1}. δ_H [400 MHz, $(CD_3)_2SO$] 2.35 (3H, s, COCH_3), 2.37 (3H, s, CH_3), 7.25 – 7.29 (1H, m, *p*-Ar-*H*), 7.41 – 7.45 (2H, m, *m*-Ar-*H*), 7.52 – 7.54 (2H, m, *o*-Ar-*H*), 11.96 (1 H, br. s, N*H*). δ_C [100 MHz, $(CD_3)_2SO$] 12.6, 20.7, 87.3, 114.9, 119.7, 125.1 (2 × C), 127.4, 129.5 (2 × C), 129.9, 133.0, 136.2, 169.2. HRMS (ESI) found $[M+H]^+$ = 241.0986 $C_{14}H_{13}N_2O_2$ requires $[M+H]^+$ = 241.0972.

*Overlaps with residual $CHCl_3$

4.3.7 Synthesis of 3-(1-carboxyalkylaminomethylene)-2-tosylacrylonitriles (2-[(2-cyano-2-tosylvinyl)amino] acids)

General method for the synthesis of 2-[(2-cyano-2-tosylvinyl)amino] acids

To a solution of (*p*-toluenesulfonyl)acetonitrile (5.36 g, 30 mmol, 1 equiv.) and the appropriate α-amino acid (1.05 equiv.) in isopropanol (80 mL) was added triethyl orthoformate (7.5 mL, 45 mmol, 1.50 equiv.). The reaction mixture was refluxed under nitrogen until the starting material was absent by TLC. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was dissolved in DCM and extracted into aq. $NaHCO_3$ (3 × 50 mL) and the aqueous extracts acidified with dil. HCl (2 M, aq.). The product was then extracted with EtOAc (3 × 50 mL), dried (Na_2SO_4) and the solvent removed *in vacuo* to yield the 2-[(2-cyano-2-tosylvinyl)amino] acid.

The following compounds were synthesised by the above method.

2-[(2-Cyano-2-tosylvinyl)amino]acetic acid, 3.82a From glycine (3.54 g, 47.2 mmol) as a brown solid from EtOAc/hexane (1.27 g, 10 %). m.p. 205 – 207 °C. ν_{max} 3300, 3231, 2937, 2205, 1713, 1626, 1302, 1234, 1131, 669, 597 cm^{-1}. δ_H [400 MHz, $(CD_3)_2SO$] 2.40 (3H, s, C*H*$_3$), 4.11 (2H, d, *J* = 5.9 Hz, NHC*H*$_2$COOH), 7.44 (2H, d, *J* = 8.2 Hz, *m*-Ts-*H*), 7.70 (2H, d, *J* = 8.2 Hz, *o*-Ts-*H*), 8.01 (1H, d, *J* = 14.6 Hz, CC*H*), 8.95 (1H, dt, *J* = 5.9, 14.6 Hz, N*H*), 13.07 (1H, br. s, COO*H*). δ_C [100 MHz, $(CD_3)_2SO$] 21.5, 49.4, 81.9, 114.6, 126.6 (2 × C), 130.4 (2 × C), 140.3, 143.9, 159.6, 171.1. HRMS (ESI) found $[M+NH_4]^+$ = 298.0858 $C_{12}H_{16}N_3O_4S$ requires $[M+NH_4]^+$ = 298.0856.

2-[(2-Cyano-2-tosylvinyl)amino]propanoic acid, 3.82b From DL-alanine (2.81 g, 31.5 mmol) as a brown powder from DCM (1.63 g, 18 %). m.p. 155 – 157 °C. ν_{max} 3288, 3229, 3035, 2926, 2204, 1714, 1633, 1343, 1288, 1140, 666 cm^{-1}. δ_H [400 MHz, $(CD_3)_2SO$] 1.39 (3H, d, *J* = 7.2 Hz, C*H*$_3$), 2.40 (3H, s, PhC*H*$_3$), 4.39 – 4.46 (1H, m, NHC*H*COOH), 7.44 (2H, d, *J* = 8.2 Hz, *m*-Ts-*H*), 7.70 (2H, d, *J* = 8.2 Hz, *o*-Ts-*H*), 7.97 (1H, d, *J* = 14.5 Hz, CC*H*), 9.13 (1H, dd, *J* = 8.1, 14.5 Hz, N*H*). δ_C [100 MHz, $(CD_3)_2SO$] 17.6, 21.5, 57.2, 81.5, 114.7, 126.7 (2 × C), 130.4 (2 × C), 140.3, 143.9, 157.8, 173.3. HRMS (ESI) found $[M+H]^+$ = 295.0746 $C_{13}H_{15}N_2O_4S$ requires $[M+H]^+$ = 295.0747.

2-[(2-Cyano-2-tosylvinyl)amino]-2-phenylacetic acid, 3.82c From DL-2-phenylglycine (4.76 g) as a red solid (0.85 g, 8 %). ν_{max} 3297, 3034, 2204, 1728, 1621, 1288, 1140, 667, 515 cm^{-1}. δ_H [400 MHz, $(CD_3)_2SO$] 2.39 (3H, s, PhC*H*$_3$), 5.59 (1H, d, *J* = 7.8 Hz, NHC*H*COOH), 7.36–7.44 (7H, m, *m*-Ts-*H*, Ar-*H*), 7.66 (2H, d, *J* = 8.3 Hz, *o*-Ts-*H*), 8.00 (1H, d, *J* = 14.2 Hz, CC*H*), 9.72 (1H, dd, *J* = 7.8, 14.2 Hz, N*H*), 13.45 (1H, br. s, COO*H*). δ_C [100 MHz, $(CD_3)_2SO$] 21.5, 65.0, 82.4, 114.5, 126.7 (2 × C), 128.7 (2 × C), 128.9, 129.2 (2 × C), 130.4 (2 × C), 136.7, 140.0, 144.0, 157.1, 171.3. HRMS (ESI) found $[M+H]^+$ = 357.0903 $C_{18}H_{17}N_2O_4S$ requires $[M+H]^+$ = 357.0904.

4.3.8 Synthesis of Pyrroles: Cyclisation of 3-(1-carboxyalkylaminomethylene)-2-tosylacrylonitriles (2-[(2-cyano-2-tosylvinyl)amino] acids)

General method for the cyclisation of 2-[(2-Cyano-2-tosylvinyl)amino] acids

The 2-[(2-cyano-2-tosylvinyl)amino] acid was dissolved in acetic anhydride (30 mL) prior to the addition of triethylamine (7 equiv.). The mixture was refluxed until the emission of CO_2 was complete (limewater bubbler) and allowed to cool to room temperature. The brown solution was poured into water (400 mL), stirred for 1 h and extracted with DCM (5 × 50 mL). The organic extracts were washed with water (2 × 100 mL), aq. $NaHCO_3$ (5 × 50 mL) and water (100 mL). The dried (Na_2SO_4) solvent was removed under reduced pressure and the products were isolated by flash column chromatography.

The following compounds were synthesised by the above method.

Cyclisation of 2-[(2-Cyano-2-tosylvinyl)amino]acetic acid, 3.82a From 2-[(2-cyano-2-tosylvinyl)amino]acetic acid (0.70 g, 2.5 mmol) flash column chromatography [50 % EtOAc in hexane] provided only N-*acetyl*-N-*(1-acetyl-4-tosyl-1*H-*pyrrol-3-yl)acetamide* **3.84a** as a yellow solid (0.12 g, 15 %). m.p. 144 – 147 °C. ν_{max} 3375, 3166, 3113, 2980, 1739, 1730, 1687, 1323, 1148, 678, 591 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.22 (3H, s, NHCOC*H*$_3$), 2.42 (3H, s, Ts-C*H*$_3$), 2.54 (3H, s, NCOC*H*$_3$), 7.33 (2H, d, *J* = 8.2 Hz, *m*-Ts-*H*), 7.75 (1H, d, *J* = 2.6 Hz, 5-*H*), 7.78 (2H, d, *J* = 8.2 Hz, *o*-Ts-*H*), 7.92 (1H, d, *J* = 2.6 Hz, 2-*H*), 8.61 (1H, br. s, N*H*). δ_C (100 MHz, $CDCl_3$) 21.6, 22.1, 23.9, 110.0, 119.7, 120.8, 123.3, 126.7 (2 × C), 130.1 (2 × C), 139.1, 144.8, 167.1, 167.7. HRMS (ESI) found $[M+H]^+$ = 321.0904 $C_{15}H_{17}N_2O_4S$ requires $[M+H]^+$ = 321.0904.

Cyclisation of 2-[(2-Cyano-2-tosylvinyl)amino]propanoic acid, 3.82b From 2-[(2-cyano-2-tosylvinyl)amino]propanoic acid (0.88 g, 3 mmol) flash column chromatography [50 % EtOAc in hexane] provided initially N-*acetyl*-N-*(1-acetyl-2-methyl-4-tosyl-1*H-*pyrrol-3-yl)acetamide* **3.83b** as an orange oil (0.32 g, 28 %). ν_{max} 2928, 1716, 1368, 1316, 1140, 667, 582 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.21 [6H, s, N(COC*H*$_3$)$_2$], 2.24 (3H, s, C*H*$_3$), 2.42 (3H, s, Ts-C*H*$_3$), 2.65 (3H, s, NCOC*H*$_3$), 7.30 (2H, d, *J* = 8.2 Hz, *m*-Ts-*H*), 7.72 (2H, d, *J* = 8.2 Hz, *o*-Ts-*H*), 7.83 (1H, s, 5-*H*). δ_C (100 MHz, $CDCl_3$) 12.0, 21.7, 23.6, 26.1 (2 × C), 120.8, 123.3, 124.7, 127.8 (2 × C), 129.9 (2 × C), 132.7, 137.3, 144.9, 168.6, 172.3 (2 × C). HRMS (ESI) found $[M+H]^+$ = 377.1166 $C_{18}H_{21}N_2O_5S$ requires $[M+H]^+$ = 377.1166. Further elution provided N-*(1-acetyl-2-methyl-4-tosyl-1*H-*pyrrol-3-yl)acetamide* **3.84b** as an off-white powder (0.30 g, 30 %). m.p. 167 – 169 °C. ν_{max} 3133, 1729, 1321, 1138, 664, 580, 560 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.11 (3H, NHCOC*H*$_3$), 2.30 (3H, s, C*H*$_3$), 2.40 (3H, s, Ts-C*H*$_3$), 2.58 (3H, s, NCOC*H*$_3$), 7.14 (1H, br. s, N*H*COCH$_3$), 7.29 (2H, d, *J* = 8.2 Hz, *m*-Ts-*H*), 7.66 (1H, s, 5-*H*), 7.74 (2H, d, *J* = 8.2 Hz, *o*-Ts-*H*). δ_C (100 MHz, $CDCl_3$) 13.6, 21.6, 23.2, 23.7, 118.3, 122.1, 123.5, 127.0 (2 × C), 129.9 (2 × C), 130.7, 138.2, 144.6, 168.2, 168.6. HRMS (ESI) found $[M+H]^+$ = 335.1061 $C_{16}H_{19}N_2O_4S$ requires $[M+H]^+$ = 335.1060.

Cyclisation of 2-[(2-Cyano-2-tosylvinyl)amino]-2-phenylacetic acid, 3.82c From 2-[(2-cyano-2-tosylvinyl)amino]-2-phenylacetic acid (0.53 g, 1.5 mmol) flash column chromatography [50 % EtOAc in hexane] provided initially N-*acetyl*-N-*(1-acetyl-2-phenyl-4-tosyl-1*H-*pyrrol-3-yl)acetamide* **3.83c** as orange crystals (0.11 g, 17 %). m.p. 211 – 212 °C. ν_{max} 3139, 1749, 1717, 1704, 1313, 1230, 1152, 673, 609, 535 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.13 [6H, s, N(COC*H*$_3$)$_2$], 2.23 (3H, s, NCOC*H*$_3$), 2.43 (3H, s, Ts-C*H*$_3$), 7.16 (2H, m, *o*-Ar-*H*), 7.32 (2H, *J* = 8.1 Hz, *m*-Ts-*H*), 7.36–7.42 (3H, m, *m*-Ar-*H*, *p*-Ar-*H*), 7.76 (2H, d, *J* = 8.2 Hz, *o*-Ts-*H*), 8.12 (1H, s, 5-*H*). δ_C (100 MHz, $CDCl_3$) 21.7, 24.8, 26.1 (2 × C), 122.1, 124.4, 124.8, 127.9 (2 × C), 128.9, 129.0 (2 × C), 129.2 (2 × C), 129.9 (3 × C), 133.1, 137.4, 144.8, 167.9, 172.5 (2 × C) HRMS (ESI) found $[M+Na]^+$ = 461.1140 $C_{23}H_{22}N_2NaO_5S$ requires $[M+Na]^+$ = 461.1142. Further elution provided N-*(1-acetyl-2-phenyl-4-tosyl-1*H-*pyrrol-3-yl)acetamide* **3.84c** as an off-white powder (0.11 g, 19 %). m.p. 176 – 177 °C. ν_{max} 3144, 1749, 1661, 1511, 1309, 1153, 662, 541 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.93 (3H, s, NHCOC*H*$_3$), 2.14 (3H, s, NCOC*H*$_3$), 2.42 (3H, s, Ts-C*H*$_3$), 6.74 (1H, br. s, N*H*COCH$_3$), 7.29–7.40 (7H, *m*-Ts-*H*, Ar-*H*), 7.80 (2H, d, *J* = 8.2 Hz, *o*-Ts-*H*), 8.00 (1H, s, 5-*H*). HRMS (ESI) found $[M+H]^+$ = 397.1218 $C_{21}H_{21}N_2O_4S$ requires $[M+H]^+$ = 397.1217.

4.3.9 Synthesis of 2-(1-carboxyalkylaminomethylene)dibenzoylmethanes (2-[(2-benzoyl-3-oxo-3-phenylprop-1-en-1-yl)amino] acids)

2-[(Dimethylamino)methylene]-1,3-diphenylpropane-1,3-dione, 3.87 To dibenzoylmethane (11.19 g, 50 mmol) was added DMFDMA (16.6 mL, 125 mmol, 2.5 equiv.) and the mixture was stirred at reflux under nitrogen for 30 hours. The reaction mixture was allowed to cool to room temperature overnight. The mixture was diluted with brine and the product extracted with EtOAc (3 × 75 mL). The combined organic extracts were washed with brine (2 × 100 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure. The product was recrystallised from EtOH to afford an orange solid (6.84 g, 49 %). m.p. 129 – 131°C (lit. m.p. 120 °C [82JHC1275]). ν_{max} 1648, 1558, 1322, 697, 684 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.78 [3H, br. s, $N(CH_3)_a(CH_3)_b$], 3.27 [3H, br. s, $N(CH_3)_a(CH_3)_b$], 7.17–7.21 (4H, m, *m*-Ar-*H*), 7.25–7.28 (2H, m, *p*-Ar-*H*), 7.58 (4H, br. s, *o*-Ar-*H*), 7.66 (1H, s, CC*H*). δ_C (100 MHz, $CDCl_3$) 42.4, 47.6, 111.5, 127.9 (2 × C), 129.0, 131.1 (2 × C), 140.9, 158.1, 194.9 (2 × C). HRMS (ESI) found $[M+H]^+$ = 280.1334 $C_{18}H_{18}NO_2$ requires $[M+H]^+$ = 280.1332.

General method for the synthesis of 2-[(2-benzoyl-3-oxo-3-phenylprop-1-en-1-yl)amino] acids

To 2-[(dimethylamino)methylene]-1,3-diphenylpropane-1,3-dione (2.79 g, 10 mmol) in EtOH (50 mL) was added a solution of the appropriate amino acid (12 mmol, 1.2 equiv.) and $NaOAc{\cdot}3H_2O$ (1.63 g, 12 mmol, 1.2 equiv.) in water (20 mL). The reaction was stirred at reflux for 19 hours and allowed to cool to room temperature. The solvent was removed under reduced pressure and ice-water was added to the residue (50 mL). The solution was acidified (2 M HCl) and extracted with EtOAc (3 × 75 mL). The combined organic extracts were washed with water (50 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure.

2-[(2-Benzoyl-3-oxo-3-phenylprop-1-en-1-yl)amino]acetic acid 3.88a From glycine (0.91 g) as a yellow solid which was recrystallised from EtOAc/hexane (1.66 g, 54 %). m.p. 209 – 211. ν_{max} 3061, 2779, 1717, 1637, 1514, 1212, 889, 723, 708 cm^{-1}. δ_H [400 MHz, $(CD_3)_2SO$] 4.25 (2H, d, *J* = 6.0 Hz, NHCH_2COOH), 7.20–7.24 (2H, m, *m*-Ar-*H*), 7.27–7.35 (5H, *o*-Ar-*H*, *m*-Ar-*H*, *p*-Ar-*H*), 7.38–7.42 (1H, m, *p*-Ar-*H*), 7.54–7.56 (2H, m, *o*-Ar-*H*), 7.81 (1H, d, *J* = 14.2 Hz, CC*H*), 10.24 (1H, dt, *J* = 6.0, 14.2 Hz, N*H*), 13.02 (1H, br. s, COO*H*). δ_C [100 MHz, $(CD_3)_2SO$] 50.0, 109.8, 128.2 (4 × C), 128.5 (2 × C), 129.4 (2 × C), 130.70, 131.7, 140.3, 141.7, 161.3, 171.3, 194.2, 195.0. HRMS (ESI) found $[M+H]^+$ = 310.1073 $C_{18}H_{16}NO_4$ requires $[M+H]^+$ = 310.1074.

2-[(2-Benzoyl-3-oxo-3-phenylprop-1-en-1-yl)amino]propanoic acid, 3.88b From DL-alanine (1.07 g) as a yellow solid which was recrystallised from EtOAc/hexane (1.60 g, 50 %). m.p. 179 – 180 °C. ν_{max} 2980, 2885, 1732, 1635, 1515, 729, 698 cm^{-1}. δ_H [400 MHz, $(CD_3)_2SO$] 1.48 (3H, d, *J* = 7.2 Hz, C*H*$_3$), 4.48 (1H, dq, *J* = 7.2, 7.5 Hz, NHC*H*COOH), 7.20–7.23 (2H, m, *m*-Ar-*H*), 7.26–7.35 (5H, m, *o*-Ar-*H, m*-Ar-*H, p*-Ar-*H*), 7.38–7.41 (1H, m, *p*-Ar-*H*), 7.55–7.57 (2H, m, *o*-Ar-*H*), 7.90 (1H, d, *J* = 14.0 Hz, CC*H*), 10.54 (1H, dd, *J* = 7.5, 14.0 Hz, N*H*), 13.33 (1H, br. s, COO*H*). δ_C [100 MHz, $(CD_3)_2SO$] 19.4, 56.2, 109.9, 128.2 (4 × C), 128.5 (2 × C), 129.5 (2 × C), 130.7, 131.8, 159.4, 173.4, 194.2, 195.1. HRMS (ESI) found $[M+H]^+$ = 324.1230 $C_{19}H_{18}NO_4$ requires $[M+H]^+$ = 324.1230.

2-[(2-Benzoyl-3-oxo-3-phenylprop-1-en-1-yl)amino]-2-phenylacetic acid, 3.88c From DL-2-phenylglycine (1.81 g) as a yellow powder which was recrystallised from EtOAc/hexane (2.20 g, 57 %). m.p. 187 – 188 °C. ν_{max} 3032, 1739, 1638, 1612, 1233, 716, 687 cm^{-1}. δ_H [400 MHz, $(CD_3)_2SO$] 5.65 (1H, d, *J* = 7.2 Hz, NHC*H*COOH), 7.20–7.49 (15H, m, Ar-*H*), 7.82 (1H, d, *J* = 13.8 Hz, CC*H*), 10.98 (1H, dd, *J* = 7.2, 13.8 Hz, N*H*) δ_C [100 MHz, $(CD_3)_2SO$] 63.5, 110.4, 127.8 (2 × C), 128.2 (4 × C), 128.5 (2 × C), 129.1, 129.7 (2 × C), 129.8 (2 × C), 130.9, 131.9, 137.5, 139.9, 141.3, 159.0, 171.5, 194.1, 195.3. HRMS (ESI) found $[M+H]^+$ = 386.1387 $C_{24}H_{20}NO_4$ requires $[M+H]^+$ = 386.1387.

4.3.10 Synthesis of Pyrroles: Cyclisation of 2-(1-carboxyalkylaminomethylene)dibenzoylmethanes (2-[(2-benzoyl-3-oxo-3-phenylprop-1-en-1-yl)amino] acids)

General Method for the Cyclisation of 2-[(2-Benzoyl-3-oxo-3-phenylprop-1-en-1-yl)amino] acids

The 2-[(2-benzoyl-3-oxo-3-phenylprop-1-en-1-yl)amino] acid was dissolved in acetic anhydride (30 mL) prior to the addition of triethylamine (7 equiv.). The mixture was refluxed until the emission of CO_2 was complete (limewater bubbler) and allowed to cool to room temperature. The brown solution was poured into water (400 mL), stirred for 1 h and extracted with DCM (5 × 50 mL). The organic extracts were washed with water (2 × 100 mL), aq. $NaHCO_3$ (5 × 50 mL) and water (100 mL). The dried (Na_2SO_4) solvent was removed under reduced pressure and the products were isolated by flash column chromatography or recrystallisation.

The following compounds were synthesised by the above method.

Cyclisation of 2-[(2-Benzoyl-3-oxo-3-phenylprop-1-en-1-yl)amino]acetic acid, 3.88a From 2-[(2-benzoyl-3-oxo-3-phenylprop-1-en-1-yl)amino]acetic acid (1.55 g, 5 mmol) recrystallisation from EtOAc/hexane provided *1-(3-benzoyl-4-phenyl-1*H*-pyrrol-1-yl)ethan-1-one* **3.89a** as pale orange crystals (0.95 g , 66 %). m.p. 101 – 102 °C. ν_{max} 2980, 1731, 1638, 1215, 758, 698 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.60 (3H, s, NCOC*H*$_3$), 7.26–7.30* (3H, m, 4-*m*-Ar-*H*, 4-*p*-Ar-*H*), 7.34–7.43 (5H, m, 5-*H*, 4-*o*-Ar-*H*, 3-*m*-Ar-*H*), 7.50–7.54 (1H, m, 3-*p*-Ar-*H*), 7.68 (1H, d, *J* = 1.1 Hz, 2-*H*), 7.82–7.84 (2H, m, 3-*o*-Ar-*H*). δ_C (100 MHz, $CDCl_3$) 22.2, 118.3, 125.5, 126.0, 127.3, 128.2 (2 × C), 128.3 (2 × C), 128.4 (2 × C), 129.6 (2 × C), 130.0, 132.7, 132.9, 138.5, 167.5, 191.2. HRMS (ESI) found $[M+H]^+$ = 290.1176 $C_{19}H_{16}NO_2$ requires $[M+H]^+$ = 290.1176.

*overlaps with residual $CHCl_3$

Cyclisation of 2-[(2-Benzoyl-3-oxo-3-phenylprop-1-en-1-yl)amino]propanoic acid, 3.88b From 2-[(2-benzoyl-3-oxo-3-phenylprop-1-en-1-yl)amino]propanoic acid (1.54 g, 4 mmol) recrystallisation from EtOAc/hexane provided *1-(4-benzoyl-2-methyl-3-phenyl-1*H*-pyrrol-1-yl)ethan-1-one* **3.89b** as a yellow solid (1.08 g, 75 %). m.p. 138 – 139 °C. δ_H (400 MHz, $CDCl_3$) 2.49 (3H, s, C*H*$_3$), 2.60 (3H, s, NCOC*H*$_3$), 7.19–7.23 (3H, m, 3-*o*-Ar-*H*, 3-*p*-Ar-*H*), 7.26–7.30* (2H, m, 3-*m*-Ar-*H*), 7.32–7.36 (2H, m, 4-*m*-Ar-*H*), 7.45–7.49 (2H, m, 5-*H*, 4-*p*-Ar-*H*), 7.75–7.77 (2H, m, 4-*o*-Ar-*H*). δ_C (100 MHz, $CDCl_3$) 13.8, 24.2, 125.5, 125.7, 126.9, 127.0, 128.0 (2 × C), 128.1 (2 × C), 129.5 (2 × C), 130.1 (2 × C), 130.8, 132.3, 133.4, 138.6, 169.5, 191.1. HRMS (ESI) found $[M+H]^+$ = 304.1332 $C_{20}H_{18}NO_2$ requires $[M+H]^+$ = 304.1332.

*overlaps with residual $CHCl_3$

Cyclisation of 2-[(2-Benzoyl-3-oxo-3-phenylprop-1-en-1-yl)amino]-2-phenylacetic acid, 3.88c From 2-[(2-benzoyl-3-oxo-3-phenylprop-1-en-1-yl)amino]-2-phenylacetic (1.96 g, 5 mmol) flash column chromatography [25 % EtOAc in hexane] provided *1-(4-benzoyl-2,3-diphenyl-1*H*-pyrrol-1-yl)ethan-1-one* **3.89c** as a yellow solid (1.52 g, 82 %). m.p. 119 – 121 °C. ν_{max} 1739, 1648, 1322, 1194, 726, 695 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.20 (3H, s, NCOC*H*$_3$), 7.04–7.11 (5H, m, 2-*o*-Ar-*H*, 2-*m*-Ar-*H*, 2-*p*-Ar-*H*), 7.25–7.33* (5H, m, 3-*o*-Ar-*H*, 3-*m*-Ar-*H*, 3-*p*-Ar-*H*), 7.38–7.42 (2H, m, 4-*m*-Ar-*H*), 7.49–7.53 (1H, m, 4-*p*-Ar-*H*), 7.82 (1H, m, 4-*o*-Ar-*H*). δ_C (100 MHz, $CDCl_3$) 25.3, 125.1, 126.5, 126.7 (2 × C), 127.6 (2 × C), 128.3 (4 × C), 128.5, 128.7, 129.6 (2 × C), 130.2, 131.1 (2 × C), 132.0, 132.3, 132.5, 132.9, 138.6, 169.2, 191.1. HRMS (ESI) found $[M+H]^+$ = 366.1489 $C_{25}H_{20}NO_2$ requires $[M+H]^+$ = 366.1489.

*overlaps with residual $CHCl_3$

3-(Dimethylamino)-1,2-diphenylprop-2-en-1-one, 3.93 To deoxybenzoin (14.72 g, 75 mmol) was added DMFDMA (25 mL, 188 mmol, 2.5 equiv.) and the reaction mixture stirred at reflux under nitrogen for 19 hours. The mixture was allowed to cool to room temperature overnight, diluted with brine and the product extracted with EtOAc (3 × 75 mL). The combined organic extracts were washed with brine (2 × 100 mL) and water (1 × 100 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure. The product was recrystallised from EtOAc/hexane to afford a yellow solid (15.55 g, 82%). m.p. 131 – 133 °C [lit. m.p. 127 – 129 °C (79JOC835)]. ν_{max} 3020, 2914, 1615, 1544, 1299, 775, 701, 666 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.71 [6H, s, N(CH_3)$_2$], 7.15–7.33* (8H, m, *o*-Ar-*H,* 2 × *m*-Ar-*H,* 2 × *p*-Ar-*H*), 7.35 (1H, s, CC*H*), 7.42–7.45 (2H, m, *o*-Ar-*H*). δ_C (100 MHz, $CDCl_3$) 43.6 (2 × C), 112.0, 126.3, 127.6 (4 × C), 128.7 (2 × C), 129.2, 132.1 (2 × C), 137.3, 141.8, 153.8, 194.8. HRMS (ESI) found $[M+H]^+$ = 252.1383 $C_{17}H_{18}NO$ requires 252.1383.

Attempted synthesis of 2-[(3-oxo-2,3-diphenylprop-1-en-1-yl)amino]-2-phenylacetic acid, 3.94c To 3-(dimethylamino)-1,2-diphenylprop-2-en-1-one (6.28 g, 25 mmol) in EtOH (70 mL) was added a solution of DL-2-phenylglycine (4.54 g, 30 mmol, 1.2 equiv.) and $NaOAc{\cdot}3H_2O$ (4.08 g, 30 mmol, 1.2 equiv.) in water (20 mL). The reaction mixture was stirred at reflux for 16 hours and allowed to cool to room temperature. The solvent was removed under reduced pressure and ice-water was added to the residue (50 mL). The solution was acidified (2 M HCl) and extracted with EtOAc (3 × 75 mL). The combined organic extracts were washed with water (50 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure to afford deoxybenzoin as a yellow solid (4.26 g).

Chapter 5

Conclusions

Chapter 5 Conclusions

5.1 Chapter 2 Conclusions

1. A range of diethyl 2-(1-carboxyalkylaminomethylene)malonates has been prepared either by transamination of diethyl (dimethylaminomethylene)malonate or condensation of diethyl (ethoxymethylene)malonate with α-amino acids. Many of these compounds are novel or have been fully characterised for the first time. No evidence for enamine-imine tautomerism was observed by ^{1}H NMR spectroscopy. The enamine form is the preferred tautomer.
2. Preliminary studies of the Zav'yalov pyrrole synthesis involving the acylative cyclodehydration-decarboxylation sequence of 2-(1-carboxyalkylaminomethylene)malonates have been extended. It was found that good to moderate yields of 3-acetoxypyrroles were obtained from the enaminomalonates derived from glycine or simple alkyl-substituted amino acids. In certain cases the cyclisation also provided, unexpectedly, the corresponding 3-ethoxypyrrole derivative in up to 20 % yield.
3. The structure of ethyl 1-acetyl-4-ethoxy-5-ethylpyrrole-3-carboxylate was determined by X-ray crystallography. Although the bond lengths and bond angles are comparable to those of other pyrroles, it was found that the 1-acetyl group is oriented to minimise steric interaction with the adjacent (C-5) ethyl group.
4. Enamino malonates derived from α-aminoalkanedioic acids, aspartic acid (1,2-disposed carboxyl groups) and glutamic acid (1,3-disposed carboxyl groups) reacted anomalously, *via* five-membered intermediates, the former provided only diethyl (acetamidomethylene)malonate *via* a formal retro-Michael elimination of maleic anhydride. However, the enaminomalonate derived from glutamic acid provided a 5-acetylpyrrolidin-2-one, the product of a Dakin-West-type rearrangement.
5. In complete contrast to the behaviour of the diacid, the enaminoester derived from glutamic acid 5-methyl ester cyclised as expected upon treatment of Ac_2O-Et_3N to give a mixture of the 3-acetoxy- and 3-ethoxypyrroles.
6. The asparagine-derived enaminomalonate cyclised to afford both the acetoxy- and ethoxypyrrole-2-acetonitrile derivatives. An isosuccinimide intermediate has been proposed to account for formation of the acetonitrile side chain. Although the ^{1}H and ^{13}C

NMR spectra and HRMS data were consistent with the structure of ethyl 4-acetoxy-1-acetyl-5-cyanomethylpyrrole-3-carboxylate, the IR spectrum did not exhibit a ν_{CN} band. Thus, definitive confirmation of the structure was obtained by X-ray crystallography. The enaminomalonate derived from the homologous amide, glutamine was not dehydrated to a nitrile and instead formation of the acetoxypyrrole proceeded with concomitant *N*-acetylation of the amide function.

7. Low yields of the 4-acetoxypyrrole and 4-ethoxypyrrole-3-esters were obtained from the enaminomalonate derived from methione sulfoxide. In this case the cyclisation proceeded with a regioselective Pummerer arrangement to generate an *O*,*S*-acetal function.
8. Secondary α-amino acids, apart from L-proline, could not be induced to condense with diethyl (ethoxymethylene)malonate; cyclodehydration of the proline derivative failed to give a tractable product.
9. Several mechanisms for the formation of the 4-acetoxypyrrole-3-carboxylates have been considered. Attempts to intercept the aminomethylene ketene (intermediate **B** in Scheme 2.36) were unsuccessful. No evidence supporting the β-acylation of the enamine by mixed anhydride (intermediate **A**, Scheme 2.36) was obtained. The failure to intercept any of the 1,4-oxazepine **F** (Scheme 2.37) with a dipolarophile discounts the 1,5-dipolar cyclisation pathway for formation of the ethoxypyrrole. On this basis, the mechanisms depicted in Schemes 2.38 and 2.39 satisfactorily account for pyrrole ring formation *via* either the carboxylate anion or the enolate of a mixed anhydride. A ^{13}C labelling experiment established that the carboxyl group of the starting materials was not retained in the product. Evidence that cyclisation of diethyl 2-(1-carboxyethylaminomethylene)malonate in Ac_2O to ethyl 4-acetoxy-1-acetyl-5-methylpyrrole-3-carboxylate (**2.13b**) proceeds *via* a münchnone intermediate was obtained *via* a trapping experiment with dimethyl acetylenedicarboxylate, which provided a novel *N*-alkenylpyrrole. The structure of the latter was confirmed by X-ray crystallography. Whilst formation of the pyrrole esters from the cyclisation of the enaminomalonates may invoke more than one pathway, the intermediacy of a münchnone clearly represents a significant route (based on the yield of the DMAD cycloadduct) as shown in Scheme 2.56. It is not yet clear why the cyclisations of in Ac_2O-Et_3N favour formation of the 3-ethoxypyrroles. It was also demonstrated in one case that the acetoxypyrroles readily undergo a [4+2] cycloaddition – [4+2] cycloreversion sequence.

10. Cyclisation of the Dane salt derived from ethyl acetoacetate and glycine is reported for the first time. Ring closure onto the β-position of the enaminoester occurs although the yield of the product is poor. An additional pyrrole-3-carboxylic ester was formed as a by-product.
11. Attempts to generate a ketene intermediate by an "unambiguous" route from diethyl 2-(1-carboxyethylaminomethylene)malonate were unsuccessful. This area merits further investigation.
12. A novel oxazolidin-5-one was obtained from the attempted Zav'yalov reaction of diethyl 2-[(1-carboxy-1-methyl)ethylaminomethylene]malonate. The α,α-disubstitution pattern prevents münchnone formation and the reaction proceeds instead *via* conjugate addition of the carboxylate anion to the methylenemalonate function.

5.2 Chapter 3 Conclusions

1. Nucleophilic vinylic substitution of the ethoxymethylene derivatives of ethyl cyanoacetate and malononitrile with α-amino acids has been used to synthesise a range of ethyl 2-(1-carboxyalkylaminomethylene)cyanoacetates and 2-(1-carboxyalkylaminomethylene)malononitriles, respectively. Although the former were obtained as mixtures of (*E*)- and (*Z*)-isomers, distinction between the isomers by ^{1}H NMR spectroscopy was facile.
2. The isomeric mixtures of ethyl 2-(1-carboxyalkylaminomethylene)cyanoacetates cyclised upon treatment with Ac_2O-Et_3N in a regiospecific manner to afford mixtures of ethyl 4-acetamido-1-acetyl-5-(un)substitutedpyrrole-3-carboxylates and the 4-acetamido-derivative. None of the diacetamidopyrrole was obtained from the 2-(1-carboxymethylaminomethylene)cyanoacetates however in this case trace amounts of 4-acetoxy-1-acetylpyrrole-3-carbonitrile and 1-acetyl-4-ethoxypyrrole-3-carbonitrile (ratio 0.08:1) were also formed.
3. The acylative cyclisation of (*E*)- and (*Z*)- ethyl 2-(1-carboxyethylaminomethylene)cyanoacetate provided both the acetamido- and imidopyrroles. However, a small amount of a 2,3-dihydropyrrole, resulting from acylative cyclisation onto the β-position of the (aminomethylene)cyanoacetate was obtained. Products resulting from incorporation of the carbonyl moiety were not observed in the malonate series. The structure of the 2,3-dihydropyrrole was established as ethyl

(2*R**,2*S**)-1-acetyl-3-cyano-2,4-diacetoxy-5-methyl-2,3-dihydropyrrole-3-carboxylate by X-ray crystallography.

4. The condensation of β-ketonitriles with triethyl orthoformate and α-amino acids has provided access to a range of 2-alkanoyl- and 2-aroyl-3-(1-carboxyalkylamino)acrylonitriles. Mixtures of (*E*)- and (*Z*)-isomers were obtained from these reactions. The acylative cyclisations of these compounds have been investigated. It was found that the distribution of products was dependent upon the nature of the amino acid substituent. Thus:
    i. The 2-alkanoyl- and 3-aroyl-3-(1-carboxy-1-phenylmethylamino)acrylonitriles furnished mixtures of 3-acyl-4-diacetamidopyrroles and 3-acyl-4-acetamidopyrroles, in which the latter predominated. Good overall yields of products were obtained.
    ii. In contrast the 3-(1-carboxyethylamino)acrylonitriles provided little of the 3-acylpyrroles, instead the cyclisation involved an enamine β-acylation to afford, after concomitant ketonic hydrolysis, 4-acetoxy-1-acetyl-5-methylpyrrole-3-carbonitrile in good yields.
    iii. Acylative cyclisation of the 2-alkanoyl- and 3-aroyl-3-(1-carboxymethylamino)acrylonitriles is complex and up to four products have been obtained from these reactions. Noteworthy is the formation of 1-acetyl-4-alkyl(aryl)pyrrole-3-carbonitriles in addition to 4-acetoxy-1-acetylpyrrole-3-carbonitrile. In two examples 3-acetamido-6-aryl-5-cyanopyran-2-ones were isolated.

A mechanism to account for formation of the 3-acyl-4-(di)acetamidopyrroles has invoked tautomerism of the enamino acid to an iminoketene species (for which there is a literature precedent) and cyclisation to the product *via* the enolate of a mixed anhydride. The tautomerism step facilitates interconversion between (*E*)- and (*Z*)-enamino acids and the imine (Scheme 3.53). Direct cyclisation onto the nitrile function is possible in the mixed anhydride of the (*E*)-isomer (Scheme 3.54). Although there are satisfactory mechanisms to account for formation of all of the products, the nature of the product distribution is less easy to rationalise. For example, the differing outcomes in the cyclisations of the 2-acyl-3-(1-carboxyalkylamino)acrylonitriles derived from phenylglycine (Table 3.14), alanine (Table 3.15) and glycine (Table 3.16).

5. Ethyl 2-(1-carboxyethylaminomethylene)cyanoacetate when cyclised with Ac_2O in the presence of DMAD provided a mixture of ethyl 1-acetyl-4-diacetamido-5-methylpyrrole-3-carboxylate and dimethyl 1-acetyl-5-methylpyrrole-3,4-dicarboxylate. It was established that the latter is formed *via* [4+2] cycloaddition of DMAD to the initially formed 4-acetamidopyrrole (Scheme 3.15). This behaviour is in complete contrast to that shown by diethyl 2-(1-carboxyethylaminomethylene)malonate that provided an *N*-alkenylpyrrole *via* a münchnone intermediate. None of the *N*-alkenylpyrrole was observed when 2-benzoyl-3-(1-carboxy-1-phenylmethylamino)acrylonitrile was heated with DMAD in acetic anhydride; the sole product was 1-acetyl-3-benzoyl-4-diacetamido-5-phenylpyrrole, derived by acylative cyclisation onto the nitrile function.
6. A 1,4-oxazepin-2-one intermediate has been proposed to account for the formation of the 3-acetamido-6-aryl-5-cyanopyran-2-ones [16. (iii)]. Unambiguous synthesis of the 6-phenyl derivative was accomplished by conjugate addition of $PhCOCH_2CN$ to methyl 2-acetamido-3-(dimethylamino) acrylate.
7. Acylative cyclisation of 2-benzoyl-3-(1-carboxyalkylamino)crotononitriles has been investigated. Whereas the 3-(1-carboxyethylamino)crotononitrile provided 4-acetoxy-1-acetyl-2,5-dimethylpyrrole-3-carbonitrile as the only isolable product, the 3-(1-carboxy-1-phenylmethylamino)crotononitrile provided a mixture of products. A compound characterised by the ^{1}H and ^{13}C NMR and NOESY experiments as 4-acetoxy-1-benzoyl-2-methyl-5-phenylpyrrole-3-carbonitrile is the result of sequential 1,5-benzoyl migrations of a 3*H*-pyrrole intermediate.
8. Aminomethylenation of (*p*-toluenesulfonyl)acetonitrile provided access to a range of 3-(1-carboxyalkylamino)-2-tosylacrylonitriles, as single isomers. Cyclisation of the latter follows the expected course and provided access to the hitherto 3-diacetamido-4-tosyl- and 3-acetamido-4-tosylpyrroles.
9. The synthesis and cyclisation of 2-(1-carboxyalkylaminomethylene)dibenzoylmethane derivatives has been investigated. The pyrrole products, formed in good yields, result from ring closure onto the ketone carbonyl function. These pyrrole-forming reactions, in contrast to the behaviour of the 2-benzoyl-3-(1-carboxyalkylamino)acrylonitriles that often cyclise *via* β-acylation of the enamine function with sequential hydrolytic cleavage of the benzoyl moiety. Pyrrole formation from the 2-(1-carboxyalkylaminomethylene)dibenzoylmethanes provides a complementary

approach to 5-(un)substituted-3-benzoyl-4-phenylpyrroles to the existing protocols that involve the conjugate addition of TosMIC and α-substituted anions to chalcones.

Chapter 6

References

Chapter 6 References

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Chapter 7

Appendices

Chapter 7 Appendices

Appendix 1

Figure 7.1 Crystal Data and Structure Refinement for Ethyl 1-acetyl-4-ethoxy-5-ethyl-1*H*-pyrrole-3-carboxylate **2.19c**.

```
Bond precision:  C-C = 0.0094 A          Wavelength=1.54178

Cell:          a=4.5787(7)        b=10.6290(14)     c=14.129(2)
               alpha=99.546(12)   beta=94.601(11)   gamma=96.965(11)
Temperature:   150 K

                 Calculated                Reported
Volume           669.55(17)                669.55(17)
Space group      P -1                      P -1
Hall group       -P 1                      -P 1
Moiety formula   C13 H19 N O4              ?
Sum formula      C13 H19 N O4              C13 H19 N O4
Mr               253.29                    253.29
Dx,g cm-3        1.256                     1.256
Z                2                         2
Mu (mm-1)        0.768                     0.768
F000             272.0                     272.0
F000'            272.89
h,k,lmax         5,12,17                   5,12,16
Nref             2476                      2336
Tmin,Tmax        0.991,0.992               0.770,0.880
Tmin'            0.926

Correction method= MULTI-SCAN

Data completeness= 0.943          Theta(max)= 68.565

R(reflections)= 0.1186( 1323)     wR2(reflections)= 0.3067( 2336)

S = 1.048                 Npar= 167
```

Table 7.1 Bond Lengths (Å) and Angles (°) for Ethyl 1-acetyl-4-ethoxy-5-ethyl-1*H*-pyrrole-3-carboxylate **2.19c**.

	Length (Å)		Angle (°)		Angle (°)
C1–C2	1.3473	C1–N1–C4	109.05	H7A–C7–C8	110.4
C1–N1	1.4243	C1–N1–C12	125.81	H7B–C7–C8	110.4
N1–C4	1.3794	C4–N1–C12	125.09	C7–C8–H8A	109.47
C4–C3	1.3633	C2–O1–C7	112.62	C7–C8–H8B	109.47
C3–C2	1.4325	C9–O2–C11	116.24	C7–C8–H8C	109.47
C11–C3	1.4647	N1–C1–C2	105.73	H8A–C8–H8B	109.47
C11–O3	1.2149	N1–C1–C5	126.41	H8A–C8–H8C	109.47
C11–O2	1.3296	C2–C1–C5	127.73	H8B–C8–H8C	109.47
O2–C9	1.4468	O1–C2–C1	123.08	O2–C9–H9A	110.34
H9B–C9	0.99	O1–C2–C3	126.55	O2–C9–H9B	110.34
H9A–C9	0.99	C1–C2–C3	110.16	O2–C9–C10	106.92
C10–H10B	0.98	C2–C3–C4	106.45	H9A–C9–H9B	108.57
C10–H10C	0.98	C2–C3–C11	131.27	H9A–C9–C10	110.34
C10–H10A	0.98	C4–C3–C11	122.19	H9B–C9–C10	110.34
		N1–C4–C3	108.6	C9–C10–H10A	109.47
		N1–C4–H4	125.7	C9–C10–H10B	109.47
		C3–C4–H4	125.7	C9–C10–H10C	109.47
		C1–C5–H5A	108.95	H10A–C10–H10B	109.47
		C1–C5–H5B	108.95	H10A–C10–H10C	109.47
		C1–C5–C6	113.16	H10B–C10–H10C	109.47
		H5A–C5–H5B	107.75	O2–C11–O3	122.68
		H5A–C5–C6	108.95	O2–C11–C3	113.09
		H5B–C5–C6	108.95	O3–C11–C3	124.21
		C5–C6–H6A	109.47	N1–C12–O4	120.16
		C5–C6–H6B	109.47	N1–C12–C13	115.79
		C5–C6–H6C	109.47	O4–C12–C13	124.04
		H6A–C6–H6B	109.47	C12–C13–H13A	109.47
		H6A–C6–H6C	109.47	C12–C13–H13B	109.47
		H6B–C6–H6C	109.47	C12–C13–H13C	109.47
		O1–C7–H7A	110.4	H13A–C13–H13B	109.47
		O1–C7–H7B	110.4	H13A–C13–H13C	109.47
		O1–C7–C8	106.61	H13B–C13–H13C	109.47
		H7A–C7–H7B	108.62		

Appendix 2

Figure 7.2 Crystal Data and Structure Refinement for Ethyl 4-acetoxy-1-acetyl-5-cyano-1*H*-pyrrole-3-carboxylate **2.24**.

Bond precision: C-C = 0.0043 A Wavelength=1.54178

Cell:	a=13.0070(6)	b=7.4288(3)	c=13.9720(5)
	alpha=90	beta=92.381(2)	gamma=90
Temperature:	150 K		

	Calculated	Reported
Volume	1348.90(10)	1348.90(10)
Space group	P 21/n	P 21/n
Hall group	-P 2yn	-P 2yn
Moiety formula	C13 H14 N2 O5	?
Sum formula	C13 H14 N2 O5	C13 H14 N2 O5
Mr	278.26	278.26
Dx,g cm-3	1.370	1.370
Z	4	4
Mu (mm-1)	0.903	0.903
F000	584.0	584.0
F000'	586.08	
h,k,lmax	15,8,16	15,8,16
Nref	2387	2340
Tmin,Tmax	0.835,0.914	0.770,0.880
Tmin'	0.835	

Correction method= MULTI-SCAN

Data completeness= 0.980 Theta(max)= 66.592

R(reflections)= 0.0805(1822) wR2(reflections)= 0.2496(2340)

S = 1.059 Npar= Npar = 213

Table 7.2 Bond Lengths (Å) and Angles (°) for Ethyl 4-acetoxy-1-acetyl-5-cyano-1*H*-pyrrole-3-carboxylate **2.24**.

	Length (Å)		Angle (°)		Angle (°)
N1–C4	1.379(4)	C4–N1–C1	108.8(2)	C12–C11–H11B	109.5
N1–C1	1.401(4)	C4–N1–C13	125.1(3)	H11A–C11–H11B	109.5
N1–C13	1.429(3)	C1–N1–C13	125.9(3)	C11'–C12'–H12A	109.5
N2–C6	1.145(4)	C7–O1–C2	118.3(2)	C11'–C12'–H12B	109.5
O1–C7	1.372(4)	C10–O3–C11	116.2(4)	H12A–C12'–H12B	109.5
O1–C2	1.385(3)	C2–C1–N1	107.0(3)	C11'–C12'–H12C	109.5
O2–C7	1.194(4)	C2–C1–C5	127.3(3)	H12A–C12'–H12C	109.5
O3–C10	1.330(5)	N1–C1–C5	125.6(2)	H12B–C12'–H12C	109.5
O3–C11	1.464(6)	C1–C2–O1	123.3(3)	O5–C13–N1	119.1(3)
O4–C10	1.208(4)	C1–C2–C3	109.2(2)	O5–C13–C14	124.9(3)
O5–C13	1.204(4)	O1–C2–C3	126.9(3)	N1–C13–C14	116.0(3)
C1–C2	1.344(4)	C4–C3–C2	106.1(3)	C13–C14–H14A	109.5
C1–C5	1.504(4)	C4–C3–C10	122.7(3)	C13–C14–H14B	109.5
C2–C3	1.441(4)	C2–C3–C10	130.9(3)	H14A–C14–H14B	109.5
C3–C4	1.360(4)	C3–C4–N1	108.9(3)	C13–C14–H14C	109.5
C3–C10	1.468(4)	C3–C4–H4	125.6	H14A–C14–H14C	109.5
C4–H4	0.9500	N1–C4–H4	125.6	H14B–C14–H14C	109.5
C5–C6	1.464(4)	C6–C5–C1	113.2(3)	C11–C12–H12D	109.5
C5–H5A	0.9900	C6–C5–H5A	108.9	C11–C12–H12E	109.5
C5–H5B	0.9900	C1–C5–H5A	108.9	H12D–C12–H12E	109.5
C7–C8	1.482(4)	C6–C5–H5B	108.9	C11–C12–H12F	109.5
C8–H8A	0.9800	C1–C5–H5B	108.9	H12D–C12–H12F	109.5
C8–H8B	0.9800	H5A–C5–H5B	107.8	H12E–C12–H12F	109.5
C8–H8C	0.9800	N2–C6–C5	179.7(4)	C12'–C11'–O3'	114.8(15)
C10–O3'	1.396(17)	O2–C7–O1	122.3(3)	C12'–C11'–H11C	108.6
C11–C12	1.516(6)	O2–C7–C8	127.6(3)	O3'–C11'–H11C	108.6
C11–H11A	0.9900	O1–C7–C8	110.1(3)	C12'–C11'–H11D	108.6
C11–H11B	0.9900	C7–C8–H8A	109.5		
C12'–C11'	1.33(2)	C7–C8–H8B	109.5		
C12'–H12A	0.9800	H8A–C8–H8B	109.5		
C12'–H12B	0.9800	C7–C8–H8C	109.5		
C12'–H12C	0.9800	H8A–C8–H8C	109.5		
C13–C14	1.486(4)	H8B–C8–H8C	109.5		
C12–H12D	0.9800	O4–C10–O3	122.4(3)		
C12–H12E	0.9800	O4–C10–O3'	127.2(7)		
C12–H12F	0.9800	O4–C10–C3	123.5(3)		
C11'–O3'	1.431(19)	O3–C10–C3	113.9(3)		
C11'–H11C	0.9900	O3'–C10–C3	108.0(7)		
C11'–H11D	0.9900	O3–C11–C12	106.2(4)		

Appendix 3

Figure 7.3 Crystal Data and Structure Refinement for Dimethyl 1-[3-ethoxy-2-(ethoxycarbonyl)-3-oxoprop-1-en-1-yl]-2,5-dimethyl-1*H*-pyrrole-3,4-dicarboxylate **2.65**.

```
Bond precision:  C-C = 0.0029 A          Wavelength=0.71073

Cell:          a=8.6719(8)       b=11.1287(10)     c=11.2488(11)
               alpha=64.219(2)   beta=75.291(3)    gamma=77.595(2)
Temperature:   150 K

                Calculated                Reported
Volume          938.68(15)                938.68(15)
Space group     P -1                      P -1
Hall group      -P 1                      -P 1
Moiety formula  C18 H23 N O8              ?
Sum formula     C18 H23 N O8              C18 H23 N O8
Mr              381.37                    381.37
Dx,g cm-3       1.349                     1.349
Z               2                         2
Mu (mm-1)       0.107                     0.107
F000            404.0                     404.0
F000'           404.25
h,k,lmax        12,15,16                  12,15,16
Nref            5779                      5747
Tmin,Tmax       0.989,0.989               0.770,0.880
Tmin'           0.989

Correction method= MULTI-SCAN

Data completeness= 0.994          Theta(max)= 30.613

R(reflections)= 0.0618( 3650)     wR2(reflections)= 0.1472( 5747)

S = 1.037                 Npar= 250
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Table 7.3 Bond Lengths (Å) and Angles (°) for Dimethyl 1-[3-ethoxy-2-(ethoxycarbonyl)-3-oxoprop-1-en-1-yl]-2,5-dimethyl-1*H*-pyrrole-3,4-dicarboxylate **2.65**.

	Length (Å)		Length (Å)		Angle (°)		Angle (°)
N1–C1	1.388(2)	C7–H7A	0.9800	C1–N1–C4	109.97(13)	C4–C10–H10A	109.5
N1–C4	1.392(2)	C7–H7B	0.9800	C1–N1–C11	127.45(13)	C4–C10–H10B	109.5
N1–C11	1.407(2)	C7–H7C	0.9800	C4–N1–C11	122.45(13)	H10A–C10–H10B	109.5
O1–C6	1.205(2)	C9–H9A	0.9800	C6–O2–C7	116.76(14)	C4–C10–H10C	109.5
O2–C6	1.340(2)	C9–H9B	0.9800	C8–O4–C9	115.14(15)	H10A–C10–H10C	109.5
O2–C7	1.446(2)	C9–H9C	0.9800	C15–O6–C19	115.87(14)	H10B–C10–H10C	109.5
O3–C8	1.198(2)	C10–H10A	0.9800	C13–O7–C22	115.88(14)	C12–C11–N1	125.77(15)
O4–C8	1.340(2)	C10–H10B	0.9800	C2–C1–N1	106.98(14)	C12–C11–H11	117.1
O4–C9	1.447(2)	C10–H10C	0.9800	C2–C1–C5	129.82(15)	N1–C11–H11	117.1
O5–C15	1.198(2)	C11–C12	1.334(2)	N1–C1–C5	122.88(15)	C11–C12–C13	119.61(15)
O6–C15	1.328(2)	C11–H11	0.9500	C1–C2–C3	108.06(14)	C11–C12–C15	126.43(15)
O6–C19	1.460(2)	C12–C13	1.490(2)	C1–C2–C6	122.59(15)	C13–C12–C15	113.90(14)
O7–C13	1.328(2)	C12–C15	1.491(2)	C3–C2–C6	128.69(15)	O8–C13–O7	124.79(16)
O7–C22	1.455(2)	C19–C21	1.477(3)	C4–C3–C2	107.84(14)	O8–C13–C12	122.64(16)
O8–C1	1.203(2)	C19–H19A	0.9900	C4–C3–C8	125.24(15)	O7–C13–C12	112.57(14)
C1–C2	1.365(2)	C19–H19B	0.9900	C2–C3–C8	126.35(15)	O5–C15–O6	124.80(17)
C1–C5	1.490(2)	C20–C22	1.495(3)	C3–C4–N1	107.14(14)	O5–C15–C12	123.09(17)
C2–C3	1.437(2)	C20–H20A	0.9800	C3–C4–C10	131.66(15)	O6–C15–C12	112.11(14)
C2–C6	1.466(2)	C20–H20B	0.9800	N1–C4–C10	120.90(14)	O6–C19–C21	107.58(17)
C3–C4	1.362(2)	C20–H20C	0.9800	C1–C5–H5A	109.5	O6–C19–H19A	110.2
C3–C8	1.477(2)	C21–H21A	0.9800	C1–C5–H5B	109.5	C21–C19–H19A	110.2
C4–C10	1.489(2)	C21–H21B	0.9800	H5A–C5–H5B	109.5	O6–C19–H19B	110.2
C5–H5A	0.9800	C21–H21C	0.9800	C1–C5–H5C	109.5	C21–C19–H19B	110.2
C5–H5B	0.9800	C22–H22A	0.9900	H5A–C5–H5C	109.5	H19A–C19–H19B	108.5
C5–H5C	0.9800	C22–H22B	0.9900	H5B–C5–H5C	109.5	C22–C20–H20A	109.5
				O1–C6–O2	123.47(16)	C22–C20–H20B	109.5
				O1–C6–C2	124.88(16)	H20A–C20–H20B	109.5
				O2–C6–C2	111.59(14)	C22–C20–H20C	109.5
				O2–C7–H7A	109.5	H20A–C20–H20C	109.5
				O2–C7–H7B	109.5	H20B–C20–H20C	109.5
				H7A–C7–H7B	109.5	C19–C21–H21A	109.5
				O2–C7–H7C	109.5	C19–C21–H21B	109.5
				H7A–C7–H7C	109.5	H21A–C21–H21B	109.5
				H7B–C7–H7C	109.5	C19–C21–H21C	109.5
				O3–C8–O4	123.52(16)	H21A–C21–H21C	109.5
				O3–C8–C3	125.05(17)	H21B–C21–H21C	109.5
				O4–C8–C3	111.41(15)	O7–C22–C20	107.96(16)
				O4–C9–H9A	109.5	O7–C22–H22A	110.1
				O4–C9–H9B	109.5	C20–C22–H22A	110.1
				H9A–C9–H9B	109.5	O7–C22–H22B	110.1
				O4–C9–H9C	109.5	C20–C22–H22B	110.1
				H9A–C9–H9C	109.5	H22A–C22–H22B	108.4
				H9B–C9–H9C	109.5		

Appendix 4

Figure 7.4 Crystal Data and Structure Refinement for (2*R**,3*S**)-1-Acetyl-3-cyano-3-(ethoxycarbonyl)-5-methyl-2,3-dihydro-1*H*-pyrrole-2,4-diyl diacetate **3.11**.

```
Bond precision:  C-C = 0.0024 A          Wavelength=0.71073

Cell:           a=16.2079(10)    b=10.3606(7)         c=20.6562(13)
                alpha=90         beta=96.0907(15)     gamma=90
Temperature:    300 K

                 Calculated                Reported
Volume           3449.1(4)                 3449.1(4)
Space group      C 2/c                     C 2/c
Hall group       -C 2yc                    -C 2yc
Moiety formula   C15 H18 N2 O7             ?
Sum formula      C15 H18 N2 O7             C15 H18 N2 O7
Mr               338.31                    338.31
Dx,g cm-3        1.303                     1.303
Z                8                         8
Mu (mm-1)        0.104                     0.104
F000             1424.0                    1424.0
F000'            1424.86
h,k,lmax         21,13,27                  21,13,27
Nref             4377                      4332
Tmin,Tmax        0.975,0.979               0.770,0.880
Tmin'            0.969

Correction method= MULTI-SCAN

Data completeness= 0.990          Theta(max)= 28.512

R(reflections)= 0.0490( 3064)     wR2(reflections)= 0.1498( 4332)

S = 1.018                 Npar= 251
```

Table 7.4 Bond Lengths (Å) and Angles (°) for (2*R**,3*S**)-1-Acetyl-3-cyano-3-(ethoxycarbonyl)-5-methyl-2,3-dihydro-1*H*-pyrrole-2,4-diyl diacetate **3.11**.

	Length (Å)		Length (Å)		Angle (°)		Angle (°)
N1–C6	1.135(2)	C13–H13B	0.9600	C15–N3–C14	126.15(15)	O5–C15–C16	121.79(17)
N3–C15	1.383(2)	C13–H13C	0.9600	C15–N3–C1	123.38(15)	N3–C15–C16	117.56(17)
N3–C14	1.415(2)	C15–C16	1.490(3)	C14–N3–C1	110.24(11)	C15–C16–H16A	109.5
N3–C1	1.4543(19)	C16–H16A	0.9600	C12–O3–C3	117.16(13)	C15–C16–H16B	109.5
O2–C7	1.186(2)	C16–H16B	0.9600	O7–C1–N3	107.91(10)	H16A–C16–H16B	109.5
O3–C12	1.367(2)	C16–H16C	0.9600	O7–C1–C2	112.37(11)	C15–C16–H16C	109.5
O3–C3	1.3811(18)	C17–C18	1.476(3)	N3–C1–C2	105.18(11)	H16A–C16–H16C	109.5
O4–C12	1.195(2)	C18–H18A	0.9600	O7–C1–H1	110.4	H16B–C16–H16C	109.5
O5–C15	1.209(2)	C18–H18B	0.9600	N3–C1–H1	110.4	O6–C17–O7	121.39(15)
O6–C17	1.1988(19)	C18–H18C	0.9600	C2–C1–H1	110.4	O6–C17–C18	127.29(17)
C1–O7	1.4212(17)	C10–O1	1.464(3)	C6–C2–C3	110.54(12)	O7–C17–C18	111.31(14)
C1–C2	1.5641(18)	C10–C11	1.466(5)	C6–C2–C7	111.08(12)	C17–C18–H18A	109.5
C1–H1	0.9800	C10–H10A	0.9700	C3–C2–C7	110.76(13)	C17–C18–H18B	109.5
C2–C6	1.473(2)	C10–H10B	0.9700	C6–C2–C1	113.06(12)	H18A–C18–H18B	109.5
C2–C3	1.508(2)	C11–H11A	0.9600	C3–C2–C1	101.18(11)	C17–C18–H18C	109.5
C2–C7	1.543(2)	C11–H11B	0.9600	C7–C2–C1	109.83(11)	H18A–C18–H18C	109.5
C3–C14	1.322(2)	C11–H11C	0.9600	C14–C3–O3	125.07(14)	H18B–C18–H18C	109.5
C8–C14	1.490(2)	C10'–O1'	1.481(15)	C14–C3–C2	113.17(13)	O1–C10–C11	107.5(3)
C8–H8A	0.9600	C10'–C11'	1.57(2)	O3–C3–C2	121.44(12)	O1–C10–H10A	110.2
C8–H8B	0.9600	C10'–H10C	0.9700	N1–C6–C2	179.00(18)	C11–C10–H10A	110.2
C8–H8C	0.9600	C10'–H10D	0.9700	O2–C7–C2	122.99(14)	O1–C10–H10B	110.2
O7–C17	1.3615(19)	C11'–H11D	0.9600	C14–C8–H8A	109.5	C11–C10–H10B	110.2
C12–C13	1.482(3)	C11'–H11E	0.9600	C14–C8–H8B	109.5	H10A–C10–H10B	108.5
C13–H13A	0.9600	C11'–H11F	0.9600	H8A–C8–H8B	109.5	C10–C11–H11A	109.5
				C14–C8–H8C	109.5	C10–C11–H11B	109.5
				H8A–C8–H8C	109.5	H11A–C11–H11B	109.5
				H8B–C8–H8C	109.5	C10–C11–H11C	109.5
				C17–O7–C1	114.97(11)	H11A–C11–H11C	109.5
				O4–C12–O3	121.23(16)	H11B–C11–H11C	109.5
				O4–C12–C13	128.07(18)	O1'–C10'–C11'	105.9(12)
				O3–C12–C13	110.68(17)	O1'–C10'–H10C	110.6
				C12–C13–H13A	109.5	C11'–C10'–H10C	110.6
				C12–C13–H13B	109.5	O1'–C10'–H10D	110.6
				H13A–C13–H13B	109.5	C11'–C10'–H10D	110.6
				C12–C13–H13C	109.5	H10C–C10'–H10D	108.7
				H13A–C13–H13C	109.5	C10'–C11'–H11D	109.5
				H13B–C13–H13C	109.5	C10'–C11'–H11E	109.5
				C3–C14–N3	109.92(13)	H11D–C11'–H11E	109.5
				C3–C14–C8	125.48(16)	C10'–C11'–H11F	109.5
				N3–C14–C8	124.59(15)	H11D–C11'–H11F	109.5
				O5–C15–N3	120.6(2)	H11E–C11'–H11F	109.5