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Combinatorial, heterocyclic and guanidine chemistry

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COMBINATORIAL, HETEROCYCLIC AND GUANIDINE CHEMISTRY

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ABSTRACT

The research in this thesis covers two areas: (i) combinatorial chemistry involving the synthesis of solid-phase supported reagents and approaches to compound libraries; and (ii) synthetic approaches and purification methods for heterocyclic guanidines.

A range of solid-phase supported reagents were prepared and an analytical protocol for such materials was established. Products contained mainly aldehyde, alcohol, oxime and nitro functional groups and were synthesised from Merrifield resin with good levels of substituent loading. These reagents were then used in further synthesis. Five combinatorial libraries were synthesised comprising of ureas, thioureas, sulfonamides, dihydropyrimidines and cyano acrylic methyl esters. Reactions achieved were in moderate to good yield and the use of scavenger resins, as an alternative route, in some cases, proved successful.

As a result of purification problems associated with solution-phase methods, the synthesis of cyclic guanidines was investigated with the aim of producing such compounds by solid-phase methodologies. Three solid-phase approaches to producing cyclic guanidines were attempted; however the cleavage step proved unsuccessful in each case. Silylation was then carried out successfully with crude products in good yield; unfortunately purification resulted in deprotection of the alcohol.

The reaction of guanidine and epoxide in the presence of base yielded cyclic guanidines. A five-membered guanidine heterocycle was produced in a maximum of 33 % yield, from several reactions, and greater than 90 % purity. In a similar approach 7-membered monomeric and dimeric cyclic guanidines were synthesised. Additional equivalents of epoxide and base were added after initial alkylation of the guanidine to bias the products formed. It was hoped that the dimer species could be elucidated further by achieving greater yields and could also be useful for further synthetic approaches. The biasing was promising and dimeric material was produced in greater amounts, such that 1 equivalent of reagent gave a ratio of 70: 30, 2 equivalents gave 37: 63 and 3 equivalents gave 22: 78 of monomer to dimer.

DEDICATION

For Dad, Mum and Del – for love, belief and encouragement

GROWTH[1]

When we plant a rose seed in the earth, we notice it is small,
but we do not criticise it as "rootless and stemless".
We treat it as a seed,
giving it all the water and nourishment required of a seed.

When it firsts shoots up out of the earth,
we don't condemn it as immature and underdeveloped,
nor do we criticise the buds for not being open when they appear.
We stand in wonder at the process taking place,
and give the plant the care it needs at each stage of its development.

The rose is a rose from the time it is a seed to the time it dies.
Within it, at all times, it contains its whole potential.
It seems to be constantly in the process of change:
Yet at each state, at each moment, it is perfectly all right as it is.

A flower is not better when it blooms than when it is merely a bud;
At each stage it is the same thing
- a flower in the process of expressing its potential

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Leaving the best for last I express my love and gratitude to Trevor and Anne -my parents for always being there and for financial and emotional support throughout my life, to my brother David – miles apart but so alike, and to Delwyn for his love, friendship and sense of humour.

ABBREVIATIONS AND DEFINITIONS

AcOH	Acetic acid
AIDS	Acquired immune deficiency syndrome
Ar	Aromatic
ATR	Attentuated total reflectance
br	Broad
Boc	tert-Butoxycarbonyl
BTF	Benzo trifluoride
Bu	Butyl
° C	Degrees centigrade
Cbz	Benzyloxycarbonyl
CI	Chemical Ionisation
δ	Chemical shift
CLND	Chemiluminescent nitrogen detector
DIC	*N,N*'-diisopropylcarbodiimide
DMAP	4-(*N,N*-dimethylamino)pyridine
DMF	Dimethyl formamide
DMSO	Dimethylsulphoxide
DNA	Deoxyribonucleic acid
d	Doublet
DPPP	1,3-Bis(diphenylphosphino)propane
DRIFTS	Diffuse reflectance infrared fourier transform spectroscopy
Δ	Heat, reflux
ELSD	Evaporative light scattering detector
EPR	Electron paramagnetic resonance
eq./equiv.	Mole equivalent(s)
Et	Ethyl
EtOAc	Ethyl acetate
FTIR	Fourier transform infrared spectroscopy
ν	Frequency
h	Hour(s)
HCl	Hydrochloric acid
HPLC	High Performance liquid chromatography

HIV	Human immuno deficiency virus
HOBT	1-Hydroxybenzotriazole hydrate
HRMS	High resolution mass spectrometry
Hz	Hertz (sec^{-1} or cycles per second)
IUPAC	International Union of Pure and Applied Chemistry
J	Coupling constant
MAS	Magic angle spinning
MALDI	Matrix assisted laser desorption/ionisation
MBHA	*p*-Methylbenzhydrylamine resin
*m*CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
MeOH	Methanol
MHz	Megahertz
m.p.	Melting point
MsCl	Mesyl chloride
ml	Millilitre(s)
min	Minute(s)
Mol/mmol	Moles/millimoles
m	Multiplet
KO^tBu	Potassium tertiary butoxide
KBr	Potassium bromide
$NaBH_4$	Sodium borohydride
NaH	Sodium hydride
NH_4OAc	Ammonium acetate
NMR	Nuclear magnetic resonance
NEt_3	Triethylamine
Petrol	Petroleum spirit 40 - 60 °C
Ph	Phenyl
PA-FTIR	Photoacoustic infrared spectroscopy
Pol	Polymer base resin
PPh_3	Triphenylphosphine
ppm	Parts per million
q	Quartet
RT	Room temperature

sat.	Saturated
s	Singlet
str	Stretch
^{t}BDMSCl	tert-Butyldimethylsilyl chloride
^{t}Bu	tert-Butyl
^{t}BuOH	tert-Butanol
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
t	triplet
cm^{-1}	Wavenumber(s)
w	Weak intensity

CONTENTS

INTRODUCTION

OVERVIEW

The aims of this thesis were to produce novel solid-phase supported reagents in order to develop new nitrogen containing heterocyclic compounds and to investigate solid-phase approaches to heterocyclic guanidines. The following three chapters are intended as a background to the work carried out. Prior to carrying out the research it was necessary to gain an understanding of combinatorial chemistry, which involved a lengthy literature review on the topic. The first chapter therefore describes the basic approaches used and discusses the problems involved in the analysis of solid-phase supported reagents.

It became apparent in the course of the research that solid-phase synthetic approaches to heterocycles were not leading to yields and purity that were significantly improved. Solution-phase library synthesis was then adopted in an attempt to make interesting and potentially biologically active molecules. Chapter 2 discusses solid and solution-phase methods for the synthesis of heterocycles deemed relevant to the research carried out.

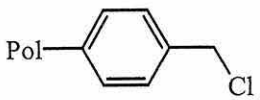
The final part of the research focussed on the synthesis of heterocyclic guanidines by solid-phase techniques. The solid-phase approaches again proved to be unsuccessful and solution-phase methods were adopted to better effect. Chapter 3 is intended as a background to synthetic approaches of heterocyclic guanidines.

CHAPTER 1 – COMBINATORIAL CHEMISTRY

1.1. DEVELOPMENT OF COMBINATORIAL CHEMISTRY

Combinatorial synthesis can be defined by 'the ability to generate large numbers of chemical compounds quickly'.[2] Essentially combinatorial synthesis can involve reactions carried out with either solid-phase supported substrates or those in solution that are run in parallel. Solid-phase reactions are those which are carried out on a non-soluble polymeric material that acts as a support for the reaction and eliminates by-products. Solid and solution-phase reactions can be run in parallel producing tens to hundreds of compounds at a time, thus challenging the traditional methods for producing organic compounds. The literature on combinatorial chemistry is expansive and many authors have summarised this field in books and reviews.[2–7]

Solid-phase synthesis has developed significantly since first reported by Merrifield in 1963.[8] Merrifield was particularly interested in the synthesis of peptides and his Nobel Prize winning invention enabled peptides to be synthesised on a polymeric support. Chloromethyl polystyrene **[1]** was the polymer chosen and the reason behind its application was its insolubility in a range of solvents. A reaction could be carried out upon the polymer that enabled excess reagents and by-products to be removed by filtration, leaving the product bound to the polymer. The reactions proved to be reliable and efficient and his work led to developments in the rather novel approach with initial studies geared towards peptide synthesis. Chemists focussed on the technologies already in place using peptide and oligonucleotide solid-phase approaches to synthesise other compounds; however, it was apparent that further methods would need to be developed.



[1]

Figure 1. Merrifield Resin

This chapter discusses the principles behind combinatorial chemistry, the analytical methods applicable and common terminology used.

1.2. COMMON TERMINOLOGY USED IN COMBINATORIAL CHEMISTRY

The development of this new chemical strategy has meant that new terms and approaches have been outlined. A glossary of terms commonly used in combinatorial chemistry was recently published by IUPAC.[9] The following terminology is relevant to the discussion of this and the following chapters.

Array Synthesis is a type of parallel synthesis whereby reaction vessels remain in a set configuration throughout the duration of a reaction.

Backbone is a term used to describe a linear scaffold, such as a repeating polymer unit.

Building Blocks are interchangeable reagents applicable to a combinatorial library that are incorporated in the final product.

Cleavage refers to the removal of the desired product from the polymeric support.

Combinatorial is defined by: (i) relation to or involving combinations; (ii) the arrangement of, operation on and selection of discrete elements belonging to finite sets.

Combinatorial Chemistry adopts a combinatorial (combined) approach to compound synthesis.

Crosslinking is a term for connection between strands of polymers. It is important in combinatorial chemistry as the degree of crosslinking can effect the ability of a polymer to swell in solvents.

Dendrimer is a regular branched polymer that can be used as a soluble support and applied to combinatorial chemistry. Compound isolation is achieved by size-exclusion chromatography. Attachment to solid-supports can significantly increase polymer loading.

Diversity is a measure of the differences between a combinatorial library or set of building blocks and can be the physical or biological properties of molecules.

Fluorous Synthesis is a solution-phase approach that uses highly fluorinated compounds that will partition out of aqueous and organic solvents into fluorinated ones.

High-Throughput Screening (HTS) is a rapid method for determining the activity of vast numbers of products, such as a combinatorial library, by parallel assays in multi-well plates.

Linker is a term used to describe the functional part of a solid-support that can bind to the polymer and be synthetically modified and released by a cleavage reaction.

Loading refers to the amount of the functional group per unit mass of solid-support.

Macroporous resins contain permanent pores enabling reactions to proceed irrespective of the swelling properties of a solvent.

Magic Angle Spinning is an NMR concept whereby the tube is spun at a specific angle that cancels out line broadening and inhomogeneities within the sample.

Mesh Size refers to the density of wires in a sieve. Such sieves are commonly used in particle size analysis and resin beads are available in different ranges of mesh size, most commonly 100 - 200 and 200 - 400 mesh.

Parallel Synthesis is the preparation of a compound set or library simultaneously in different reaction vessels.

A **Pin** is a rather novel technique involving an elongated tip that acts as the solid-support. Several pins can be inserted into solvents or reagents allowing library preparation to occur on the tip.

Pool/Split (split/pool; split & mix; divide, couple, recombine; portion/mix, orthogonal chemistry) is an approach used in library synthesis. The solid-support is split into portions, which are reacted with a particular building block molecule. The solid-supports are then pooled into a multicomponent mixture and the process of division, reaction and pooling repeated for several reaction steps and thus the potential number of products is endless, essentially a new compound could be achieved on each resin bead.

Residue refers to an identifiable portion of the product from a combinatorial reaction that originates from the building block or a portion of it.

The **Resin** is the insoluble polymeric material that allows for reactions to occur on its support and allows for ease of purification by filtration. The resin is commonly represented in literature by a bead, such as ●-NH_2.

A **Scavenger Resin** is a solid-supported reagent that reacts with undesired reagents (excess or by-product) and removes them from solution. Scavenger resins can also be applied as alternative reagents, such as polymer bound pyridine, to drive the reaction without the need of harmful compounds.

The **Tea-Bag** approach incorporates the solid-support within a porous mesh allowing reactions to occur but retaining the polymer within the mesh. The polymeric support is easily collected and none is lost through filtration techniques.

1.3. SOLID-PHASE COMBINATORIAL CHEMISTRY

Solid-phase synthesis has many advantages over traditional solution-phase methods; resin bound products can be easily collected by filtration and a simple cleaving reaction results in removing the desired compound from the polymer. Solid-phase reactions often employ the use of excess reagents that drive the reaction to completion; excess material is removed by filtration and can potentially be purified and reused, as can the polymeric support. The term 'solid-phase' gives the impression that reactions are carried out on a rigid, solid material, however in practice resins are designed to act like a gel in solvents making the reactive sites more accessible and therefore behave in a similar manner to a solution.

The use of solid-supports in organic synthesis has been shown to depend upon the following three requirements:[2]

1) A cross-linked, insoluble, but solvent-swellable polymeric material that is inert to the conditions of synthesis.
2) Some means of linking the substrate to this solid-phase that permits selective cleavage of some or all of the product from the solid-support during synthesis for analysis of the extent of reaction(s) and ultimately to give the final product.
3) A successful synthetic procedure that is compatible with the linker and the solid-phase.

Früchtel and Jung discussed the advantages of organic synthesis on solid-supports.[10] The following main advantages are apparent:

1) Reaction procedures are simplified by the elimination of time consuming purification and isolation steps by binding product to a polymeric support. Excess reagents can also be used and removed by filtration.
2) The thermodynamics of reactions can be improved by using excess reagents and yield can be increased.
3) The polymeric support can be regenerated after the cleavage step.

4) Reactions can be carried out in high dilution and side-reactions and polymer cross-linking is eliminated when a low polymeric loading is used, typically <0.8 mmol/g.

The most widely researched and applied polymer in solid-phase synthesis is cross-linked polystyrene. Small spherical resin beads are frequently used. The beads are usually 80 – 200 μm in diameter. The resin is reacted with a suitable reagent to produce a functional group bound to the resin that provides good linkage for further reagents. Polymer cross-linking plays an important role in solid-phase supported reagents. Cross-linking is necessary for polymer strength; however too much cross-linking will decrease the swelling properties of the polymer to solvents, thus making functional groups on the resin less accessible to reactants. Resins are generally microporous or macroporous. Microporous resins have a low level of cross-linking and therefore have good swelling capability in solvents. A macroporous resin contains a permanent network of pores that are independent of the state of swelling of the resin.[2]

Several different practical techniques have been applied to organic reactions adopting the use of solid-supports:[2,3]

- Micro- and macroporous polystyrene resin is cheap and can be functionalized with a relatively high loading. It is commonly used for polypeptide and small molecule synthesis.
- Polystyrene resin coated with polyethylene glycol spacers has been shown to improve the swelling properties of the polymer in aqueous solutions; however products are expensive, mechanically less stable and have a lower resin loading.
- Collection of polymers by filtration can be responsible for the loss of resin beads and affect the yield of a reaction. The 'Tea Bag' approach was designed to contain the polymer within a porous polypropylene bag, thus allowing reactions to occur and eliminating resin loss by filtration. In practice this method is commonly used for parallel library synthesis.
- Similarly, the Diversomer® approach was designed for this purpose. The resin beads are encapsulated in glass tubes with frittes at the bottom end. Tubes are inserted into reagents and solvents in order for reactions to occur. Hobbs DeWitt

et al. discuss the Diversomer® method and the areas of combinatorial chemistry it has been applied to.[11,12] The publications depict a laboratory set-up for this method. Polyethylene crowns can also be attached to pins and these dipped into reactions in a similar manner to the Diversomer® approach.

- A further application, not necessarily combinatorial, employs solid-phase supported reagents, such as bases, to replace organic reagents used in a particular synthetic step.[13] The use of an organic base in a reaction can often produce unwanted by-product that may be difficult to separate from the product. Adopting the use of a polymer bound base eliminates the presence of by-products and reduces the amount of purification required for a particular compound. The resin bound base can be removed by simple filtration. The principle may have even more benefit when it is considered that several polymeric bound reagents may be used in a reaction at one time, unlike traditional chemistry. Different resin beads will not react with each other, as organic reagents will, due to the fact that the reagent is contained within the beads.

1.4. SOLUTION-PHASE COMBINATORIAL CHEMISTRY

The automation of synthetic chemistry is a very appealing process to the industrial chemist due to the ability to generate vast numbers of compounds rapidly. The possibility of producing many compounds in series would certainly be preferable to traditional solution-phase chemistry. Solution-phase combinatorial chemistry employs orthogonal (pool/split approach) organic chemistry; however, like the solid-phase equivalent, reactions are run in series with a vast library of compounds being produced and purified in a relatively short time.

Solution-phase combinatorial synthesis has been widely applied in industry. Automated reaction systems are now available and they are able to handle hundreds of reactions *in situ*. The automated synthesiser may even include a purification station, whereby several compounds can be passed through a flash column and UV detection will determine the product containing fractions. Industrial applications of solution-phase chemistry often produce small quantities of material (mg scale). The principle of

producing libraries of compounds quickly is geared at improving the prospects of lead discovery.

1.5. ANALYTICAL METHODS IN COMBINATORIAL CHEMISTRY

Perhaps the most challenging aspect of solid-phase combinatorial chemistry is the analysis associated with the confirmation that reagents have become bound to polymers. Techniques used in solution-phase reaction analysis are simply not applicable. Alternative methods are constantly being investigated and a summary of those available is reported.[14-16] The publications discuss the main analytical methods that can be used in combinatorial chemistry and can be applied to polymeric supports and solution-phase libraries.

1.5.1. Infrared Spectroscopy

Fourier Transform Infrared Spectroscopy (FTIR) is perhaps the easiest and most useful method for analysing solid-phase supported reagents.[14] Functional groups can be easily identified and separated from the base polymer resonances by subtracting spectra. The application of this technique to solid-phase supported reagents requires the standard method of grinding of polymeric samples with potassium bromide followed by the forming of a pelletized mixture of the two components, usually requiring 1 % of product to KBr. This method is the easiest and most effective for the analysis of resin bound reagents; however problems arise in forming the pressed film and it is difficult to quantify the amount of material bound to the polymer. It is important, in forming a film, that it is not too thick and impenetrable, nor too thin and easily damaged.

IR spectroscopy of solid-phase supported reagents with 'Real-Time Monitoring' of reactions was reported.[17-22] Infrared spectroscopy was adapted to analyse a flattened polymer bead.[17] Monitoring could be achieved by removing a single polymer bead at regular intervals from a reaction. The method proved to be quick and highly sensitive and spectra obtained were of significantly improved resolution. Flattening or pressing a single resin bead can enhance spectral resolution. The utilisation of an attentuated total reflectance (ATR) microscope provides the means for a small fraction of the polymer surface to be analysed.

Advances in infrared techniques such as Diffuse Reflectance Infrared Fourier Transform Spectroscopy (DRIFTS) enable the analysis of a single polymer bead to be carried out, thus eliminating the difficulties associated with forming a KBr pellet. Many solid substances exhibit diffuse reflection, in that incident light is scattered in many directions, as opposed to specular or mirror-like reflection. DRIFTS can be used to measure absorbance and reflection at any reflective angle. Sofia and co-workers outline the monitoring of solid-phase reactions by DRIFTS.[23] The reduction of azido monosaccharides was thus monitored to observe the disappearance of the azide absorption band.

Ellis, Lubell *et al.* discuss a non-destructive method of analysing polymers by Photoacoustic Infrared Spectroscopy (PA-FTIR).[24] Spectroscopic enhancements by photoacoustic methods was shown to remove baseline artefacts such as those that occur as a result of light scattering and reflectance. The approach was applied to three different resin-bound amino esters and several reaction steps where functional group changes occur.

Other infrared applications include the removal of bound water molecules by drying, providing enhanced spectral resolution. Labelled substrates can be identified by IR spectroscopy, similar to approaches used in NMR spectroscopy. In this way IR can be used quantitatively to measure the deuterium content of an immobilised substrate and thus monitor the progress and yield of reactions.[25]

1.5.2. Nuclear Magnetic Resonance Spectroscopy

Recent developments have provided a method for analysing polymers by solid-state NMR spectroscopy.[14] Magic angle spinning (MAS) is commonly used to obtain high resonance ^{1}H-NMR spectra of polymer bound substrates. Solid-state NMR is therefore a useful tool for monitoring solid-phase reactions. Techniques are now available that can confirm functional groups bound to resins; however, although a useful tool, the analysis of polymer bound reagents by NMR can be time consuming and a powerful NMR machine is required.

New approaches in NMR have enabled single resin beads to be analysed by direct ^{1}H observation in a CP/MAS (cross polarised magic angle spinning) probe that has clearly shown resonances that could be assigned to a characteristic molecule in a Tentagel™-type resin.[14]

Shapiro and his team report several NMR methodologies applicable to combinatorial chemistry and in particular MAS and tandem techniques.[26-31] One such example discusses the enhanced resolution that can be obtained using MAS NMR for combinatorial chemistry.[29] A spin-echo MAS NMR of isoleucine on Wang resin swollen in DMF was illustrated with excellent resolution. Tartar *et al.* also report MAS NMR monitoring of the Heck reaction by solid-phase synthesis again using solvent, 'gel-phase', swollen resins.[32] The method provided a useful technique for monitoring multi-step reactions. MAS has also been applied to poly(ethylene glycol)-grafted polystyrene Tentagel™ resins where comparable resolution to that in the liquid-phase was achieved by gel-phase NMR.[33]

The gel-phase approach was again reported by Gani *et al.*; however in this case ^{19}F-NMR spectroscopy was used to quantitatively identify the extent of conversion of resins.[34] The approach was used to quantify the reaction of Merrifield resin with 2- and 4-fluorophenol. The spectra clearly showed separate resonances that could be assigned to the corresponding fluorophenol bound resins. Sarkar *et al.* report a non-destructive method of single bead analysis by NMR.[35] A ^{13}C labelled single bead was detected by ^{1}H-NMR(HMQC) in a two coil high-resolution MAS probe.

Another example of NMR application to combinatorial chemistry describes the liquid-phase monitoring of combinatorial reactions.[36] Polyethylene glycols were used as a soluble matrix for the combinatorial approach; ^{1}H-NMR could uniquely confirm product formation without destruction of the polymer or involving cleavage reactions.

Standard NMR techniques are also advancing rapidly and can be applied to combinatorial chemistry. These include:[14]

(i) Gradient Field technology

(ii) J-resolved 2D spectra

(iii) Reduction of inhomogeneous line broadening

Reaction monitoring was also demonstrated, by Cilli *et al.*, utilising spin label EPR spectra.[37] EPR spectra show a strong dependency on the method of labelling adopted. In this case EPR was used to successfully monitor chain-chain association in a solvated polymer matrix.

1.5.3. Chromatography

Chromatographic methods, such as high performance liquid chromatography (HPLC), are difficult to achieve on solid-phase supported reagents, as the majority of techniques require samples to be in solution. The technique is, therefore, of use in solution-phase approaches but is not likely to be of use to solid-phase supported reagents now or in the future. A recent development, geared towards the challenges of high throughput solution-phase library synthesis, has provided a new application of HPLC by means of a chemiluminescent nitrogen detector (CLND). Essentially this destructive detector oxidises nitrogen-containing compounds into NO and then uses ozone to excite NO to nitrogen dioxide.[14] CLND does have some limitations yet it has provided excellent results for specific compounds.

Iterative size-exclusion chromatography was coupled with liquid chromatographic mass spectrometry to identify complexes in combinatorial chemistry, used in the screening of solution-phase libraries.[38] Bioaffinity selection was achieved utilising fast SEC spin columns to good effect, the only restriction on the type of ligand being whether it was amenable to electrospray ionisation.

1.5.4. Mass Spectrometry

Mass Spectrometry is frequently used in the characterisation of solution-phase combinatorial libraries. It can currently only be applied to materials removed from polymeric support and is therefore of little benefit in confirming solid-supported reagents. Techniques that are useful for solution-phase compound libraries include fourier transform mass spectrometry and gas chromatography coupled with mass spectrometry.

Electrospray mass spectrometry is the only useful method to date for providing any analysis on material cleaved from solid-supported reagents. The technique is sensitive enough to determine the molecular weight of material cleaved from a single resin bead. McKeown and co-workers discuss an electrospray mass spectrometry approach involving the development of a dual linker, based on a photolabile carbamate, which has the ability to release an amine that is MS sensitising.[39]

MALDI (Matrix assisted laser desorption/ ionisation) mass spectrometry is used to screen entire solution-phase libraries. Bradley and co-workers report the application of MALDI mass spectrometry to solid-phase combinatorial synthesis.[40-43] Essentially any given chemistry can be carried out and analysed by MALDI –TOF mass spectrometry providing the reaction is compatible with the Rink linker used.[40] Application to several (10-100) or single beads was achieved. The method was applied to the synthesis of Lysobactin and Katanosin analogues to good effect.[41] Products in each case were cleaved from single beads by treatment with TFA.

CHAPTER 2 – HETEROCYCLE SYNTHESIS

2.1 BACKGROUND

Heterocycles are cyclic compounds in which at least one of the atoms in the ring is non-carbon. The heteroatom is commonly nitrogen, oxygen or sulfur but other examples can include atoms such as B, Si, P, Sn and As.[44] Classification of heterocycles falls under two categories, nonaromatic and aromatic and ring sizes have been reported for three-, four-, five-, six-, seven-, eight-membered, and greater, or bicyclic and fused heterocycles. Literature on heterocyclic chemistry is widely reported and several good books covering synthetic approaches are available.[45-49] Recent advances in solid-supported heterocyclic synthesis have been discussed in a review by Franzén.[50]

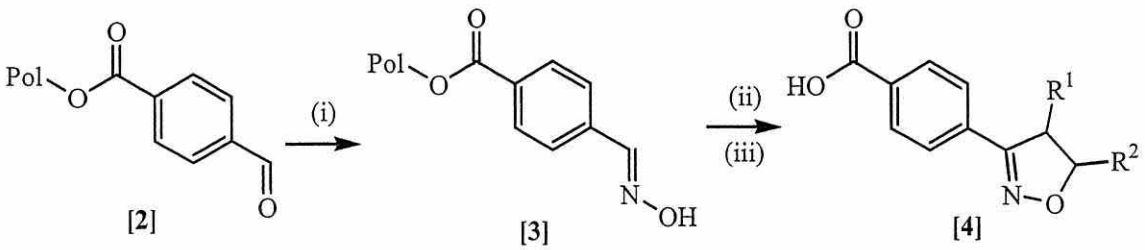
Due to the vast literature published on approaches to heterocycles, this section aims to discuss mainly 5- and 6-membered heterocyclic synthesis and fused or bicyclic heterocycle synthesis. Focus in this section is towards research that involved aspects of solid-phase and solution-phase synthesis of heterocycles that was deemed relevant to the research; it excludes guanidine synthesis (discussed in Chapter 3).

2.2. FIVE MEMBERED HETEROCYCLES

Many examples of 5-membered heterocycles can be found in nature and are useful in pharmaceutical applications. Interest in the following examples was due to the fact that the novel resins could be produced and used in further synthetic approaches towards heterocycles.

2.2.1. Synthesis of Isoxazolines

A polymer-supported oxime was investigated by Cheng and Mjalli in the synthesis of Δ^2-isoxazolinones, which are important pharmacophores in medicinal chemistry.[51] The oxime can be converted into a nitrile oxide using bleach in THF, and this is then trapped by an alkene (Scheme 1).

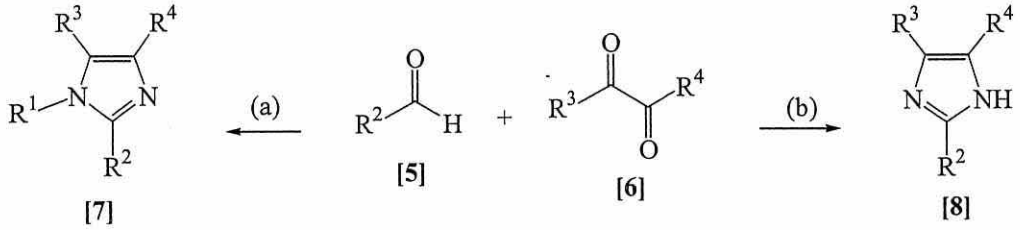


Scheme 1. (i) $NH_2OH.HCl$, Et_3N, MeOH, r.t.; (ii) Bleach / THF, $R^1(CH=CH)R^2$; (iii) 20 % TFA / CH_2Cl_2.

Thus 4-formylbenzoic acid was coupled to the benzyl alcohol of Wang resin using standard DIC / DMAP conditions. The aldehyde resin **[2]** was converted into oxime **[3]** on reaction with hydroxylamine and base. A 1,3-diploar cycloaddition reaction was achieved on addition of bleach with a range of alkenes. Cleavage of product from resin by treatment with TFA in dichloromethane afforded the desired Δ^2-isoxazolinones as a single product **[4]**. Δ^2-Isoxazolinone synthesis was also achieved by polymer supported dipolarophiles with improved yield, again forming only the single product.

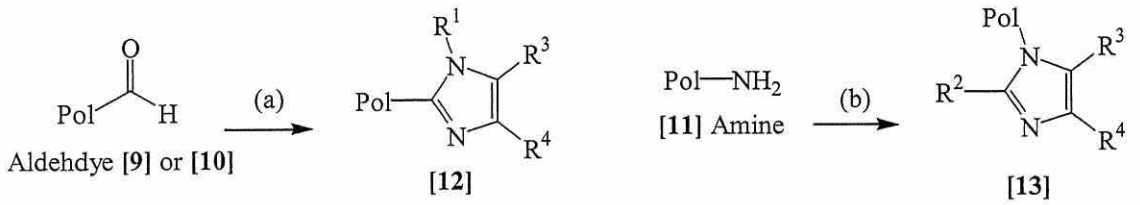
2.2.2. Synthesis of Imidazoles

Traditional solution-phase syntheses of imidazoles (Scheme 2) produce crude products **[8]** and much purification is required.



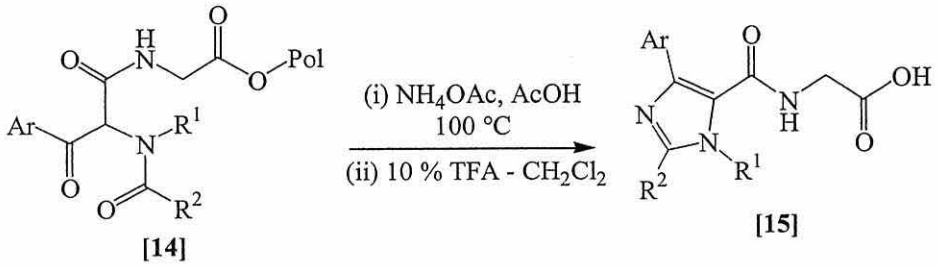
Scheme 2. (a)R^1NH_2, NH_4OAc, AcOH, Δ; (b) NH_4OAc, AcOH, Δ.

The above reaction, by Mjalli *et al.*, was compared to the equivalent solid-phase synthesis, which required a large excess of reagents to drive the reaction to completion.[52] The research demonstrated the reaction *via* three different linkers, two aldehyde bound resins, 4-hydroxybenzaldeyde **[9]** and carboxybenzaldehyde **[10]**, and an amine **[11]**. Excellent yields and purity of products **[13]** were obtained after cleavage from the resin (Scheme 3).



Scheme 3. (a) R^1NH_2, NH_4OAc, R^3COCOR^4, AcOH, 100 °C, 4 h; (b) R^2CHO, NH_4OAc, $R^3COCO\ R^4$, AcOH, 100 °C, 4 h.

Similarly Mjalli reported imidazole synthesis *via* α-(*N*-acyl-*N*-alkylamino)-β-ketoamides on Wang resin.[53] Aliphatic amino acids were formylated and bound to Wang resin, which was then dehydrated to provide **[14]**. α-(*N*-Acyl-*N*-alkylamino)-β-ketoamides **[15]** were thus produced after removal from the resin (Scheme 4).

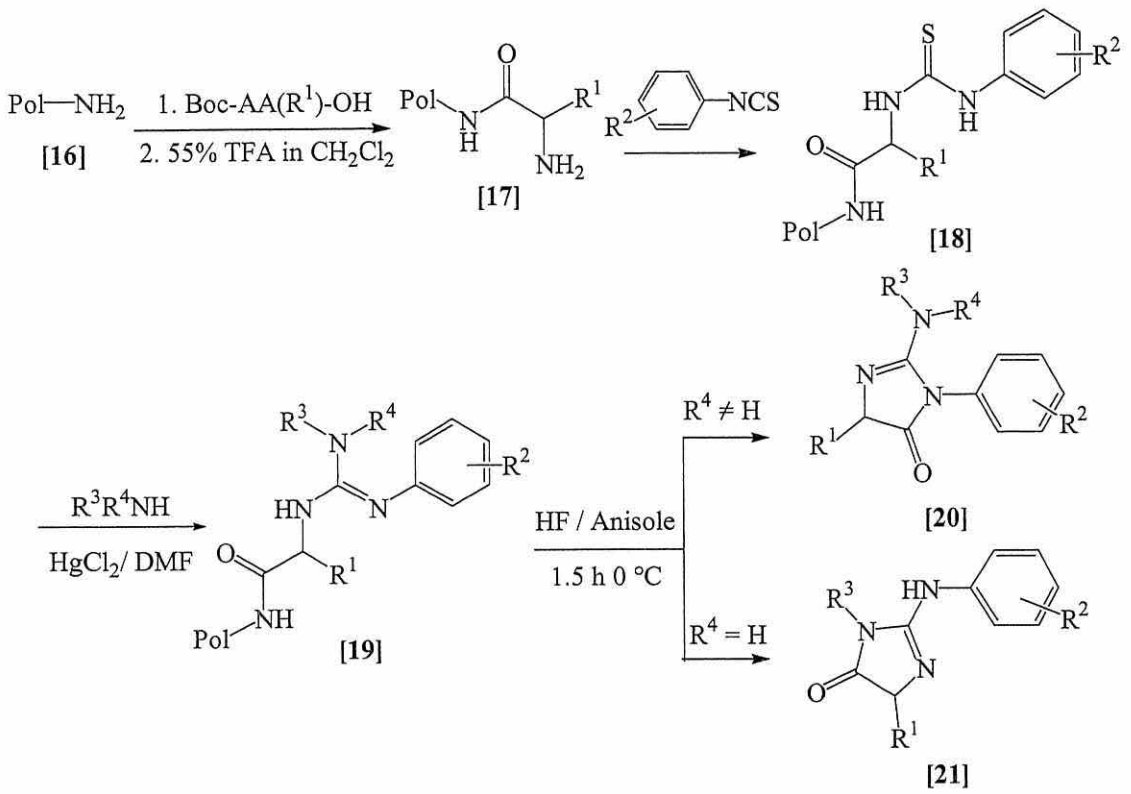


Scheme 4. α-(*N*-Acyl-*N*-alkylamino)-β-ketoamide synthesis

Initial production of **[14]** took 3 days to achieve and treatment with ammonium acetate required up to 20 hours for completion; however, cleavage occurred in under 20 minutes. The imidazoles were produced in low to moderate yield (16 – 56 %) and the reaction was a significant improvement to traditional solution-phase multi-step synthesis.

2.2.3. Synthesis of Imidazolones

The application of parallel solid-phase synthesis *via* 'Tea Bag' methodology was reported by Houghten *et al.*[54] The method also reports the utilisation of *p*-methylbenzhydrylamine (MBHA) resin in the rather novel approach illustrated in Scheme 5.



Scheme 5. Imidazolones Synthesis - BocAA(R^1)OH is a Boc protected amino acid.

Thus a Boc amino acid was coupled to MBHA resin, the protecting group was removed and the resultant resin was treated with an isothiocyanate to yield a polymer supported thiourea **[18]**. Guanidine products **[19]** were then acquired by treating the thiourea bound resin with $HgCl_2$ and an amine in DMF overnight. Cyclization and cleavage were achieved simultaneously upon treatment with HF / anisole, yielding the imidazolones **[20]** or **[21]**. Yields were again excellent, up to 100 %, and purity was also good. The approach was applied to 40 amino acids, 20 isothiocyanates and 20 amines, yielding a library of potentially 16,000 compounds.

2.3. SIX MEMBERED HETEROCYCLES

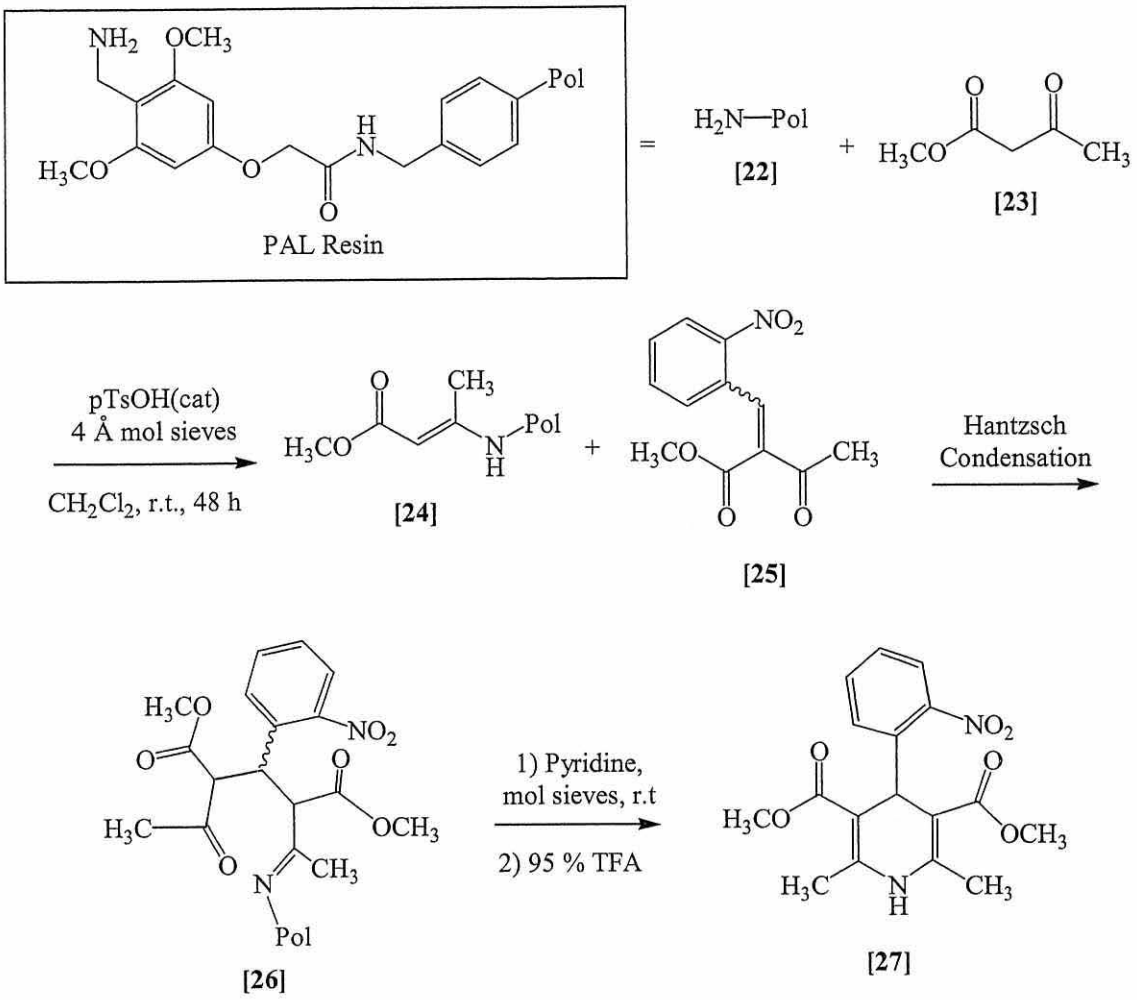
As in the case of 5-membered heterocycles, this project sought to develop methods for producing solid-supported reagents that could be used to produce 6-membered heterocycles that were expected to have pharmaceutical or agrochemical applications. As much of the work using solid supports proved unsuccessful solution-phase methods were then adopted.

2.3.1. Pyridine and Dihydropyridine Synthesis

Pyridines are usually synthesised by Hantzch's method, which involves the condensation of a β-ketoester with an aldehyde in aqueous ammonia.[45-49] The dihydropyridine structure can be found in many biologically interesting and active molecules. Compounds of this nature have been used in medicine since 1975 and are frequently used to treat diseases of a cardiovascular nature including hypertension, cardiac arrhythmias and angina.

2.3.1.1. Solid-Phase Synthesis of Nifedipine

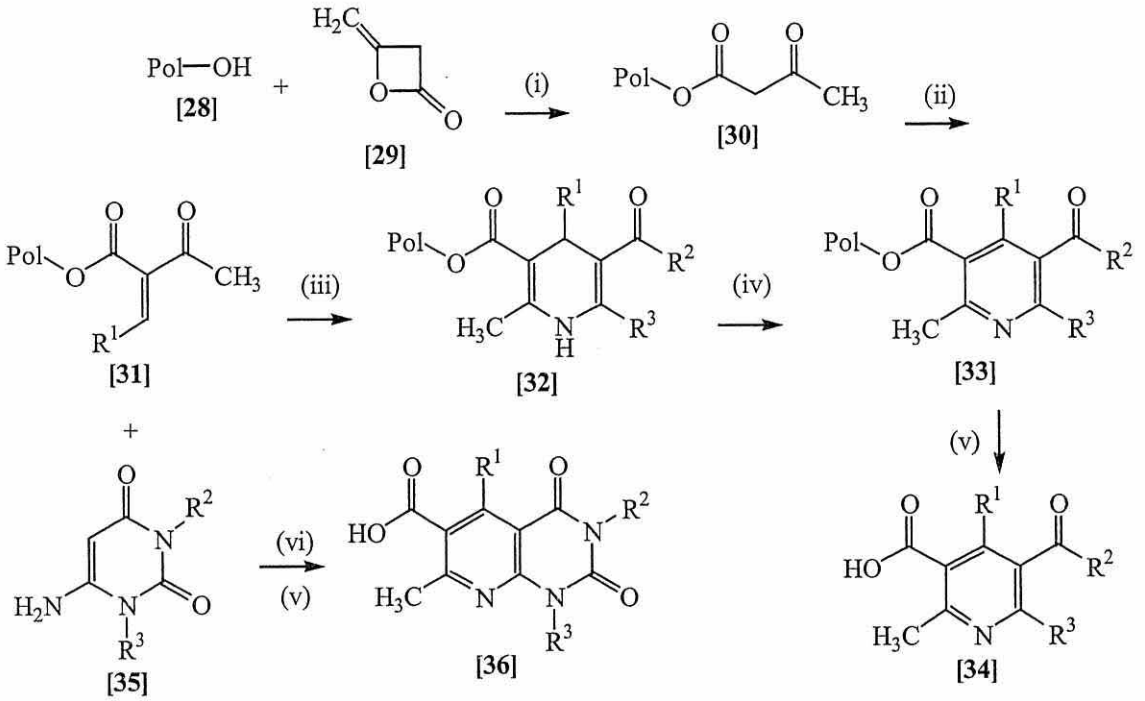
One of the most significant medical applications of pyridine synthesis was the discovery of Nifedipine **[27]**. This is a calcium channel modulator effective in the treatment of angina due to the ability it has to increase coronary blood flow. Recent advances have demonstrated the solid-phase synthesis of drugs such as **[27]** (Scheme 6).[55]



Scheme 6. Solid-phase Synthesis of Nifedipine

The approach adopted utilised acid cleavable NH_2-Pol **[22]** (depicted as PAL resin but also possible as Rink resin) using an excess of ethyl acetoacetate in dichloromethane with a catalytic amount of *p*-toluene sulfonic acid. Molecular sieves were added, as a dehydrating agent and the reaction stirred for 48 hours. Enamino ester bound resin **[24]** was then subjected to a Hantzsch type heterocyclic condensation reaction with an arylidene ester to yield the Michael adducts **[26]**. The addition of pyridine as a basic solvent and further molecular sieves followed by an acidic cleavage yielded the desired dihydropyridine, Nifedipine **[27]**, in 70 % yield (80 % purity). Further investigations on the solid-phase synthesis of Nifedipine have proved that Rink is the preferred resin, as cleavage can be achieved at low concentrations of trifluoracetic acid.

A similar method was adopted by Gordeev *et al.*, employing Rink resin in the synthesis of a library of 1,4-dihydropyridines **[32]** and pyridines **[34]** and **[36]**.[56] Their Knoevenagel condensation of immobilised β-keto esters with aldehydes is depicted in Scheme 7.

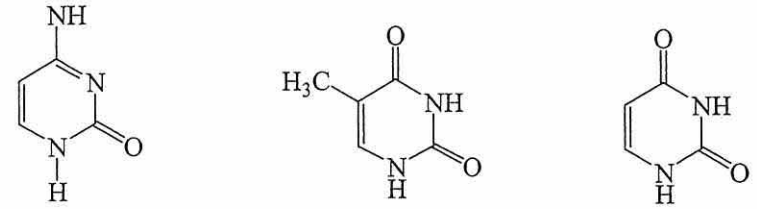


Scheme 7. (i) DMAP, CH_2Cl_2; (ii) R^1CHO, piperidine cat., ^iPrOH, benzene, Δ; (iii) $R^2OCOCHCR^3NH_2$ (*e.g.* methyl aminocrotonate), DMF, Δ; (iv) CAN, Me_2NCOMe; (v) TFA / CH_2Cl_2; (vi) DMF, Δ, CAN, Me_2NCOMe.

Acetoacetylation of polymer bound hydroxyl resins **[28]**, such as Wang or Sasrin, was achieved by reaction with diketene **[29]**. Knoevenagel condensation of **[30]** with an aldehyde resulted in the formation of benzylidine resin **[31]**, followed by heterocyclisation *via* a Hantzsch-type reaction with methyl aminocrotonate (R^2 = OMe, R^3 = Me) to afford the corresponding 1,4-dihydropyridine **[32]**. Oxidation of resin bound **[32]** and subsequent cleavage yielded products **[34]** in good to excellent purity and yield (where reported).[56]

2.3.2. Synthesis of Pyrimidines

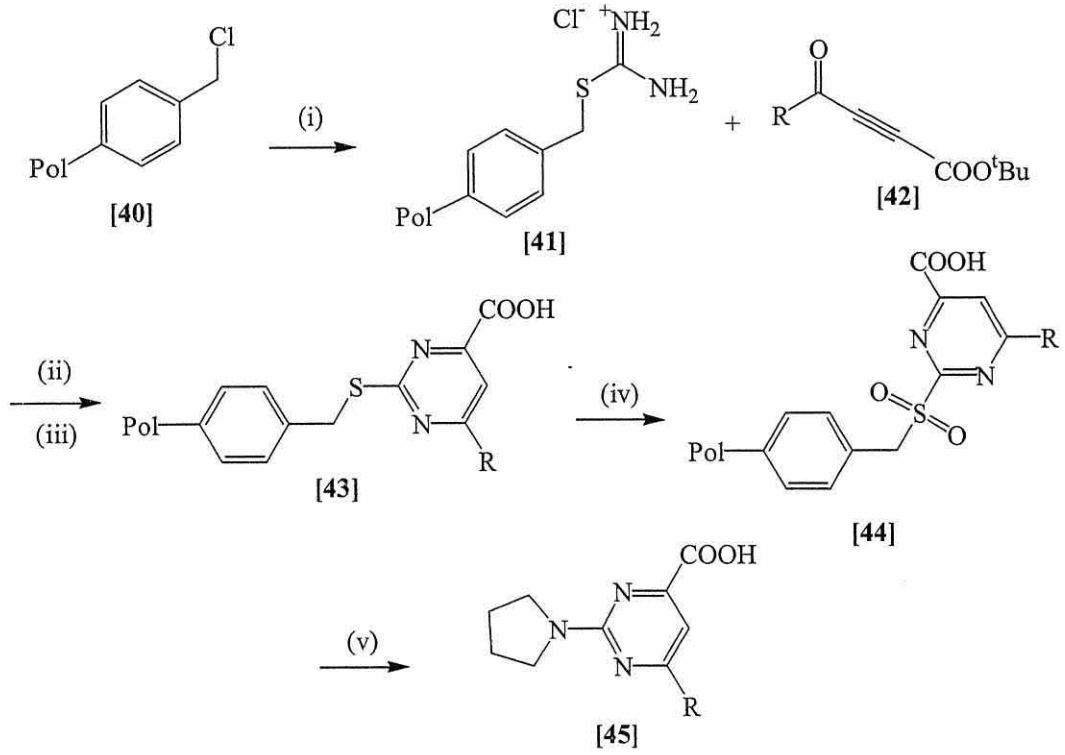
The pyrimidine substructure is of great importance in nature as it is a component within nucleic acids.[57] Cytosine **[37]**, thymine **[38]** and uracil **[39]** are all essential to the way our bodies function (Figure 2).



[37] Cytosine **[38]** Thymine **[39]** Uracil

Figure 2. Nucleoside bases

Obrecht and co-workers reported the synthesis of structurally diverse pyrimidines from Merrifield resin *via* a multi-step sequence (Scheme 8).[58]



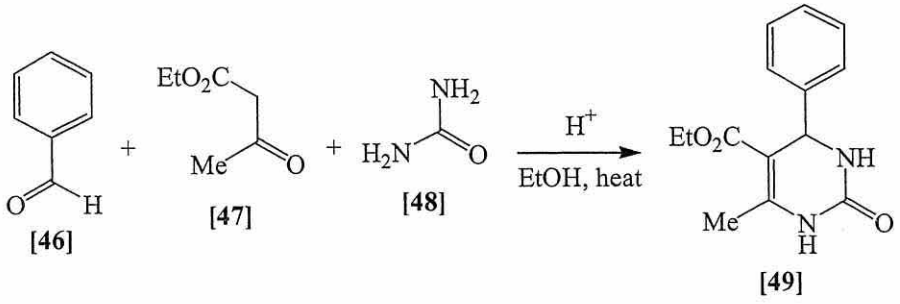
Scheme 8. (i) Thiourea, dioxane / EtOH 4:1, 85 °C, 15 h; (ii) $(^{i}Pr)_2EtN$, DMF, r.t., 24 h; (iii) 50 % CF_3COOH, CH_2Cl_2, r.t., 15 h; (iv) *m*CPBA, CH_2Cl_2, 15 h; (v) pyrrolidine, dioxane, r.t., 6 h.

Thiourea was bound to Merrifield resin as the thiouronium salt **[41]**, which was in turn reacted with acetylenic ketones in a condensation reaction to yield the corresponding pyrimidine carboxylic acids **[43]**. Interestingly the cleavage step of this reaction, producing **[45]** in excellent yield and purity, differed from traditional TFA methodologies. Similar approaches in solution used ammonolysis and alcoholysis to obtain products; however these conditions proved too harsh for the polymer bound equivalent and products were of low purity. The key step in cleavage was the formation of sulfone **[44]** by oxidation of the alkylthio group of **[43]** on treatment with *m*CPBA. Products **[45]** were then easily removed from the polymer by pyrrolidine in dioxane at room temperature.

2.3.3. Synthesis of Dihydropyrimidines

Dihydropyrimidines have proved to have similar pharmacological effects to dihydropyridine calcium channel blockers. There are extensive publications on solution-phase synthetic approaches to dihydropyrimidines. Perhaps the most direct is the Biginelli multicomponent condensation reaction.[59]

Multicomponent condensation reactions such as the Ugi [60-63] and Biginelli [63-75] reactions are commonplace in organic synthesis. Biginelli reported his multicomponent reaction in 1893.[59] The reaction classically involves the catalysed cyclo-condensation of benzaldehyde **[46]**, ethyl acetoacetate **[47]** and urea **[48]** in the presence of hydrochloric acid, depicted in Scheme 9. Crystalline product **[49]** appears on cooling the reaction mixture to room temperature. The research of Kappe over recent years has provided many examples of the classic Biginelli reaction used in the synthesis of dihydropyrimidines.[75-78]

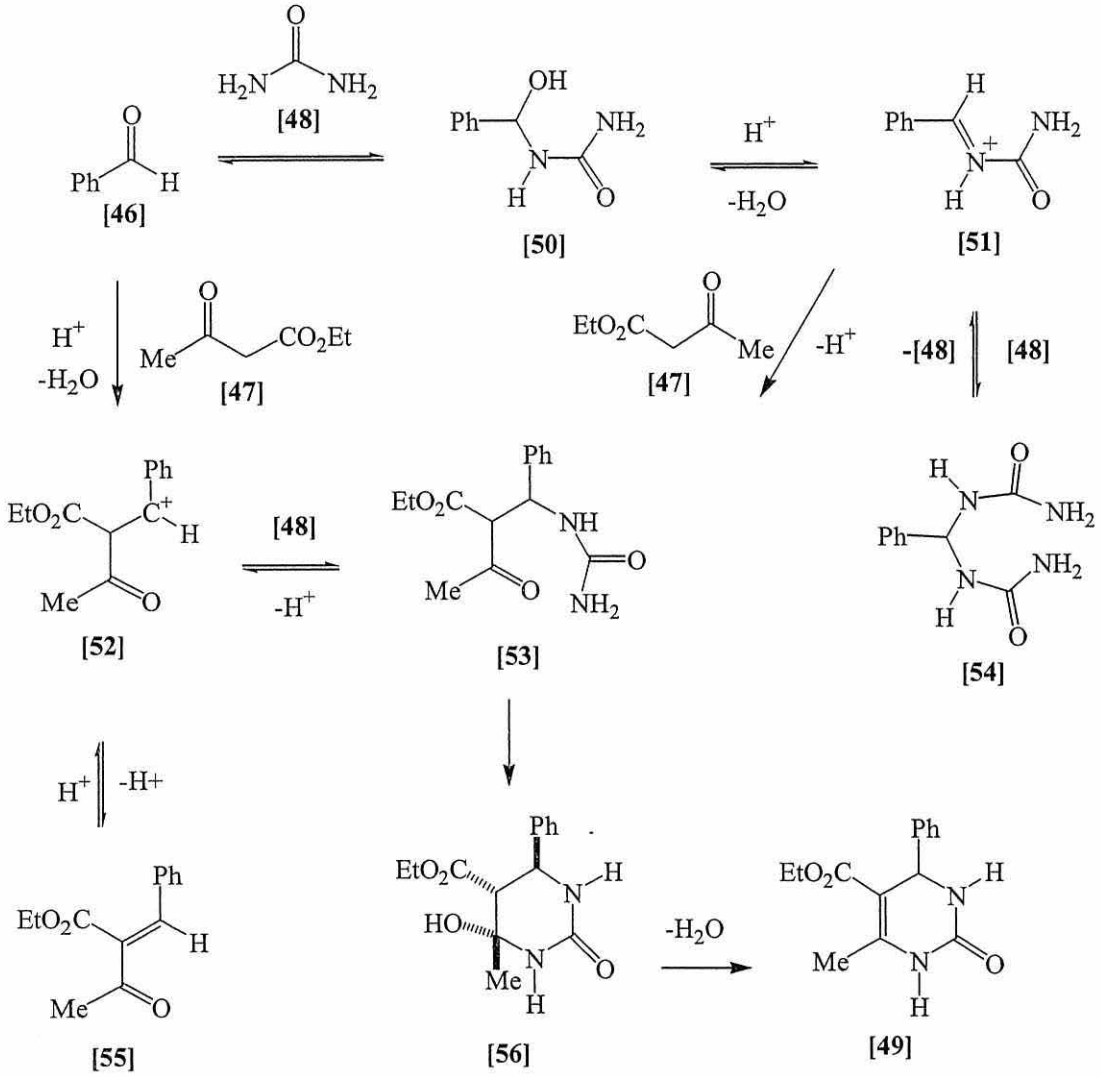


[46] [47] [48] [49]

Scheme 9. The Biginelli condensation reaction

2.3.3.1. The Mechanism of the Biginelli Reaction

The complete mechanism of the Biginelli reaction has not been defined with great clarity or scientific conviction. Many scientists have provided theories of the mechanism for 30 years. A comprehensive review by Kappe illustrates likely mechanistic routes to product (Scheme 10).[75]



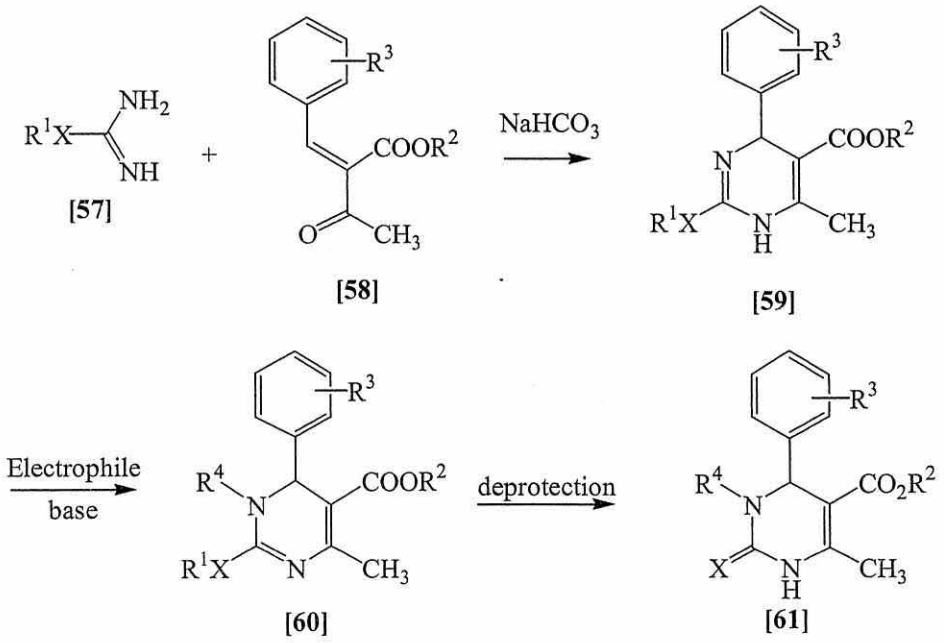
Scheme 10. Proposed Mechanism of the Biginelli Reaction

It was initially proposed that the bisureide **[54]** was the first intermediate formed in a condensation reaction with benzaldehyde **[46]** and urea **[48]**.[75] Sweet and Fissekis suggested that an acid-catalysed aldol reaction occurs between benzaldehyde **[46]** and ethyl acetoacetate **[47]** to yield a carbenium ion **[52]**.[79] Kappe and his team investigated this theory by trapping experiments followed by ^{1}H- and ^{13}C-NMR spectroscopy. NMR

spectroscopy provides some insight into the mechanistic debate by proving that the key step is the acid-catalysed reaction forming the *N*-acyliminium ion **[51]**. The reaction is likely to proceed by interception of the iminium ion by ethyl acetoacetate **[47]**, *via* the enol tautomer, to yield an open-chain ureide **[53]** which cyclizes to form hexahydro-pyrimidine **[56]**. A further acid-catalysed reaction takes place, eliminating water to form the desired product **[49]**.[79]

2.3.3.2. Other Solution-Phase Approaches to Dihydropyrimidines

Atwal *et al.* have reported that 2-heteroalkyl-1,4-dihydropyrimidines mimic the biological effects of dihydropyridines.[65,66] Previously their research had shown the potent vasorelaxant activity of such compounds *in vitro*; however, the structures had lower affinity for the dihydropyridine receptor than similar dihydropyridines. Modification of the original methods proved effective, producing a compound with enhanced calcium channel blocking potency. Scheme 11 illustrates the synthetic approach to dihydropyrimidines.



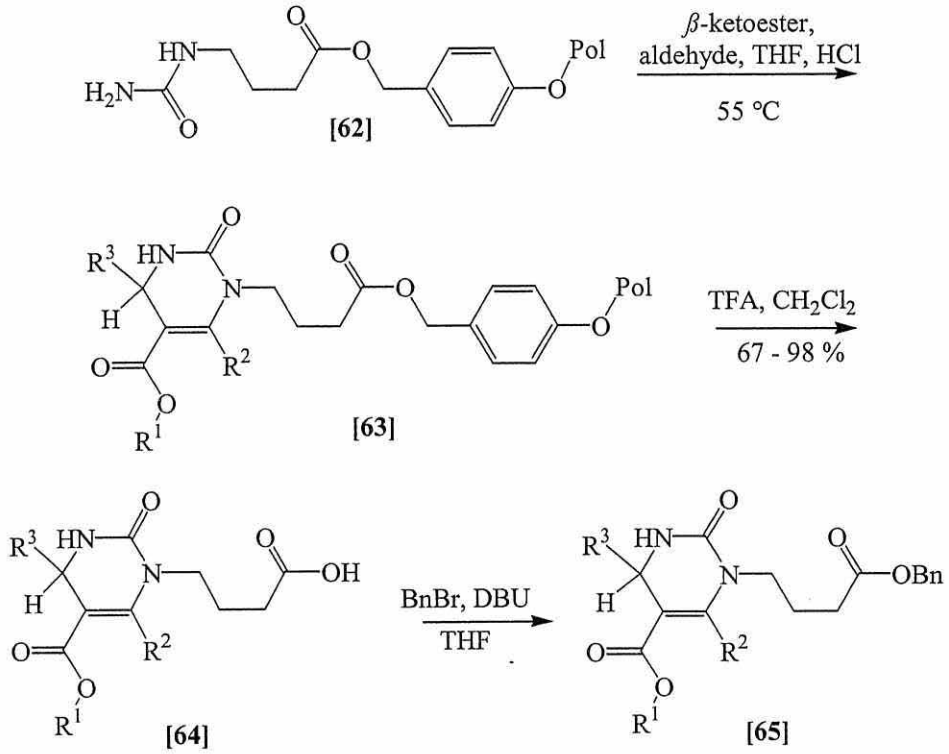
Scheme 11. Dihydropyrimidine Synthesis, X = N, O, S

A series of twenty three 3-substituted-4-aryl-1,4-dihydropyrimidinecarboxylic acid esters, *e.g.* **[61]**, were successfully produced by this method, some of which proved to

have significantly more potency with regard to calcium channel blocking than previously reported 2-hetero-1,4-dihydropyrimidines.

2.3.3.3. Solid-Phase Synthesis of Dihydropyrimidines

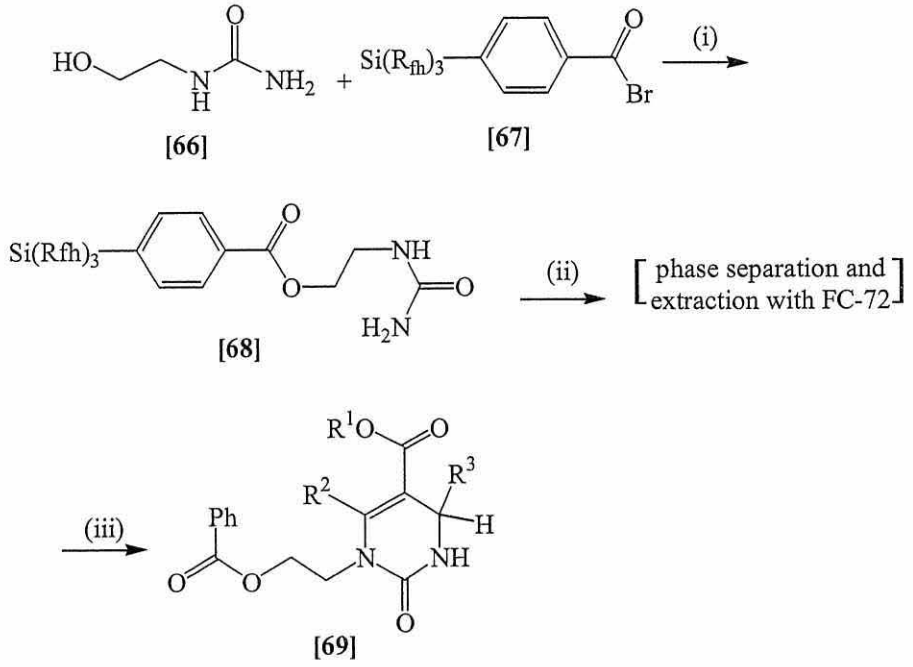
Wipf and Cunningham reported a novel protocol for Biginelli condensations, yielding dihydropyrimidines **[65]**, using a solid-support derived from Wang resin.[67] The protocol has been demonstrated for substituted β-ketoesters, aldehydes and ureas and is illustrated in Scheme 12.



Scheme 12. Solid-phase Synthesis of Dihydropyrimidines

The reaction proceeded in excellent overall yield, with products **[65]** ranging from 67 - 93 % yield, compared to 54 - 86 % for the equivalent traditional solution-phase reactions. A library of 10 dihydropyrimidines was synthesised by this route. Potentially this method could be applied to the synthesis of a more extensive library. The commercial availability of large numbers of aldehydes and the relatively straightforward synthesis of the reaction components makes this synthetic approach of benefit.

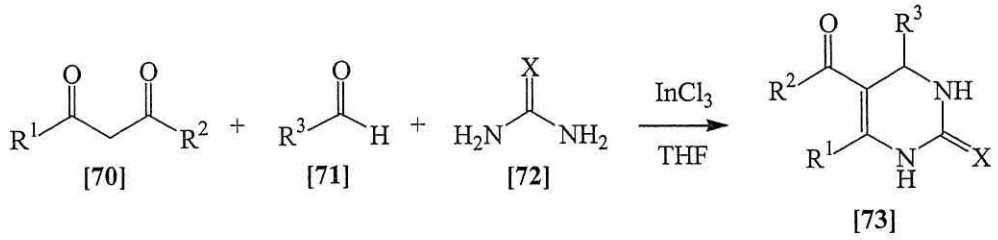
Wipf also demonstrated a method for applying the Biginelli reaction utilising fluorous phase methodologies.[68] The rather novel approach, although not solid-phase synthesis, enables a highly fluorinated molecule to partition into the fluorous phase in liquid-liquid extraction between fluorinated and non-fluorinated organic solvents (Scheme 13).



Scheme 13. (i) NEt_3, DMAP, dioxane / BTF, 35 °C, 22 h.; (ii) $R^1OC(O)CH_2C(O)R^2$, R^3CHO, HCl, THF / BTF, 50 °C, 3 d.; (iii) TBAF, THF / BTF, 25 °C, 0.5 h. $R_{fh} = C_{10}F_{21}CH_2CH_2$-

Fluorous synthesis in reality differs very little from solid-phase synthesis; fundamentally, the reaction occurs on a fluorous substrate as opposed to a polymer supported one.

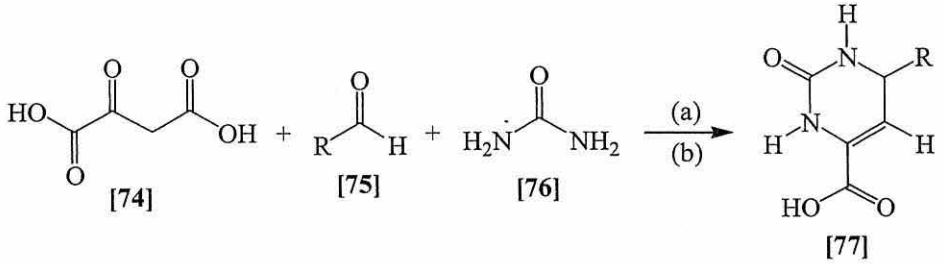
Ranu *et al.* describe an interesting alternative to the classic Biginelli reaction to produce dihydropyrimidinones **[73]**.[69] The drawback to the multi-component condensation reaction is the low yields obtained when substituted aromatic and aliphatic aldehydes are used. Other research teams have attempted using protic acids (HCl),[70] strong Lewis acids (BF_3), acetic acid and other additives.[71] Indium(III) chloride is a powerful Lewis acid that has been used in regio- and chemo-selective reactions. Ranu's team has replaced the classic acid used in the Biginelli reaction with indium(III) chloride to good effect (Scheme 14).



Scheme 14. Indium (III) Chloride application to Biginelli Reaction, X = O, S

Typically a β-dicarbonyl **[70]**, aldehyde **[71]** and urea **[72]** in THF are heated under reflux with 10 mol % of $InCl_3$. Yields obtained range from 75 – 95 % in all 38 reactions and compounds are over 95 % pure by ^{1}H-NMR spectroscopy. The method significantly improves previously reported yields of such compounds.

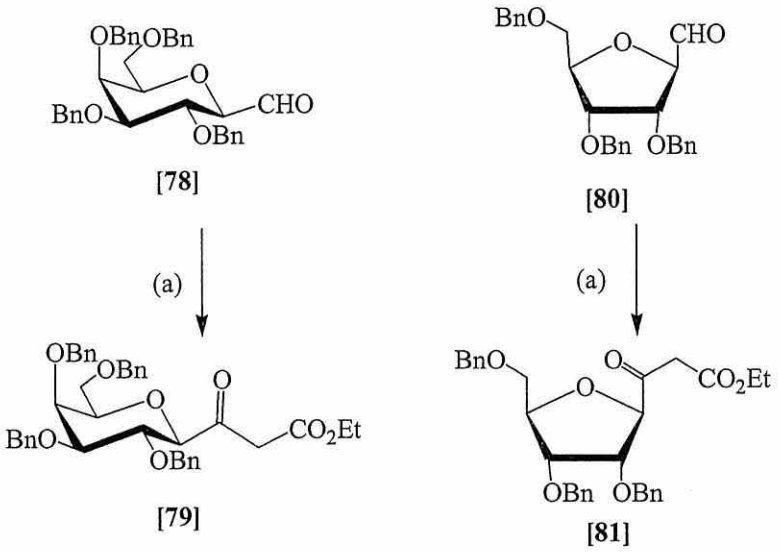
A further approach to dihydropyrimidinones, and in particular a 5-unsubstituted derivative, was demonstrated by Bussolari and McDonnell.[72] Cyclocondensation reactions were carried out on oxalacetic acid with urea and several aldehydes (Scheme 15). Heating under reflux with trifluoroacetic acid in dichloroethane proved an extremely efficient reaction producing dihydropyrimidinones **[77]** in better yields than their alternative method using sulfuric acid. The presence of a carboxylic acid group provided scope for further synthetic transformations.



Scheme 15. (a) cat. H_2SO_4, absolute EtOH, Δ, 12 h., (b) cat. TFA, DCE, Δ, 12 h.

Dondoni *et al.* describe the synthesis of *C*-glycosylated dihydropyrimidine libraries using Lewis acid catalysis.[73] This type of dihydropyrimidine had been little investigated previously and interest lay in the potential such compounds have in increasing bioavailability and water solubility. The reaction is in essence a Biginelli cyclo-condensation with the replacement of β-keto esters with *C*-glycosyl β-keto esters. Anomeric sugar aldehydes, β-linked galactopyranoside **[78]** and ribofuranoside **[80]**,

were converted into *C*-glycosyl *β*-keto esters **[79]** and **[81]** by reaction with ethyl diazoacetate and boron trifluoride etherate (Scheme 16).

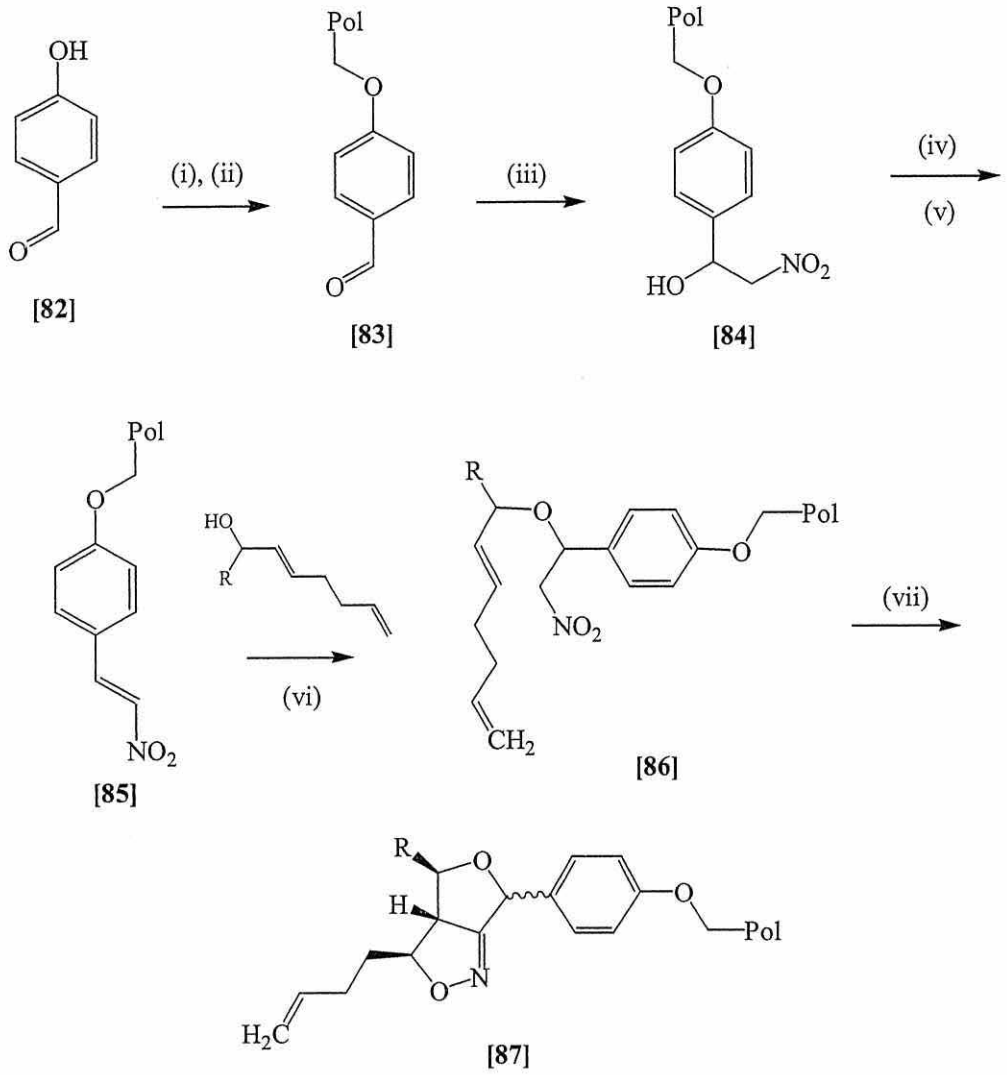


Scheme 16. (a) Ethyl diazoacetate, $BF_3.Et_2O$. 4 Å MS, CH_2Cl_2, 0 °C, 10 min.

β-Linked galactopyranoside **[78]** and ribofuranoside **[80]** were then used in a model Biginelli type reaction with ethyl acetoacetate and urea promoted by CuCl and $BF_3.Et_2O$ in acetic acid. *C*-Galactosyl dihydropyrimidine derivatives were produced in a mixture of diastereomers, with varying ratios determined by ^{1}H-NMR spectroscopy. Yields were modest, with the greatest yield of 92 % obtained in the reaction of **[81]** with benzaldehyde and urea. Sugar aldehydes and keto esters are readily available and therefore a combinatorial library of glycosylated dihydropyrimidines is highly feasible. Further research into the production of these molecules is of interest for biological applications.[73]

2.4. FUSED HETEROCYCLES

Aldehydes can undergo many synthetic transformations such as condensations and acylations. Much well established aldehyde chemistry has been successfully carried out using solid-phase supported reagents. Kurth *et al.* report the electrophilic cyclization of tetrahydrofuroisoxazolinones to synthesise cyclic ethers, such as **[87]**, using solid-phase synthesis (Scheme 17).[80]

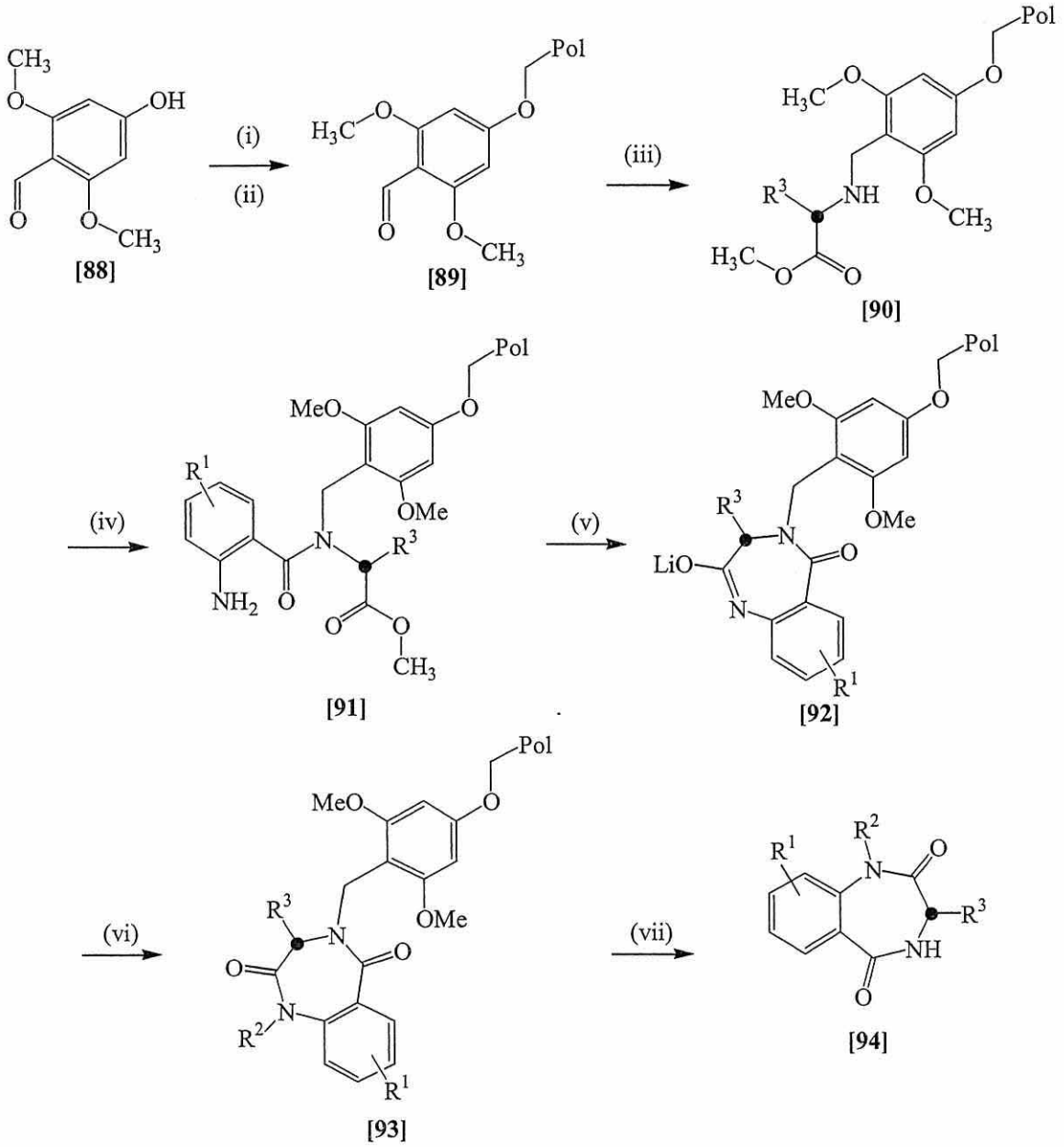


Scheme 17. (i) NaOH, DMSO, 90 °C, 6 h; (ii) Merrifield Resin; (iii) CH_3NO_2, EtOH, THF, r.t., 15 h; (iv) MsCl, CH_2Cl_2, 0 °C; (v) Et_3N; (vi) KOH, THF, -41 °C; (vii) PhNCO, Et_3N, benzene, r.t.

The reaction of 4-hydroxybenzaldehyde **[82]** and NaOH in DMSO with Merrifield resin yielded the corresponding polymer supported 4-(benzyloxy)benzaldehyde **[83]**. Nitroaldol condensation of **[83]** yielded polymer supported alcohol **[84]**, followed by dehydration yielding β-nitrostyrene bound polymer **[85]**. Michael addition of dienol alkoxides to **[85]** resulted in nitro ether bound polymers **[86]**. The final transformation in this reaction sequence involved the removal of water from **[86]** with phenyl isocyanate, which then undergoes an intramolecular 1,3-dipolar cycloaddition yielding **[87]**. Electrophilic cyclization of the resulting heterocycles **[87]**, which was optimised using dichloromethane as solvent and iodine monobromide in the cleavage step, yielded

a small library of cyclic ethers in poor to reasonable yields with the best results obtained when R was a phenyl group.

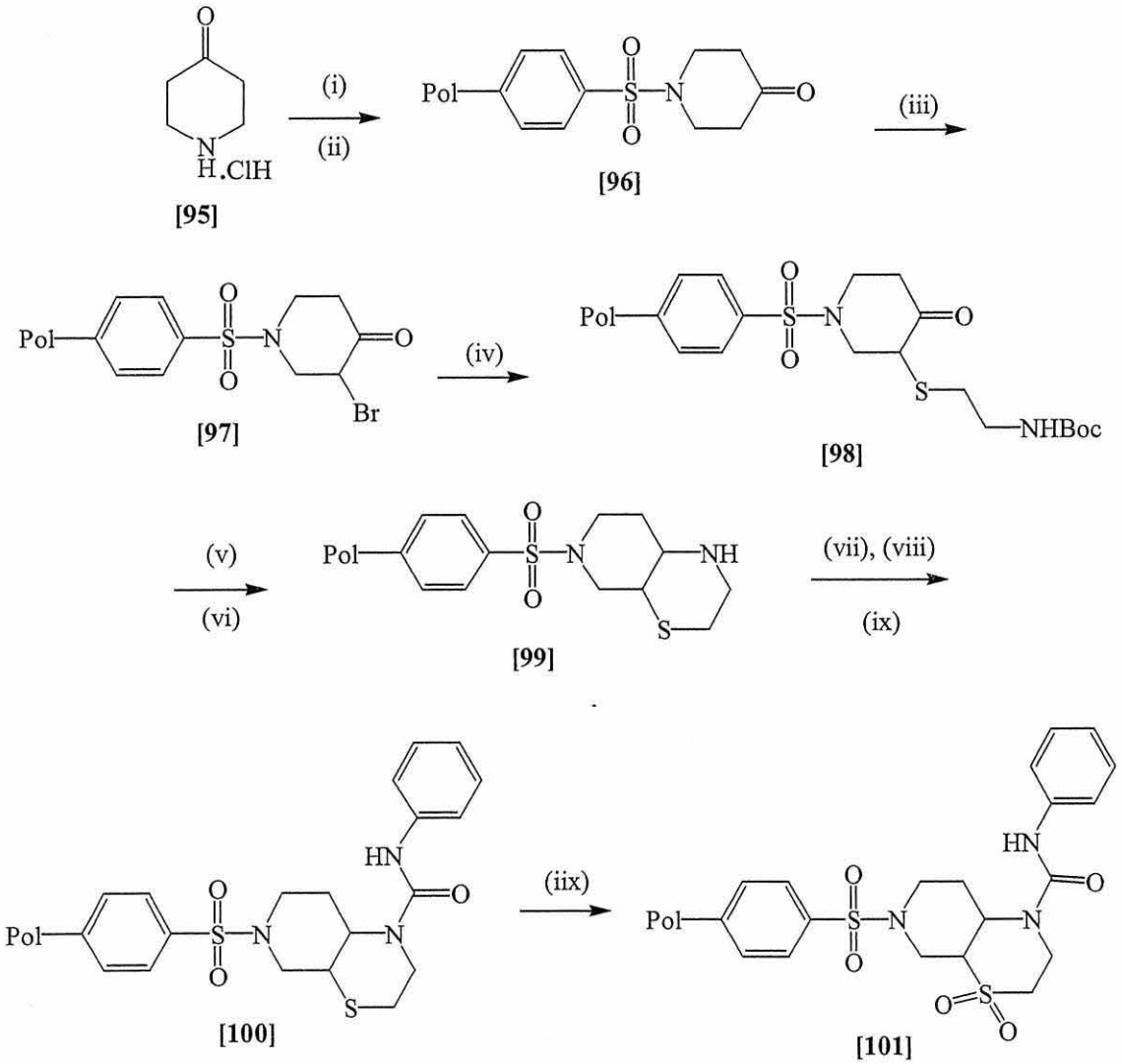
A similar approach involving a benzaldehyde linkage was demonstrated by Ellman *et al.* (Scheme 18).[81] 1,4-Benzodiazepines have been well documented over recent years in pharmaceutical screening. Ellman used an aldehyde linker in a multi-step reaction to synthesise diverse 1,4-benzodiazepine-2,5-diones, *e.g.* **[94]**.



Scheme 18. (i) NaH, DMF; (ii) Merrifield resin, 50 °C, 36 h; (iii) α-amino ester, $NaBH(OAc)_3$, 1 % HOAc, DMF; (iv) anthranilic acid, EDC, NMP; (v) lithium salt, THF / DMF, r.t., 30 h; (vi) R^2X; (vii) TFA / Me_2S / H_2O

This method gave good yield and minimal racemization (position • in scheme) occurs during acylation at step (iii) as determined by chiral HPLC, with optimal results obtained when $R^1 = NO_2$, R^2 = ethyl and $R^3 = CH_2CH(CH_3)_2$ (92 %).

Piperidines and morpholines have been shown to be active fungicides. In particular the thiomorpholine substructure exhibits beneficial applications to medicine and agriculture. A six-step synthesis of a library of piperidino-thiomorpholine derivatives, *e.g.* compound **[101]**, was demonstrated by Ley *et al.* (Scheme 19).[82]



Scheme 19. (i) RSO_2Cl, Pol-DMAP, CH_2Cl_2; (ii) amberlyst 15 Pol-SO_3H; (iii) Pol-Br_2, toluene; (iv) *N*-Boc-2-mercaptoamine, amberlyst A21 (Pol-NMe_2), THF; (v) TFA / CH_2Cl_2; (vi) Pol-$N^+Me_3CNBH_3^-$, MeOH; (vii) PhNCO, CH_2Cl_2; (viii) Pol-NH_2; (ix) amberlyst 15 Pol-SO_3H; (iix) dimethyldioxirane, acetone.

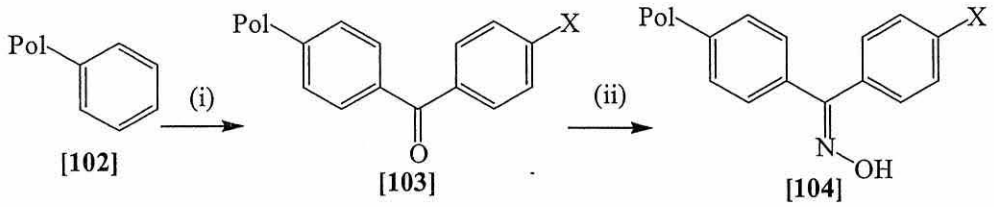
A thirty-two component library of ureas was produced *via* this multi-step reaction and all products required no chromatographic purification and were produced in good yield. The reaction also proved to be applicable for use in an automated system.

2.5. MISCELLANEOUS SOLID-PHASE COMBINATORIAL APPROACHES

The following section describes literature deemed particularly relevant to the research carried out in this thesis.

2.5.1. Solid-supported Oximes

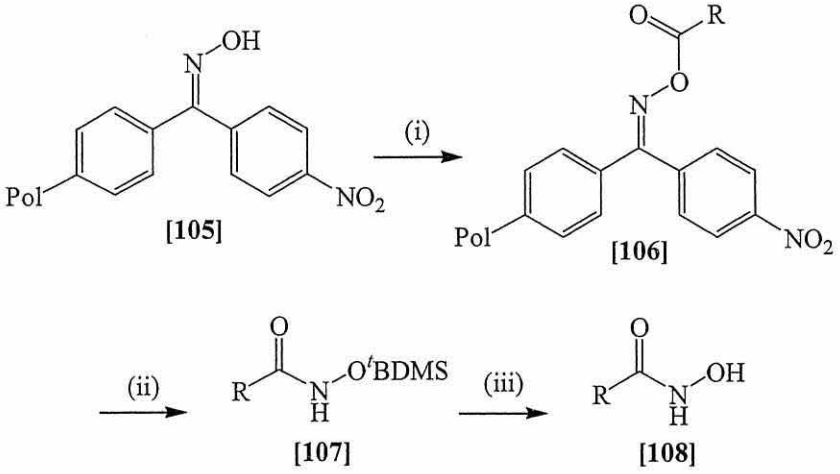
Amine production is commonplace in combinatorial chemistry. It is widely known that oximes can be reduced by catalytic hydrogenation to the corresponding amines. Several research teams have developed methods for producing polymer bound oximes to good effect. Kaiser and DeGrado have prepared polymer bound oxime ethers and used these as supports in the synthesis of peptides.[83,84] A series of substituted benzophenone oximes were attached to polystyrene divinyl benzene resin and each support was tested for preparing peptides (Scheme 20).[83]



Scheme 20. (i) *p*-XC_6H_4COCl, $AlCl_3$; (ii) NH_2OH, HCl, pyridine
X = OMe, H, Cl, NO_2.

The stability of the oxime linker was tested by submitting the polymer bound oximes to a condensation reaction with BocLeu.H_2O, using DCC as a condensing agent. Peptide yields ranged from moderate to excellent and purities were also shown to be high. Kaiser and DeGrado further illustrated peptide synthesis using the oxime bound resin in synthesising longer protected peptides.[84]

Golebiowski and Klopfenstein illustrated hydroxamic acid synthesis.[85] Hydroxamic acid derivatives can inhibit matrix metalloproteinases and act as a unique deacetylase of lipid A biosynthesis. The reaction (Scheme 21) provides building blocks **[108]**, which can be used in further synthesis to produce biologically interesting molecules.

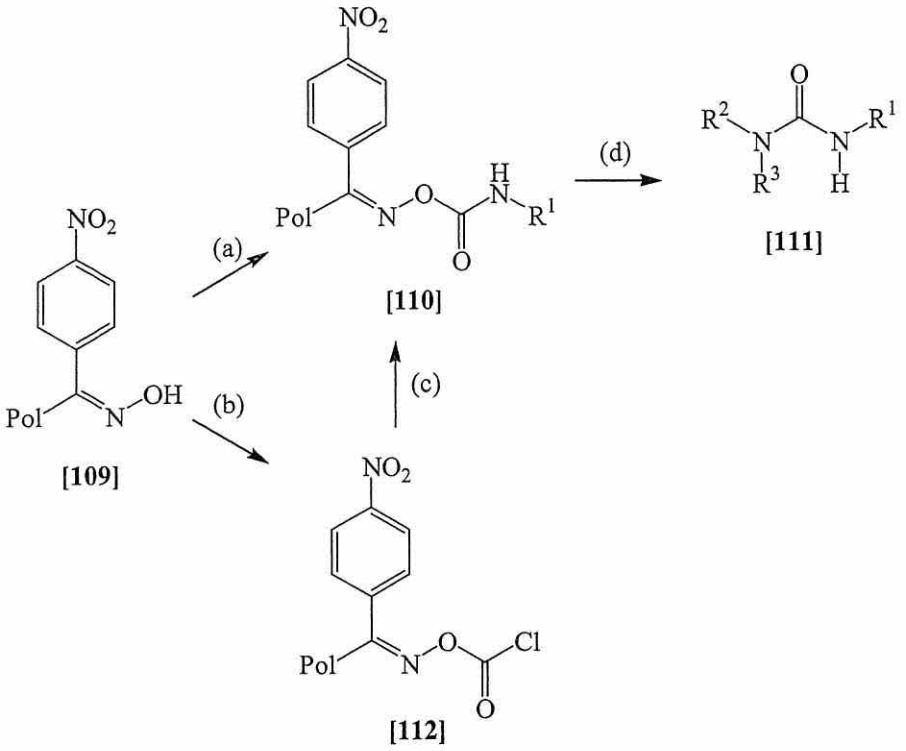


Scheme 21. (i) RCOOH, DIC, CH_2Cl_2; (ii) ^{t}BDMSONH$_2$; (iii) TFA / H_2O

Oxime bound resin **[105]** undergoes *O*-acylation to yield **[106]** which is treated with *tert*-butyldimethylsilyl hydroxylamine to produce *O*-protected hydroxamic acid **[107]**. Cleavage with trifluoroacetic acid removes the protecting group and products **[108]** were obtained in yields ranging from excellent to poor and purities were very good.

2.5.2. Urea Synthesis

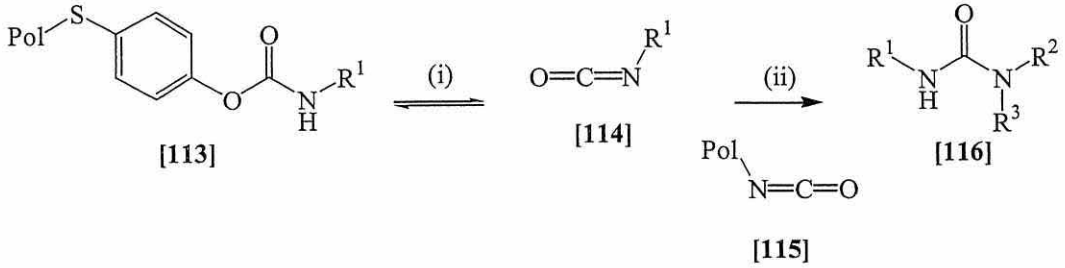
The urea substructure is commonly found within biologically active compounds, such as dihydropyrimidines (see page 21). Literature on the solid-phase production of ureas has utilised many routes to the final product. Scialdone and co-workers have made use of a resin bound oxime in the synthesis of ureas.[86] Products **[111]** were successfully synthesised from the oxime *via* two possible routes, and the product was cleaved on reaction with an amine without the need for standard solid-phase cleavage with trifluoroacetic acid (Scheme 22).



Scheme 22. (a) R^1NCO, CH_2Cl_2; (b) triphosgene, CH_2Cl_2, r.t.; (c) R^1NH_2, CH_2Cl_2, r.t.; (d) CH_2Cl_2, R^2R^3NH, toluene, 80 °C.

The reaction produced both high yield and purity from a diverse series of amines. Optimum results were obtained in the reaction when R^1NH_2 was 2-aminopyridine and R^2R^3NH was morpholine, with 99 % yield and 97 % purity.

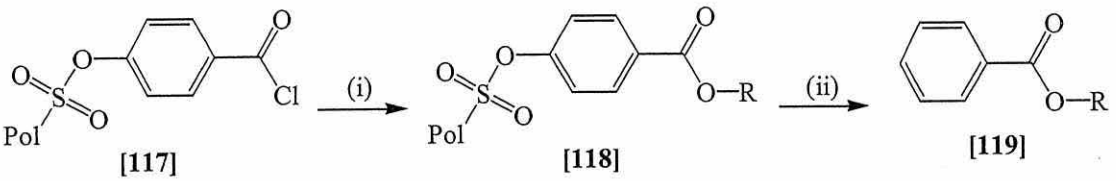
Dressman *et al.* were able to synthesise urea libraries using two different polymer bound resins; a diversifiable thiophenoxy carbonyl linker **[113]** and polymer bound isocyanates **[115]** (Scheme 23).[87]



Scheme 23. (i) base; (ii) HNR^2R^3

Urea production was achieved with a wide range of yields with optimum levels of purity. The reaction had the added advantage of mild cleavage conditions and the resins could be regenerated for use in future synthesis.

Wustrow *et al.* have exemplified the use of arylsulfonates in solid-phase synthesis.[88] The reactions and applications associated with this functional group are well reported for traditional solution-phase methodologies; however, they are somewhat limited in their application to solid-phase chemistry. Wustrow outlined the reductive cleavage of resin bound arylsulfonates (Scheme 24).



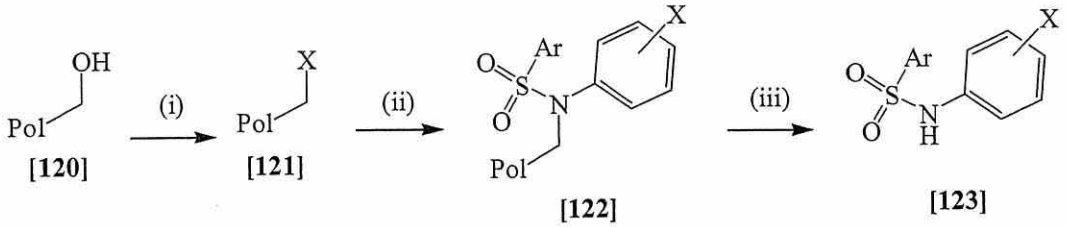
[117] [118] [119]

Scheme 24. (i) ROH, NEt_3, CH_2Cl_2; (ii) NEt_3, formic acid, $Pd(OAc)_2$, DPPP, 110-140 °C.

The approach outlined worked exceptionally well for electron rich aromatic systems and could also be applied effectively to electron poor aromatic structures. The yields obtained for benzoate esters were moderate; however, applying this methodology to benzamides produced lower yields. Formic acid also appeared to give better results for cleavage than trifluoroacetic acid.

2.5.3. Sulfonamide Synthesis

Sulfonamide and amide synthesis was reported by Raju and Kogan making use of halomethyl resins to obtain compounds such as **[123]**.[89] Wang resin was used in this three-step reaction (Scheme 25).



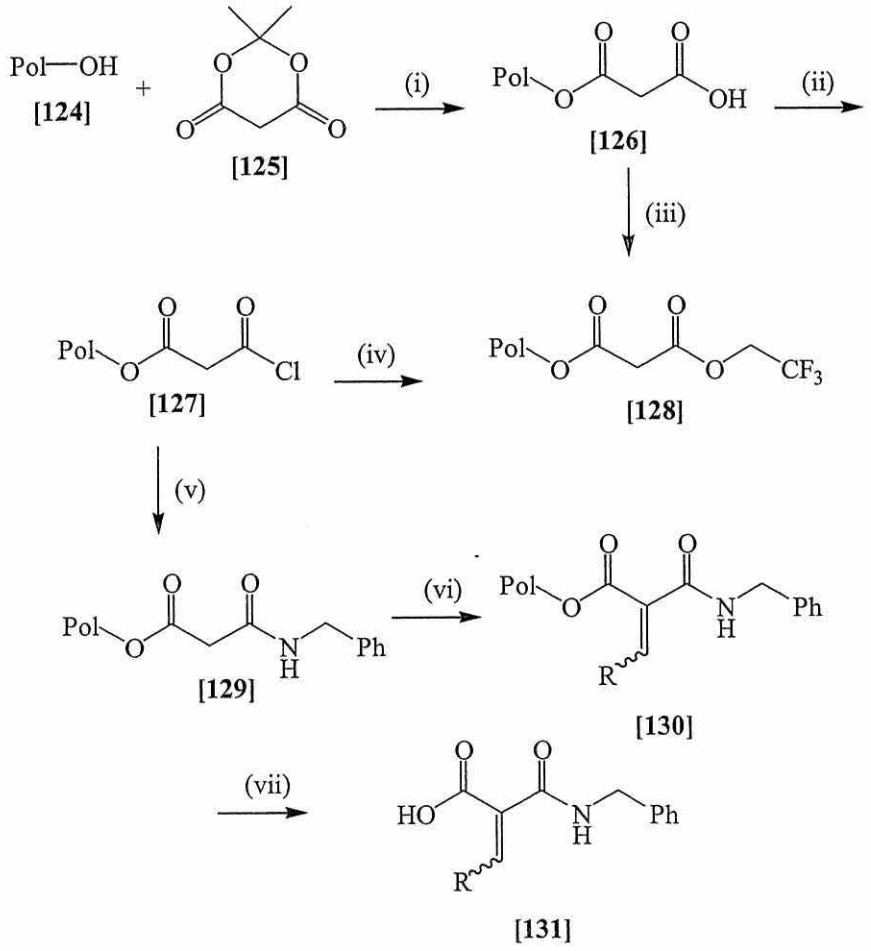
[120] [121] [122] [123]

Scheme 25. (i) $SOCl_2$, CH_2Cl_2, 0 °C, 45 min; (ii) $ArNHSO_2Ar$, NaH, DMF, r.t., 24 h; (iii) TFA / H_2O 95:5, r.t., 24 h.

Sulfonamides were produced in varying yields and purities with optimum results obtained when X was nitro. Amides could be produced in a similar method; however step (ii) of the reaction involved treatment of **[121]** with Ar_2COCl, DIEA in THF at room temperature for 8 hours. Amide yields were moderate to good but purities were greater than the equivalent sulfonamide product.

2.5.4. Acids and Esters in Solid-phase Synthesis

Acids and esters are good building blocks for many reactions. The Knoevenagel condensation of unsymmetrical malonamic esters **[129]** and malonates was exemplified by Hamper *et al.* (Scheme 26).[90]



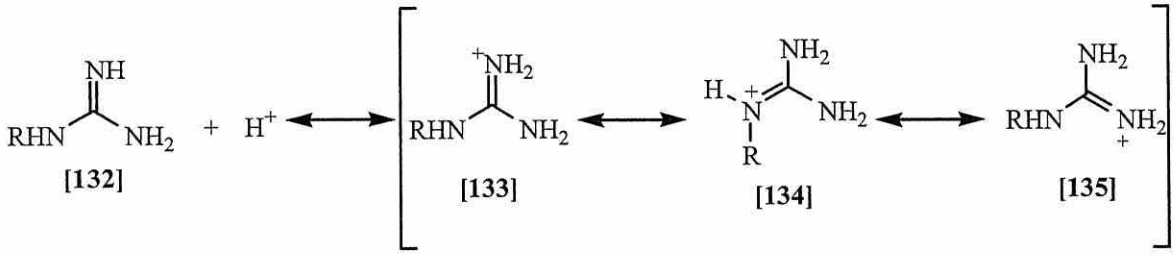
Scheme 26. (i)THF, 65 °C; (ii) $(COCl)_2$, CH_2Cl_2; (iii) CF_3CH_2OH, DIC, DMAP; (iv) CF_3CH_2OH; (v) benzylamine; (vi) RCHO, piperidine acetate, toluene, 85 °C; (vii) TFA.

Reaction of **[129]** with aldehydes and piperidine acetate in toluene, followed by cleavage with trifluoracetic acid led to the production of methylene malonic acid-amides **[131]**. Purification of the products **[131]** was achieved by column chromatography and mixtures of the E:Z isomeric malonate monoacids were observed.

CHAPTER 3 - GUANIDINE CHEMISTRY

3.1. BACKGROUND

Guanidine containing molecules have been of interest to the synthetic chemist for many years due to their ability to bind anions, their wide range of biological activity and because they are recognised by enzymes.[91] Guanidine itself is a by-product of protein metabolism and is found in urine. The guanidine moiety is found in arginine, the α-amino acid and the conjugate acid of guanidine has a pKa of 13.2. The strong basicity of guanidines can be explained by the stability of the cation after protonation. Resonance within the π-system results in delocalisation and hence stabilises the guanidinium ion. The resonance forms of a protonated guanidine are illustrated below (Scheme 27).



Scheme 27. Resonance forms of the guanidinium ion

Classically guanidine synthesis has involved the reaction of an amine with an electrophilic amidine species and commonly used guanylating species include pyrazole-1-carboxamide **[136]**, protected thiourea **[137]** and *S*-alkylthioureas such as **[138]**.

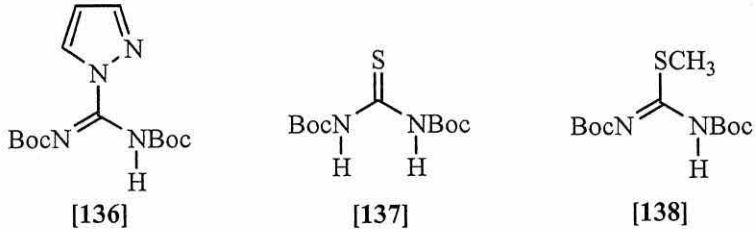


Figure 3. Common guanylating reagents

Guanidine synthesis has been widely examined due to the presence of the guanidine moiety in many natural products and its potential medical benefits. Many approaches have been identified and summarised.[92] Due to the vast literature in this area this

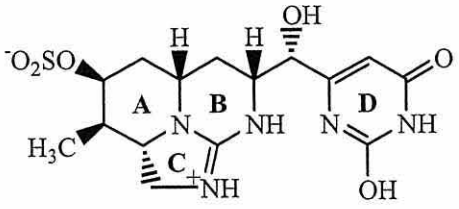
chapter will concentrate on guanidine synthesis under the following categories: natural products containing guanidines, guanidine protecting group chemistry and solid-phase approaches.

3.2. GUANIDINES IN NATURE

Many aquatic ecosystems contain blue-green algae, cyanobacteria, which, upon analysis, have been shown to possess the guanidine sub-structure among the natural products they contain.[93] Cyanobacteria contain many toxins which fall into two main categories, neurotoxins and hepatotoxins. The two types of toxins can be distinguished by an intraperitoneal mouse assay: an acute dose of a neurotoxin will lead to respiratory arrest within 2-30 minutes, whereas lethal dosing of mice with a hepatotoxin leads to severe haemorrhage within 45 minutes. Neurotoxins include the alkaloids saxitoxin, neosaxitoxin and anatoxin and the guanidine methyl phosphate ester anatoxin-a(*S*).[92, 93] Hepatotoxins include the peptides microcystins, nodularins and the guanidinium alkaloid cylindrospermopsin.[93, 94]

3.2.1. Cylindrospermopsin

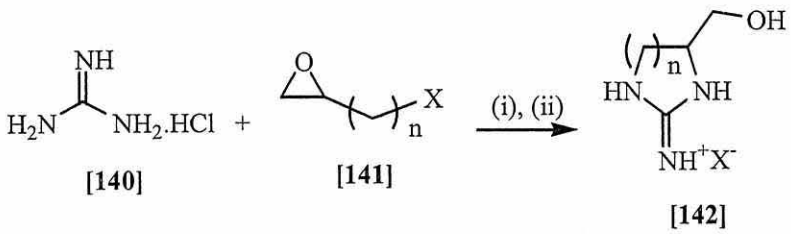
Drinking waters in Australia were contaminated by toxins from cyanobacteria, later determined to contain the compound cylindrospermopsin (a toxin produced from *A. ovalisporum*), which led to a serious outbreak of hepatoenteritis.[95] Cylindrospermopsin was first isolated from *Cylindrosperopsis raciborskii* and more recently from *Umezakia natans* and *Aphanizomenon ovalisporum*. Cylindrospermopsin **[139]** exists as a zwitterionic molecule containing tricyclic guanidine and uracil moieties as represented in Figure 4.



[139]

Figure 4. Cylindrospermopsin

Several multi-step synthetic approaches to cylindrospermopsin have been reported in the literature and there is also an interest at Bangor within the Murphy research group. A recent publication from this group reports an approach to the 5-membered guanidine heterocycle found in cylindrospermopsin **[139]** *via* an intramolecular epoxide ring opening reaction (Scheme 28).[96] Further details of this process are reported in the results and discussion section of this thesis.

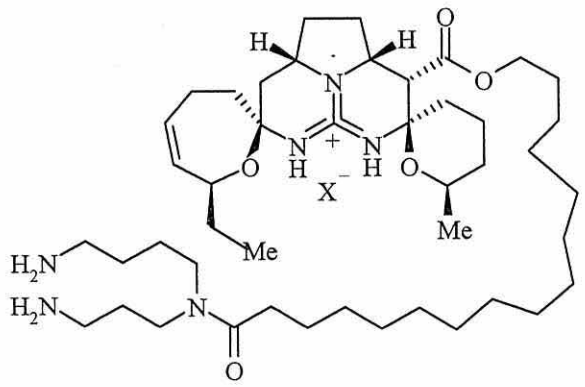


[140] **[141]** **[142]**

Scheme 28. (i) ^{t}BuOH, 16 h, r.t.; (ii) KO^{t}Bu, 60 °C, 24 h. X = Br

3.2.2. Ptilomycalin A

The tricyclic structure of cylindrospermopsin is also found within ptilomycalin A. This is a natural product found in sponges such as the Caribbean sponges *Ptilocaulis spiculifer* and *Batzella sp.* and the Red Sea sponge *Hemmimycale sp.* and was also recently observed in the starfish *Fronia manilis*.[97] The structure of ptilomycalin A **[143]** is shown in Figure 5.

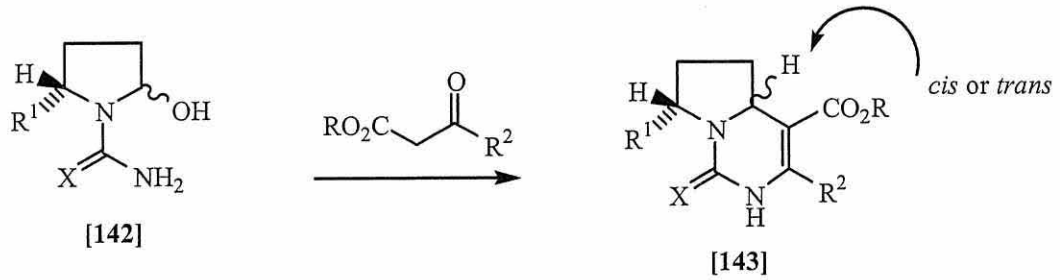


[143]

Figure 5. Ptilomycalin A

Many synthetic approaches towards ptilomycalin A and compounds of this nature have been reported.[98] McDonald and Overman reported the synthesis of 1-oxo and 1-imino

hexahydropyrrolo[1,2-c]pyrimidines **[145]** by Biginelli condensation reactions.[99] The research focussed around determining whether the free hydroxy group of the derivative used to synthesise ptilomycalin A was key to the stereochemistry of product formation, as illustrated in the following scheme.

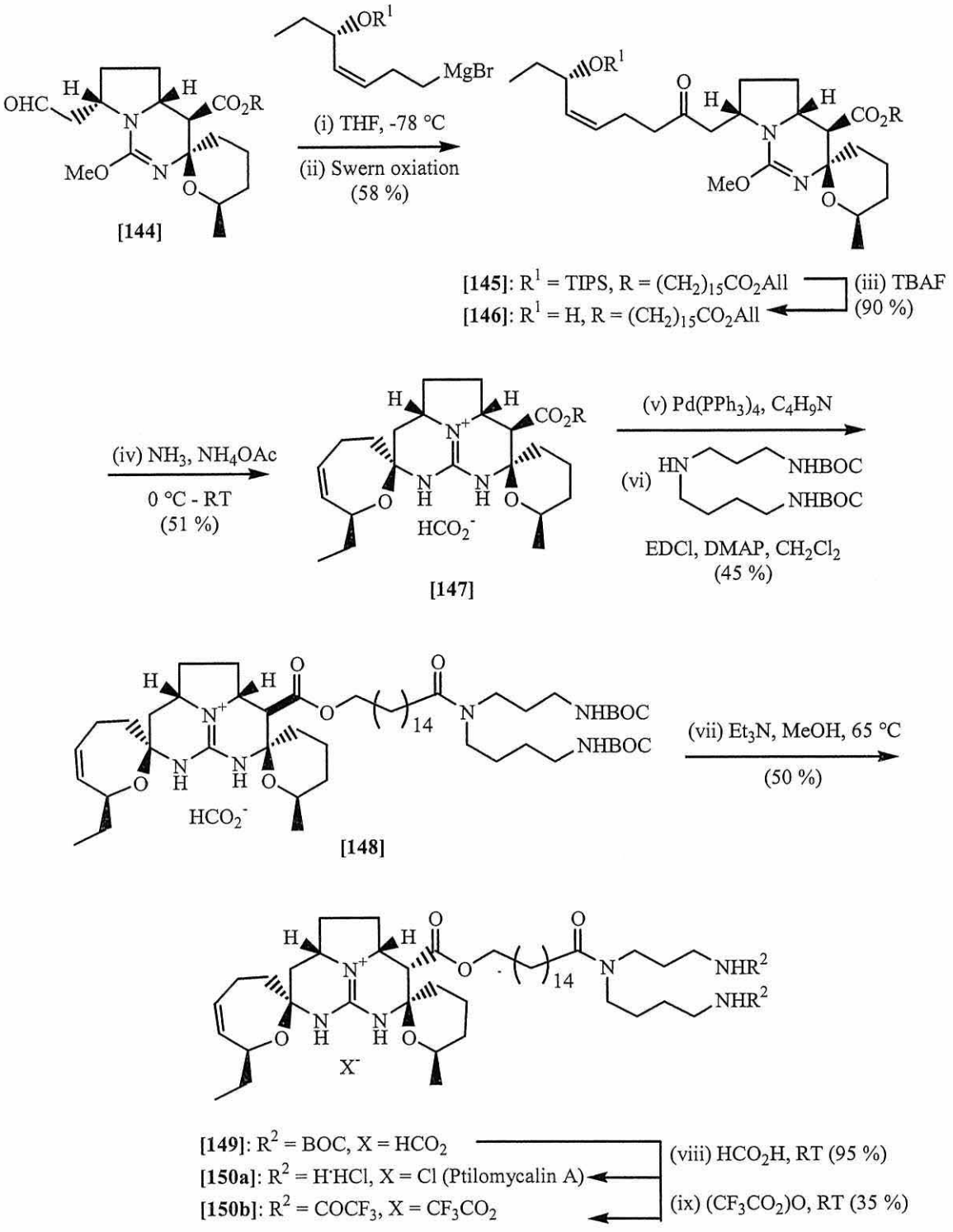


Scheme 29. Synthesis of oxo and 1-iminohexahydropyrrolo[1,2-c]pyrimidines

X = O, NR

The paper demonstrated that stereoselection in 1-oxo and 1-imino hexahydropyrrolo-[1,2-c]pyrimidines is highly dependent on the reaction conditions and the nature of X. *Cis*-selection is favoured for urea and *N*-sulfonyl guanidine functionality in the X group. *Trans*-selectivity is favoured when condensation occurs in the presence of poly-phosphate ester (PPE).

Further to this work, the total synthesis of ptilomycalin A was reported by Overman *et al. via* the key intermediate **[146]**, which was synthesised using the methodology outlined in Scheme 30.[100]



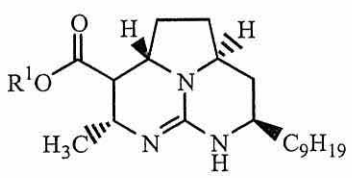
Scheme 30. Total Synthesis of Ptilomycalin A

The first key stage was to synthesise the tricyclic guanidinium species **[149]**. After the addition of the Grignard reagent, **[146]** was subjected to Swern oxidation to produce **[147]** in 58 % yield. The silyl protecting group, TIPS, was removed by treatment with tetrabutyl-ammonium fluoride (TBAF). Cyclization to the tricyclic guanidine was

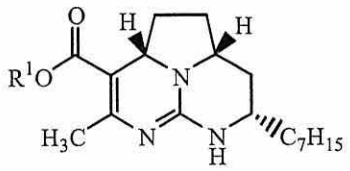
achieved by exposure to ammonia and ammonium acetate, affording **[149]**. Following the removal of the allyl ester group by palladium catalysis, the next stage required the addition of protected spermidine (step (vi)). Compound **[150]** was produced in 45 % yield in the presence of EDCI and DMAP in dichloromethane. Epimerisation to **[150]** was achieved by treatment with triethylamine in boiling methanol. Ptilomycalin A **[152a]** was produced, by removal of the Boc protecting groups and anion exchange, in 95 % final yield by 8 reaction steps from **[146]**. Conversion to the trifluoroacetate derivative **[152b]** was used to establish the specific rotation, which was identical to the value reported for the natural product.[100]

3.2.3. Batzelladine Alkaloids

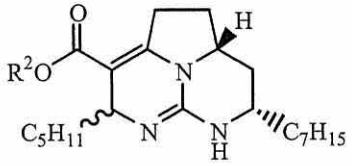
The batzelladines A – E are further examples of marine natural products found in sponges. All five batzelladines were isolated from the Caribbean sponge *Batzella sp.* and are depicted in **[153]-[157]**.[101,102]



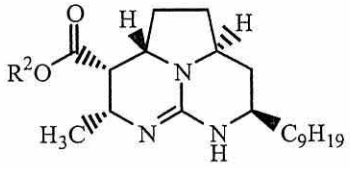
[153] Batzelladine A



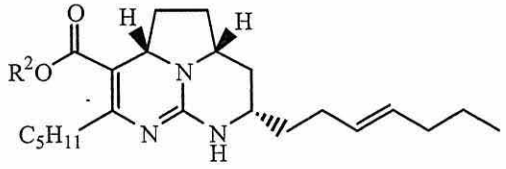
[154] Batzelladine B



[155] Batzelladine C



[156] Batzelladine D



[157] Batzelladine E

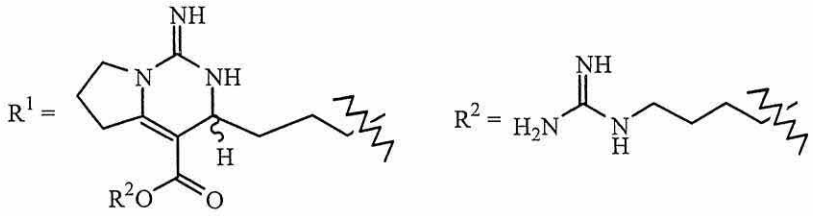
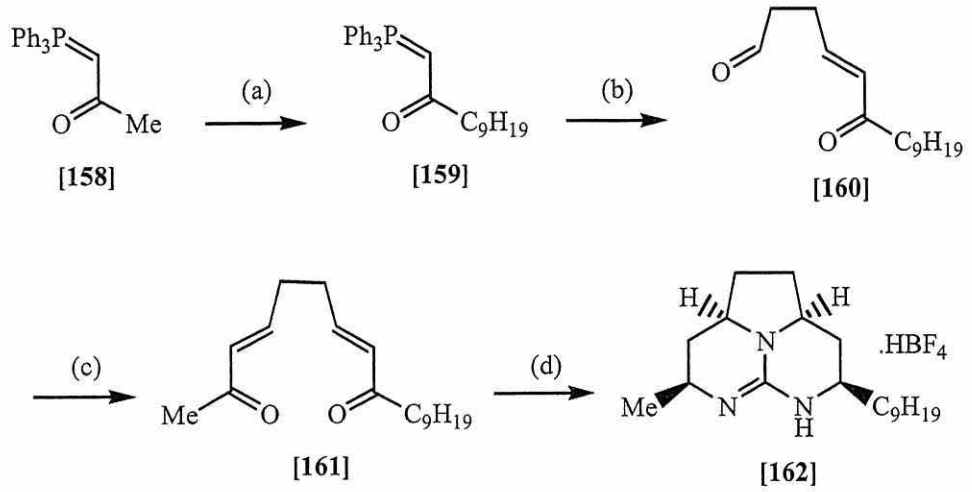


Figure 6. Batzelladine Alkaloids

Batzelladines have proved of interest due to the biological activity they possess, especially with respect to anti-HIV activity. Murphy *et al.* demonstrated the synthesis of the tricyclic guanidine core of batzelladine D **[156]** depicted in the following scheme.[101]

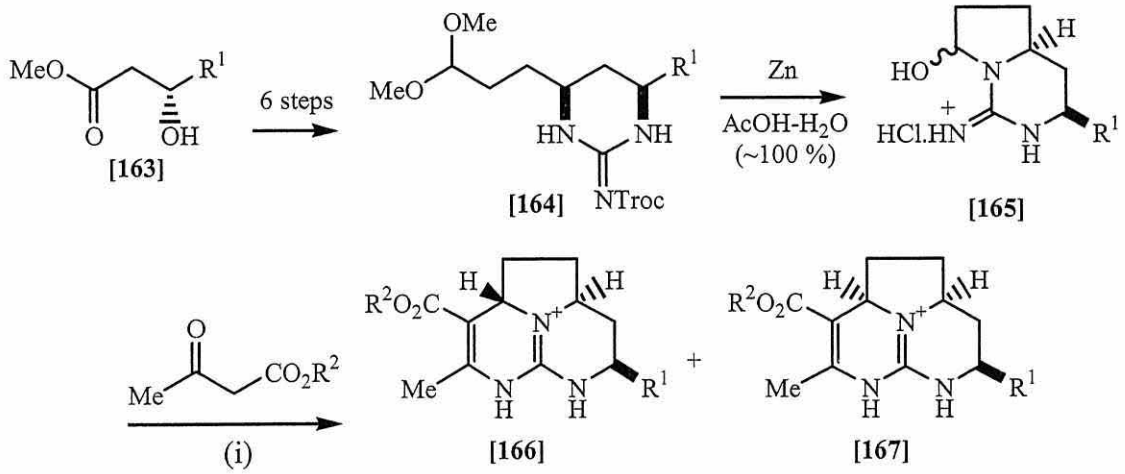


[158] [159] [160] [161] [162]

Scheme 31. (a) ^{n}BuLi/-78 °C; then $C_8H_{17}I$/r.t./16 h.; (b) 3 eqv. succinaldehyde/THF/ 24 h. (c) $MeCOCHPPh_3$/DCM/24 h.; (d) (i) guanidine/DMF/0 °C – r.t./5 h.; (ii) 3:1:3 DMF/H_2O/MeOH, then $NaBH_4$/16 h.; (iii) HCl. (iv) sat. aq. $NaBF_4$.

The phosphorane **[158]** was deprotonated with *n*-butyl lithium followed by alkylation with *n*-octyl iodide to yield the phosphorane **[159]**. Further reaction with an excess of succinaldehyde yielded aldehyde **[160]**, which was then treated with phosphorane **[158]** to produce the desired ketone **[161]**. Guanidine was then reacted with ketone **[161]** in DMF for 5 hours, reduced, acidified and finally subjected to ion exchange yielding the fluoroborate **[162]**. This methodology compares well with the other reported approaches in that the procedure requires only 4 reaction steps to achieve the synthesis of very closely related structures to the natural materials.

Overman *et al.* report synthetic approaches to establish the correct stereochemical assignment of batzelladine alkaloids.[103] The key synthetic step involved a Biginelli cyclization. Retrosynthetic analysis identified the 2-undecanone derivative **[163]** as a suitable starting reagent (Scheme 32).

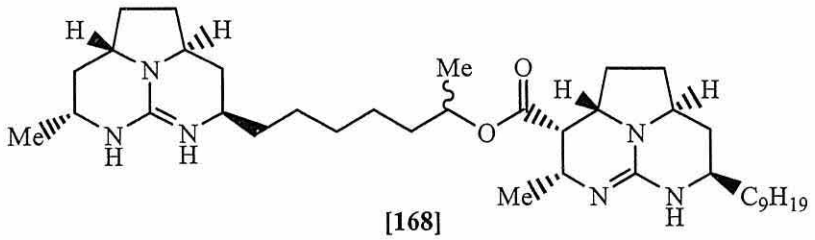


Scheme 32. Batzelladine A derivative synthesis, $R^1 = C_9H_{19}$, R^2 = Me or $CH_2CH{=}CH_2$, (i) Acid = HOAc, HCl, CF_3CO_2H; base = morpholine or none; solvent = CF_3CH_2OH, DMF, THF, cyclohexane, CH_3CN, $Cl(CH_2)_2Cl$; temperature = 40, 66, 80, 85 or 90 °C.

β-Hydroxyester **[163]** was converted into **[164]** in moderate yield. Bicycle **[165]** formed on reaction with zinc in aqueous acetic acid. The next step was carried out with various reaction conditions. Biginelli cyclization reactions were used to produce tricyclic guanidines **[166]** and **[167]**. A yield of 95 % was obtained, with poor stereoselectivity, when R^2 was methyl in the presence of morpholine and acetic acid in dichloroethane at 90 °C.[102]

3.2.4. Batzelladine F

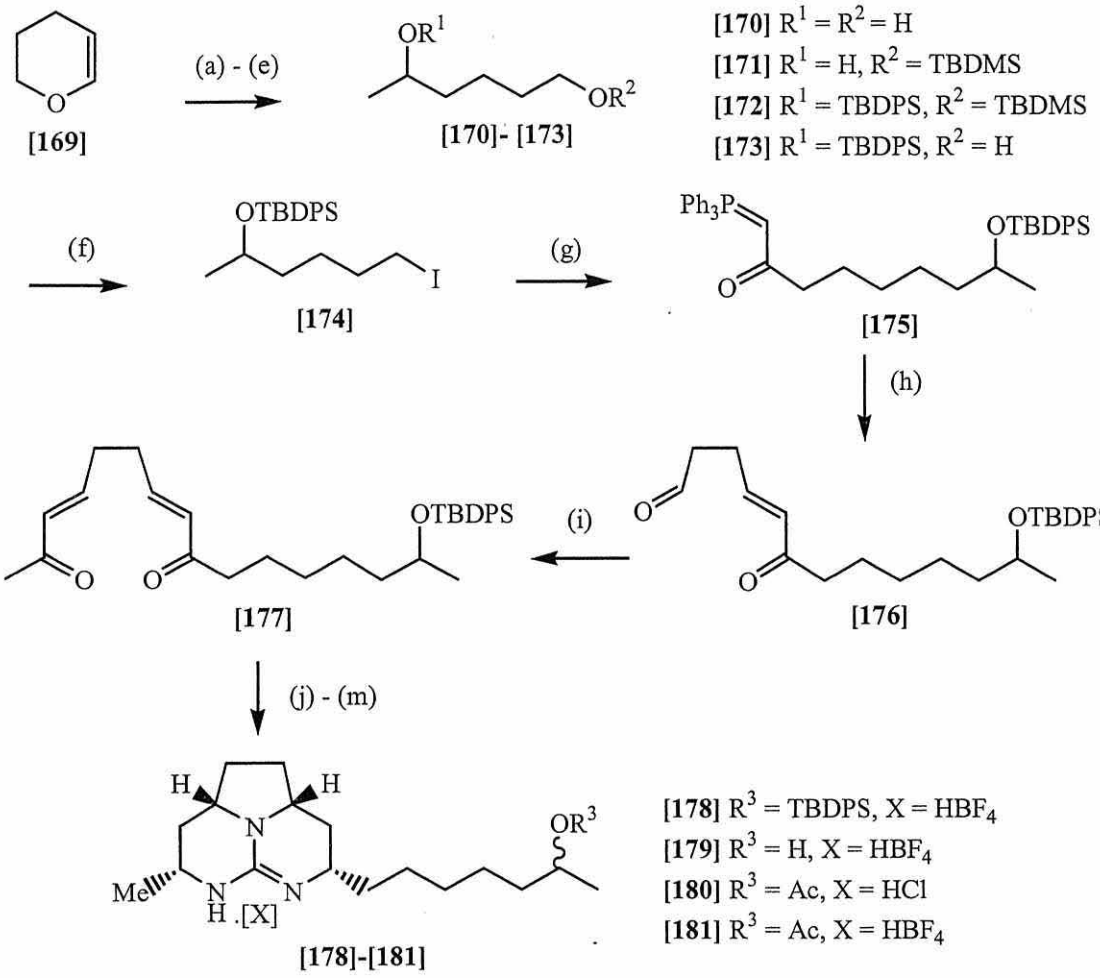
Several new batzelladine structures have been isolated and the proposed structure of one of these, batzelladine F, is shown below **[168]**.[104] Murphy *et al.* wished to confirm the structure of this and to establish the stereochemistry.[105]



[168]

Figure 7. Proposed structure of Batzelladine F

The molecule was particularly interesting as it contained two tricyclic guanidine units and only one of them had the classic ester function present within batzelladines A – E. The synthetic approach in Scheme 33 was used to synthesise the left hand side of batzelladine F in order to determine the stereochemistry.

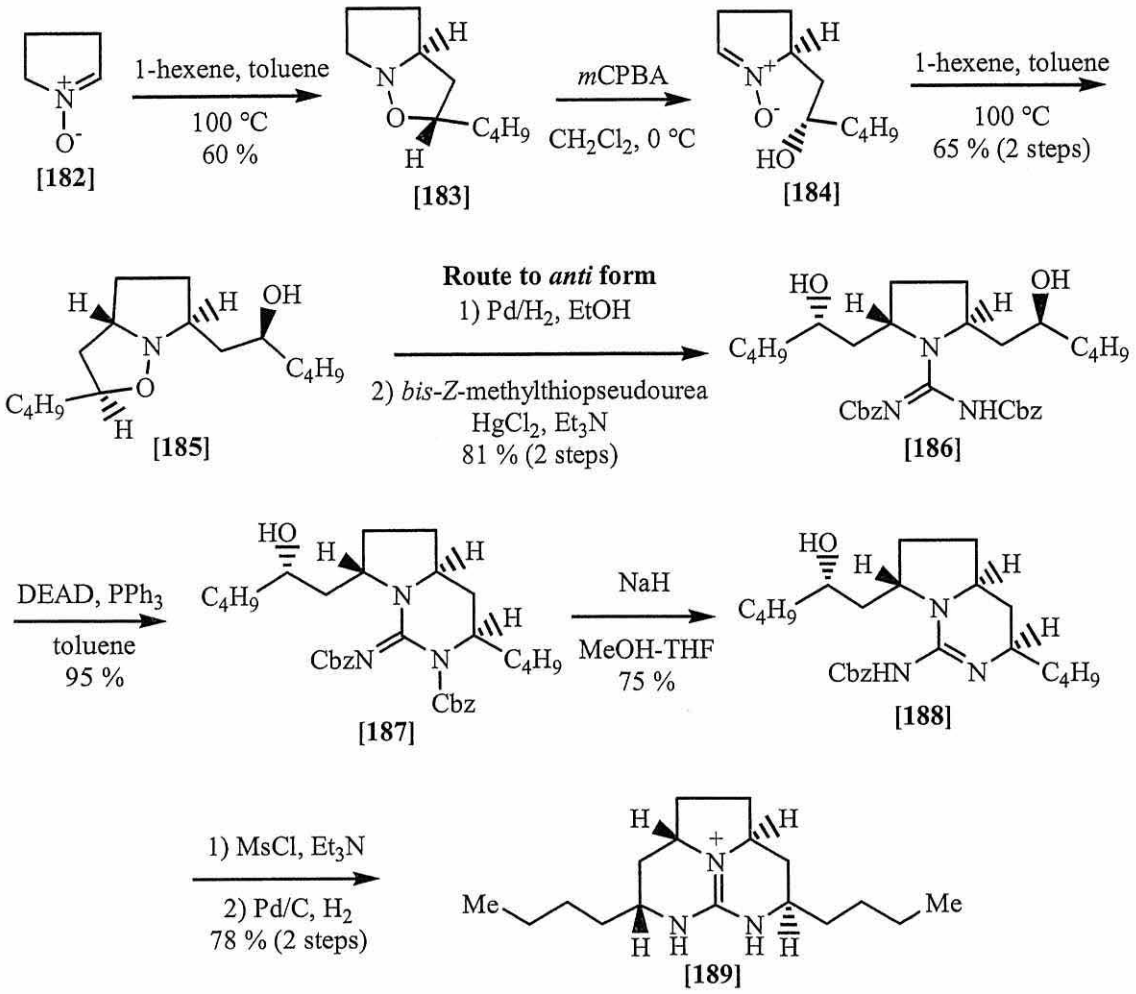


Scheme 33. (a) HCl/H_2O/reflux, 92 %; (b) MeMgCl/THF/reflux, 95 %; (c) ^{t}BDMSCl/ Imid./DCM/24 h, 92%; (d) ^{t}BDPSCl/imidazole/DCM, 89 %; (e) PyHTos/DCM, 91 %; (f) (i) MsCl/NEt_3/DCM/24 h; (ii) NaI/acetone/24 h, 67 %; (g) $CH_3COCHPPh_3$/BuLi/ THF/-78 °C – r.t.; (h) succinaldehyde/DCM/ 24 h, 54 %; (i) $CH_3COCHPPh_3$/DCM/24 h, 91 %; (j) (i) guanidine/DMF/0 °C/5 h; (ii) 3:1:3 DMF/H_2O/MeOH, then $NaBH_4$/16 h; (iii) HCl (aq); (iv) sat. aq. $NaBF_4$; **[178]**, 29 % overall; (k) (i) MeOH/HCl; (ii) sat. aq. $NaBF_4$; **[179]**, 91 %; (l) Ac_2O/Py, then HCl (2N); **[180]**, 41 %. (m) sat. aq. $NaBF_4$; **[181]**, quantitative.

Dihydropyran **[169]** was hydrolysed and treated with methyl magnesium chloride to yield diol **[170]** ($R^1 = R^2 = H$), which was then converted into the mono-protected

product **[173]** (R^1 = ^{t}BDPS, R^2 = H). Mesylation and reaction with sodium iodide yielded **[174]**, which was further reacted with a phosphorane,[105] producing **[175]**. Treatment of this with succinaldehyde proceeded in 54 % yield to give **[176]**, which was further reacted with the phosphorane,[105] giving rise to the *bis*-enone **[177]**. Guanylation of **[177]** followed by reduction and counter ion exchange produced **[178]**. Deprotection and acetylation yielded **[180]** or **[181]** in 41 % yield. ^{13}C-NMR comparison between the resulting product and the reported data for batzelladine F **[168]** showed a strong correlation. Spectroscopic assignments indicated that batzelladine F has an all *cis*- arrangement of hydrogens in the tricyclic guanidine.

Nagasawa *et al.* had a similar interest in establishing the stereochemistry of batzelladine F some years later.[106] Their approach, however, involved the use of a nitrone as a starting point for the synthesis and they were able to synthesise *anti*- and *syn*- products corresponding to the left-hand side of batzelladine F. Essentially they developed a synthetic method for the stereoselective synthesis of *anti*- and *syn*-fused tricyclic guanidines that has potential for producing many other examples (Scheme 34).

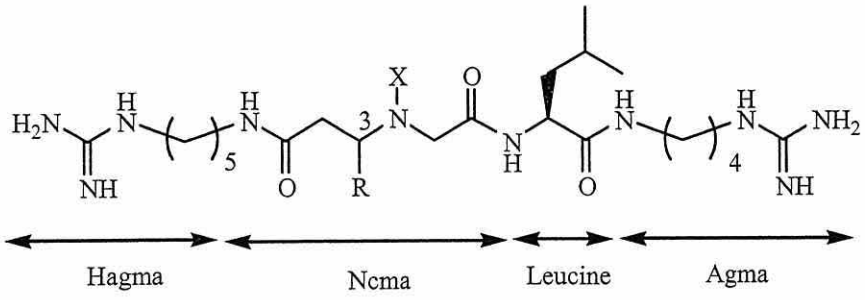


Scheme 34. Approaches towards Batzelladine F

The structures of the *anti*-product **[189]** and the corresponding *syn*-product were analysed by ^{13}C-NMR spectroscopy and, on comparison with spectra of the batzelladines, confirmed Murphy's conclusion that the left-hand side tricyclic guanidine has an all *cis* arrangement of hydrogens.

3.2.5. Minelamine A

Minelamine A is a guanidine peptide found in the marine tunicate *Didemnum rodriguesi*.[107] This proved to be a rich source of structurally diverse and biologically potent marine metabolites and among the first sulfamic acid guanidine derivatives to be found in nature. The peptide-like minelamines (Figure 8) are comprised of leucine and amino-di-acid 3-(*N*-carboxymethyl)amino decanoic acid (Ncma). Minelamine **[190]**, to date, includes 6 forms, listed in Table 1.



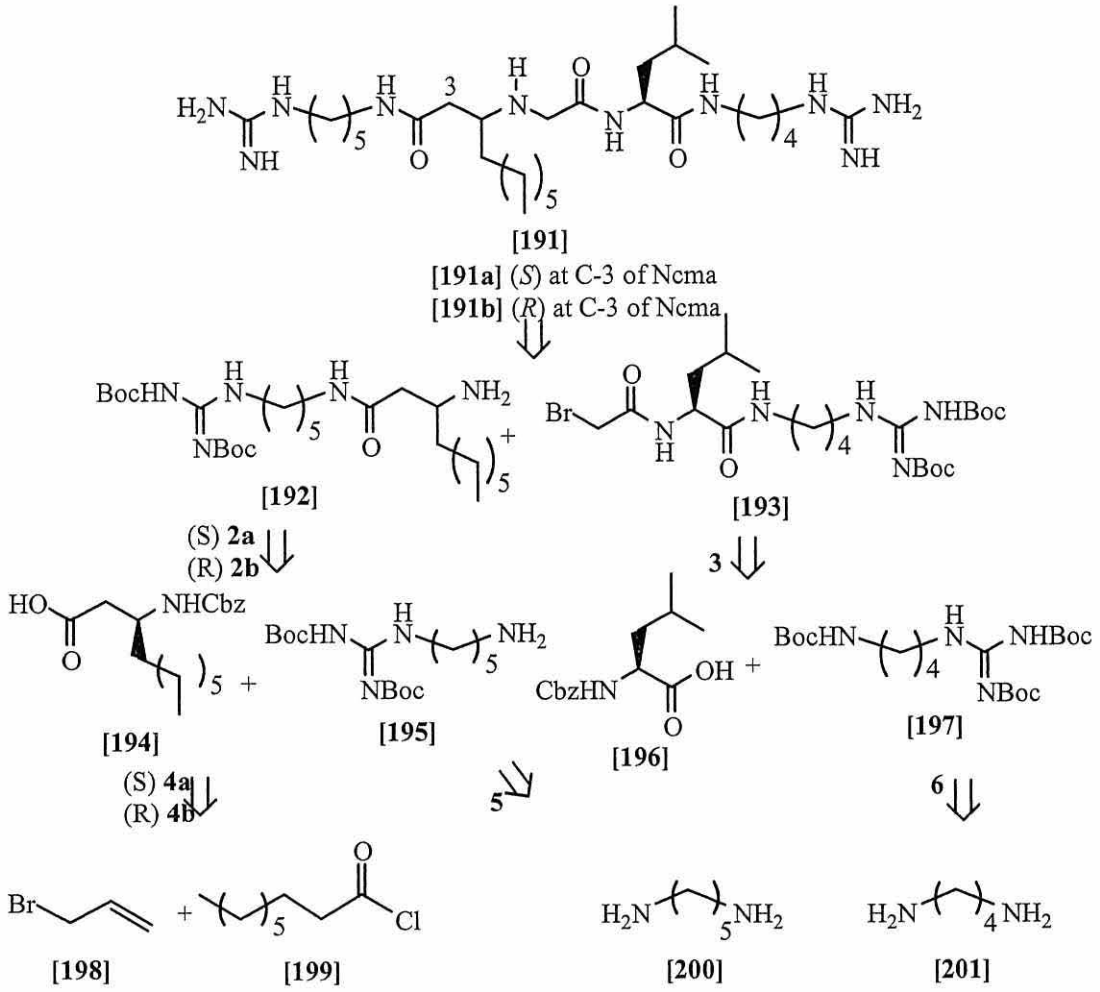
[190]

Figure 8. Basic structure of Minelamine

Minelamine	X	R
A	H	C_7H_{15}
B	H	C_8H_{17}
C	H	C_9H_{19}
D	SO_3H	C_7H_{15}
E	SO_3H	C_8H_{17}
F	SO_3H	C_9H_{19}

Table 1.

Synthetic strategies towards such compounds employ the use of Boc and Cbz protecting groups as is commonplace in guanidine synthesis (discussed in more detail later in this chapter). The synthetic approach of Muñoz *et al.* is illustrated in the following retrosynthetic scheme (Scheme 35).[107] The configuration of the C-3 carbon in the Ncma component had not been established at the time of their research.



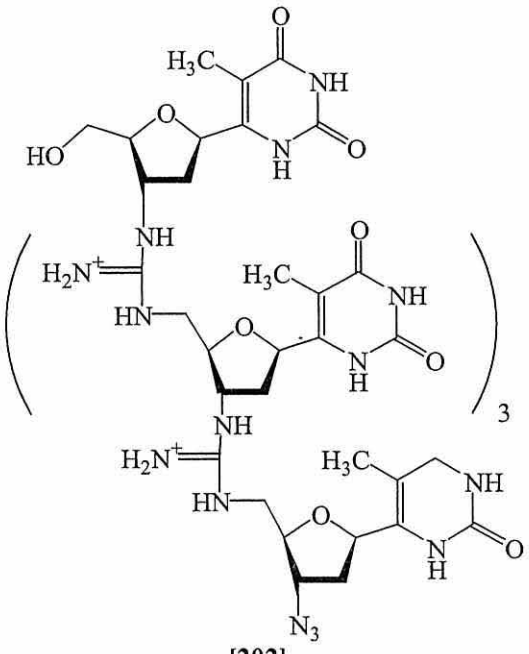
Scheme 35. Retrosynthetic analysis of Minelamine A

Many steps were required to yield the desired minelamine A derivative. Comparison of **[191a]** and **[191b]** with natural minelamine A proved difficult to achieve as minor differences in chemical shift were observed. The ^{13}C-NMR spectrum of minelamine A was most similar to **[191b]**, thus it was proved that the stereochemical configuration of minelamine A is 3*R*, 2*S* (R = Ncma).

3.2.6. Deoxyribonucleic Guanidine

Further examples of guanidine containing compounds possessing biological activity are deoxyribonucleic and ribonucleic guanidines; these antisense and antigene agents are oligonucleoside analogues that can arrest translational and transcriptional level cellular processes by binding to RNA or DNA. Luo and Bruice discuss the replacement of phosphodiester linkages of a polyaninon DNA/RNA with guanidine linkers yielding DNG/RNG.[108]

A key synthetic strategy in antisense compound design is to incorporate neutral internucleoside linkages that will prevent the repulsion that occurs between negatively charged phosphate diester backbones in double helix DNA. Solution-phase methodologies have been used to synthesise deoxynucleic guanidines (DNGs) to good effect. Figure 9 represents a pentameric deoxynucleic guanidine structure incorporating a positively charged oligomer.

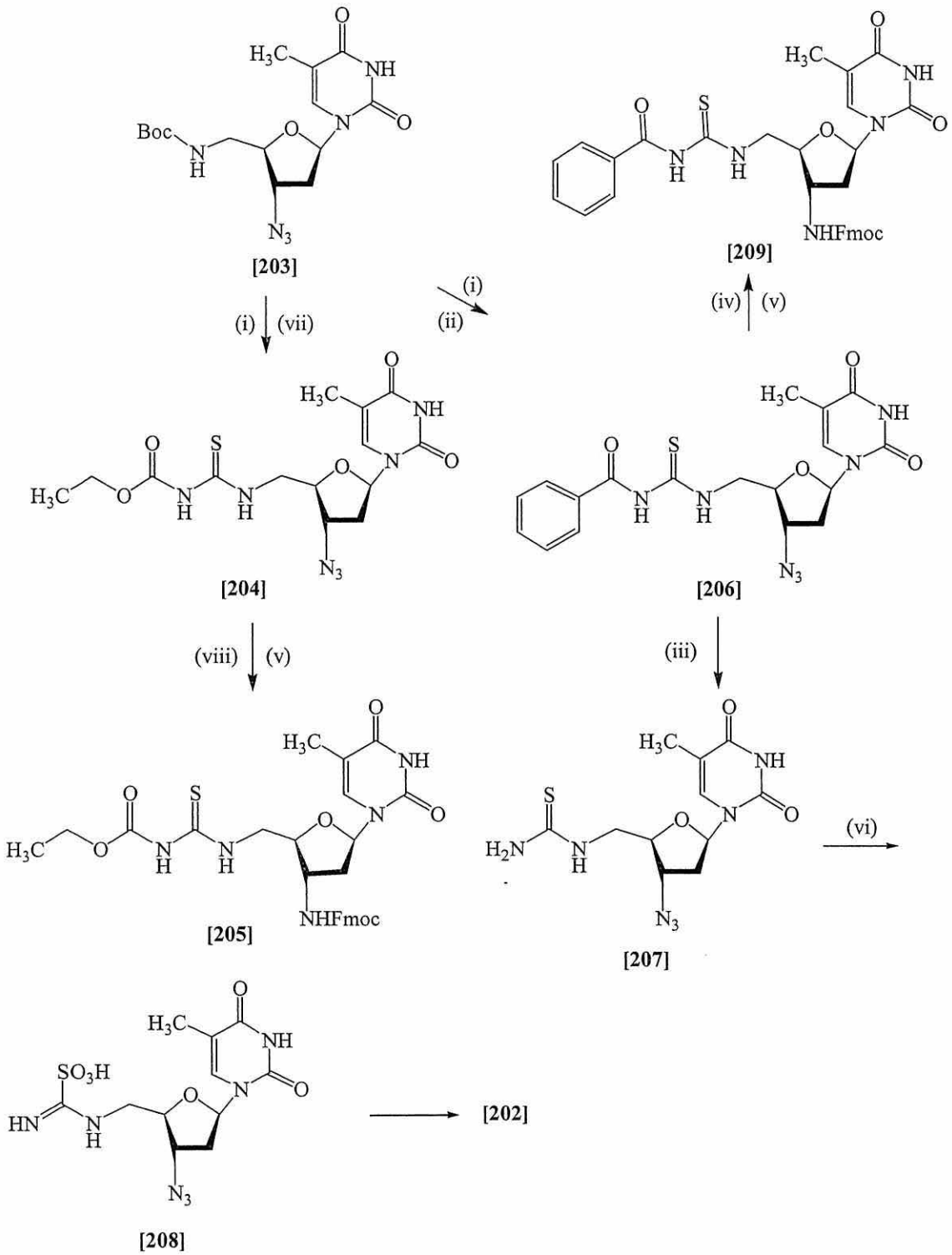


[202]

Figure 9. Deoxyribonucleic Guanidine

The methods identified to date have proved unsuccessful in synthesising longer chain DNGs. A solid-phase method to DNG synthesis is outlined by Bruice *et al.*[109] Solid-phase approaches to guanidine compounds are discussed in more detail later in this

chapter. Several monomers were synthesised for the solid-phase approach, as depicted in Scheme 36.[109]

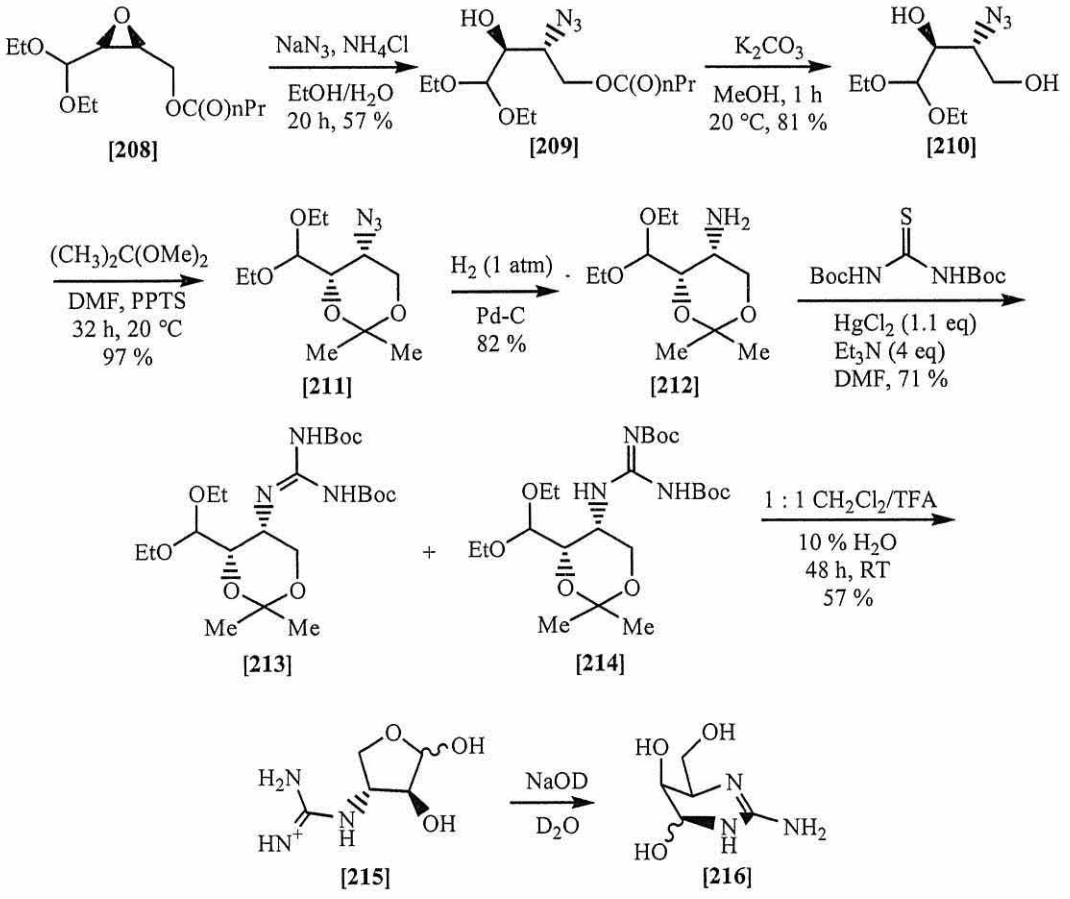


Scheme 36. (i) 20 % TFA/DCM; (ii) benzoyl isothiocyanate, DCM; (iii) Na_2CO_3, 2:1 MeOH/H_2O; (iv) H_2S, pyridine; (v) 9-fluorenylmethyl chloroformate, DCM, NEt_3; (vi) peracetic acid; (vii) trichloroethoxycarbonyl isothiocyanate, NEt_3, DCM; (viii) H_2, 10 % Pd/C, EtOH.

The solid-phase approach was based on equivalent solution-phase methods. Extension of the oligomer was achieved by binding **[208]** with Rink peptide amide resin loaded with a 3′-amino thymidyl nucleoside. Coupling *via* displacement of the sulfonyl group gave rise to the guanidine linkage. The 3′-azide was reduced with hydrogen sulfide in pyridine and the process was repeated. Although results were promising the method failed to produce chain lengths longer than those produced by solution-phase methods.

3.2.7. Guanidino Sugars

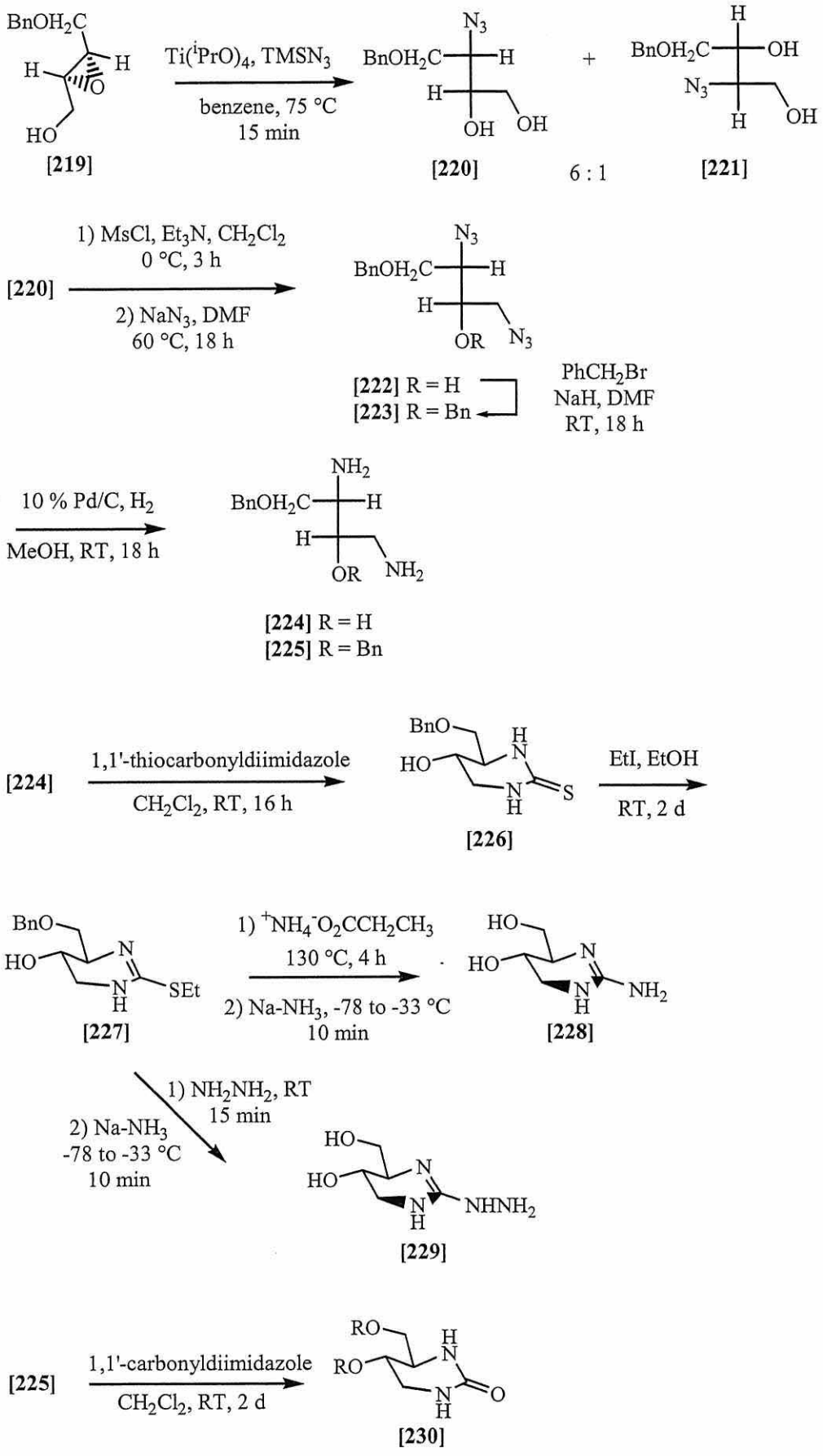
Metabolic disorders, such as diabetes, can be treated using glycosidase inhibitors.[110] These compounds are designed to mimic the transition state, or a transient intermediate in a process occurring at an enzyme's active site. Chemically they contain hydroxyl groups, a protonated heteroatom and a cyclic conformation that mimics the sugar moiety. Commonly, pyrrolidine and piperidine azasugars and amidines of monosaccharides have been reported in this role. Scheme 37 shows a reported method for guanidino-sugar synthesis.



Scheme 37. Guanidino-sugar synthesis

In this synthesis epoxide **[210]** was regioselectively ring opened to yield 2-hydroxy-3-azido product **[211]**, followed by the removal of butyrate on treatment with K_2CO_3 in methanol, affording diol **[212]**. Protected diol **[213]** was then hydrogenated to produce amine **[214]**. Subsequent protection of the guanidine derivative was achieved by treatment with *N,N'-bis-tert*-butoxycarbonyl thiourea yielding tautomers **[215]** and **[216]**. The protecting group was removed by treatment with trifluoroacetic acid and water producing α- and β-furanose anomers **[217]** as visible by the ^{1}H-NMR in D_2O. Raising the pH from 5 to 11 by treatment with NaOD gave rise to the predominantly neutral cyclic guanidine sugar **[218]**. The work lends itself towards further applications, as potentially such guanidine containing compounds within tetrahydropyrimidines should be better inhibitors of galactosidase; studies are ongoing.[110]

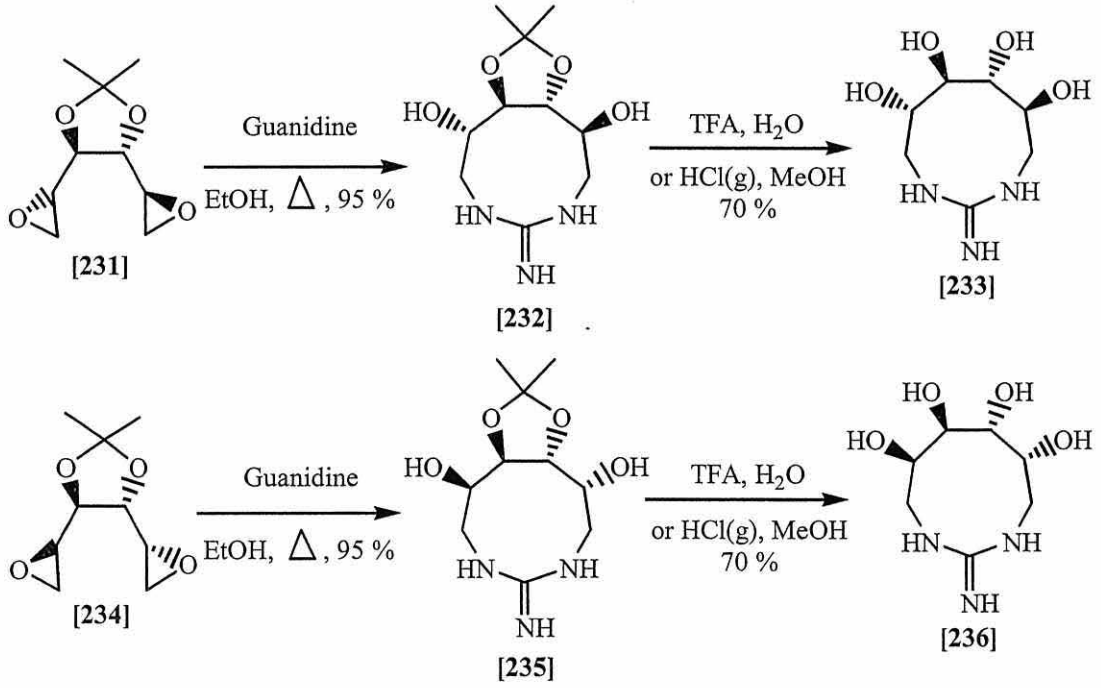
A similar investigation into guanidine analogues of deoxysugars directed towards the synthesis of glycomimetics was reported.[111] An enantioselective route to **[228]** and **[229]** is illustrated in Scheme 38.



Scheme 38. Enantioselective deoxysugar synthesis

Once again epoxide ring opening was adopted and the synthetic approach was similar to previous reports, however ring formation differed considerably. The amine intermediate **[224]** was reacted with 1,1′-thiocarbonyldiimidazole, which resulted in the formation of thiourea **[226]**. A similar reaction was carried out with amine intermediate **[225]** and 1,1′-carbonyldiimidazole; however, the amine was not fully converted into the desired urea **[230]**. *S*-Ethyl thiourea **[227]**, formed on reaction of **[226]** with ethyl iodide, underwent a substitution reaction with ammonium propionate or hydrazine to afford **[228]** or **[229]** respectively.

Azasugars, such as the polyhydroxylated forms of pyrrolidines, piperidines and indolizidines, have proved to selectively inhibit the oligosaccharide processing enzymes. Similarly, cyclic amidino, amidrazino and guanidino-sugars have proved interesting due to their ability to mimic the partial positive charge of the putative transition state of glycosidase hydrolysis. Le Merrer and co-workers report C_2-symmetrical polyhydroxylated cyclic guanidines **[233]** and **[236]** (Scheme 39).[112,113]



Scheme 39. C_2-symmetrical polyhydroxylated cyclic guanidines

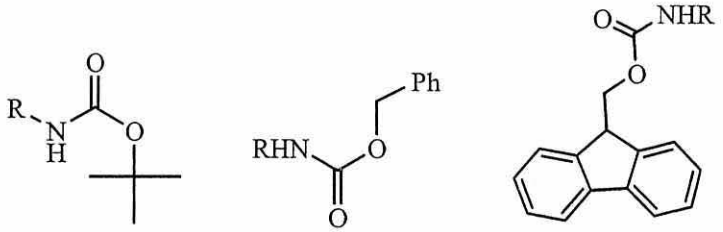
Products are formed *via* nucleophilic ring opening of L-iditol or D-mannitol *bis*-epoxide by guanidine in 95% yield. The biological activity of these guanidino sugars was evaluated. Unfortunately the examples reported were weak inhibitors of glycosidases.

Encouraging results were obtained when a substituent such as *N*-butyl or *N*-glucosyl was present in place of the guanidine proton.

Effective inhibitors of glycosidases were found to be neutral, transition-state analogues that can be protonated upon binding.[114] The research showed that cyclic guanidino sugars as inhibitors are pH dependent, with the most potent inhibitor, the tetrahydropyrimidine form, being neutral.

3.3. PROTECTING GROUP CHEMISTRY IN GUANIDINE SYNTHESIS

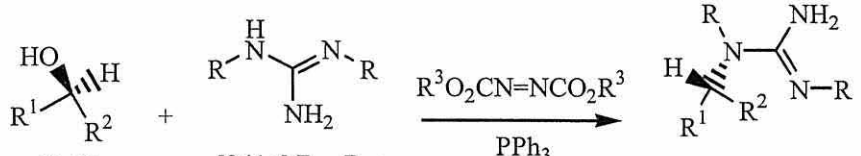
Protecting groups designed and used to block the reactivity of a particular functionality are commonplace in guanidine synthesis.[115] Frequently used protecting groups include Boc, Cbz and Fmoc (Figure 10).



[237] Boc **[238]** Cbz **[239]** Fmoc

Figure 10. Protecting groups used in guanidine chemistry

One particular example employing the use of protecting groups in guanidine synthesis involved the conversion of alcohols by a Mitsunobu reaction.[116] Cbz and Boc protected guanidines were chosen as nucleophiles for the protocol depicted below (Scheme 40).



[240]

[241a] R = Boc
[241b] R = Cbz

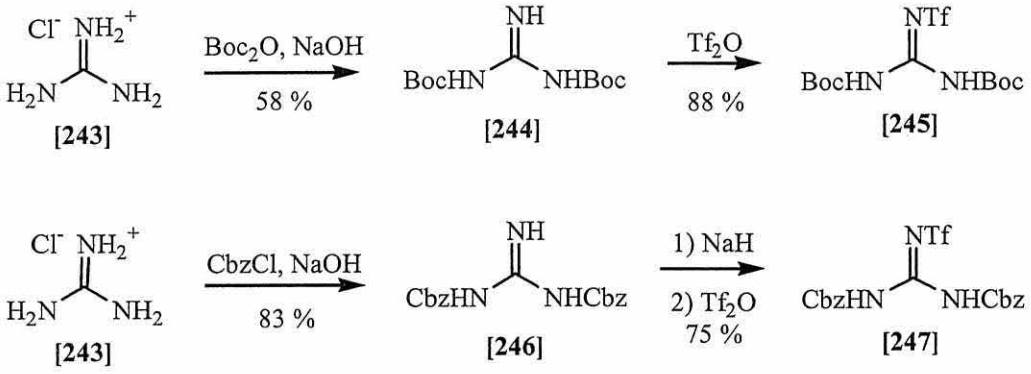
[242a] R = Boc
[242b] R = Cbz

Scheme 40. Mitsunobu and guanidine protection

N,N'-bis(*tert*-Butoxycarbonyl)guanidine (Boc) **[241a]** and *N,N'-bis*(benzyloxycarbonyl) guanidine (Cbz) **[241b]** were reacted with a range of primary and secondary alcohols, in excess, in the presence of azodicarboxylate-PPh_3 complex to yield desired products

[242a] and **[242b]**. This provides a useful route to guanidines, avoiding the classic amine route. Excellent yields were obtained throughout, most in excess of 95 %.

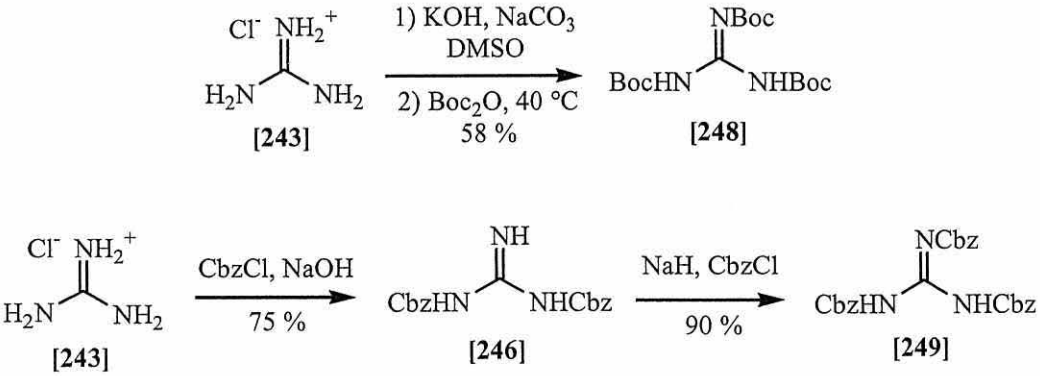
Di-protected triflyl-guanidines have been illustrated as a new type of guanylating reagent.[117] Two examples of such, *N,N′-bis*-Boc-*N″*-triflylguanidine **[245]** and *N,N′-bis*-Cbz-*N″*-triflylguanidine **[247]** are stable crystalline compounds allowing further synthetic approaches to be achieved with ease and efficiency.



Scheme 41. Triflyl group protection of guanidine hydrochloride

Subsequent guanylation of a range of amines produced protected guanidines in excellent yield under mostly mild conditions.

Following this research, Goodman *et al.* reported the equivalent *N*-Boc and *N*-Cbz alternatives to triflyl diurethane protected guanidines, as depicted in Scheme 42.[118]

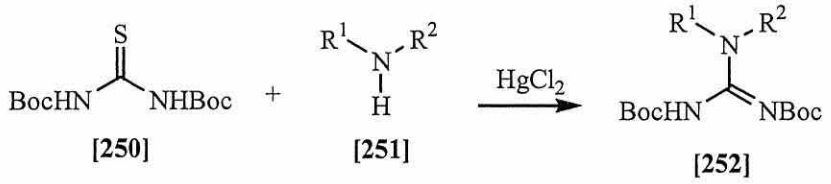


Scheme 42. Tris- protected guanidines

N,N′,N″-Tris-Boc-Guanidine **[248]** and *N,N′,N″-tris*-Cbz-guanidine **[249]** can be used to convert alcohols into guanidines in one step. Synthetically, they were applied as guanylating reagents in Mitsunobu reactions giving rise to protected alkylated

guanidines. The approach provides a method for one step conversion of alcohols into protected guanidines in good to excellent yield.

Alternatively guanidines may be prepared from thioureas. Cunha *et al.* have investigated *N*-benzoyl activation in $HgCl_2$ promoted guanylation reactions with thioureas.[119] In order to convert thioureas into guanidines, adopting the mercuric chloride protocol, it was necessary to use a highly activated, strongly electron withdrawing thiourea (Scheme 43).



[250] [251] [252]

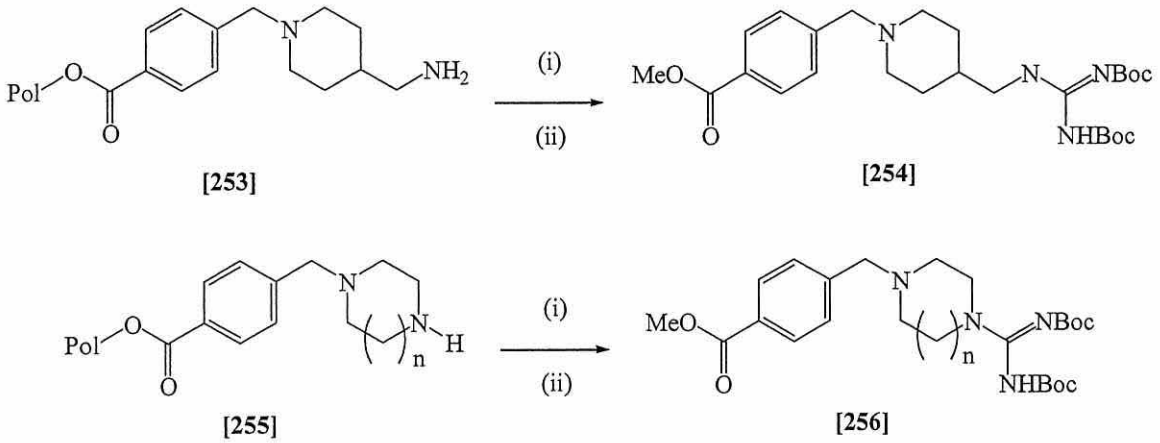
Scheme 43. Guanidine preparation from thiourea

N,N''-bis-Boc Thioureas can be readily converted into guanidines; however, problems may arise when guanidines containing different substituents are of interest. Guanidines were also prepared from *N*-benzoyl thioureas (benzoyl isothiocyanate method) providing yet more potential for future synthesis.[119]

3.4. SOLID-PHASE SYNTHESIS

Solid-phase synthesis is now being widely applied to guanidine chemistry, often as a result of difficulties arising from product purification in solution-phase reactions. Liquid-phase combinatorial synthesis was used to prepare *N,N-bis*-Boc protected guanidines on a soluble polymer, poly(ethylene glycol) (PEG).[120]

PEG is soluble in organic solvents but can be precipitated in certain cases. During the reaction the product is covalently bonded to the polymer and purification is simply achieved by precipitation and filtration. The strategy is illustrated in Scheme 44.[120]

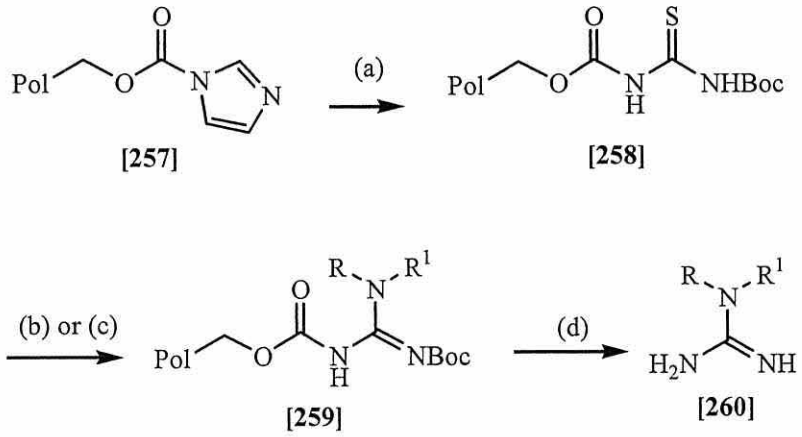


Scheme 44. Protected guanidines on a soluble support

(i) Guanylating reagent; (ii) Resin cleavage

The guanylating agents used were the three classical reagents listed previously (Figure 3) and resin cleavage was achieved by KCN in methanol. The Boc protecting groups were then removed by standard deprotection with trifluoroacetic acid in dichloromethane. Purity and yields of products were excellent with yields in excess of 75% for the 12 reactions carried out.

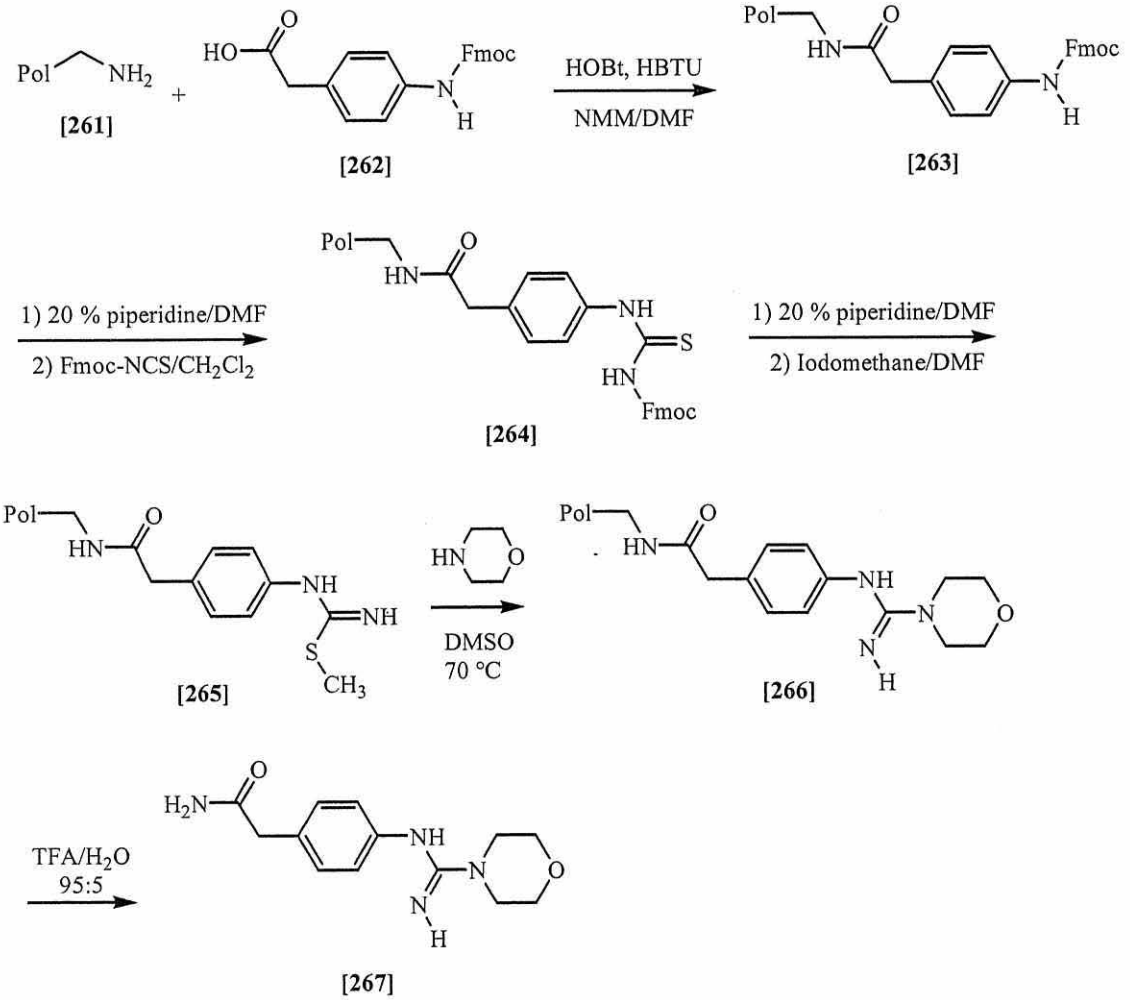
Josey *et al.* developed a novel linker applicable to alkyl-, acyl- and aryl guanidine production.[121] Functionalized thioureas were bound to Wang resin forming a carbamate linkage. Sulfur displacement by primary and secondary amines afforded resin bound guanidines, the preparation and cleavage of which are depicted in the Scheme below.



Scheme 45. (a) (i) Thiourea, NaH, THF, (ii) **[257]**, THF, (iii) $(Boc)_2O$, THF; (b) RR^1NH, Et_3N, NMP or CH_2Cl_2; (c) ArR^1NH, 2-chloro-1-methylpyridinium iodide, Et_3N, NMP; (d) TFA, $^iPr_3SiH$, CH_2Cl_2.

Carbonyl diimidazole resin **[257]**, prepared from Wang resin,[122,123] was added to a deprotonated thiourea in THF and subjected to protection with *N,N″*-di-*tert*-butyldicarbonate yielding **[258]**. Primary and secondary amines were reacted with **[259]** in the presence of base, producing resin bound protected guanidines **[260]**. Standard cleavage with trifluoroacetic acid afforded yields of greater than 85 % and products of 90 % purity.

A different approach to di-substituted guanidines involves the conversion of polymer bound aryl or alkyl amines into methyl isothioureas.[124] Commercially available Rink amide resin MBHA (represented by Pol-CH_2-NH_2) was adopted, as shown in the following Scheme.

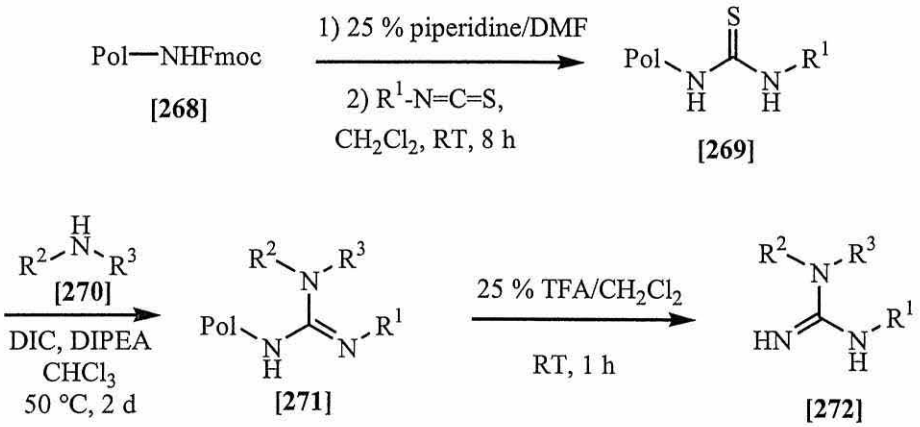


Scheme 46. Di-substituted guanidine synthesis

Rink amide MBHA resin **[261]** was treated with an amino acid **[262]**, HOBt, HBTU and NMM in DMF resulting in the corresponding resin bound product **[263]**. The protecting

group was removed by a 20 % solution of piperidine in DMF, followed by exposure to Fmoc-NCS, affording **[264]**. Further removal of the protecting group was followed by treatment with iodomethane, yielding resin bound methyl isothiourea **[265]**. In the example above, morpholine was added in DMSO and heating at 70 °C, produced resin bound guanidine **[266]**, which was cleaved by TFA/H_2O (95:5) to afford **[267]**. Morpholine was one of 5 amines used in the study. Moderate to good yields and purity were obtained throughout and the method exemplifies the potential for di-substituted guanidine synthesis.

Rink amine resin was once again used in the solid-phase synthesis of substituted guanidines.[125] *Tris*-substituted guanidines were synthesised *via* an isothiocyanate group following the thiourea route to guanidines, as depicted in the following Scheme.

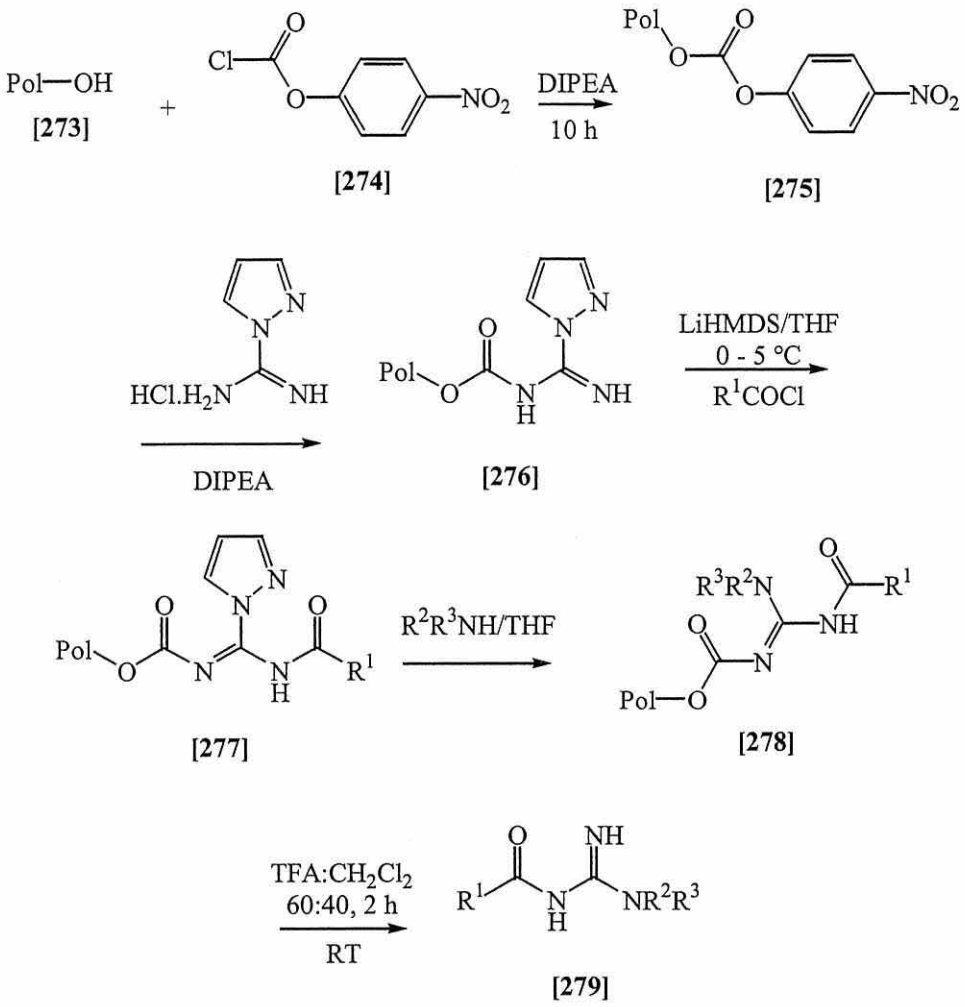


Scheme 47. Tri-substituted guanidine synthesis

Compound **[268]** was deprotected in piperidine and reacted with an isothiocyanate to yield resin bound thiourea **[269]**, which was guanylated on addition of amine **[270]**, yielding resin bound guanidine **[271]**. Standard cleavage was achieved by trifluoroacetic acid in dichloromethane affording *tris*-substituted guanidines **[272]**. Yields again were excellent in most cases.

Fan and his team reported the solid-phase synthesis of *N*-acyl, *N*-alkyl/aryl di-substituted guanidines.[126] Strategically the synthesis involves the modification of Wang resin to a more activated resin followed by treatment with 1-*H*-pyrazole-1-carboxamidine. The resultant resin is deprotonated, acylated and reacted with amines to yield the polymer bound product. Standard cleavage is achieved by treatment with

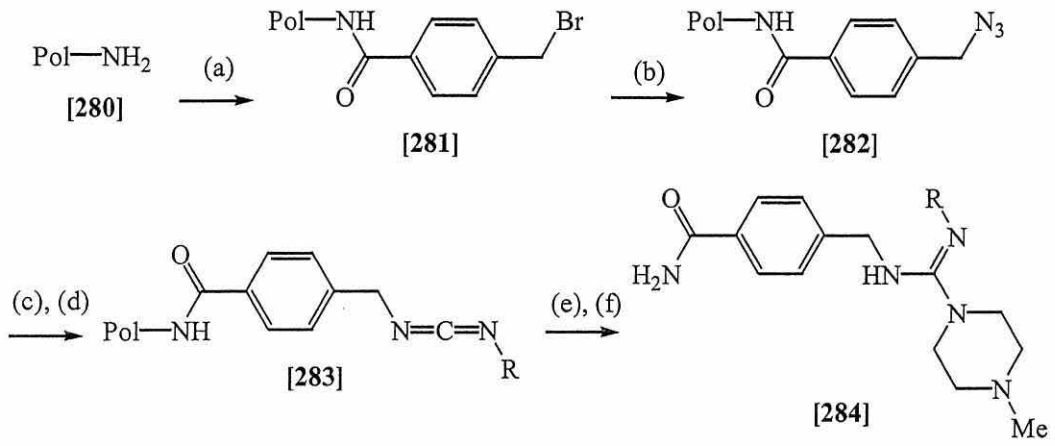
trifluoroacetic acid/ dichloromethane (60:40). Scheme 48 illustrates the approach to these di-substituted guanidines.



Scheme 48. Di-substituted guanidine synthesis

Yields obtained were moderate to good (61 – 88 %) and even poorly nucleophilic amines also produced moderate yields. The methodology provides a good basis for more complex guanidine synthesis.

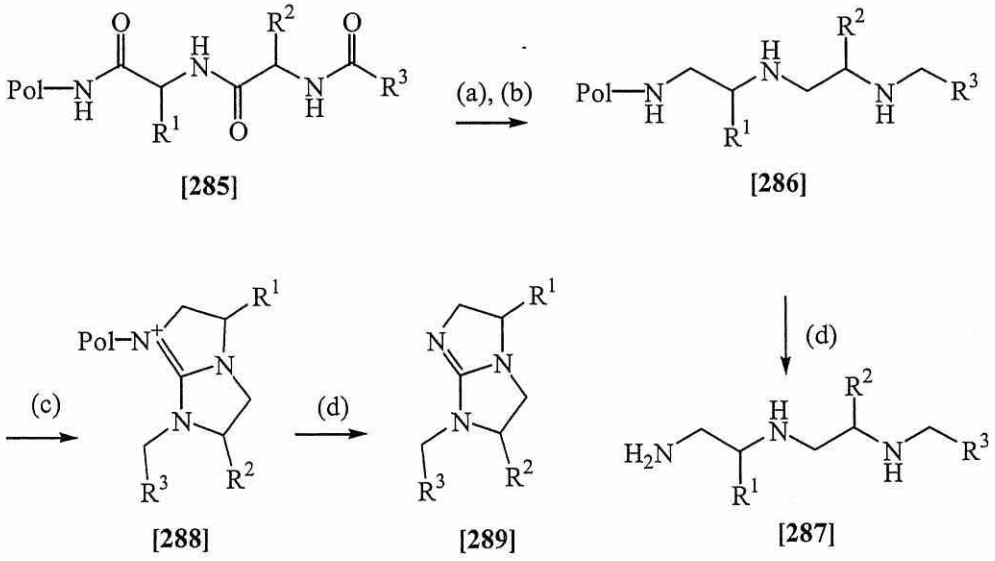
The final example of non-cyclic guanidine synthesis discussed herein illustrates an alternative approach.[127] A library of 5000 compounds was successfully synthesised by the method outlined in the following Scheme.



Scheme 49. (a) $BrCH_2C_6H_4CO_2H$, DIC, HOBt, DMF, 16 h, 25 °C; (b) NaN_3, DMSO, 18 h, 60 °C; (c) PhNCS, THF; PPh_3, THF, 4 h, 25 °C; (e) *N*-methylpiperazine, DMSO, 16 h; (f) 95 % TFA/H_2O, 1 h.

Rink amide resin was also used in the synthesis of this large library of guanidines, replacing R groups and Rink resin for more diverse resin amides. The yields were excellent, however some purification was required.

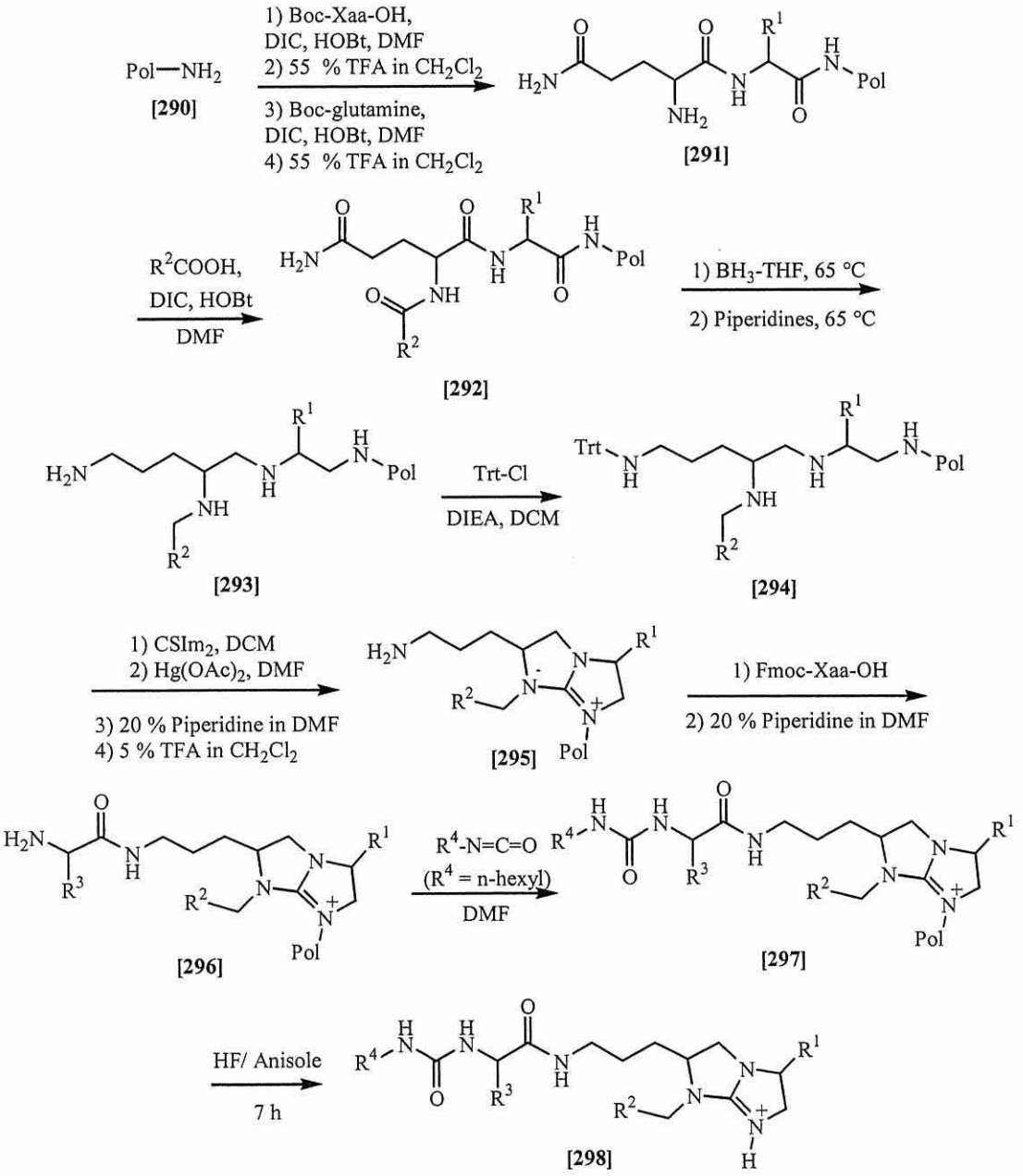
Houghten and co-workers reported a solid-phase method for tri-substituted bicyclic guanidines.[128] Resin bound *N*-acetylated dipeptides are reduced by borane-THF followed by a cyclization of triamine with thiocarbonyldiimidazole, as depicted in Scheme 50.



Scheme 50. (a) BH_3-THF, $B(OH)_3$, $B(OCH_3)_3$, 65 °C, 72 h; (b) piperidine, 65 °C, 24 h; (c) $CSIm_2$ in CH_2Cl_2, 16 h; (d) HF, 0 °C, 9 h.

The reaction proved to be an efficient method for the reduction of peptides to polyamines. Crude products were formed in excess of 95 % purity and yields were greater than 70 %.

Houghten has been responsible for many advances in combinatorial approaches to heterocycles.[129] One such approach involved the synthesis of bicyclic guanidines from reduced *N*-acylated dipeptides. It involves the coupling of a Boc-amino group to *p*-methylbenzhydrylamine (MBHA) resin, depicted in Scheme 51.

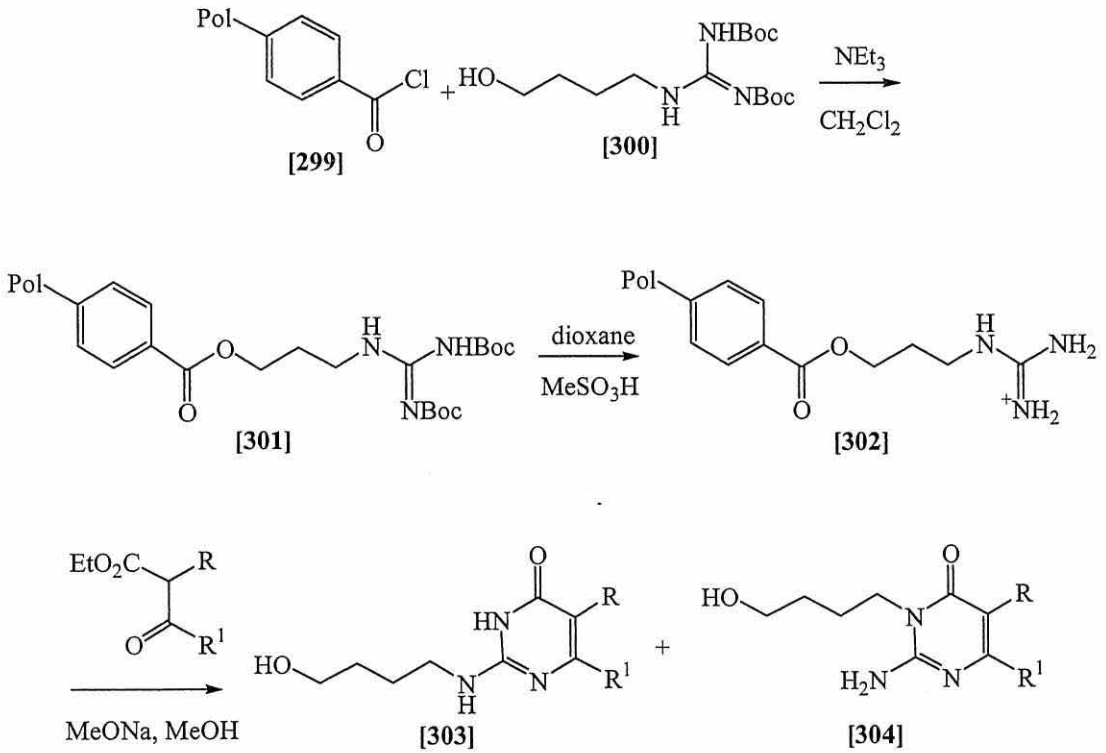


Scheme 51. Bicyclic guanidine synthesis.

Boc-Xaa-OH, Fmoc-Xaa-OH and Boc-glutamine are protected amino acids

Urea-linked tethered bicyclic guanidine products were produced in good to excellent yield and purity. The library contained 47,600 compounds (35 x R^1, 40 x R^2, 34 x R^3) but the characterisation and assessment of any biological activity within these molecules was not reported.

Pyrimidinones were discussed in the previous chapter due to their potential as anti-HIV agents; in particular, uracils and pyrimidinones substituted at C-5 and C-6 positions have been highlighted in the field of antiviral chemotherapy. Such compounds can be modified to include a guanidine moiety by simply replacing the oxygen or sulfur atom with nitrogen, though the methodology is slightly more complex. The solid-phase synthesis of such compounds was demonstrated by Botta *et al.*,[130,131] as depicted in Scheme 52.



Scheme 52. Pyrimidinone guanidine derivatives

The evaluation of such compounds as non-nucleoside reverse transcriptase inhibitors, in biological tests, gave interesting anti-reverse-transcriptase profiles. Molecular modelling studies were used to demonstrate the importance the C-5 substituent has on conformational changes that lead to a catalytically inactive enzyme. This synthetic approach has provided a new lead for future synthetic studies.[130, 131]

CHAPTER 4 - SYNTHETIC APPROACHES TO SOLID-PHASE SUPPORTED REAGENTS

4.1. AIMS & BACKGROUND

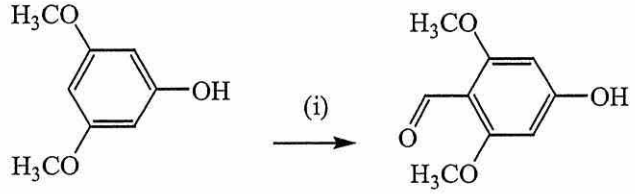
The overall objective of this part of the project was to synthesise solid-phase supported reagents for application in the synthesis of fine chemicals. A secondary aim was to develop methods for quantitative and qualitative analysis of solid-phase supported reagents, as this has proved to be the most challenging area of solid-phase synthesis. In particular the project aimed to produce heterocyclic compounds, discussed in chapter 5, in the hope that they would prove to be highly active with respect to agrochemical or pharmaceutical purposes. Solid and solution-phase methods of combinatorial chemistry would be examined in order to produce novel organic chemicals. Solid-phase products would be prepared by cleavage from the polymeric support and solution-phase products achieved by running a series of reactions in parallel.

4.2. GENERAL

The analysis of solid-supported reagents is commonly achieved by Infrared Spectroscopy and FTIR was used to analyse the solid-phase supported reagents described in this work. Raman spectroscopy was used to further clarify product formation or to detect specific functional groups present. Visual inspection of solid-supported reagents by simple microscopy was used as a method of determining the purity of solid-phase supported reagents due to the visibility of crystalline impurities in samples. The percentage of material loaded onto resins was determined by microanalysis. The loading of material is usually low as at high loadings interactions between functional groups are more significant. Loadings are either determined by conversion to a sulfur or nitrogen containing derivative or by assumption that the all functional sites in commercial resins are transformed in reactions. Loading values take into consideration a margin of error and, in some cases, batch variability. Scialdone *et al.* detail a method for the calculation of combinatorial resin loading in sulfur derived resins by microanalysis.[86]

4.3. BENZALDEHYDE DERIVED RESIN SYNTHESIS

The first approach involved the production of an aldehyde resin, as the aldehyde functionality could be widely applied in many syntheses. Albericio and co-workers outline the preparation of 4-hydroxy-2,6-dimethoxybenzaldehyde, which was used in the synthesis of the equivalent bound resin.[132] 3,5-Dimethoxyphenol **[305]** and phosphorous oxychloride were mechanically stirred at 0 °C and DMF was added over 30 minutes and the reaction stirred at room temperature for 15 h. Work-up of the reaction comprised of the addition of crushed ice and water to quench the reaction. The acidic aqueous phase contained the product, which formed as a precipitate when the solution was basified to afford the desired product **[306]** in poor yield (26 %).

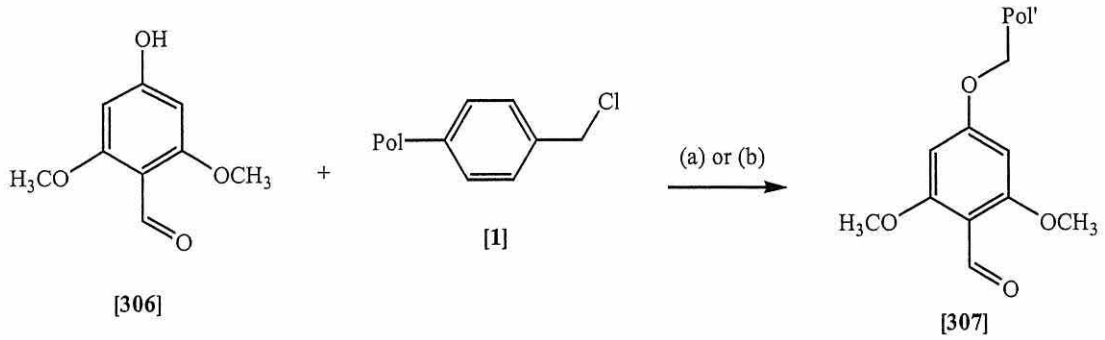


[305] **[306]**

Scheme 53. (i) $POCl_3$, 0 °C, DMF, 30 min, r.t., 15 h.

The ^{1}H-NMR spectrum obtained for **[306]** was in agreement with literature. Peaks were found at δ_H 10.0 (OC*H*), 6.05 (Ar*H*), 3.75 (OCH_3) and 2.8 ppm (O*H*) (literature 10.16, 6.09 and 3.76 ppm). FTIR spectroscopy clarified the presence of the carbonyl absorption at 1584 cm^{-1}. The melting point of the product was 222 - 224 °C, compared to 224 - 226 °C reported in the literature.[132]

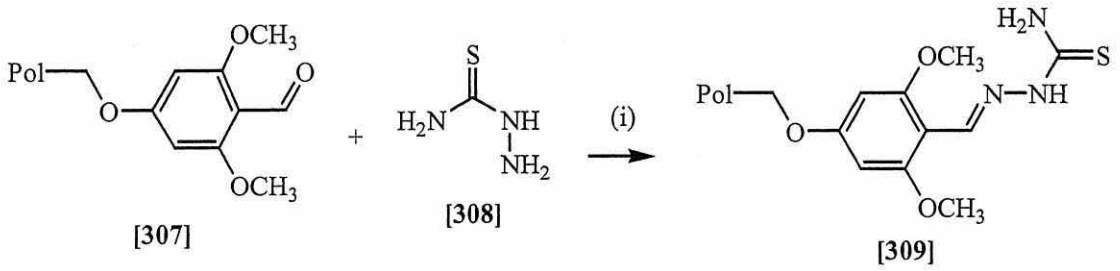
The next step involved binding the alcohol functional group to Merrifield resin. The synthesis of 4-hydroxy-2,6-dimethoxybenzaldehdye bound resin was demonstrated by Thompson and Ellman.[133] They showed the solid-phase synthesis of 1,4-benzodiaz-epine-2,5-diones *via* a multi-step reaction sequence, the key step being the production of the aldehyde bound resin. 4-Hydroxy-2,6-dimethoxybenzaldehdye **[306]** was reacted with Merrifield resin **[1]** in the presence of a base to achieve an ether linkage to the polymer support (Scheme 54).[133]



Scheme 54. (a) NaOH, DMSO, r.t., 30 min, 85 °C, 72 h; (b) NaOMe, MeOH, rot evap, DMSO, r.t., 30 min, 85 °C, 72 h.

4-Hydroxy-2,6-dimethoxybenzaldehyde **[306]** was first dissolved in DMSO and a solution of sodium hydroxide added in order to achieve alkoxide displacement of the chloride. This was then added, dropwise, to a pre-swollen suspension of Merrifield resin **[1]** in DMSO. Warming the reaction to 50 °C for 72 hours was deemed sufficient for product formation. The resin was collected by filtration, washed with a variety of solvents and oven dried. Two methods of production for the title compound **[307]** have been outlined (method (a) or (b) above), each providing a successful synthesis of the aldehyde bound resin with similar results and spectra obtained.

FTIR spectroscopy was used to confirm the completion of the reaction. A strong carbonyl absorption at 1686 cm^{-1} and a C-H stretch at 2727 cm^{-1} clarified the presence of the aldehyde. Aromatic CH stretching vibrations were found at 3024 cm^{-1}; however this may be due to Merrifield resin resonances. The asymmetric and symmetric C-O-C stretches from the methoxy groups were present at 1254 cm^{-1} and 1027 cm^{-1}, respectively. The spectrum contained no alcohol peak as would be present within the starting material. Further analytical information was achieved by Raman analysis. The aromatic methoxy group gave a Raman band at 1333 cm^{-1} and the carbonyl was faintly visible at 1682 cm^{-1}. The loading of the resin was calculated to range between 0.70 and 1.10 mmol/g as determined by conversion into the thiosemicarbazide bound derivative for which sulfur analysis can be used to directly calculate the resin loading (Scheme 55).[85]



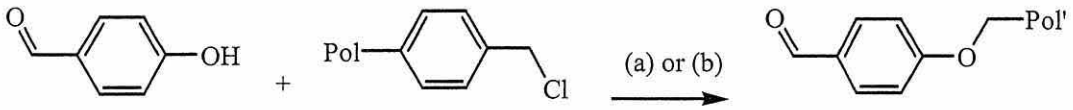
Scheme 55. (i) MeOH, r.t., 72 h.

4-Hydroxy-2,6-dimethoxybenzaldehyde bound resin **[307]** was reacted with an excess of thiosemicarbazide **[308]** in methanol to yield 4-(2-(aminothioxomethyl)amino-2-azavinyl)-3,5-dimethoxy phenol bound resin **[309]**. This method was adopted as it would provide a novel resin of thiouronium nature and would also allow the loading of the aldehyde bound resin **[307]** to be determined. The reaction proceeded efficiently and was driven to completion by the addition of excess reagents. The resin was collected by filtration and washed with copious amounts of solvent (MeOH, CH_2Cl_2 and water).

Analysis of **[309]** at this stage again showed that it contained high levels of sulfur, determined by microanalysis. The resin was examined by microscopy and several large crystals were clearly visible, believed to be excess thiosemicarbazide. The resin was submitted to Soxhlet extraction in methanol. This was deemed to be a sufficient purification procedure for this compound, as subsequent microanalysis was within the acceptable loading levels for this resin, estimated from commercial Merrifield resin loading. The sulfur content of this resin was found to be 0.88 mmol/g (2.8 % loading by content), which was consistent when repeated. FTIR spectroscopy showed a broad absorption at 3179 cm^{-1}, due to the N-H stretch. Absorptions were also visible at 1645 cm^{-1}, due to asymmetric N-H bending and at 1165 cm^{-1}, due to the thiocarbonyl group. 4-Hydroxy-2,6-dimethoxybenzaldehdye **[307]** bound resin was used in further synthetic approaches in this thesis to synthesise novel polymer bound compounds.

A similar approach to the production of 4-hydroxy-2,6-dimethoxybenzaldehdye bound resin was outlined by Kurth *et al.* [80] The ether linkage was again used to produce a resin bound aldehyde that would prove useful in future synthetic transformations. This approach was adopted to yield another aldehyde linked resin in a similar method to the

production of **[307]**. 4-Hydroxybenzaldehyde **[310]** was reacted with Merrifield resin **[1]** in the presence of a base to yield the polymer bound aldehyde **[311]** (Scheme 56).



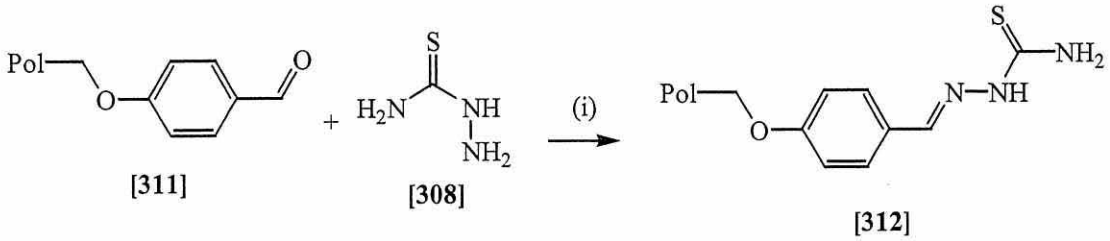
[310] [1] [311]

Scheme 56. (a) NaOMe, MeOH, rot evap, DMSO, r.t., 30 min, 85 °C, 72 h.; (b) NaOMe, MeOH, rot evap, DMF, r.t., 30 min, 85 °C, 72 h.

In order to produce these resins the phenoxide derivative of the aldehyde was produced prior to the addition of Merrifield resin **[1]**, by the addition of sodium methoxide in methanol. The production of the aldehyde resin **[311]** was carried out by two similar routes using different solvents. The use of DMSO or DMF was equally effective in producing **[311]**, although the resins differed in loading, determined by sulfur content analysis after derivatization to the thiosemicarbazide derivative. The loadings were 0.4 mmol/g in the DMSO reaction and 1.7 mmol/g when DMF was used; however this may be attributed to the levels of thiosemicarbazide that successfully reacted and bound to the resin. Washing with copious quantities of methanol, water and dichloromethane was a sufficient purification procedure for this resin as no crystalline impurities were visible by microscopy.

Product confirmation was achieved by FTIR spectroscopy of KBr discs and this was compared with published results.[80] The carbonyl resonance occurred at 1699 cm^{-1} compared to 1698 cm^{-1} and an unclear aldehyde C-H stretch was observed at 2726 cm^{-1} (literature found 2725 cm^{-1}). The O-H resonance from **[310]** was absent from the spectrum, clarifying that the alcohol had bound to Merrifield resin **[1]**. Structural elucidation of **[311]** was further confirmed by Raman analysis, which contained a weak carbonyl resonance at 1697 cm^{-1}.

Conversion of **[311]** to the corresponding thiosemicarbazide derivative, similar to Scheme 55, would provide a thiouronium bound resin and establish the loading of the aldehyde (Scheme 57).

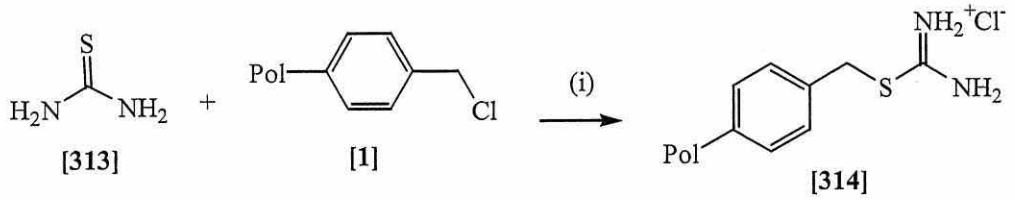


Scheme 57. (i) MeOH, r.t., 72 h.

The same conditions outlined in Scheme 55 were applied to the less substituted aldehyde **[311]**. The resin was washed with solvent (MeOH, CH_2Cl_2 and water) to remove excess reagents and was shown to contain higher levels of sulfur than expected, determined by microanalysis. Submission of **[312]** to Soxhlet extraction in methanol was sufficient to remove the excess reagents, apparent on examination of the resin by microscopy. FTIR spectroscopy of 4-(2-((aminothioxomethyl)amino)-2-azavinyl)phenol bound resin **[312]** confirmed product formation. The spectrum showed distinct bands at 3185, 1620 and 1161 cm^{-1} corresponding to N-H stretching, asymmetric N-H bending and thiocarbonyl absorption, respectively. Microanalysis of the resin found 5.5 % sulfur content equating to a loading of 1.7 mmol/g, which was far higher than the value obtained for the more substituted aldehyde equivalent. These thiosemicarbazide bound resins are now available for use in further synthesis.

4.4. SOLID-PHASE SUPPORTED THIOUREA SYNTHESIS

Pyrimidine derivatives have been shown to possess a wide range of beneficial properties. Obrecht *et al.* demonstrated the synthesis of diverse pyrimidines by solid-phase combinatorial chemistry.[58] Ureas can be converted into the corresponding halide salts by a simple S_N2 reaction with alkyl halides. It was decided to investigate the formation of a thiouronium bound approach to pyrimidine synthesis. The published method involved the reaction of thiourea with Merrifield resin in a mixture of dioxane and ethanol (4:1). This was modified, successfully, in this research and a cheaper solvent used. Thiourea **[313]** was dissolved in tetrahydrofuran and reacted with pre-swollen Merrifield resin **[1]** to yield thiouronium bound resin **[314]** (Scheme 58).



Scheme 58. (i) THF, 85 °C, 36 h.

The conversion of Merrifield resin to the thiouronium salt is an efficient process due to the excellent ability of sulfur to act as a nucleophile. A five-fold excess of thiourea was used to drive this reaction to completion. Excess reagents were removed by washing with solvent (MeOH, CH_2Cl_2 and water).

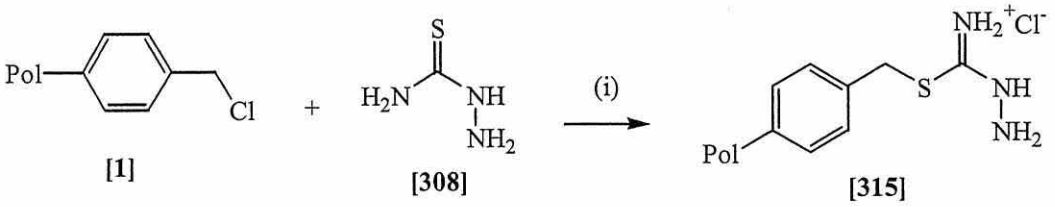
Preliminary analysis of the resin by FTIR spectroscopy showed it to contain excess starting reagent, as the spectra differed little from that of **[313]**. This was further confirmed by microanalysis, which yielded a calculated loading that was far greater than that of Merrifield resin **[1]**, by sulfur content. The resin was subsequently submitted to Soxhlet extraction in methanol for 6 hours to remove excess reagents that were contaminating it and hence affecting the microanalysis. The resin was further washed with solvents to ensure complete removal of impurities. Analysis of the resin (post Soxhlet) by microanalysis gave a loading of 1.39 mmol/g, which would suggest that full conversion of the chlorine sites on the commercial Merrifield resin had occurred and that the resin could be used in further synthesis.

The FTIR spectra after Soxhlet correlated well with the published results and confirmed the identity of **[314]**.[58] Important IR resonances were found at 3024 cm^{-1}, which was broad due to N^+H stretches, reported at 3040 cm^{-1}. This broad band hid the polystyrene resonance due to Merrifield resin. An absorption band at 1654 cm^{-1} (lit. 1643 cm^{-1}) was likely to be due to asymmetric N-H bending within this molecule. An absorption at 697 cm^{-1} (exp. 700 cm^{-1}) was due to the C-S linkage stretching vibration.

The reaction was repeated, yielding similar loading values and an alternative, larger mesh size of Merrifield resin was used which also produced the thiouronium bound resin. This was done in order to enhance the range and diversity of products that could be produced on a large commercial scale.

4.5. SYNTHESIS OF THIOSEMICARBAZIDE BOUND RESIN

The principle outlined by Obrecht should also be applicable to groups similar to thiourea.[58] The above methodology was therefore adapted towards thiosemicarbazide **[308]** to yield the resin bound derivative **[315]** (Scheme 59).



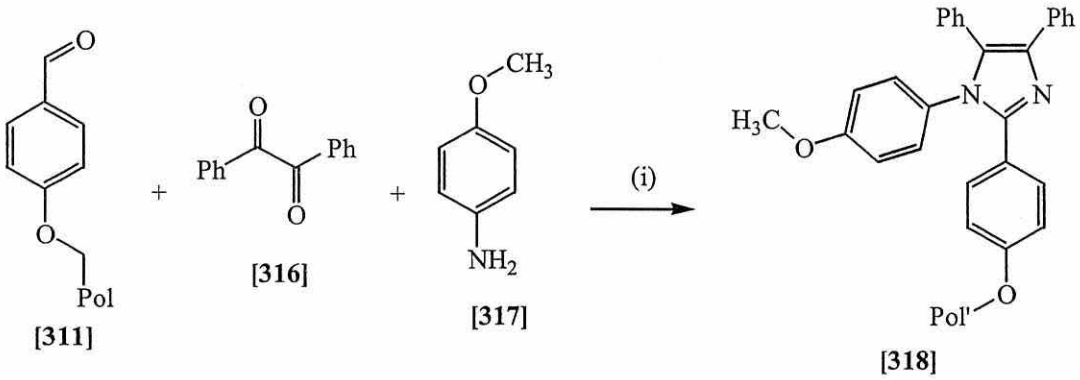
Scheme 59. (i) MeOH, r.t., 48 h.

The reaction proceeded by displacement of the halide on Merrifield resin producing the thiosemicarbazide derivative and was deemed complete after 48 h and the resin analysed by FTIR spectroscopy. Previous resins containing sulfur and nitrogen were found to contain impurities after washing with large amounts of solvent and this resin also contained impurities. It was therefore submitted to Soxhlet extraction.

Analysis by FTIR spectroscopy then confirmed the formation of the desired resin **[315]**. Clear bands were located at 3180, 1620 and 698 cm^{-1} corresponding to N-H stretching, asymmetric N-H bending and sulfide absorption respectively. Microanalysis gave 4.8 % sulfur (1.5 mmol/g loading) which was comparable to the commercial Merrifield resin starting reagent **[1]**. This approach had not been reported in the literature previously and it was hoped that such a functional group would be attractive for use in further combinatorial approaches to yield heterocycles, although no examples were attempted in the course of this thesis.

4.6. IMIDAZOLE DERIVATIVE SYNTHESIS

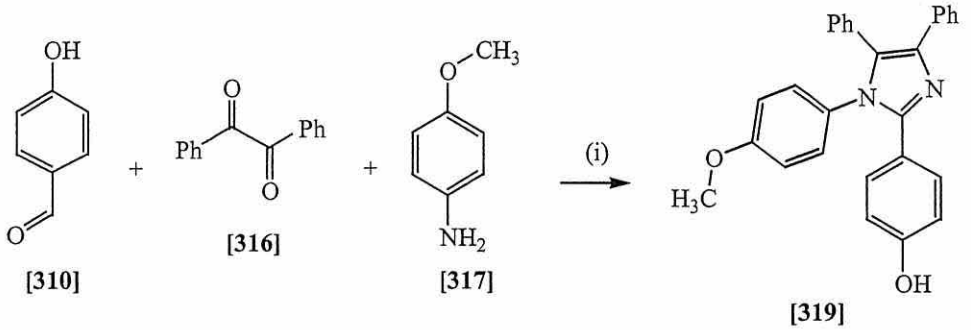
Condensation reactions are well established in orthogonal chemistry (pool/split); however, in solution-phase imidazoles are often highly impure and require extensive purification. Mjalli *et al.* were able to synthesise imidazoles on a solid-support.[51] Wang resin was converted into an aldehyde or amine and the resins were subjected to appropriate reaction conditions to produce the resin bound imidazole. It was believed that the modification of this approach using the resins previously synthesised would yield similar results. 4-Hydroxybenzaldehyde bound resin **[311]** should, in theory, react under acidic conditions to yield similar compounds. Resin **[311]** was reacted with benzil **[316]**, *p*-anisidine **[317]** and ammonium acetate in glacial acetic acid to yield **[318]** in an approach previously reported in literature (Scheme 60).[52]



Scheme 60. (i) NH_4OAc, AcOH, 85 °C, 24 h.

The condensation reaction led to the formation of polymer bound imidazole **[318]**, which was washed with copious amounts of solvents (MeOH, CH_2Cl_2 and water). Structural elucidation was achieved by FTIR spectroscopy. Absorption in the region of 3082 cm^{-1} was attributed to the CH stretches within the imidazole and the peak at 2848 cm^{-1} was due to the polystyrene base resin and overlap of other aromatic C-H stretches due to the phenyl groups of the imidazole. Absorptions of medium intensity were observed at 1597 and 1450 cm^{-1} due to ring stretching vibrations and a broad band at 1243 cm^{-1} was probably due to the C-O stretch from the methoxy group. Further elucidation by Raman spectroscopy showed the presence of bands at 1572, 1594 and 1622 cm^{-1} corresponding to the 5-membered ring of the imidazole. Microanalysis of the nitrogen content found the loading of the resin to be 0.72 mmol/g (0.5 % nitrogen content), which was lower than the starting resin loading of 1.7 mmol/g.

In order to establish the advantages of the previous method (Scheme 61) and possibly to give further structural clarification, the corresponding solution-phase reaction was carried out. *p*-Hydroxybenzaldehyde **[310]** was reacted with benzil **[316]**, *p*-anisidine **[317]** and ammonium acetate in glacial acetic acid and refluxed for 6 h (Scheme 61).

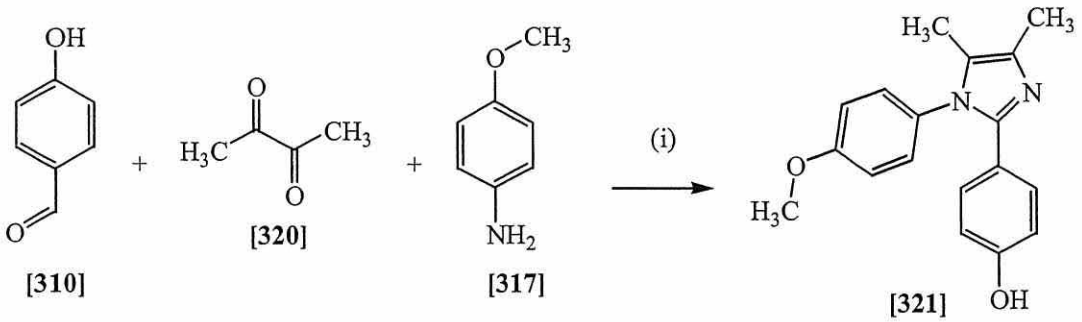


[310] **[316]** **[317]** **[319]**

Scheme 61. (i) NH_4OAc, AcOH, 85 °C, 6 h.

The resultant solution was diluted with NaCl solution. The product **[319]** formed as a dense grey solid, which was collected by filtration. This was followed by several recrystallisations; however all failed to provide an adequately pure product that could be properly characterised. This was disappointing as **[319]** was unreported in the literature. The ^{1}H-NMR spectrum showed promising peaks at 3.0 ppm correlating to OH, 4.7 ppm representing the three methoxy protons and also 7.0 ppm integrating to approximately 18 protons for the aromatic rings; however the spectrum was poorly resolved and it was obvious that trace quantities of starting reagents were present. The yield of impure product obtained was 25 %. This compound was previously unreported; however, the approach and similar compounds are reported.[52]

The approach adopted in the previous reaction was repeated using 2,3-butanedione **[320]** instead of benzil to synthesise the imidazole **[321]** (Scheme 62).[52]



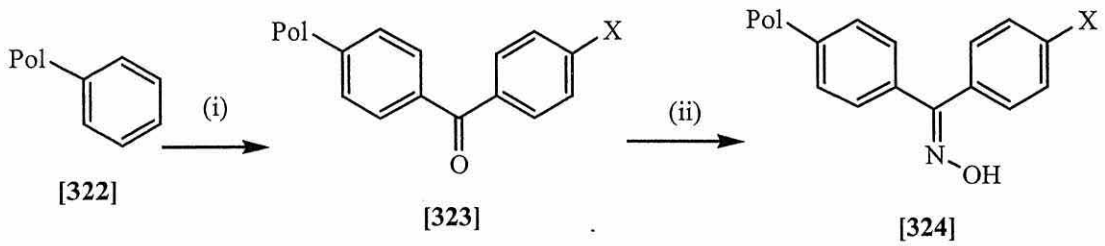
[310] **[320]** **[317]** **[321]**

Scheme 62. (i) NH_4OAc, AcOH, 85 °C, 6 h.

4-Hydroxybenzaldehyde **[310]**, 2,3-butanedione **[320]**, ammonium acetate and *p*-anisidine **[317]** were refluxed in glacial acetic acid for 6 h. Work-up was again achieved by adding brine when a dense black solid formed. The solid was collected by filtration and washed with petrol. FTIR spectroscopy found that the product contained no characteristic peaks correlating to an alcohol or heterocyclic stretching bands, as expected for an imidazole. ^{1}H-NMR spectroscopy provided an unresolved spectrum and failed to give any of the characteristic signals expected for **[321]**, such as an OH or OCH_3 group.

4.7. SOLID SUPPORTED OXIME SYNTHESIS

Amine production by combinatorial methods is well established, such as the reduction of oximes into the corresponding amine by catalytic hydrogenation. Kaiser and DeGrado prepared polymer bound oxime ethers and used these as supports in the synthesis of peptides.[83,84] A series of substituted benzophenone oximes were attached to polystyrene divinyl benzene resin **[322]** and each support was tested for preparing peptides (Scheme 63).

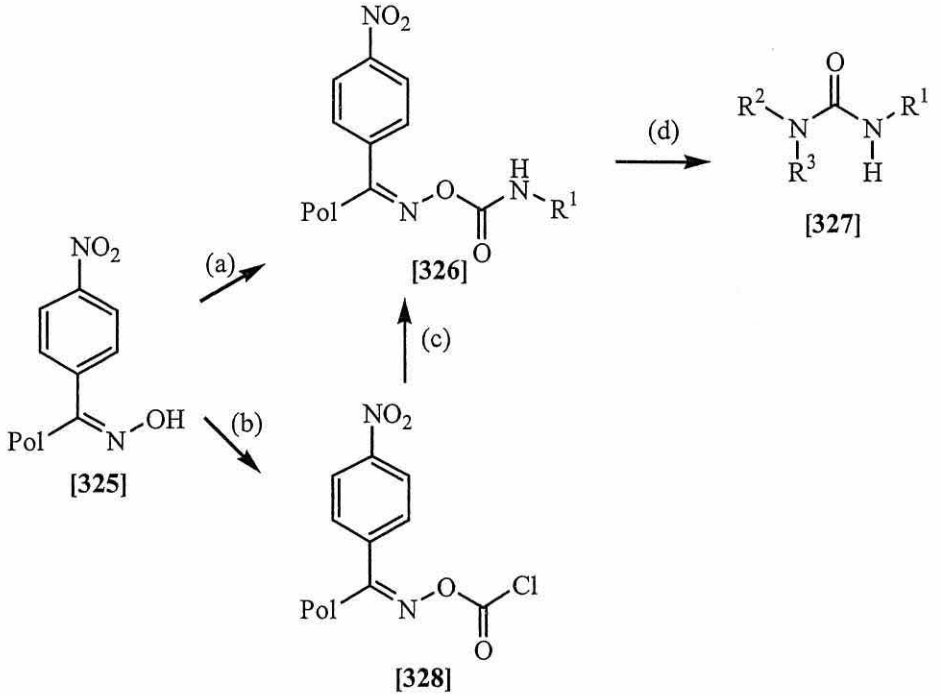


[322] **[323]** **[324]**

Scheme 63. (i) *p*-XC_6H_4COCl, $AlCl_3$; (ii) NH_2OH, HCl, pyridine.
X = OMe, H, Cl, NO_2.

The stability of the oxime linker was tested by submitting the polymer bound oximes to a condensation reaction with a Boc-protected amino acid, using DCC as a condensing agent. Peptide yields ranged from moderate to excellent and purities were shown to be high. Kaiser and DeGrado further illustrated peptide synthesis using the oxime bound resin as a support in synthesising longer chain length protected peptides.[84]

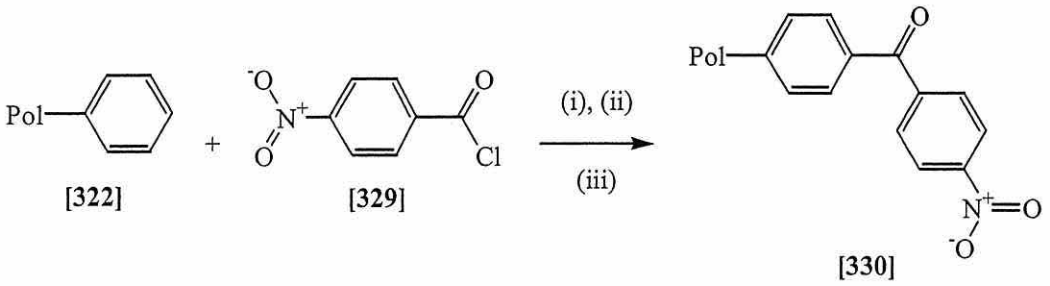
Scialdone and co-workers also made use of the resin bound oxime.[86] Ureas were successfully synthesised from the oxime *via* two possible routes, without the need for cleavage with trifluoroacetic acid (Scheme 64).



Scheme 64. (a) R^1NCO, CH_2Cl_2; (b) triphosgene, CH_2Cl_2, r.t.; (c) R^1NH_2, CH_2Cl_2, r.t.; (d) CH_2Cl_2, R^2R^3NH, toluene, 80 °C.

The reaction produced both high yield and purity from a diverse series of amines and initiatiated investigation into the production of oxime bound resins. Oximes such as **[324]** could therefore be applied to this approach.

It was decided to repeat the approach of Kaiser and Degrado [83,84] to produce an oxime bound resin and use the resin to produce amines in a similar manner to that of Scialdone *et al.*[86] The first step in producing a polymer bound oxime was to synthesise a ketone bound resin. Polystyrene(co-divinyl)benzene resin **[322]** was reacted with *p*-nitro-benzoyl chloride **[329]** in the presence of aluminium chloride in 1,2-dichloroethane to produce 4-(nitrophenyl)phenylmethanone bound resin **[330]** (Scheme 65).

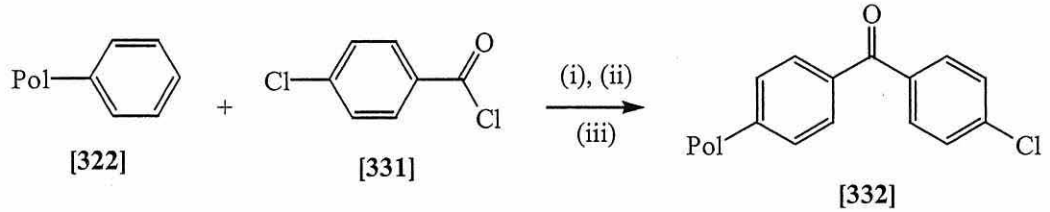


Scheme 65. (i) 1,2-Dichloroethane, r.t., 30 min; (ii) $AlCl_3$, r.t., 1 h.; (iii) Δ, 3 h.

Resin **[322]** was pre-swollen in 1,2-dichloroethane and stirred under nitrogen. *p*-Nitrobenzoyl chloride **[329]** was then added and the reaction stirred for a further 30 min. Aluminium chloride was added slowly and the resultant mixture stirred for 1 h at room temperature, followed by reflux for 3 h. The resin was collected and washed with copious amounts of water to ensure complete removal/ quenching of the excess aluminium chloride, which was easy to distinguish from the polymer beads as large white clusters. Further washing with MeOH, CH_2Cl_2 and more water yielded resin **[330]**. This still contained aggregates of $AlCl_3$ on examination by microscopy. Quenching the excess $AlCl_3$ was aided by stirring the resin in water at 60 °C.

Comparison of the FTIR spectrum of the resin obtained and the published results gave excellent correlation.[86] The carbonyl absorption expected at 1665 cm^{-1} was clearly visible at 1664 cm^{-1}. The nitro group showed two bands at 1527 cm^{-1} (lit. 1525 cm^{-1}) and 1310 cm^{-1} (lit. 1310 cm^{-1}) due to the asymmetric and symmetric NO_2 stretches, respectively. Raman spectroscopy clarified the NO_2 presence with a band at 851 cm^{-1}. Microanalysis was used to establish the loading of the resin and found 0.6 % nitrogen content corresponding to 0.43 mmol/g loading. Polystyrene resin, as supplied, has no associated loading value.

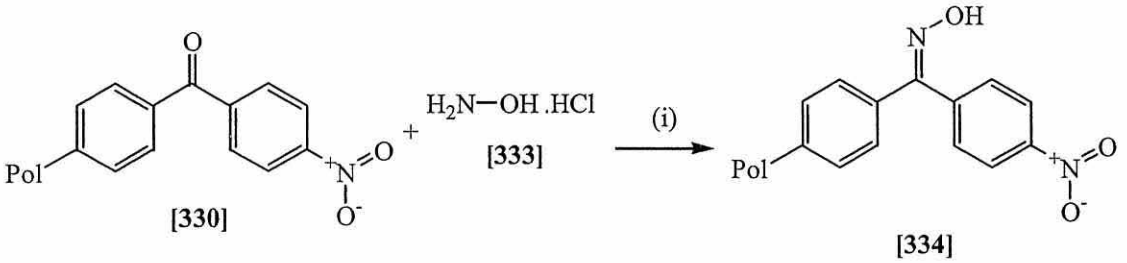
The reaction previously illustrated could be applied to other benzoyl chlorides. *p*-Nitrobenzoyl chloride was replaced with *p*-chlorobenzoyl chloride (Scheme 66).[86]



Scheme 66. (i) 1,2-Dichloroethane, r.t., 30 min; (ii) $AlCl_3$, r.t., 1 h.; (iii) 85 °C, 24 h.

The production of 4-(chlorophenyl)-phenyl-methanone bound resin **[332]** gave rise to similar purification problems to the previous reaction. Washing the resin with copious amounts of water, MeOH and CH_2Cl_2 yielded an impure product, with aluminium chloride residues visible within the resin sample. Stirring the resin in hot water (60 °C) was sufficient to remove by-products. The resin was then further washed with MeOH and CH_2Cl_2 to remove moisture from the sample and oven dried (50 °C) to yield **[332]**. 4-(Chlorophenyl)-phenyl-methanone bound resin gave a similar IR spectra to the *p*-nitrobenzoyl chloride equivalent. The main absorption bands were at 2727 cm^{-1} corresponding to the *HC*O stretch and the carbonyl was clearly visible at 1688 cm^{-1}.

The oxime reaction described by Kaiser and DeGrado involved the treatment of an aldehyde or ketone with hydroxylamine hydrochloride.[83,84] 4-Methylphenyl 4-nitro-phenyl ketone bound resin **[330]** was treated with hydroxylamine **[333]** in methanol to obtain the corresponding oxime (Scheme 67).

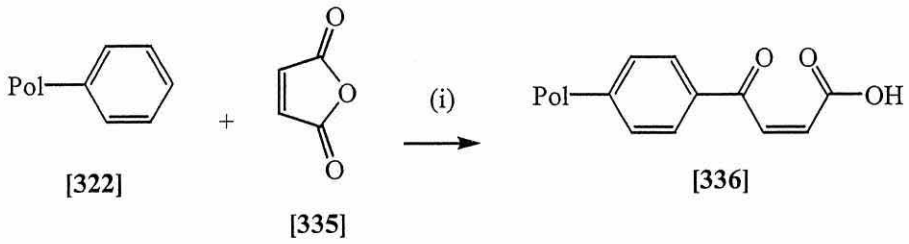


Scheme 67. (i) MeOH, pyridine, reflux, 100 h.

The reaction used excess reagents and the addition of pyridine drove it to completion and literature suggested that 24 h reflux was sufficient for conversion to **[334]**.[83,84] A sample of the resin was taken at various intervals over a 5-day period and complete conversion of the ketone to oxime was observed on day 5. Comparison of FTIR spectra with the published results confirmed the formation of **[334]**.[83,84] A broad oxime absorption band was apparent at 3504 cm^{-1} (lit. 3530 cm^{-1}) due to the OH group. The carbonyl absorption at 1664 cm^{-1} was negligible and the reaction was deemed complete. Raman spectroscopy showed the NO_2 group to be present at 851 cm^{-1}.

4.8. SOLID SUPPORTED ACID SYNTHESIS

Hamper *et al.* [90] reported the binding of malonic acid to Wang resin by refluxing with Meldrum's acid in THF and, similarly, Gordeev *et al.* [56] have demonstrated the binding of a β-keto ester to Wang resin with diketene and DMAP in dichloromethane. This led to the investigation into the synthesis of acid bound resins. The reaction of maleic anhydride **[335]** with polystyrene divinyl benzene resin **[322]** in the presence of aluminium chloride was expected to yield the acid bound resin **[336]** (Scheme 68).

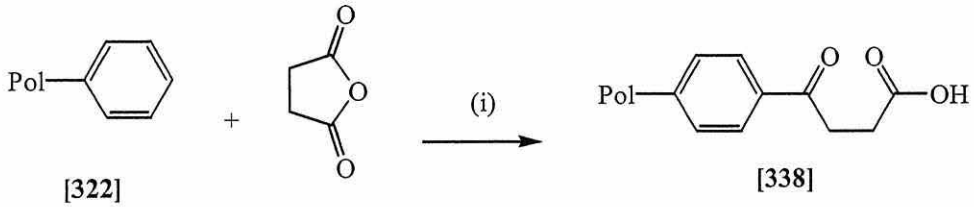


[322] **[335]** **[336]**

Scheme 68. (i) CH_2Cl_2, $AlCl_3$, 85 °C, 24 h.

The reaction was stirred for 24 h at 85 °C and the resultant resin collected by filtration and washed with copious quantities of water, MeOH and CH_2Cl_2, which was sufficient to remove aluminium chloride by-products. FTIR spectroscopy proved the reaction to be unsuccessful due to the lack of carbonyl and alcohol absorptions expected for resin bound **[336]**.

Simultaneously the above reaction was carried out replacing maleic anhydride **[335]** with succinic anhydride **[337]** with the aim of producing a similar acid bound resin **[338]** under the same conditions (Scheme 69).



[322] **[337]** **[338]**

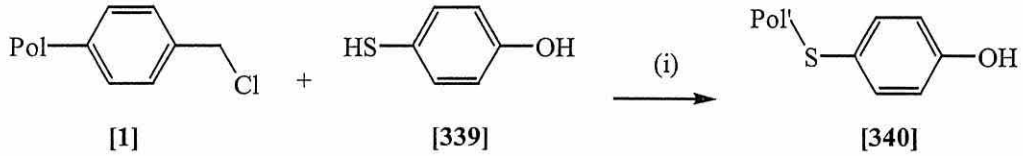
Scheme 69. (i) CH_2Cl_2, $AlCl_3$, 85 °C, 24 h.

The resin was collected by filtration and washed with copious amounts of water, followed by subsequent washing with MeOH and CH_2Cl_2, which was sufficient to

remove the excess reagents and by-products from the resin. FTIR spectroscopy also proved this reaction to be unsuccessful as the compound showed no characteristic carbonyl or alcohol absorbtions and was similar to the starting material.

4.9. FORMAMIDE SYNTHESIS

The production of ureas *via* solid-phase organic chemistry was exemplified by Dressman *et al.*[87] Interest in this approach stemmed from the potential of their resin to produce ureas and the added benefit of resin reclamation after cleavage. The first step in synthesis was the production of hydroxythiophenol bound resin **[340]**. Merrifield resin **[1]** was reacted with *p*-hydroxythiophenol **[339]** and potassium hydroxide in DMF (Scheme 70).



[1] **[339]** **[340]**

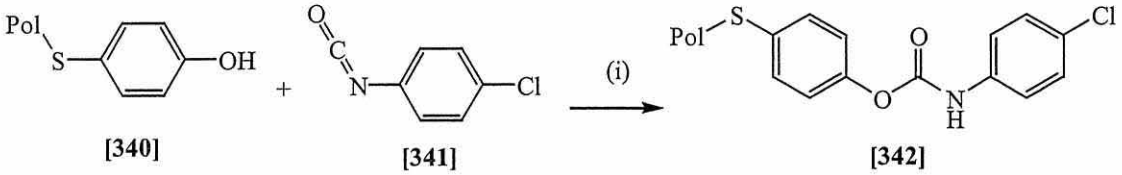
Scheme 70. (i) DMF, KOH, 85 °C, 24 h.

Merrifield resin **[1]** was swollen in DMF prior to the addition of potassium hydroxide, which had been fully dissolved in DMF before addition. *p*-Hydroxy-thiophenol **[339]** was added and the reaction was stirred at 85 °C for 24 h. The method adopted the use of a six-fold excess of alcohol and a 4-fold excess of potassium hydroxide. The reaction occurs at the more acidic thiol functional group to produce resin **[340]**, which was collected by filtration and washed with copious amounts of solvent (water, MeOH and CH_2Cl_2).

Analysis of the resin by FTIR spectroscopy and comparison with the literature by microanalysis confirmed product formation.[87] The resin **[340]** showed an alcohol absorption at 3386 cm^{-1} and also a band at 693 cm^{-1} corresponding to the C-S linkage. Raman analysis and the subtraction of spectra confirmed the loss of the carbon-chlorine stretch at 678 cm^{-1}. The resin contained 5.6 % sulfur which corresponded to 1.79 mmol/g loading, which was far higher than the original literature reported value (0.93 mmol/g) but was comparable with Merrifield resin (1.5 – 2.0 mmol/g). The resin was

sufficiently pure for use in further synthesis, as there were no crystalline impurities visible by microscopy.

The work of Dressman *et al.*, as outlined previously, was used to synthesise ureas.[87] The paper reports the reaction of *p*-hydroxythiophenol bound resin with *p*-nitrophenyl chloroformate and *N*-methyl morpholine in dichloromethane to produce *p*-nitrophenyl carbonate resin, which was the building block for further synthesis. The reaction of 4-chlorophenyl isocyanate **[341]** with *p*-hydroxythiophenol bound resin **[340]** was carried out, as it would provide a useful intermediate **[342]** in further synthesis (Scheme 71).

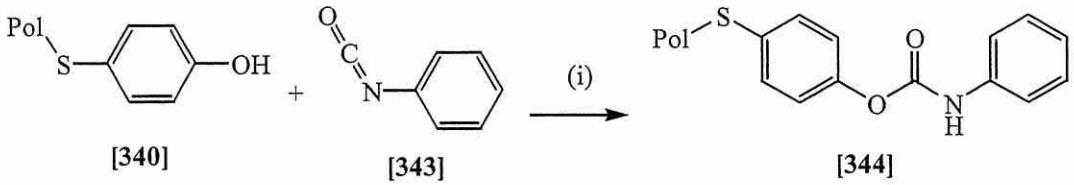


[340] **[341]** **[342]**

Scheme 71. (i) Toluene, pyridine, 85 °C, 18 h.

4-Chlorophenyl isocyanate **[341]** reacted with *p*-hydroxythiophenol bound resin **[340]** to produce the corresponding carbamate **[342]**. Collection of the resin by filtration followed by subsequent washing with large amounts of solvent (water, MeOH and CH_2Cl_2) was sufficient for purification. FTIR spectroscopy gave a clear indication of the carbamate resin formation. The O-H stretch at 3386 cm^{-1} had vanished and a distinct carbonyl peak at 1723 cm^{-1} was present. The C-S linkage was also still present at 694 cm^{-1} and absorptions at 3300 cm^{-1} and 1596 cm^{-1} were representative of N-H stretching and bending, respectively. The loading was assumed to be 1.79 mmol/g, established by sulfur analysis of the starting *p*-hydroxythiophenol bound resin **[340]**.

The above reaction was repeated on phenyl isocyanate **[343]** by reaction with *p*-hydroxy-thiophenol bound resin **[340]** and pyridine in toluene at 85 °C for 18 h (Scheme 72).



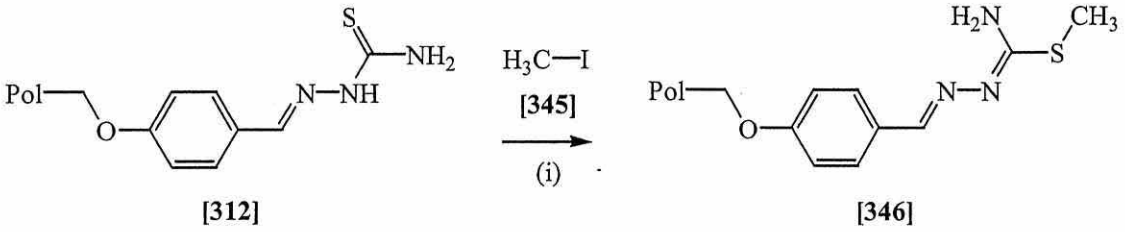
[340] **[343]** **[344]**

Scheme 72. (i) Toluene, pyridine, 85 °C, 18 h.

Collection of the resin **[344]** by filtration followed by subsequent washing with copious amounts of solvent (water, MeOH and CH_2Cl_2) was sufficient for purification. Analysis by FTIR spectroscopy and comparison with the spectrum obtained for the previous resin proved this reaction to be successful. The carbamate resin **[344]** showed N-H absorptions at 3327 cm^{-1} and 1594 cm^{-1} corresponding to the N-H stretch and bend, respectively. The O-H absorption was absent and the C-S linkage was present at 696 cm^{-1}. The loading was assumed to be 1.79 mmol/g as determined by sulfur analysis of the starting *p*-hydroxythiophenol bound resin **[340]**. The resin was then used in further synthesis, which is demonstrated in the solution-phase section of this thesis.

4.10. MODIFICATION OF THIOSEMICARBAZIDE RESIN

Miocque *et al.* have investigated approaches to triazole synthesis.[134] They demonstrated the reaction of a thiosemicarbazone derivative with methyl iodide and further reaction with iron (III) chloride to produce a triazole. Thiosemicarbazide bound resins **[309]** and **[312]** were anticipated to react in a similar manner. Resin **[312]** was reacted with methyl iodide **[345]** in methanol in an attempt to produce the methylated product **[346]** for use in further synthesis (Scheme 73).

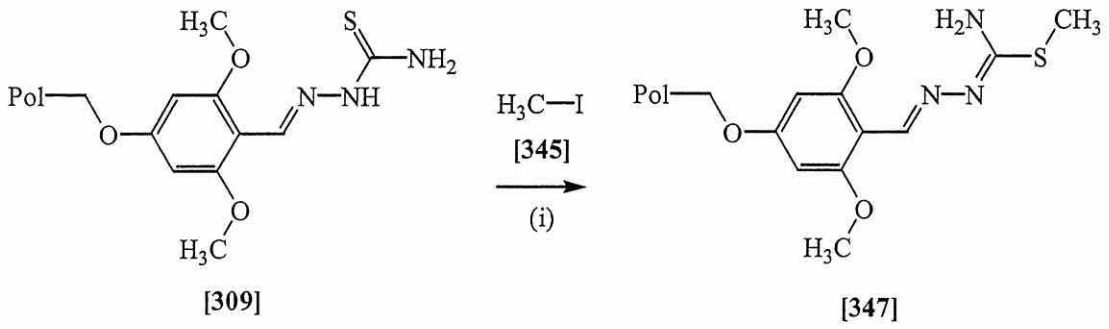


[312] **[346]**

Scheme 73. (i) MeOH, r.t., 18 h.

The thiosemicarbazide resin **[312]** was pre-swollen in methanol and a ten-fold excess of methyl iodide **[345]** was used to drive the reaction to completion. The resin was collected by filtration and washed with water, MeOH and CH_2Cl_2. Analysis of the resin by FTIR spectroscopy showed the reaction to be unsuccessful, as the spectrum showed no significant differences from that of the starting reagent **[312]**.

Simultaneously to the previous reaction (Scheme 75) 4-(2-(aminothioxomethyl)-amino-2-azavinyl)-3,5-di-methoxyphenol bound resin **[309]** was reacted with methyl iodide **[345]** under the same reaction conditions (Scheme 74).

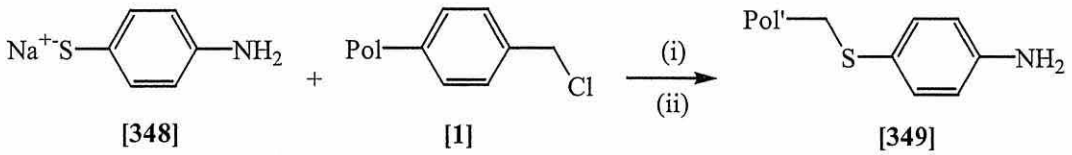


Scheme 74. (i) MeOH, r.t., 18 h.

A ten-fold excess of methyl iodide was again used to drive the reaction to completion. The resin was collected by filtration and washed with large amounts of solvents (water, MeOH, CH_2Cl_2). FTIR spectroscopy of the product **[347]** showed the reaction had been unsuccessful, as again the spectrum was unaltered from the starting resin spectrum **[309]**.

4.11. SYNTHESIS OF 4-AMINOBENZENE-1-THIOL BOUND RESIN

The amine functional group has many applications in synthetic chemistry. An amine bound to a resin would be useful for combinatorial chemistry as many synthetic transformations could be achieved. Sodium methoxide in methanol was reacted with 4-aminothiophenol and the solution concentrated *in vacuo*, yielding **[348]** which was further reacted with pre-swollen Merrifield resin **[1]** in DMF to produce 4-aminobenzene-1-thiol bound resin **[349]** (Scheme 75).



Scheme 75. (i) MeOH, NaOMe, rot evap; (ii) DMF, 85 °C, 24 h.

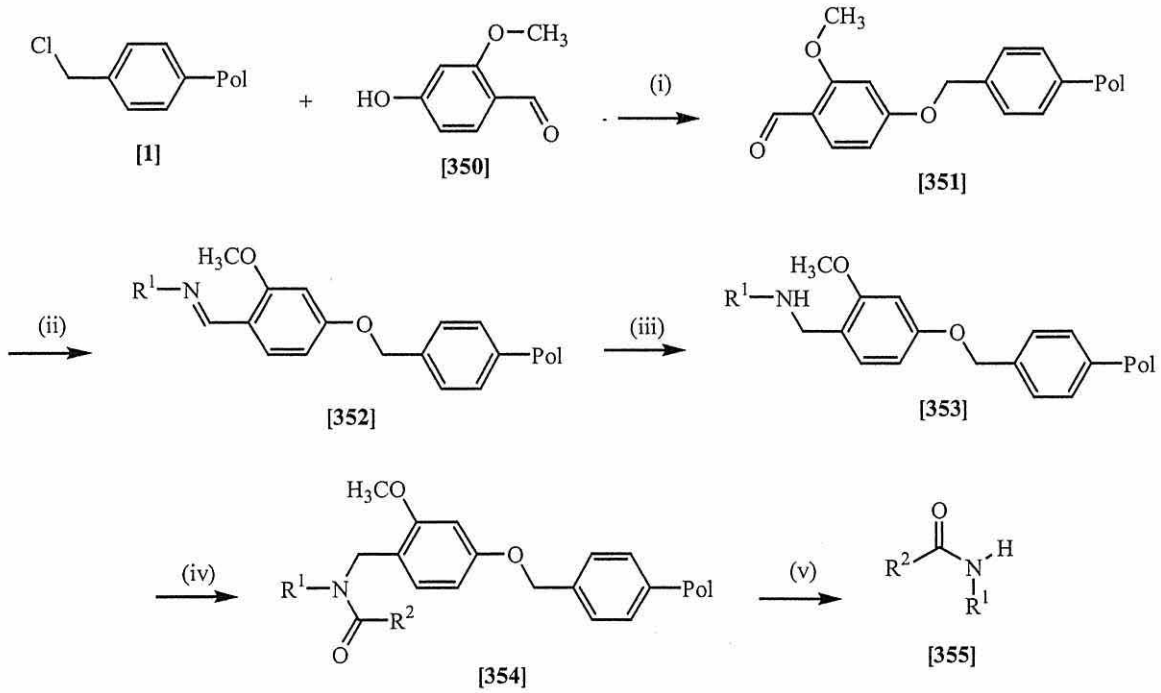
The reaction was deemed complete after 24 h at 85 °C and only a 4-fold excess of reagents was used. Resin **[349]** was collected and washed with copious amounts of solvent (water, MeOH, CH_2Cl_2) to remove excess reagents.

The resin **[349]** was analysed by FTIR spectroscopy and the reaction proved successful due to absorptions at 3500 cm^{-1} and 3379 cm^{-1} corresponding to asymmetric and symmetric stretching of the amine. The N-H bend absorption was present at 1596 cm^{-1} and a C-S linkage occurred at 696 cm^{-1}, however due to the complex fingerprint region it was difficult to detect the loss of a C-Cl stretch.

4.12. CONCLUSIONS AND FURTHER WORK

It has been demonstrated, in this section, that solid-phase synthetic reagents were synthesised successfully and, in some cases, were put to further use in producing organic reagents. At the time of this work two resins were used to produce organic reagents and the remaining resins became commercially available by Menai Organics Limited in a new product range. Unfortunately it was shown that these products arising from the resins could be produced in far greater yields *via* solution-phase methods. It was concluded that, for the purposes of a small chemical company, the use of combinatorial resins to produce fine chemicals is not particularly advantageous. This led to the decision to produce novel resins that would have commercial benefit to the company and would be offered to larger pharmaceutical companies. Companies using automated methods, where scale of product is not as important as the development of compounds, can rapidly produce new compounds that may prove of pharmaceutical benefit.

Sarantakis and Bicksler report the linkage of a similar aldehyde to resins **[307]** and **[311]** reported in this work to produce produce sec-amides involving aldehyde **[350]** and reaction with Merrifield resin (Scheme 76).[135]



Scheme 76. (i) NaOMe, DMF, N_2, 60 - 70 °C, 20 h; (ii) R^1NH_2, THF, r.t. 18 h; (iii) $NaBH_4$, THF-EtOH, 6 - 8 h; (iv) R^2COX, NEt_3; (v) TFA/CH_2Cl_2

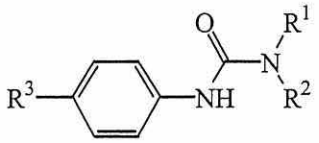
The yields of amides **[355]** in the literature for this reaction varied from moderate to good and further studies are in progress for optimisation of the full potential of this methodology.[135] Cleavage conditions were relatively mild (30 % TFA in CH_2Cl_2) and the reaction proceeded to completion with a five-fold excess of primary amine. Further studies also indicated that the use of one equivalent of methyl orthoformate as a dehydrating agent assisted in driving the reaction to completion. Further novel aldehyde bound resins, that could have been applied to the above method or to the synthesis of dihydropyrimidines (reported in the solution-phase synthesis chapter), would provide an interesting further project.

The project was geared towards the production of heterocyclic or cyclic compounds, with the aim that these may prove of benefit to the agrochemical or pharmaceutical industry. Future work in this area could involve solid-phase synthetic approaches utilising the Biginelli and Ugi multi-component reactions. Weber *et al.* report the optimisation of biological activity of combinatorial libraries by genetic algorithm and this could be adopted by using an aldehyde or amine bound resin. [60]

CHAPTER 5- SOLUTION-PHASE COMBINATORIAL CHEMISTRY

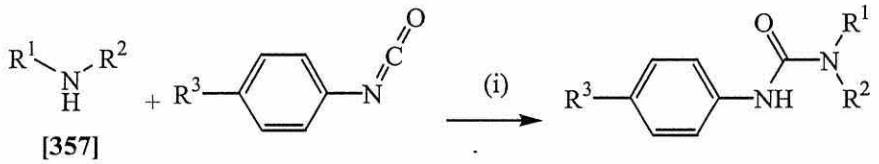
5.1. SYNTHETIC APPROACHES TO UREAS

5.1.1. Urea Derivative Synthesis [87]



[357]

The aim of this research was to synthesise a library of urea derivatives by solution-phase methods and to investigate alternative solid-phase approaches. The urea moiety is often found in biologically active compounds and the solid-phase synthesis of such compounds has been widely reported in the literature.[87, 134, 136-143] One particular example, reported by Dressman *et al.*, involved the production of urea derivatives from an isocyanate bound resin.[87] The reaction of a phenylisocyanate with compounds R^1R^2NH to yield formamides proceeds quickly and *via* mild reaction conditions, as summarised in the following Scheme.



[357] [358] [356]

Scheme 77. (i) Toluene, 85 °C, 1 h.

The above reaction was carried out with a series of different amines and two phenyl-isocyanates, with products **[359]** – **[366]** formed after heating for one hour at 85 °C. The reactions produced urea derivatives in excellent yields with optimum results obtained for chlorophenyl derivatives. Recrystallisation, when required, was achieved using CH_2Cl_2 / petrol and compounds were proven by CHN microanalysis or high-resolution mass spectrometry. The following table summarises the results obtained for this series of reactions (Table 2).

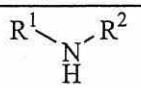
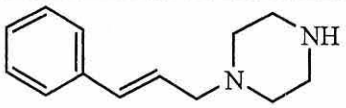
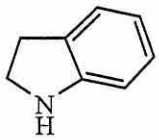
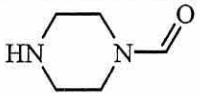
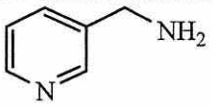
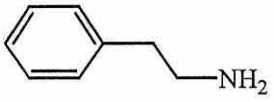
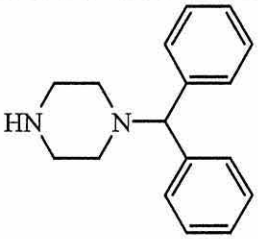
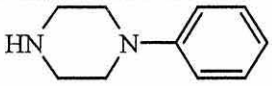
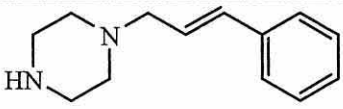
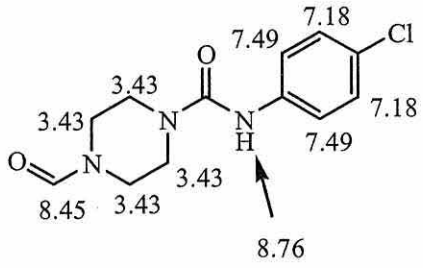
	 [357]	R^3	Yield (%)
[359]		Cl	91
[360]		Cl	94
[361]		Cl	94
[362]		Cl	92
[363]		H	82
[364]		Cl	92
[365]		Cl	79
[366]		H	85

Table 2. Urea Derivatives.

The FTIR spectra obtained for all products showed significant variability, particularly for the N-H stretch of the urea moiety and the carbonyl stretching frequency. The N-H stretch of compounds containing a chlorophenyl was considerably lower than those without or those with piperidine functionality. The highest N-H stretching value was observed for **[363]**, which has two free N-H protons. The C=O stretch occurred at ca 1650 cm^{-1} for all compounds. At the time of the research compound **[362]** had been

previously reported in the literature as having a melting point of 171 – 173 °C, which was similar to that obtained of 170 – 172 °C.

^{1}H-NMR spectroscopy showed wide variation due to the significant differences in structure; however, similarities were observed. Products containing the piperidine structure typically displayed two separate signals for both groups of 4 protons. They ranged from 3.63 – 2.60 ppm representative of the NCH_2 nearest to carbonyl and 3.43 – 1.60 ppm for the other NCH_2 resonance. Compound **[364]** was analysed only by 60 MHz NMR and the piperidine resonance was poorly resolved. Samples that were subjected to ^{13}C-NMR analysis showed significant similarities in resonance. The C=O was located consistently at ca. 155 ppm and the piperazine group ranged from 52.7 – 43.5 ppm. A representative ^{1}H-NMR interpretation of compound **[361]** is depicted in Figure 11.



[361]

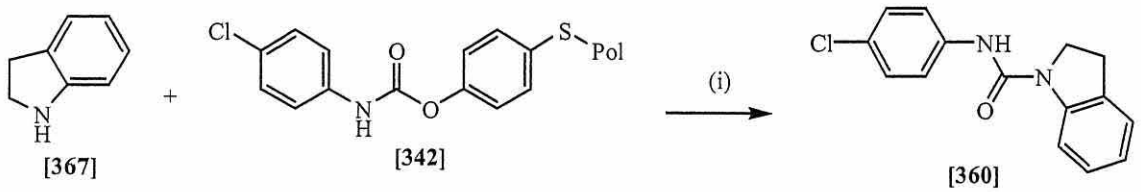
Figure 11. ^{1}H-NMR interpretation of compound **[361]**

The formation of compound **[361]** was the best result obtained for this reaction series with a yield of 94 %. Analysis by ^{13}C-NMR found, in particular, signals at 161.2 and 154.7 correlated to the aldehyde CH and the CO respectively. These were further supported by a strong carbonyl absorption at 1635 cm^{-1}.

5.1.2. Synthesis of *N*-(4-Chlorophenyl)indolinylformamide [87]

The next approach was to attempt to make a urea derivative by a similar method to that outlined by Dressman *et al.* using solid-phase synthesis.[87] Compound **[360]**, *N*-(4-chlorophenyl)indolinylformamide, was produced in excellent yield (94 %) and purity by solution-phase methods. Purity of the product synthesised by solid-phase methods could therefore be determined by comparison of spectra. The solid-phase equivalent of

this reaction was carried out using previously synthesised resin **[342]**. *N*-(4-Chlorophenyl)(4-thio-phenoxy)formamide bound resin **[342]** was reacted with **[367]** in the presence of triethylamine in dichloromethane / toluene (Scheme 78).



[367] [342] [360]

Scheme 78. (i) CH_2Cl_2, toluene, NEt_3, 85 °C, 48 h.

The conditions for this reaction were similar to the solution-phase equivalent, except that a base was required to assist in product formation and an excess of indoline **[367]** was used. The reaction is particularly advantageous as the thiol bound resin **[340]** is cleaved on the formation of product and therefore the reaction does not require acidic cleavage. The resin was collected by filtration and the washings collected and concentrated to dryness to yield the desired urea, which was washed with petrol. The cleaved product was obtained in 62 % yield, which was significantly lower than the 94 % solution-phase equivalent.

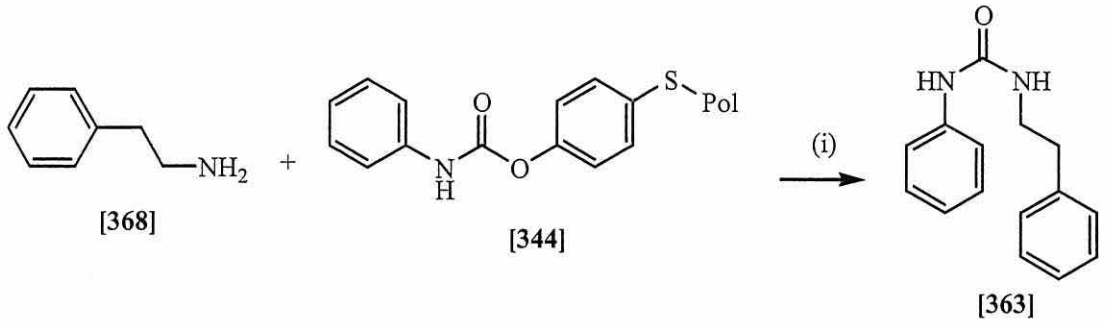
Compound **[360]** melted between 170 - 175 °C, which was lower than that from the solution-phase reaction (175 - 180 °C). Comparison of spectrum obtained showed the products were identical and the solid-phase reaction had been successful.

The reaction was particularly advantageous due to the recoverable reagents from the cleavage step of the reaction. The *p*-hydroxythiophenol bound resin was recovered and could be re-used in further synthesis. Although the approach adopted was of lower yield than the solution-phase equivalent, this reaction could be employed for more complex molecules or for reactions with low yield in the solution-phase.

5.1.3. Synthesis of 1-Phenethyl-3-phenyl Urea [87]

It was next decided to carry out a similar reaction to the above (Scheme 78), using the non-chloro derivative resin **[344]** and 2-phenylethylamine **[368]** to produce a urea that was not synthesised *via* the solution-phase route demonstrated in the previous section. Phenyl-carbamic acid 4-mercapto-phenyl ester bound resin **[344]** was reacted

with 2-phenylethylamine **[368]** in the presence of base to yield 1-phenethyl-3-phenyl urea **[369]** (Scheme 79).



Scheme 79. (i) CH_2Cl_2, toluene, NEt_3, 85 °C, 48 h.

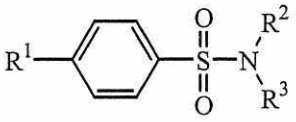
The resin was removed by filtration and the cleaved product was collected in solution, which was evaporated to yield **[369]**. Recrystallisation was achieved using dichloromethane / petrol. The reaction was carried out on 5 g of loaded resin, assumed to be 1.5 mmol/ g, and the yield obtained was 1.48 g (82 %). Compound **[363]** melted between 133 – 138 °C.

FTIR spectroscopy of **[363]** showed a clear C=O absorption at 1649 cm^{-1}. The ^{1}H-NMR spectrum confirmed the presence of 10 aromatic hydrogens at 6.94 ppm and also showed the two CH_2 groups within this molecule. The ^{13}C-NMR spectrum further confirmed the desired product with particular resonances at 156.3 (CO), 41.1 ($NHCH_2$) and 36.1 (CH_2).

Preparation of urea derivatives by solid-phase methods did indeed produce the desired compounds; however, the equivalent solution-phase reaction gave significantly greater yields. A combinatorial approach involving fluorous electrophilic scavenger resins also produced good yields in solution-phase combinatorial urea synthesis.[142]

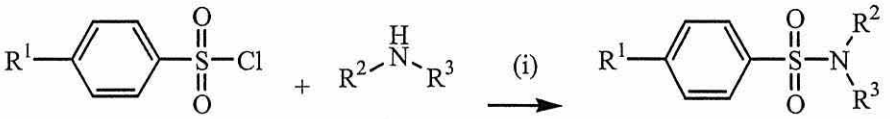
5.2. SYNTHETIC APPROACHES TO SULFONAMIDES

5.2.1. Solution-phase Sulfonamide Synthesis



[369]

It was decided to investigate the synthesis of sulfonamides with the aim of producing diverse sulfonyl ureas. Classically sulfonamides were produced by reaction of amines with a sulfonyl chloride derivative, which can then be converted, over copper (I) chloride, into sulfonamides **[370]**.[144] These have been found to have pharmacological significance and are of particular benefit in the treatment of diabetes.[145, 146] A series of such reactions was performed on a 1: 1 basis to yield, *via* the following scheme, the desired sulfonamides using excess pyridine to drive the reaction to completion (Scheme 80).



[370] [371] [369]

Scheme 80. (i) Pyridine, 85 °C, 18 h. or CH_2Cl_2, aq. $NaHCO_3$, 85 °C, 4 h.

Pyridinium chloride precipitated in solution and could easily be separated from the products. The speed of reactions varied and these were deemed to be complete when no further solid formed. Recrystallisation was achieved by dichloromethane/petrol. The yields of products **[373]** – **[383]** are shown in Table 3.

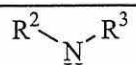
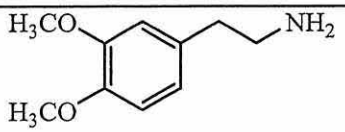
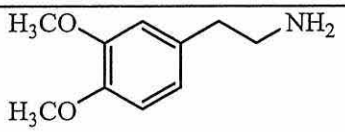
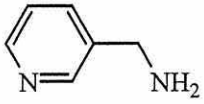
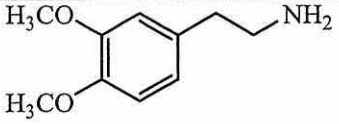
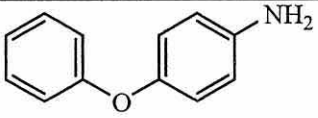
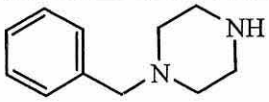
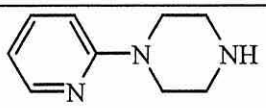
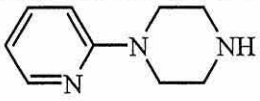
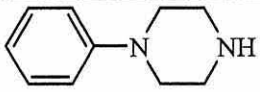
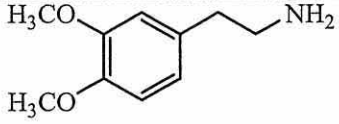
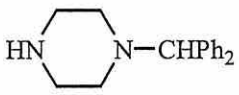
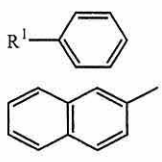
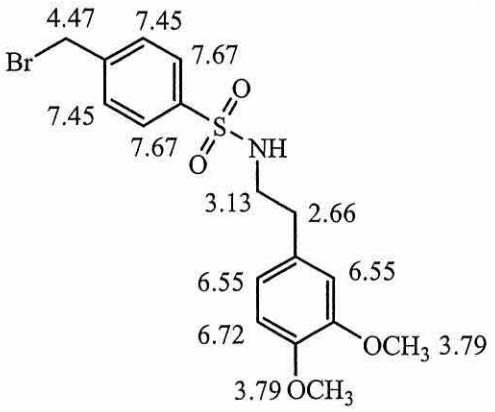
	 [371]	R^1	Yield (%)
[372]		Cl	56
[373]		CH_2Br	72
[374]		H	65
[375]		$NHCOCH_3$	12
[376]		$NHCOCH_3$	88
[377]		$NHCOCH_3$	22
[378]		$NHCOCH_3$	22
[379]		I	37
[380]		I	37
[381]		I	40
[382]			58

Table 3. Sulfonamide Synthesis

The products **[372]** – **[382]** were obtained in moderate to good yields and purity and no further recrystallisation or chromatographic techniques were necessary.

Spectrally the compounds were quite different due to the wide range of possible structures for this library of compounds. On comparison of FTIR spectroscopy, peaks occurring at approximately 1350 and 1160 cm^{-1} were assigned as S=O stretching vibrations, if apparent, and often there was evidence of the broad NH stretching between 3200 and 3350 cm^{-1}. Several ^{1}H-NMR spectra showed the presence of the NH group(s), commonly between 12 and 10 ppm, as a broad singlet. The ^{1}H-NMR spectra found the piperazine group protons as two separate signals, the four protons nearest the sulfonyl located between 3.6 and 2.2 ppm with the remaining four protons visible between 3.0 and 1.5 ppm. ^{13}C-NMR spectra (where obtained) gave further confirmation of product formation and in particular clarified the C=O in compound **[379]**. A representative interpretation of the shifts for one of the library members, compound **[372]**, is shown in Figure 12.



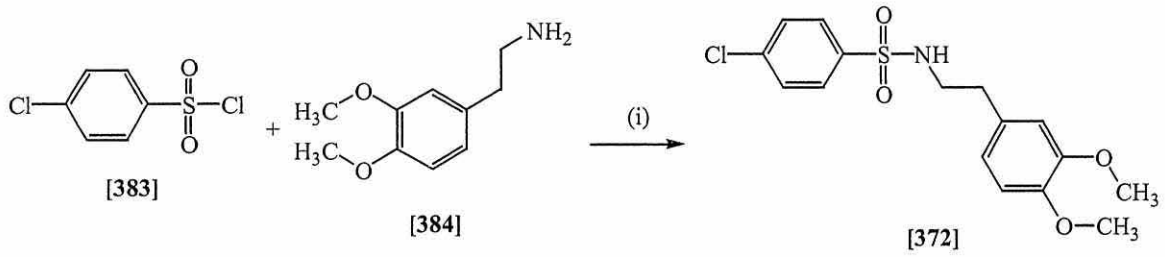
[372]

Figure 12. ^{1}H-NMR interpretation of the chemical shifts for compound **[372]**

Compound **[373]** was produced in 72 % yield and provided the best resolved proton spectrum of the series. The spectrum was similar to those obtained for compounds **[372]** and **[381]**, as these also contained the 2-(3,4-dimethoxyphenyl)ethylamine substructure.

5.2.2. Scavenger Resin Synthesis of (2-(3,4-Dimethoxyphenyl)ethyl)((4-chlorophenyl)sulfonyl)amine [372]

Sulfonamide synthesis was demonstrated in the previous reaction series by solution-phase methods involving the use of pyridine to drive the reactions to completion. It was decided to investigate an alternative route employing the use of a scavenger resin in a similar reaction. Commercially available poly(4-vinyl)pyridine scavenger resin in dichloromethane was expected to yield the same compounds by reaction of 4-chlorobenzene sulfonyl chloride **[383]** with 2-(3,4-dimethoxyphenyl)-ethylamine **[384]** (Scheme 81).

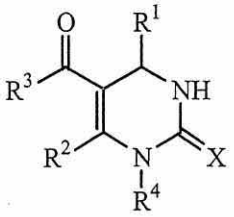


Scheme 81. (i) CH_2Cl_2, poly(4-vinyl)pyridine, 85 °C, 4 h.

The scavenger resin again produced an identical compound to **[372]** in 45 % yield, which was lower than the product from the solution-phase equivalent (56 %). Spectra correlated well, although the scavenger approach was only analysed by 60 MHz NMR; however further studies of this methodology were abandoned as solution-phase yields were greater and this method, although less hazardous, appeared to be of little benefit.

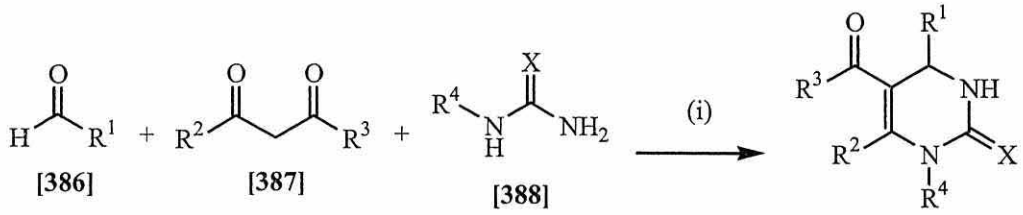
5.3. SYNTHETIC APPROACHES TO DIHYDROPYRIMIDINES

5.3.1. Solution-phase Dihydropyrimidin-one and -thione Synthesis



[385]

The Biginelli multicomponent condensation reaction has been known for more than 100 years and is discussed in more detail in Chapter 2 of this thesis.[59, 63-75] Essentially it is a multicomponent condensation that proceeds by acid catalysis. It was the aim of this section to produce a library of dihydropyrimidines that would possibly prove of medical benefit. Several aldehydes, acetoacetates and thioureas were reacted at 85 °C in methanol with hydrochloric acid to yield pyrimidines (Scheme 82).



[386] [387] [388] [385]

Scheme 82. (i) MeOH, c. HCl, 85 °C, 5 - 18 h.

The aldehyde **[386]** was dissolved in methanol and acetoacetate **[387]** and thiourea **[388]** were added and the reaction stirred. Hydrochloric acid (ca 5 drops) was then added and the reaction further stirred and heated to 85 °C for up to 18 hours, until a solid formed. Purification was commonly achieved by extraction in hot methanol (60 °C), followed by recrystallisation. Products **[389]** – **[397]** were obtained in moderate to good yield and deemed of sufficient purity after recrystallisation.

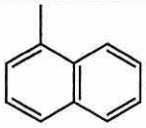
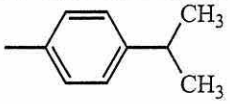
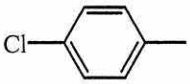
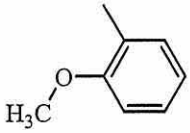
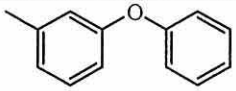
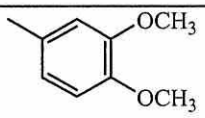
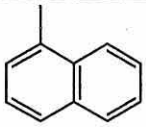
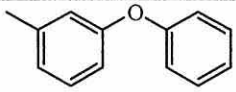
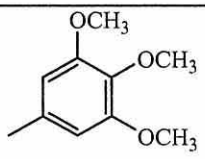
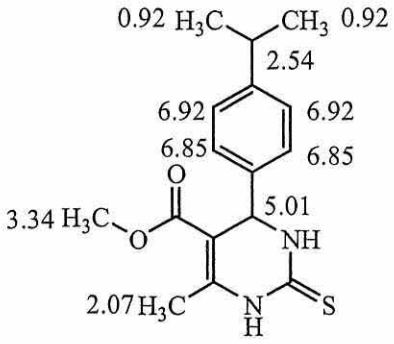
	R^1	R^2	R^3	R^4	X	Yield (%)
[389]		CH_3	OCH_2CH_3	H	S	26
[390]		CH_3	OCH_3	H	S	60
[391]		CH_3	OCH_3	H	S	43
[392]		CH_3	OCH_3	H	S	49
[393]		CH_3	OCH_3	H	S	23
[394]		CH_3	OCH_3	H	S	40
[395]		CH_3	OCH_3	H	S	45
[396]		CH_3	OCH_3	H	O	39
[397]		Ph	OCH_2CH_3	H	O	32

Table 4. Dihydropyrimidine Synthesis

FTIR was used to initially detect the NH stretch and, where contained, the carbonyl stretching frequency. The symmetric and asymmetric NH stretches occurred between ca. 3330 and 3230 cm^{-1} and 3200 and 3100 cm^{-1} and the NH bend at 1574 – 1596 cm^{-1} Characterisation by ^{1}H-NMR spectroscopy was sufficient to confirm product formation. The spectra clearly showed the presence of two broad NH singlets, usually between 10.5 and 8.5 ppm. Integrals for aromatic protons were accurate for all compounds. The CH proton on the pyrimidine core was evident between 5 and 6 ppm and occasionally

displayed a doublet, which can only be explained by the possibility of splitting by the neighbouring nitrogen proton; however this is inconclusive as this was not apparent in all spectra. ^{13}C-NMR was used to further confirm product formation and indeed the CO resonance was displayed at ca. 165 ppm. Compounds produced from thiourea showed strong peaks at ca. 174 ppm correlating to the C=S group. Figure 13 shows a representative example of the ^{1}H-NMR interpretation of compound **[390]**.



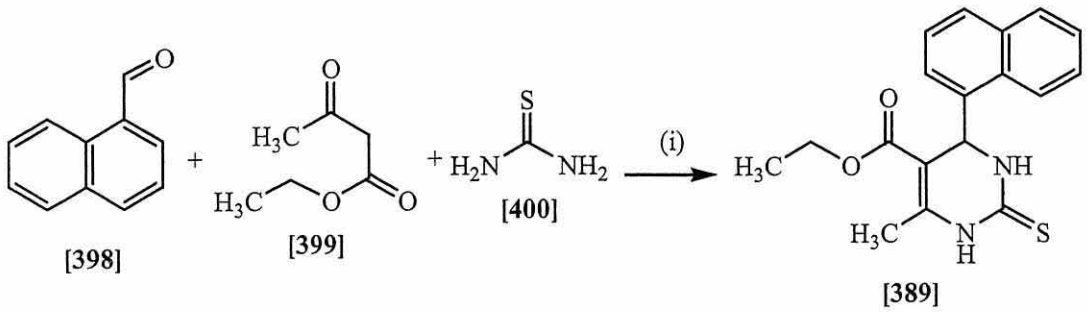
[390]

Figure 13. ^{1}H-NMR interpretation of the chemical shifts for compound **[390]**

Compound **[390]** was produced in the highest yield for this compound library (60 %). Characteristic signals were also observed in the ^{13}C-NMR spectra of this compound with CS and CO occurring at 174.5 and 166.0 respectively. Further elucidation was achieved by FTIR, which confirmed the NH stretching absorption band at 3184 cm^{-1} and the carbonyl stretch at 1706 cm^{-1}.

5.3.2. Attempted Synthesis of 6-Methyl-4-naphthalen-1-yl-2-thioxo-1,2,3,4-tetra-hydro-pyrimidine-5-carboxylic Acid Ethyl Ester [389]

It was decided to investigate a scavenger resin approach to dihydropyrimidine synthesis, again involving the use of poly(4-vinylpyridine) resin in hydrochloride form. 6-Methyl-4-naphthalen-1-yl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester **[389]** was selected from the previous reactions due to the poor yield obtained. Scheme 83 represents the scavenger resin approach to this compound.



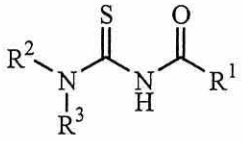
[398] [399] [400] [389]

Scheme 83. (i) MeOH, poly(4-vinylpyridine) hydrochloride, 85 °C, 8 h.

1-Naphthaldehdye **[398]** was dissolved in methanol and ethyl acetoacetate **[399]** and thiourea **[400]** were added and the reaction stirred. Poly(4-vinylpyridine) hydrochloride was then added and the reaction heated at 85 °C for 8 hours. A sticky residue formed that was difficult to remove from the resin. The beads were washed with copious quantities of solvents and the solutions concentrated *in vacuo*. An oil formed, which looked entirely different to the solid produced in the solution-phase reaction for **[389]**. Several attempts were made to purify the oil by chromatography and recrystallisation. Analysis of the oil by FTIR and ^{1}H-NMR gave no indication of the desired product formation and the methodology was abandoned.

5.4. THIOUREA CHEMISTRY

5.4.1. Derivative Synthesis



[401]

Thioureas have long been investigated for medical purposes, KF31327 (Figure 14) has demonstrated selective inhibitory activity against cGMP-specific phospho-diesterase (PDE V) and is therefore attractive in the treatment or relief of cardiovascular conditions such as thrombosis, angina pectoris and hypertension.[146] The synthesis of alternative thiourea derivatives is therefore of importance.

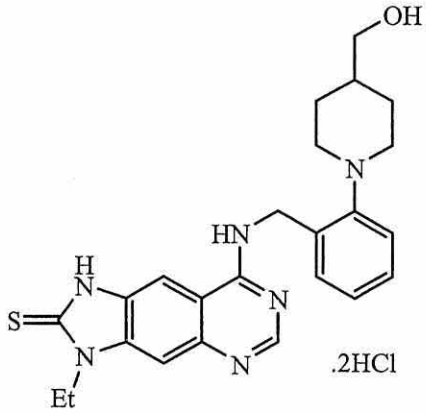
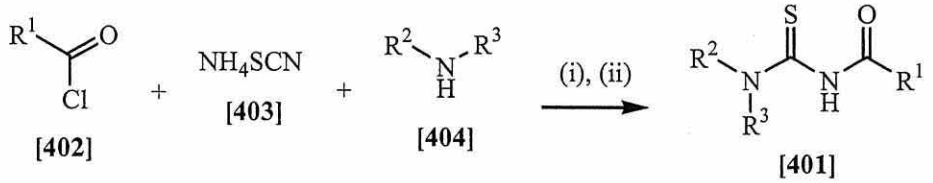


Figure 14. Structure of KF31327

Carbonyl chlorides **[402]** are renowned for their reactivity. The reaction of a series of carbonyl chlorides with ammonium thiocyanate **[403]** and an amine **[404]** produces the title compounds (Schemes 84).



Scheme 84. (i) Acetone, r.t. 1 h.; (ii) 85 °C, 30 min.

A small library of thiourea derivatives **[405] - [411]** was successfully synthesised *via* the method outlined above. The results are depicted in the following table (Table 5).

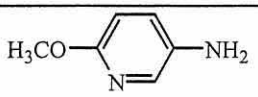
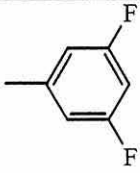
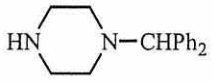
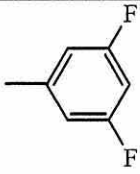
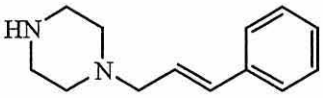
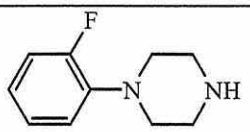
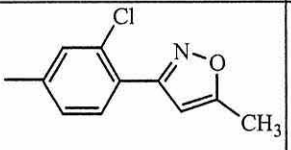
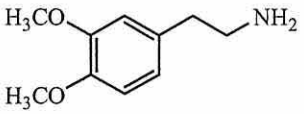
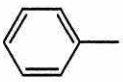
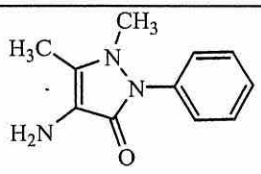
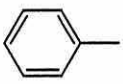
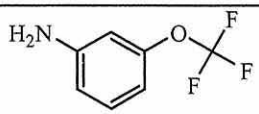
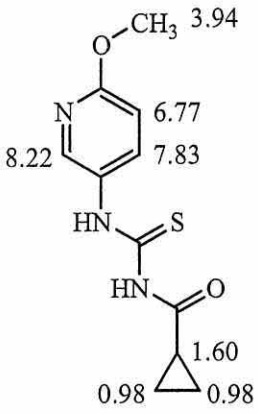
	R^1	R^2, R^3 N H **[405]**	**Yield (%)**
[405]			60
[406]			24
[407]			35
[408]			32
[409]			38
[410]			47
[411]			59

Table 5. Thiourea Derivatives

Products **[405] - [411]** were synthesised in moderate to good yield in all cases. Product confirmation was achieved by FTIR and ^{1}H-NMR spectroscopy. The FTIR spectra showed a wide variability as a result of the different R groups within the products. The NH stretching bands fell in the range of 3420 to 3176 cm^{-1} and the NH bend between 1584 and 1516 cm^{-1}. The =C-H stretch occurred at approximately 3020 cm^{-1} for all products. The carbonyl band also showed wide variability, ranging from 1694 to

1647 cm^{-1}. The ^{1}H-NMR spectra confirmed the presence of the NH group, in most cases occurring between 12 and 8 ppm. Further confirmation was achieved by ^{13}C-NMR, which clarified C=S and C=O groups at ca. 180 ppm and 160 ppm, respectively. A representative interpretation of the ^{1}H-NMR of compound **[405]** is depicted in the following Figure.

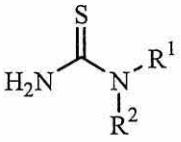


[405]

Figure 15. ^{1}H-NMR interpretation of the chemical shifts of compound **[405]**

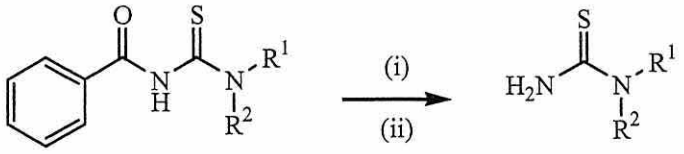
Optimum yields were obtained for this particular example of urea synthesis with compound **[405]** produced in 60 % yield. ^{13}C-NMR gave further confirmation of product formation with signals at 179.5 and 175.1 correlating to CS and CO, respectively. The carbonyl was confirmed at the 1683 cm^{-1} and NH stretch and bending absorptions occurred at 3177 and 1534 cm^{-1}.

5.4.2. Preparation of Thioureas from Derivatives



[412]

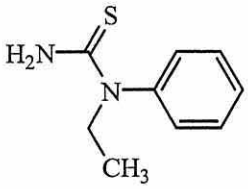
The previous reaction was of interest due to the potential medical / biological benefit of compounds containing the thiourea structure. It was decided to investigate methods for preparing thioureas that could be used in other syntheses, such as the Biginelli reaction. The method outlined below involves the cleavage of the benzoyl group from the thiourea derivative (Scheme 85).



[413] [412]

Scheme 85. (i) Potassium hydroxide, water; (ii) MeOH, reflux, 4 h.

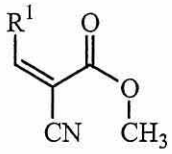
Synthetically the preparation of thioureas by this method would appear straightforward; however, product purification was exceptionally difficult to achieve and only compound **[414]**, depicted below, was successfully prepared by this method in satisfactory purity.



[414]

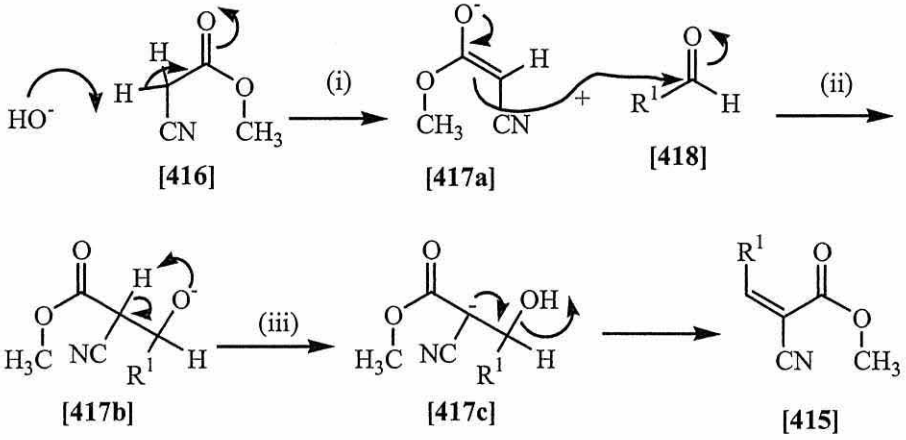
The compound was pure by CHN microanalysis. Analysis by FTIR showed the lack of a C=O from the benzoyl group and a broad NH stretch from the NH_2 group was obvious at 3166 cm^{-1}. ^{1}H-NMR also confirmed the formation of thiourea by the presence of a broad NH_2 peak, integrating to 2 protons at 5.59 ppm. The presence of the ethyl group was confirmed by the two resonances at 4.18 (2H, q, J = 7.3 Hz, CH_2CH_3), 1.19 (3H, t, J = 7.3 Hz, CH_3CH_2). ^{13}C-NMR indicated the CS group at 181.6.

5.5. PREPARATION OF CYANO ACRYLIC ACID METHYL ESTERS



[415]

The final example of library synthesis within this thesis aimed to produce an array of cyano methyl acrylic esters **[415]**. Such structures were synthesised for potential use in further synthesis, as they are highly reactive species. Scheme 86 depicts this Knoevenagel method of synthesis.



Scheme 86. (i) MeOH, NaOAc, reflux, 3 h.

A small library of compounds **[419]** – **[425]** was synthesised. Table 6 shows the results obtained.

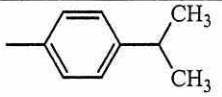
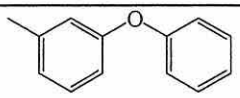
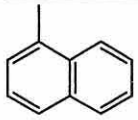
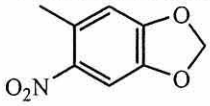
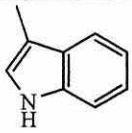
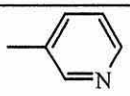
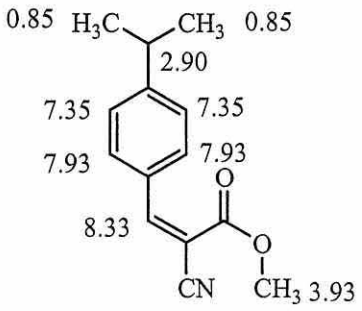
	R^1	Yield (%)
[419]		60
[420]		66
[421]		62
[422]		53
[423]		42
[424]		83
[425]		74

Table 6. Cyano acrylic acid methyl esters

Compounds were obtained in good yield and reasonable purity in most cases; however, improved methods of purification require investigation, as the carbon content by CHN, in some cases, was significantly higher than expected.

FTIR analysis was particularly useful for this range of compound as two strong vibrational modes should be clearly visible in spectra. Indeed the carbonyl group was apparent in all molecules at ca. 1700 – 1740 cm^{-1}, raised by its proximity to the methyl ester. The C≡N group occurred, as expected, between 2230 and 2200 cm^{-1}. ^{1}H-NMR also gave some correlation, particularly for the OCH_3 group, which was found between 2.9 and 3.8 ppm as a singlet. Compound **[419]** was analysed by ^{13}C-NMR, which gave probable indication of the presence of carbonyl (163.3 ppm) and nitrile (115.8 ppm) within the compound. A representative interpretation of the ^{1}H-NMR spectra of compound **[419]** is illustrated in the following Figure.



[419]

Figure 16. ^{1}H-NMR interpretation of the chemical shifts for compound **[419]**

Compound **[419]** was synthesised in a good yield of 60 %. The product was elucidated further by ^{13}C-NMR analysis, which clearly showed a CO signal at 163.3 ppm and a CN signal at 115.8 ppm. The absorptions of these two functionalities were also clearly visible by FTIR spectroscopy with the nitrile at 2225 cm^{-1} and the carbonyl at 1742cm^{-1}.

5.6. CONCLUSIONS AND FURTHER WORK

Solution-phase methods were successfully used to synthesise five libraries of compounds, including ureas and thioureas, sulfonamides, dihydropyrimidines and cyano acrylic acid methyl esters. In most examples the products were obtained in moderate to good yield and good purity and many had been previously unreported in the literature. The results from the biological screening of these compounds are still awaited.

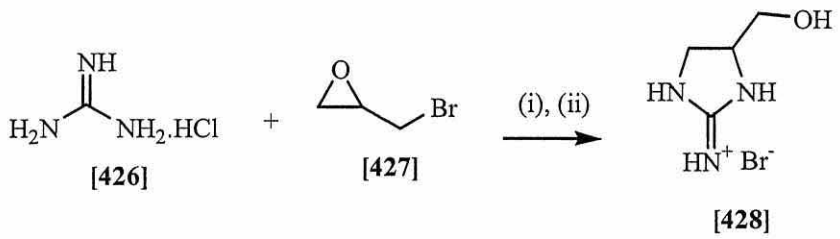
The synthesis of urea derivatives was attempted by solid and solution-phase methods, both to good effect. The solution-phase method adopting chlorophenyl isocyanate in the production of **[360]** proceeded with a 30 % increase in yield compared to the solid-phase equivalent. Interestingly, however, the similar approach involving phenyl isocyanate produced **[363]** in 82 % yield. The surprisingly good yield suggests potential for this solid-phase approach in future synthesis. This procedure may be adopted in the future in low yielding reactions in solution-phase or on reactions that have failed by other methods.

Interestingly the production of a novel thiourea **[414]** in section 5.4.2 could provide much potential in further synthetic approaches. The Biginelli multicomponent condensation reaction was highlighted earlier (Chapter 2) in the production of dihydropyrimidines that have shown potential as calcium channel blockers. **[414]** and other new ureas and thioureas could be applied to the Biginelli reaction to produce a larger library of dihydropyrimidines, with the potential of producing a better calcium channel blocker or prove to be of some pharmaceutical benefit.

CHAPTER 6 - GUANIDINE SYNTHESIS

6.1. AIMS & BACKGROUND

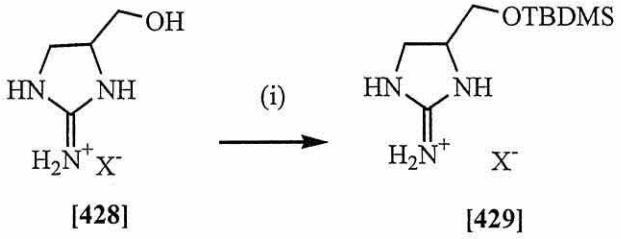
Previous work by Thornhill focussed on epoxide ring opening reactions using guanidine to produce monocyclic guanidines, which are related structures to known glycosidase inhibitors.[97] His research was directed towards identifying the mechanism and scope of these reactions. For example, he found that the reaction of guanidine with *epi*-bromohydrin led to the 5-exo-cyclised product **[428]** (Scheme 87).



Scheme 87. (i) ^{t}BuOH, 16 h, r.t.; (ii) KO^{t}Bu, 60 °C, 24 h.

Thornhill reported that monocyclic guanidines **[428]** were readily synthesised by this approach, however, he found that purification of these highly polar materials was problematic and led to low yields.[97] We wished to investigate alternative methods of purifying these compounds *via* the following routes:

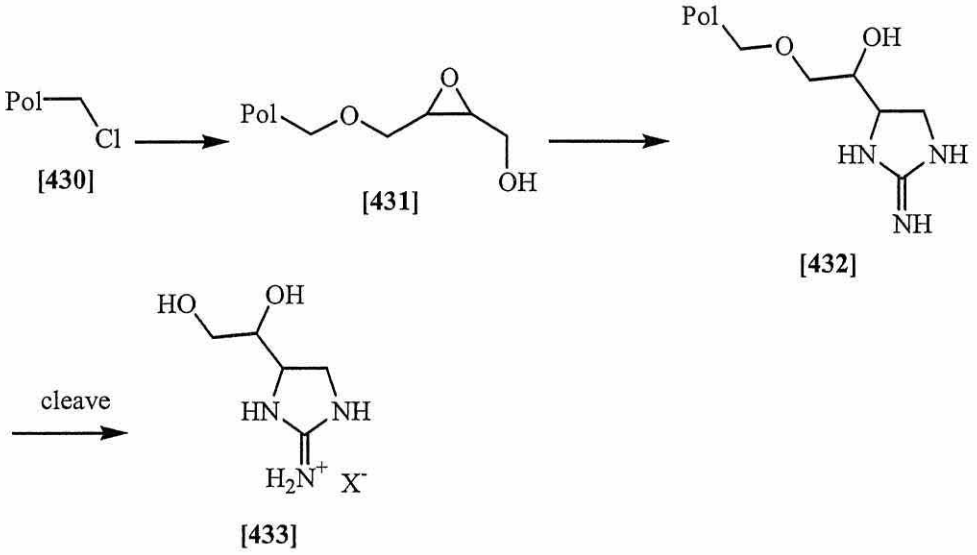
1) Silylation. The silyl ether has become one of the most commonly used alcohol protecting group in organic synthesis due to its ease of formation and the selectivity with which it can be removed. The purification of the five-membered cyclic salts **[429]** had proven disappointing by silylation with *tert*-butyldimethylsilyl chloride in DMF with a catalytic amount of imidazole, producing the desired product **[429]** however only in 10 % yield (Scheme 88).[97]



Scheme 88. (i) dry DMF, 0 °C, imidazole, ^{t}BDMSCl, 0 °C – r.t., overnight.

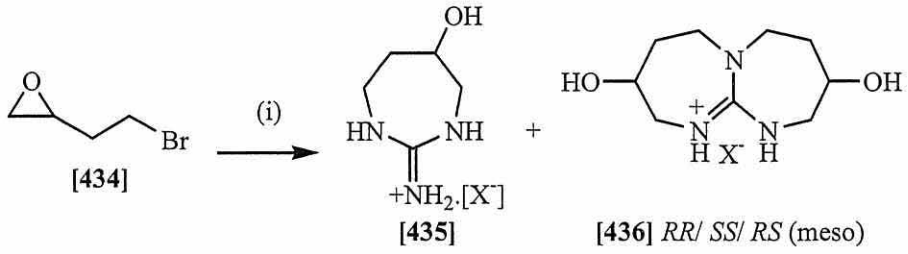
It was intended to investigate methods of improving this yield by firstly repeating this work and varying the stoichiometry of the reagents and also by using alternative silyl protecting groups.

2) Solid-Phase Synthesis. Guanidine synthesis has been exemplified over recent years in solid-phase synthetic approaches. [119-128] The production of the five-membered cyclic *via* combinatorial methodology would be investigated with the aim of improving the purity of the desired product, outlined by the following Scheme.



Scheme 89. Summarised Solid-Phase Approach to Cyclic Guanidines

3) The third aim of the guanidine related research also stemmed from previous findings of Thornhill.[97] He attempted to produce the 6-membered derivative of the guanidino sugar; however his results showed that the equivalent reaction led to the formation of the 7-membered guanidino monocycle **[435]**. Small amounts of dimeric materials were also present as observed by NMR spectroscopy. These were later found to comprise of both racemic *RR* and *SS* dimers and the *RS* meso dimer **[436]** products (Scheme 90).



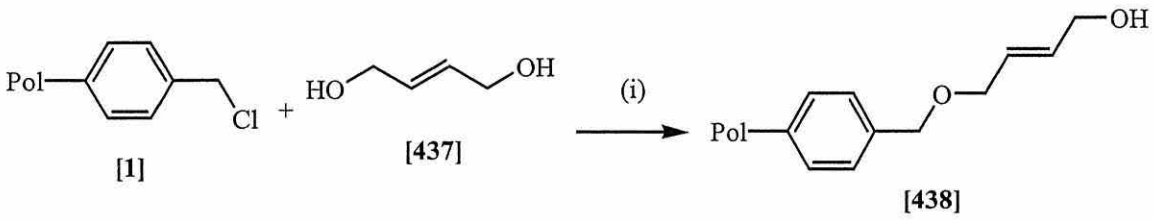
Scheme 90. (i) (a) ^{t}BuOH, guanidine, ^{t}BuOH, r.t., 36 h, (b) KO^{t}Bu, 60 °C, 96 h.

The goal was to attempt to bias the reaction outlined above to produce more of the dimeric product, which would open avenues in the production of C_2-symmetric chiral guanidines.

6.2. SOLID-PHASE SYNTHESIS

6.2.1. Merrifield Linkage Approach

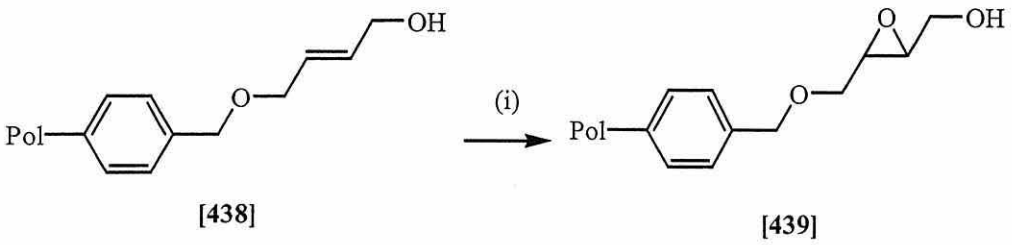
In order to prepare a resin bound guanidine it was first necessary to modify a commercially available combinatorial resin that could be modified and subjected to similar reaction conditions to the equivalent solution-phase methods. The binding of alcohols to Merrifield resin **[1]** was achieved successfully in the solid-phase synthesis section of this thesis (Chapter 4) and to good effect in the literature (Chapter 2). 2-Butene-1,4-diol was chosen as the alcohol as it could be further converted to an epoxide.



Scheme 91. (i) NaH, THF, 0 °C – r.t., overnight

The resin **[1]** was pre-swollen in tetrahydrofuran and added to a suspension of sodium hydride (petrol washed, THF suspension) and 2-butene-1,4-diol **[437]**. The reaction was stirred at room temperature overnight, after which time the resin **[438]** was washed with copious amounts of solvent and dried *in vacuo*. Infrared analysis clarified the presence of the desired alcohol functionality at 3500 cm^{-1} and could also suggest the presence of an asymmetric alkene C=C stretch at 1600 cm^{-1}, although this is more likely to be the polystyrene base resin stretch. A strong absorption at 1263 cm^{-1} correlates with a C-O stretch, either due to the COC or COH groups, present within this molecule. The reaction was deemed successful and the product subjected to further reactions.

The second stage of this sequence is the epoxidation of resin **[438]**, which was achieved by using *m*-chloroperoxybenzoic acid (*m*CPBA) which had been used in the previous solution-phase chemistry (Scheme 92).

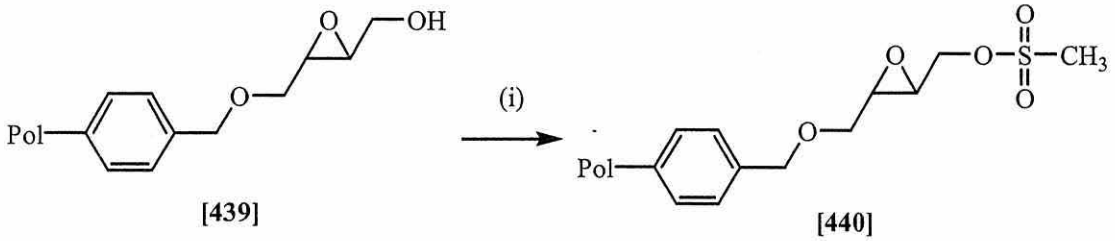


[438] [439]

Scheme 92. (i) *m*CPBA, CH_2Cl_2, 0 °C – r.t., overnight.

The reaction appeared to be a success on analysis of the FTIR of product **[439]**, however the presence of epoxide on a polymer bound substrate could not be determined definitively by IR analysis, or by other techniques. A broad OH stretch was present at 3423 cm^{-1} and the C=C band had almost disappeared, suggesting complete conversion of alkene to epoxide. It was hoped that subsequent reactions would confirm the structures of the polymeric intermediates.

The next stage in the synthesis was the conversion of alcohol **[439]** into the mesylate **[440]** which was chosen as a suitable leaving group as it gave good results in the related solution-phase chemistry. Thus the resin **[439]** was pre-swollen in dichloromethane and treated with methanesulfonyl chloride in the presence of triethylamine to give the desired mesylate **[440]** (Scheme 93).



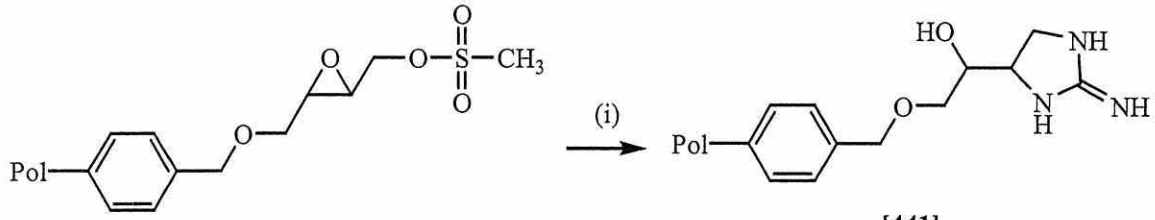
[439] [440]

Scheme 93. (i) Methanesulfonylchloride, NEt_3, CH_2Cl_2, 0 °C – r.t., overnight.

The difficulties in confirming the presence of the product **[440]** were again exemplified by the use of FTIR, however the sulfonate appeared to be present as indicated by bands at 1350 and 1150 cm^{-1} in the FTIR spectrum of the resin. This was deemed to be sufficient evidence for the presence of the product and it was hoped that final structural proof would be demonstrated at the end of the synthesis.

With the resin **[440]** in hand we were in a position to attempt the guanidine cyclization which would yield heterocycle **[441]**. Thus the polymer **[440]** was swollen in ^tBuOH,

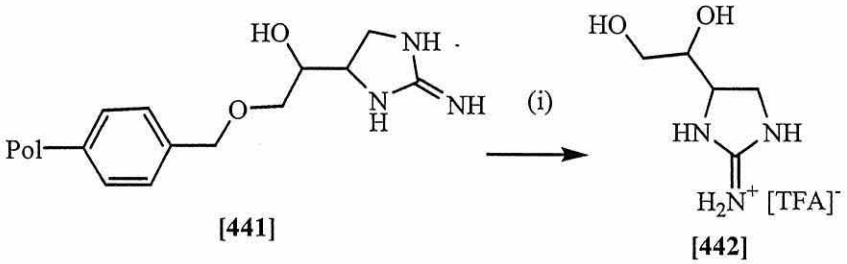
following which, a pre-prepared solution of guanidine was added and the mixture stirred at room temperature for 18 hours. The resultant mixture was treated with 1.75 eq of KO^{t}Bu and further heated to 60 °C overnight. The resin was collected by filtration, washed and dried *in vacuo*.



Scheme 94. (i) ^{t}BuOH, guanidine in ^{t}BuOH, KO^{t}Bu, 18 h, r.t.

IR analysis of the product gave a broad band at 3420 cm^{-1}, which suggested the presence of an alcohol (broad) and possibly an NH, which could indicate the formation of **[441]**. Further elucidation was required, therefore attention was focussed towards the cleavage of the product from the resin.

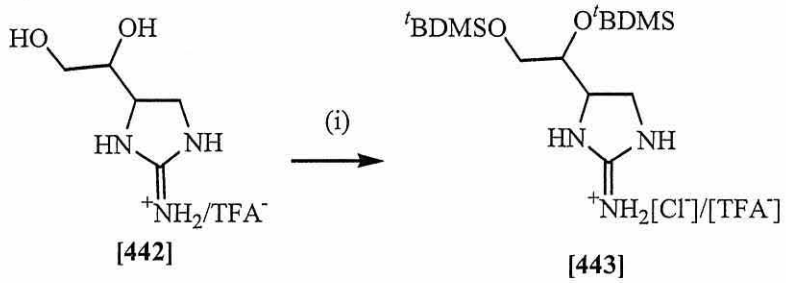
Previous solution-phase chemistry had shown that similar cyclic guanidines to the expected product **[442]** are stable to concentrated trifluoroacetic acid. Sample resin **[441]** was treated with a 20% solution of trifluoroacetic acid in CH_2Cl_2 for 18 hours and the crude product isolated by filtration from the resin.



Scheme 95. (i) Trifluoroacetic acid, CH_2Cl_2, r.t., 18 h.

Analysis of the crude product by ^{1}H-NMR was not promising as the spectrum was complex and TLC analysis indicated the presence of several highly polar compounds. In an attempt to simplify the purification purify this product a similar approach to that of Thornhill was adopted by attempting to convert the product into the corresponding the silylated derivative **[443]**, which should be less polar than **[442]** (Scheme 96).[97] Thus

the guanidine salt **[442]** was silylated with ^{t}BDMSCl and imidazole in DMF for 18 hours.



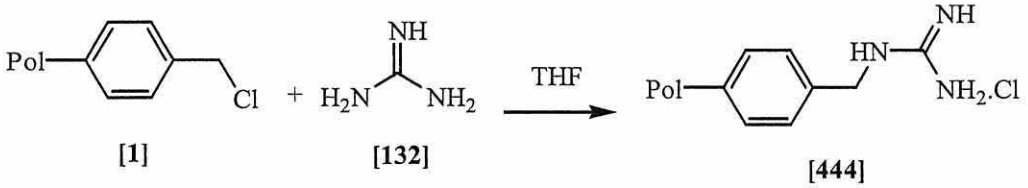
[442] **[443]**

Scheme 96. (i) ^{t}BDMSCl, DMF, imidazole, 0 °C – r.t., 18 h.

The guanidine salt **[442]** was thus dissolved in DMF and cooled to 0 °C, after which time a solution of ^{t}BDMSCl and imidazole in DMF were added. The reaction was allowed to warm to room temperature and stirred in an inert atmosphere overnight. After work-up and drying 80 mg of product was obtained. After ion exchange and work up a low polarity product was obtained. Upon analysis of ^{1}H-NMR the reaction was deemed unsuccessful when compared to similar products produced by solution-phase methods and it was apparent that silylation had therefore not occurred, as none of the characteristic ^{t}BDM signals were apparent and this approach was abandoned.

6.2.2. Solid-phase Guanidinium Linkage Route

The failure of the previous synthetic route, led to the reappraisal of initial methodology and the investigation of a different strategy. The previous route involved binding the epoxide to a solid-support and reacting this with guanidine, the new approach was to reverse this situation and attach the guanidine moiety to the resin.



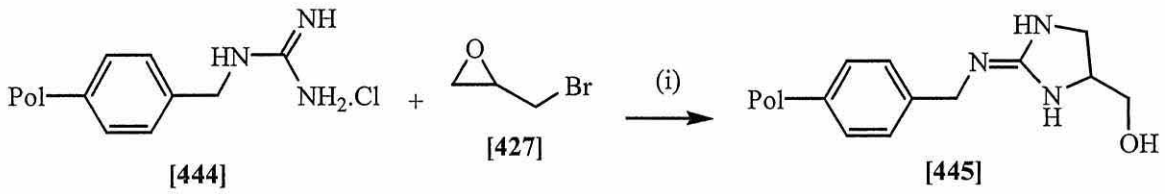
[1] **[132]** **[444]**

Scheme 97. Production of guanidine bound resin.

A sample of Merrifield resin **[1]** was thus pre-swollen in THF and a solution of guanidine **[132]** in THF added. The reaction was heated to 60 °C overnight, cooled and the resin collected by filtration, washed and dried *in vacuo*.

Analysis of the product **[444]** by FTIR proved promising, showing the presence of a broad band at 3400 cm^{-1}, which was assigned as NH stretching, a band at 1597 cm^{-1} which was attributed to the C=N stretch in the guanidine.

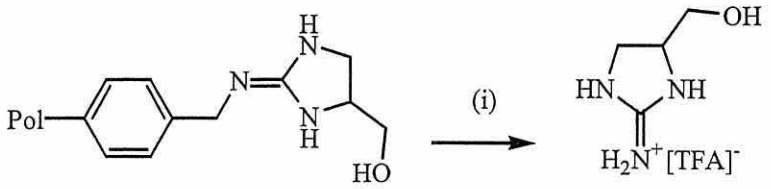
With this polymer in hand, the next step was to investigate its reaction with *epi*-bromohydrin **[427]** using similar conditions to those developed for the solution-phase chemistry (Scheme 98).



[444] **[427]** **[445]**

Scheme 98. (i) KO^{t}Bu, ^{t}BuOH, r.t., 18hr; (ii) **[429]**, r.t., 18 hr; (iii) KO^{t}Bu, 60 °C, 18 h.

Thus potassium *tert*-butoxide was added to a stirred suspension of **[444]** in THF followed by the addition of a slight excess of *epi*-bromohydrin **[427]**. After stirring for 18 hours overnight at room temperature, a further portion of KO^{t}Bu was added and the reaction heated to 60 °C and stirred overnight. At this point the reaction was cooled and the resin collected by filtration, followed by washing and drying *in vacuo*. On analysis of the polymer by FTIR it was difficult to say conclusively that any reaction had occurred. The spectrum obtained for the product was not significantly different to the original spectra for the bound guanidine derivative **[444]**. It was decided to attempt to cleave the product from the resin in an effort to determine if the synthesis had indeed worked.



[445] **[446]**

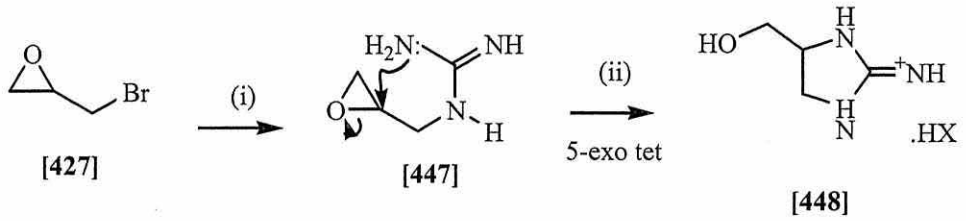
Scheme 99. (i) Trifluoroacetic acid, CH_2Cl_2, reflux, 8 h.

The product was then treated with a solution of trifluoroacetic acid in dichloromethane and stirred for 8 hours. After work up only a small quantity of material was obtained which, on analysis by ^{1}H-NMR, was show to be a complex mixture which did not have any of the signals expected for the product.

6.3. APPROACHES TO IMPROVING THE PURIFICATION OF 5-MEMBERED GUANIDINO SUGARS

6.3.1. Preparation of (2-Iminoimidazolidin-4-yl)methanol Salts

Previous work by Thornhill demonstrated a methodology for the preparation of guanidine heterocycles by the intramolecular nucleophilic ring opening of epoxides by guanidine.[97] For example the guanidinium salt **[448]** was readily prepared using this methodology (Scheme 100).



[427] **[447]** **[448]**

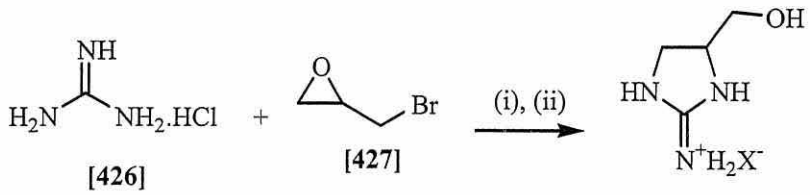
Scheme 100. (i) **[426]**, ^{t}BuOH, 5 °C, KO^{t}Bu, 30 min, **[434]**, RT, 18 h; (ii) KO^{t}Bu, 60 °C, 24 h.

This work also investigated the mechanism of the reaction as potentially both the 6-endo-tet and 5-exo-tet cyclization products may have been produced, despite the fact that the 6-endo reaction is disfavoured.[97] The studies clearly demonstrated that the 5-membered product was formed exclusively as shown by extensive ^{1}H-NMR studies.

The aim of investigating this reaction was to attempt to determine a method of purification of the products obtained, as previous work has been problematic in this respect.

Synthetically the route is identical to the previous method such that guanidine hydrochloride was suspended in ^{t}BuOH and cooled (5°C) whereupon potassium tert-butoxide was added and the reaction stirred for 30 minutes. Following this *epi*-bromohydrin was added and the mixture allowed to warm to room temperature and stirred overnight. A further portion of KO^{t}Bu was added to deprotonate the guanidinium salts formed in the first step and the reaction was then heated to 60 °C for 16 hours. Several methods of work up were investigated in order to establish what effects they would have and which would give both optimum yields and the highest purity.

The reaction work-up results in the formation of a range of inorganic salts, which are difficult to remove from the product. We thus added a range of acids to the reaction on work up to investigate which would give the most readily purified organic product (Table 7).



Scheme 101. (i) ^{t}BuOH, KO^{t}Bu, 18 hrs RT; (ii) KO^{t}Bu, 60 °C, 18 h; (iii) work up (see Table 7)

	Guanidine HCl eq	**KO^{t}Bu**	**Work up Method**	**Chromatography**	**Yield (%)**
1	1.2	2	Removal of ^{t}BuOH *in vacuo*, addition of MeOH (20 ml) and glacial acetic acid (0.84 ml, 14.6 mmol, 2 eq) in MeOH (10 ml). Sodium acetate (5.99 g, 73 mmol, 10 eq) added, stirred RT 1 hr.	Due to the large quantities of material obtained from this reaction and the number of visible spots of similar Rf, purification was not carried out or proceeded further.	30 %
2	1.2	1.1 x 2	Methanolic HCl (1 ml Acetyl chloride: 9 ml dry MeOH) was added at 0 °C, stirred for 10 minutes, solvent removed *in vacuo*.	Dry loading: 100% $CHCl_3$, 5% MeOH: $CHCl_3$, 10%, 15%, 20%, 25%, 30%, 50%, 70%, 100% MeOH.	42 %
3	1.2	1.1 x 2	Methanolic HBr (1 ml Acetyl bromide: 9 ml dry MeOH) was added at 0 °C, stirred for 10 minutes, solvent removed *in vacuo*.	Dry loading: 100% $CHCl_3$, 2% MeOH: $CHCl_3$, 5%, 10%, 20%, 30%, 40%, 50%, 70%, 100% MeOH.	impure
4	1.2	1.1 x 2	Methanolic TFA (5 ml Trifluoroacetic acid: 15 ml dry MeOH) was added at 0 °C, stirred for 10 minutes, solvent removed *in vacuo*.	Dry loading: 100% Et_2O, 100% $CHCl_3$, 5% MeOH: $CHCl_3$, 10%, 20%, 25%, 30%, 50%, 70%, 100% MeOH.	44 %

Table 7.

The work-up with methanolic HCl gave a product which could be purified by column chromatography in chloroform/methanol (eluting in 20% MeOH in $CHCl_3$). On analysis of the product by ^{1}H- and ^{13}C-NMR it was apparent that considerable amounts of impurities were present in the product even after repeated chromatography. A similar situation was found when methanolic HBr was employed in the work-up, this method also led to a considerably lower yield of product.

By far the best method of work-up was found to be that in which methanolic TFA was employed. This gave a salt which was easily separated from inorganic by-products by chromatography (eluting in 30 - 100% MeOH in $CHCl_3$) and was obtained in 44% yield with greater than 90 % purity.

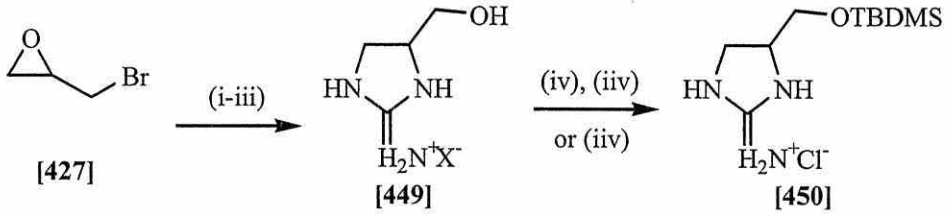
The purified compound was analysed by FTIR, which gave a broad OH peak at 3352 cm^{-1} and a C=N stretch at 1552 cm^{-1}. Analysis of ^{1}H-NMR spectra found 5 separate signals, which would suggest an ABX coupling pattern expected for the product. Signals were found at 4.30 (1H, m, C*H*), 3.93 (1H, br t, J = 10.1 Hz, CH*H*), 3.84 (1H, dd, J = 4.2, 12.1 Hz, CH*H*) 3.77 (1H, dd, J = 5.2, 10.1 Hz, CH*H*) and 3.73 (1H, dd, J = 6.1, 12.1 CH*H*). The ^{13}C-NMR spectrum of **[449]** gave signals at 45.73 (CH_2), 57.7 (CH_2), 63.48 (CH) and 158.77 (C) which were in agreement with the literature values.[96] Finally, high-resolution MS gave a mass of 116.0825 daltons which is in close agreement with the expected value of 116.0824 daltons.

The successful development of a suitable work up procedure will enable the preparation of multi-gram quantities of **[449]** and related guanidines; however the problem of final purification of these materials still remains.

6.3.2. Silylation of (2-Iminoimidazolidin-4-yl)methanol Salts

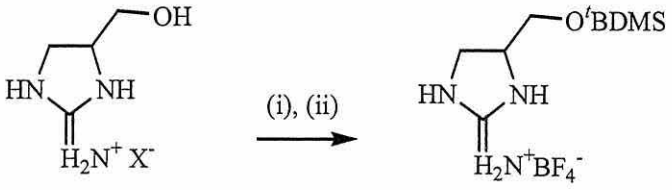
As noted the product **[449]** was found to contain trace impurities, which may arise from the presence of mixed counter-ions resulting from work-up. A strategy previously employed by Thornhill [97] was to make a derivative, which will be less polar and easier to purify. Additionally the preparation of a derivative, which is soluble in common organic solvents, is obviously advantageous and enables the multiple counter-ions to be exchanged to a single ion, which removes ambiguity.

Previous attempts had employed silyl-protecting groups, which had shown some success and two general approaches were used. Either the silylation process was applied to the crude reaction product **[449]** before column chromatography or the reaction product was semi-purified by chromatography before silylation was attempted. Both methods gave the required silylated derivative **[450]** when ^{t}BDMSCl was utilised, however the yields were low and the purification was again surprisingly difficult (Scheme 102).



Scheme 102. (i) ^{t}BuOH, guanidine, ^{t}BuOH, stir 36 h, RT; (ii) KO^{t}Bu, 60 °C, 96 h; (iii) (a) 0 °C, MeOH, TFA, stir 5 min; (b) 0 °C, Methanolic HCl, stir 5 min; (iv) column chromatography; (iiv) dry DMF, 0°C, imidazole, ^{t}BDMSCl, 0°C – RT, overnight.

It was decided to repeat this work to establish the reproducibility of the results using the purified guanidinium trifluoroacetate **[449]**. Thus **[449]** was treated with tert-butyldimethylsilyl chloride in the presence of imidazole in DMF, followed by an aqueous work up and to give the silylated derivative **[450]** which was ion-exchanged by stirring with a solution of sodium tetrafluoroborate. (Scheme 103).



[449] **[450]**

Scheme 103. (i) dry DMF, 0 °C, imidazole, ^{t}BDMSCl, 0 °C – RT, overnight; (ii) $CHCl_2$, sat. $NaBF_4$ solution, RT, 18 h.

	Silylating agent (eq.)	Reagents (eq.)	Work up Method	Chromatography	Yield (%)
1	^{t}BDMSCl (5 eq.)	imidazole (5 eq.) DMF, Et^iPr_2N (1 eq), DMAP (0.1 eq).	Water added and product extracted into EtOAc, washed with aq. Bromide, H_2O and brine. Dried over $MgSO_4$ and concentrated *in vacuo*. Cation exchange with $NaBF_4$.	Dry loading: 100% $CHCl_3$, 2% MeOH: $CHCl_3$, 2.5%, 3%, 4%, 4.5%, 5%, 25%, 50%, 100% MeOH.	5 %
2	^{t}BDMSCl (1.5 eq.)	Imidazole (2 eq.) DMF	Product diluted in EtOAc, washed with H_2O, brine, H_2O. Aq layers back extracted in $CHCl_3$. Cation exchange with $NaBF_4$.	Columned twice, both dry loading. 1. 100% $CHCl_3$, 2% MeOH:$CHCl_3$, 4%, 6%, 7%, 8%, 10%, 20%, 100% MeOH. 2. 100% Et_2O, 100% $CHCl_3$, 0.5% MeOH: $CHCl_3$, 20%.	5 %
3	^{t}BDMSCl (1.5 eq.)	Imidazole (2 eq.) DMF	Product diluted with EtOAc, washed with H_2O, brine, lithium bromide, dried over $MgSO_4$, concentrated *in vacuo*. Cation exchange with $NaBF_4$. Dried over $MgSO_4$, concentrated *in vacuo*.	Dry loading: 100 % $CHCl_3$, 2 % MeOH: $CHCl_3$, 4 %, 6 %, 8 %, 10 %, 20 %, 100 % MeOH.	33 %

Table 8.

In the first attempt (entry 1), an excess of silylating agent was employed in an attempt to ensure complete reaction of the substrate. This gave a good crude yield of chloroform soluble product which was purified by chromatography on silica gel which gave a diminished yield of **[450]**; the reason for this low yield was not readily apparent.

The second attempt (entry 2) again gave a good crude yield of the product, but on purification by column chromatography several impurities were found to be present, therefore repeated chromatography was attempted. This unfortunately led to the formation of a very pure product but in very low yield. On repeating the method in entry 2, a good crude yield of the product was obtained and it was subjected to a modified chromatography protocol (entry 3). This method allowed the desired product **[450]** to be prepared in a moderate 33 % yield and high purity (>95% by NMR).

Confirmation of the structure of **[450]** was given from the spectroscopic data. FTIR gave a broad alcohol stretch at ca. 3300 cm^{-1} whilst the ^{1}H-NMR spectrum had signals at 0.0 and 0.8 ppm corresponding to the silyl protecting group with corresponding signals at -5.52 and 25.69 in the signals for the ^{13}C-NMR spectrum. High resolution MS gave a mass at 230.1687, which corresponds well with the expected mass of 230.1689.

Despite a more rigorous approach to purification in this work, the yields obtained and the purity of the product were still low. It was thus concluded that the silyl protecting group was being cleaved from the molecule during chromatography and a mechanism was proposed in which the adjacent guanidine is involved in an anchimeric manner (Figure 17).

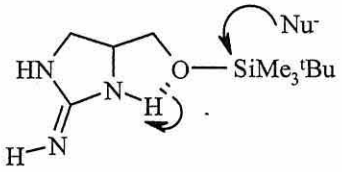
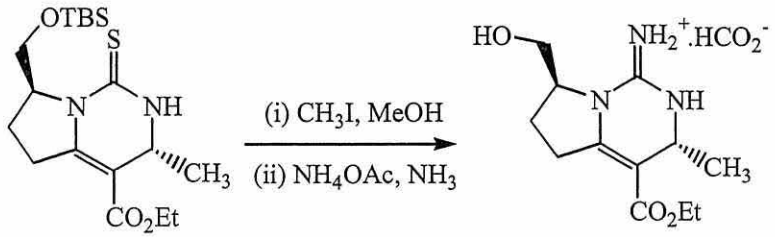


Figure 17. Deprotection of Cyclic Guanidine.

This mechanism might explain the difficulties experienced in obtaining the silylated product and support for it was found in a publication by Elliott and Long, where a similar deprotection is observed. They describe the cleavage of an OTBS ether during guanylation of the thiourea **[451]** to give **[452]**.[148]



[451] [452]

Scheme 104. Silyl deprotection of alcohol

They proposed a similar intermediate **[453]** in which the guanidine is involved in the cleavage of the protecting group (Figure 18).

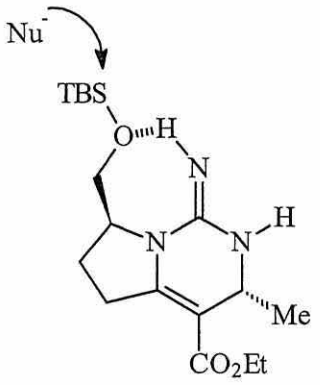
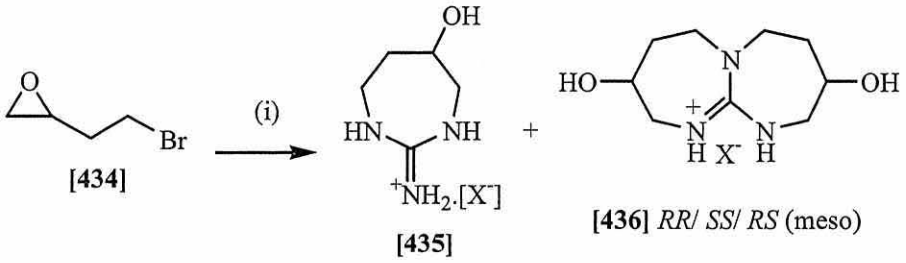


Figure 18. Silylated intermediate **[453]**

As a result of this work, it was decided to abandon this approach on improving the purification of such guanidine compounds *via* a silylation method, as these groups are too labile. Investigation into improving the purity of cyclic guanidine compounds in the future would rely on chromatography.

6.4. PREPARATION OF SEVEN MEMBERED AND BICYCLIC GUANIDINES

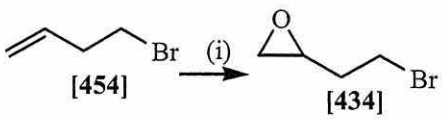
Following the investigations into the synthesis of the 5-membered cyclic guanidines by ring opening of epoxides, it was decided to investigate the formation of larger guanidine containing heterocycles. A preliminary investigation had already been performed in which the bromo epoxide **[434]** was reacted with guanidine under identical conditions to those previously reported for the 5-membered system. Interestingly this reaction led to the formation of two products identified as the monocyclic 7-membered guanidine **[435]** and a bicyclic compound **[436]** which was composed of the enantiomeric *RR/SS* and the meso-(*RS*)-heterocycles (Scheme 105).[97]



Scheme 105. (i) (a) ^{t}BuOH, guanidine HCl, ^{t}BuOH, 5 °C – RT, 18 h.
(b) KO^{t}Bu, RT, 24 h.

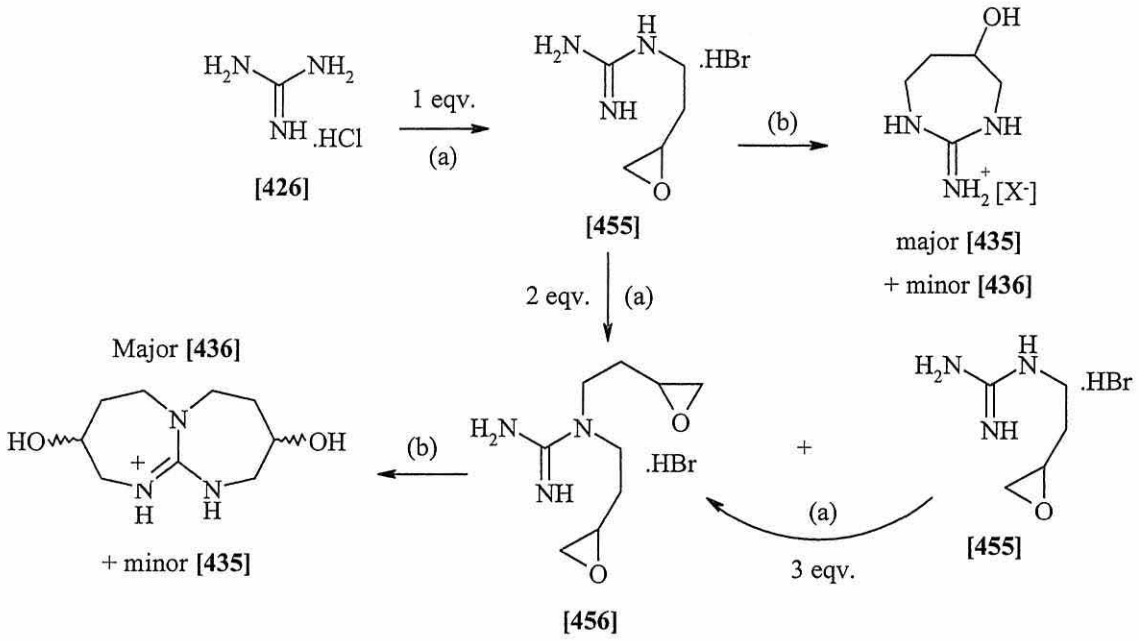
The focus of the previous investigation was the optimisation of formation of the seven-membered product and the investigation into the cyclization mode of this reaction. It was decided to reinvestigate this work but focus on the formation of the bicyclic products by attempting to bias the reaction conditions, and to develop a new work up procedure to aid purification and separation.

Preparation of the bromoepoxide **[434]** was straightforward and involved the *m*CPBA epoxidation of 4-bromobut-1-ene **[454]** in dichloromethane, which proceeded in 84 % yield. Analysis of the ^{1}H-NMR of the product included signals at 2.4 (CH), 2.7 (CH) and 3.0 (CH) ppm whilst the ^{13}C-NMR gave signals at 46.95 (CH) and 50.62 (CH_2) ppm, both of which were indicative of the epoxide functional group.[149]



Scheme 106. (i) *m*CPBA, CH_2Cl_2, 0 °C – RT, 18 h.

The next step in this sequence was the cyclization of the epoxide with guanidine. Previous preparations had been carried out utilising free guanidine, however it was decided to adopt the same approach used for the 5-membered cyclic guanidine and to use guanidine hydrochloride. The reaction sequence for this process is shown below (Scheme 107).



Scheme 107. **Reaction Conditions A:** (i) **[426]**, ^{t}BuOH, 5 °C, KO^{t}Bu, 30 min, **[434]**, RT, 18 h; (ii) KO^{t}Bu, 60 °C, 24 h.

Reaction Conditions B: (i) **[426]**, ^{t}BuOH, 5 °C, KO^{t}Bu, 30 min, **[434]**, RT, 18 h; (ii) KO^{t}Bu, 30 min, **[434]**, RT, 18 h; (iii) KO^{t}Bu, 60 °C, 24 h.

Reaction Conditions C: (i) **[426]**, ^{t}BuOH, 5 °C, KO^{t}Bu, 30 min, **[434]**, RT, 18 h; (ii) KO^{t}Bu, 30 min, **[434]**, RT, 18 h; (iii) KO^{t}Bu, 30 min, **[434]**, RT, 18 h; (iv) KO^{t}Bu, 60 °C, 24 h.

Guanidine hydrochloride was thus treated with KO^{t}Bu in ^{t}BuOH to give free guanidine. Epoxide **[434]** was then added to give the alkylated guanidine salt **[455]**. This was followed by the addition of a further equivalent of base to give product **[435]** after 24 hours, which could then be isolated at this point in 43 % yield (see entry A in table 9). Alternatively, at the stage where **[455]** is present, a further 1-equivalent (entry B, table 9) or 2-equivalents (entry C, table 9) of epoxide could be added, together with base, to give the bis-alkylated salt **[456]**. On stirring, this yields the monomeric **[435]** and dimeric products **[436]** in varying amounts, as shown in Table 9. The crude ^{1}H-NMR

data obtained in each of the reactions was not particularly informative, as there was little to differentiate between the 7-*endo* product and the double addition bicyclic product. The analysis of the crude products by ^{13}C-NMR gave a better indication of the production of both products and it was also possible to estimate the ratios of monomeric **[435]** to dimeric **[436]**.

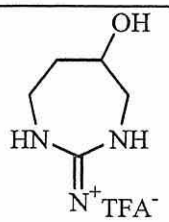
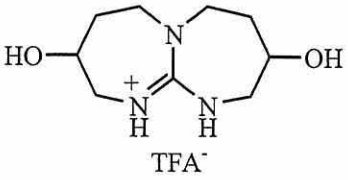
	 **[435]**		 **[436]**	
Reaction Conditions	**Ratio (%)**	**Yield (%)**	**Ratio (%)**	**Yield (%)**
A	70	43 %	30	-
B	37	-	63	24 %
C	22	n.d.	78	-

Table 9.

From the crude NMR it was possible to determine the chemical shifts of **[435]** and **[436]**, as shown in Figure 19.

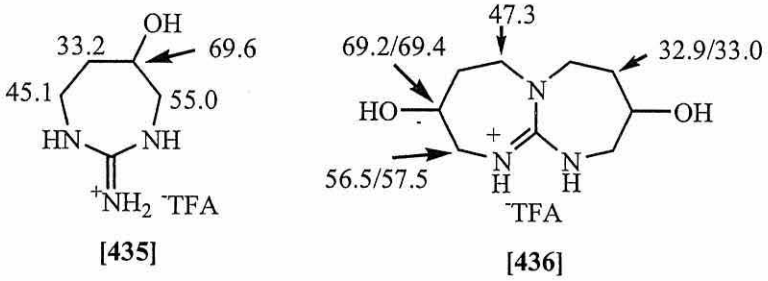


Figure 19. ^{13}C-NMR shifts of hydrogen environments

It is important to note that **[436]** was obtained as a mixture of diastereomers (ratio ca. 1:1), hence the pairing of the signals in Figure 19. The ^{13}C-NMR spectra for the three reactions (entries A, B and C) are shown in figures 20 – 22. Signals have been assigned on each spectrum with M representative of monomeric and D representative of dimeric signals.

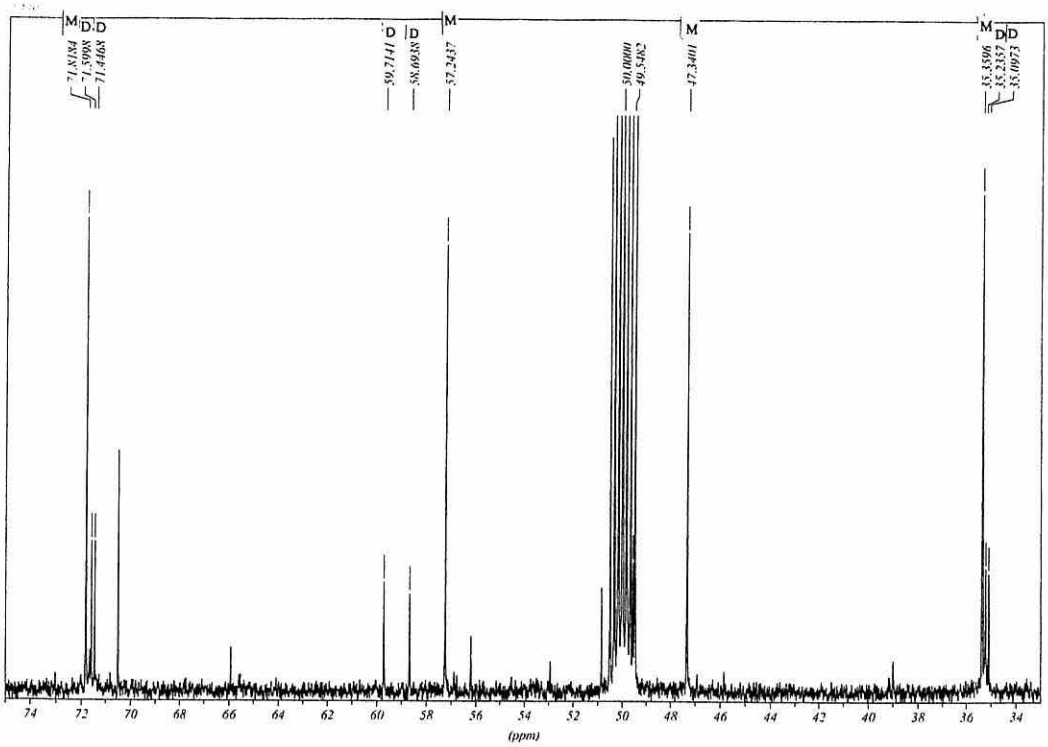


Figure 20. ^{13}C-NMR spectrum: 1 equivalent of epoxide, entry A in Table 9. (signals at 50 ppm are for the solvent d_4-MeOH)

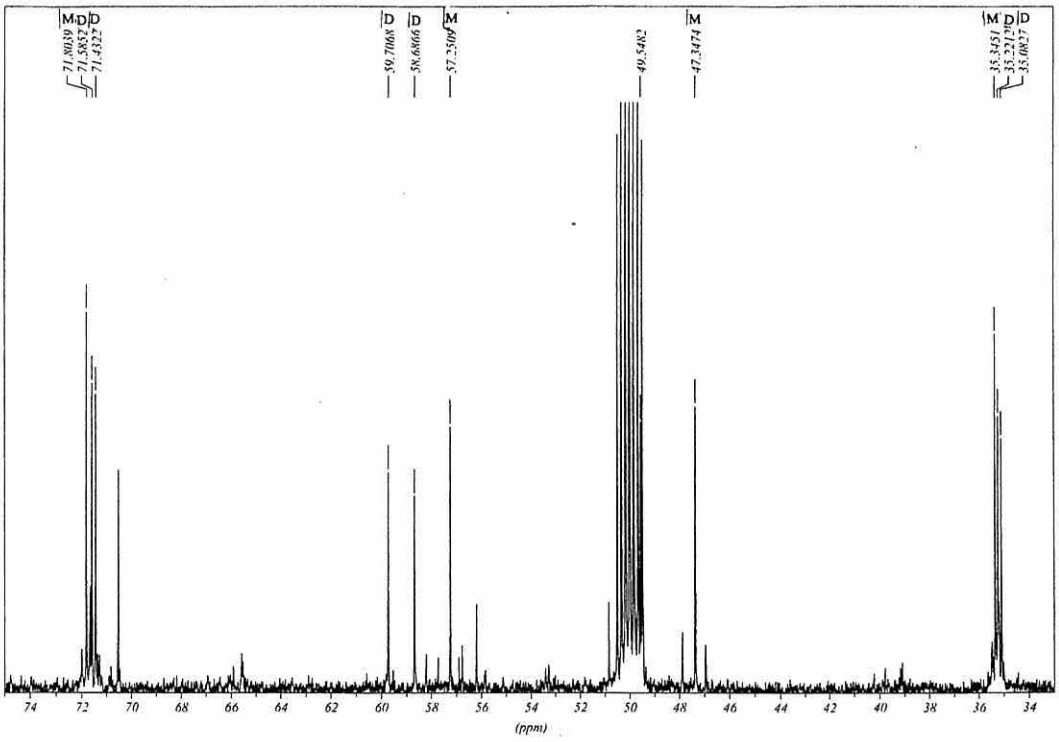


Figure 21. ^{13}C-NMR spectrum: 2 equivalents of epoxide, entry B in Table 9.

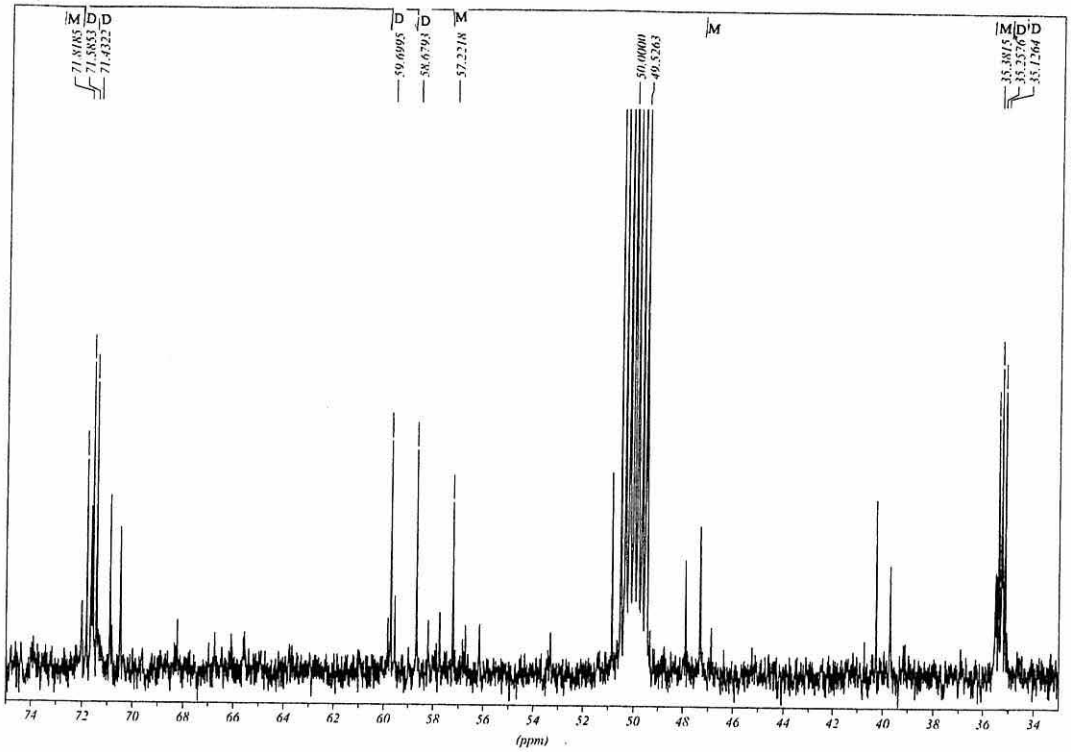


Figure 22. ^{13}C-NMR spectrum: 3 equivalents of epoxide, entry C in Table 9.

It is apparent, from these results, that the additional epoxide and base have had a significant effect on the ratios of product produced in the reactions. The reaction with one equivalent of epoxide shows predominantly the 7-membered product **[435]** (70:30), whereas when 2 equivalents were used the product was predominantly **[436]** (37:63). A further equivalent did give more of the dimer but at the expense of purity, as this reaction was highly contaminated by impurities, as seen by the ^{13}C-NMR spectrum.

At this stage the crude products from entries A and B were purified by column chromatography. The products resulting from entry C were not purified further, due to the high levels of contamination and therefore a yield was not obtained.

The monomeric product **[435]** was isolated in 43 % yield from a graduated solvent system of MeOH/$CHCl_3$. Analysis of **[435]** by ^{1}H-NMR spectroscopy found signals at δ = 4.61 - 4.71 (2 x CH), 3.28 - 4.13 (4 x CH_2) and 1.59 - 2.23 (2 x CH_2), which together with IR resonances at 3346 cm^{-1} (OH) and 1500 cm^{-1} (C=N) proved product formation. Analysis of pure **[435]** by ^{13}C-NMR found signals at δ = 34.4 (CH), 46.9 (CNH), 57.2 (CNH), 71.0 (COH) and 157.8 (C=N) and final proof was given by mass spectrometry,

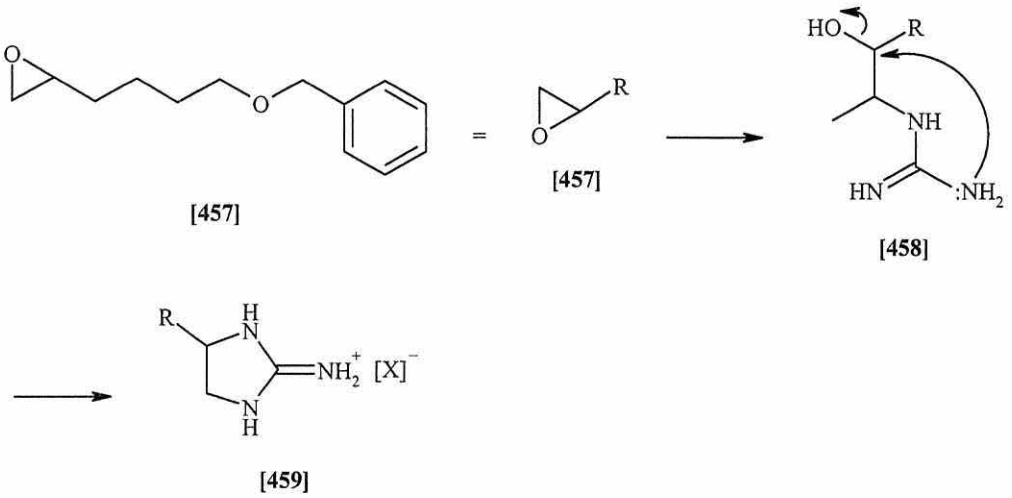
which found 130 daltons, which is comparable to the accurate mass of 130.1684 expected for [$C_5H_{12}N_3O$].

The dimeric product **[436]** was isolated by column chromatography (MeOH/$CHCl_3$) in 24 % yield and the structure also confirmed by IR and NMR. IR was used merely to confirm the presence of a broad OH, found at 3300 cm^{-1} and C=N, found at 1500 cm^{-1}. ^{1}H-NMR gave signals at δ = 4.7 (2 x C*H*-OH), 3.2 - 3.9 (4 x CH_2-N) and 1.7 - 2.25 (2 x CH_2-C). Evidence of the structure was more apparent on analysis of the ^{13}C-NMR, which gave strong correlation with the bicyclic guanidine. The trifluoroacetate derivative displayed signals at δ = 32.9/33.0 (*C*H-OH), 47.3 (*C*H_2-NH), 56.5/57.5 (CH-*C*H_2NH), 69.2/69.4 (*C*H_2-CH-OH) and 158.6 ppm (C-N).

In conclusion this work has been successful as the synthesis of **[435]** and **[436]** were both achieved in a selective manner and in 45 % and 24 % yields respectively. The yield of **[436]** is low and is likely to be a mixture of diastereomers. Repeating the reaction, in future synthetic approaches with an enantiopure epoxide, could improve the yields and be easier to purify.

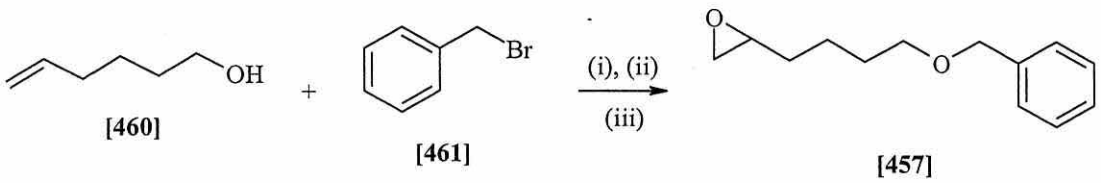
6.5. AN ALTERNATIVE APPROACH TO 5-MEMBERED GUANIDINE HETEROCYCLES

In order to extend the range and applicability of our methodology it was envisaged that the reaction between guanidine and the epoxide **[457]** would lead to the β-hydroxy guanidine **[458]**. Displacement of the hydroxy group in **[458]** would lead to the 5-membered guanidine heterocycle **[459]** (Scheme 108).



Scheme 108. Summarised cyclic guanidine approach.

The substrate chosen was epoxide **[457]**, which was prepared in two steps from 5-hexen-1-ol **[460]** (Scheme 109).[149]

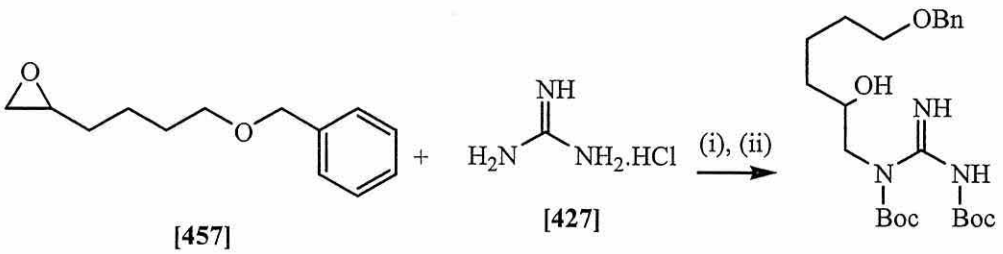


Scheme 109. (a) (i) Sodium hydride, THF, 0 °C, 5 min. (ii) benzyl bromide, TBAI, reflux, 18 h, (iii) *m*CPBA, CH_2Cl_2, 0°C – RT, 18 h.

The intermediate formed on reaction of 5-hexen-1-ol **[460]** and benzyl bromide **[461]** was confirmed by IR, which clearly showed the lack of the OH group expected for **[460]**. The next step in this reaction sequence was the formation of the appropriate epoxide **[457]**, which was achieved by treatment with *meta*-chloroperoxybenzoic acid, resulting in 95 % overall yield of product. The ^{1}H-NMR of epoxide **[457]** contained

signals at 2.7–3 ppm (3 H), which together with the lack of alkene signals at 6.0 and 5.2, confirmed the preparation of **[457]**.

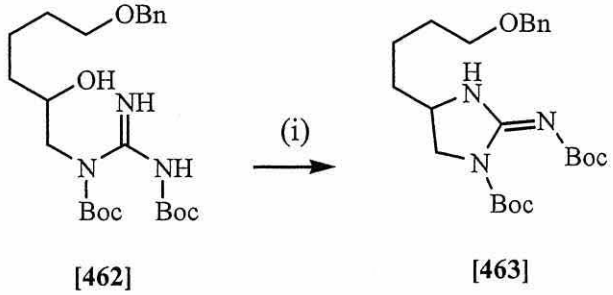
The reaction of **[457]** with guanidine hydrochloride was followed by Boc protection of the crude reaction mixture. Chromatographic purification gave the β-hydroxy guanidine **[462]** in 36 % overall yield (Scheme 110).



Scheme 110. (c) (i)KO^{t}Bu, ^{t}BuOH, 5 °C, 30 min, 60 °C, 18 h. (ii) Boc_2O, NEt_3, 48 h, RT

The proton spectrum of **[462]** was not particularly useful in the identification of product. Signals were found at δ = 7.25 for the Ph and at 4.49 for the benzyl CH_2 together with t-butyl signals at δ = 1.3. ^{13}C-NMR was more useful, showing three quaternary carbons at 161.6, 156.3 and 153.8 corresponding to the two BocN groups on the guanidine. This, together with five CH_2 signals at 44.5, 31.9, 29.4, 28.1 and 22.2, a C*H*OH signal at 83.1, the *t*-butyl groups at 28.4 and 27.7 and the phenyl CHs at 128.3, 127.6 and 127.7. Final proof was given by the mass spectrum which gave a [M+H] at 466, which has an accurate mass at 466.2917, which was identical to that predicted for $C_{24}H_{40}O_6N_3$ [M+H$^+$].

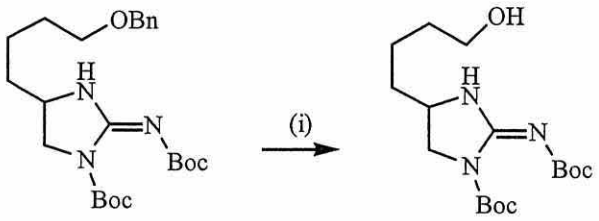
The success of the previous reaction led to the investigation of the cyclization of **[463]** under Mitsunobu conditions (Scheme 111).



Scheme 111. (i) PPh_3, DIAD, Toluene, H_2O, 0 °C – RT, 48 h.

On following the reaction by TLC the starting material was still present after several hours and no new compounds were visible. It was assumed that the reaction was either not working or was slow to proceed. Further PPh_3 and DIAD were added, which resulted in the disappearance of the starting material over 16 hours. After work up, however, only a complex mixture was formed which was inseparable by chromatography.

It was hoped that the removal of the benzyl group from the crude product would assist in purification, as this would alter the polarity of the product. It was thus decided to remove the benzyl group by hydrogenation using H_2 and palladium on charcoal (Scheme 112).



[463] **[464]**

Scheme 112. (i) Pd/ C, EtOAc, H_2, RT, 18 h.

Structural elucidation of the above product was inconclusive on analysis of ^{1}H-NMR, which gave little evidence of the functional groups expected for compound **[464]**. This product again proved difficult to purify by chromatography and recrystallisation. Further attempts of this synthesis failed to produce the desired compound and this methodology was abandoned. At this stage it is impossible to ascertain whether the cyclic product **[463]** had formed, prior to hydrogenation. The method had initially proven promising, with the success of the protected guanidine reaction. We were unable to conclude whether the heterocycle had formed in the intended Mitsunobu reaction and the work was not continued due to the lack of time.

6.6. CONCLUSIONS AND FURTHER WORK

Approaches towards the solid-phase synthesis of guanidine heterocycles proved disappointing and, though promising results were obtained for binding the guanidine functionality to a solid-support, we were unable to identify the products we had hoped to achieve by such methods.

It had been hoped that the yields of the silylation reactions of the 5-membered cyclic guanidine could be improved to aid in purification, however in all cases a good crude yield was obtained. Unfortunately purification is a problem as the silyl protecting group is cleaved on chromatography. Scope for future work in this approach could involve alternative protection methods and investigation of other purification routes.

The production of the 7-membered monocyclic and bicyclic guanidines was successful and it was possible to isolate both products in moderate yield and over 90 % purity. A similar approach could be applied in future synthetic methods towards guanidine heterocycles. In particular this opens avenues for enantio-pure compounds, as the use of a chiral epoxide will lead to a single enantiomer. This work is currently ongoing in Bangor.

Finally, our attempts at producing alternative guanidine heterocycles were encouraging as the first three stages of the synthesis were successful; however the hetero-cyclization using DIAD was not a success. Despite this, the reaction could be further investigated by using an alternative method of purification in the protection stage and investigating the cyclization in more detail.

CHAPTER 7 - CONCLUSIONS

The work within this thesis was aimed towards (i) the synthesis of solid-phase supported reagents and approaches to compound libraries and (ii) the synthesis and purification methods of heterocyclic guanidines. Both were achieved successfully, such that novel solid-supported reagents were prepared, new compounds were produced from solid- and solution-phase library synthesis and heterocyclic guanidines were synthesised and a purification method for such compounds developed that was of significant improvement to previously published attempts.[97]

Approaches towards solid-phase supported reagents proved successful, in that a total of 16 resins were prepared and the structures confirmed by IR and Raman analysis. Most of the solid-phase supported reagents described herein were previously unreported; however, literature examples were prepared and modified in some cases. In two examples the resins were used in further syntheses to successfully produce organic reagents. It was shown, however, that these compounds could be produced in far greater yields *via* solution-phase methods. It is concluded that combinatorial resins can be used to produce fine chemicals, although in the examples investigated it did not prove particularly advantageous. Solid-phase synthesis would appear to lend itself more towards producing organic reagents for screening purposes or where solution-phase methods have proven unsuccessful and therefore conventional solution-phase methods should be adopted in cases where yield is important.

An example of producing a large array of compounds for screening purposes future work in solid-phase synthetic approaches could involve the Biginelli and Ugi multi-component reactions. Weber *et al* [60] report the optimisation of biological activity of combinatorial libraries by genetic algorithm and this could be adopted by using an aldehyde or amine bound resin, which provides scope for vast quantities of compounds.

The synthesis of urea derivatives was attempted by solid and solution-phase methods, both to good effect. The solution-phase method adopting chlorophenyl isocyanate in the production of **[360]** proceeded with a 30 % increase in yield compared to the solid-phase equivalent. Interestingly the similar solid-phase approach involving phenyl

isocyanate offered **[363]** in 82 % yield. The surprisingly good yield would suggest potential for this solid-phase approach in future synthesis.

Solution-phase methods were also successfully used to synthesise five libraries of compounds, including ureas and thioureas, sulphonamides, dihydropyrimidines and cyano acrylic acid methyl esters. In most cases the products were obtained in moderate to good yield and good purity and in several cases were previously unreported. The products were screened for biological activity, unfortunately the results from screening these compounds for biological activity are not known at present.

The most successful library was produced from the Biginelli multicomponent reaction. Altering the aldehyde, urea/thiourea and acetoacetate could potentially provide a library of several thousands of compounds, thus increasing the number of compounds screened for biological activity and possibly providing a compound of pharmaceutical benefit. Section 5.4.2 demonstrated the preparation of a novel thiourea **[414]**. This compound could be applied to the Biginelli reaction in the future, therefore increasing the dihydropyrimidine library.

Solid-phase synthetic approaches towards guanidine heterocycles proved promising, such that it was possible to successfully bind guanidine to a solid-support, proven by IR analysis. Cyclization was then carried out via epoxidation of the guanidine, followed by removal of the product by acidic cleavage. Analysis of the product from the cyclization reaction was inconclusive, as the IR spectrum was similar to the spectrum obtained for the guanidine bound reagent. The resin was therefore subjected to TFA and the cleaved product analysed by ^{1}H-NMR; however, the spectra was complex and lacked any of the characteristic signals expected for the cyclic guanidine.

The 5-membered (2-iminoimidazolidin-4-yl) methanol salts were synthesised successfully and in far greater yields than previously reported.[97] Approaches towards improving the purification of such compounds were initially focussed on silyl protection, which is a well established method for protecting alcohols. Unfortunately the method failed as the silyl-protecting group was cleaved on chromatographic purification. The work up and chromatographic purification of (2-iminoimidazolidin-4-yl) methanol salts was therefore investigated and modified with optimum yield and

purity obtained when methanolic TFA was used in work up and column chromatography was best achieved with a graduated solvent system of $MeOH/CHCl_3$.

The synthesis of the 7-membered mono and bicyclic guanidines was successful and both products were isolated in moderate yield and over 90 % purity. It was possible to bias the reaction with additional reagents and hence alter the ratios of monomer **[435]** to dimer **[436]** produced. A similar approach could be applied in future synthetic approaches towards related guanidine heterocycles. In particular this opens avenues for enantiopure compounds, as the use of chiral epoxides will lead to single enantiomers. Approaches of this nature are currently ongoing in the Murphy research group at Bangor.

Finally attempts to use an alternative methodology to synthesise guanidine heterocycles were encouraging. A previously unreported Boc-protected guanidine **[462]** was prepared and confirmed by NMR and MS. The Mitsunobu cyclization step of this method did not prove successful and the approach was therefore abandoned.

GENERAL EXPERIMENTAL

Reagents and Solvents

Merrifield peptide resin (200 – 400 mesh, 2 % crosslinked 1 – 1.5 mmol/g) and poly(styrene-co-vinylbenzene) (200 – 400 mesh, 2 % crosslinked) were obtained from Aldrich. Other reagents were obtained from suppliers, and solvents, unless otherwise stated, were used as supplied. When required, drying of solvents was achieved using standard literature methods,[150] in particular methanol was dried over calcium hydride, stirred overnight and distilled. THF drying took place over sodium wire and was distilled when required and used immediately.

Chromatography

TLC was performed on Polygram Sil G/UV 254 using a suitable elution system for each reaction. Column Chromatography was carried out on Matrix Silica gel (35-70 μm) or by using neutral, basic or acidic alumina supplied by Supelco, where appropriate, eluting with a sufficient solvent system.

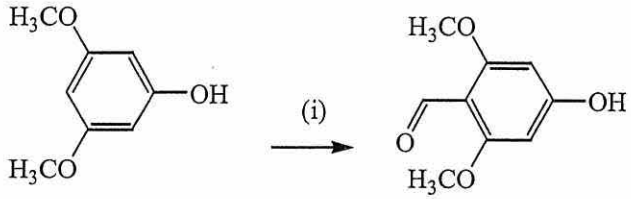
Analytical Methods

Melting points were recorded on Gallenkamp capillary apparatus. A Bruker EM-60 NMR or AC250 MHz NMR spectrometer was used to perform NMR analysis of organic compounds and spectra were recorded in deuterated chloroform ($CDCl_3$), dimethyl sulfoxide (D_6DMSO), deuterated methanol (CD_3OD) and trifluoroacetic acid. Chemical shifts are quoted as δ values (ppm) relative to tetramethylsilane as an internal standard and spin couplings are given as J values (Hz). FTIR spectroscopy was used to perform infrared analysis of organic and polymer bound reagents; spectra were recorded as a thin film or obtained in nujol or a KBr pellet. Perkin Elmer Paragon 1000 FT-IR apparatus was used to record IR data. Raman analysis was carried out on Reneshaw Ramascope Imaging Microscopy at the Laboratory of Government Chemists, with spectra normalised to $1000cm^{-1}$.

CHAPTER 8 - PREPARATION OF SOLID-PHASE SUPPORTED REAGENTS

8.1. BENZALDEHYDE DERIVED RESIN SYNTHESIS

8.1.1. Preparation of 4-Hydroxy-2,6-dimethoxybenzaldehyde [306] [132]



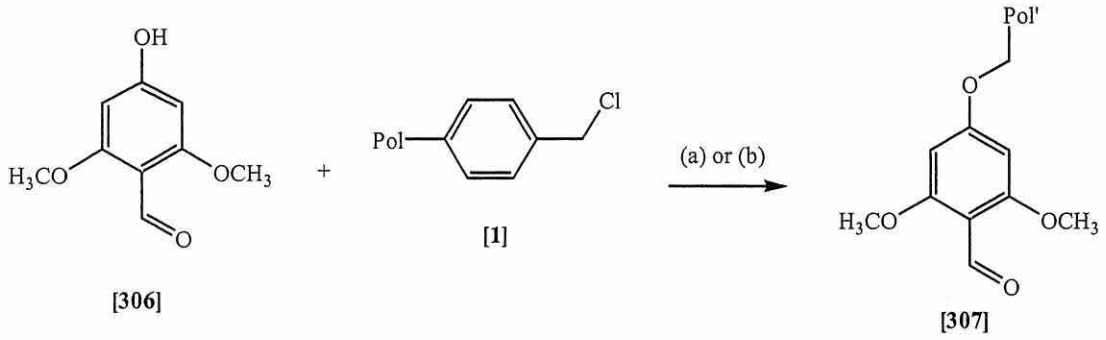
[305] [306]

(i) $POCl_3$, 0 °C, DMF, 30 min, r.t., 15 h.

3,5-Dimethoxyphenol (20 g, 0.1 mol) and phosphorous oxychloride (24 ml, 0.3 mol, 2.0 eq) were mechanically stirred at 0 °C and DMF (15 ml, 0.2 mol) was added portionwise over 30 min. The mixture was warmed to room temperature and stirred for 15 h. Crushed ice (300 g) was added and the mixture was stirred until an aqueous solution had formed. The acidic aqueous phase was washed with ether (3 x 200ml) and filtered to remove a tan residue. The filtrate was brought to pH 6 with a 19N solution of sodium hydroxide (ca 500 ml), adding this portionwise. A dense precipitate formed which was filtered and washed with ether to yield the desired product.

Yield 6.17 g (26 %). **m.p.** 230 – 234 °C (lit: 222 – 224 °C). **FT IR:** ν_{max} **(cm^{-1})** 2726 (HCO), 1584 (C=O). **^{1}H-NMR:** δ_H 10.0 (1H, s, *H*CO), 6.05 (2H, m, Ar*H*), 3.75 (3H, s, OC*H*$_3$).[132]

8.1.2. 4-Hydroxy-2,6-Dimethoxybenzaldehyde Bound Resin [307] [132]



(a) NaOH, DMSO, r.t., 30 min, 85 °C, 72 h;

(b) NaOMe, MeOH, rot evap, DMSO, r.t., 30 min, 85 °C, 72 h.

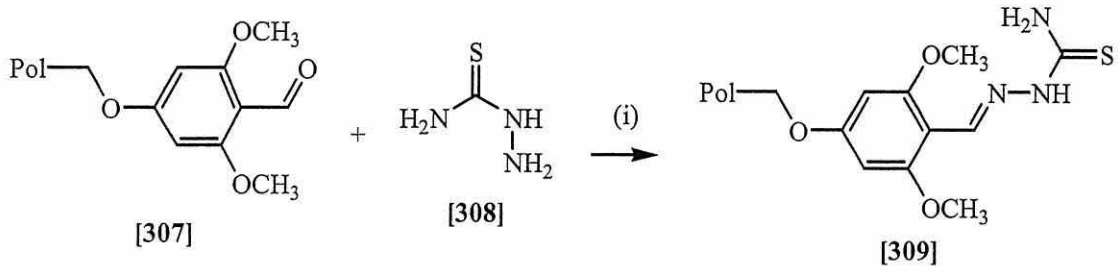
(a) 4-Hydroxy-2,6-dimethoxybenzaldehyde (5.00 g, 27.5 mmol) in dimethyl sulfoxide (13 ml) was added to a solution of sodium hydroxide (1.21 g, 30.3 mmol, 1.10 eq) in dimethyl sulfoxide (40 ml) and the resultant alkoxide solution stirred for 30 min at room temperature. The red alkoxide solution was added portionwise to a suspension of pre-swollen Merrifield resin (10.20 g) in dimethyl sulfoxide (22 ml). The reaction was warmed to 50 °C, stirred for 72 h and left to cool at room temperature. The resin was collected by filtration and washed with methanol (500 ml), dichloromethane (500 ml), water (500 ml), dichloromethane (200 ml) and further methanol (200 ml) and oven dried at 50 °C to yield desired the resin.

Yield 7.20 g. **FT IR:** ν_{max} **(cm^{-1})** 3024 (ArH), 2727 (HCO), 1686 (C=O), 1254 (C-O-C), 1026 (C-O-C). **Loading (mmol /g)** 0.70 – 1.10 as determined by sulfur content analysis by conversion to the corresponding sulfur containing thiosemicarbazide derivative (see later).

(b) Sodium methoxide (0.760 g, 13.6 mmol, 1.10 eq) was dissolved in methanol (30 ml) and 4-hydroxy-2,6-dimethoxybenzaldehyde (2.48 g, 13.6 mmol, 1.10 eq) was added and the solution was evaporated to dryness. The solid was re-dissolved in DMSO (50 ml), stirred and heated to 85 °C for 30 min. The resultant solution was added to a suspension of pre-swollen Merrifield resin (7.75 g, 12.4 mmol) in DMSO (50 ml) and heated to 85 °C for 72 h. The resin was collected by filtration and washed with methanol (500 ml), dichloromethane (500 ml), water (500 ml), dichloromethane (200 ml) and methanol (200 ml) and dried in an oven at 50 °C to yield the desired resin.

Yield 6.94 g. **FT IR:** ν_{max} **(cm^{-1})** 3024 (ArH), 2727 (HCO), 1686 (C=O), 1254 (C-O-C), 1027 (C-O-C). **Loading (mmol /g)** 0.70 – 1.10 as determined by sulfur content analysis by conversion to the corresponding sulfur containing thiosemicarbazide derivative.

8.1.3. 4-(2-(Aminothioxomethyl)amino-2-azavinyl)-3,5-dimethoxyphenol Bound Resin [309]

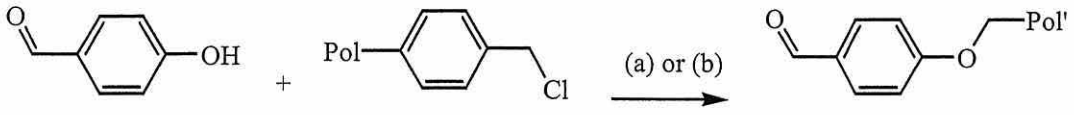


(i) MeOH, r.t., 72 h.

4-Hydroxy-2,6-dimethoxybenzaldehyde resin **[307]** (1.0 g, assume 1.6 mmol/g) was swollen in methanol (20 ml) and thiosemicarbazide (0.9 g, 10 mmol) was added and the reaction stirred at room temperature for 72 h. The resin suspension was transferred to a filter and washed with methanol (100 ml), dichloromethane (100 ml), water (100 ml), dichloromethane (100 ml) and methanol (100 ml), then dried *in vacuo* and placed in oven at 50 °C overnight to yield the desired product.

Yield 1.06 g. **FT IR:** ν_{max} **(cm^{-1})** 3180 (NH), 1645 (NH), 1165 (C=S). **Microanalysis** S: 2.82 %. **Loading (mmol /g)** 0.88.

8.1.4. Preparation of 4-Hydroxybenzaldehyde Bound Resin [311]



[310] [1] [311]

(a) NaOH, DMSO, r.t., 30 min, 85 °C, 72 h;

(b) NaOMe, MeOH, rot evap, DMF, r.t., 30 min, 85 °C, 72 h.

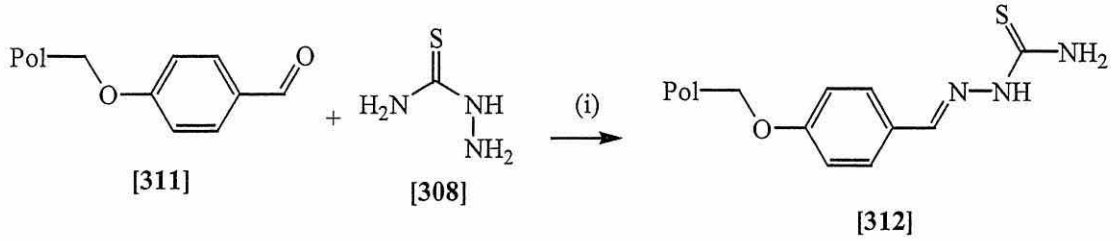
(a) *p*-Hydroxybenzaldehyde (6.16 g, 50.4 mmol) in DMSO (15 ml) was added to a solution of potassium hydroxide (3.17 g, 56.5 mmol) in DMSO (80 ml) The resulting alkoxide solution was stirred for 30 min at room temperature. The red solution was then added portionwise to a suspension of pre-swollen Merrifield resin (18.50 g, 2% loading) in DMSO (40 ml) and the solution stirred at 50 °C for 24 h. The resin suspension was filtered and washed with methanol (500 ml), dichloromethane (500 ml), water (500 ml), dichloromethane (200 ml) and further methanol (200 ml). Resin **[311]** was dried in an oven at 50 °C. Purification of the resin was achieved by Soxhlet extraction with methanol for 8 h.

Yield 17.08 g. **FT IR:** ν_{max} **(cm^{-1})** 2726 (HCO), 1699 (C=O). **Loading (mmol /g)** 0.40 as determined by conversion to the thiosemicarbazide derivative resin.

(b) Sodium methoxide (8.64 g, 160 mmol, 20.0 eq) was dissolved in methanol (100 ml) and *p*-hydroxybenzaldehyde (8.97 g, 160 mmol, 20.0 eq) was added and the resultant mixture evaporated to dryness. The solid was re-dissolved in DMF (80 ml) and heated to 85 °C for 30 min and then added to a suspension of pre-swollen Merrifield resin (5 g, 8 mmol, 2% loading) in DMF (80 ml). The resin was collected by filtration and washed with methanol (500 ml), dichloromethane (500 ml), water (500 ml), dichloromethane (200 ml) and methanol (200 ml) and oven dried at 50 °C.

Yield 17.08 g. **FT IR:** ν_{max} **(cm^{-1})** 2720 (HCO), 1698 (C=O). **Loading (mmol /g)** 1.70 as determined by conversion to the corresponding thiosemicarbazide derivative.

8.1.5. 4-(2-((Aminothioxomethyl)amino)-2-azavinyl)phenol Bound Resin [312]



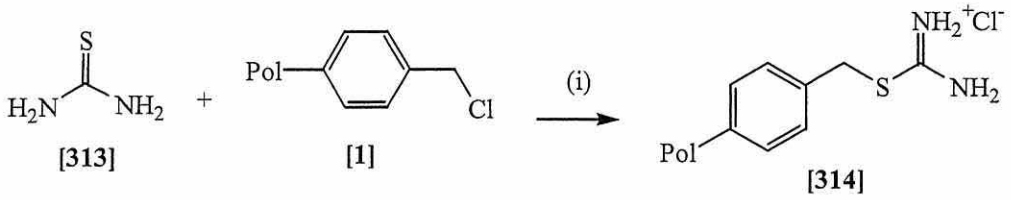
(i) MeOH, r.t., 72 h.

p-Hydroxybenzaldehyde resin **[311]** (1.0 g, 1.6 mmol) was pre-swollen in methanol (20 ml) and thiosemicarbazide (0.9 g, 10 mmol) in methanol (20 ml) was added and the mixture stirred at room temperature for 48 h. The resin suspension was transferred to a filter washed with methanol (100 ml), dichloromethane (100 ml), water (100 ml), dichloromethane (100 ml) and methanol (100 ml) then oven dried at 50 °C to yield impure desired resin. The sample was subjected to Soxhlet extraction in methanol for 8 h then further oven dried at 50 °C to yield pure resin **[312]**.

Yield 1.36 g. **FT IR:** ν_{max} **(cm^{-1})** 3186 (NH), 1621 (NH), 1161 (C=S). **Microanalysis** S: 5.46 %. **Loading (mmol /g)** 1.7.

8.2. PREPARATION OF SOLID-PHASE SUPPORTED THIOUREA DERIVATIVES

8.2.1. Thiouronium Bound Resin [314]



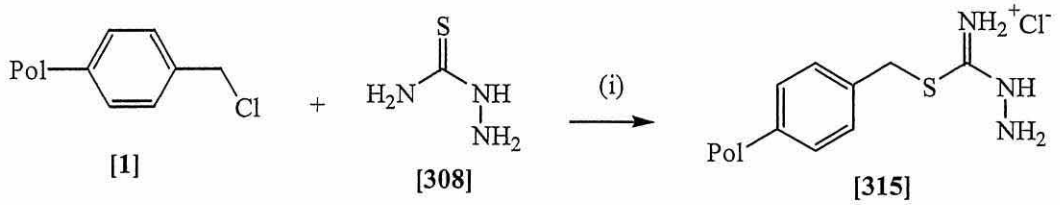
[313] [1] [314]

(i) THF, 85 °C, 36 h.

Merrifield resin (10.0 g, 34.0 mmol) was pre-swollen in THF (70 ml) and thiourea (12.9 g, 170 mmol) was added. The resultant suspension was stirred at 85 °C for 36 h. The resin was cooled to room temperature, transferred to a filter and washed with methanol (500 ml), dichloromethane (500 ml), water (500 ml), dichloromethane (200 ml) and methanol (200 ml) and oven dried at 50 °C. Purification of the resin was achieved by Soxhlet extraction in methanol overnight. The resin was further oven dried at 50 °C.

Yield 11.14 g. **FT IR:** ν_{max} **(cm^{-1})** 3024 (NH), 1654 (NH), 697 (C-S). **Microanalysis** S: 4.46 %. **Loading (mmol /g)** 1.39.

8.3. PREPARATION OF THIOSEMICARBAZIDE BOUND RESIN [315]



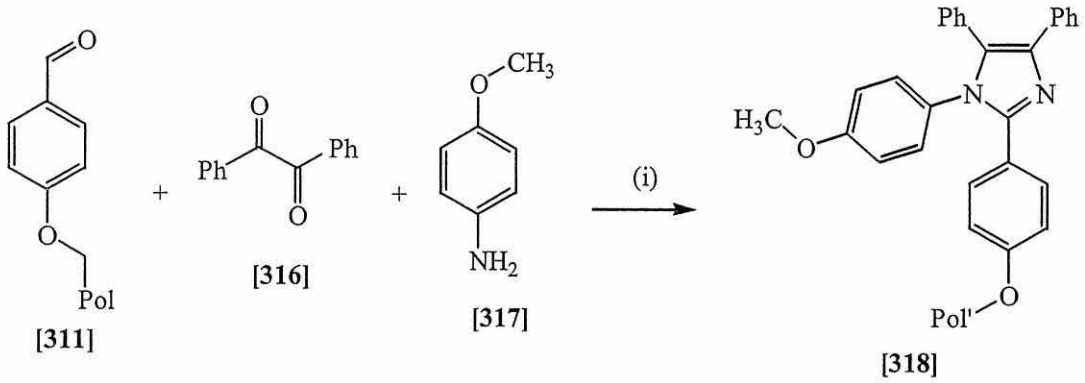
(i) MeOH, r.t., 48 h.

Merrifield resin (5.0 g, 8.0 mmol) was pre-swollen in methanol (25 ml) and thiosemicarbazide (7.29 g, 80.0 mmol, 10.0 eq) in methanol (25 ml) was added. The mixture was stirred at room temperature for 48 h. Resin **[315]** was collected by filtration and washed with methanol (500 ml), dichloromethane (500 ml), water (500 ml), dichloromethane (200 ml) and methanol (200 ml), then oven dried at 50 °C to yield the desired product.

Yield 7.50 g. **FT IR:** ν_{max} **(cm^{-1})** 3180 (NH), 1620 (NH), 699 (C-S). **Microanalysis** S: 4.8 %. **Loading (mmol /g)** 1.5.

8.4. PREPARATION OF IMIDAZOLE DERIVATIVES [52]

8.4.1. 4-(1-Methoxyphenyl)-4,5-diphenylimidazol-2-yl)phenol Bound Resin [318]

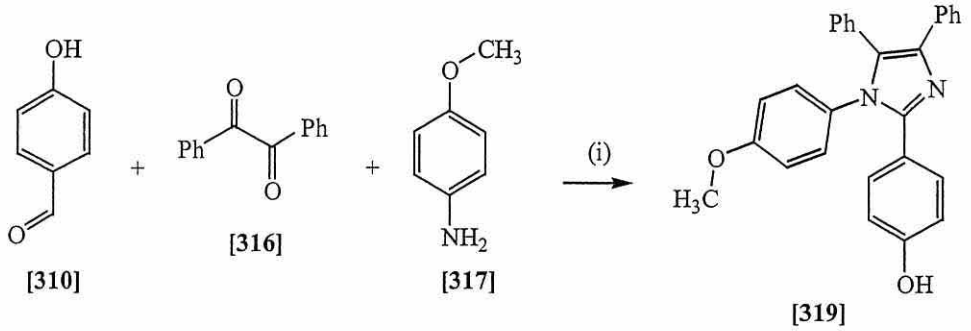


(i) NH_4OAc, AcOH, 85 °C, 24 h

p-Hydroxybenzaldehyde resin (5.0 g, 8.0 mmol), benzil (33.6 g, 169 mmol, 20.0 eq), ammonium acetate (0.86 g, 11 mmol, 1.4 eq) and *p*-anisidine (19.7 g, 160 mmol, 20.0 eq) were dissolved in acetic acid (60 ml) and heated to 85 °C for 24 h. The resin was collected by filtration, then washed with methanol (500 ml), dichloromethane (500 ml), water (800 ml), dichloromethane (200 ml) and methanol (200 ml). The resin **[318]** was oven dried at 50 °C to yield the resin bound imidazole.

Yield 6.89 g. **FT IR:** ν_{max} **(cm^{-1})** 2849 (Ar-H), 1243 (C-OMe). **Microanalysis** N: 0.5 %. **Loading (mmol /g)** 0.72.

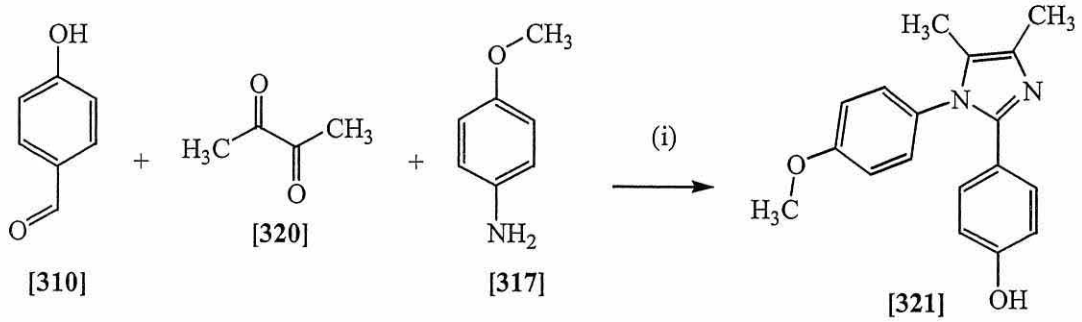
8.4.2. 4-(1-Methoxyphenyl)-4,5-dimethylimidazol-2-yl)phenol [319]



(i) NH_4OAc, AcOH, 85 °C, 24 h.

p-Hydroxybenzaldehyde (5.00 g, 40.0 mmol), benzil (11.8 g, 56.0 mmol, 1.40 eq), ammonium acetate (4.4 g, 56 mmol, 1.4 eq) and *p*-anisidine (7.0 g, 56 mmol, 1.4 eq) were refluxed in acetic acid (70 ml) for 6 h. The reaction was cooled to room temperature and the liquid then transferred to a large flask where water (copious) and salt were added. A black oil formed which could not be purified further. Analysis of this reaction by ^{1}H-NMR showed it to have been unsuccessful. Peaks at 3.0, 4.7 and 7.0 ppm suggested the product had formed; however the spectra was poorly resolved and trace quantities of starting reagents were visible.

8.4.3. 4-(1-Methoxyphenyl)-4,5-diphenylimidazol-2-yl)phenol [321]



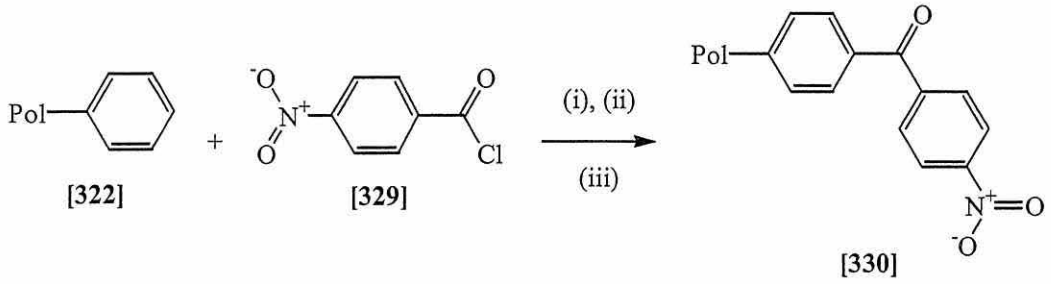
(i) NH_4OAc, AcOH, 85 °C, 24 h.

p-Hydroxybenzaldehyde (5.0 g, 40 mmol), 2,3-butanedione (4.9 g, 56 mmol, 1.4 eq), ammonium acetate (4.4 g, 56 mmol, 1.4 eq) and *p*-anisidine (7.0 g, 56 mmol, 1.4 eq) were refluxed in glacial acetic acid for 6 h (100 °C). The reaction was cooled to room temperature and the liquid then transferred to a large flask where copious amounts of water (500 ml) and salt were added. The solid was collected by filtration. Water was added to the filtrate and further solid dropped out. This in turn was filtered. The first filtrate was found to be the desired product upon analysis by proton NMR. Further interpretation by CHN analysis proved the product **[321]** to be impure. The product was recrystallised in MeOH/water, followed by washing with petrol and then oven dried at 50 °C. Recrystallisation failed to produce a product of adequate purity, although spectrally the product had proved promising.

Yield 4.26 g (25 %). **m.p.** 310 - 312 °C. **^{1}H-NMR:** δ_{ppm} 3.0 (1H, br s, OH), 4.7 (3H, s, OCH_3), 7.0 (18H, m, ArH).

8.5. SOLID SUPPORTED OXIME PREPARATION [83,84]

8.5.1. Preparation of 4-(Nitrophenyl)-phenyl-methanone Bound Resin [330]

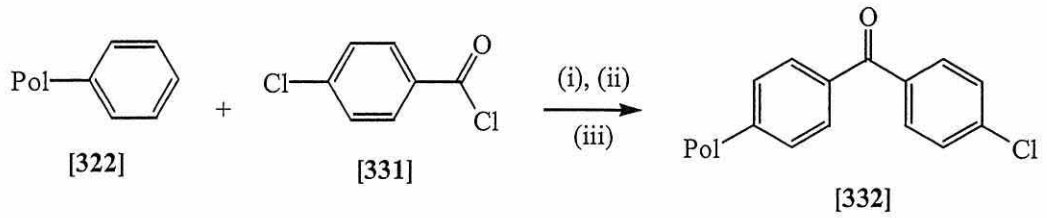


(i) 1,2-dichloroethane, r.t., 30 min; (ii) $AlCl_3$, r.t., 1 h.; (iii) Δ, 3 h.

Polystyrene divinyl benzene (4.34 g, 1.00 % cross-linked) was pre-swollen in 1,2-dichloroethane (70 ml). The resultant suspension was stirred under nitrogen and *p*-nitrobenzoyl chloride (0.93 g, 5.0 mmol) was added and the reaction further stirred for 30 min. Aluminium chloride (1.0 g, 7.5 mmol) was added slowly and the resultant mixture stirred for 1 h at room temperature. The reaction was then heated to 85 °C for 3 h on a water bath. The resin was collected by filtration, then washed with water (500 ml), methanol (500 ml), dichloromethane (200 ml), water (200 ml) and methanol (200 ml) and oven dried at 50 °C to yield the desired product **[330]**.

FT IR: ν_{max} **(cm^{-1})** 2727 (HCO), 1666 (C=O). **Microanalysis** N: 0.60 %. **Loading (mmol /g)** 0.43.

8.5.2. Preparation of 4-Chlorophenyl-4-phenyl Ketone Bound Resin [332] [83,84]



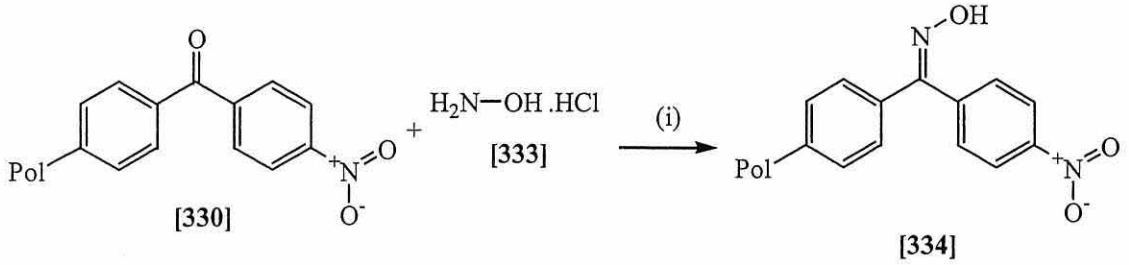
[322] [331] [332]

(i) 1,2-dichloroethane, r.t., 30 min; (ii) $AlCl_3$, r.t., 1 h.; (iii) 85 °C, 24 h.

Polystyrene divinyl benzene resin (4.34 g, 1.00 % cross-linked) was pre-swollen in 1,2-dichloroethane (70 ml). The resultant suspension was stirred for 10 min and *p*-chlorobenzoyl chloride (0.87 g, 5.0 mmol) was added and the reaction further stirred for 30 min at room temperature. Aluminium chloride (1.0 g, 7.5 mmol) was added in small portions over 15 min and the resultant mixture heated at 85 °C for 24 h. The resin was filtered, then washed with methanol (500 ml), copious quantities of water (800 ml), dichloromethane (200 ml), water (200 ml), MeOH (200 ml) and hot MeOH (100 ml), then oven dried at 50 °C.

Yield 4.54 g. **FT IR:** ν_{max} **(cm^{-1})** 2727 (HCO), 1654 (C=O). **Loading (mmol /g)** 0.70 – 1.10. Assumed to be in a similar range to the equivalent nitro resin.

8.5.3. Preparation of (Hydroxyimino)-(4-phenyl)-(4-nitrophenyl) Methane Bound Resin [334] [83,84]



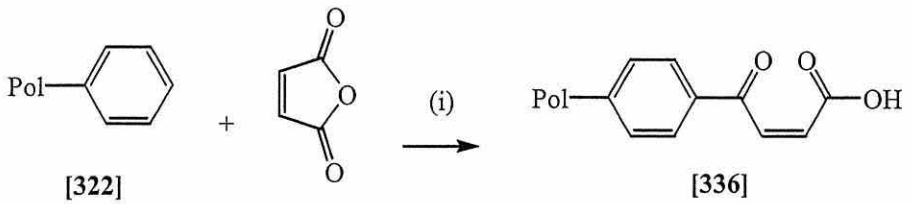
(i) MeOH, pyridine, reflux, 100 h.

p-Nitrobenzoylated resin (4.38 g) was pre-swollen in methanol (50 ml) and hydroxylamine hydrochloride (12 g, 0.23 mol) and pyridine (6 ml) were added to the suspension and the resultant refluxed for 100 h. The resin was filtered and washed with methanol (500 ml), water (500 ml), dichloromethane (200 ml), water (200 ml), dichloromethane (200 ml), methanol (200 ml) and hot MeOH (100 ml), then oven dried at 50 °C

Yield 4.19 g. **FT IR:** ν_{max} **(cm^{-1})** 2727 (HCO), 1664 (C=O). **Microanalysis** N: 2.4 %. **Loading (mmol /g)** 0.43.

8.6. SOLID SUPPORTED ACID SYNTHESIS

8.6.1. Attempted Preparation of 4-(4-Phenyl)-4-oxobut-2-enoic Acid Resin [336]

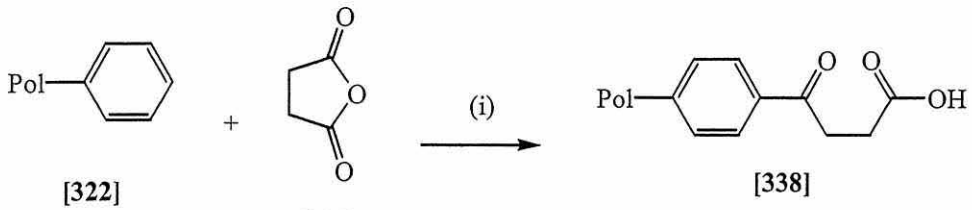


[322] [335] [336]

(i) CH_2Cl_2, $AlCl_3$, 85 °C, 24 h.

Polystyrene divinyl benzene resin (5.00 g, 1.00 % cross-linked) was pre-swollen in dichloromethane (100 ml) and maleic anhydride (0.980 g, 10.0 mmol) and aluminium chloride (2.0 g, 15 mmol) were added. The resultant mixture was heated at 85 °C for 24 h. The resin was filtered and washed with copious amounts of water (500 ml) to eliminate excess aluminium chloride present as solid residue. The resin was then washed with methanol (200 ml), dichloromethane (200 ml), water (200 ml), dichloromethane (100 ml) and methanol (100 ml) and placed in an oven at 50 ° C to dry. FTIR analysis of the resin showed the reaction had been unsuccessful, as no characteristic alcohol and carbonyl peaks were present.

8.6.2. Attempted Preparation of 4-(4-Phenyl)-4-oxobutanoic Acid Resin [338]



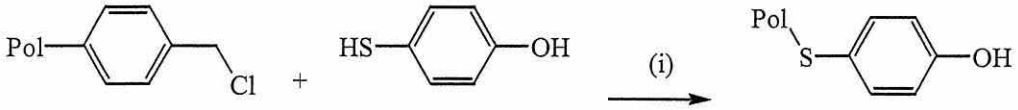
[322] [337] [338]

(i) CH_2Cl_2, $AlCl_3$, 85 °C, 24 h.

Polystyrene divinyl benzene resin (5.00 g, 1.00 % cross-linked) was swollen in dichloromethane (100 ml) and succinic anhydride (1 g, 10 mmol) and aluminium chloride (2.00 g, 15 mmol) were added. The resultant was heated at 85 °C for 24 h. The resin was filtered and washed with copious amounts of water (500 ml) to eliminate excess aluminium chloride. The resin was then washed with methanol (200 ml), dichloromethane (200 ml), water (200 ml), dichloromethane (100 ml) and methanol (100 ml) and placed in an oven to dry. Analysis of **[338]** by FTIR also proved this reaction to be unsuccessful, as again the spectra contained none of the characteristic peaks for an alcohol or carbonyl.

8.7. FORMAMIDE SYNTHESIS

8.7.1. Preparation of Polymer Bound 4-Hydroxythiophenol [340] [87]



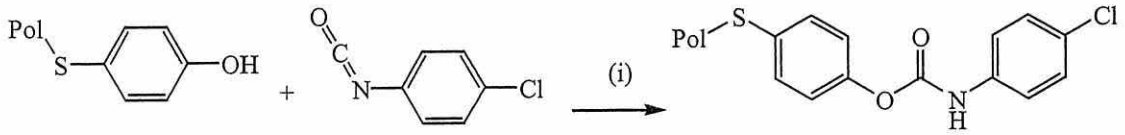
[1] [339] [340]

(i) DMF, KOH, 85 °C, 24 h.

Merrifield resin (2.0 g, 3.2 mmol, 1.6 mmol/g) was pre-swollen in DMF. Potassium hydroxide pellets (0.71 g, 45 mmol) were crushed and dissolved in DMF. 4-hydroxythiophenol (2.50 g) was added to the Merrifield suspension and heated at 85 °C for 20 min. The KOH solution was then added and the flask heated for a further 24 h. The resin was filtered, washed with DMF (100 ml) and water (100 ml), then stirred in water for 10 min, filtered and washed with DMF (100 ml) and water (100 ml). The resin was stirred in 1N HCl for 10 min, filtered and washed sequentially with water (200 ml), methanol (200 ml), dichloromethane (100 ml) and methanol (100 ml). Oven drying at 50 °C yielded the desired resin.

Yield 1.89 g. **FT IR:** ν_{max} **(cm^{-1})** 3386 (OH), 693 (C-S). **Microanalysis** S: 5.6 %. **Loading (mmol /g)** 1.79 determined from sulfur content.

8.7.2. Preparation of *N*-(4-Chlorophenyl)(4-thiophenoxy)formamide Resin [342]



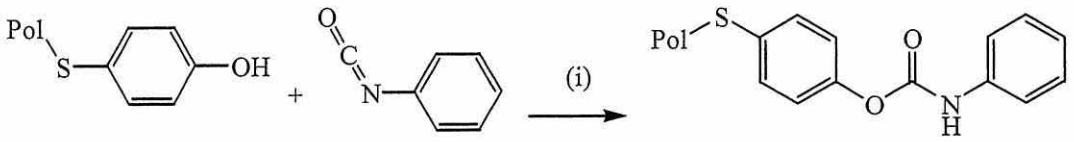
[340] [341] [342]

(i) toluene, pyridine, 85 °C, 18 h.

4-Hydroxythiophenol resin (1.89 g, 1.75 mmol/g) was swollen in toluene. 4-Chlorophenyl isocyanate (2.70 g, 17.6 mmol, 10.0 eq) was added to the suspension together with a catalytic amount of pyridine (ca 1 ml). The resultant mixture was heated at 85 °C for 18 h. The mixture was allowed to cool, then washed with dichloromethane (200 ml), water (500 ml), dichloromethane (200 ml) and methanol (200 ml). The resin was then placed in an oven at 50 °C to dry overnight.

Yield 1.72 g. **FT IR:** ν_{max} **(cm^{-1})** 3300 (NH), 1723 (C=O), 1596 (NH) 694 (C-S) **Loading (mmol /g)** 1.79. Assumed to be the same as the starting resin **[340]**.

8.7.3. Preparation of (4-Thiophenoxy)-*N*-benzamide Resin [344]



[340] [343] [344]

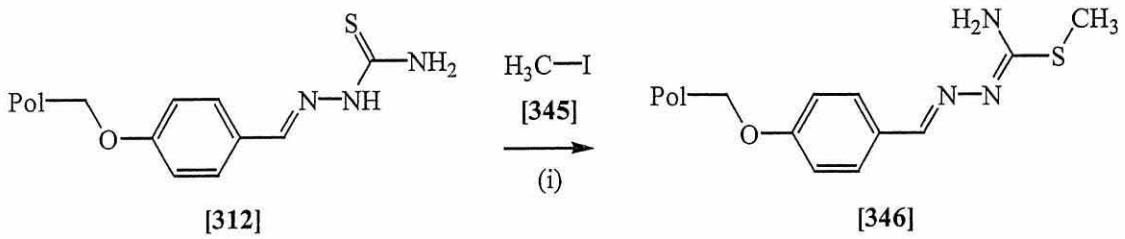
(i) toluene, pyridine, 85 °C, 18 h.

4-Hydroxythiophenol bound resin (5.00 g, 8.75 mmol, 1.75 mmol/g) was swollen in toluene (50 ml) and phenylisocyanate (10.4 g, 87.5 mmol, 10.0 eq) and a catalytic amount of pyridine (ca 1 ml) were added. The resultant mixture was then heated at 85 °C for 18 h. The mixture was allowed to cool and the resin collected by filtration and washed with dichloromethane (200 ml), water (500 ml), dichloromethane (200 ml) and methanol (200 ml). The resin was then placed in an oven at 50 °C and dried overnight.

Yield 4.94 g. **FT IR:** ν_{max} **(cm^{-1})** 3327 (NH), 1702 (C=O), 1594 (NH), **Loading (mmol /g)** 1.79. Assumed to be the same as the starting resin **[340]**.

8.8. ATTEMPTED TRIAZOLE SYNTHESIS

8.8.1. Preparation of 4-[(Methylsulfanylmethyl-azo)-methyl]-phenol Resin [346]

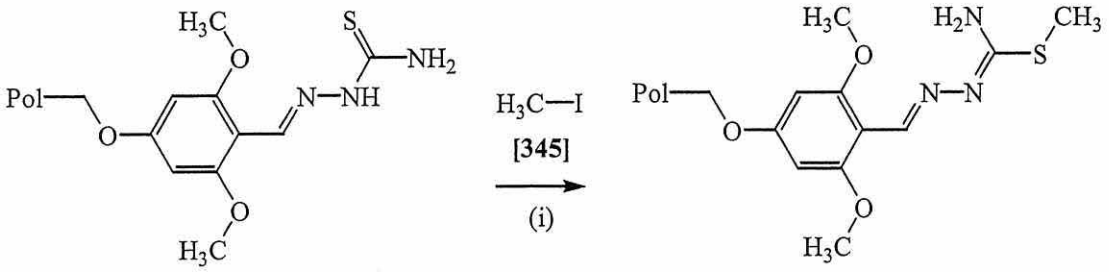


[312] [346]

(i) MeOH, r.t., 18 h.

Thiosemicarbazide bound resin (5.00 g, 1.50 mmol/g) was swollen in methanol (100ml) and iodomethane (2.7 g, 19 mmol, 2.5 eq) was added. The reaction was sealed and stirred at room temperature for 18 h. The resin was collected by filtration and washed with methanol (200 ml), dichloromethane (200 ml), water (200 ml), dichloromethane (200 ml) and methanol (200 ml), then oven dried at 50 °C. FTIR analysis found the reaction had been unsuccessful, as obvious NH bands were still present.

8.8.2. Preparation of 4-(2,3-Diaza-4-methylthiobuta-1,3-dienyl)-1-phenol Resin [347]

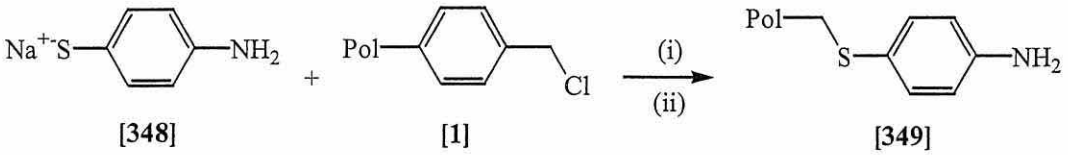


[309] [347]

(i) MeOH, r.t., 18 h.

Thiosemicarbazide bound resin (1.02 g, 1.50 mmol/g) was swollen in methanol (20 ml) and methyl iodide (1.27 g, 8.98 mmol, 6.00 eq) was added. The reaction was stirred and placed on heat bath for 24 h at 85 °C. The resin was allowed to cool and transferred to a filter. The resin was then washed with methanol (200 ml), dichloromethane (200 ml), water (200 ml), dichloromethane (200 ml) and methanol (200 ml) and oven dried at 50 °C. FTIR analysis also proved this reaction to be unsuccessful as the resin differed little from the starting resin **[309]**.

8.9. PREPARATION OF 4-AMINOBENZENE-1-THIOL BOUND RESIN [349]



[348] [1] [349]

(i) MeOH, NaOMe, rot evap; (ii) DMF, 85 °C, 24 h.

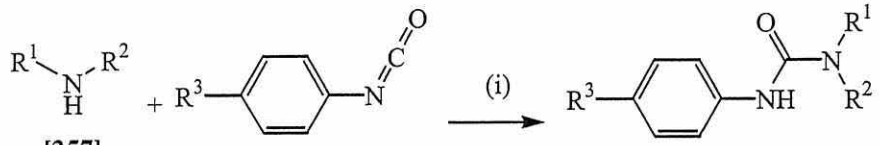
4-Aminothiophenol (5.00 g, 40.0 mmol) and sodium methoxide (2.08 g, 40.0 mmol) were dissolved in methanol (100 ml) and evaporated to dryness. The solid formed was dissolved in DMF (50 ml) and added to pre-swollen Merrifield resin (6.25 g, 1.60 mmol/g) in DMF (50 ml). The resultant mixture was stirred and heated to 85 °C for 24 h. The resin was transferred to a filter and washed with methanol (200 ml), dichloromethane (200 ml), water (200 ml) and finally with dichloromethane (200 ml) and placed in oven to dry at 50 °C to yield **[349]**. FTIR proved the resin had formed with peaks for the amine and a C-S linkage.

Yield 6.13 g. **FT IR:** ν_{max} **(cm^{-1})** 3500 (NH), 3379 (NH), 1596 (NH), 696 (C-S). **Microanalysis** S: 6.05 %. **Loading (mmol /g)** 1.6.

CHAPTER 9 - SOLUTION-PHASE COMBINATORIAL CHEMISTRY

9.1 SYNTHETIC APPROACHES TO UREAS

9.1.1. Preparation of Urea Derivatives



[357] [358] [356]

(i) Toluene, 85 °C, 1 h.

General Procedure: *trans*-Cinnamylpiperazine **[357]** (4.00 g, 19.8 mmol) was dissolved in toluene (20 ml) and 4-chlorophenyl isocyanate **[358]** (3.04 g, 19.8 mmol) was added. The resultant reaction was heated at 85 °C for 1 h, when a solid was formed. The solid was collected by filtration and washed with petrol to yield the title compounds. Recrystallisation, when required, was achieved using CH_2Cl_2/ Petrol.

9.1.1.1. *N*-(4-Chlorophenyl)-(4-(3-phenylprop-2-enyl)piperazinyl) formamide [359]

R^1/R^2 = *trans*-Cinnamylpiperazine, R^3 = Cl.

Yield 6.42 g (91 %). **m.p.** 167– 171 °C. **FT IR:** ν_{max} **(cm^{-1})** 3313 (NH), 3083 (=C-H), 1635 (C=O), 1590 (NH). **^{1}H-NMR (250 MHz, $CDCl_3$):** δ_H 7.41 (2H, d, J = 4.0 Hz, Ar*H*), 7.32 (4H, m, Ar*H*), 7.24 (3H, m, Ar*H*), 6.55 (1H, d, J = 7.9 Hz, C*H*Ph), 6.47 (1H, s, NH), 6.23 (1H, dt, J = 7.9, 3.3 Hz, C*H*CH_2), 3.53 (4H, s, CH_2NC=O), 3.21 (2H, d, J = 3.3 Hz, CH_2CH), 2.55 (4H, s, CH_2NCH_2). **Microanalysis** $C_{20}H_{22}ClN_3O$ requires C: 67.50, H: 6.23, N: 11.81 %, found C: 67.7, H: 6.2, N: 11.9 %.

9.1.1.2. *N*-(4-Chlorophenyl)indolinylformamide [360]

R^1/R^2 = Indoline, R^3 = Cl

Yield 8.60 g (94 %). **m.p.** 175 – 180 °C. **FT IR:** ν_{max} **(cm^{-1})** 3374 (NH), 3020 (=C-H), 2948 (CH), 1658 (C=O), 1586 (NH). **^{1}H-NMR (250 MHz, $CDCl_3$):** δ_H 7.85 (1H, s, N*H*), 7.66 (1H, d, J = 8.2 Hz, Ar*H*), 7.26 (2H, d, J = 8.9 Hz, Ar*H*), 7.01 – 6.89 (4H, m,

Ar*H*), 6.67 (1H, d, J = 7.6 Hz, Ar*H*), 3.83 (2H, t, J = 8.6 Hz, NC*H*$_2$CH), 2.90 (2H, t, J = 8.6 Hz, C*H*$_2$CH$_2$). **Microanalysis** $C_{15}H_{13}ClN_2O$ requires C: 66.06, H: 4.80, N: 10.27 %, found C: 66.0, H: 4.7, N: 10.3 %.

9.1.1.3. *N*-(4-Chlorophenyl)(4-formylpiperazinyl)formamide [361]

R^1/R^2 = 1-Formylpiperazine, R^3 = Cl

Yield 8.78 g (94 %). **m.p.** 165 –169 °C. **FT IR:** ν_{max} **(cm^{-1})** 3291 (NH), 3020 (=C-H), 2851 (CH), 1635 (C=O), 1590 (NH). **^{1}H-NMR (250 MHz, $CDCl_3$):** δ_H 8.76 (1H, s, N*H*), 8.07 (1H, *H*C=O), 7.49 (2H, d, J = 8.9 Hz, Ar*H*), 7.26 (2H, d, J = 8.9 Hz, Ar*H*), 3.43 (8H, m, C*H*$_2$N). **^{13}C-NMR:** δ_C 161.2 (HCO), 154.7 (CO), 139.4 (CNH), 121.0 - 128.3 (Ar), 44.6 (NCH_2), 43.5 (NCH_2). **Microanalysis** $C_{12}H_{14}ClN_3O_2$ requires C: 53.84, H: 5.27 N: 15.7 %, found C: 53.6, H: 5.3, N: 15.4 %.

9.1.1.4. ((4-Chlorophenyl)amino)-*N*-(3-pyridylmethyl)formamide [362]

R^1/R^2 = 3-(Aminomethyl)pyridine, R^3 = Cl

Yield 8.89 g (92 %). **m.p.** 170-172 °C (lit. 171-173 °C). **FT IR:** ν_{max} **(cm^{-1})** 1660 (C=O). **^{1}H-NMR (250 MHz, $CDCl_3$):** δ_H 8.80 (1H, s, N*H*), 8.53 (1H, d, J = 1.6 Hz, Ar*H*), 8.44 (1H, dd, J = 4.8, 1.6 Hz, Ar*H*), 7.69 (1H, d, J = 7.7 Hz, Ar*H*), 7.41 (2H, m, Ar*H*), 7.33 (1H, dd, J = 4.8, 7.7 Hz, Ar*H*), 7.24 (2H, m, Ar*H*), 6.75 (1H, t, J = 5.8 Hz, N*H*), 4.31 (2H, d, J = 5.8 Hz, C*H*$_2$N). **^{13}C-NMR:** δ_C 155.2 (HCO), 148.8 (CH, pyr), 148.1 (CH, pyr), 139.5 (ArC), 135.9 (CH, pyr), 135.1 (ArC, pyr), 128.6 (2eq, ArC), 124.8 (ArC), 123.5 (ArC), 119.4 (2eq ArC), 38.6 (CH_2). **Microanalysis** $C_{13}H_{12}ClN_3O$ requires C: 59.66, H: 4.62 N: 16.06 %, found C: 59.5, H: 4.6, N: 15.9 %.

9.1.1.5. 1-Phenethyl-3-phenyl-urea [363]

R^1/R^2 = 2-Phenylethylamine, R^3 = H

Yield 1.48 g (82 %). **m.p.** 133 - 138 °C. **FT IR:** ν_{max} **(cm^{-1})** 3345 (NH), 3024 (=C-H), 1646 (C=O). **^{1}H-NMR (250 MHz, $CDCl_3$):** δ_H 7.37 (1H, d, J = 3.8 Hz, Ar*H*), 7.29 - 7.17 (8H, m, Ar*H*), 6.97 (1H, dt, J = 5.8, 3.8 Hz, Ar*H*), 3.42 (2H, t, J = 3.5 Hz,

CH_2NH), 2.77 (2H, t, J = 3.5 Hz, CH_2). **^{13}C-NMR:** δ_C 156.3 (CO), 139.1, 138.9 (2 x ArC), 129.0, 128.9, 128.8, 128.5 (4 x ArCH), 126.3 (2 eq ArCH), 123.0, 122.9 (2 x ArCH), 119.9, 119.5 (2 x ArCH), 41.1 ($NHCH_2$), 36.1 (CH_2). **HRMS ($M+H^+$)** $C_{15}H_{17}N_2O$ requires 241.1341, found 241.1312.

9.1.1.6. 4-Benzhydryl-piperazine-1-carboxylic acid (4-chlorophenyl)amide [364]

R^1/R^2 = 1-Benzhydrylpiperazine, R^3 = Cl

Yield 8.89 g (92 %) **m.p.** 251 – 253 °C. **FT IR:** ν_{max} **(cm^{-1})** 1655 (C=O) **^{1}H-NMR (250 MHz, $CDCl_3$):** δ_H 7.54 (1H, s, N*H*), 6.85 - 6.48 (14H, m, Ar*H*), 3.55 (1H, s, C*H*Ph_2), 2.62 (4H, t, J = 5.0 Hz, CH_2NCO), 1.63 (4H, t, J = 5.0 Hz, CH_2NCH). **Microanalysis** $C_{24}H_{24}ClN_3O$ requires C: 71.01, H: 5.96 N: 10.35 %, found C: 71.2, H: 6.1, N: 10.8 %.

9.1.1.7. 4-Phenyl-piperazine-1-carboxylic acid (4-chlorophenyl)amide [365]

R^1/R^2 = 1-Phenylpiperazine, R^3 = Cl

Yield 79 % **m.p.** 182 - 185 °C. **FT IR:** ν_{max} **(cm^{-1})** 3271 (NH), 3019 (=C-H), 2920 (CH), 1651 (C=O), 1593 (NH). **^{1}H-NMR (250 MHz, $CDCl_3$):** δ_H 7.35 – 6.90 (9H, m, Ar*H*), 6.66 (1H, s, N*H*), 3.63 (4H, t, J = 5.0 Hz, CH_2NCO), 3.20 (4H, t, J = 5.0 Hz, CH_2NPh). **^{13}C-NMR:** δ_C 154.8 (CO), 150.7 (ArC), 137.5 (ArC), 129.3 (ArC), 128.9 (2eq ArCH), 128.23 (ArCH), 128.19 (ArCH), 121.4 (ArCH), 121.2 (ArCH), 120.6 (ArCH), 116.6 (2eq ArCH), 49.2 (2eq $NHCH_2$), 44.0 (2eq CH_2). **HRMS ($M+H^+$)** $C_{17}H_{19}ClN_3O$ requires 316.1217, found 316.1182.

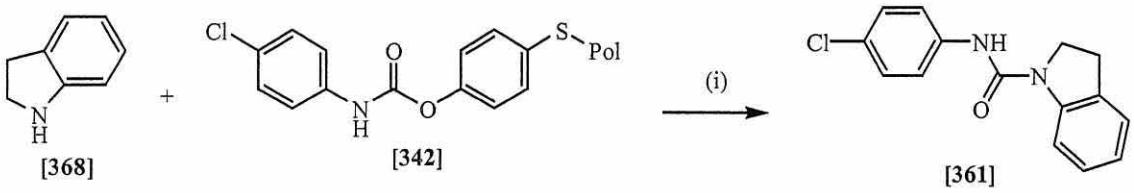
9.1.1.8. 4-(3-Phenyl-allyl)-piperazine-1-carboxylic acid phenylamide [366]

R^1/R^2 = *trans*-Cinnamylpiperazine, R^3 = H

Yield 9.15 g (85 %). **m.p.** 99 - 101 °C. **FT IR:** ν_{max} **(cm^{-1})** 3325 (NH), 3012 (=C-H), 1646 (C=O). **^{1}H-NMR (250 MHz, $CDCl_3$):** δ_H 7.42 - 7.26 (10H, m, Ar*H*), 7.03 (1H, t, J = 6.7 Hz, C*H*), 6.55 (1H, s, N*H*), 6.22 (1H, dt, 7.9, 3.3 Hz, C*H*CH_2), 3.53 (4H, t, J = 4.9 Hz, 2 x NCH_2), 3.21 (2H, d, J = 6.7 Hz, CH_2), 2.54 (4H, t, J = 4.9 Hz, 2 x CH_2NCO).

^{13}C-NMR: δ_C 155.0 (CO), 139.0 (ArC), 133.7 (ArC), 128.9 (2eq, CH), 128.6 (2eq ArCH), 127.7 (2eq ArCH), 126.4 (2eq ArCH), 125.6 (ArCH), 123.1 (ArCH), 120.1 (2eq ArCH), 60.9 (CH_2), 52.7 (2eq $NHCH_2$), 44.0 (2eq CH_2). **HRMS ($M+H^+$)** $C_{20}H_{24}N_3O$ requires 322.1919, found 322.1910.

9.1.2. Solid-phase Synthesis of *N*-(4-Chlorophenyl)indolinylformamide [360]



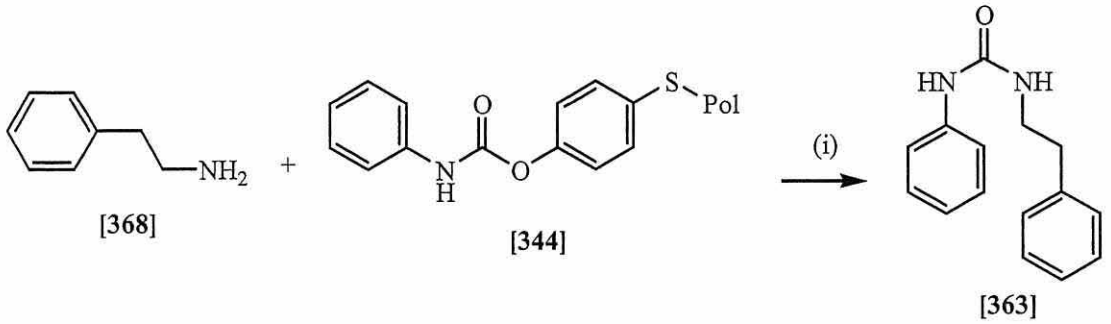
[368] [342] [361]

(i) CH_2Cl_2, toluene, NEt_3, 85 °C, 48 h.

N-(4-Chlorophenyl)(4-thiophenoxy)formamide bound resin (1.72 g, 3.03 mmol) **[342]** was pre-swelled in dichloromethane (10 ml) and further taken up in toluene (20 ml). Indoline (0.72 g, 6.0 mmol, 2.0 eq) **[367]** was added followed by triethylamine (1 ml). The reaction was stirred and heated to 85 °C for 48 h. The resin was collected by filtration and washed with water (200 ml) and dichloromethane (200 ml). Solvents were removed from the washings in *vacuo*, producing a dense white solid. The resin was collected by filtration and found to be the 4-hydroxythiophenol bound resin **[340]**, as determined by FTIR.

Yield 0.51 g (62 %). **m.p.** 170 - 175 °C. **FT IR:** ν_{max} **(cm^{-1})** 3310 (NH), 3086 (=C-H), 1632 (C=O), 1593 (NH). **^{1}H-NMR (60 MHz, $CDCl_3$):** δ_H 7.60 (1H, s, N*H*), 7.45 - 6.9 (8H, m, Ar*H*), 4.02 (2H, t, CH_2NC=O), 2.84 (2H, t, CH_2CH) (poor resolution).

9.1.3. Solid-phase Synthesis of 1-Phenethyl-3-phenyl Urea [363]



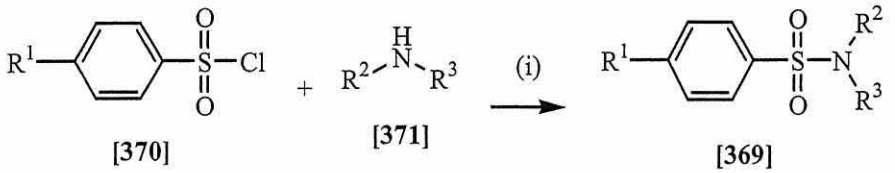
(i) CH_2Cl_2, toluene, NEt_3, 85 °C, 48 h.

(4-Thiophenoxy)-*N*-benzamide resin (5.00 g) was swollen in dichloromethane (20 ml) and 2-phenylethylamine (3.63 g, 30.0 mmol) in toluene (50 ml) was added followed by triethylamine (1 ml). The resultant mixture was stirred and heated at 85 °C for 24 h. The mixture was allowed to cool to room temperature and then the resin removed by filtration and washed with water (200 ml) and dichloromethane (200 ml). The washings were concentrated in *vacuo* to yield the solid product. As with the previous reaction 4-hydroxythiophenol resin **[340]** was regenerated after product cleavage.

Yield 1.48 g (82 %). **m.p.** 133 – 138 °C. **FT IR: ν_{max} (cm^{-1})** 3327 (NH), 3000 (=C-H), 1649 (C=O), 1595 (NH). **^{1}H-NMR (250 MHz, $CDCl_3$): δ_H** 7.37 (1H, d, J = 3.8 Hz, Ar*H*), 7.29 – 7.17 (8H, m, Ar*H*), 6.97 (1H, dt, J = 5.8, 3.8 Hz, Ar*H*), 3.42 (2H, t, J = 3.5 Hz, CH_2NH), 2.77 (2H, t, J = 3.5 Hz, CH_2). **^{13}C-NMR: δ_C** 156.3 (CO), 139.2 (ArC), 138.9 (ArC), 129.0 (ArCH), 128.9 (2eq ArCH), 128.8 (2eq ArCH), 128.5 (ArCH), 126.3 (ArCH), 123.0 (ArCH), 119.9 (ArCH), 119.5 (ArCH), 41.1 (CH_2), 36.1 (CH_2).

9.2. SULFONAMIDE SYNTHESIS

9.2.1. Solution-phase Synthesis



[370] [371] [369]

(i) Pyridine, 85 °C, 18 h.

General Preparation: 4-Chlorobenzenesulfonyl chloride (sulfonyl chloride **[370]**, 1 eq) (5.82 g, 27.6 mmol) was added to 2-(3,4-dimethoxyphenyl)ethylamine (amine **[371]**, 1 eq) (5.00 g, 27.6 mmol) in pyridine (50 ml). The mixture was stirred and heated at 85 °C for 24 h. A yellow solid formed which was recrystallised by dissolving in methanol (100 ml) and slowly adding water until a solid formed. The solid was collected by filtration and recrystallisation achieved from dichloromethane/petrol.

9.2.1.1. 4-Chloro-*N*-[2-(3,4-dimethoxy-phenyl)-ethyl]-benzenesulfonamide [372]

R^1 = Cl, R^2 = 2-(3,4-Dimethoxyphenyl)ethylamine, R^3 = H

Yield 5.45 g (56 %). **m.p.** 92 - 95 °C. **^{1}H-NMR (250 MHz, $CDCl_3$):** δ 7.68 (2H, d, J = 8.5 Hz, Ar*H*), 7.42 (2H, d, J = 8.5 Hz, Ar*H*), 6.72 (1H, d, J = 8.0 Hz, Ar*H*), 6.62 - 6.55 (2H, m, Ar*H*), 3.84 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.14 (2H, t, J = 6.8 Hz, NHCH_2), 2.68 (2H, t, J = 6.8 Hz, CH_2CH$_2$). **Microanalysis** $C_{16}H_{18}ClNO_4S$ requires C: 54.01, H: 5.10 N: 3.94 %, found C: 53.8, H: 5.0, N: 4.0 %.

9.2.1.2. 4-Bromomethyl-*N*-[2-(3,4-dimethoxyphenyl)ethyl] benzene sulfonamide [373]

R^1 = CH_2Br, R^2 = 2-(3,4-Dimethoxyphenyl)ethylamine, R^3 = H

Yield 8.2 g (72 %). **m.p.** 95 - 100 °C. **^{1}H-NMR (250 MHz, $CDCl_3$):** δ_H 7.67 (2H, d, J = 8.0 Hz, Ar*H*), 7.45 (2H, d, J = 8.0 Hz, Ar*H*), 6.74 – 6.55 (3H, m, Ar*H*), 4.47 (2H, s, CH_2Br), 3.82 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.13 (2H, t, J = 6.6 Hz, NHCH_2), 2.66 (2H, t, J = 6.6 Hz, CH_2CH$_2$). **Microanalysis** $C_{17}H_{20}BrNO_4S$ requires C: 49.28, H: 4.87 N: 3.38 %, found C: 49.5, H: 4.8, N: 3.4 %.

9.2.1.3. *N*-Pyridin-3-yl-methyl-benzenesulfonamide [374]

R^1 = H, R^2 = 3-Aminomethylpyridine, R^3 = H

Yield 7.42 g (65 %). **m.p.** 127 - 129 °C. **FT IR:** ν_{max} **(cm^{-1})** 3020 (=C-H), 1584 (NH) 1323, 1160 (S=O). **^{1}H-NMR (250 MHz, $CDCl_3$):** δ_H 8.41 (1H, d, J = 4.0 Hz, Ar*H*), 8.35 (1H, s, N*H*), 7.87 – 7.82 (2H, m, Ar*H*), 7.63 – 7.45 (4H, m, ArH), 7.18 (1H, dd, J = 7.9, 4.9 Hz, Ar*H*), 6.12 (1H, t, J = 6.1 Hz, N*H*), 4.14 (2H, d, J = 6.1 Hz, CH_2). **^{13}C-NMR:** δ_C 148.84, 148.78 (2 x ArCH pyr), 139.8 (ArC), 136.0 (ArCH pyr), 132.8 (ArC pyr), 132.5 (ArCH), 129.2 (2eq ArCH), 127.0 (2eq ArCH), 123.7 (ArCH pyr), 44.6 ($NHCH_2$). **Microanalysis** $C_{12}H_{12}N_2O_2S$ requires C: 58.05, H: 4.87 N: 11.28 %, found C: 57.9, H: 4.9, N: 11.4 %.

9.2.1.4. *N*-(4-Phenethylsulfamoyl-phenyl)-acetamide [375]

R^1 = Acetamido, R^2 = 2-Phenylethylamine, R^3 = H

Yield 0.65 g (12 %). **m.p.** 131 - 134 °C. **FT IR:** ν_{max} **(cm^{-1})** 3279 (NH), 3026 (=C-H), 2937 (CH), 1683 (C=O), 1592 (NH), 1371 (S=O), 1156 (S=O). **^{1}H-NMR (250 MHz, $CDCl_3$):** δ_H 7.71 – 7.59 (4H, m, Ar*H*), 7.20 – 7.08 (5H, m, Ar*H*/N*H*), 6.99 (2H, d, J = 7.9 Hz, Ar*H*), 3.01 (2H, t, J = 7.0 Hz, NHCH_2), 2.63 (2H, t, J = 7.0 Hz, CH_2CH_2), 2.07 (3H, s, H_3CC=O). **^{13}C-NMR:** δ_C 169.4 (CO), 142.7 (ArC), 138.3 (ArC), 128.7 (ArC), 128.3 (2eq ArCH), 127.7 (2eq ArC), 126.3 (2eq ArCH), 119.0 (ArCH), 113.6 (2eq ArCH), 44.1 ($NHCH_2$), 35.7 (CH_2), 24.3 (CH_3). **HRMS (M+Na$^+$)** $C_{16}H_{18}N_2NaO_3S$ requires 341.0936, found 341.0932.

9.2.1.5. *N*-[4-(4-Phenoxy-phenylsulfamoyl)-phenyl]-acetamide [376]

R^1 = Acetamido, R^2 = 4-Phenoxyaniline, R^3 = H

Yield 5.75 g (88 %). **m.p.** 143 - 148 °C. **FT IR:** ν_{max} **(cm^{-1})** 3306 (NH), 3017 (=C-H), 1682 (C=O), 1590 (NH), 1316 (S=O), 1156 (S=O). **^{1}H-NMR (250 MHz, $CDCl_3$):** δ 10.31 (1H, s, N*H*), 10.05 (1H, s, N*H*), 7.71 (2H, d, J = 4.4 Hz, Ar*H*), 7.64 (2H, d, J = 4.4 Hz, Ar*H*), 7.37 - 7.33 (2H, m, Ar*H*), 7.12 - 7.06 (3H, m, Ar*H*), 6.93 - 6.89 (4H, m, Ar*H*), 2.07 (3H, s, CH_3C=O). **^{13}C-NMR:** δ_C 169.5 (CO), 157.4 (ArC), 153.5 (ArC), 143.6 (ArC), 133.8 (ArC), 133.4 (ArC), 130.5 (2eq ArCH), 128.4 (2eq ArCH), 123.7

(ArCH), 123.2 (2eq ArCH), 120.0 (2eq ArCH), 119.0 (2eq ArCH), 118.9, 118.6 (2 x ArCH), 24.6 (CH_3). **HRMS ($M+H^+$)** $C_{20}H_{19}N_2O_4S$ requires 383.1066, found 383.1061.

9.2.1.6. *N*-[4-(4-Benzyl-piperazine-1-sulfonyl)-phenyl]-acetamide [377]

R^1 = Acetamido, R^2/R^3 = 1-Benzylpiperazine

Yield 1.38 g (22 %). **m.p.** 249 - 252 °C. **^{1}H-NMR (60 MHz, $CDCl_3$): δ_H** 10.54 (1H, s, N*H*), 7.95 – 7.10 (9H, m, Ar*H*), 4.5 (2H, s, CH_2Ph), 2.36 (8H, m, 4 x CH_2), 1.90 (CH_3C=O). **HRMS ($M+H^+$)** $C_{19}H_{24}N_3O_3S$ requires 374.1538, found 374.1545.

9.2.1.7. *N*-[4-(4-Pyridin-2-yl-piperazine-1-sulfonyl)-phenyl]-acetamide [378]

R^1 = Acetamido, R^2/R^3 = 1-(2-Pyridylpiperazine)

Yield 1.37 g (22 %). **FT IR: ν_{max} (cm^{-1})** 3347 (NH), 3019 (=C-H), 1705 (C=O), 1537 (NH). **^{1}H-NMR (250 MHz, $CDCl_3$): δ_H** 10.38 (1H, s, N*H*), 8.07 (1H, dd, J = 2.4, 0.6 Hz, Ar*H* pyr), 7.82 (2H, d, J = 4.4 Hz, Ar*H*), 7.68 (2H, d, J = 4.4 Hz, Ar*H*), 7.51 (1H, m, Ar*H* pyr), 6.80 (1H, d, J = 4.4 Hz, Ar*H* pyr), 6.38 (1H, dd, J = 3.5, 2.4 Hz, Ar*H* pyr), 3.36 (1H, s, N*H*), 3.57 (4H, t, J = 2.4 Hz, $(SO_2)NCH_2$), 2.89 (4H, t, J = 2.4 Hz, $PhNCH_2$) 2.09 (3H, s, CH_3C=O). **^{13}C-NMR: δ_C** 169.5 (CO), 158.7 (ArC), 147.8 (ArCH pyr), 144.1 (ArC), 138.2 (ArCH pyr), 129.3 (ArC), 128.5 (2eq ArCH), 119.1 (2eq ArCH), 114.0 (ArCH pyr), 108.0 (ArCH pyr), 46.0 (2eq CH_2), 44.5 (2eq CH_2), 24.6 (CH_3). **Microanalysis** $C_{12}H_{12}N_2O_2S$ requires C: 56.65, H: 5.59 N: 15.54 %, found C: 56.7, H: 5.6, N: 15.5 %.

9.2.1.8. 1-(4-Iodo-benzenesulfonyl)-4-pyridin-2-yl-piperazine [379]

R^1 = I, R^2/R^3 = 1-(2-Pyridyl)piperazine

Yield 2.1 g (37 %). **FT IR: ν_{max} (cm^{-1})** 3019 (=C-H), 1359 (S=O), 1168 (S=O). **^{1}H-NMR (250 MHz, $CDCl_3$): δ_H** 7.87 (1H, dd, J = 5.2, 1.8 Hz, Ar*H* pyr), 7.63 (2H, d, J = 8.6 Hz, Ar*H*), 7.30 - 7.22 (3H, m, Ar*H*), 6.51 - 6.40 (2H, m, Ar*H* pyr), 3.32 (4H, t, J = 4.6 Hz, $(SO_2)NCH_2$), 2.84 (4H, t, J = 4.6 Hz, $PhNCH_2$). **^{13}C-NMR: δ_C** 157.9 (ArC pyr), 147.0 (ArCH pyr), 138.2 (ArC), 137.9 (2eq ArCH), 137.0 (ArCH pyr), 134.8 (ArC pyr), 128.7 (2eq ArCH), 113.9 (ArCH pyr), 107.4 (ArCH pyr), 100.6 (ArCI), 45.5 (2eq CH_2), 44.5 (2eq CH_2). **HRMS ($M+H^+$)** $C_{15}H_{17}IN_3O_2S$ requires 430.0086, found 430.0062.

9.2.1.9. 1-(4-Iodo-benzenesulfonyl)-4-phenyl-piperazine [380]

R^1 = I, R^2/R^3 = 1-Phenylpiperazine

Yield 2.10 g (37 %). **m.p.** 98 - 101 °C. **FT IR:** ν_{max} **(cm^{-1})** 3019 (=C-H), 2820 (CH), 1341, 1168 (S=O). **^{1}H-NMR (250 MHz, $CDCl_3$):** δ_H 8.06 (2H, d, J = 4.1 Hz, Ar*H*), 7.52 (2H, d, J = 4.1 Hz, Ar*H*), 7.22 (1H, d, J = 3.6, Ar*H*), 7.19 (1H, d, J = 3.6 Hz, Ar*H*), 6.90 (2H, d, J = 4.0 Hz, Ar*H*), 6.80 (1H, t, J = 3.6 Hz, Ar*H*), 3.19 (4H, t, J = 2.5 Hz, $(SO_2)NCH_2$), 3.01 (4H, t, J = 2.5 Hz, $PhNCH_2$). **^{13}C-NMR:** δ_C 150.8 (ArC), 138.9 (ArC), 134.8 (2eq ArCH), 129.6 (2eq ArCH), 129.5 (2eq ArCH), 120.2 (ArCH), 116.5 (2eq ArCH), 102.4 (ArCI), 48.4 (2eq CH_2), 46.3 (2eq CH_2). **Microanalysis** $C_{16}H_{17}IN_2O_2S$ requires C: 44.87, H: 4.00 N: 6.54 %, found C: 44.9, H: 4.1, N: 6.8 %.

9.2.1.10. *N*-[2-(3,4-Dimethoxy-phenyl)-ethyl]-4-iodo-benzenesulfonamide [381]

R^1 = I, R^2 = 2-(3,4-Dimethoxyphenyl)ethylamine, R^3 = H

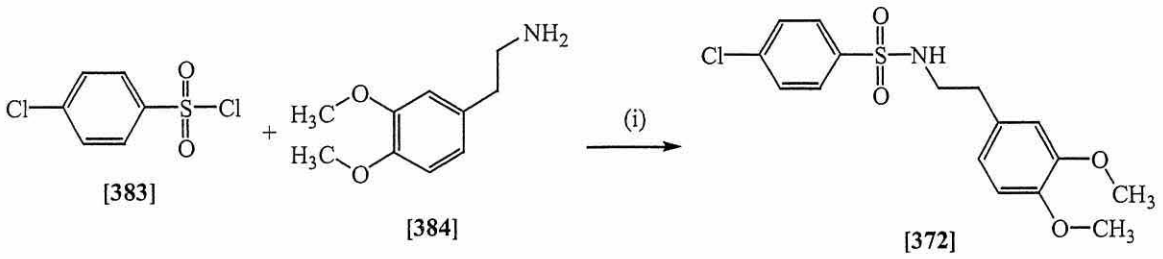
Yield 2.35 g (40 %). **m.p.** 98 - 104 °C. **FT IR:** ν_{max} **(cm^{-1})** 3260 (NH), 3021 (=C-H), 2959 (CH), 1329 (S=O), 1160 (S=O). **^{1}H-NMR (250 MHz, $CDCl_3$):** δ_H 7.84 (2H, d, J = 4.3 Hz, Ar*H*), 7.50 (2H, d, J = 4.3 Hz, Ar*H*), 6.78 (1H, d, J = 4.0 Hz, Ar*H*), 6.63 (1H, d, J = 4.0 Hz, Ar*H*), 6.59 (1H, s, Ar*H*), 3.84 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.20 (2H, m, $NHCH_2$), 2.73 (2H, t, J = 3.3 Hz, CH_2CH_2). **^{13}C-NMR:** δ_C 149.2 (ArC), 148.0 (ArC), 139.6 (ArC), 138.3 (2eq ArCH), 129.8 (ArC), 128.5 (2eq ArCH), 120.7 (ArCH), 111.7 (ArCH), 111.4 (ArCH), 99.9 (ArCI), 56.0, 55.9 (2 x CH_3), 44.3 ($NHCH_2$), 35.3 (CH_2). **HRMS ($M+Na^+$)** $C_{16}H_{18}INNaO_4S$ requires 469.9899, found 469.9884.

9.2.1.11. 1-Benzhydryl-4-(naphthalene-2-sulfonyl)-piperazine [382]

R^1 = Naphthalene-sulfonyl chloride, R^2/R^3 = 1-Benzhydrylpiperazine

Yield 58 %. **m.p.** 133 - 135 °C. **FT IR:** ν_{max} **(cm^{-1})** 3022 (=C-H), 2817 (CH), 1347 (S=O), 1165 (S=O). **^{1}H-NMR (250 MHz, $CDCl_3$):** δ_H 8.36 (1H, s, Ar*H*), 7.97 (3H, m, Ar*H*), 7.81 - 7.63 (3H, m, Ar*H*), 7.34 - 7.14 (11H, m, Ar*H*), 4.4 (1H, s, $CHPh_2$), 2.2 (4H, m, $(SO_2N(CH_2)_2)$), 1.5 (4H, m, $(CH_2)_2NCH$). **HRMS ($M+H^+$)** $C_{27}H_{27}N_2O_2S$ requires 443.1793, found 443.1780.

9.2.2. Scavenger Resin Synthesis of (2-(3,4-Dimethoxyphenyl)ethyl)((4-chlorophenyl)sulfonyl)amine [372]

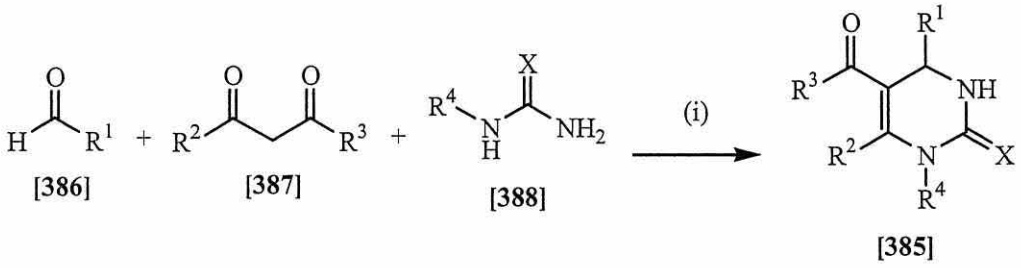


(i) CH_2Cl_2, poly(4-vinyl)pyridine, 85 °C, 4 h.

4-Chlorobenzenesulfonyl chloride (4.66 g, 22.1 mmol) **[383]** was dissolved in dichloromethane (30 ml) and added to a solution of 2-(3,4-dimethoxyphenyl) ethylamine (4.00 g, 22.09 mmol) **[384]**. Poly(4-vinyl)pyridine scavenger resin (6.97 g, 22.1 mmol) was added and the reaction was stirred and heated to 85 °C for 4 h. The deactivated scavenger resin was collected by filtration and washed with dichloromethane. Petrol was added to the filtrate and pale beige crystals formed. The product was refluxed in methanol, filtered and oven dried at 50 °C to yield the title compound.

Yield 3.04 g (45 %). **^{1}H-NMR (60 MHz):** δ_H 7.72 (2H, d, J = 8.4 Hz, Ar*H*), 7.43 (2H, d, J = 8.4 Hz, Ar*H*), 6.71 (1H, d, J = 7.9 Hz, Ar*H*), 6.52 (2H, d, J = 7.9 Hz, Ar*H*), 3.75 (3H, s, OC*H*$_3$), 3.70 (3H, s, OC*H*$_3$), 3.12 (2H, t, J = 6.7 Hz, NHC*H*$_2$), 2.65 (2H, t, J = 6.7 Hz, C*H*$_2$CH$_2$).

9.3. DIHYDROPYRIMIDIN-ONE AND –THIONE SYNTHESIS



(i) MeOH, c. HCl, 85 °C, 18 h. (X = S, O)

General Preparation: 1-Naphthaldehdye (5.00 g, 32.0 mmol) (aldehyde **[386]**) was dissolved in methanol (80 ml) and ethyl acetoacetate **[386]** (4.16 g, 32.0 mmol) and thiourea **[387]** (2.44 g, 32.0 mmol) were added and the reaction stirred. Hydrochloric acid (ca 5 drops) was then added and the reaction further stirred and was heated at 85 °C for 18 h. A solid formed which was collected by filtration and dissolved in methanol. The glass was scratched and crystals slowly formed. The solid was collected and washed with petrol to yield the title compound.

Attempted Alternative Preparation: 1-Naphthaldehdye (5.00 g, 32.0 mmol) (aldehyde **[386]**) was dissolved in methanol (50 ml) and ethyl acetoacetate **[386]** (4.16 g, 32.0 mmol) and thiourea **[387]** (2.44 g, 32.0 mmol) were added and the reaction stirred. Poly(4-vinyl)pyridine hydrochloride beads (14.70 g) were then added and the reaction further stirred and heated to 85 °C for 8 h. The resin was collected, washed with methanol (100 ml) and concentrated *in vacuo* and crystals slowly formed. The product was collected by filtration and washed with dichloromethane to yield white crystals. ^{1}H-NMR analysis of the crystals obtained proved that the reaction had been unsuccessful as the spectra contained none of the characteristic signals for such a compound.

9.3.1. 6-Methyl-4-naphthalen-1-yl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxlic acid ethyl ester [389]

[386] = 1-Naphthaldehyde, **[387]** = Ethyl acetoacetate, R^4 = H, X = S

Yield 2.66 g (26 %). **m.p.** 198 - 200 °C (impure). **FT IR:** ν_{max} **(cm^{-1})** 3293 (NH), 3167 (NH), 2996 (=C-H), 1661 (C=O) 1575 (NH). **^{1}H-NMR (250 MHz, $CDCl_3$):** δ_H 9.48 (1H, s, N*H*), 8.54 (1H, s, N*H*), 8.07 (1H, d, J = 8.2 Hz, Ar*H*), 7.68 (1H, d, J = 7.9 Hz,

Ar*H*), 7.61 - 7.20 (5H, m, Ar*H*), 6.01 (1H, d, J = 3.0 Hz, C*H*NH), 3.59 (2H, m, C*H*$_2$CH$_3$)*, 2.26 (3H, s, C*H*$_3$), 0.77 (3H, t, J = 7.0 Hz, C*H*$_3$CH$_2$). **^{13}C-NMR:** δ_C 174.0 (CS), 165.9 (CO), 144.7 (C=C), 138.6 (ArC), 133.6 (ArC), 130.1 (ArC), 128.6 - 122.9 (7 x ArCH), 101.4 (C=C), 59.7 (CH_2), 51.0 (CH), 17.7 (CH_3), 13.7 (CH_3). **HRMS (M+H$^+$)** $C_{18}H_{19}N_2O_2S$ requires 327.1167, found 327.1139.

* This signal was complex, apparently containing overlapping quartets, probably because it contains the signals for two diastereotopic hydrogens.

9.3.2. 4-(4-Isopropyl-phenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid methyl ester [390]

[386] = Isopropylbenzaldehyde, **[387]** = Methyl acetoacetate, R^4 = H, X = S

Yield 7.5 g (60 %). **m.p.** 185 - 187 °C. **FT IR:** ν_{max} **(cm^{-1})** 3184 (NH), 3019 (=C-H), 2963 (CH), 1706 (C=O) 1562 (NH). **^{1}H-NMR (250 MHz, $CDCl_3$):** δ_H 9.47 (1H, s, N*H*), 8.80 (1H, s, N*H*), 6.92 (2H, d, J = 8.2 Hz, Ar*H*), 6.85 (2H, d, J = 8.2 Hz, Ar*H*), 5.01 (1H, d, J = 3.7 Hz, C*H*NH), 3.34 (3H, s, OC*H*$_3$), 2.54 (1H, m, C*H*(CH$_3$)$_2$), 2.07 (3H, s, C*H*$_3$), 0.92 (6H, d, J = 7.0 Hz (C*H*$_3$)$_2$CH). **^{13}C-NMR:** δ_C 174.5 (CS), 166.0 (CO), 148.1 (C=C), 144.5 (ArC), 140.7 (ArC), 126.9 – 126.1 (4 x ArCH), 101.5 (C=C), 54.6 (CH), 50.9 (CH_3), 33.5 (CH), 23.7 (2eq CH_3), 17.6 (CH_3). **HRMS (M+H$^+$)** $C_{16}H_{21}N_2O_2S$ requires 305.1324, found 305.1318.

9.3.3. 4-(4-Chloro-phenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid methyl ester [391]

[386] = 4-chlorobenzaldehyde, **[387]** = Methyl acetoacetate, R^4 = H, X = S

Yield 5.50 g (43 %). **FT IR:** ν_{max} **(cm^{-1})** 3310 (NH), 3185 (NH), 3023 (=C-H), 2951 (CH), 1670 (C=O) 1573 (NH). **^{1}H-NMR (250 MHz, $CDCl_3$):** δ_H 10.30 (1H, s, N*H*), 9.60 (1H, s, N*H*), 7.30 (2H, m, Ar*H*), 7.20 (2H, m, Ar*H*), 5.19 (1H, d, J = 1.9 Hz, C*H*NH), 3.56 (3H, s, OC*H*$_3$), 2.30 (3H, s, C*H*$_3$). **^{13}C-NMR:** δ_C 174.8 (CS), 165.9 (CO), 145.9 (C=C), 142.6 (ArC), 132.9 (ArC), 131.4 (ArCH), 129.6 (ArCH), 128.8 (ArCH), 128.6 (ArCH), 100.6 (C=C), 53.8 (CH), 51.3 (CH_3), 17.7 (CH_3). **Microanalysis** $C_{13}H_{13}ClN_2O_2S$ requires C: 52.61, H: 4.42 N: 9.44 %, found C: 52.2, H: 4.5, N: 9.3 %.

9.3.4. 4-(2-Methoxy-phenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid methyl ester [392]

[386] = 2-Methoxybenzaldehyde, **[387]** = Methyl acetoacetate, R^4 = H, X = S

Yield 6.20 g (49 %). **m.p.** 246 - 249 °C. **FT IR:** ν_{max} **(cm^{-1})** 3121 (NH), 3019 (=C-H), 2952 (CH), 1713 (C=O) 1581 (NH). **^{1}H-NMR (250 MHz, $CDCl_3$):** δ_H 10.39 (1H, s, N*H*), 9.14 (1H, s, N*H*), 7.22 (1H, td, J = 8.2, 1.8 Hz, Ar*H*), 7.06 - 6.97 (2H, m, Ar*H*), 6.85 (1H, t, J = 7.3 Hz, Ar*H*), 5.51 (1H, d, J = 3.7 Hz, C*H*NH), 3.82 (3H, s, OCH_3), 3.51 (3H, s, OCH_3), 2.32 (3H, s, CH_3). **^{13}C-NMR:** δ_C 174.5 (CS), 165.7 (CO), 156.8 (ArC-O), 145.6 (C=C), 130.3 (ArC), 129.1 (ArCH), 127.5 (ArCH), 120.2 (ArCH), 111.3 (ArCH), 99.1 (C=C), 55.5 (CH_3), 50.9 (CH_3), 49.5 (CH), 17.2 (CH_3). **HRMS ($M+Na^+$)** $C_{14}H_{16}N_2NaO_3S$ requires 315.0779, found 315.0774.

9.3.5. 6-Methyl-4-(3-phenoxyphenyl)-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid methyl ester [393]

[386] = 3-Phenoxybenzaldehyde, **[387]** = Methyl acetoacetate, R^4 = H, X = S

Yield 1.12 g (23 %). **m.p.** 188 – 190 °C. **FT IR:** ν_{max} **(cm^{-1})** 3332 (NH), 3179 (NH), 3021 (=C-H), 2957 (CH), 1670 (C=O) 1574 (NH). **^{1}H-NMR (250 MHz, $CDCl_3$):** δ_H 9.16 (1H, s, N*H*), 8.51 (1H, s, N*H*), 7.28 – 7.13 (3H, m, Ar*H*), 6.97 (1H, t, J = 7.3 Hz, Ar*H*), 6.92 - 6.74 (5H, m, Ar*H*), 5.21 (1H, s, C*H*NH), 3.50 (3H, s, OCH_3), 2.22 (3H, s, CH_3). **^{13}C-NMR:** δ_C 174.5 (CS), 166.0 (CO), 157.5 (ArC-O), 156.6 (ArC-O), 144.5 (C=C), 144.2 (C=C), 130.0 – 116.8 (9 x ArCH), 101.7 (C=C), 55.0 (CH_3), 51.2 (CH_3), 17.6 (CH_3). **HRMS ($M+H^+$)** $C_{19}H_{19}N_2O_3S$ requires 355.1116, found 355.1111.

9.3.6. 4-(3,4-Dimethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid methyl ester [394]

[386] = 3,4-Dimethoxybenzaldehyde, **[387]** = Methyl acetoacetate, R^4 = H, X = S

Yield 5.60 g (40 %). **m.p.** 187 – 189 °C. **FT IR:** ν_{max} **(cm^{-1})** 3295 (NH), 3173 (NH), 3020 (=C-H), 2950 (CH), 1658 (C=O) 1576 (NH). **^{1}H-NMR (250 MHz, $CDCl_3$):** δ_H 9.17 (1H, s, N*H*), 8.57 (1H, s, Ar*H*), 6.74 - 6.64 (3H, m, Ar*H*), 5.17 (1H, s, C*H*NH), 3.68 (6H, s, 2 x OCH_3), 3.50 (3H, s, OCH_3), 2.20 (3H, s, CH_3). **^{13}C-NMR:** δ_C 174.0

(CS), 166.3 (CO), 148.8 (C=C), 143.9 (ArC-O), 143.7 (ArC-O), 135.3 (C=C), 118.7 (ArCH), 111.1 (ArCH), 109.9 (ArCH), 102.0 (C=C), 55.6 (2eq CH_3), 54.9 (CH), 51.2 (CH_3), 17.6 (CH_3). **HRMS ($M+H^+$)** $C_{15}H_{19}N_2O_4S$ requires 323.1066, found 323.1031.

9.3.7. 6-Methyl-4-naphthalen-1-yl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid methyl ester [395]

[386] = Naphthaldehyde, **[387]** = Methyl acetoacetate, R^4 = H, X = S

Yield 6.0 g (45 %). **m.p.** 239 - 242 °C **FT IR: ν_{max} (cm^{-1})** 3284 (NH), 3158 (NH), 3020 (=C-H), 1662 (C=O), 1575 (NH). **^{1}H-NMR (60 MHz): δ_H** 10.48 (1H, s, N*H*), 9.73 (1H, s, N*H*), 8.42 (1H, d, J = 7.3 Hz, Ar*H*), 7.82 - 7.47 (6H, m, Ar*H*), 6.11 (1H, s, C*H*), 3.48 (3H, s, OCH_3), 2.42 (3H, s, CH_3). **HRMS ($M+H^+$)** $C_{17}H_{17}N_2O_2S$ requires 313.1011, found 313.1005.

9.3.8. 6-Methyl-2-oxo-4-(3-phenoxy-phenyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid methyl ester [396]

[386] = 3-Phenoxybenzaldehyde, **[387]** = Ethyl acetoacetate, R^4 = H, X = O

Yield 2.68 g (39 %). **m.p.** 162 - 165 °C. **FT IR: ν_{max} (cm^{-1})** 3235 (NH), 3111 (NH), 3019 (=C-H), 2229 (C≡N), 1701 (C=O) 1583 (NH). **^{1}H-NMR (250 MHz, $CDCl_3$): δ_H** 8.32 (1H, s, N*H*), 7.60 (1H, s, N*H*), 7.29 - 7.24 (2H, m, Ar*H*), 7.17 (1H, t, J = 4.0 Hz, Ar*H*), 7.02 (1H, t, J = 3.8 Hz, Ar*H*), 6.98 (1H, d, J = 3.8 Hz, Ar*H*), 6.91 - 6.85 (3H, m, Ar*H*), 6.79 (1H, dd, J = 4.9, 0.8 Hz, Ar*H*), 5.25 (1H, s, C*H*NH), 3.53 (3H, s, OCH_3), 2.25 (3H, s, CH_3). **^{13}C-NMR: δ_C** 166.0 (CO), 157.6 (CO), 156.9 (ArCO), 153.6 (ArCO), 147.0 (ArC), 145.6 (C=C), 130.2 (ArCH), 129.8 (2eq ArCH), 123.5 (ArCH), 121.1 (ArCH), 119.1 (2eq ArCH), 117.9 (ArCH), 117.0 (ArCH), 100.8 (C=C), 55.2 (CH_3), 51.2 (CH), 18.6 (CH_3). **HRMS ($M+H^+$)** $C_{19}H_{19}N_2O_4$ requires 339.1345, found 339.1339.

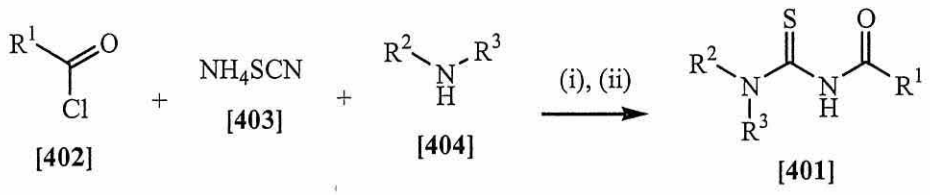
9.3.9. 2-Oxo-6-phenyl-4-(3,4,5-trimethox-phenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester [397]

[386] = 3,4,5-Trimethoxybenzaldehyde, **[387]** = Ethylbenzoyl acetate, R^4 = H, X = O

Yield 3.38 g (32 %). **FT IR:** ν_{max} **(cm^{-1})** 3323 (NH), 3202 (NH), 3018 (=C-H), 1697 (C=O), 1645 (C=O), 1596 (NH). **^{1}H-NMR (250 MHz, $CDCl_3$):** δ_H 8.95 (1H, s, N*H*), 7.15 - 7.06 (6H, m, Ar*H* and N*H*), 6.35 (2H, s, Ar*H*), 5.14 (1H, d, J = 3.0 Hz, C*H*NH), 3.59 (6H, 2s, 2 x OCH_3), 3.56 (2H, unresolved CH_2), 3.54 (3H, s, OCH_3), 0.58 (3H, t, J = 7.0 Hz, CH_3). **^{13}C-NMR:** δ_C 165.3 (CO), 153.0 (2eq ArCO), 152.9 (CO), 147.9 (C=C), 139.5 (ArC), 137.0 (ArC), 135.1 (ArC), 129.0 (ArC), 127.9 (2eq ArCH), 127.8 (2eq ArCH), 103.3 (2eq ArCH), 101.3 (C=C), 60.4 (CH_3), 59.5 (CH_3), 55.8 (2eq CH_3), 55.0 (CH), 13.4 (CH_3). **HRMS ($M+H^+$)** $C_{22}H_{25}N_2O_6$ requires 413.1713, found 413.1707.

9.4. THIOUREA CHEMISTRY

9.4.1. Thiourea Derivative Synthesis



(i) Acetone, r.t. 1 h.., (ii) 85 °C, 30 min.

General Preparation: Cyclopropane carbonylchloride (5.00 g, 48.1 mmol) **[402]** was dissolved in acetone (100 ml), ammonium thiocyanate (3.64 g, 48.1 mmol) **[403]** was added and the mixture was stirred at room temperature for 1 h. 5-Amino-2-methoxypyridine (5.94 g, 48.1 mmol) **[404]** was added and the reaction further stirred and heated for 30 min. Water (100 ml) was added and a heavy solid formed which was collected by filtration. The solid was precipitated by dissolving in methanol (100 ml) and adding water until a solid formed (repeated twice). Final recrystallisation took place by dissolving the solid in dichloromethane (100 ml) and adding petrol until a crystalline solid formed. Extracting with methanol at 85 °C removed any impurities and gave the title product in pure form.

9.4.1.1. 1-Cyclopropanecarbonyl-3-(6-methoxypyridin-3-yl)-thiourea [405]

[402] = Cyclopropane carbonyl chloride, **[404]** = 5-Amino-2-methoxypyridine

Yield 7.12 g (60 %). **m.p.** 155 – 157 °C. **FT IR:** ν_{max} **(cm^{-1})** 3177 (NH), 3020 (=CH), 1683 (C=O) 1534 (NH). **^{1}H-NMR (250 MHz, $CDCl_3$):** δ_H 12.25 (1H, s, N*H*), 9.82 (1H, s, N*H*), 8.22 (1H, d, J = 2.6 Hz, Ar*H*), 7.83 (1H, dd, J = 8.9, 2.6 Hz, Ar*H*), 6.77 (1H, d, J = 8.9 Hz, Ar*H*), 3.94 (3H, s, OCH_3), 1.60 (1H, m, $CH(CH_2)_2$), 0.98 (4H, m, $CH(CH_2)_2$). **^{13}C-NMR:** δ_C 179.5 (CO), 175.1 (CS), 162.6 (ArC), 143.0 (ArCH), 136.0 (Ar), 128.3 (ArCH), 110.7 (ArCH), 53.8 (OCH_3), 15.7 (CH), 10.1 (2eq CH_2). **HRMS (M+H$^+$)** $C_{11}H_{14}N_3O_2S$ required 252.0807, found 252.0801.

9.4.1.2. *N*-(4-Benzhydrylpiperazine-1-carbothioyl)-2,6-difluorobenzamide [406]

[402] = 2,6-Difluorobenzoyl chloride, **[404]** = 1-Benzhydrylpiperazine

Yield 1.81 g (24 %). **m.p.** 187 - 188 °C. **FT IR:** ν_{max} **(cm^{-1})** 3176 (NH), 3021 (=C-H), 1694 (C=O), 1540 (NH). **^{1}H-NMR (250 MHz, $CDCl_3$):** δ_H 7.46 - 7.12 (12H, m, Ar*H*), 6.89 (1H, t, J = 8.2 Hz, Ar*H*), 4.39 (1H, s, C*H*Ph$_2$), 3.65 (2H, s, C*H*$_2$NH), 3.25 (2H, s, C*H*$_2$N), 2.53 (4H, s, N(C*H*$_2$)$_2$). **^{13}C-NMR:** δ_C 183.3 (CS), 166.4 (CO), 163.3 (ArC), 162.6, 162.4 (2 x ArCF), 147.8 (2eq ArC), 138.2 (ArCH), 134.2 (4eq ArCH), 133.3 (4eq ArCH), 132.7 (2eq ArCH), 117.7, 117.4 (2 x ArCH), 79.8 (CH), 46.6 – 43.3 (4 x NCH_2). **Microanalysis** $C_{25}H_{23}F_2N_3OS$ requires C: 66.50, H: 5.13 N: 9.31 %, found C: 66.2, H: 5.1, N: 9.3 %.

9.4.1.3. 2,6-Difluoro-*N*-[4-(3-phenylallyl)piperazine-1-carbothioyl]-benzamide [407]

[402] = 2,6-Difluorobenzoyl chloride, **[404]** = *trans*-1-Cinnamylpiperazine

Yield 35 %. **m.p.** 141 - 143 °C. **^{1}H-NMR (250 MHz, $CDCl_3$):** δ_H 7.49 - 7.22 (6H, m, Ar*H*), 6.96 (2H, t, J = 8.2 Hz, Ar*H*), 6.53 (1H, d, J = 15.9 Hz, C*H*), 6.20 (1H, dt, J = 15.9, 6.7 Hz, C*H*), 4.24, 3.76 (2 x 2H, m, C*H*$_2$NC=S), 3.22 (2H, d, J = 6.7 Hz, C*H*$_2$), 2.68 (4H, t, J = 4.9 Hz, C*H*$_2$NC=S). **^{13}C-NMR:** δ_C 177.3 (CS), 162.1 (CO), 156.6, 158.0 (2 x ArCF), 136.5 (ArCH), 133.9 (ArC), 128.6 (2eq ArCH), 127.7 (CH, ArCH), 126.4 (2eq ArCH), 125.4 (CH), 112.7 (ArC), 112.4, 112.1 (2 x ArCH), 60.4 (4 NCH_2), 52.2 (CH_2). **Microanalysis** $C_{21}H_{21}F_2N_3OS$ requires C: 62.82, H: 5.27 N: 10.47 %, found C: 63.1, H: 5.4, N: 10.6 %.

9.4.1.4. *N*-[4-(2-Fluorophenyl)-piperazine-1-carbothioyl]-4-iodobenzamide [408]

[402] = 4-Iodobenzoylchloride, **[404]** = 1-(2-Fluorophenyl)piperazine

Yield 3.15 g (32 %). **m.p.** 148 - 150 °C. **FT IR:** ν_{max} **(cm^{-1})** 3258 (NH), 3017 (=C-H), 1671 (C=O), 1533 (NH). **^{1}H-NMR (250 MHz, $CDCl_3$):** δ_H 8.55 (1H, s, N*H*), 7.87 (2H, d, J = 8.6 Hz, Ar*H*), 7.59 (2H, d, J = 8.6 Hz, Ar*H*), 7.10 - 6.94 (4H, m, Ar*H*), 4.47 (4H, 2s, 2 x C*H*$_2$NCS), 3.27 (4H, 2s, 2 x C*H*$_2$NCH$_2$). **^{13}C-NMR:** δ_C 178.9 (CS), 162.6 (CO), 154.8 (ArCF), 138.3 (2eq ArCH), 131.8 (ArC), 129.1 (2eq ArCH), 128.9 (ArC), 124.6

(ArCH), 123.5 (ArCH), 119.4 (ArCH), 116.3 (ArCH), 100.7 (Ar CI), 51.5 (2eq NCH_2), 50.2 (2eq NCH_2). **HRMS (M+H$^+$)** $C_{18}H_{18}FIN_3OS$ requires 470.0199, found 470.0194.

9.4.1.5. 1-[3-(2-Chlorophenyl)-5-methylisoxazole-4-carbonyl]-3-[2-(3,4-dimethoxy-phenyl)-ethyl]-thiourea [409]

[402] = 3-(2-Chlorophenyl)-5-methyl-isoxazole-4-carbonyl chloride,
[404] = 2-(3,4-Dimethoxyphenyl)ethylamine

Yield 38 %. **m.p.** 78 – 80 °C. **FT IR: ν_{max} (cm^{-1})** 3378 (NH), 3252 (NH), 3019 (=C-H), 1676 (C=O) 1516 (NH). **^{1}H-NMR (250 MHz, $CDCl_3$): δ_H** 8.05 (1H, s, N*H*), 7.65 (1H, m, Ar*H*), 7.59 (1H, m, Ar*H*), 7.55 - 7.53 (2H, m, Ar*H*), 6.84 - 6.77 (3H, m, Ar*H*), 3.90 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.81 (3H, m, N*H* and CH_2), 2.92 (2H, t, J = 3.5 Hz, CH_2), 2.79 (3H, s, CH_3). **HRMS (M+H$^+$)** $C_{22}H_{23}ClN_3O_4S$ requires 460.1080, found 460.1098.

9.4.1.6. 1-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-3-phenyl acetyl thiourea [410]

[402] = Phenylacetyl chloride, **[404]** = 4-Aminoantipyrine

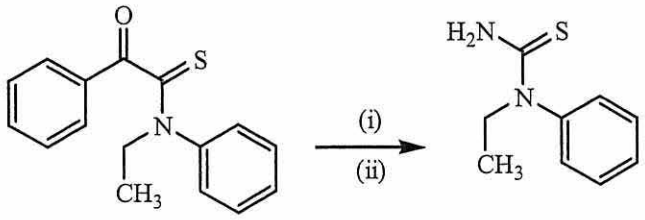
Yield 47 %. **m.p.** 205 – 207 °C. **FT IR: ν_{max} (cm^{-1})** 3180 (NH), 3019 (=C-H), 1694, 1647 (C=O), 1518 (NH). ^{1}H-NMR (250 MHz, $CDCl_3$): **δ_H** 7.55 - 7.29 (10H, m, Ar*H*), 3.90 (2H, s, CH_2Ph), 3.11 (3H, s, NCH_3), 2.17 (3H, s, CH_3). **HRMS (M+H$^+$)** $C_{20}H_{21}N_4O_2S$ requires 381.1385, found 381.1365.

9.4.1.7. 1-Phenylacetyl-3-(3-trifluoromethoxy-phenyl) thiourea [411]

[402] = Phenylacetyl chloride, **[404]** = 3-Trifluoromethoxyaniline

Yield 59 %. **FT IR: ν_{max} (cm^{-1})** 3384 (NH), 3180 (NH), 3020 (=C-H), 1690 (C=O) 1532 (NH). **^{1}H-NMR (250 MHz, $CDCl_3$): δ** 12.57 (1H, s, N*H*), 11.80 (1H, s, N*H*), 7.91 (1H, s, Ar*H*), 7.53 - 6.93 (8H, m, Ar*H*), 3.38 (2H, s, CH_2Ph). **Microanalysis** $C_{16}H_{13}F_3N_2O_2S$ requires C: 54.23, H: 3.70 N: 7.91 %, found C: 54.1, H: 3.8, N: 7.4 %.

9.4.2. Preparation of 1-Ethyl-1-phenyl-thiourea [414]



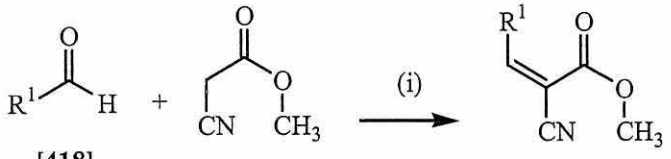
[413a]

(i) Potassium hydroxide, water; (ii) MeOH, reflux, 4 h.

3-Benzoyl-1-ethyl-1-phenyl-thiourea (6.80 g, 23.9 mmol) **[413a]** was added to a solution of potassium hydroxide (2.68 g, 47.8 mmol, 2.00 eq) in water (100 ml). Methanol (10 ml) was added to aid dissolving and the resultant mixture was refluxed for 4 h. Upon cooling the reaction mixture was added to water (100 ml) and acidified with hydrochloric acid until a thick white precipitate formed. The solid was collected by filtration and purification achieved by gently heating in methanol at 85 °C and washing with petrol.

Yield 38 %. **m.p.** 103 - 105 °C. **FT IR:** ν_{max} **(cm^{-1})** 3392 (NH), 3166 (NH), 3020 (=C-H), 1586 (NH bend). **^{1}H-NMR (250 MHz, $CDCl_3$):** δ_H 7.39 (2H, m, Ar*H*), 7.53 - 7.22 (3H, m, Ar*H*), 5.59 (2H, s (br), NH_2), 4.18 (2H, q, J = 7.3 Hz, CH_2CH_3), 1.19 (3H, t, J = 7.3 Hz, CH_3CH_2). **^{13}C-NMR:** δ_C 181.6 (CS), 162.6 (ArC), 143.0 (ArCH), 136.0 (Ar), 128.3 (ArCH), 50.5 (CH_2), 12.9 (CH_3). **HRMS ($M+H^+$)** $C_9H_{12}N_2S$ requires 180.0721, found 181.0794.

9.5. PREPARATION OF CYANO ACRYLIC ACID METHYL ESTERS



[418] [416] [415]

(i) MeOH, NaOAc, reflux, 3 h.

General Preparation: 3,4-Dimethoxybenzaldehyde (8.00 g, 48.1 mmol) **[418]** was dissolved in methanol (60 ml) and methyl cyanoacetate (4.77 g, 48.1 mmol, 1.00 eq) **[416]** and sodium acetate (3.95 g, 48.1 mmol, 1.00 eq) were added. The resultant mixture was refluxed for 3 h, then cooled and added to water (200 ml), upon which a heavy precipitate formed. Recrystallisation was achieved by gently heating in methanol, at 85 °C and adding water until the solid precipitated. Products were washed with petrol and oven dried at 50 °C.

9.5.1. 2-Cyano-3-(4-isopropyl-phenyl)-acrylic acid methyl ester [419]

[418] = 4-Isopropylbenzaldehyde

Yield 60 %. **m.p.** 43 - 45 °C. **FT IR:** ν_{max} **(cm^{-1})** 3023 (=C-H), 2963 (CH), 2225 (C≡N), 1742 (C=O). **^{1}H-NMR (250 MHz, $CDCl_3$):** δ_H 8.33 (1H, s, C*H*), 7.93 (2H, d, J = 8.2 Hz, Ar*H*), 7.35 (2H, d, J = 8.2 Hz, Ar*H*), 3.93 (3H, s, OCH_3), 2.90 (1H, m, C*H*$(CH_3)_2$), 1.27 (6H, d, J = 7.0 Hz, 2 x CH_3). **^{13}C-NMR:** δ_C 163.3 (CO), 155.2 (C=CH), 151.1 (Ar), 131.5 (Ar), 127.4 – 125.8 (4 x ArCH), 115.8 (CN), 101.1 (C=C), 53.4 (OCH_3), 34.3 (*CH*$(CH_3)_2$), 23.7, 23.5 (CH(*CH*$_3)_2$). **HRMS (M+H$^+$)** $C_{14}H_{16}NO_2$ requires 230.1181, found 230.1176.

9.5.2. 2-Cyano-3-(3-phenoxy-phenyl)-acrylic acid methyl ester [420]

[418] = 3-Phenoxybenzaldehyde

Yield 66 %. **m.p.** 88 - 90 °C. **FT IR:** ν_{max} **(cm^{-1})** 3020 (=C-H), 2230 (C≡N), 1732 (C=O). **^{1}H-NMR (250 MHz, $CDCl_3$):** δ_H 8.20 (1H, s, C*H*Ph), 7.75 (1H, d, J = 7.6 Hz,

Ar*H*), 7.53 - 7.16 (7H, m, Ar*H*), 7.04 (1H, d, J = 7.6 Hz, Ar*H*), 3.93 (3H, s, OCH_3). **HRMS (M+Na$^+$)** $C_{17}H_{13}NNaO_3$ requires 302.0793, found 303.0822.

9.5.3. 2-Cyano-3-naphthalen-1-yl-acrylic acid methyl ester [421]

[418] = 1-Naphthaldehyde

Yield 62 %. **m.p.** 99 - 101 °C. **FT IR: ν_{max} (cm^{-1})** 3064 (=C-H), 2954 (CH), 2225 (C≡N), 1732 (C=O). **^{1}H-NMR (250 MHz, $CDCl_3$): δ_H** 9.21 (1H, s, C*H*Ph), 8.32 (1H, d, J = 7.3 Hz, Ar*H*), 8.03 (2H, d, J = 8.0 Hz, Ar*H*), 7.92 (1H, d, J = 7.3 Hz, Ar*H*), 7.67 - 7.56 (3H, m, Ar*H*), 4.00 (3H, s, OCH_3). **HRMS (M+H$^+$)** $C_{15}H_{12}NO_2$ requires 238.0868, found 238.0832.

9.5.4. 2-Cyano-3-(6-nitro-benzo[1,3]dioxol-5-yl)-acrylic acid methyl ester [422]

[418] = 6-Nitropiperonal

Yield 53 %. **m.p.** 160 - 162 °C. **FT IR: ν_{max} (cm^{-1})** 3055 (C-H), 3020 (=C-H), 2229 (C≡N), 1739 (C=O). **^{1}H-NMR (250 MHz, $CDCl_3$): δ_H** 8.66 (1H, s, C*H*Ph), 7.73 (1H, s, Ar*H*), 7.24 (1H, s, Ar*H*), 6.25 (2H, s, OCH_2O), 3.97 (3H, s, OCH_3). **HRMS (M+Na$^+$)** $C_{12}H_8N_2NaO_6$ requires 299.0280, found 299.0247.

9.5.5. 2-Cyano-3-(1H-indol-3-yl)-acrylic acid methyl ester [423]

[418] = Indole-3-carboxaldehyde

Yield 3.3 g (42 %). **m.p.** 183 - 185 °C. **FT IR: ν_{max} (cm^{-1})** 3264 (NH), 3020 (=C-H), 2213 (C≡N), 1699 (C=O) 1571 (NH). **^{1}H-NMR (250 MHz, $CDCl_3$): δ_H** 11.61 (1H, s, N*H*), 8.56 (1H, s, C*H*), 8.53 (1H, s, C*H*), 7.74 (1H, m, Ar*H*), 7.40 (1H, m, Ar*H*), 7.27 - 7.21 (2H, m, Ar*H*), 3.84 (3H, s, OCH_3). **HRMS (M+H$^+$)** $C_{13}H_{11}N_2O_2$ requires 227.0821, found 227.0815.

9.5.6. 2-Cyano-3-pyridin-3-yl-acrylic acid methyl ester [424]

[418] = 3-Pyridinecarboxaldehyde

Yield 7.32 g (83 %). **m.p.** 126 - 128 °C. **FT IR:** ν_{max} **(cm^{-1})** 3021 (=C-H), 2234 (C≡N), 1736 (C=O). **^{1}H-NMR (250 MHz, $CDCl_3$):** δ_H 8.91 (1H, d, J = 1.8 Hz, Ar*H*), 8.74 (1H, dd, J = 4.9, 2.0 Hz, Ar*H*), 8.54 (1H, dt, J = 8.2, 1.8 Hz, Ar*H*) 8.19 (1H, s, C*H*), 7.45 (1H, dd, J = 8.2, 4.9 Hz, Ar*H*), 3.65 (3H, s, OCH_3). **HRMS (M+Na$^+$)** $C_{10}H_8N_2NaO_2$ requires 211.0483, found 211.0472.

9.5.7. 2-Cyano-3-thiophen-3-yl-acrylic acid methyl ester [425]

[418] = Thiophene-3-carboxaldehyde

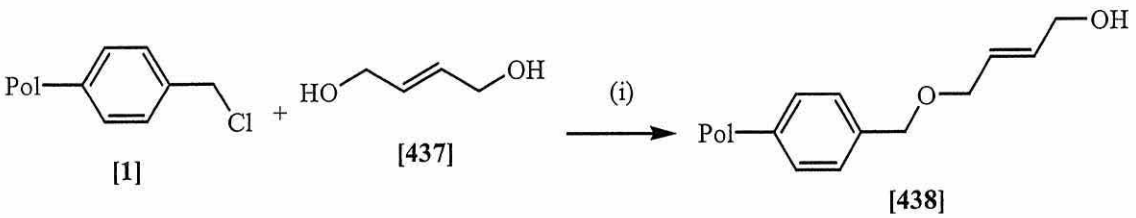
Yield 6.4 g (74 %). **m.p.** 98 - 100 °C. **FT IR:** ν_{max} **(cm^{-1})** 3016 (=C-H), 2956 (CH), 2225 (C≡N), 1733 (C=O). **^{1}H-NMR (250 MHz, $CDCl_3$):** δ_H 8.25 (1H, s, C*H*) 8.19 (1H, s, C*H*), 7.86 (1H, d, J = 4.9 Hz, C*H*), 7.45 (1H, dd, J = 4.9, 2.8 Hz, C*H*), 3.93 (3H, s, OCH_3). **Microanalysis** $C_9H_7NO_2S$ requires C: 55.94, H: 3.65 N: 7.25 %, found C: 55.5, H: 3.8, N: 7.6 %.

CHAPTER 10 - GUANIDINE SYNTHESIS

10.1. SOLID-PHASE TECHNIQUES

10.1.1. Merrifield Linkage Approach

10.1.1.1. Preparation of 2-Butene-1,4-diol Bound Resin [438]



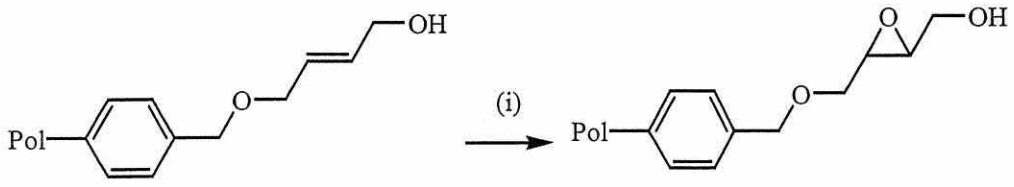
[1] [437] [438]

(i) NaH, THF, 0 °C – RT, overnight

Sodium hydride (0.77 g, 32 mmol, 2.0 eq) was washed with petroleum ether and suspended in dry THF (30 ml). The suspension was cooled to 0 °C and 2-butene-1,4-diol **[437]** (6.6 ml, 80 mmol, 5.0 eq) was added slowly, over 20 minutes, under Argon. The resultant suspension was warmed to room temperature and a pre-swollen suspension of Merrifield resin **[1]** (5.0 g, 16 mmol) in dry THF (40ml) was added. The reaction was stirred overnight at room temperature, then the resin was collected by filtration and washed with THF (200 ml), water (500 ml), methanol (200 ml) and ether (100 ml) and the resin then dried *in vacuo*.

Yield 4.72 g **FT IR:** ν_{max} **(cm^{-1})** 3500 (O-H), 1600 (C=CH), 1263 (C-O). **Loading (mmol /g)** 1.6. Assumed to be the same as the starting resin **[1]**.

10.1.1.2. Preparation of (3-Hydroxymethyl-oxiranyl)methanol Bound Resin [439]



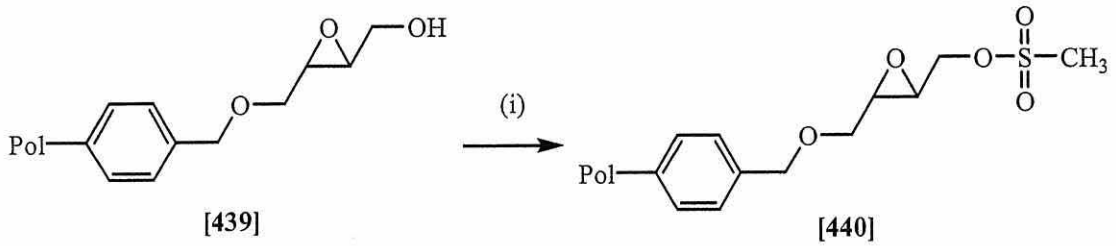
[438] [439]

(i) *m*CPBA, CH_2Cl_2, 0 °C – RT, overnight

2-Butene-1,4-diol bound resin **[438]** (1.00 g, 1.60 mmol) was pre-swollen in dichloromethane (50 ml) and the suspension cooled to 0 °C. *m*-Chloroperoxybenzoic acid (0.83 g, 4.8 mmol, 3.0 eq) was added gradually, over 2 minutes, and the reaction allowed to warm to room temperature and stirred overnight. The resin was collected by filtration and washed with water (400 ml), CH_2Cl_2 (200 ml) and ether (200 ml) and dried *in vacuo*.

Yield 1.00 g **FT IR:** ν_{max} **(cm^{-1})** 3423 (O-H), 1259 (C-O). **Loading (mmol /g)** 1.6. Assumed to be the same as the starting resin **[1]**.

10.1.1.3. Preparation of Methanesulfonic Acid 3-Hydroxymethyl-oxiranylmethyl Ester Bound Resin [440]



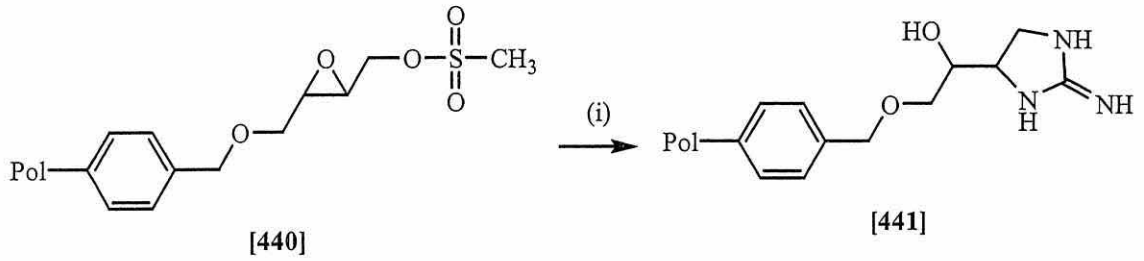
[439] [440]

(i) Methanesulfonylchloride, NEt_3, CH_2Cl_2, 0 °C – RT, overnight

Epoxide bound resin **[439]** (1.0 g, 1.6 mmol) was pre-swollen in dry dichloromethane (30 ml) and cooled to 0 °C. Triethylamine (0.35 ml, 4.8 mmol, 3.0 eq) and methanesulfonylchloride (0.37 ml, 4.8 mmol, 3.0 eq) were added and the reaction stirred and allowed to warm to room temperature overnight. The resin was collected by filtration and washed with water (500 ml), CH_2Cl_2 (200 ml) and ether (200 ml) and dried *in vacuo*.

Yield 1.00 g **FT IR:** ν_{max} **(cm^{-1})** 1350 (S=O), 1259 (C-O), 1150 (S=O). **Loading (mmol /g)** 1.6. Assumed to be the same as the starting resin **[1]**.

10.1.1.4. Preparation of 2-Ethoxy-1-(2-imino-imidazolidin-4-yl)ethanol Bound Resin [441]



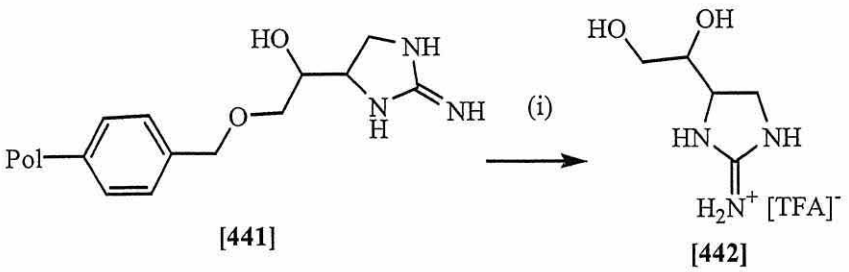
[440] [441]

(i) ^{t}BuOH, guanidine in ^{t}BuOH, KO^{t}Bu, 18 h, r.t.

Resin **[440]** (1.0 g, 1.6 mmol) was pre-swollen in *tert*-butanol (5 ml) and a solution of guanidine (0.17 g, 2.8 mmol, 1.8 eq) in *tert*-butanol (5 ml) was added and the reaction allowed to stir at room temperature overnight. Potassium *tert*-butoxide (0.32 g, 1.8 eq) was added and the reaction heated to 60 °C overnight. The resin was collected by filtration and washed with dichloromethane (200 ml), water (200 ml), further dichloromethane (100 ml) and ether (100 ml) and dried *in vacuo*.

Yield 1.00 g **FT IR:** ν_{max} **(cm^{-1})** 3420 (N-H, O-H overlap), 1257 (C-O). **Loading (mmol /g)** 1.6. Assumed to be the same as the starting resin **[1]**.

10.1.1.5. Attempted Preparation of 1-(2-Imino-imidazolidin-4-yl)-ethane-1,2-diol Trifluoroacetic Acid Salt [442]

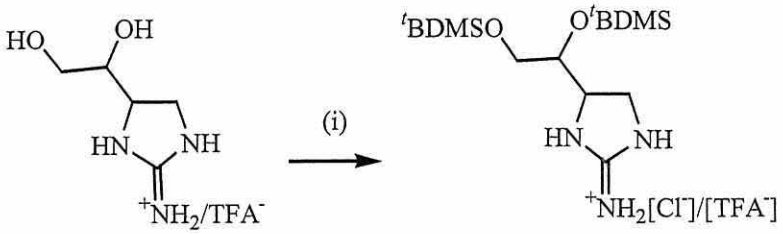


[441] [442]

(i) Trifluoroacetic acid, CH_2Cl_2, RT, 18hr

2-Ethoxy-1-(2-imino-imidazolidin-4-yl)-ethanol bound resin **[442]** (1.00 g) was stirred in a solution of trifluoroacetic acid in dichloromethane (2 ml: 8 ml) overnight. The resin was collected by filtration and washed with chloroform (100 ml), dichloromethane (50 ml) and methanol (100 ml). The collected solvent fractions were dried over $MgSO_4$ and concentrated *in vacuo* to yield the supposed compound **[443]** (112 mg). From the analysis of the product by ^{1}H-NMR it was unclear whether **[443]** had been obtained and thus the crude material was taken onto the following silylation stage unpurified.

10.1.1.6. Attempted Silylation of 1-(2-Imino-imidazolidin-4-yl)-ethane-1,2-diol Trifluoroacetic Acid Salt [443]



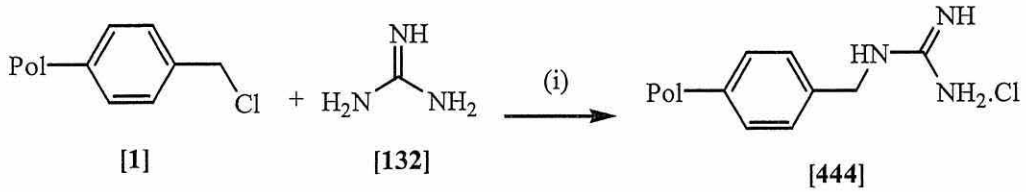
[442] [443]

(i) ^{t}BDMSCl, DMF, imidazole, 0 °C – RT, 18 h.

Crude 4-(1,2-dihydroxy-ethyl)-imidazolidin-2-ylidene ammonium salt **[442]** (180 mg) was dissolved in dry DMF (10 ml) and cooled to 0 °C. A solution of *tert*-butyldimethylsilyl chloride (0.30 g, 3.0 eq, 2.1 mmol) and imidazole (0.15 g, 3.2 eq, 2.2 mmol) in dry DMF (5 ml) was added. The reaction was allowed to warm to room temperature and stirred an inert atmosphere overnight. The reaction was diluted with ethylacetate (30 ml) and washed with water (2 x 100 ml), brine (2 x 100 ml) and a saturated lithium bromide solution (2 x 100 ml). The aqueous layers were then combined and back extracted with chloroform (100 ml), The combined organic fractions were washed with lithium bromide solution (2 x 100 ml), dried over $MgSO_4$ and concentrated *in vacuo*, further dissolved in chloroform (15 ml) and stirred with a saturated $NaBF_4$ solution overnight. The resulting organic fraction was again dried over $MgSO_4$ and concentrated *in vacuo* to yield 80 mg of product. Upon analysis of ^{1}H-NMR the reaction was deemed unsuccessful as a complex spectrum was obtained that gave no indicative signals for the silyl groups.

10.1.2. Solid-phase Guanidinium Linkage Route

10.1.2.1. Preparation of Guanidine Bound Resin [444]



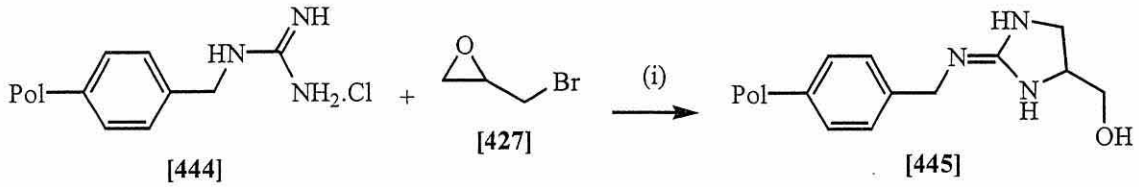
[1] [132] [444]

(i) THF, 60 °C, 18 h.

Merrifield resin **[1]** (1.0 g, 1.6 mmol) was pre-swollen in dry THF (5 ml) and a solution of guanidine **[132]** (0.24 g, 4.0 mmol, 2.5 eq) in dry THF (5 ml) was added. The resulting suspension was heated to 60 °C overnight. The suspension was cooled to room temperature and collected by filtration, with subsequent washing with dichloromethane (2 x 100 ml), chloroform (2 x 100 ml) and ether (2 x 100 ml) and dried *in vacuo*.

Yield 1.00 g **FT IR:** ν_{max} **(cm^{-1})** 3400 (N-H), 1597 (N-H). **Loading (mmol /g)** 1.6. Assumed to be the same as the starting resin **[1]**.

10.1.2.2. Preparation of (2-Iminoimidazolidin-4-yl)methanol Bound Resin [445]

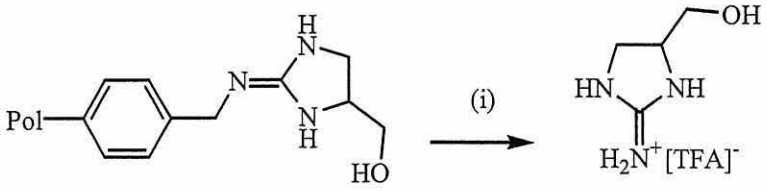


[444] [427] [445]

(i) KO^{t}Bu, ^{t}BuOH, RT, 18hr; (ii) KO^{t}Bu, 60 °C, 18 h.

Guanidine hydrochloride bound resin **[444]** (1.0 g, 1.6 mmol/g) was pre-swollen in *tert*-butanol under argon and KO^{t}Bu (0.22 g, 1.3 eq, 2.0 mmol) was added. The reaction was stirred at room temperature for 30 minutes, after which time *epi*-bromohydrin **[427]** (0.30 ml, 2.0 eq, 3.2 mmol) was added and the reaction was further stirred overnight. A second portion of KO^{t}Bu (0.22 g, 1.3 eq, 2.0 mmol) was added and the reaction heated to 60 °C overnight. Once cooled the resin was collected by filtration, washed with dichloromethane (2 x 100 ml), chloroform (2 x 100 ml) and ether (2 x 100 ml) and dried *in vacuo*. Analysis of the product **[445]** by FTIR showed that there was no significant difference to the bound guanidine derivative and therefore cleavage was performed in order to ascertain the success of the reaction.

10.1.2.3. Cleavage of (2-Iminoimidazolidin-4-yl)methanol Trifluoroacetate [446]



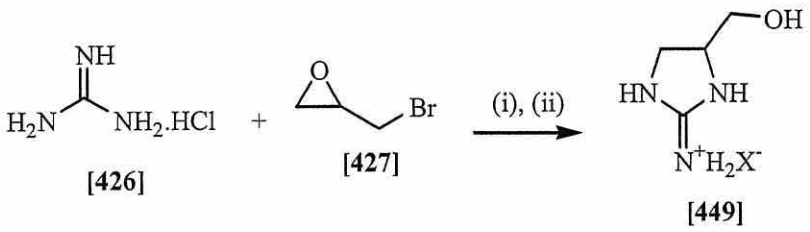
[445] [446]

(i) Trifluoroacetic acid, CH_2Cl_2, reflux, 8 h.

Polymer bound cyclic guanidine **[445]** (1.00 g) was swollen in a solution of trifluoroacetic acid in dichloromethane (4 ml: 16 ml) and refluxed for 8 hours. The resin was collected by filtration and washed with dichloromethane (200 ml), chloroform (200 ml) and methanol (100 ml). The organic washings were combined and concentrated *in vacuo*. Upon analysis by ^{1}H-NMR spectroscopy the reaction was deemed unsuccessful due to the lack of expected signals when compared to spectra obtained for the solution-phase equivalent reaction (section 10.2.1. (2-iminoimidazolidin-4-yl)methanol salts).

10.2. SOLUTION-PHASE GUANIDINE CHEMISTRY

10.2.1. (2-Iminoimidazolidin-4-yl)methanol Salts [449] [97]



(i) ^{t}BuOH, 5 °C, KO^{t}Bu, 30 min; (ii) **[427]**, ^{t}BuOH, RT, 18 h; (iii) KO^{t}Bu, 60 °C, 18 h.

General Procedure: - Guanidine hydrochloride **[426]** (0.84 g, 8.8 mmol, 1.2 eq) was dissolved in dry ^{t}BuOH (12 ml) and cooled to 5 °C. KO^{t}Bu (0.90 g, 8.0 mmol, 1.1 eq) was added and the reaction stirred for 30 minutes. *Epi*-bromohydrin **[427]** (0.63 ml, 7.3 mmol) was added slowly in dry ^{t}BuOH (20 ml) and the reaction allowed to warm to room temperature and stirred overnight. Further KO^{t}Bu (0.90 g, 8.0 mmol, 1.1 eq) was added and the reaction heated to 60 °C and stirred overnight. The reaction was cooled to room temperature and worked up by the following methods:

1). Removal of ^{t}BuOH *in vacuo* followed by the addition of MeOH (20 ml) and glacial acetic acid (0.84 ml, 14.6 mmol, 2 eq) in MeOH (10 ml). Sodium acetate (5.99 g, 73.0 mmol, 10.0 eq) was added, after stirring at room temperature for 30 minutes, followed by further stirring for 30 minutes. TLC analysis indicated that the product was highly polar and was inseparable from baseline salts. The product was obtained in 30 % yield.

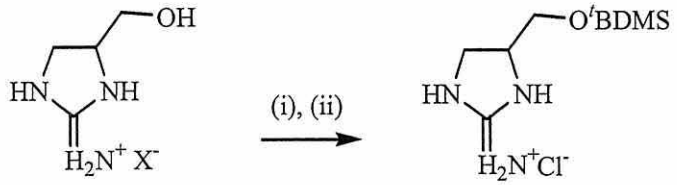
2). Methanolic HCl (1 ml acetyl chloride: 9 ml dry MeOH) was added at 0 °C and stirred for 10 minutes, followed by the removal of solvent *in vacuo*. Purification was carried out by dry loading onto a silica column with a graduated solvent system of 100 % $CHCl_3$, 5 % MeOH: $CHCl_3$, 10 % MeOH: $CHCl_3$, 15 % MeOH: $CHCl_3$, 20 % MeOH: $CHCl_3$, 25 % MeOH: $CHCl_3$, 30 % MeOH: $CHCl_3$, 50 % MeOH: $CHCl_3$, 70 % MeOH: $CHCl_3$, 100 % MeOH. The product eluted in fractions 15 - 20 (15 - 20 % MeOH, 40 ml fractions) with an Rf = 0.19 (20 % MeOH: $CHCl_3$). The product was obtained in 42 % yield.

3). Methanolic HBr (1 ml acetyl bromide: 9 ml dry MeOH) was added at 0 °C and stirred for 10 minutes, followed by the removal of solvent *in vacuo*. Purification was carried out by dry loading onto a silica column with a graduated solvent system of 100 % $CHCl_3$, 2 % MeOH: $CHCl_3$, 5 % MeOH: $CHCl_3$, 10 % MeOH: $CHCl_3$, 20 % MeOH: $CHCl_3$, 30 % MeOH: $CHCl_3$, 40 % MeOH: $CHCl_3$, 50 % MeOH: $CHCl_3$, 70 % MeOH: $CHCl_3$, 100 % MeOH. The product eluted in fractions 18 – 32 (20 – 50 % MeOH, 40 ml fractions) with an Rf = 0.14 (20 % MeOH: $CHCl_3$). The product was shown to contain trace impurities even after column chromatography and this approach was abandoned and the yield could not be determined.

4). Methanolic TFA (5 ml trifluoroacetic acid: 15 ml dry MeOH) was added at 0 °C and stirred for 10 minutes, followed by the removal of solvent *in vacuo*. Purification was carried out by dry loading onto a silica column with a graduated solvent system of 100 % Et_2O, 100 % $CHCl_3$, 5 % MeOH: $CHCl_3$, 10 % MeOH: $CHCl_3$, 20 % MeOH: $CHCl_3$, 25 % MeOH: $CHCl_3$, 30 % MeOH: $CHCl_3$, 50 % MeOH: $CHCl_3$, 70 % MeOH: $CHCl_3$, 100 % MeOH. The product was obtained in 44 % yield (3.12 g) and eluted in fractions 56 – 75 (20 – 100% MeOH, 40 ml fractions) with an Rf = 0.12 (20 % MeOH: $CHCl_3$).

FT IR: ν_{max} (cm^{-1})	3352 (br, OH), 1552 (C=N).
^{1}H-NMR: δ_{ppm} (250 MHz, CD_3OD)	4.30 (1H, m, C*H*), 3.93 (1H, br t, J = 10.1 Hz, CH*H*), 3.84 (1H, dd, J = 4.2, 12.1 Hz, CH*H*) 3.77 (1H, dd, J = 5.2, 10.1 Hz, CH*H*) and 3.73, (1H, dd, J = 6.1, 12.1 CH*H*).
^{13}C-NMR: δ_{ppm}	45.73 (CH_2), 57.7 (CH_2), 63.48 (CH), 158.77 (C=N).
MS (CI): m/z	116 (40 % $[M+H]^+$)
HRMS	$C_4H_{10}N_3O^+$ $[M+H^+]$, requires 116.0824, found 116.0825.

10.2.2. (2-Iminoimidazolidin-4-yl)-4-methyl-(*tert*-butyldimethylsilyloxy) Hydrochloride [450] [97]



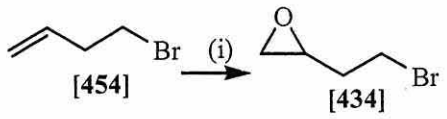
[449] [450]

(i) dry DMF, 0 °C, imidazole, ^{t}BDMSCl, 0 °C – RT, overnight;
(ii) $CHCl_2$, sat. $NaBF_4$ solution, RT, 18 h.

General Procedure: To a cooled (0 °C) solution of (2-iminoimidazolidin-4-yl) methanol bromide **[449]** (0.35 g, 1.8 mmol) in dry DMF (2 ml) was added ^{t}BDMSCl (0.41 g, 2.7 mmol, 1.5 eq) and imidazole (0.24 g, 3.6 mmol, 2.0 eq) and the reaction stirred overnight reaching room temperature. The mixture was diluted with $CHCl_3$ (30 ml) and stirred with water (20 ml) for 30 minutes. The organic layer collected and washed with water (2 x 20 ml), brine (2 x 20 ml) and sat. lithium bromide (2 x 20 ml), dried over $MgSO_4$ and evaporated *in vacuo*. The crude oil was dissolved in CH_2Cl_2 (20 ml) and stirred with aq. $NaBF_4$ solution (sat., 20 ml) overnight. The aqueous fraction was extracted with $CHCl_3$ (20 ml). The organic fractions were combined, dried over $MgSO_4$ and concentrated *in vacuo* to yield crude product as a yellow oil (550 mg). Purification was carried out by column chromatography eluting with a graduated solvent system of 100 % $CHCl_3$, 2 % MeOH: $CHCl_3$, 4 % MeOH: $CHCl_3$, 6 % MeOH: $CHCl_3$, 8 % MeOH: $CHCl_3$, 10 % MeOH: $CHCl_3$, 20 % MeOH: $CHCl_3$, 100 % MeOH. Yields are reported in table 7 (page 140), the product eluted at Rf = 0.13 (10 % MeOH: $CHCl_3$, 2- 4 % MeOH, fractions 8 - 13).

FT IR: ν_{max} (cm^{-1})	2950 (CH), 1685 (C=N).
^{1}H-NMR: δ_{ppm}	0.0 (6H, s, 2 x CH_3), 0.8 (9H, s, 3 x CH_3), 3.45 (2H, dd, 2 x CH
(250 MHz, CD_3OD)	5, J = 5.4, 9.8 Hz), 3.55 (1H, d, CH-1', J = 5.4 Hz), 3.65 (1H, t, CH-1', J = 9.8 Hz), 4.0 (1H, m, CH-4).
^{13}C-NMR: δ_{ppm}	-5.52 (CH_3), 18.11 (C), 25.69 (CH_3), 45.19 (CH_2-5), 56.33 (CH_2-1'), 64.25 (CH-4), 160.42 (C=N).
MS (CI): m/z	230 (100 %[M^+])
HRMS	$[C_{10}H_{24}ON_3Si]^+$ requires 230.1689 daltons found 230.1687.

10.2.3. 2-(2-Bromo-ethyl)-oxirane [434] [149]

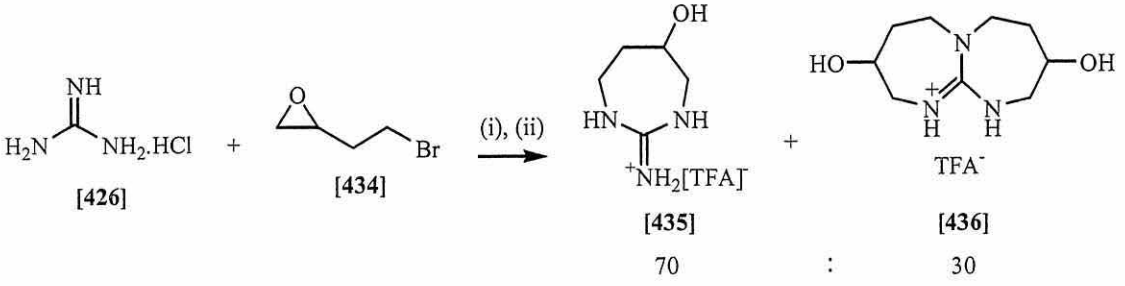


(i) *m*CPBA, CH_2Cl_2, 0 °C – RT, 18 h.

4-Bromobutane (5.00 g, 37.0 mmol) was dissolved in dry dichloromethane (20 ml) and cooled to 0 °C whereupon *meta*-chloroperoxybenzoic acid (12.8 g, 74.0 mmol, 2.00 eq) was added and the reaction stirred overnight at room temperature. The resultant mixture was concentrated *in vacuo*, passed through a pad of $MgSO_4$ and washed with CH_2Cl_2 (200 ml). The organic phase was washed with sat. aq. sodium metabisulfite (4 x 30 ml) then sat. aq. sodium hydrogen carbonate (3 x 30 ml), dried over $MgSO_4$ and concentrated *in vacuo* to achieve the title compound in 84 % yield (4.70 g).

FT IR: ν_{max} (cm^{-1})	2994 (s, CH), 1265 (s, CO)
^{1}H-NMR: δ_{ppm}	2.0 (2H, m, CH_2), 2.4 (1H, m, CH), 2.7 (1H, m, CH), 3.0 (1H, m,
(250 MHz, CD_3OD)	CH), 3.5 (2H, t, CH_2, J = 7.2 Hz).
^{13}C-NMR: δ_{ppm}	29.00 (CH_2), 35.65 (CH_2), 46.95 (CH_2), 50.62 (CH).

10.2.4. 5-Hydroxy-[1,3]diazepan-2-ylidene-ammonium Trifluoroacetate [435] [97]

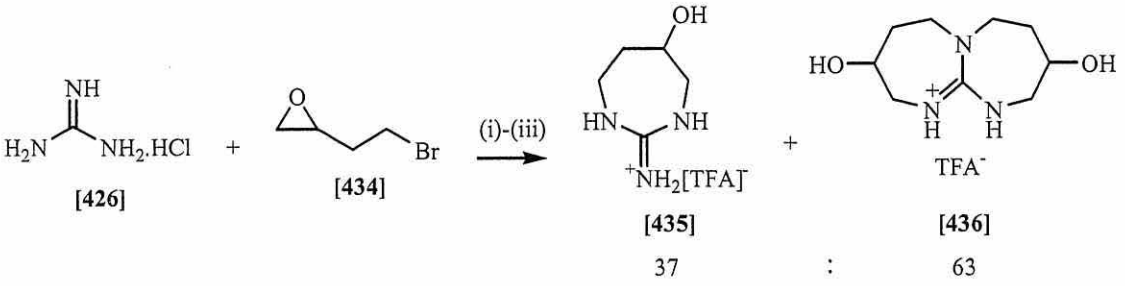


(i) **[426]**, ^{t}BuOH, 5 °C, KO^{t}Bu, 30 min, **[434]**, RT, 18 h; (ii) KO^{t}Bu, 60 °C, 24 h.

Guanidine hydrochloride (0.58 g, 6.1 mmol) was dissolved in dry *tert*-butanol (10 ml) and cooled (5 °C). Potassium *tert*-butoxide (0.75 g, 6.7 mmol, 1.1 eq) was added and the reaction stirred for 30 minutes. 1,2-Epoxy-4-bromobutane (1.0 g, 6.7 mmol, 1.1 eq) was added dropwise and the reaction stirred overnight to room temperature. A further portion of potassium *tert*-butoxide (0.75 g, 6.7 mmol, 1.1 eq) was added and the reaction heated to 60 °C and stirred for 24 hours. The resultant mixture was cooled to 0 °C, treated with methanolic TFA (9 ml MeOH: 1 ml trifluoroacetic acid) and stirred for 10 minutes. Solvent was removed *in vacuo* and the crude material passed through a Celite pad, eluting with 80 % MeOH in $CHCl_3$. A crude NMR was obtained to estimate the ratio of **[435]**:**[436]** and then the material was submitted to column chromatography with a graduated solvent system of 100 % $CHCl_3$, 5 % MeOH, 10 % MeOH, 15 % MeOH, 20 % MeOH, 30 % MeOH, 50 % MeOH, 70 % MeOH, 100 % MeOH. The desired product **[435]** was produced in 43 % yield, Rf = 0.12 (20 % MeOH: $CHCl_3$) in column fractions 27 – 33 (50 – 70 % MeOH, 7 ml fractions).

FT IR: ν_{max} (cm^{-1})	3346 (br, OH), 1500 (C=N)
^{1}H-NMR: δ_{ppm} (250 MHz, CD_3OD)	4.61 - 4.71 (2H, m, 2 x CH), 3.28 - 4.13 (8H, m, 4 x CH_2), 1.59 - 2.23 (4H, m, 2 x CH_2). Crude NMR showing both **[435]** and **[436]**.
^{13}C-NMR: δ_{ppm}	34.4 (*CH_2*-CH), 46.9 (*CH_2*-NH), 57.2 (NH-*CH_2*-CH), 71.0 (*CH*-OH), 157.8 (C=N).
MS (CI): m/z	130 (30 % $[MH]^+$)

10.2.5.a. Preparation of 5-Hydroxy-[1,3]diazepan-2-ylidene-ammonium Trifluoro-acetate [435] and 3,8-Dihydroxy-2,4,5,6,7,8,9,10-octahydro-3H-5a,10-diaza-1-azonia-heptalene Trifluoroacetate [436] using 2 equivalents of 1,2-Epoxy-4-bromo-butane [97]

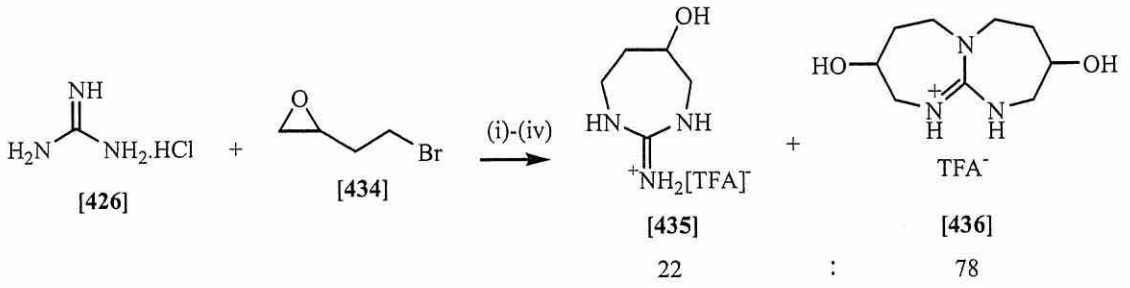


(i) **[426]**, ^{t}BuOH, 5 °C, KO^{t}Bu, 30 min, **[434]**, RT, 18 h; (ii) KO^{t}Bu, 30 min, **[434]**, RT, 18 h; (iii) KO^{t}Bu, 60 °C, 24 h.

Guanidine hydrochloride (0.58 g, 6.1 mmol) was dissolved in dry *tert*-butanol (10 ml) and cooled (5 °C). Potassium *tert*-butoxide (0.75 g, 6.7 mmol, 1.1 eq) was added and the reaction stirred for 30 minutes. 1,2-Epoxy-4-bromobutane **[434]** (1.0 g, 6.7 mmol, 1.1 eq) was added dropwise and the reaction stirred overnight reaching room temperature. A further portion of potassium *tert*-butoxide (0.75 g, 6.7 mmol, 1.1 eq) was added and the reaction stirred for 30 minutes. A second equivalent of 1,2-epoxy-4-bromobutane **[434]** (1.0 g, 6.7 mmol, 1.1 eq) was added and the reaction stirred for a 24 hours. A third portion of potassium *tert*-butoxide (0.75 g, 6.7 mmol, 1.1 eq) was added and the reaction was heated to 60 °C for 24 hours. The resulting reaction mixture was cooled to 0 °C, treated with methanolic TFA (9 ml MeOH: 1 ml TFA) and stirred for 10 minutes. The solvent was removed *in vacuo* and the crude material passed through a Celite pad, eluting with 80 % MeOH in $CHCl_3$. A crude NMR was obtained at this stage and showed the ratio of monomer **[435]** to dimer **[436]** to be 37 : 63 (NMR discussion - refer to text on Page 127). The crude material was then submitted to column chromatography eluting with a graduated solvent system of 1 % MeOH: $CHCl_3$, 5 % MeOH: $CHCl_3$, 10 % MeOH: $CHCl_3$, 20 % MeOH: $CHCl_3$, 30 % MeOH: $CHCl_3$, 40 % MeOH: $CHCl_3$, 50 % MeOH: $CHCl_3$, 70 % MeOH: $CHCl_3$, 90 % MeOH: $CHCl_3$ and 100 % MeOH. The dimeric product eluted in 90 % MeOH (Rf = 0.16 20 % MeOH: $CHCl_3$). The yield of **[436]** was found to be 12 %.

FT IR: ν_{max} (cm^{-1})	3300 (br, OH), 2952 (s, CH) 1210 (w, CH)
^{1}H-NMR: δ_{ppm}	4.7 (2H, m, 2 x CH), 3.9 - 3.2 (8H, m, 4 x CH_2), 2.25 - 1.7 (4H,
(250 MHz, CD_3OD)	m, 2 x CH_2). Crude NMR showing both **[435]** and **[436]**.
^{13}C-NMR: δ_{ppm}	158.6 (C=N), 69.4 (*CH_2*-CH), 69.2 (*CH_2*-CH), 57.5 (N-*CH_2*-CH), 56.5 (N-*CH_2*-CH), 47.3 (2 x *CH_2*-N), 33.0 (*CH*-OH), 32.9 (*CH*-OH).

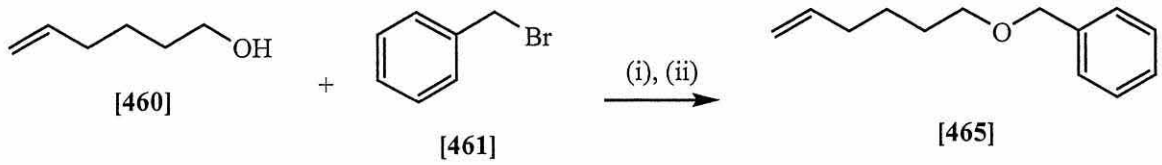
10.2.5.b. Preparation of 5-Hydroxy-[1,3]diazepan-2-ylidene-ammonium Trifluoro-acetate [435] and 3,8-Dihydroxy-2,4,5,6,7,8,9,10-octahydro-3H-5a,10-diaza-1-azonia-heptalene Trifluoroacetate [436] using 3 equivalents of 1,2-Epoxy-4-bromobutane [97]



(i) **[426]**, ^{t}BuOH, 5 °C, KO^{t}Bu, 30 min, **[434]**, RT, 18 h; (ii) KO^{t}Bu, 30 min, **[434]**, RT, 18 h; (iii) KO^{t}Bu, 30 min, **[434]**, RT, 18 h; (iv) KO^{t}Bu, 60 °C, 24 h.

Guanidine hydrochloride **[426]** (0.58 g, 6.1 mmol) was dissolved in dry *tert*-butanol (10 ml) and cooled (5 °C). Potassium *tert*-butoxide (0.75 g, 6.7 mmol, 1.1 eq) was added and the reaction stirred for 30 minutes. 1,2-Epoxy-4-bromobutane **[434]** (1.0 g, 6.7 mmol, 1.1 eq) was added drop-wise and the reaction stirred overnight reaching room temperature. A further portion of potassium *tert*-butoxide (0.75 g, 6.7 mmol, 1.1 eq) was added and the reaction stirred for 30 minutes. A second equivalent of 1,2-epoxy-4-bromobutane **[434]** (1.0 g, 6.7 mmol, 1.1 eq) was added and the reaction stirred overnight. A third portion of potassium *tert*-butoxide (0.75 g, 6.7 mmol, 1.1 eq) was added and the reaction again left to stir for 30 minutes. A third portion of 1,2-epoxy-4-bromobutane **[435]** (1.0 g, 6.7 mmol, 1.1 eq) was added and the reaction stirred at room temperature. A final equivalent of potassium *tert*-butoxide (0.75 g, 6.7 mmol, 1.1 eq) was added and the reaction mixture was heated to 60 °C for 24 hours. The resulting reaction mixture was cooled to 0 °C, treated with methanolic TFA (9 ml MeOH: 1 ml TFA) and stirred for 10 minutes. Solvent was removed *in vacuo* and the crude material passed through a Celite pad, eluting with 80 % MeOH in $CHCl_3$. A crude NMR was obtained indicating that the products were present in a ratio of 22 **[435]** : 78 **[436]**. The reaction was not purified by column chromatography as high levels of contamination were present in the crude NMR and therefore a yield was unobtainable.

10.2.6. Hex-5-enyloxymethyl-benzene [465] [149]



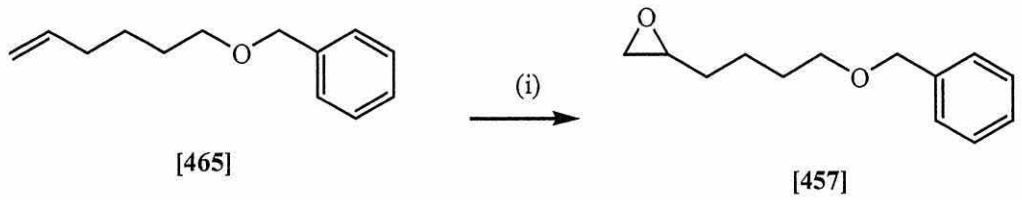
[460] + [461] → [465]

(i) Sodium hydride, THF, 0 °C, 5 min. (ii) Benzyl bromide, TBAI, reflux, 18 h.

Sodium hydride (1.68 g, 70.0 mmol, 1.4 eq) was washed with petroleum ether, dried and suspended in dry THF (10 ml). A solution of 5-hexen-1-ol (5.00 g, 49.9 mmol) in dry THF (5 ml) was added slowly at 0 °C. TBAI (100 mg) was then added and the reaction was refluxed overnight. The reaction was cooled to room temperature, quenched with MeOH (100 ml) and concentrated *in vacuo*. Petroleum ether (40 ml) and water (40 ml) were added and the separated organic phase washed with water (2 x 30 ml), brine (2 x 30 ml), dried over $MgSO_4$ and concentrated *in vacuo* to yield a pale oil. Yield 10.05 g (98 %). The product was identical when compared to the literature data.

FT IR: ν_{max} (cm^{-1})	3074 (C=H), 2926 (CH), 1586 (C=C), 1244 (C-O), 990 (C-H).
^{1}H-NMR: δ_{ppm} (250 MHz, CD_3OD)	7.3 (5H, m, Ar*H*), 5.8 (1H, m, C*H*), 5.0 (2H, m, CH_2), 4.5 (2H, m, OCH_2), 3.5 (2H, t, J = 6 Hz, C*H*), 2.1 (2H, m, C*H*), 1.5 (2H, m, C*H*).

10.2.7. 2-(4-Benzyloxy-butyl)-oxirane [457] [149]



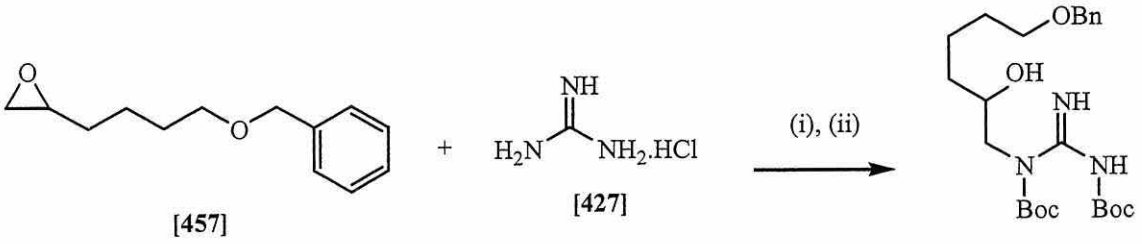
[465] [457]

(i) *m*CPBA, CH_2Cl_2, 0 °C – RT, 18 h.

Hex-5-enyloxymethyl-benzene (5.00 g, 26.3 mmol) was dissolved in dry CH_2Cl_2 (15 ml) and cooled to 0 °C. *m*CPBA (4.5 g, 53 mmol, 2.0 eq) was added portion-wise and the reaction stirred overnight reaching room temperature. The reaction was diluted with $CHCl_3$ (30 ml) and washed with sat. $NaHCO_3$ (30 ml), sodium metabisulfite (2 x 30 ml), further $NaHCO_3$ (2 x 30 ml) and dried over $MgSO_4$ to yield 6.08g (95 %) of yellow oil. The product was identical when compared to the literature data.

FT IR: ν_{max} (cm^{-1})	3071 (C=H), 2924 (CH), 1592 (C=C), 1239 (C-O), 990 (C-H).
^{1}H-NMR: δ_{ppm} (250 MHz, CD_3OD)	7.40 – 7.26 (5H, m, Ar*H*), 4.5 (2H, m, OCH_2), 3.5 (2H, t, J = 6 Hz, C*H*), 2.9 (1H, m, C*H*), 2.75 (1H, t, J = 4 Hz, C*H*), 2.45 (1H, t, J = 4 Hz, C*H*), 1.5 (6H, m, CH_2).

10.2.8. *N*-(6-Benzyloxy-2-hydroxy-hexyl)-*bis*-Boc-guanidine [462]

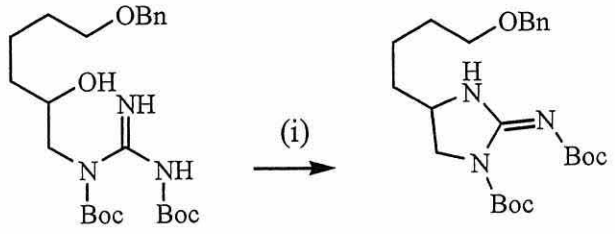


(i)KO^{t}Bu, ^{t}BuOH, 5 °C, 30 min, 60 °C, 18 h. (ii) BOC_2O, NEt_3, 48 h, RT

KO^{t}Bu (1.52 g, 13.6 mmol, 1.40 eq) was added to a cooled (0 °C) solution of guanidine hydrochloride (1.40 g, 14.7 mmol, 1.50 eq) in *t*ert-butanol (5 ml) and the reaction stirred for 30 minutes. 2-(3-Benzyloxy-propyl)-oxirane (2.0 g, 9.7 mmol) in *tert*-butanol (5 ml) was added and the reaction allowed to warm to room temperature, followed by heating at 60 °C overnight. The reaction mixture was allowed to cool to room temperature and di-*tert*-butyl dicarbonate (7.04 g, 32.3 mmol, 2.20 eq) and triethylamine (4.50 ml, 32.3 mmol, 2.20 eq) were added and the reaction stirred overnight. The resultant was concentrated *in vacuo* and purification was carried out by dry loaded column chromatography eluting with a graduated solvent system of 100 % Petrol, 5 % Et_2O: Petrol, 10 % Et_2O: Petrol 15 % Et_2O: Petrol, 20 % Et_2O: Petrol, 25 % Et_2O: Petrol, 30 % Et_2O: Petrol, 50 % Et_2O: Petrol, 100 % Et_2O, 10 % EtOAc: Et_2O, 50 % EtOAc: Et_2O. The product was obtained in 36 % yield (0.81 g) and eluted at Rf = 0.2 (100 % EtOAc) from fractions 20 – 35 (20 – 30 % Et_2O, 40 ml fractions).

^{1}H-NMR: δ_{ppm} (250 MHz, CD_3OD)	7.45 - 7.25 (7H, m, 2 x NH and Ph), 4.52 (1H, m, C*H*OH), 4.49 (2H, s, OC*H*$_2$Ph), 3.45 (2H, t, J = 7.0 Hz, OC*H*$_2$), 3.38 (1H, dd, J = 14.5, 4.5 Hz, C*H*HN), 3.21 (1H, dd, J = 14.5, 8.5 Hz, CH*H*N), 1.8-1.4 (7H, m, 3 x CH_2 and OH), 1.48, 1.47 (18H, 2 x s, 2 x ^{t}Bu).
^{13}C-NMR: δ_{ppm}	161.5 (C), 156.3 (C), 153.8 (C), 128.3 (2 x CH), 127.6 (2 x CH), 127.7 (CH), 83.1 (CH), 78.5 (C), 75.6 (C), 72.8 (CH_2), 69.9, (CH_2), 44.5 (CH_2), 31.9 (CH_2), 29.4 (CH_2), 28.4 (tBu), 27.7 (tBu), 22.2 (CH_2).
MS (CI): m/z	466 (100 % [M+H])
HRMS	$C_{24}H_{40}N_3O_6$ [M+H$^+$], requires 466.2917, found 466.2917.

10.2.9. 4-(4-Benzyloxy-butyl)-*bis*-Boc-imidazolidin-2-ylideneamine [463]

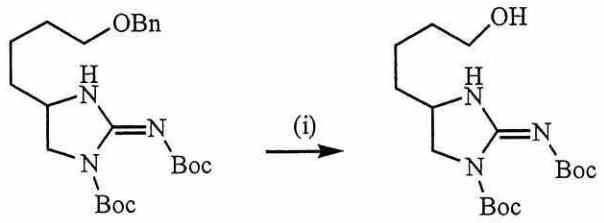


[462] [463]

(i) PPh_3, DIAD, toluene, 0 °C – RT, 48 h, (ii) PPh_3, DIAD, H_2O, RT, 18 h.

Triphenylphosphine (0.30 g, 1.1 mmol, 1.5 eq) was added to *N*-(6-benzyloxy-2-hydroxy-hexyl)-*bis*-Boc-guanidine (0.35 mg, 0.80 mmol) in dry toluene (8 ml), the reaction cooled (0 °C) and diisopropylazodicarboxylate (0.23 ml, 1.1 mmol, 1.5 eq) added slowly, drop-wise. The reaction was allowed to warm to room temperature and stirred for 2 days. TLC showed the reaction to be incomplete and further triphenylphosphine (0.30 mg, 1.1 mol, 1.5 eq) and diisopropyl azodicarboxylate (0.23 ml, 1.1 mmol, 1.5 eq) were added and the reaction stirred overnight. Water (5 ml) was added and the resultant stirred for 30 minutes and concentrated *in vacuo*. Purification was carried out by column chromatography eluting with a graduated solvent system of 100 % Petrol, 10 % Et_2O: Petrol, 20 % Et_2O: Petrol, 30 % Et_2O: Petrol, 40 % Et_2O: Petrol, 50 % Et_2O: Petrol, 60 % Et_2O: Petrol, 70 % Et_2O: Petrol, 100 % Et_2O. Analysis of the fractions obtained failed to confirm product formation and the promising fractions (20 - 22, 50 % Petrol: Ether) were combined and subjected to hydrogenation.

10.2.10. 2-*tert*-Butoxycarbonylimino-4-(4-hydroxy-butyl)-imidazolidine-1-carboxylic Acid *tert*-butyl Ester [464]



[463] [464]

(i) Pd/ C, EtOAc, H_2, RT, 18 h.

4-(4-Benzyloxy-butyl)-*bis*-Boc-imidazolidin-2-ylideneamine (200 mg) was dissolved in ethyl acetate (3 ml) and Pd/C (100 mg) was added. A balloon of hydrogen gas was flushed through the round bottomed flask and further hydrogen gas supplied from a balloon *via* a septum inlet. The reaction was then stirred vigorously overnight. TLC of the reaction and the NMR of the isolated product were complex and indicative of an unsuccessful reaction.

CHAPTER 11 - REFERENCES

1. W. T. Gallway, *www.empnet.com/nancydl/scr.html*
2. N. K Terrett, *Combinatorial Chemistry*, **1998**, Oxford University Press.
3. I. M. Chaiken and K. D. Janda, *Molecular Diversity and Combinatorial Chemistry: Libraries and Drug Discovery*, **1996**, American Chemical Society.
4. A. R. Vaino, K. D. Janda, *J. Comb. Chem.*, **2000**, *2*, 579.
5. L. A. Thompson and J. A. Ellman, *Chem. Rev.*, **1996**, *96*, 555.
6. G. Lowe, *Chem. Soc. Rev.*, **1995**, 309.
7. F. Balkenhohl, C. von dem Bussche-Hünnefeld, A. Lansky, C. Zechel, *Angew. Chem. Int. Ed. Engl*, **1996**, *35*, 2288.
8. R. B. Merrifield, *J. Am. Chem. Soc.*, **1963**, *85*, 2149.
9. D. Maclean, J. J. Baldwin, V. T. Ivanov, Y. Kato, A. Shaw, P. Schneider, E. M. Gordon, *Pure Appl. Chem.*, **1999**, *71*, 2349.
10. J. S. Früchtel and G. Jung, *Angew. Chem. Int. Ed. Engl.*, **1996**, *35*, 17.
11. S. Hobbs DeWitt, J. S. Kiely, C. J. Stankovic, M. C. Schroeder, D. M. Reynolds Cody, M. R. Pavia, *Proc. Natl. Acad. Sci. USA*, **1993**, *90*, 6909.
12. S. Hobbs DeWitt, A. W. Czarnik, *Acc. Chem. Res.*, **1996**, *29*, 114.
13. S. V. Ley, I. R. Baxendale, R. M. Bream, P. S. Jackson, A. G. Leach, D. A. Longbottom, M. Nesi, J. S. Scott, R. L. Stoner, S. J. Taylor, *J. Chem. Soc. Perkin Trans.*, **2000**, *23*, 3815.
14. W. L. Fitch, *Molecular Diversity*, **1999**; *4*, 39.
15. D. Gorse, A. Rees, M. Kaczorek, R. Lahana, *Drug Discovery Today*, **1999**, *4*, 257.
16. I. Hughes, G. Hunter, *Combinatorial Chemistry*, **2001**, 243.
17. B. Yan, G. Kumaravel, *Tetrahedron*, **1996**, *52*, 843.
18. B. Yan, G. Kumaravel, H. Anjaria, A. Wu, R. C. Petter, C. F. Jewell, Jr., J. R. Wareing, *J. Org. Chem.*, **1995**, *60*, 5736.
19. B. Yan, J. B. Fell, G. Kumaravel, *J. Org. Chem.*, **1996**, *61*, 7467.
20. B. Yan, Q. Sun, J. R. Wareing, C. F. Jewell, Jr., *J. Org. Chem.*, **1996**, *61*, 8765.
21. B. Yan, Q. Sun, *J. Org. Chem.*, **1998**, *63*, 55.
22. B. Yan, *Combinatorial Chemistry*, **2002**, 328.
23. T. Y. Chan, R. Chen, M. J. Sofia, B. C. Smith, D. Glennon, *Tetrahedron Lett.*, **1997**, *38*, 2821.

24. F. Gosselin, M. Di Renzo, T. H. Ellis, W. D. Lubell, *J. Org. Chem.*, **1996**, *61*, 7980.
25. K. Russell, D. C. Cole, F. M. McLaren, D. E. Pivonka, *J. Am. Chem. Soc.*, **1996**, *118*, 7941.
26. R. C. Anderson, J. P. Stokes, M. J. Shapiro, *Tetrahedron Lett.*, **1995**, *36*, 5311.
27. R. C. Anderson, M. A. Jarema, M. J. Shapiro, J. P. Stokes, M. Ziliox, *J. Org. Chem.*, **1995**, *60*, 2650.
28. J. Chin, B. Fell, M. J. Shapiro, J. Tomesch, J. R. Wareing, A. M. Bray, *J. Org. Chem.*, **1997**, *62*, 538.
29. M. J. Shapiro, J. Chin, R. E. Marti, M. A. Jarosinski, *Tetrahedron Lett.*, **1997**, *38*, 1333.
30. J. Chin, J. B. Fell, M. A. Jarosinski, M. J. Shapiro, J. R. Wareing, *J. Org. Chem.*, **1998**, *63*, 386.
31. J. Chin, B. Fell, S. Pochapsky, M. J. Shapiro, J. R. Wareing, *J. Org. Chem.*, **1998**, *63*, 1309.
32. I. E. Pop, C. E. Dhalluin, B. P. Déprez, P. C. Melnyk, G. M. Lippens, A. L. Tartar, *Tetrahedron*, **1996**, *52*, 12209.
33. G. C. Look, C. P. Holmes, J. P. Chinn, M. A. Gallop, *J. Org. Chem.*, **1994**, *59*, 7588.
34. D. Stones, D. J. Miller, M. W. Beaton, T. J. Rutherford, D. Gani, *Tetrahedron Lett.*, **1998**, *39*, 4875.
35. S. K. Sarkar, R. S. Garigipati, J. L. Adams, P. A. Keifer, *J. Am. Chem. Soc.*, **1996**, *118*, 2305.
36. J. Shey, C. Sun, *Tetrahedron Lett.*, **2002**, *43*, 1725.
37. E. M. Cilli, R. Marchetto, S. Schreier, C. R. Nakaie, *Tetrahedron Lett.*, **1997**, *38*, 517.
38. R. G. Davis, R. J. Anderegg, S. G. Blanchard, *Tetrahedron*, **1999**, *55*, 11653.
39. S. C. McKeown, S. P. Watson, R. A. E. Carr, P. Marshall, *Tetrahedron Lett.*, **1999**, *40*, 2407.
40. B. J. Egner, G. J. Langley, M. Bradley, *J. Org. Chem.*, **1995**, *60*, 2652.
41. M. Davies, M. Bradley, *Tetrahedron*, **1997**, *53*, 8565.
42. B. J. Egner, M. Bradley, *Tetrahedron*, **1997**, *53*, 14021.
43. V. Swali, G. J. Langley, M. Bradley, *Combinatorial Chemistry*, **1999**, 337.

44. A. Streitweiser, C. H. Heathcock, E. M. Kosower in *Introduction to Organic Chemistry*, **1992**, *4th Edition*, 1083, Macmillan Publishing Company.
45. J. A. Joule, K. Mills in *Heterocyclic Chemistry*, **2000**, *4th Edition*, Blackwell Science Ltd.
46. T. L. Gilchrist in *Heterocyclic Chemistry*, **1992**, *2nd Edition*, Longman Scientific & Technical.
47. J. A. Joule, G. F. Smith in *Heterocyclic Chemistry*, **1978**, *2nd Edition*, Chapman & Hall.
48. M. Sainsbury in *Heterocyclic Chemistry*, **2001**, The Royal Society of Chemistry.
49. D. T. Davies in *Aromatic Heterocyclic Chemistry*, **1992**, Oxford University Press.
50. R. G. Franzén, *J. Comb. Chem.*, **2000**, *2*, 195.
51. J. Cheng, A. M. M. Mjalli, *Tetrahedron Lett.*, **1998**, *39*, 939.
52. S. Sarshar, D. Siev, A. M. M. Mjalli, *Tetrahedron Lett.*, **1996**, *37*, 835.
53. C. Zhang, E. J. Moran, T. F. Woiwode, K. M. Short, A. M. M. Mjalli, *Tetrahedron Lett.*, **1996**, *37*, 751.
54. Y. Yu, J. M. Ostresh, R. A. Houghten, *J. Comb. Chem.*, **2001**, *3*, 521.
55. D. V. Patel, M. F. Gordeev, B. P. England, E. M. Gordon, *Molecular Diversity and Combinatorial Chemistry: Libraries and Drug Discovery*, **1996**, *7*, 58.
56. M. F. Gordeev, D. V. Patel, J. Wu, E. M. Gordon, Tetrahedron Lett., **1996**, *37*, 4643.
57. R. J. Simmons, *Chemistry of Biomolecules: An Introduction*, **1992**, The Royal Society of Chemistry.
58. D. Obrecht, C. Abrecht, A. Grieder, J. M. Villagordo, *Helv. Chim. Acta*, **1997**, *80*, 65.
59. P. Biginelli, *Gazz. Chim. Ital.*, **1893**, *23*, 360.
60. L. Weber, S. Wallbaum, C. Broger, K. Gubernator, *Angew. Chem. Int. Ed. Engl.*, **1995**, *34*, 2280.
61. P. A. Tempest, S. D. Brown, R. W. Armstrong, *Angew. Chem. Int. Ed. Engl.*, **1996**, *35*, 640.
62. K. M. Short, B. W. Ching, A. M. M. Mjalli, *Tetrahedron Lett.*, **1996**, *37*, 7489.
63. A. Struder, P. Jeger, P. Wipf, D. P. Curran, *J. Org. Chem.*, **1997**, *62*, 2917.
64. H. Cho, M. Ueda, K. Shima, A. Mizuno, M. Hayashimatsu, Y. Ohnaka, Y. Takeuchi, M. Hamaguchi, K. Aisaka, T. Hidaka, M. Kawai, M. Takeda, T.

Ishihara, K. Funahashi, F. Satoh, M. Morita, T. Noguchi, *J. Med. Chem.*, **1989**, *32*, 2399.

65. K. S. Atwal, G. C. Rovnyak, S. D. Kimball, D. M. Floyd, S. Moreland, B. N. Swanson, J. Z. Gougoutas, J. Schwartz, K. M. Smilie, M. F. Malley, *J. Med. Chem.*, **1990**, *33*, 2629.
66. G. C. Rovnyak, K. S. Atwal, A. Hedberg, S. D. Kimball, S. Moreland, J. Z. Gougoutas, B. C. O'Reilly, J. Schwartz, M. F. Malley, *J. Med. Chem.*, **1992**, *35*, 3254.
67. P. Wipf, A. Cunningham, *Tetrahedron Lett.*, **1995**, *36*, 7819.
68. A. Studer, P. Jeger, P. Wipf, D. P. Curran, *J. Org. Chem.*, **1997**, *62*, 2917.
69. B. C. Ranu, A. Hajra, U. Jana, *J. Org. Chem.*, **2000**, *65*, 6270.
70. J. Lu, H. R. Ma, *Synlett.*, **2000**, 63
71. E. H. Hu, D. R. Sidler, D. P. Curran, *J. Org. Chem.*, **1998**, *63*, 3454.
72. J. C. Bussolari, P. A. McDonnell, *J. Org. Chem.*, **2000**, *65*, 6777.
73. A. Dondoni, A. Massi, S. Sabbatini, *Tetrahedron Lett.*, **2001**, *42*, 4495.
74. E. Gößnitzer, G. Feierl, U. Wagner, *Eur. J. Pharm. Sci.*, **2002**, *15*, 49.
75. C. O. Kappe, *J. Org. Chem.*, **1997**, *62*, 7201.
76. C. O. Kappe, *Molecules*, **1998**, *3*, 1.
77. C. O. Kappe, S. F. Falsone, *Synlett.*, **1998**, 718.
78. C. O. Kappe, *Acc. Chem. Res.*, **2000**, *33*, 879.
79. F. Sweet, J. D. Fissekis, *J. Am. Chem. Soc.*, **1973**, *95*, 8741.
80. X. Beebe, C. L. Chiappari, M. M. Olmstead, M. K. Kurth, N. E. Schore, *J. Org. Chem.*, **1995**, *60*, 4204.
81. C. G. Boojamra, K. M. Burow, J. A. Ellman, *J. Org. Chem.*, **1995**, *60*, 5742.
82. J. Habermann, S. V. Ley, J. S. Scott, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3127.
83. W. F. Degrado, E. T. Kaiser, *J. Org. Chem.*, **1980**, *45*, 1295.
84. W. F. Degrado, E. T. Kaiser, *J. Org. Chem.*, **1982**, *47*, 3258.
85. A. Golebiowski, S. Klopfenstein, *Tetrahedron Lett.*, **1998**, *39*, 939.
86. M. A. Scialdone, S. W. Shuey, P. Soper, Y. Hamuro, D. M. Burns, *J. Org. Chem.*, **1998**, *63*, 4802.
87. B. A. Dressman, U. Singh, S. W. Kaldor, *Tetrahedron Lett.*, **1998**, *39*, 3631.
88. S. Jin, D. P. Holub, D. J. Wustrow, *Tetrahedron Lett.*, **1998**, *39*, 3651.
89. B. Raju, T. P. Kogan, *Tetrahedron Lett.*, **1997**, *38*, 4965.
90. B. C. Hamper, S. A. Kolodziej, A. M. Scates, *Tetrahedron Lett.*, **1998**, *39*, 2047.

91. P. Gund, *J. Chem. Ed.*, **1972**, *49*, 100.

92. Y. Yamamoto, S. Kojima, *Synthesis and Chemistry of Guanidine Derivatives*, Vol. 2, John Wiley and Sons Ltd., **1991**,485.

93. A. Sukenik, C. Rosin, R. Porat, B. Teltsch, R. Banker, S. Carmeli, *Israel J. Plant Sci.*, **1998**, *46*, 109.

94. W. W. Carmichael, *The Toxins of Cyanobacteria. Sci. Am.*, **1994**, *January 270*, 64.

95. I. J. McAlpine, R. W. Armstrong, *Tetrahedron Lett.*, **2000**, *41*, 1849.

96. M. Dennis, L. M. Hall, P. J. Murphy, A. J. Thornhill, R. Nash, A. L. Winters, M. B. Hursthouse, M. E. Light, P. Horton, *Tetrahedron Lett.*, **2003**, *44*, 3075.

97. A. J. Thornhill, *PhD. Thesis*, University of Wales Bangor, **2000**.

98. K. Nagasawa, A. Georgieva, T. Nakata, *Tetrahedron*, **2000**, *56*, 187.

99. A. I. McDonald, L. E. Overman, *J. Org. Chem.* **1999**, *64*, 1520.

100. D. S. Coffey, A. I. McDonald, L. E. Overman, M. H. Rabinowitz, P. A. Renhowe, *J. Am. Chem. Soc.*, **2000**, *122*, 4893.

101. G. P. Black, P. J. Murphy, N. D. A. Walsh, *Tetrahedron*, **1998**, *54*, 9481.

102. G. P. Black, P. J. Murphy, N. D. A. Walsh, D. E. Hibbs, M. B. Hursthouse, K. M. A. Malik, *Tetrahedron Lett.*, **1996**, *37*, 6943.

103. A. S. Franklin, S. K. Ly, G. H. Mackin, L. E. Overman, A. J. Shaka, *J. Org. Chem.*, **1999**, *64*, 1512.

104. A. D. Patil, A. J. Freyer, P. B. Taylor, B. Carte, G. Zuber, R. K. Johnson, D. J. Faulkner, *J. Org. Chem.*, **1997**, *62*, 1814.

105. G. P. Black, P. J. Murphy, A. J. Thornhill, N. D. A. Walsh, C. Zanetti, *Tetrahedron*, **1999**, *55*, 6547.

106. K. Nagasawa, H. Koshino, T. Nakata, *Tetrahedron Lett.*, **2001**, *42*, 4155.

107. A. Expósito, M. Fernández-Suá, T. Iglesias, L. Muñoz, R. Riguera, *J. Org. Chem.* **2001**, *66*, 4206.

108. J. Luo, T. C. Bruice, *J. Am. Chem. Soc.* **1998**, *120*, 1115.

109. B. A. Linkletter, I. E. Szabo, T. C. Bruice, *J. Am. Chem. Soc.* **1999**, *121*, 3888.

110. C. H. Fotsch, C-H. Wong, *Tetrahedron Lett.*, **1994**, *35*, 3481.

111. A. W. –Y. Chan, B. Ganem, *Tetrahedron Lett.*, **1995**, 36, 811.

112. L. Gauzy, Y. Le Merrer, J-C. Depezay, *Synlett.*, **1998**, 402.

113. Y. Le Merrer, L. Gauzy, C. Gravier-Pelletier, J-C. Depezay, *Bioorg. Med. Chem.*, **2000**, *8*, 307.

114. V. Le, C-H. Wong, *J. Org. Chem.*, **2000**, *65*, 2399.
115. J. Robertson, *Protecting Group Chemistry*, Oxford Science Publications, **2000**.
116. D. S. Dodd, A. P. Kozikowski, *Tetrahedron Lett.*, **1994**, *35*, 977.
117. K. Feichtinger, C. Zapf, H. L. Sings, M. Goodman, *J. Org. Chem.*, **1998**, *63*, 3804.
118. K. Feichtinger, H. L. Sings, T. J. Baker, K. Mathews, M. Goodman, *J. Org. Chem.*, **1998**, *63*, 8432.
119. S. Cunha, M. B. Costa, H. B. Napolitano, C. Lariucci, I. Vencato, *Tetrahedron*, **2001**, *57*, 1671.
120. J. Shey, C. Sun, *Synlett.*, **1998**, 1423.
121. J. A. Josey, C. A. Tarlton, C. E. Payne, *Tetrahedron Lett.*, **1998**, *39*, 5899.
122. J. R. Hauske, P. Dorff, *Tetrahedron Lett.*, **1995**, *36*, 1589.
123. A. S. Hernandez, J. C. Hodges, *J. Org. Chem.*, **1997**, *62*, 3153.
124. P. C. Kearney, M. Fernandez, J. A. Flygare, *Tetrahedron Lett.*, **1998**, *39*, 2663.
125. M. Li, L. J. Wilson, D. E. Portlock, *Tetrahedron Lett.*, **2001**, *42*, 2273.
126. A. K. Ghosh, W. G. J. Hol, E. Fan, *J. Org. Chem.* **2001**, *66*, 2161.
127. T. P. Hopkins, J. M. Dener, A. M. Boldi, *J. Comb. Chem.*, **2002**, *4*, 167.
128. J. M. Ostresh, C. C. Schoner, V. T. Hamashin, A. Nefzi, J. Meyer, R. A. Houghten, *J. Org. Chem.*, **1998**, *63*, 8622.
129. A. N. Acharya, A. Nefzi, J. M. Ostresh, R. A. Houghten, *J. Comb. Chem.*, **2001**, *3*, 189.
130. E. Nizi, M. Botta, F. Corelli, F. Manetti, F. Messina, G. Maga, *Tetrahedron Lett.*, **1998**, *39*, 3307.
131. M. Botta, F. Corelli, G. Maga, F. Manetti, M. Renzulli, S. Spardari, *Tetrahedron*, **2001**, *57*, 8357.
132. F. Albericio, N. Kneib-Cordonier, S. Biancalana, L. Gera, R. I. Masada, D. Hudson, G. Barany, *J. Org. Chem.*, **1990**, *55*, 3730.
133. L. A. Thompson, J. A. Ellman, *Tetrahedron Lett.*, **1994**, *35*, 9333.
134. A. Minot, H. Moskowitz, M. Miocque, *Synthesis*, **1979**, 52.
135. D. Sarantakis, J. J. Bicksler, *Tetrahedron Lett.*, **1997**, *38*, 7325.
136. A. Nefzi, J. M. Ostrech, J. Meyer, R. A. Houghten, *Tetrahedron Lett.*, **1997**, *38*, 931.
137. A. Nefzi, N. A. Ong, R. A. Houghten, *Tetrahedron Lett.*, **2000**, 41, 5441.

138. G. T. Wang, Y. Chen, S. Wang, R. Sciotti, T. Sowin, *Tetrahedron Lett.*, **1997**, *38*, 1895.

139. M. A. Scialdone, S. W. Shuey, P. Soper, Y. Hamuro, D. M. Burns, *J. Org. Chem.*, **1998**, *63*, 4802.

140. S. Bräse, S. Dahmen, M. Pfefferkorn, *J. Comb. Chem.*, **2000**, *2*, 710.

141. M. Scroeder, J. M. Hamby, C. J. C. Connolly, P. J. Grohar, R. T. Winters, M. R. Barvian, C. W. Moore, S. L. Boushelle, S. M. Crean, A. J. Kraker, D. L. Driscoll, P. W. Vincent, W. L. Elliott, G. H. Lu, B. L. Batley, T. K. Dahring, T. C. Major, R. L. Panek, A. M. Doherty, H. D. Hollis Showalter, *J. Med. Chem.*, **2001**, *44*, 1915.

142. W. Zhang, C. H. Chen, T. Nagashima, *Tetrahedron Lett.*, **2003**, 44, 2065.

143. D. Fattori, P. D'Andrea, M, Porcelloni, *Tetrahedron Lett.*, **2003**, 44, 811.

144. J. Cervelló, T. Sastre, *Synthesis*, March **1990**, 221.

145. H. E. Lebovitz, M. N. Feinglos, *Diabetes Care*, **1978**, *1*, 189.

146. WO9808848A1, *March 5*, **1998**.

147. M. Xue, B. H. Long, C. Fairchild, K. Johnston, W. C. Rose, J. F. Kadow, D. M. Vyas, S. Chen, *Bioorg. Med. Chem. Lett.*, **2000**, *10*, 1327.

148. M. C. Elliott, M. S. Long, *Tetrahedron Lett.*, **2002**, *43*, 9191.

149. M. Muehlbacher, C. Poulter, J. Dale, *J. Org. Chem.* **1998**, *53*, 1026.

150. M. Casey, J. Leonard, B. Lygo, G. Procter, *Advanced Practical Organic Chemistry*, **1990**, Blackie Ltd.