Novel pyridinium linkers for solid phase synthesis

Novel Pyridinium Linkers for Solid Phase Synthesis.

By

Sweta Ramesh Ladwa

A Doctoral Thesis

Submitted in partial fulfilment of the requirements

For the award of

Doctor of Philosophy of Loughborough University

(May 2004)

Acknowledgements

I would like to start by thanking Dr. George Weaver, my supervisor and friend over the last 4 years. The support, guidance, advice and sheer enthusiasm for this project has made this work possible and enjoyable. I could not have asked for a better supervisor. Thank you.

I would like to thank Dr. Nicole Hamblin, my industrial supervisor at GSK over the last three years. Thank you for all the support and advice over the last few years, especially during my time at GSK. It has been an invaluable experience.

I would also like to thank the rest of the Weaver group, whom I worked with for their help and advice. Also to all the organic staff, especially Dr. Steve Christie and Professor Ray Jones for all their help during group meeting sessions and general chemistry queries. To all the laboratory technicians and especially the technical staff for all their help, including Dr. Tim Smith and Dr. Mark Edgar (NMR), Mr Alastair Daley (CHN, LC-MS, everything else), Mr John Kershaw (Mass Spectrometry) and Mr John Spray (glass blower). Everyone in laboratories F001, F009 and F402 also deserve a big thank you for my making my time during my PhD so enjoyable. I would also like to thank Dr. Paul Kelly for his constant support and encouragement over the last few years.

And now to my friends, I would first like to thank all my friends who I started University with back in 1996, you know who you are! Thank you for all the encouragement over the last few years. You'll be pleased to know I am paying taxes now! Thank you to all the friends I made during my PhD, Stella James, Suzanne Dilly, Dave Leach, Anthony Fletcher, Emma Kendrick, Emma Ross, Steve Aucott and Ross Fryatt, to name a few. Thank you for your friendship, encouragement and everything else over the last few years. I would also like to thank Sam Hollands (best friend) and James Mason for their help, friendship, encouragement and support over the last few years. Fantastic friends are always hard to find, but I managed to, so thank you to you all.

I would like to especially thank my parents, Ramesh and Prabha Ladwa and my brother, Mahin Ladwa for everything. Without their support throughout my education, none of this would be possible.

Lastly I would thank the EPSRC and GSK for the greatly appreciated financial support in the form of a project studentship, which has enabled this project to be completed.

Abstract

This thesis describes the synthesis of novel pyridinium linkers for solid phase synthesis. In the first instance, Merrifield resins were employed to attach a pyridine substrate on which alkylation and arylation reactions were extensively studied. Reactions of this type were initially attempted in solution phase using pyridine and DMAP to act as the linker mimic. Successful results were obtained in both solution and solid phase.

A variety of amine nucleophiles were investigated to study ring- opening reactions of the pyridinium ring. Amines were successfully isolated from solution phase reactions. Attempted cleavage reactions of solid-supported pyridinium compounds were less successful.

Fmoc Rink amide resin was employed, onto which a pyridine acid was attached. This support could act as a 'pre' linker resin, thus enabling us to analyze synthetic steps during reaction sequences. Alkylation reactions were successfully carried out on this type of support, enabling propanamide adducts to be isolated and analyzed by LC-MS. A number of these alkylated resins were then employed to investigate cyclization reactions to build quinoline and benzopyran derivatives. Initial LC-MS studies showed that these compounds had been synthesized on the pyridinium ring, although uncyclized intermediates were detected.

A study was carried out into the synthesis of vinyl pyridinium salts in solution phase. This was with a view to eventually transfer the processes to solid support. We studied the synthesis of unsubstituted and substituted salts and some of their reactions. A phenyl vinyl pyridinium salt was isolated and we were able to obtain an X-ray structure to study the conformation of the phenyl and pyridinium rings.

Keywords: *Pyridinium, Linkers, Solid phase, Cyclization, Alkylation, Solution phase.*

Table of Contents

Table of Contents 0
1 Introduction 1
1.1 General Introduction 1
1.2 History of Combinatorial and Solid Phase Chemistry 4
1.3 Solid Phase and Soluble Polymers for Combinatorial Synthesis 15
1.3.1 Solid-phase Supports 16
1.3.1.1 Polystyrene- based Resins 16
1.3.1.2 PEGylated resins 19
1.3.1.3 Cross-linked acrylamide resins 20
1.3.2 Soluble Polymeric Supports 22
1.3.2.1 Separation Techniques for Soluble Polymeric Supports 23
1.3.2.2 Classification of Soluble Polymers 24
1.4 Linkers for Solid Phase Chemistry 28
1.4.1 Acid Labile Linkers 30
1.4.2 Base- labile linkers 37
1.4.3 Photolabile-linkers 39
1.4.4 Oxidative/Reductive Linkers 45
1.4.4.1 Reductive Methods 45
1.4.4.2 Oxidative Methods 48
1.5 Summary 51
2 Results and Discussion 52
2.1 Synthesis of pyridine linkers using Merrifield Resins 52
2.2 Solution phase reactions 53
2.3 Cleavage strategies of solution-phase reactions 61
2.4 Alkylation and cyclization reactions of pyridine linker resins 67
2.5 Cleavage strategies for solid supports 70
2.6 The use of 'pre' linker resins 73
3 Vinyl Pyridinium Salts: Synthesis and Applications 86
3.1 Introduction 86
3.2 Synthesis of *N*-vinylpyridinium salts 88
3.3 Synthesis of aryl-vinyl pyridinium salts 102
4 Conclusion 111
4.1 Summary and Future work 111
5 Experimental 113
6 References 163
APPENDIX (I) 171

Abbrevations

AIBN	azo-bis-(isobutyronitrile)
atm.	atmosphere
BHA	benzhydrylamine
bn	benzyl
t-Boc	*t*-butoxycarbonyl
Bpoc	2-(*p*-biphenyl)-2-propyloxycarbonyl
Bu^t	tertiary butyl
BuLi	butyl lithium
CAN	ammonium cerium(IV) nitrate
Cbz	benzyloxycarbonyl
cm^{-1}	wave number
m-CPBA	3-chloroperoxybenzoic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCCI	*N, N'*- dicyclohexylcarbodiimide
DCM	dichloromethane
DDQ	2, 3-dichloro-5,6-dicyanobenzoquinone
DIPEA	diisopropylamine
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
d.p	decimal places
eq.	equivalents
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
Fmoc	9-fluorenylmethyloxycarbonyl
GC-MS	gas chromatography-mass spectrometry
g	gram(s)
h	hour(s)
HBr	hydrogen bromide
HCl	hydrogen chloride
HF	hydrogen fluoride

IR	infra-red
KHMDS	potassium hexamethyldisilazide
KOH	potassium hydroxide
LC-MS	liquid chromatography-mass spectrometry
LDA	lithium diisopropylamine
Me	methyl
MeOH	methanol
min	minute(s)
ml	millilitre
mmol	millimole(s)
mp	melting point
m/z	mass to charge ratio
NaOMe	sodium methoxide
NBHA	nitrobenzhydrylamine
NMP	1-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
PEG	poly(ethylene)glycol
PEGA	poly(ethylene)glycol dimethylacrylamide
Ph	phenyl
PhMe	toluene
ppm	parts per million
PVA	poly(vinyl)alcohol
PyBrop	benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate
PyBrop	bromo-tris-pyrrolidinophosphonium hexafluorophosphate
RP-HPLC	reverse phase- high performance liquid chromatography
RT	room temperature
s	second(s)
SPE	solid phase extraction
TBAF	tetra-*n*–butylammonium fluoride
TBD	7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
Temp	temperature

TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
Tos	tosylate
UV-vis	ultra violet-visible

1 Introduction

1.1 General Introduction

A fundamental aim of organic synthesis involves the creation of new carbon containing substances. From its early beginnings, organic synthesis has been carried out by targeting one molecule at a time. During the last decade of the twentieth century, a new concept was developed, which involved the synthesis of a collection of molecules at one time. This concept, known as combinatorial chemistry allowed a large number of chemical compounds to be generated very quickly in one pot, thus increasing productivity. This is in contrast to traditional organic chemistry, where several synthetic steps may be involved to synthesize a single compound, thus requiring a number of reactions. ***Figure 1*** shows this contrast.

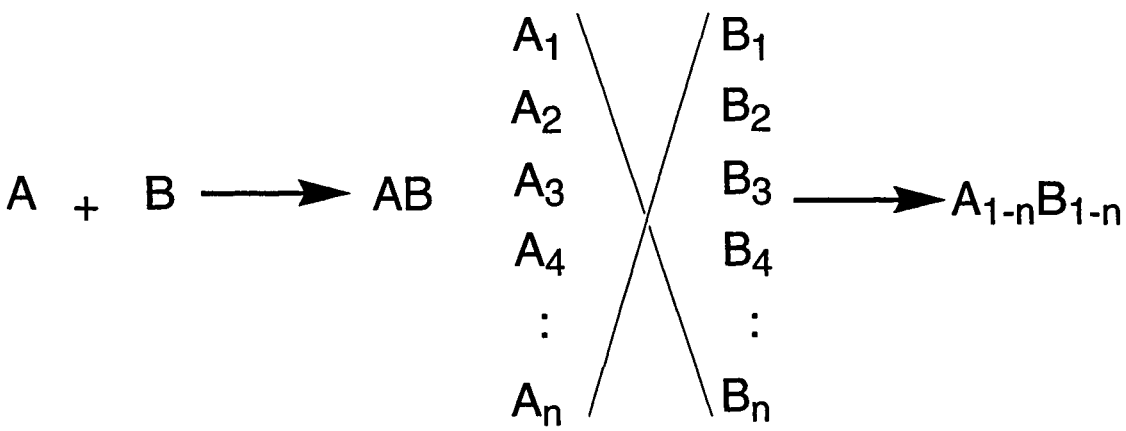


Figure 1

Thus more compounds could be generated in a 'library' than the number of steps involved in the synthesis itself and combinatorial chemistry has become an important tool within the pharmaceutical industry. Drug discovery is an expensive and lengthy process. It can take up to five years from project initiation to a potential drug being nominated for research and development. The synthesis of exploratory compounds can often be the slowest step and pressures within the pharmaceutical industry to speed up the drug discovery process have meant that combinatorial chemistry has become a high priority concept.

Today, as well as being utilized within the pharmaceutical industry, it has rapidly been encompassed in academia and the fine chemical industry. The ability to synthesize libraries of either mixtures or single compounds has become of great importance. Alongside this, high-speed purification techniques and characterization strategies have also been developed which can be utilized with the synthetic chemistry. The use of combinatorial chemistry is not only restricted to solid supports, where the chemistry is carried out on a polymeric framework, from which the desired product is eventually released, but can also be utilized in solution phase. Although each area holds its own advantages and disadvantages, both methods are widely used to synthesize large libraries of compounds.

Solid phase chemistry holds many benefits. Firstly, large excesses of reagents may be employed which can be used with the solid supports to accelerate and drive reactions to completion. The use of these excess reagents is possible because they can be conveniently removed at the end of a reaction by filtration and washing of the resin beads. Any by-products of the reactions, which are not attached to the resin itself, can also be washed away, leaving only the desired material on the resin beads. Solid phase chemistry can also be automated through robotics, much more so than traditional solution-phase chemistry. This plays a vital role, especially in the pharmaceutical industry where high-throughput chemistry remains a laborious task. Combinatorial chemistry encompasses the use of the 'split-mix' strategy, which was developed by Furka[1] and this concept will be discussed in Section 1.2.

Also, as well as the use of solution phase reagents to build structures on solid supports, the reagent can also be the supported component in the reaction mixture. This can be particularly beneficial if the reagent is persistent, such as phosphines[2], toxic, such as chromates[3], or just expensive, such as palladium[4]. The reactant can then be easily removed from the reaction mixture, allowing: -

- Persistent reagents to be removed completely and effortlessly.
- Toxic reagents to be removed without leaving residues.
- Expensive reagents to be easily recovered and regenerated.

The removal of toxic reagents is particularly important, as it allows the user to contain and dispose of the hazardous material easily, and often renders the substance non-toxic. There is also potential for industries that are concerned about toxic residues, such as the pharmaceutical industry, to use a wider scope of reactions.

Related to this type of application, solid supports can also be used as scavengers. In a normal solution phase reaction, undesired by-products or unreacted material may be removed by the addition of a polymer, which picks up the contaminant, which can then be removed by filtration.

Although the insoluble nature of the resin is an advantage at the purification stage, it can also be a liability at the reaction stage. For example, the heterogeneous reaction conditions of solid phase prevent monitoring of progress by classical methods such as TLC. Also, tedious optimization of reaction protocols is sometimes required to obtain good yields in solid phase reactions. Other disadvantages include the cost of the solid supports; they are expensive. Also typical loading capacities range from 1.0 to 2.5 mmol/g. This results in effective molecular weights of 1 000 to 10 000, making large scale or even multi-gram solid phase synthesis impractical, although very high loading resins have recently been developed to overcome this. Bradley *et al.*[5] reported the synthesis of dendrimers using solid support techniques. The synthesis of two polyamidoamine (PAM- AM) supports were reported, which were synthesized using TentaGel resin. Loadings were calculated to be between 2.3-2.8 mmol/g.

In summary, the principal advantages of solid phase and combinatorial technology are the ease of purification, either by the ability to hold onto the product and wash it, or through being able to 'fish out' desirable or undesirable components of the reaction by the use of supported reagents or post reaction by the use of scavengers. The increased control of hazardous materials whilst polymer-supported is also a major advantage, allowing otherwise detrimental reactions to be carried out harmlessly. Other advantages, such as the production of fewer side reactions[6], or additional stability, particularly with organometallic reagents[7], have been observed for some reactions.

1.2 History of Combinatorial and Solid Phase Chemistry

Combinatorial and solid phase chemistry, though a relatively new field of chemistry has its earliest origins in solid phase peptide synthesis. Merrifield[8] pioneered the first solid phase work in 1963, where his method depended on the use of an insoluble polymer or solid support to facilitate the synthesis of polypeptides. The idea was demonstrated by the synthesis of the tetrapeptide L-leucyl-L-alanyl-glycyl-L-valine. He demonstrated that the sample, which was prepared on the resin, was identical to that prepared using the standard *p*-nitrophenyl ester procedure[9], which was carried out in solution phase. ***Figure 2*** shows the steps used to synthesize one peptide bond on the solid support.

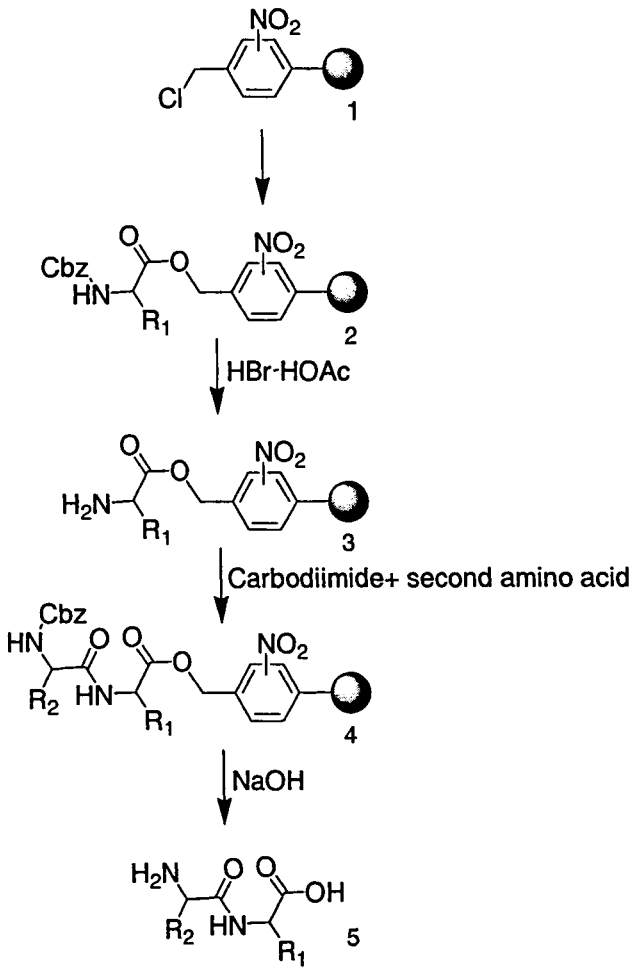
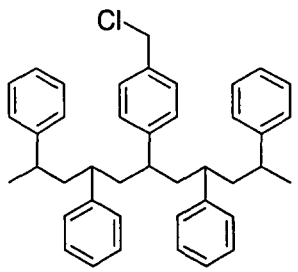


Figure 2

The solid support originally used by Merrifield consisted of beads of a copolymer prepared from styrene and 2% 1,4-divinylbenzene. These were treated with

chloromethyl methyl ether and tin(IV) chloride, which gave a resin in which 10% of the aromatic rings bore chloromethyl (-CH_2Cl) groups. See ***Figure 3***.



6

Figure 3

The polymer was in the form of 200-400 mesh beads, which possessed a porous gel structure. The polymer swelled in some solvents including DCM, which allowed the diffusion of reagents throughout the polymer. The polymer was cross-linked to a degree of 2%. Cross-linking of 8% and 16% was also investigated. These were both found to be too rigid, thus preventing reagents from entering the matrix of the polymer. This resulted in slow and incomplete reactions on the resins. Lower cross-linking, i.e. 1% produced fragile beads, which proved to be troublesome during the filtration process, where the beads disintegrated.

In his publication[8], Merrifield established the advantages of his solid phase synthesis. He reported these to be the simplification of the manipulations required in peptide synthesis, which resulted in shorter reaction times and higher yields. This was found to be due mainly to the fact that intermediates did not have to be isolated and purified.

The advances in polymerization techniques also provided new opportunities in organic chemistry. Before the acceptance of suspension polymerization, 'popcorn' polymers were developed[10]. These polymers had a low level of cross-linking, but were highly insoluble, with little or no swelling properties. This polymerization technique was used to generate early examples of polymers, which presented themselves in two macromolecular forms. The first type was found to be dense and glassy in appearance. This was defined as a 'glassy' polymer. It was found

to be extremely soluble in benzene. The second, which was termed the 'popcorn' polymer, was found to be low in density and had a greater porosity, this allowing solvents and reagents to pass freely within the polymeric framework.

In 1959, Letsinger[10] showed that substituted styrene compounds, possessing boron functional groups could be synthesized and subjected to polymerization. From the diethyl tartrate ester of *p*-vinylbenzeneboronic acid, styrene and diallyl maleate, a 'popcorn-type' copolymer was obtained. This copolymer was found to be highly insoluble, however it reacted with phenylenediamine to give a dihydrobenzoboradiazole derivative and hydrogen peroxide cleaved the carbon-boron bonds to give a boron-free polymer. See ***Figure 4.***

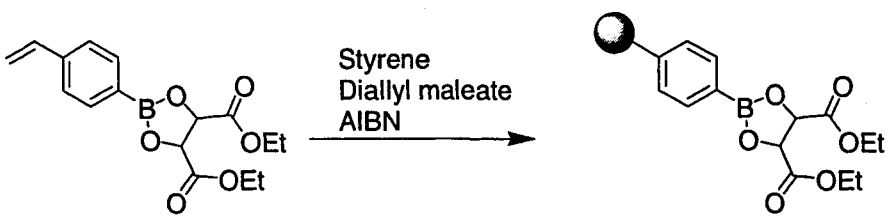


Figure 4 An example of 'popcorn' polymer

After Merrifield's publication, Letsinger[11] published a report on the synthesis of a dipeptide, using a 'popcorn' polymer[12] utilizing the same principles as Merrifield. He established that polymers with 0.1-0.5% cross-linking could be synthesized, which allowed easier diffusion of starting reagents through the polymer, without the disintegration problems of Merrifield's beads.

Since the time of Letsinger and Merrifield, it has been realized that this approach could be used to synthesize many different compounds, not only peptides. In the early 1970s the group of Leznoff[13] reported the use of polymer supports to synthesize monotrityl ethers of symmetrical diols. This was achieved by using functionalized insoluble polymers to selectively block one functional group of a completely symmetrical difunctional compound. Frechet[14] has reviewed the synthesis and applications of organic polymers as supports and protecting groups. Camps[15], Patchornik[16] and Rapoport[17] have also reported the use of solid phase

supports in this decade. Camps[18] reported a solid phase synthesis of a pharmaceutically important benzodiazepine.

In the 1980s Houghten[19] demonstrated the use of the 'teabag' concept. The 'teabag' is a polypropylene mesh bag with dimensions of approx. 15 x 20 mm. This bag was filled with resin beads, after which the bag was then sealed. The mesh allowed solvents and solids to enter readily, but it had holes small enough so that the resin beads would not escape. The principle behind the use of this 'bag' was to allow the synthesis of multimilligram quantities of a specific peptide sequence in each bag, while to save time, bags could be combined in the same pot for common chemical steps. By combining common reaction steps, considerable time could be saved in preparing many different peptides.

Also in this decade, Frank and co-workers[20] synthesized collections of oligonucleotides and, later peptides on circles of cellulose paper. In Australia, Geysen[21] and co-workers demonstrated that libraries of peptides could be prepared on functionalized polypropylene pins. This was carried out by immersing them sequentially into various solutions of activated amino acids held in the wells of a microtitre plate.

During this time, Furka and co-workers[1] came up with an elegant and ingenious strategy for combinatorial synthesis. This concept was known as the 'split-mix' or 'split and pool' method. For example, if 10 000 compounds were to be synthesized using traditional organic methods, 10 000 reactions vessels would be required. If three synthetic steps were used to create trimers, then 30 000 reaction steps would be required. Using Furka's concept, the task of making 10 000 compounds was less laborious. In this case only 27 reaction vessels would be needed. The basic idea was as follows; a quantity of resin was divided into an equal number of portions and each of these portions was individually reacted with a different monomeric material. To synthesize a peptide library for example, the monomers used would be amino acids, suitably protected with a Boc or Fmoc group at the *N*-terminus. The individual portions would be recombined, thoroughly mixed with an appropriate coupling agent, and then divided again into equal portions. Reactions with a further set of reagents could be carried out, for

example following a deprotection step which would reveal the next key functional group. This would give a complete set of dimeric products. This process could be repeated as many times as necessary (for a total of n times). ***See Figure 5.***

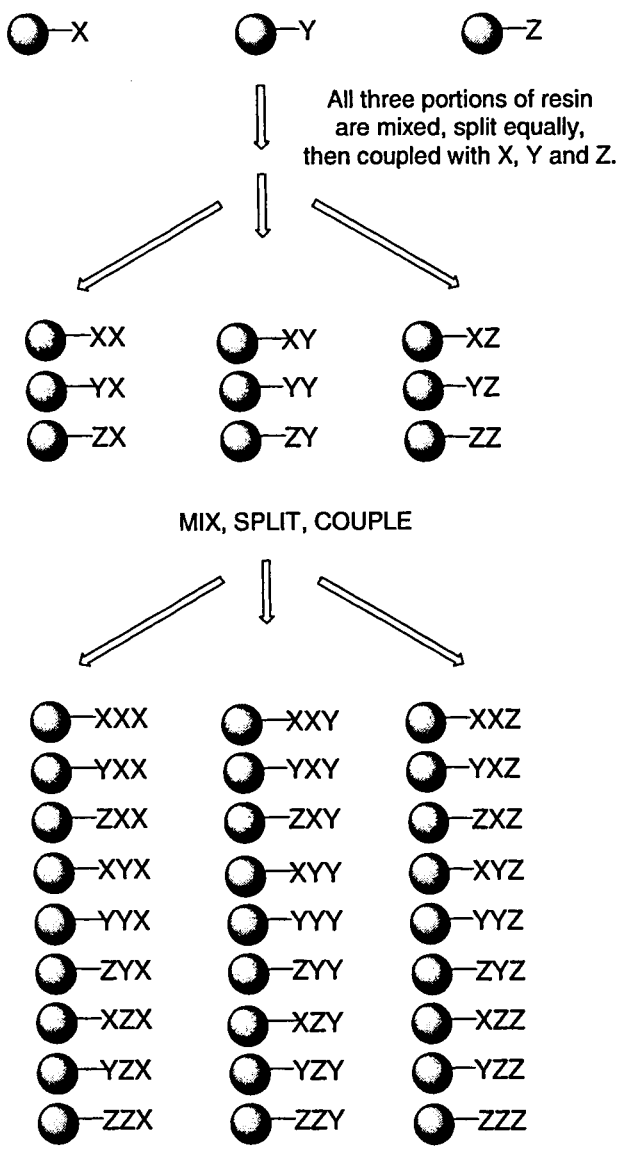


Figure 5 Split-mix method for the synthesis of 27 trimers[22]

The figure above shows a simple example of a 3 x 3 x 3 library, giving all 27 combinations of trimers. This 'split-mix' method provides a key role, especially in the pharmaceutical industry, as this type of chemistry allows for a large number of compounds to be synthesized at one time. From these compounds, active molecules can be identified by deconvolution.

The group of Lam[23] independently developed the same technique and this work was published in 1991. This strategy, along with Houghten's[19] work led to the concept of "one bead-one compound". This led to the promise of delivery of millions of compounds, which would be synthesized simultaneously on beads, and with unprecedented rapidity[22].

During the late 1970s, alternative strategies were investigated, which encompassed solution and solid phase together. It was found that certain polymers were soluble in certain solvents, but would precipitate efficiently from others[24]. Reactions on these types of polymers were carried out in homogeneous solutions, still providing the convenience of purification by simple filtration. By replacing insoluble cross linked resins with soluble polymer supports, the familiar reaction conditions of classical organic chemistry are reinstated, and yet product purification is still facilitated through application of macromolecular properties. This methodology, in essence avoids the difficulties of solid phase synthesis, such as the rigidity and fragility of the solid beads, while preserving its positive aspects. The group of Bayer[25, 26] first used this term 'liquid phase' synthesis to contrast the differences between solid phase peptide synthesis and a method of synthesis on soluble PEG. They used this method to demonstrate the synthesis of peptides, ***see Figure 6***. To the carboxylic acid of the *C*-terminal amino acid was bound a polymeric protecting group. This would endow the growing peptide chain with good solubility. PEG was found to be very useful for this purpose. Besides this, the polymeric group had the advantage that from the beginning of the synthesis, the reagents and the growing peptide chain differed in molecular size. This made is possible for separation of the growing peptide chain at every step. The easiest way to achieve this separation was by dialysis under membrane filtration[27]. It was found that the advantages of solid phase were still preserved, with the further advantage that the growing peptide chain could be purified as often as desired, without cleavage from the polymer support.

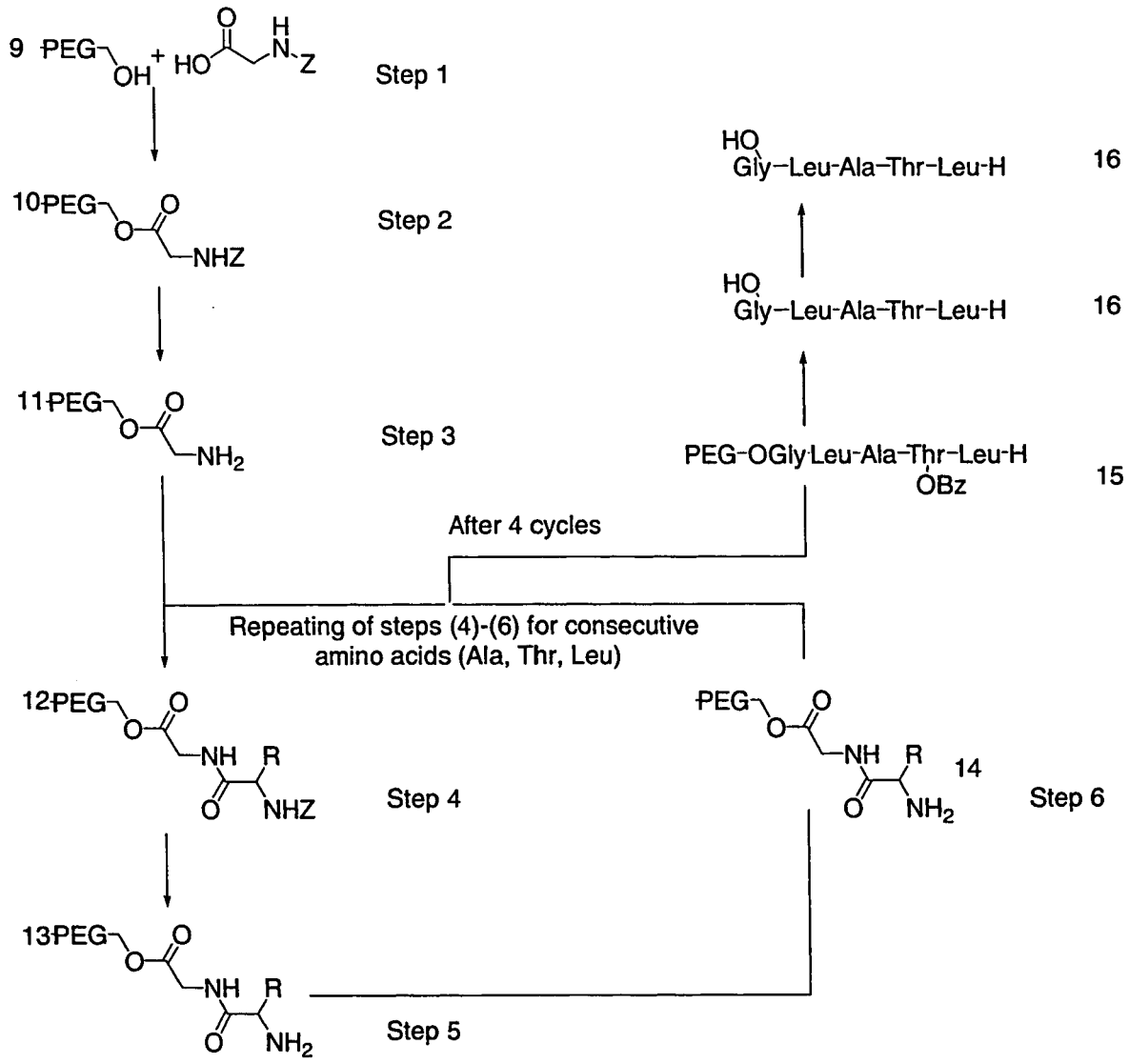


Figure 6 Flow chart for the synthesis of HO-Gly-Leu-Ala-Thr-Leu.

In 1965[28], the synthesis of a tetrapeptide was achieved using a soluble polymer support. During this procedure, many problems were encountered as well as during subsequent peptide syntheses. The reactions were carried either using dioxane or DMF as the solvent. To precipitate the polymer out of solution, water was added to the reaction mixture. This resulted in co-precipitation of some of the reagents, which caused a problem in purification. By carrying out the reaction in DMF and then pouring the polymer into water, precipitation of reagents eventually solved the problem of co-precipitation, but it did cause the precipitation of the polymer to be incomplete, as the polymer chain became elongated by the growing peptide. Gel filtration[29] solved this problem. This maximized polymer retrieval from the reaction. This in turn allowed shorter chain lengths of polymer to be used. Another problem that occurred was that of cross-linking. The linear

polystyrenes employed were chloromethylated to allow attachment of the peptides. However, as the initial peptide attachment step was incomplete, some of the chloromethyl groups remained[24]. After several synthetic steps were completed, cross-linking between the chloromethyl groups could become sufficient to cause the polymer to become insoluble. While the reaction was continued in a heterogeneous manner, this uncontrolled cross-linking made the technique unreliable. This problem was largely overcome by the polymerization of styrene with chloromethyl polystyrene. A polymer was produced with virtually no cross-linking. When this was used to support the amino acid leucine, the coupling reaction was carried out in 86-89% yield[30].

These soluble polymers showed an additional advantage over insoluble polymers. The addition of pre-formed oligopeptides, typically 3-10 residues could be carried out on a growing peptide chain on a soluble polymer with the same efficiency as a single residue. This was not possible with the more rigid insoluble polymers due to the inability of larger molecules to penetrate the pores. This caused the coupling yields to decrease as the chain length of the oligopeptides increased[31].

Since this time, various linear polymers have been screened for this process. From this, PEG has emerged as the predominant soluble polymer. The properties and applications of this polymer support will be discussed in Section 1.3.2.

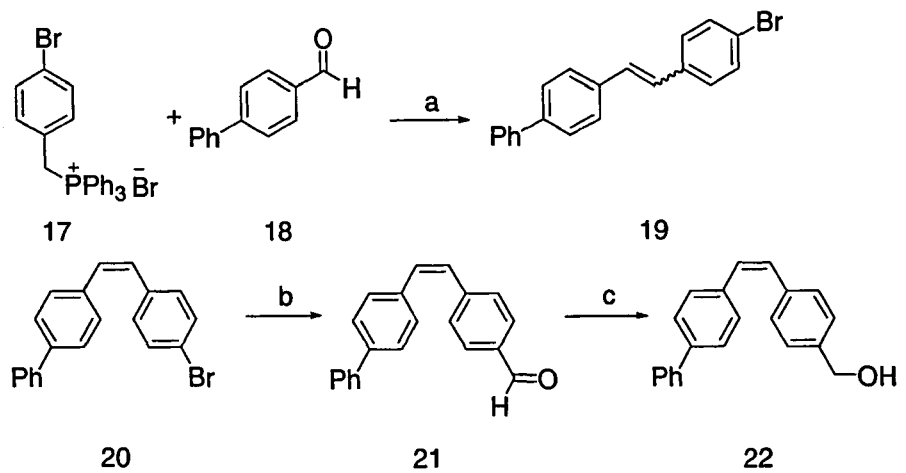
In 1973, Rink[32] reported the use of soluble linear polystyrene as a support for a Merrifield-type synthesis. It was recognized that the advantages of solid phase synthesis could be maintained, while allowing classical organic conditions to be utilized.

Automated solid-phase organic synthesis (SPOS) has emerged as an important tool in organic synthesis and medicinal chemistry[33]. From the early 1990s, there has been an explosion in chemical reports addressing all aspects of combinatorial and solid phase chemistry. In response to the limitations mentioned earlier, alternative methods have been introduced. For example, fluorous synthesis[34] and dendrimer-supported organic synthesis[35], involves the attachment of a reactant

molecule to a 'phase tag', which facilitates product isolation by a phase-transfer event (solvent-induced precipitation or liquid-liquid partition).

The group of Wilcox[36] reported a separation process, which was caused by a change in solubility that would be caused not by a change in solvent or environment, but by a change in the structural ancillary portion of the desired product. This auxiliary was termed a 'precipiton' and this was defined as a group of atoms or molecular fragment, which could be isomerized after a reaction to facilitate precipitation or phase transfer of the attached product. One class of precipiton, which was described, included molecular fragments, which could exist in two isomeric forms; one form was freely soluble in a given solvent, the other insoluble in the same solvent. A product attached to such an auxiliary could be directly isolated from a reaction mixture by isomerization of the ancillary group to generate the insoluble isomer of the product. The precipitated product could then be isolated by filtration or centrifugation.

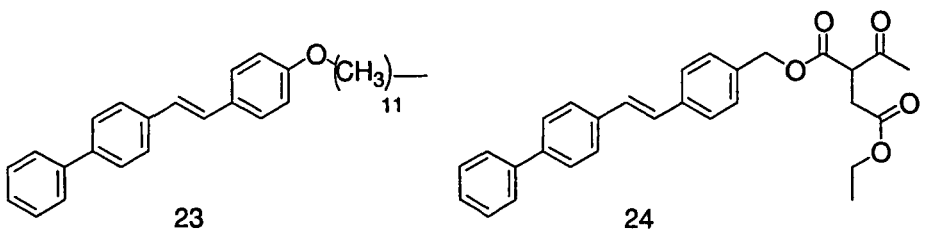
The search for precipitons started with stilbene analogues. cis-Stilbenes can be more soluble than trans-stilbenes[37, 38]. The biphenyl-derived alkenes (*E*)-**19** and (*Z*)-**20** were prepared via a Wittig reaction. ***See Figure 7.***



a) KHMDS, THF, -78 °C, 81%
b) i) *t*BuLi, THF, -78 °C; ii) DMF, -78 °C - 0 °C, 97%;
c) $NaBH_4$, EtOH, 0 °C, 98%.

Figure 7 The preparation of biphenyl analogues for use as 'precipitons'

Alkene **22** was found to be freely soluble in common organic solvents such as EtOAc, THF, Et_2O, DCM, $CHCl_3$ and PhMe. The solubility of the (*E*) isomer was found to be the opposite in these solvents. The dodecyl ether (*E*)-**23** and the *ß*-ketoester (*E*)-**24** were also prepared, see ***Figure 8***, and their solubilities were measured in the solvents listed above. This was carried out to assess the effect that attached product like groups might have on the solubility of the precipiton. It was found that the dodecyl group had no measurable effect on the solubility of the (*E*) isomer, but the *ß*-ketoester functionality increased the solubility of the (*E*) isomer in EtOAc and THF. Fortunately, regardless of the nature of the appended fragment, the (*E*) isomers remained virtually insoluble in Et_2O and in hexanes and MeOH.



23

24

Figure 8

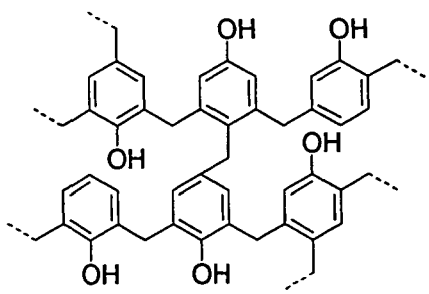
This method of using precipitons has been applied to the synthesis of a range of compounds, including isoxalines[39] and ß-ketoesters[40].

It is worth mentioning that before the use of solid supports was applied to the synthesis of peptides in organic chemistry, they were originally used as ion-exchange resins. In the mid-nineteenth century[41], agricultural chemists discovered the process of ion exchange. They recognized that ammonium salts were removed from manure and replaced by calcium salts, by running the manure through clay-based soil. This process was defined as base-exchange. This process was applied to both ammonium and potassium fertilizers. It was found that the active cations in the fertilizer were retained by clay-based soil, even though the anions were washed through the subsoil. Natural clays usually contain an alumino-silicate skeleton, together with a selection of cations[41]. Some natural clays are still employed in synthetic chemistry, i.e., montmorillonite, which contains an expanding layer lattice, allowing ions to move freely within the structure.

Artificial alumino-silicates were developed early in the twentieth century and used in the water-softening process.

Zeolites, both natural and synthetic, have also been utilized in cation exchange[42]. The structure of zeolites makes them ideal for diffusion of substances to the active sites within the structure. They have a rigid structure, which contains open pores and channels. The use of zeolites is limited as they are sensitive to both acidic and basic conditions.

In 1935[42], the first completely synthetic ion exchange resin was developed. In this process, dihydric phenols were heated with formaldehyde to perform a poly-condensation reaction, where H_2O is eliminated between the CH_2O and the H-atoms *ortho* and *para* to the OH groups. The resulting polymeric resin **25** contained phenolic hydroxyl groups, which gave the resin a weakly acidic nature. The resin demonstrated the exchange of hydroxyl protons for other cations in a solution. However, due to the weakness of the acidity of the phenolic protons, the exchange was limited to highly basic solutions. ***See Figure 9.***



25

Figure 9 An example of an 'ion exchange' resin

The resin was modified to contain a strongly acidic group ($-SO_3H$) in the place of the phenol hydroxyl group by substitution of benzenesulfonic acid for phenol in the preparation. These acid resins overcome the problems of the original resin. Anion exchange resins were then produced in analogous fashion by the condensation of *m*-phenylene-diamine with formaldehyde[42].

The development of polymerization techniques allowed ion exchange resins to be developed further. It was found that cross-linked polystyrene could undergo

quantitative sulfonation with concentrated sulphuric acid. It was from this, and the birth of suspension polymerization that "Dowex 50" was produced. This resin, which was marketed by the Dow Chemical Company in 1945, was the first commercial ion exchange resin to consist of beads, i.e., uniform spherical particles[42]. From this, anion exchange resins soon followed with the arrival of "Amberlite IRA-400". This consisted of cross-linked polystyrene with an attached quaternary ammonium salt[42].

Since this time, a range of both cation and anion exchange resins has been developed and additional ranges have been marketed. Cross linked polyacrylic acid and polymethacrylic acid resins have also been developed. Commercial resins are now produced exclusively in bead form[42], and are available in varying sizes and degrees of cross-linking. An important quality of ion exchange resins is regeneration. When the resin is saturated with removed ions, it may usually be washed with the appropriate acid or base to regenerate the active functional group. An example of this is that a strong cation exchange will require a strong acid to remove the collected cations, and so to regenerate the acid functionality.

1.3 Solid Phase and Soluble Polymers for Combinatorial Synthesis

In the last decade, polymeric supports have revolutionized organic chemistry. They have also become the major driving force for combinatorial chemistry and laboratory automation. As previously mentioned, Merrifield[8] was the first to report peptide synthesis on polystyrene supports. Until the late 1980s, polymer supports were mainly used for special applications, such as peptide and oligonucleotide synthesis. In these cases, the polymer support had to be stable towards coupling and deprotection reactions.

In the last ten years, a large number of supports have been reported. There are three main requirements that are essential for the use of solid supports for organic synthesis: -

- A polymer, which is able to swell in a suitable solvent, but is inert to the reaction conditions. The polymer used is usually insoluble and a cross-linked matrix.
- A substrate linker must be used which attaches the substrate to the solid support. This will also allow cleavage of the final product from the solid support. Also selective cleavage of a different linker could be used for the release of some, or the entire product to allow analysis during a synthesis.
- A suitable method must be used to be able to carry out the reaction on the solid support.

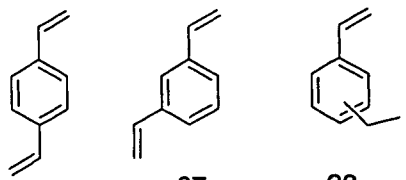
1.3.1 Solid-phase Supports

1.3.1.1 Polystyrene- based Resins

Polystyrene was the first solid support to be used in the preparation of peptides. Functionalized polystyrenes are available as linear non cross-linked and as cross-linked polymers. The latter, also known as PS resins are among the most popular used, in solid-phase organic synthesis. Nowadays, numerous types of polystyrene resins are commercially available.

Suspension polymerization is the process which is used to prepare both macroporous and microporous resin beads. Macroporous resins are highly cross-linked, possessing a permanent porous inner skeleton. Initially macroporous resins were used as ion-exchange resins, which are made up of poly(styrene co-divinyl benzene) co-polymers. Nowadays, they can be used as chromatographic materials and for continuous flow synthesis in columns[43]. They are prepared by suspension polymerization of monomers, examples of which are styrene and vinylpyridine, with a porogen agent[30, 44], generating the pores within the resin beads. The porogen will remain within the beads during the polymerization. The internal porous structure of the resin beads is due to the presence of this agent. Once the process of polymerization is complete, the porogen is removed to leave a hard opaque bead. The nature of these porogens can differ, i.e., they can be non-crosslinked polymers or simply solvents[45]. The cross-linking reagent is another key component of the polymerization process. The most commonly used

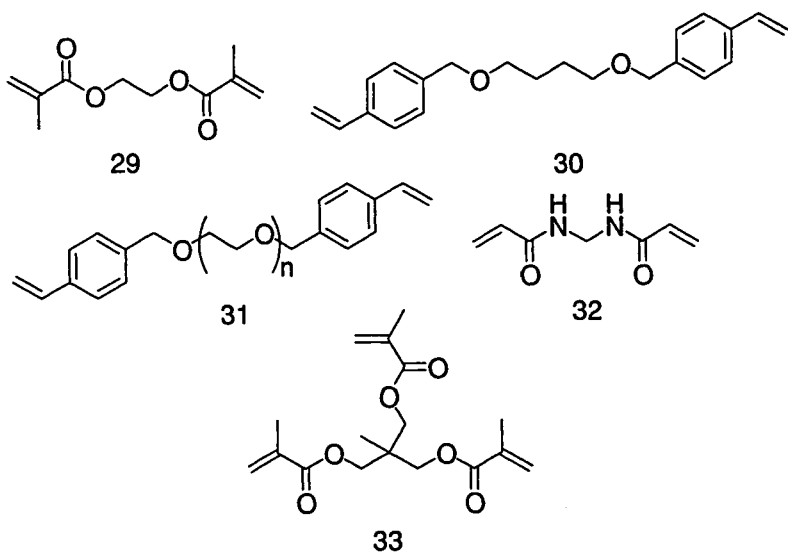
cross-linking agents are divinylbenzenes (DVB), which usually is a mixture of three chemical species: 27% *m*-DVB **27**, 53% *p*-DVB **26** and 20% ethyl vinyl-benzenes **28**. See ***Figure 10.***



26 27 28

Figure 10 Different grades of DVB used as cross- linking reagents

Other cross-linking agents, which are used often in the polymerization process, are ethylene glycol dimethylacrylate **29** and methylene bisacrylamide **32.** ***See Figure 11.*** Recently 1,4-bis(vinylbenzyloxy)butane **30** has been introduced as a cross linking reagent[46].



29 30 31 32 33

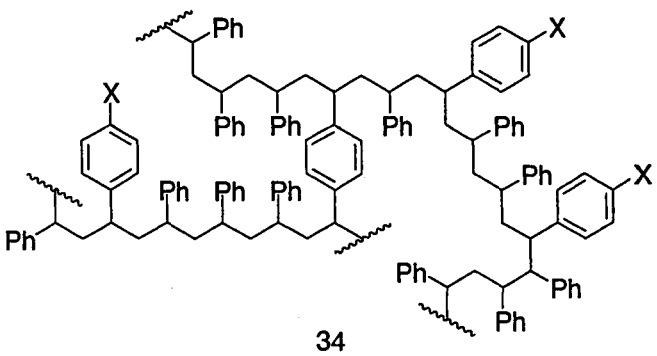
Figure 11 Cross- linking reagents utilized in suspension polymerization

In comparison, microporous resin beads are weakly cross-linked in nature. Again, these are obtained by suspension polymerization of styrene and divinylbenzene. This is carried out in the presence of a porogen reagent, which results in a homogenous network. Stirring conditions and the amount of stabilizing agent[47] helps to control the size of the beads. For microporous resin beads, the nature of the cross-linking agent and the exact amount of crossing linking is vital, as these can have a large effect on how well the beads will swell in solvent. Common

cross-linking is usually 1-2%, however beads with less cross-linking have been studied[48].

Suspension polymerization, which is used to synthesize these types of beads, involves the suspension of an organic phase into an aqueous phase[49, 50]. The organic phase consists of a monomer, a radical initiator, a cross-linking agent and potentially a co-monomer. The organic phase forms an emulsion under stirring. This is carried out in the presence of a polymeric surfactant. The size of the initial droplets is adjusted during this process. A multiple sieving process separates the beads, which differ in size and the size of the beads is usually given as a mesh number (number of sieve holes per inch).

The degree of cross-linking must be sufficient to give the resin beads mechanical strength and stability, but not so much that that swelling of the bead will be prevented when immersed in a solvent. Swelling is an important feature of polystyrene resins, as this gives an indication of the internal flexibility of the polymer backbone, **34**. ***See Figure 12.***



34

X = any suitable functionality

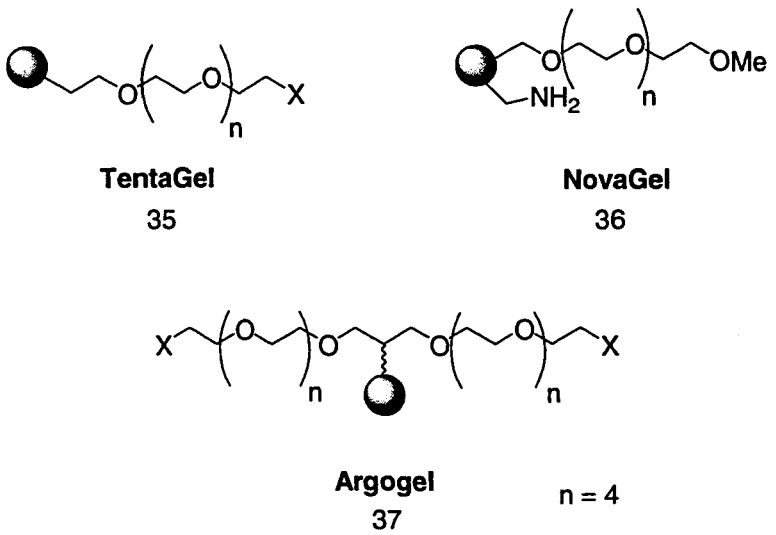
Figure 12 Internal structure of polystyrene

This type of resin can be used for most types of chemistry. Investigations have shown that the beads are not perfectly inert. MacDonald and co-workers[51] have shown that impurities were present in the final compounds, arising from both the resin and compound synthesis. Various reactions were carried out to try and solve this problem. An example of this was to pre-wash the beads numerous times,

followed by drying. This was found to have a positive effect on the quality of the final compounds. However the final products still needed purification.

1.3.1.2 PEGylated resins

Merrifield type resins are still the most widely used in combinatorial chemistry today. As discussed these types of resin do have their limitations, one of the most important being the lack of swelling in polar protic solvents. This limitation led to the design of a resin, which was made of a 1% polystyrene matrix, onto which polyethylene glycol chains were grafted[52, 53]. A notable example of this is TentaGel® resin, **35**. This consists of PEG, which is tethered to cross-linked polystyrene through an ether link. Advantages of this type of support are the combination of properties of PEG, together with the insolubility and handling characteristics of the insoluble beads. ***See Figure 13.***



TentaGel
35

NovaGel
36

Argogel
37

n = 4

Figure 13

TentaGel® and other PEGylated resins are found to be more polar than their Merrifield counterparts. This enables the use of these supports in a broad range of solvents, ranging from trifluoroethanol to hexanes[54]. It is worth noting that the loading density on PEGylated resins such as TentaGel® is far less than standard Merrifield supports, typically ranging from 0.15-0.40 mmol/g. It has also been observed that loss and release of the PEG graft can occur on addition of strong acids, for example, the use of TFA, which as a standard deprotection reagent, can

also cleave the benzylic ether PEG bond. This problem has been solved by the modification of the TentaGel® resin by Porco[55, 56]. A PEG spacer has been tethered to the polystyrene backbone through an ether linkage. This modified resin has been found to be insensitive to acidic and basic conditions.
Other PEGylated resins have been reported. NovaGel®[56] **36** is another example of a PEGylated resin, which unlike TentaGel® contains active sites located on the polystyrene backbone as opposed to the end of the chains. The consequence of this is that swelling properties are excellent and a higher loading density can also be achieved.

ArgoGel®[55, 57] **37** is another similar PEGylated resin. This has been found to have slightly higher loading capacities, typically up to 0.5 mmol/g, due to the fact that every site has two PEG chains on it.

1.3.1.3 Cross-linked acrylamide resins

Polyacrylamide polymers are the next class of solid supports to be discussed. Sheppard and co-workers[58] carried out the original designs for these types of supports. The group wanted a support, which would closely mimic the properties of the peptide chains, which were to be synthesized. This would thus improve solubility properties, allowing the use of more polar protic solvents, i.e., DMF and NMP. An example of this type of resin is the pepsyn-K resin[58]. ***See Figure 14.***

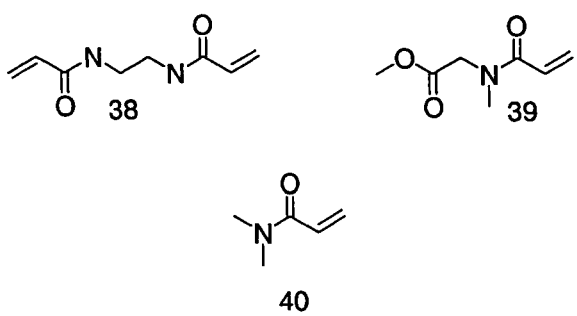


Figure 14

It is comprised of an *N,N*-dimethylacrylamide backbone **40**, which is cross-linked with *N,N'*-bis-acryloylethylenediamine, **38** and functionalization through

acryloylsarcosine methyl ester, **39**. Up until now, this type of resin has only been utilized for peptide synthesis.

The PEGA[59, 60] support, **44** is obtained by an inverse suspension copolymerization technique. The reagents employed are *N,N*-dimethylacrylamide, acryloylsarcosine ethyl ester **41** and bis-2-acrylamidoprop-1-yl-PEG 1900, **42**. Silicon oil is used as a dispersing medium. This support was found to have good swelling properties as well as mechanical stability. Larger molecules such as peptides are able to diffuse through the polymer well[61]. Batch and continuous-flow methods have both been found to be suitable for this type of resin[62]. ***See Figure 15.***

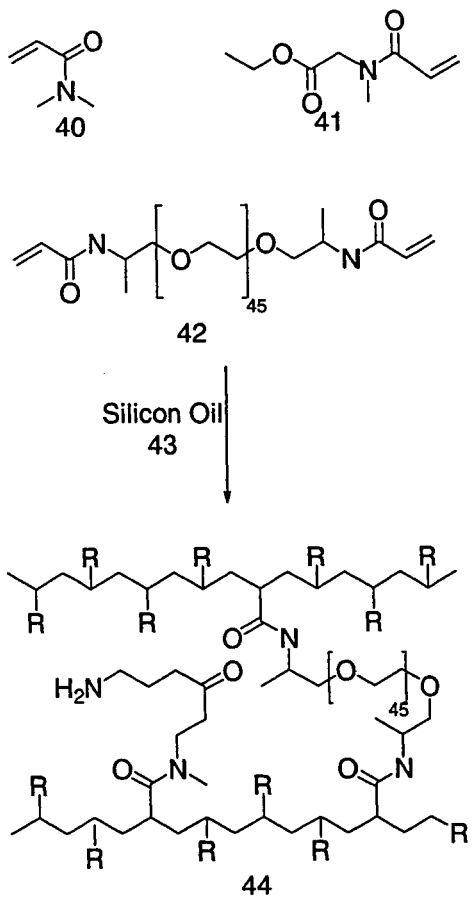


Figure 15

Developments into polyacrylamide resins have led to the synthesis of the poly(*N*-acryloylpyrrolidine) (PAP) resin[63], ***Figure 16***. Compared to other supports in this category, peptide syntheses can be carried out in polar solvents[64]. The synthesis of this support is carried out using suspension polymerization, using *N*-acryloylpyrrolidine, **45**, which is the monomer unit, *N*-acryloyl-1-6-diaminohexane,

46, which is the functionalization reagent and *N,N'*-bis(acryloyl)-1,2-diaminoethane, **47**, which is the cross linker. All these reagents are dispersed in a mixture of hexane and carbon tetrachloride[63]. The resin is found to have excellent swelling properties in solvents such as water, MeOH and DCM. A large number of compounds have been reported using this type of resin[65].

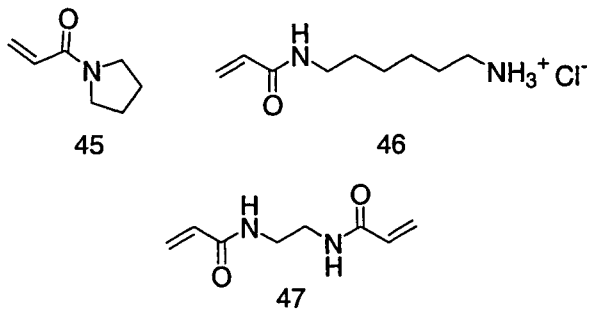


Figure 16

1.3.2 Soluble Polymeric Supports

In comparison to solid supports, soluble non cross-linked polymers give rise to homogenous reaction conditions. The term 'liquid-phase' refers to methodologies that incorporate a soluble macromolecular carrier to facilitate the isolation of a desired product. Advantages of the use of soluble polymer supports were discussed in Section 1.2. As well as employing classical organic chemistry conditions, these polymers allow characterization of reaction mixtures by routine analytical methods. Spectroscopic techniques such as NMR, IR and UV-vis can be used to monitor reactions, without having to cleave the compound off the polymer first[66]. This provides a non-destructive method of analysis, as aliquots can be returned to the reaction mixture.

Polymers employed as soluble supports for liquid phase synthesis must: -[24]

- Be commercially available or rapidly and conveniently prepared.
- Demonstrate good chemical and mechanical stabilities.
- Provide appropriate functional groups for easy attachment of organic moieties.
- Exhibit high solubilizing power in order to dissolve molecular entities with low solubilities and permit the development of a general synthetic

methodology independent of the physicochemical properties of target compounds.

Problems, which occur when using heterogeneous reaction conditions, such as non-linear kinetic behaviour and solvation problems can be overcome by using soluble polymeric supports.

1.3.2.1 Separation Techniques for Soluble Polymeric Supports

Some polymers have been found to be soluble in certain solvents, but would precipitate efficiently out of others. This property of the support would provide a convenient method of separation of the polymer-product conjugate from the reaction mixture on completion of a synthesis, while leaving excess reagents and by-products behind. Some polymers can be recrystallized to minimize inclusion complexes, which can form during the precipitation process. As with any recrystallization process, the correct choice of solvent and temperature must be made for satisfactory recovery of the suppport[67]. This method is the most common mode of separation used with this type of resin. Other methods have been reported which demonstrate product isolation for macromolecules of differing size. **Table 1** below summarizes briefly the available techniques, which are available for the separation of soluble polymeric supports. Methods such as dialysis[68], ultrafiltration[69], size exclusion chromatography[70], filtration through a silica cartridge[71], filtration[72] and liquid- liquid phase separation[72] have all been found suitable for use in automation. ***See Table 1.***

For further discussions on these methods, see references stipulated above. An important point to note is that although the soluble polymeric material is separated from the soluble impurities in precipitation, any impurities, which are attached within the matrix of the polymeric substance, will not be removed. Impurities such as incomplete reaction products, which have formed on the chain or any side-reactions, will still be attached to the polymer. This can be corrected by complete optimization of reaction conditions and also driving the reaction to completion.

Parameter	Dialysis	Ultrafiltration	SEC	Filtration through silica cartridge	Precipitation/ Filtration	Liquid-liquid phase separation
Separation by	Hyd. Vol*.	Hyd. Vol*.	Hyd. Vol*.	Hyd. Vol*. /polarity	Solubility	Phase. Dist. Coeff§.
Minimum Mol weight of polymer	>1000 g mol^{-1}	>1000 g mol^{-1}	-	-	>3000 g mol^{-1}	-
Typical sample vol.	10 ml- 1 L	1- 100 ml	<1 ml	0.1- 10 ml	1- 100 ml	10 ml- 1 L
Commercially available	Y	Y	Y	Y	-	Y
Suitable for automation	Y	Y	Y	Y	N	Y
Suitable for high throughput	N	Y	Y	Y	N	N

* Hydrodynamic volume

§ Phase distribution coefficients

Table 1 Separation techniques for soluble polymeric supports[73]

1.3.2.2 Classification of Soluble Polymers

Soluble polymeric substances can be split into two categories; the first category is terminal functionalized linear polymeric supports. These are polymers, which carry functionalities on their chain ends, i.e., PEG, which is the most commonly used polymer in liquid-phase synthesis. The second category is polyfunctional linear polymeric supports. In this case, the reactive side-group will appear on every monomer unit. An example of this is PVA. ***Figure 17*** shows soluble polymers, which have been used in liquid-phase synthesis.

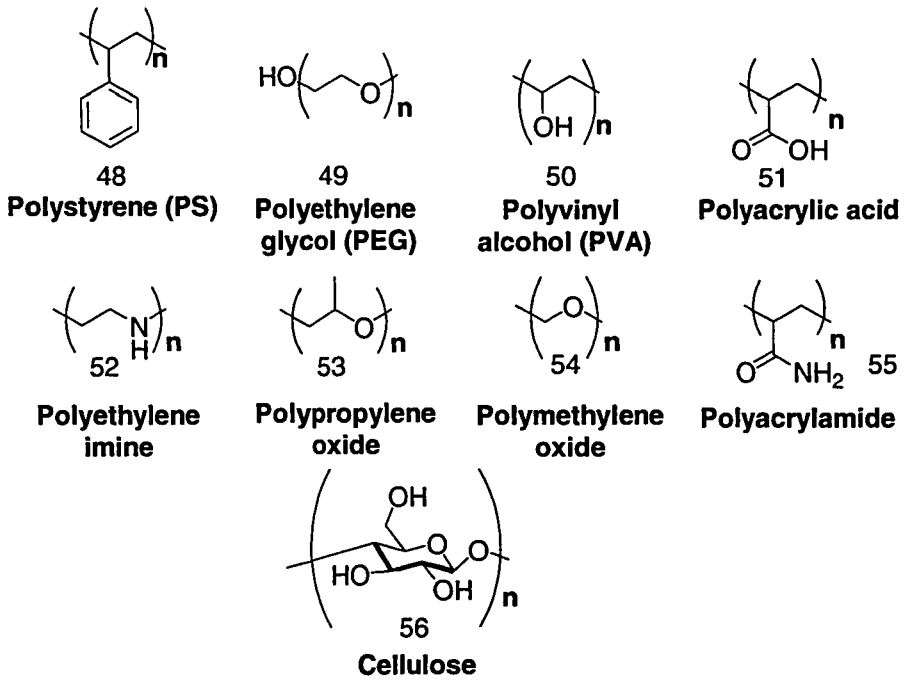


Figure 17

From the polymers listed above, PEG, **49** is by far the most common support used in liquid-phase synthesis[25, 26]. PEG exhibits broad solubility properties; it is found to be soluble in solvents, such DMF, DCM, PhMe, MeCN, water and MeOH. It shows insoluble properties in solvents such as Et_2O, isopropyl alcohol[74] and cold EtOH and MeOH. It has been found that on cooling solutions of PEG in methanol or ethanol will yield a crystalline form of the polymer. This is due to the helical structure of the polymer[75]. Analytical techniques can be used as a non-destructive method of product characterization on the polymer. In NMR spectroscopy, it has been shown that the polymer structure will not interfere with the analysis.

The synthesis of a number of peptides, including sparingly soluble oligomers[76, 77-81] has been demonstrated on PEG resin. ***Figure 18*** shows the coupling of an amino acid as part of the synthesis of a pentapeptide on the PEG polymer.

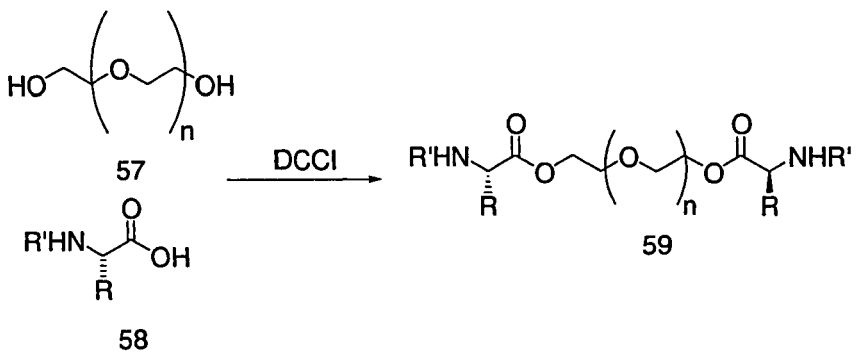


Figure 18

Direct esterification was used to carry out the attachment of amino acids. The linkage was carried out by using the coupling reagent DCCI, in DCM as the solvent. The peptide coupling yields were found to be greater than 99%, as determined by ninhydrin[24] and dansyl methods[24]. Different chain lengths were investigated and polymers of molecular weights between 10 000-20 000 were found to be suitable for longer chain oligomers. It was found that a change of solvent from DCM to DMF permitted the use of shorter polymer chain lengths. Although amino acids could be attached to the soluble polymer by direct esterification to give high coupling yields, cleavage yields were found to be low. This proved to be a major disadvantage with liquid-phase methods. The use of harsh conditions to drive the reaction to completion often caused side reactions and racemization of the peptide. This led to the development of linkers, which could be attached to the soluble polymers, which would allow the removal of the peptide chains in a more complete fashion, thus improving cleavage yields and avoiding the problem of racemization.

Figure 19 shows an example of a PEG polymer, which has attached to it a photolabile linker, **60**. This was used in a comparative study for the synthesis of a model tetrapeptide, using both solid and liquid- phase synthesis conditions[82].

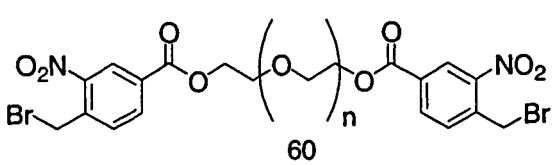


Figure 19

It was found that photolabile cleavage of the tetrapeptide from the PEG resin proceeded in 98%, compared to that of the solid phase cleavage from a cross-linked polystyrene support, which occurred in only 69%. No racemization or side reactions were observed with the PEG resin. More recent to this, Zhu and Hegedus[83] reported transesterification conditions, which allowed the cleavage of peptides, which were directly attached to the polymers supports.

While PEG is the obvious choice in most liquid-phase syntheses, it is not always suitable. This can be demonstrated by the synthesis of the prostaglandin E_2 methyl ester reported by Wentworth and Janda[84] in 1999. In this case, PEG was found to be unsuitable as it is insoluble in THF and is soluble in water, which meant aqueous extractions could not be carried out. A non cross-linked polystyrene polymer was therefore used. It was found to be soluble in THF at low temperatures, but it was insoluble in water and MeOH, thus purification could be carried out by both aqueous extraction and precipitation techniques. The overall synthesis gave the desired compound in 37% yield for the eight-step route. Observations to note are that the polymer recovery mass balance was > 97% and only one polymer bound species was detected by routine NMR analysis.

The synthesis of prostaglandin E_2 is one example of an oligonucleotide synthesis on soluble polymers supports. The synthesis described above, uses THF as the reaction solvent. More commonly, pyridine and water are used[24]. Linear polystyrene was found to be an unsuitable polymer for this type of synthesis, as the supported nucleotides did not precipitate out of pyridine solution with water. This caused poor recovery and yields. An example of this was the synthesis of a trinucleotide on linear polystyrene[85]. The recovery yield after cleavage was found to be only 11%.

Poly(vinyl) alcohol was found to be more compatible for oligonucleotide synthesis. This is due to increased solubility and better compatibility to the reaction conditions. However problems which were encountered were the number of hydroxyl groups. To avoid truncated sequences, any unreacted sites were blocked after attachment of the first nucleotide. It was found though that oligonucleotides, which contained more than five residues, caused neighbouring

chains to interact. Poor precipitation[86] was also seen when using high loading polymers, this being caused by the nucleotide chains. PEG was found to be a suitable polymer for the synthesis of these compounds. After investigating a number of techniques and looking at different linkage systems, the efficiency of this linker was demonstrated by the synthesis of an octanucleotide, which gave an overall yield of 79%[24]. This technique has been improved and has now been scaled to produce kilogram quantities of oligonucleotides. H-Phosphonates were used to allow for the recovery and recycling of the excess reagents in order to make significant cost savings, an important issue in large-scale chemical processes[87].

The synthesis of oligosaccharide molecules has also been attempted on soluble polymer supports. Problems such as poor precipitations and poor yields were seen, especially with polystyrene, PVA and polyacrylamide supports[24]. PEG has shown some signs of success, with the production of short chains, although direct transfer of solution phase conditions was needed[88].

1.4 Linkers for Solid Phase Chemistry

Linkers facilitate the attachment of building blocks or intermediates onto solid support, as well as the ultimate release of the product into solution. They can also dictate whether a compound will stay on the support for assay or whether mild or selective conditions will enable the compound to be cleaved from the support.

> **Linker:** *Bi-functional chemical moiety attaching a compound to a solid support or soluble support, which can be cleaved to release compounds from the support. A careful choice of the linker allows cleavage to be performed under appropriate conditions compatible with the stability of the compound and assay method*[89].

The earliest linkers used were developed for peptide synthesis, but in recent years, these have been modified to enable them to be used in the synthesis of non-peptide molecules. A linker can be described as a specialized protecting group, in that much of the time, a linker will tie up a functional group, only for it

reappear again. The linker is attached to the molecule being synthesized through a bond labile to cleavage conditions, e.g., silyl ethers, esters, carbamates, etc. It is attached to the solid phase polymer through a more stable bond, i.e., amides, alkyl ethers, etc. This gives an idea of the many types of linkers used and many of these will be discussed in the next section.

As mentioned earlier, an analogy can be made between linkers and protecting groups i.e., linkers perform similar functions. Many linkers that have been developed in recent years have been based on those protecting groups that are used frequently in solution phase synthesis. Many linkers have also been developed which are not based on these groups, for example traceless linkers and those which rely on ß-cleavage or cyclization[90]. The cleavage method may involve a range of chemistries to give a range of functional groups. The functional group obtained may be dependent not only on the linker, but also on the method of cleavage. ***See Figure 20.***

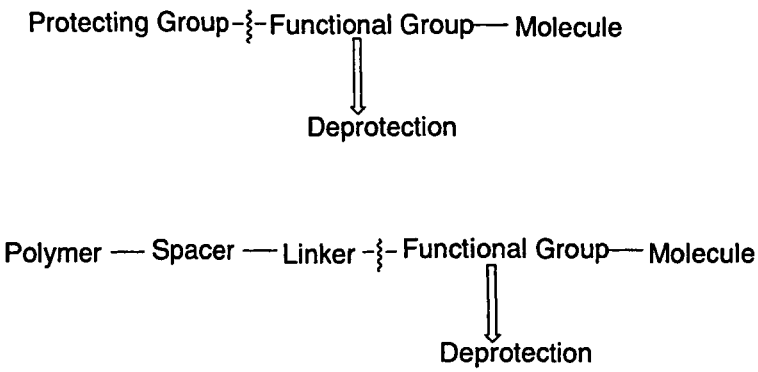


Figure 20

An ideal linker must meet a number of criteria[91]: -

- The linker would have to be cheap and readily available.
- The attachment of the starting material would have to be readily achieved and in good yield.
- The linker would be stable under the reaction conditions used in the reaction.
- Suitable cleavage would be used to ensure no damage would occur to the final product.

- The cleavage methods would not introduce impurities that are difficult to remove.

As the linker is attached to the solid support or the spacer chain, this attachment point should be able to withstand conditions during the synthesis of a molecule or the cleavage of a molecule from the solid support. Over the past 20 years, a number of linkers have been developed to enable organic syntheses to be carried out on solid supports. Linkers can be categorized in many ways- in the following sections they are categorized according to how they are cleaved. Bradley[91] and James[90] have reviewed the cleavage of these linkers.

1.4.1 Acid Labile Linkers

Acid labile linkers come under the class of 'electrophilically cleaved' linkers[91]. The use of strong acid is one of the most common methods of cleavage used in solid phase chemistry. The use of HF or more commonly TFA allows easy removal of the cleavage reagent by evaporation. The relative stability of the protonated linker controls the lability of the acid labile linker. The more stable a cation formed, the more labile the linker is to an acid. This point can be illustrated for ester linkers[90]. ***Figure 21.***

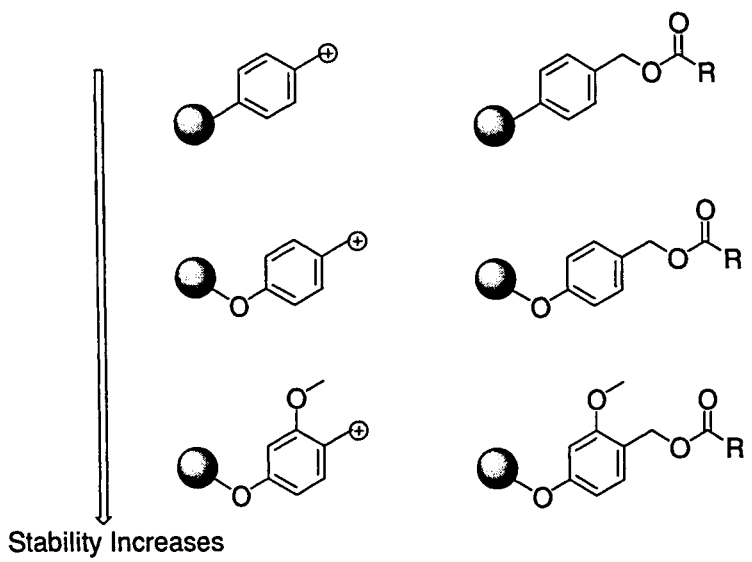


Figure 21

As the number of electron-donating groups on the benzene ring increase, the stability of the benzylic cation increases. This trend is observed when comparing hydroxymethylpolystyrene linker (Merrifield linker), which requires HF for cleavage, the Wang linker, which requires 50% TFA/DCM, and the Sasrin linker, which requires 1-3% TFA/DCM solution for cleavage.

Merrifield resin was the original support used for peptide synthesis[8]. As described earlier in Section 1.3, Merrifield resin is a cross linked polystyrene functionalized with a chloromethyl group. The synthesis of peptides involved anchorage of the free carboxylic acid of Cbz *N*-protected amino acids onto a nitrated chloromethylpolystyrene resin. The resin was nitrated as the nitro group helps destabilize the benzylic cation. Removal of the Cbz group was carried out using HBr in glacial acetic acid. It was found however found that under these conditions, which involved using 10% HBr, the ester bond linking the peptide to the resin was cleaved if no nitration was carried out. Even though nitration hindered this cleavage process, some ester bond cleavage did occur, typically 3.2% in 6h[8].

In 1964, Merrifield reported the solid phase synthesis of Bradykinin[92], ***Figure 22***. Instead of using a Cbz amino protecting group this procedure involved the use of the *t*-BOC protecting group. It was found that mild conditions such as treatment with 1M HCl could be use to remove the protecting group, in order to prepare the molecule for chain elongation. It was found that loss of the peptide from the polystyrene resin occurred to a lesser extent. Nitration of the resin was not required anymore, due to reduction in the strength of the acid employed. In Merrifield's original procedure, release of the finished peptide was carried out using HBr/TFA. The use of the *t*-BOC group instead of the Cbz group resulted in a better yield of the desired peptide, as there was little loss of the unfinished peptide, during the synthetic sequence,

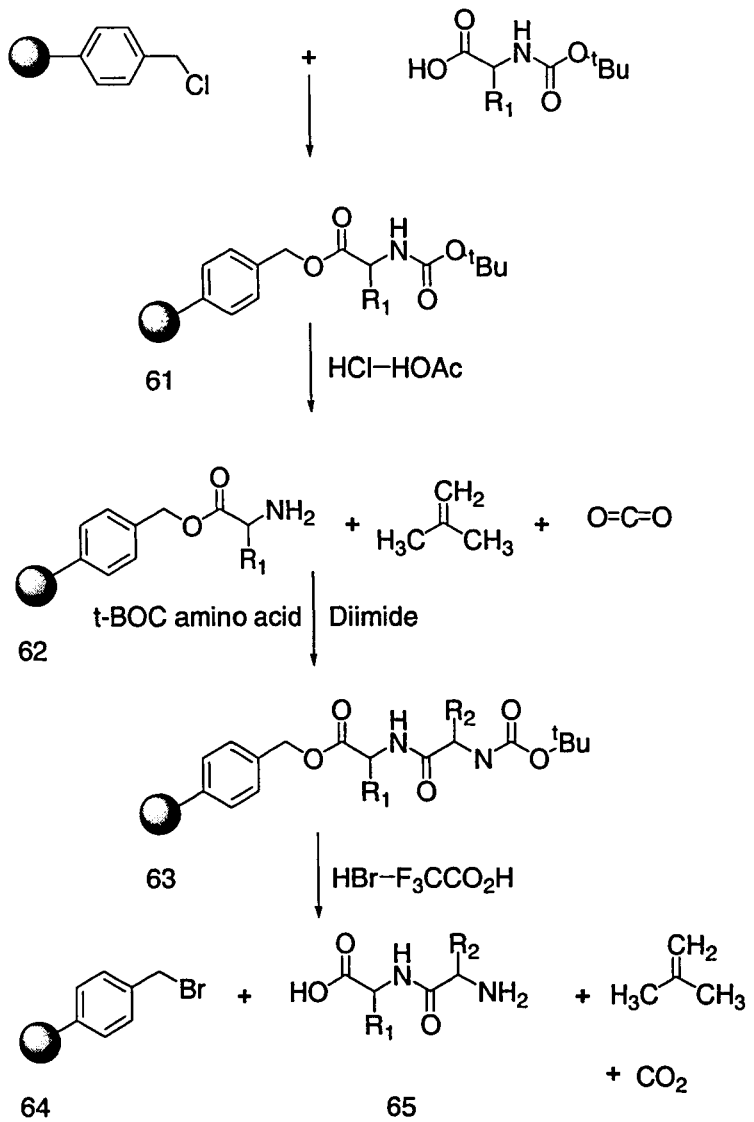


Figure 22

It was also found that the *t*-BOC group allowed HF to be utilized as a cleavage reagent for synchronous peptide cleavage and side-chain deprotection. Lenard and Robinson[93] demonstrated this method for the use in solid phase synthesis in 1967. Prior to this in 1965, the group of Sakakibara[94] showed the use of this reagent in the synthesis and release of oxytocin from fully protected nonapeptides.

Another class of linkers, which belong to the group of strong acid cleavable linkers, is the benzyloxycarbonyl linkers. Some examples are shown in ***Figure 23*** and these include benzyl carbamates.

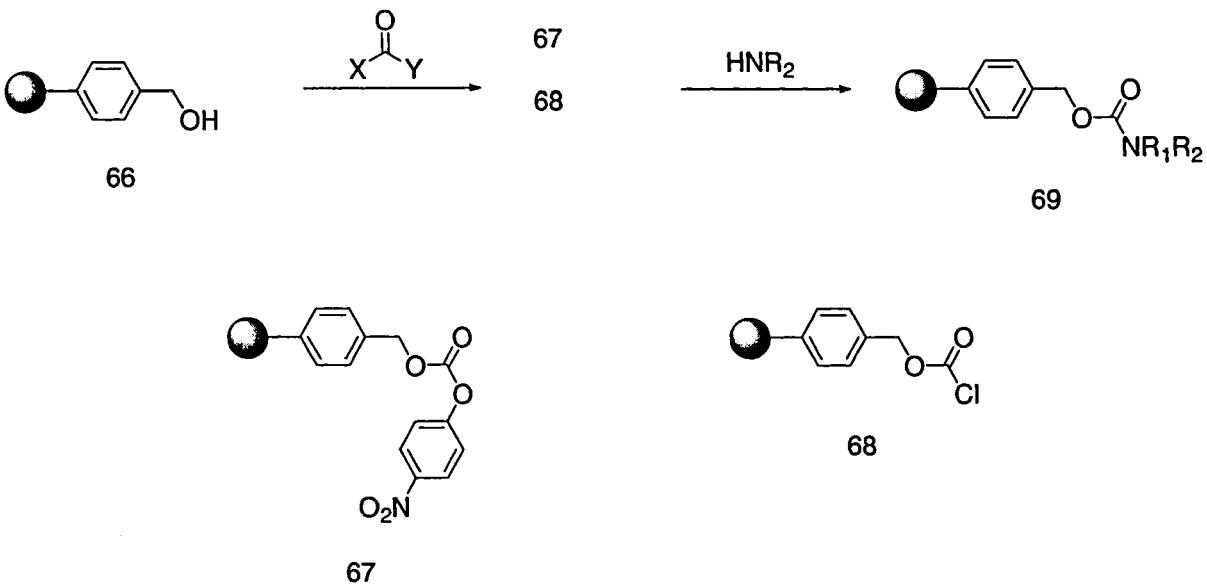
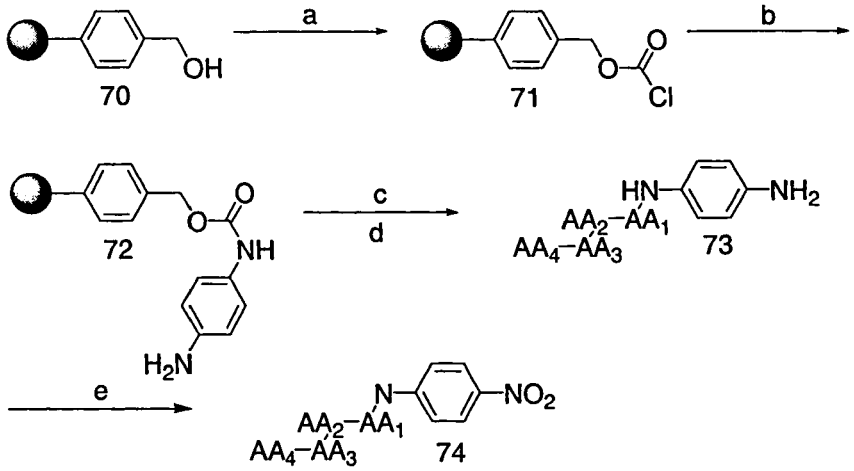


Figure 23

Merrifield resin has generally been found unsuitable for the linking of amines or carboxamides. This is because the resulting derivatives cannot be easily cleaved from the resin. Harsh conditions are generally required for this process and are often detrimental to the resulting compound. To overcome this, carbamate linkers have been developed, thus enabling amine compounds to be released under milder acidic conditions.

Burdick and co-workers[95] reported the use this type of linker in their synthesis of anilides. Standard hydroxymethyl polystyrene resin was converted to the chloroformate derivative **71** with phosgene in PhMe. This intermediate was then reacted with 1,4-phenylenediamine to give the desired resin **72**. Using standard Merrifield conditions, a tetrapeptide was built up on the amino group. Then HF was used to cleave the peptide *p*-aminoanilide from the resin, ***Figure 24***. The product was then oxidized to the corresponding 4-nitro anilide using sodium perborate ($NaBO_3.H_2O$).



a) $COCl_2$, PhMe
b) 1,4-phenylenediamine, dioxane
c) SPPS
d) HF, anisole
e) $NaBO_3.4H_2O$ (16eq.), AcOH, 18h

Figure 24

The linkers, which, have been described up to now, have all had one thing in common; strong acids such as HF have been utilized in the cleavage procedure. Although, these types of acids have been reported to be extremely effective, there are limitations. These chemicals are hazardous and generally are not used in parallel synthesis. It was previously mentioned that stability of a carbocation affects the sensitivity of a linker towards acid cleavage. With this point in mind, linkers with extra functionalities were developed, which enabled mild acid conditions to be used for the cleavage step in a reaction. In 1973, Wang[96] reported the use of a *p*-alkoxybenzyl linker for the synthesis of protected peptide fragments. See ***Figure 25***.

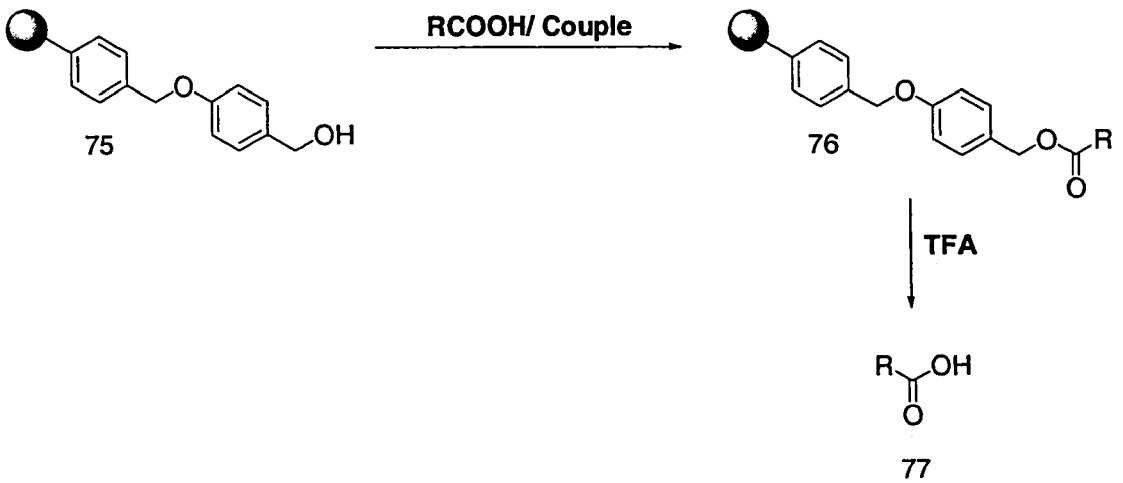


Figure 25

Wang showed that the final peptide could be cleaved using TFA. It was found that the side-chain protecting groups, which were used, namely, Tos, Bn or NO_2 were found to be stable. It was then shown that very acid-labile groups such as Bpoc could be utilized for amine group protection. The Fmoc protecting group is utilized as the protecting group. This protecting group is base-sensitive, using 20% piperidine in DMF. The Wang linker is now the standard solid support, which facilitates the synthesis of peptides. The attached ester can be cleaved using 50% TFA in DCM.

This type of linker has been used to display the synthesis of a variety of molecules. Wang linkers have been reviewed by Bradley[91] and co-workers.

In 1988, Mergler[97, 98] reported a new type of linker known by the acronym, SASRIN (super acid sensitive resin), **78**. This linker was used in the synthesis of fully protected peptides by the Fmoc/*t*-butyl method. Cleavage of these peptides required only very mild conditions, using only 0.5-1.0% TFA/DCM. ***See Figure 26.***

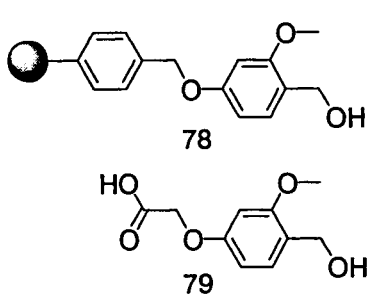
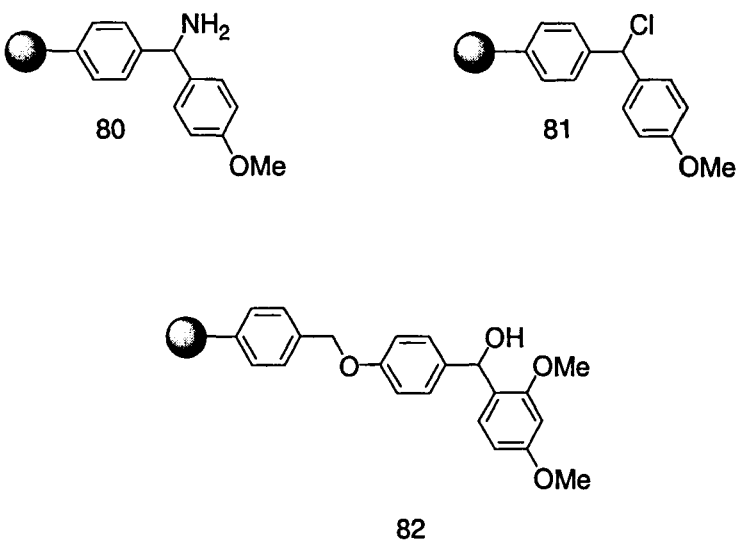


Figure 26

From the structure of this linker, it can be seen that it is very similar to that of the Wang linker. The addition of the electron donating methoxy group helps the linker to be more acid labile. This is due to the enhanced cation stabilization during the cleavage process. Prior to this, Sheppard and Williams[99] reported the unloaded linker, **79**. This was coupled to their polydimethylacrylamide resin. Mergler's method proved to yield a slightly higher loading and easier to handle resin. The main feature of this resin was the mild conditions, which could be used to cleave the peptides at the end of the synthesis in excellent yields.

In 1987, Rink[100] reported the synthesis of a linker, **82**, which went on to become one of the most widely used linkers in organic chemistry. It was based on the addition of electron donating alkoxy groups onto a benzhydryl system. It was found that on cleavage with TFA, the red solid phase cation formed was greatly stabilized. Walter[101] originally reported this type of system in 1976 utilizing a *p*-methoxybenzhydrylamine linker, **80**. Two acids were used to demonstrate cleavage of *C*-terminal phenylalanine; HF and BHA. It was found that yields were greater with HF, than with BHA. To coincide with this Brown[102] reported the use of the linker **81** for the synthesis of secondary amines. ***See Figure 27.***

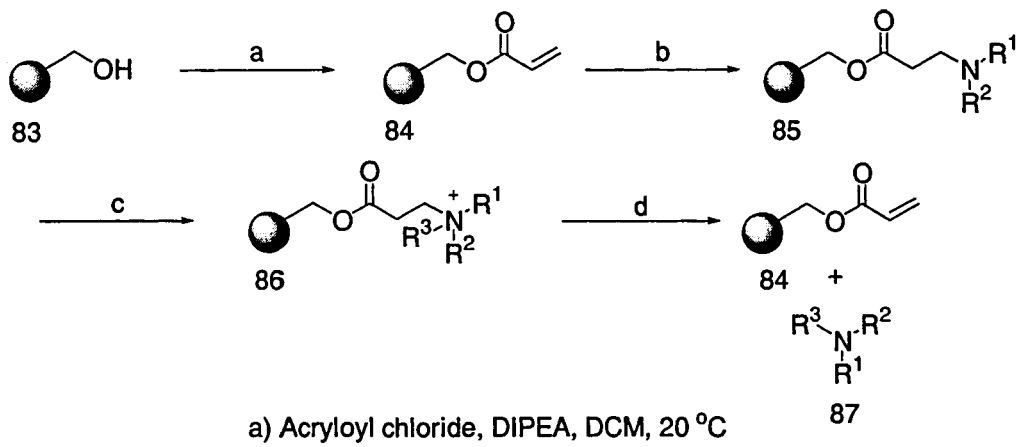


80 81 82

Figure 27

1.4.2 Base- labile linkers

There are many examples of linkers which use base as a cleavage reagent. With base- labile linkers, there are two types of cleavage which can be involved; firstly a nucleophilic addition/ elimination cleavage. An example of this can be shown using an ester linker, which is attached to hydroxymethylpolystyrene resin. On treatment with NaOH, the carboxylic acid salt will be cleaved from the resin. The use of NaOMe will yield the methyl carboxylic ester. The second type of cleavage is the use of a base to carry out an elimination or cyclization. An interesting example of this is the use of REM resin linker[103]. This linker was developed on the use of classical Michael and Hoffman reactions, ***Figure 28***.



R^1, R^3 = alkyl, R^2 = H or alkyl. X = Br, I. Where X is a secondary amine (R^3 = H) conversion to a tertiary amine is acheived by reductive alkylation on the resin using a suitable aldehyde and $NaBH(OAc)_3$ in 1 % acetic acid/ DMF for 18 h at 20 °C.

Figure 28

The strategy involved the use a hydroxymethylpolystyrene resin, which was initially derivatized with acryloyl chloride. The next step was to carry out a Michael addition using a secondary amine, which yielded a resin-bound tertiary amine. The tertiary amine was then quaternized using an alkyl halide. This was carried out to introduce another site of diversity and also activation for the facile Hoffmann elimination. This was carried out by using the base DIPEA to liberate the tertiary amine. The resin linker **84** was regenerated at the end of the synthesis. This is where part of the name originates from; as the linker is regenerated at the end of

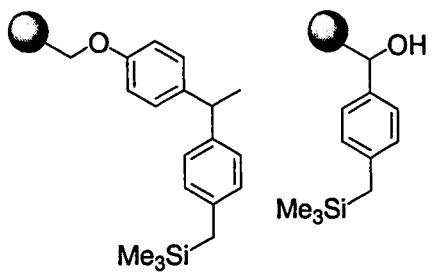
the synthesis. Functionalization is carried out via a Michael addition, thus the resin is referred to as the REM linker resin. This linker was used to demonstrate the synthesis of a number of tertiary amines. The use of the Michael addition strategy has also been used to demonstrate the synthesis of tetrahydroisoquinoline compounds

Ester linkers on resin are a common way of cleaving alcohols from a solid support. A common method to achieve this, which has been utilized by several groups, is the use of a succinate linker[104]. An example of this is the synthesis of C- terminal peptide alcohols. A succinate molecule was attached to a solid support via an amide bond. The alcohol was released on hydrolysis, with the use of ammonia in methanol or hydrazine in DMF. This type of linker has been successfully used in the synthesis of oligosaccharides.

Benzyl esters are found to be easily cleaved using 0.1M NaOH solution. Leznoff[105] reported the use of K_2CO_3 and tetrabutylammonium hydroxide in THF. He stated that his preference was more towards using K_2CO_3 as fewer by-products were obtained. Snieckus[106] and co-workers reported the use of LiOH as a cleavage reagent to provide compounds for biological screening. The use of NaOMe in MeOH/ THF was found to be an unreliable method. It was found that water was being retained within the polymer structure, causing hydroxide hydrolysis. Methyl benzoates were cleaved, which were contaminated with the corresponding acid products. Yields of 71-95% were obtained after studying various reagents. The use of TentaGel-S-OH resin has also been employed in a four-step synthesis to obtain benzofuran compounds[107]. In this case, a mixture of 1M NaOH in *i*PrOH was used to carry out the ester cleavage.

Waldmann[108] reported the development of an enzyme-labile linker in 1998. The 4-acyloxy-3-carboxybenzyloxy group was employed as a linker group, which was attached to TentaGel resin. This was found to be a suitable polymeric support due to the fact it has a polar surface and it is well solvated in aqueous medium, thus this would facilitate enzymatic cleavage of the linker. Cleavage was carried out using a lipase enzyme to release a number of different compounds.

Silyl linkers have also found be base-labile as well as acid-labile. Ramage[109] reported the synthesis of silyl linkers, which could be cleaved under basic or neutral fluoridolysis conditions to release a range of functional groups (carboxylates, alcohols and amines.) These linkers were found to be synthesized with great ease and did not require any tedious chemistry. The use of TBAF was found to give good yields of 4-bromobenzoic acid, typically around 76-78%. ***See Figure 29.***



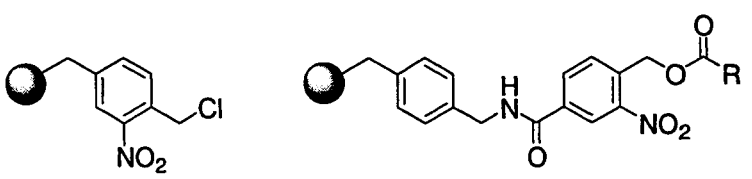
88 89

Figure 29

1.4.3 Photolabile-linkers

The development of photo-labile linkers was found to be a highly desirable concept. This type of chemistry usually takes place under neutral conditions, and offers new possibilities for orthogonal use of linkers in carbohydrate, nucleotide and peptide chemistry.

Rich and Gurwara[110] demonstrated the concept of the photo-labile linker, which was based on the *o*-nitrobenzyl protecting group, ***Figure 30.*** This linker was used in the synthesis of protected peptides and was prepared by the nitration of Merrifield resin.



90 91

Figure 30

This was carried out to increase the polarity of the resin. However it was found that excess nitration was occurring on the phenyl rings of the resin, meaning that only moderate yields were being obtained each time. This was due to poor swelling properties of the resin, particularly in low polarity solvents. This was demonstrated with the synthesis of the protected tripeptide, Boc-Ser (Bzl)-Tyr (Bzl)-Gly. Coupling of 3-nitro-4-bromomethylbenzoic acid onto an aminomethyl polystyrene resin, which was then followed by esterification gave linker **91**[111]. The use of this linker was demonstrated by the synthesis of Boc protected peptides. It was found that peptides could be released with irradiation in the region of 350 nm. These conditions were found to be not applicable to acid-labile protecting groups and amino acids would not decompose under these conditions.

It was found with these linkers that, upon photolysis cleavage, the nitro group was converted to a nitroso group by a 1,5-hydrogen abstraction, followed by insertion of an oxygen atom into a benzylic C-H bond. This led to the formation of a nitrosobenzaldehyde via the elimination of a carboxylic acid moiety. The o-nitrosobenzaldehyde was also found to be photoactive, and through cross-linking, formed a dicarboxylic acid compound. This compound acted as an internal light filter and caused reduction in yields of desired products on cleavage. Compound diffusion was a problem due to cross-linking within the resin and absorption by the diazo product was prevented. ***See Figure 31.***

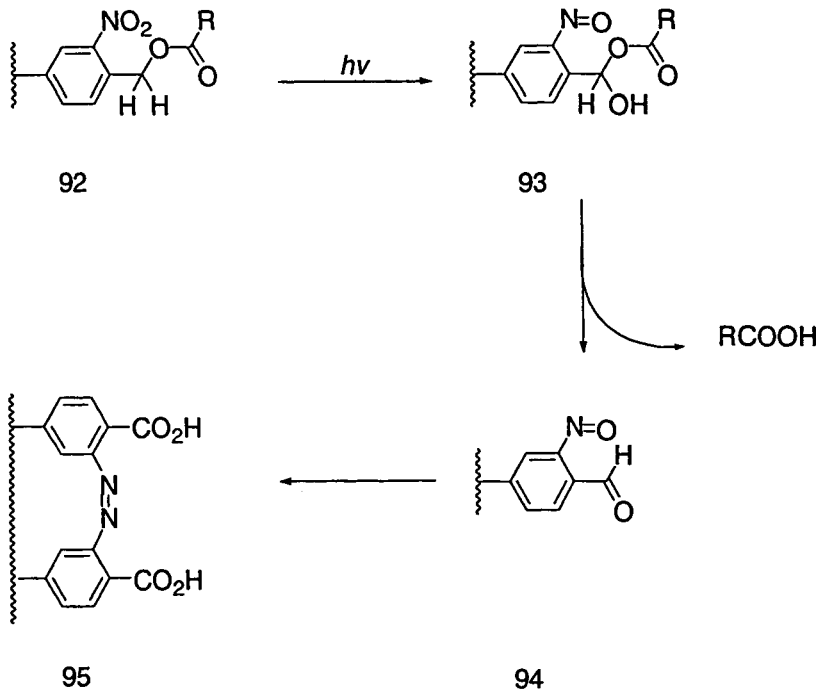


Figure 31

To overcome this problem, extra methyl groups were attached to the *o*-nitrobenzyl moiety, which gave an α-substituted *o*-nitrobenzyl linker. Pillai[112] first introduced this in 1988, whereby the functionalization of polystyrene was carried out using acetyl chloride and aluminium chloride. The resulting ketone was reduced and the alcohol was then brominated. As previously, with Rich and Gurawa's original *o*-nitrobenzyl linker[110], the nitro groups were introduced via nitration of the resin. Problems were encountered with over-nitration as before, as swelling of the resin proved to be difficult. This system was demonstrated with the synthesis of pentapeptides, which were obtained in yields of 40-50%. Other α-substituted o-nitrobenzyl linkers include the nitrobenzhydrylamine NBHA linker, which can be used for the synthesis of protected amides[113]. ***Figure 32*** shows two routes, which were explored to obtain NBHA resin. The first part of the reaction was to functionalize the polystyrene resin. This was carried out by using 2-nitrobenzoyl chloride and aluminium chloride via a Friedel-Crafts mechanism. The next step was to obtain the NBHA group. The first route involved a reduction reaction of the keto adduct **98**. This was carried out using $NaBH_4$, which yielded the corresponding hydroxy moiety, **99**. This resin was then converted to the desired resin, **101** by reacting resin **99** with HBr, followed by ammonia to give resin **101**. The second route was carried out by Leukart reductive amination of the hydroxyl

moiety, using ammonium formate and formic acid. The next step was to carry out the deformylation reaction to give the desired amine resin. This was accomplished, by treating **100** with a mixture of HCl and EtOH, which was followed by neutralization to give resin **101**.

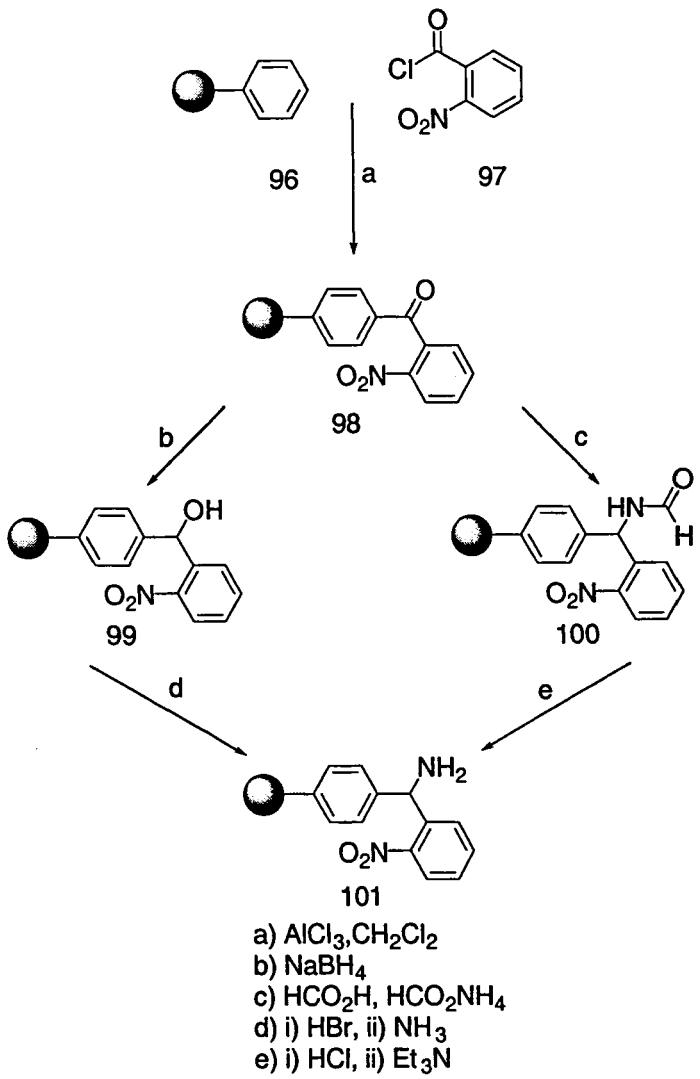
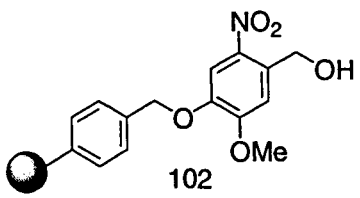


Figure 32

Many linkers based on this *o*-nitrobenzyl moiety have been reported and have been reviewed by Bradley[91].

Another group of linkers, which utilize light for the cleavage process, is based on the nitroveratryl group. It was shown that the introduction of methoxy groups para to the nitro group improves cleavage yields. It was typically shown that compounds could be released within 3 h in yields of greater that 90%. Zehavi[114] first described the synthesis of this type of light sensitive polymer. The synthesis

utilized chloromethylated styrene-divinylbenzene copolymer, to which was attached 6- nitrovanillin, through an ether linkage. After reduction of the aldehyde functions on the polymer, the alcohol polymer, which was produced, was used for the synthesis of oligosaccharides. Irradiation of the polymer at 320 nm was carried out and oligosaccharides were obtained between 10-30% yields. See ***Figure 33.***



102

Figure 33

Sheehan and co-workers[115] originally described the use of phenacyl photolabile protecting groups for the carboxyl moiety. It was found that EtOH and dioxane were the most suitable solvents to carry out cleavage reactions, as they are both good hydrogen donors. Yields between 75-100% were obtained for carboxylic acids in solution phase. Wang[116] then went on to demonstrate the use of a α-methylphenacyl ester linker, which was adapted for use on solid supports. He showed that cleavage of the peptide at 350 nm, provided protected peptides in good yields. An example of this was the tetrapeptide Z-Lys(Z)-Phe-Phe-Gly-OH which when cleaved by photolysis from the resin was obtained in yields of about 70%. This compound was shown to be identical to a compound which was used as a reference[96], but which was synthesized using an alternative route, **Figure 34.**

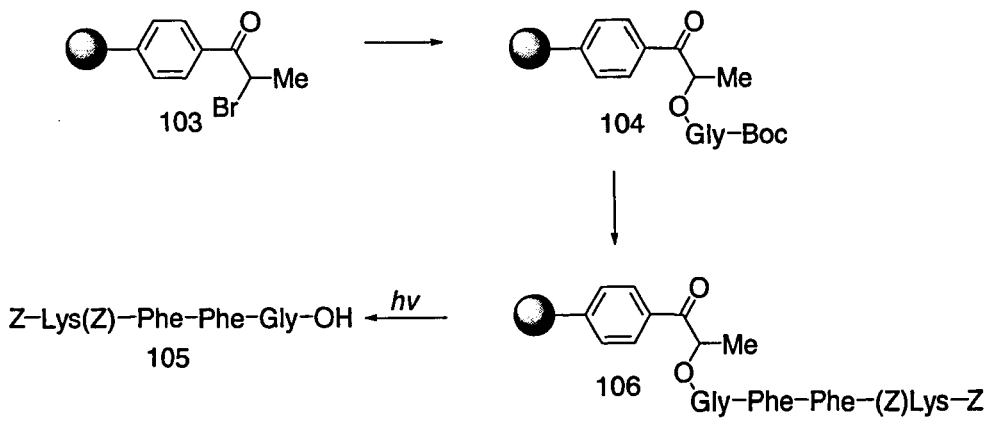
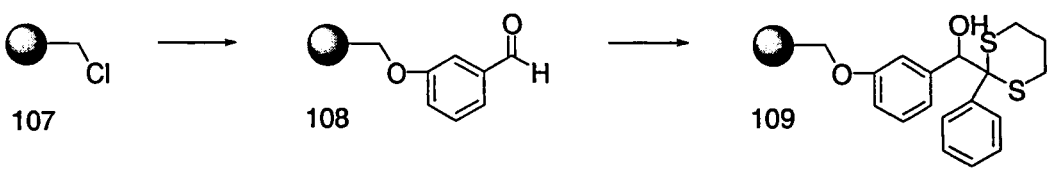


Figure 34

Chan and co-workers[117] reported the use of a photo-labile linker, which was based on the 3-methoxybenzoin protecting group described by Sheehan *et al.*[115]. It has been shown that benzoin esters are suitable photo-labile protecting groups for carboxylates and esters[118]. They used this type of linker to study methods of caging by encapsulation and also for protein studies[119].

Balasubramanian *et al.*[120] described the use of a photo-labile safety catch linker, which was also based on a benzoin-protecting group. They reported the use of dithiane protected 3-alkoxybenzoin linker, the synthesis of which is demonstrated below. The photolabile resin was synthesized as follows; 3- hydroxybenzaldehyde was attached to the chloromethylpolystyrene resin via an alkylation reaction. This resin was then reacted with the anion of 2-phenyl-1,3-dithiane to form resin **109**, ***Figure 35.***



107 108 109

Figure 35

The dithiane group was found to serve as a safety catch against premature photolysis. They studied the cleavage of Fmocß-alanine, looking at the different deprotection strategies and photolysis of the linker. Several reagents were used to carry out the deprotection of the dithiane group. It was found that photolysis at 350 nm of the mercury perchlorate salt deprotected the resin to give the peptide and gave respectable yields, typically 75%. The bis[(trifluoroacetoxy)iodo] and periodic acid resins gave yields of 65% after photolysis. ***See Figure 36.***

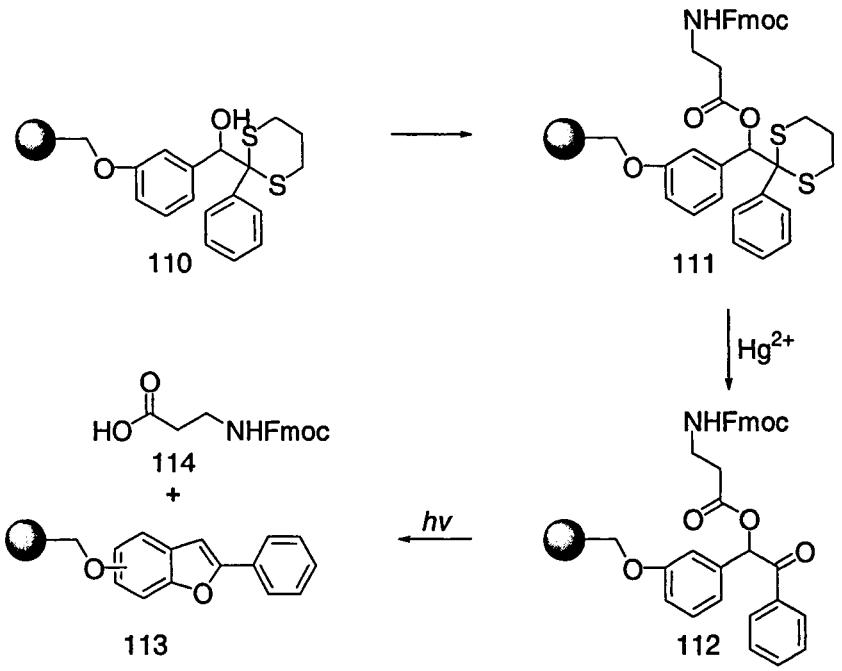


Figure 36

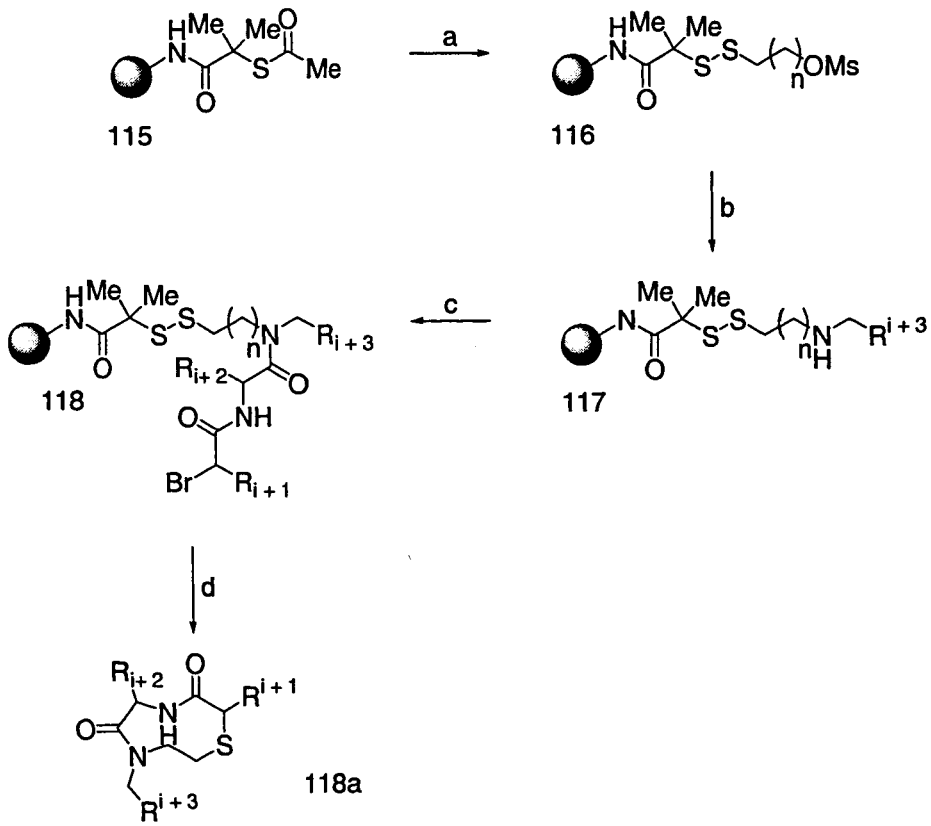
1.4.4 Oxidative/Reductive Linkers

1.4.4.1 Reductive Methods

The use of reductive methods to cleave linkers is a less common practice in solid phase chemistry. There are four reductive methods, which have been reported. Catalytic hydrogenation involves the use of hydrogen to cleave products from solid supports. The first reported method using these conditions was in 1977, where palladium(II) acetate was used to remove a pentapeptide from Merrifield resin by the reduction of a benzylic ester[121]. The peptide was obtained in 71% yield using 4 atm. of H_2 for 24 h at 40 °C with DMF as the solvent. Cyclohexene was also found to be a useful source of hydrogen for the synthesis of protected peptides. Palladium black was used in this reaction, which was generated from palladium acetate *'in situ'*[122]. Bradykinin was synthesized using these conditions in 20% yield.

The second type of reductive method used on solid phase is the reduction of disulfide bonds. Ellman and co-workers[123, 124] demonstrated an interesting example of this type of cleavage. They demonstrated the synthesis of ß-turn mimetics on polystyrene resin. ***See Figure 37.***

Linker **115** was *generated* from *S*-acetyl 2-mercapto-2-methyl propionic acid. This was then used to attach the second generation mimetic to the solid support through a hydroxyl thiol backbone component. The gem-dimethyl substituents, which are adjacent to the sulfur atom, were found to necessary as they improved the stability of the eventual disulfide bond. Treatment of the linker with 4.0 M TCEP liberated the acyclic turn mimetic, which was then treated with solid supported guanidine. This was found to act as both a solid extraction resin and a support bound catalyst. From these reactions, ß-turn mimetics were synthesized in yields between 34-61% with purities > 84%.

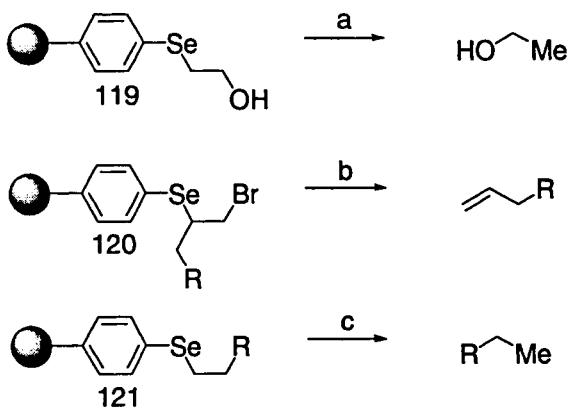


a) 1. NaOMe, 3:1 THF/ MeOH; 2. BtSS-$(CH_2)_n$-OMs
b) H_2N-R^{i+3}
c) i) Fmoc-amino acid, HATU, *i*-Pr_2EtN; ii) piperidine;
iii) halo acid, DICI, HOAt
d) i) TCEP; ii) polymer-supported guanidine

Figure 37

Linkers have also been developed which involve reductive desulfurization and deselenization techniques, to yield C-H bonds on release. Ruhland and co-workers[125] reported the first example of a reductive desulfurization/ deselenization

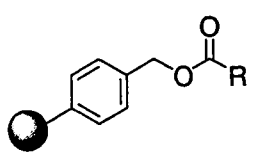
reaction on polystyrene resin. The selenide-based resin was cleaved with tributylstannane and AIBN in toluene for 12 h at 90 °C to reveal alkyl and aryl ethers. Yields of 57-83% were obtained and purities of 78-88% were achieved after purification by SPE. Nicolaou[126] used this type of resin to synthesize aliphatic and ethylenic compounds, using the same reagents, but the reaction was conducted in PhMe for 6 h at 110 °C. ***See Figure 38.***



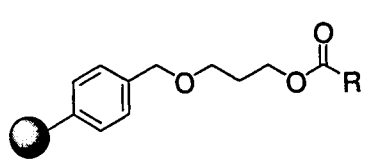
a) AIBN, Bu_3SnH, toluene, 90 °C
b) AIBN, Bu_3SnH, toluene, 110 °C
c) AIBN, Bu_3SnH, toluene, 110 °C

Figure 38

Hydride nucleophiles have also been employed to effect reductive cleavage. In this case, there is no need to use one particular linker. Direct reduction of esters, which are attached to a solid support, can be used to obtain alcohols. The use of lithium borohydride[127, 128] on the thioester linker is shown to give better yields, typically between 55-80%, compared to that when using DIBAL-H[129, 130] on linkers **122** and **123**, which give yields ranging from 20-50%, ***Figure 37.***



122



123

Figure 39

In 1999, Wang and co-workers[131] reported the use of a redox sensitive linker, which was utilized for the synthesis of *C*-terminal modified peptides. Using sodium hydrosulfite ($Na_2S_2O_4$) in water, a quinone was reduced to hydroquinone, utilizing a trimethyl-lock effect. This facilitated lactonization has been previously employed for the development of redox-sensitive prodrugs and amine protecting groups. Peptides were obtained in good yields, typically 70-89%.

1.4.4.2 Oxidative Methods

This section covers cleavage, which is carried out under oxidative conditions. There are two different approaches in this category; linkers which are sensitive to oxidation and linkers which have already been discussed, which can be cleaved under these conditions. Oxidizing agents such as DDQ, CAN and *m*-CPBA have all been utilized as suitable oxidizing reagents.

Porco[132] reported the use of non-acidic cleavage of Wang-derived ethers from solid support. ***See Figure 40.*** DDQ was used as an oxidizing reagent. This was carried out as an alternative strategy to using TFA, as this would reduce the formation of trifluoroacetate ester by-products. After the synthesis of the ether resin **125**, this was treated with DDQ. To facilitate the removal of excess DDQ and DDQH, a mixed-bed ion scavenger was used. This helped to reduce any excess DDQ, which may be in solution, thus leading to the subsequent removal of this from the product. Yields between 70-100% were obtained after cleavage.

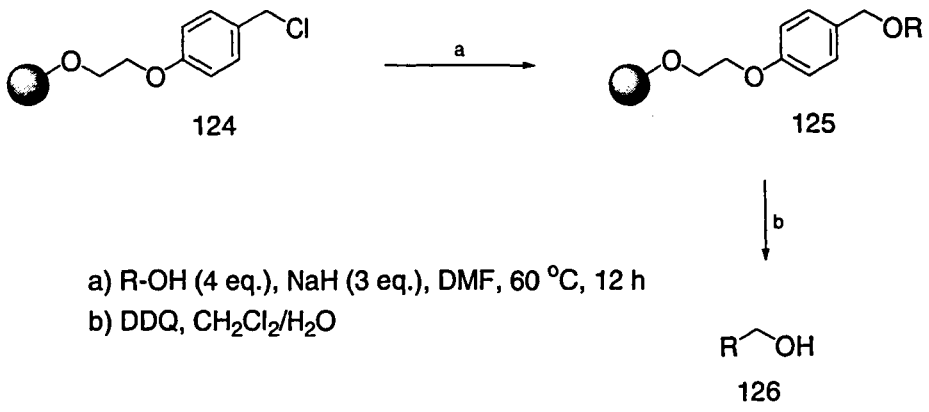


Figure 40

The use of this reagent for cleavage reactions has also been reported by Kobayashi and co-workers[133] for the synthesis of isoxazoles. Amine compounds have also been synthesized using this methodology[134].

Ozone has been found to be a suitable reagent for the cleavage of alkene bonds. This can be a versatile reaction as the double bond can be converted into three different functional groups; alcohol, aldehyde and carboxylic acids. Ozone is found to be devoid of the usual properties of oxidants, which can cause problems in solid phase reactions, i.e., low solubility, poor diffusion within the resin matrix and the formation of by-products. Another advantage with the use of ozone is that excess compound can be removed by simple degassing. This is achieved by passing argon through the reaction mixture.

Fréchet and co-workers[135] first reported ozonolysis of polymeric alkenes in 1971. They used a polystyrene resin, which had an allyl alcohol group, attached to it to build oligosaccharides. Cleavage by ozonolysis led to the release of aldehyde derivatized oligosaccharide compounds.

Mioskowski's[136] work involved stability studies of polystyrene resin towards ozonolysis conditions. Once the stability was established, ozonolysis studies were carried out on a model substrate. See ***Figure 41***.

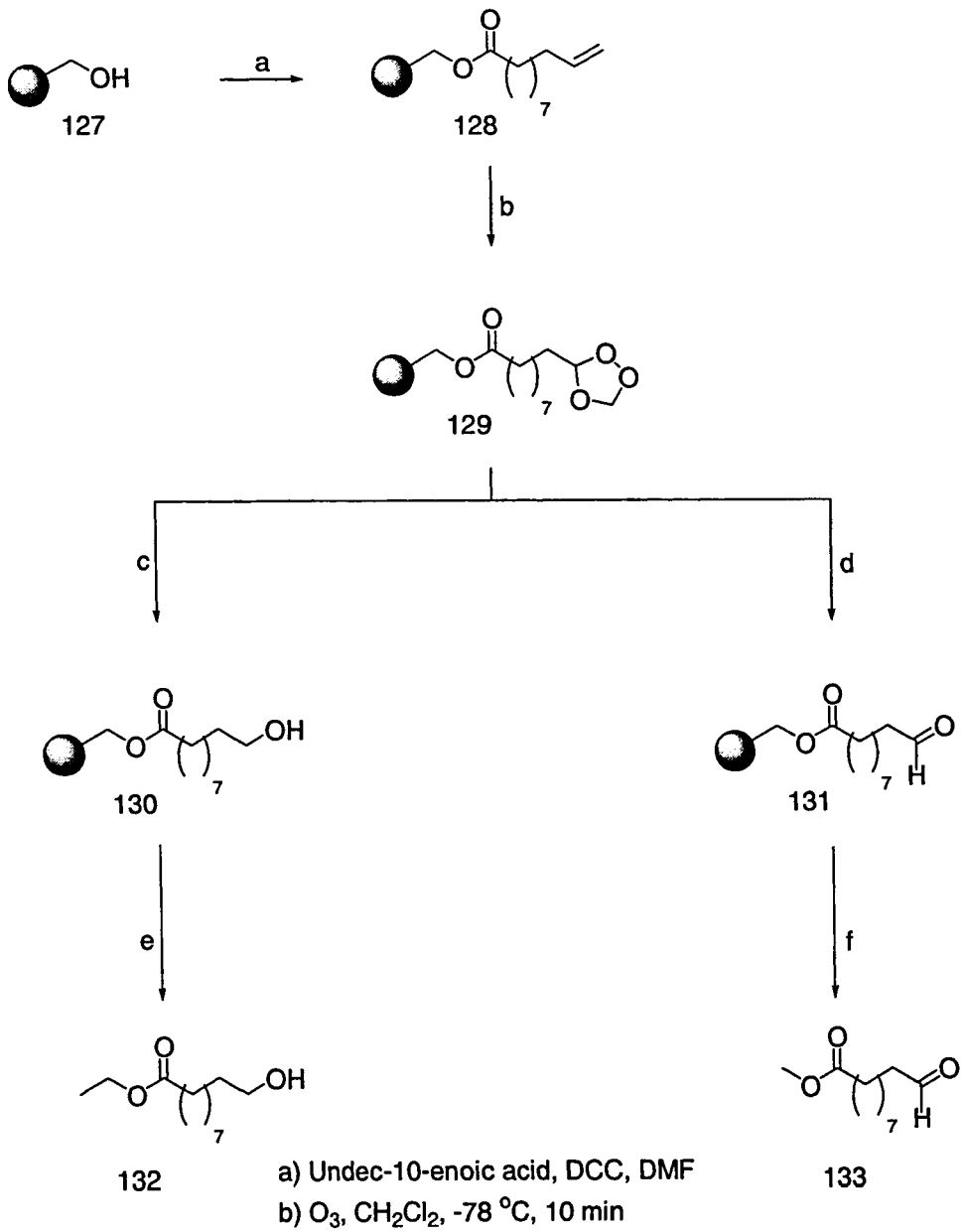
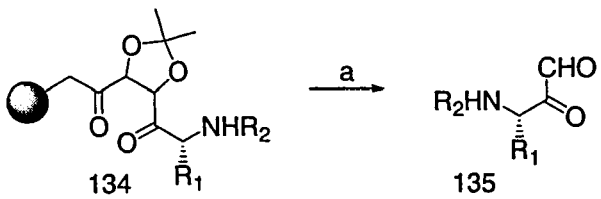


Figure 41

Yields were found to be quantitative and purities > 95% were achieved.

Fruchart[137] has reported the synthesis of *C*-terminal peptide α-oxo-aldehydes using a tartaric-based linker. By using a solid phase periodic oxidation strategy, a glyoxylyl moiety was released from the solid support. See ***Figure 42***.



a) i) TFA; ii) $NaIO_4$ (6eq.), H_2O/AcOH (2/1)

Figure 42

TFA was required to deprotect the diol functionality. After RP-HPLC purification, yields between 26-38% were achieved. These peptide α-oxo-aldehydes have been found useful as adducts in chemical ligation.

1.5 Summary

In this chapter, we have discussed combinatorial and solid phase chemistry, looking at all aspects of both these areas. A broad range of linker chemistry has been explored. Some of this chemistry will now be discussed in the next chapter.

2 Results and Discussion

2.1 Synthesis of pyridine linkers using Merrifield Resins

Initial experiments into the synthesis of a pyridine linker were carried out using a PS resin, hydroxymethylpolystyrene (100-200 mesh), 1% DVB resin. The first step was to attempt attachment of a pyridine moiety, on which the desired chemistry could be studied. It was decided to investigate the use of 4-vinylpyridine, which could act as the linker.

Initial attempts involved deprotonation of the hydroxyl group and this was carried using the base LDA. This gave an alkoxide group on the resin. It was then hoped that the addition of 4-vinylpyridine would encourage a Michael-type addition to occur on the vinyl substituent of the pyridine molecule. ***See Figure 43.***

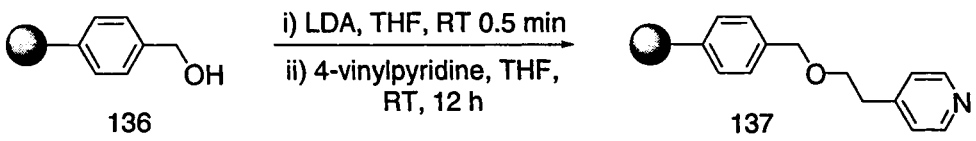


Figure 43

The reaction was carried out in THF as this has been reported to be a good swelling solvent for this type of resin. Two different reactions conditions were studied next. The first set of conditions involved the addition of both the LDA and 4-vinylpyridine to the resin at the same time, still at RT. The next set of conditions studied was the repeat addition of each reagent, performing a thorough wash of the resin between the additions of each reagent.

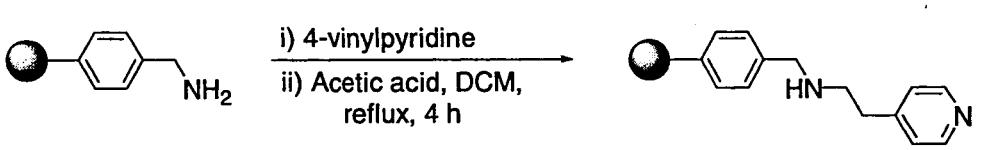
The next stage was to find a suitable method to analyze the treated resin. It was decided to employ colour tests, which would provide a qualitative method of analysis. The initial test reagent used was a molybdenum hexacarbonyl solution in THF. This was used to see if a colour change was observed between the untreated and treated resin. This may occur as the lone pair on the pyridine nitrogen could co-ordinate to the transition metal. In the case of the molybdenum solution, the beads should turn a red colour. A few drops of the solution were added to the resin beads. Initial analysis showed no colour change. It was thus concluded that either that reaction had not been successful or that the colour test

had not been successful. The latter was established by addition of a few drops of the solution to a solution of 4-vinylpyridine, which established no colour change to take place.

The next colour test reagent to be studied was a solution of cobalt(II) chloride in MeOH. A control test between the solution and 4-vinylpyridine gave a blue colour. A few drops of the solution were added to portions of the resin from each of the reaction conditions. The second set of conditions was found to give a positive result, as the resin beads gave a blue colour. Elemental analysis confirmed the presence of nitrogen on the beads. The loading was calculated to be 0.29 mmol/g.

Another example of a PS resin used to attach 4-vinylpyridine was aminomethyl polystyrene resin. Phillips[138] reported the addition of a number of primary and secondary amines to 4-vinylpyridine in solution. It was reported that addition of glacial acetic acid greatly affected the rate of addition, as well as the choice of solvent and the steric nature of the added amine. In this work, the latter would not be relevant as we were dealing with a primary amine adduct.

Our initial attempts involved the addition of 4-vinylpyridine to the resin in the presence of acid. See ***Figure 44.***



138 139

Figure 44

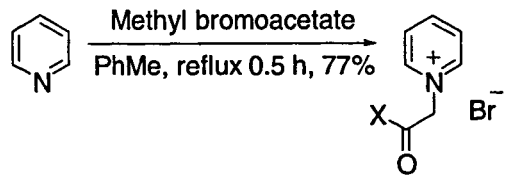
Cobalt(II) chloride showed a colour change to the treated beads, which turned blue. The reaction was deemed successful.

2.2 Solution phase reactions

The next step was to study different types of reactions on the beads. The first reactions investigated, were alkylations of the pyridine resin. The aim being to use

the pyridinium salts in cyclization reactions to construct heterocyclic rings on the pyridine nitrogen atom. These were initially studied in solution phase to optimize reaction conditions, which could then be transferred to resins **137** and **139**. These will now be discussed.

In the initial stages, pyridine was used to mimic the pyridine linker. Initial experiments, which were carried out were the literature alkylations of pyridine with methyl[139] and ethyl bromoacetate[140]. ***See Figure 45.***



140 141

141a = OMe
141b = OEt

Figure 45

A white solid was isolated in 77% yield for both reactions. ^{1}H NMR spectroscopic studies confirmed the structure of both compounds. Compounds **141a** and **141b** were both utilized in further reactions, which involve the formation of the quinolinone ring structures. ***Figure 46*** shows the reaction scheme and the proposed mechanism.

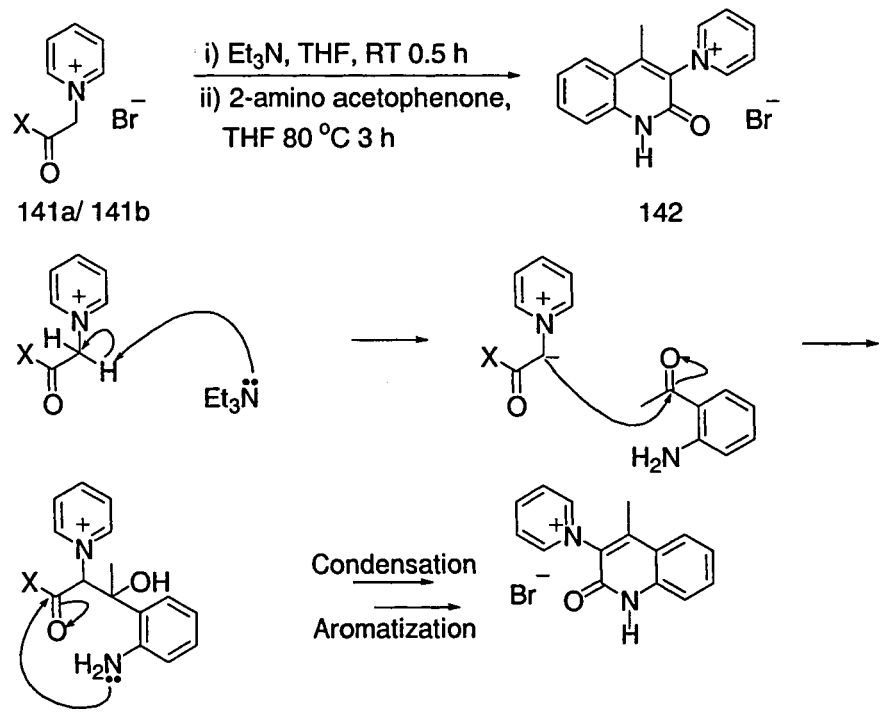
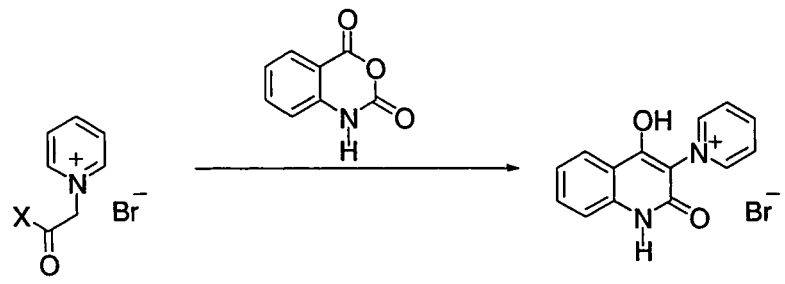


Figure 46

Et_3N was used to deprotonate the acidic proton adjacent to the pyridinium nitrogen to form the anion. It was hoped the addition of 2-aminoacetophenone would encourage a cyclization reaction to occur as indicated in ***Figure 46***. A solid was isolated in 77% yield. Analysis confirmed the solid isolated was starting material and there was no evidence that any cyclized product had been formed. The reaction was repeated, using pyridine as a base, but again no successful results were obtained. Again, starting material was isolated in 80% yield.

The next reaction employed the use of a different cyclization reagent. Isatoic anhydride[141] was employed as it was expected that the 4-carbonyl group of the isatoic anhydride would be more electrophilic than the ketonic carbonyl of the 2-amino acetophenone, thus readily allowing condensation to occur to form the quinoline derivative **143**. Loss of CO_2 would liberate a free amino group capable of cyclizing onto the ester substituent to close the six-membered pyridine ring of the quinoline. This was studied using compound **141a**. ***See Figure 47.***



141a 143

Figure 47

Table 2 shows the different reaction conditions studied. In reaction **47e**, the two starting materials were heated to a high temperature, without the presence of solvent or base to try and 'fuse' the starting materials together.

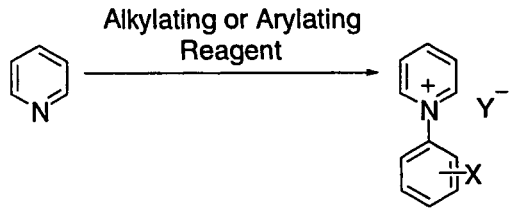
Reaction	Base used	Solvent	Temp/ °C	Time/ h	Result
47a	-	DCM	Reflux	4	50% isatoic anhydride recovered
47b	-	DMF	120	15	40% isatoic anhydride recovered
47c	-	DMF	120	30	60% isatoic anhydride recovered
47d	Et_3N	MeCN	Reflux	1	99% **143**
47e	-	-	230	0.5	Mixture of products

Table 2

Reactions **47a-c** saw the recovery of isatoic anhydride. This was confirmed by melting point analysis and ^1H NMR analysis. The melting points from each reaction were found to be around 230 °C. This is similar to the starting material. Reaction **47d** gave the best results, forming compound **143** in near quantitative yield. ^1H NMR analysis confirmed the structure of the compound. Reaction **47e** gave a brown gummy material. From ^1H NMR spectroscopy, the material could

not be identified. The final step was to see if the amine product could be cleaved from the pyridine ring. This will be discussed in Section 2.3.

In relation to this work, a number of alkylation and arylation reactions using aromatic compounds were studied. It is known that alkylation reactions with pyridine are successful and easily achievable, particularly with benzylic alkylating agents. Aromatic nucleophilic substitution reactions can sometimes require harsh conditions depending on the substitutents that are present on the aromatic ring. ***See Scheme 48.***



140 144

Figure 48

Table 3 shows the alkylating and arylating reagents and the reactions conditions used. It was observed that reactions with arylating agents with no substituents present were not successful. The alkylation reactions using the benzylic compounds were found to be successful and NMR studies confirmed this. An arylation reaction was attempted employing the use of a palladium catalyst. It was hoped that insertion of the palladium metal between the carbon-iodine bond would help the substitution of the pyridine molecule. This was found to be unsuccessful. We found that starting material was observed in the NMR spectrum. Reaction **48e** gave a low yield, 11%. It was hoped that this could be improved as the presence of the electron-withdrawing nitro groups would encourage this, as the *di*-nitro compound would be more electrophilic. This yield could not be improved. The reactions carried out using the chloropyridine compounds gave no successful results. The presence of starting materials was observed using NMR studies. 2-Chloropyridine should be reactive towards pyridine, due to the electrophilicity of this compound. Analysis showed no reaction had taken place in any of the solvents studied.

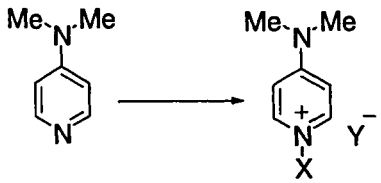
Alkylating/ Arylating reagent	Solvent	Temp/ °C	Time/ h	Yield
4-Cyanobenzyl bromide[142]	PhMe	Reflux	0.5	82% **144a**
3-(2-Bromo ethyl) indole[143]	Et_2O	50	0.5	80% **144b**
4-Bromobenzyl bromide[144]	DCM	Reflux	16	97% **144c**
4-Iodo toluene $[(C_6H_5)_3P]_4$ Pd 5 mol %	MeCN	Reflux	16	sm recovered
1-Chloro 2,4-dinitrobenzene[145]	DCM	Reflux	16	11% **144e**
2-Chloropyridine	$CHCl_3$	Reflux	16	sm recovered
2-Chloropyridine	PhMe	Reflux	16	sm recovered
2-Chloropyridine	*p*-Xylene	Reflux	16	sm recovered
2-Chloropyridine	Diglyme	Reflux	16	sm recovered
2-Chloropyridine	Ph_2O	200	0.5	sm recovered
2-Chloropyridine	-	Sealed tube @ 220	1	sm recovered
3-Chloropyridine	$CHCl_3$	Reflux	16	sm recovered
3-Chloropyridine	PhMe	Reflux	16	sm recovered
3-Chloropyridine	*p*-xylene	Reflux	16	sm recovered
3-Chloropyridine	Diglyme	Reflux	16	sm recovered
3-Chloropyridine	Ph_2O	200	0.5	sm recovered
3-Chloropyridine	-	Sealed tube @ 220	1	sm recovered
2-Chloropyrimidine	PhMe	Reflux	16	sm recovered
2-Chloroquinoline	PhMe	Reflux	16	sm recovered

Table 3

We decided to study the nucleophilic substitution reactions of pyridine further. It was decided to look at another linker mimic, DMAP. This compound is arguably more nucleophilic than pyridine due to the electron donating properties of the dimethylamino group. If the study shows that the nucleophilic displacements are successful using this adduct, then it should be possible to study the desired chemistry on polymer-bound DMAP, which is available commercially.

Due to the low reactivity of aromatic substrates towards pyridine, the use of microwave chemistry to drive these reactions to completion was explored. Microwave chemistry has been exploited for a number of years[146]. Examples of these include moisture analysis, and wet ashing procedures of biological and geological procedures. Recently this type of chemistry has been used for catalytic hydrogenation of alkenes[147], the hydrocracking of bitumen from tar sands and the degradation of polychlorinated hydrocarbons. Sealed Teflon vessels[148] have been utilized for the synthesis of organic molecules. High temperatures and pressures are readily obtained and this had led to dramatic rate enhancements and savings in reaction times. It has also allowed reactions, which are difficult to complete under normal reaction conditions, to be effected successfully.

A study was carried out into the use of DMAP as a nucleophile in aromatic nucleophilic displacement reactions using microwave activation. ***See Scheme 49*** and ***Table 4*** for the reagents used. The reaction was carried out using NMP as the solvent.



145 146

Figure 49

Reaction	Arylating reagent	Mass ion seen
49a	3-Chloroanisole	X
49b	4-Chloroanisole	X
49c	4-Chlorotoluene	X
49d	4-Iodotoluene	X
49e	4-Bromotoluene	X
49f	Ethyl-4-chloro benzoate	X
49g	3-Chloro-α-α-α-trifluorotoluene	X
49h	2-Chloro-*m*-xylene	X
49i	4-Chloro-*m*-xylene	X
49j	1-Chloro-4-nitrobenzene	X
49k	1-Iodo-4-nitrobenzene	X
49l	1-Bromo-4-nitrobenzene	X
49m	2-Chloro-5-nitrotoluene	X
49n	1-Chloro-3-nitrobenzene	X
49o	2-Chloro-3, 5-dinitropyridine	X
49p	2-Chloroquinoline	X
49q	1-Chloro isoquinoline	X
49r	2-Chlorothiophene	X
49s	2-Chloropyrimidine	X
49t	2,4-Dichloropyrimidine	X
49u	1-Fluoro-4-nitrobenzene	X
49v	1-Chloro-4-fluorobenzene	X

Table 4

It was likely that the use of arylating reagents with electron-withdrawing groups would have a greater chance of reacting with DMAP, as they would be more electrophilic. This was not the case and none of the desired materials were observed. The reaction of compounds with electron-donating groups would be more difficult, as these groups would make the compounds less electrophilic. Initial LC-MS studies showed no evidence of any successful reactions. This was

also confirmed by NMR studies. Disappointingly, the reactions were deemed unsuccessful, even with microwave irradiation.

From the solution phase results, it can be seen that successful results have been gained from the alkyation and cyclization reactions. Harsh conditions, such as microwave chemistry showed that arylation reactions, using DMAP as the nucleophile were not successful, even with strongly electron deficient substrates such as dinitropyridine. If this were the case, then pyridine would also be a poor nucleophile, as it is less nucleophilic than DMAP.

2.3 Cleavage strategies of solution-phase reactions

This section looks at the different reagents employed in solution phase to look at suitable compounds, which could eventually be used on solid phase to cleave amine compounds off the pyridine linker resins. Ukrainets *et al.* [149] showed the use of hydrazine compounds to open pyridine rings. It was decided to look at the use of this compound as well as the use of 2^{o} amines, which could also be used for this type of reaction. ***Figure 50*** shows the proposed mechanism when these amines are used.

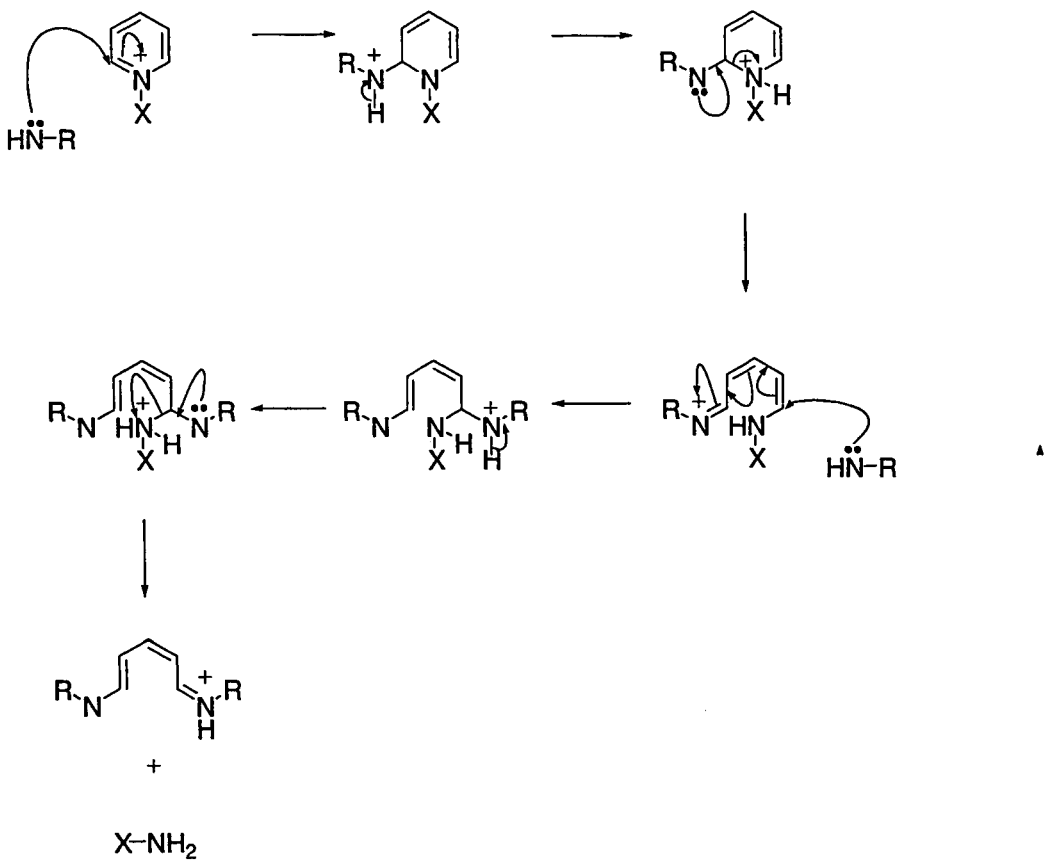


Figure 50

The first cleavage reaction attempted was the cleavage of compound **144a** to the corresponding benzylamine. ***See Figure 51.***

144a 147

Figure 51

Table 5 shows the cleavage reagents and reaction conditions used to study these reactions.

Reaction	Cleavage reagent used	Solvent	Temp/ °C	Time/ h	Yield
51a	$H_2NNH_2.H_2O$	EtOH	Reflux	4	46% **147**
51b	Me_2NNH_2	EtOH	Reflux	12	Mixture of compounds
51c	Me_2NH	DCM	Reflux	6	Mixture of compounds
51d	C_4H_9N	THF	Reflux	12	Mixture of compounds

Table 5

The use of hydrazine hydrate was found to be effective and reaction **51a** gave the desired product in 46% yield. The ^1H NMR spectrum showed the desired product, although no signal could be seen for the methylene group relative to the pyridinium salt. From ^{13}C NMR studies, the desired compound was seen and IR spectroscopy showed the presence of a cyano peak at 2226 cm^{-1}. The reaction was deemed successful.

The next reaction to be studied was the cleavage of the aminoquinolinone product **148** from the quinolinyl pyridinium **143**. ***See Figure 52.***

143 148

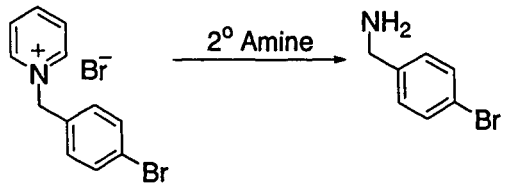
Figure 52

Reaction	Cleavage reagent used	Solvent	Temp/ °C	Time/ h	Yield
52a	Et_2NH	MeOH	Reflux	2	75% sm recovered
52b	$H_2NNH_2.H_2O$	EtOH	Reflux	4	50% **148**

Table 6

From ***Table 6***, it can be seen that hydrazine hydrate was a suitable cleavage reagent. A yellow solid was isolated in 50% yield. The compound was initially analyzed by mp. Further analysis by ^1H NMR studies showed the desired signals in the compounds spectrum. A singlet appeared at 4.37 ppm, which corresponded to the amino group. The reaction was deemed successful.

A study was carried out into the pyridinium-ring opening reactions of 1-(4-bromobenzyl) pyridinium bromide. See ***Figure 53***. We wanted to investigate three factors, i) whether the amine product was cleaved from the pyridine ring and ii) how many impurities each cleavage reagent gave and iii) which solvent system was the best for this type of reaction. The third factor is an important point as the solvent used needs to be suitable for solid support reactions.



144c 149

Figure 53

The use of four secondary amines was investigated to study the ring-opening reactions. ***Table 7*** shows the reagents used and the solvent systems that were studied. In each case, 10 eq. of each amine was used.

Reaction	Cleavage reagent used	Solvent system used
53a	Me_2NH	THF
53b	Me_2NH	DCM
53c	Me_2NH	MeOH
53d	Me_2NH	DCM: MeOH (3:1)
53e	Me_2NH	DCM: MeOH (1:1)
53f	Me_2NH	MeOH: THF (1:3)
53g	Et_2NH	THF
53h	Et_2NH	DCM
53i	Et_2NH	MeOH
53j	Et_2NH	DCM: MeOH (3:1)
53k	Et_2NH	DCM: MeOH (1:1)
53l	Et_2NH	MeOH: THF (1:3)
53m	Piperidine	THF
53n	Piperidine	DCM
53o	Piperidine	MeOH
53p	Piperidine	DCM: MeOH (3:1)
53q	Piperidine	DCM: MeOH (1:1)
53r	Piperidine	MeOH: THF (1:3)
53s	Pyrrolidine	THF
53t	Pyrrolidine	DCM
53u	Pyrrolidine	MeOH
53v	Pyrrolidine	DCM: MeOH (3:1)
53w	Pyrrolidine	DCM: MeOH (1:1)
153x	Pyrrolidine	MeOH: THF (1:3)

Table 7

All these reactions were carried out at RT. Initial analysis was carried out using GC-MS. ***Tables 8*** and ***9*** show the number of impurities shown in each reaction and the % of desired material seen by LC-MS analysis. The number of impurities was also determined by this method.

	Me_2NH (2.0 M solution in THF	Et_2NH	$C_5H_{11}N$	C_4H_9N
THF	4	1	3	2
DCM	2	2	9	8
MeOH	2	1	7	1
DCM: MeOH (3:1)	2	2	-	4
DCM: MeOH (1:1)	2	2	4	1
MeOH: THF (1:3)	3	-	3	-

Table 8 Number of impurities observed in ring-opening study

	Me_2NH (2.0 M solution in THF	Et_2NH	$C_5H_{11}N$	C_4H_9N
THF	33	0	5	57
DCM	70	61	22	21
DCM: MeOH (3:1)	57	65	6	61
DCM: MeOH (1:1)	58	63	0	42
MeOH: THF (1:3)	60	58	34	6
DCM: MeOH (3:1)	63	0	0	0

Table 9 % of 149 calculated in cleavage study

From these results, it can be seen that Me_2NH was the most suitable cleavage reagent. This showed the highest % of desired material, **149**. DCM was found to be the best solvent. It was then intended to study similar alkylation reactions of the solid-supported pyridines, and to investigate cyclization reactions of the resulting pyridinium salts to build up a range of heterocyclic products which could be released as amines by the cleavage of the pyridinum rings.

2.4 Alkylation and cyclization reactions of pyridine linker resins

The reactions discussed in Section 2.3 are these studied on the two pyridine linkers, which were discussed earlier. The reactions that were studied will initially be discussed and the cleavage strategies have been reported in Section 2.5.

The first study involved the alkylation reactions, which were previously attempted in solution phase on linkers **137** and **139**. ***See Figure 54.***

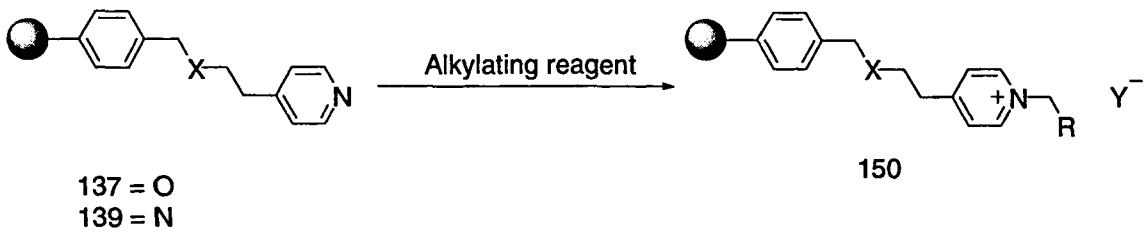


Figure 54

Table 10 shows the reactions alkylating reagents, which were used in this study.

Linker used	Alkylating reagent used	Solvent	Temp/ °C	Time/ h
137	Methyl bromoaceteate	PhMe	Reflux	2
137	Ethyl bromoacetate	PhMe	Reflux	2
137	4- Cyanobenzyl bromide	THF	Reflux	3
137	3-(2-Bromoethyl)indole	THF	Reflux	3
137	Chloroacetyl chloride	DCM (anhydrous)	RT	0.5
139	Methyl bromoacetate	PhMe	Reflux	2
139	Ethyl bromoacetate	PhMe	Reflux	2
139	4-Cyanobenzyl bromide	THF	Reflux	3

Table 10

In each reaction, once completed, a washing method was employed, which allowed the resin to swell and shrink consecutively. This was carried out in the reaction solvent, which we know allows the resin to swell and in most cases Et_2O was used to shrink the resin. It was hoped that excess reagent trapped within the matrix of the resin would be squeezed out. To look at a qualitative method of

analyzing each reaction, we employed two different tests. The first was the cobalt colour test utilized in the synthesis of the pyridine linker. For each reaction, once the beads had been washed and dried, a few drops of the cobalt solution was added. In this case, it was hoped that no colour change would occur, as this would indicate that alkylation had taken place, as the lone pair on the pyridine would be absent. Indeed this was found be true in each case. To add further evidence, a few beads were taken from each reaction, suspended in a few drops of MeCN and a few drops of silver(I) nitrate solution were added. The idea behind this was that if the alkylation reaction had taken place, halide ions would be present. On addition of the silver(I) nitrate solution, a precipitate of the silver salt should form. In each case, on the addition of the silver solution, a cloudy solution formed indicating the presence of halide ions. The reactions were deemed successful on the basis that the resins from each reaction were thoroughly washed. Traditional techniques such as TLC could not be used to follow the reactions, this being a major disadvantage of solid phase chemistry.

As in solution phase, cyclization reactions were studied on the pyridine linker resin. These were carried out using linker **137**, which was alkylated with methyl and ethyl bromoacetate. The reagents studied are described below.

The initial set of reactions investigated was the cyclization of the substituted acetate group of resin **150a/b** with 2-aminoacetophenone. ***See Figure 55.***

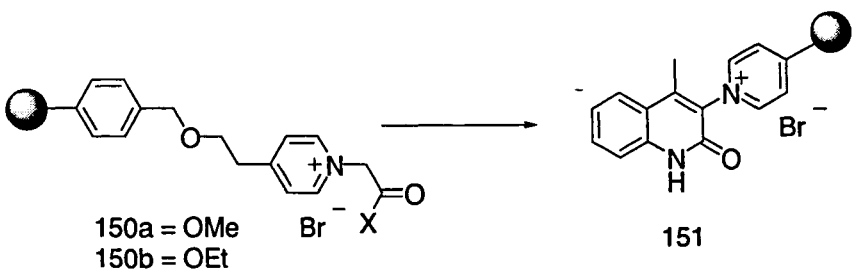


Figure 55

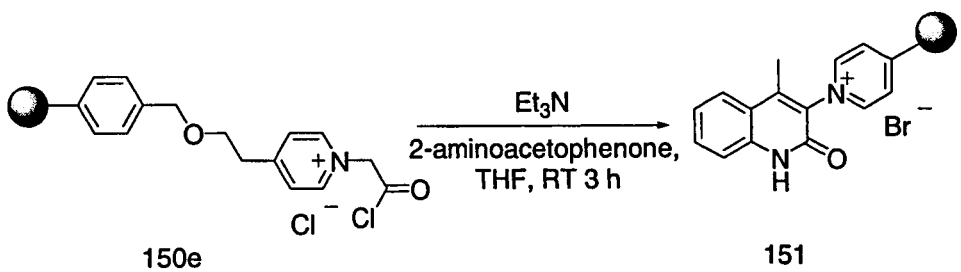
Table 11 shows the conditions studied for this reaction.

Reaction	Base used	Solvent	Temp/ °C	Time/ h
55a	DBU (3 eq.)	THF	RT	2
55b	Et_3N (3 eq.)	THF	80	3
55c	C_6H_5N (xs)	-	100	1.5
55d	C_6H_5N (xs)	-	100	12

Table 11

Once the reactions were competed, analysis by colour tests was not possible. Analysis by IR spectroscopy showed peaks around 1700 cm^{-1}, which corresponded to the carbonyl group of the quinolinone ring. There was also an increase in the weight of the resin.

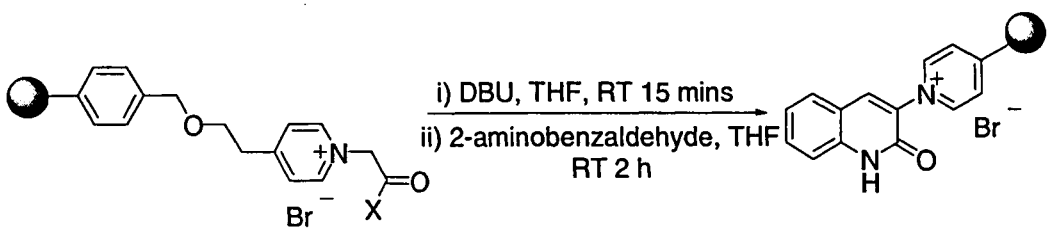
Resin **150e** was also reacted with 2-aminoacetophenone. This was prepared immediately before use due to the instability of this compound. The acid chloride resin should be more reactive than the ester group, thus likelihood of this reaction should be greater. ***See Figure 56.***



150e 151

Figure 56

The next cyclization reagent to be studied was 2-aminobenzaldehyde. ***See Figure 57.*** The expected product was also the quinolinone, with the absence of the methyl group.



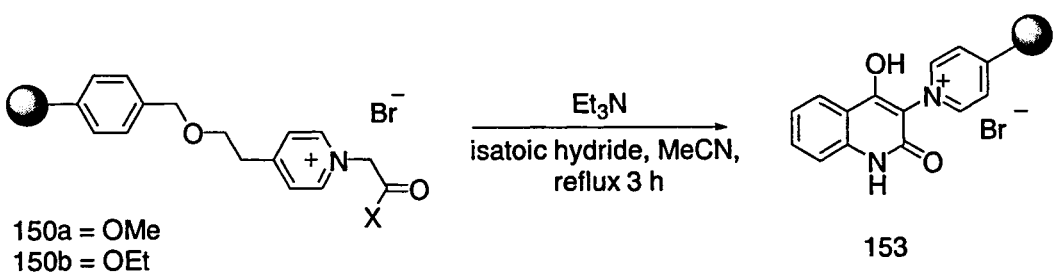
150a = OMe
150b = OEt

152

Figure 57

Analysis by IR spectroscopy showed the presence of a carbonyl group around 1640 cm^{-1}.

Figure 58 shows the cyclization reaction carried out using isatoic anhydride.



150a = OMe
150b = OEt

153

Figure 58

This was carried out using the conditions employed in solution phase. Initial analysis by IR spectroscopy showed the presence of the hydroxyl and carbonyl groups. It was not clear at this point, whether these reactions had been successful. This would be established once the cleavage procedure had been attempted.

The next section looks at the cleavage of the alkylated and cyclized products from the pyridine linkers.

2.5 Cleavage strategies for solid supports

This section deals with the cleavage reactions carried out on the pyridine linkers described in Section 2.4.

The first set of reactions investigated was the cleavage of 4-cyanobenzyl amine from linkers **150c** and **150h**. The alkylations were described in Section 2.4. It was hoped that the benzylamine would be isolated. ***See Figure 59.***

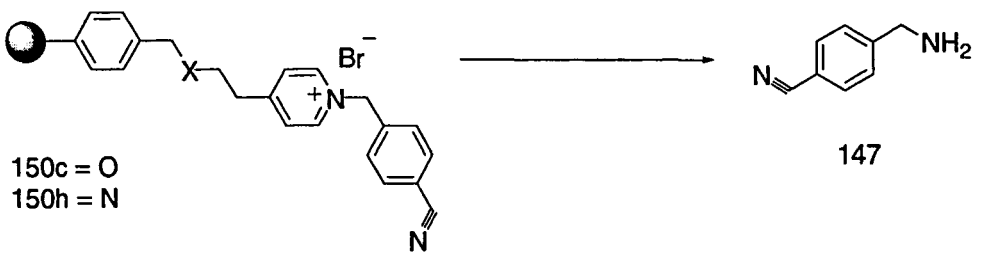


Figure 59

Table 12 showed the reaction conditions studied for this reaction.

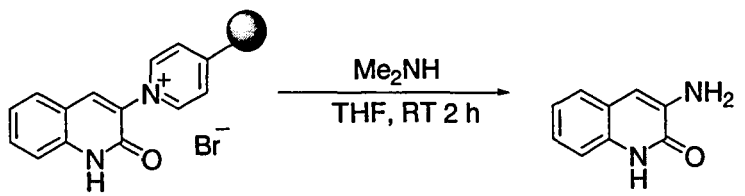
Reaction	Linker	Cleavage reagent	Solvent	Temp/ °C	Time/ h	Desired compound isolated
59a	N	$H_2NNH_2.H_2O$	EtOH	Reflux	16	Complex mixture isolated
59b	N	Me_2NH	DCM	Reflux	0.5	Complex mixture isolated
59c	N	Me_2NH	DCM	Reflux	1.0	Complex mixture isolated
59d	N	Me_2NH	DCM	Reflux	1.5	Complex mixture isolated
59e	N	Me_2NH	DCM	Reflux	2.0	Complex mixture isolated
59f	O	Me_2NH	THF	Reflux	2	None
59g	O	C_4H_9N	THF	80	1.5	None

Table 12

The use of these reagents was studied, by using the results gained in Section 2.3. Me_2NH was found to be a suitable cleavage reagent, as fewer impurities were seen in the study. Also, the volatility of the compound would permit easier isolation of the cleavage product. It was intended to compare this to the use of the

other secondary amine compounds used to cleave the benzylamine product. From the results shown in ***Table 13***, it can be seen that the desired compound had not been cleaved off the pyridine resins. ^{1}H NMR data from each reaction showed a complex mixture in each case. Pyridinium peaks were present between 7-9 ppm, but it was not possible to identify them as the desired material. This could suggest that cleavage was possibly occurring at another site, which was releasing an intact pyridinium ring. Mass spectrometry data showed no evidence of the desired parent ion being present and there was no evidence of the cyano group being present in the IR data. The reactions were deemed unsuccessful.

The next cleavage reaction studied was the cleavage of linker **152** from the reaction with aminobenzaldehyde. ***See Figure 60.*** The reaction again employed the volatile dimethylamine as the nucleophile and was carried out in THF at RT, in the hope that the aminoquinolinone **154** would be released from the resin.



152 154

Figure 60

A brown oily material was isolated. Initial analysis by IR spectroscopy showed a weak peak at 3317 cm^{-1}. This could have corresponded to the –NH_2 stretch. ^{1}H NMR spectroscopy showed no evidence of aromatic signals. The reaction was repeated using resin **152** again with pyrrolidine as the cleavage reagent and again no evidence was seen of the desired material. Pyrrolidine was seen using ^{1}H NMR and this was the only compound, which was isolated. The results were deemed unsuccessful.

In summary it was seen that the results from these studies were found to be inconclusive. This was mainly due to the fact that there are not suitable techniques to analyze the treated solid supports after each reaction step. This led to the investigation of a type of linker, which could be analyzed using more 'traditional techniques.

2.6 The use of 'pre' linker resins

As part of the ongoing efforts to improve analysis techniques for solid phase chemistry, it has been decided to investigate the use of a 'pre' linker resin, onto which could be attached another linker where the desired chemistry can then take place. Geysen and co- workers[150] reported this concept, whereby they developed an analytical construct, in which the solid supported substrate and the linker were attached through a MS sensitizer, peak splitter and a second orthogonal linker. The basic concept of this was as follows; cleavage at the linker closest to the polymer backbone could occur. This would release an analytical construct, which would have the peak splitter, the MS sensitizer and the linker on the end, on which the chemistry is carried out. This construct could then be analyzed using techniques such as LC-MS and ^{1}H NMR spectroscopy. The syntheses of these constructs meant that a multi step reaction, when carried using a solid support, could be analyzed at each individual stage. This technique was found to represent a rapid method of analysis for solid phase synthesis and could be equivalent to TLC, which is widely used in solution phase chemistry.

The solid support, which was used in this study, was Fmoc Rink amide resin, **155**. It has been found that after removal of the Fmoc protecting group, TFA can be used to cleave at the amine position. This is a favourable reaction as the benzhydryl cation that is formed is very stable. The stability partially comes from the electron donating methoxy groups, which are present on the aromatic ring. ***See Figure 61.***

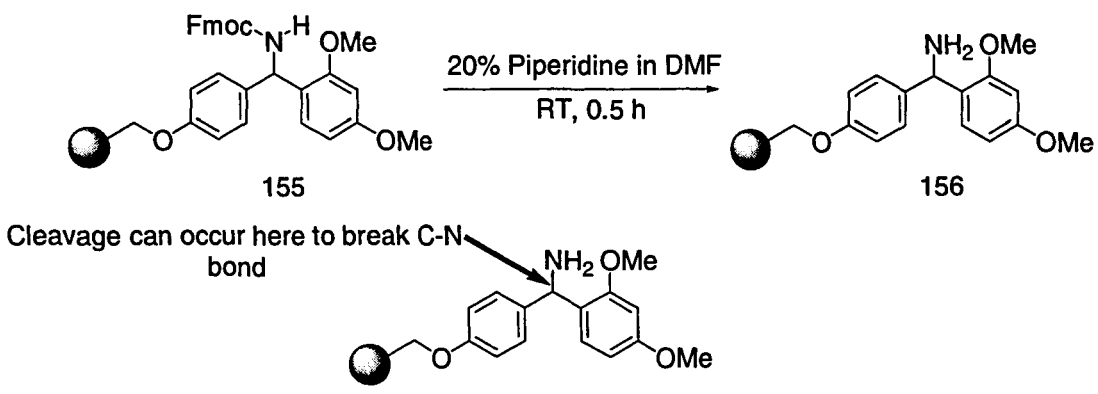


Figure 61

The first step into the synthesis of the pyridine resin was to attach a spacer chain, onto which the pyridine adduct could be attached. It was decided to employ the use of 12- hydroxydodecanoic acid, which is commercially available. ***See Figure 62.***

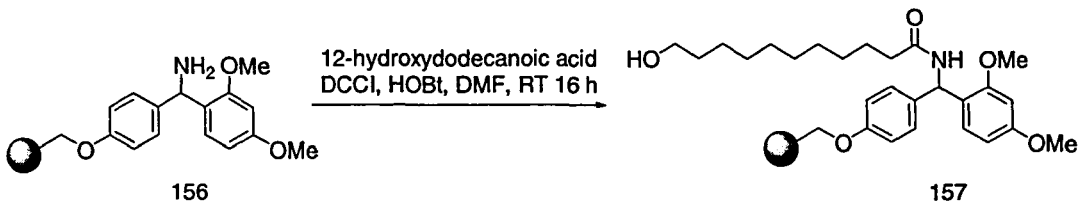


Figure 62

Initial steps involved deprotection of the amine group on the Rink resin. This was carried out using standard conditions of 20% piperidine solution in DMF. Next, using the coupling reagent DCCI and 1-hydroxybenzotriazole, 12-hydroxydodecanoic acid was attached to the resin via an amide coupling reaction. The reaction was initially carried at RT. Initial IR spectroscopy results showed that there was a shift of the N-H peak from 3446 cm^{-1} in the untreated starting resin to 3328 cm^{-1} in the treated resin. From this initial analysis, it could be deemed that the reaction may have been successful and that the amine had in fact been converted to an amide.

It was decided to try cleavage at the 'pre' linker to confirm whether the spacer chain had been attached to the Rink resin. This would release the amide product, **158**. ***See Figure 63.***

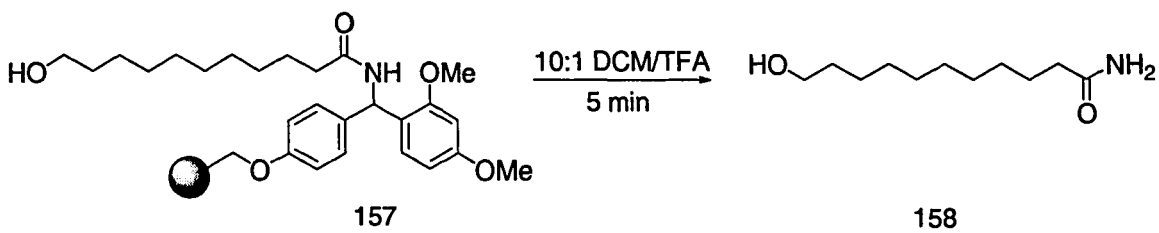


Figure 63

This was carried out by taking a few of the treated resin beads and adding drops of TFA in DCM. On addition of the acid, the beads turned a red colour. This was expected due to the generation of the stabilized benzhydryl cation. The cleaved material was initially analyzed by GC-MS. Results from this analysis showed no

evidence of the desired parent ion. This indicated that the reaction might have not been successful. It is possible that the column used for the GC analysis was not suitable and that the material had in fact not passed through the column. Analysis of the material by LC- MS using a suitable column also failed to show the desired material. This was also confirmed by ^{1}H NMR spectroscopy, which failed to show the presence of the dodecamide product. The reaction was deemed unsuccessful.

The reaction was repeated with 12-hydroxydodecanoic acid using various different conditions. These are summarized in ***Table 13*** below:

Coupling reagents used	Time/ h	Temperature/ °C	Parent ion seen in LC-MS spectrum?
DCCI	4	RT	X
DCCI	8	RT	X
DCCI	20	RT	X
PyBop	8	RT	X
PyBop	20	RT	X

Table 13

Disappointingly, reactions with either DCCI or PyBop as coupling reagents gave no successful results. It was decided to investigate different acids, which could be coupled onto the resin. We decided to look at spacer chains, which incorporated the pyridine adduct as well as the acid portion. This would mean one less synthetic step would be involved in the synthesis of the pyridine linker resin. The spacer chain would create a short chain between the 'pre' linker and linker on which the chemistry would be carried out.

The first compound of this type, which was studied, was 4-(pyridin-4-yl)butyric acid, the synthesis of which was reported by Klein *et al*[151]. This compound incorporated the pyridine adduct, on which the desired chemistry could be studied. At the other end of the molecule, a carboxylic acid group was present. This could be used to attach the compound onto the Rink amide resin via an amide coupling as previously attempted.

The first part of obtaining the desired acid was the synthesis of the intermediate diethyl 2-[2-(pyridin-4-yl)ethyl]propanedioate, **160**. ***See Figure 64.***

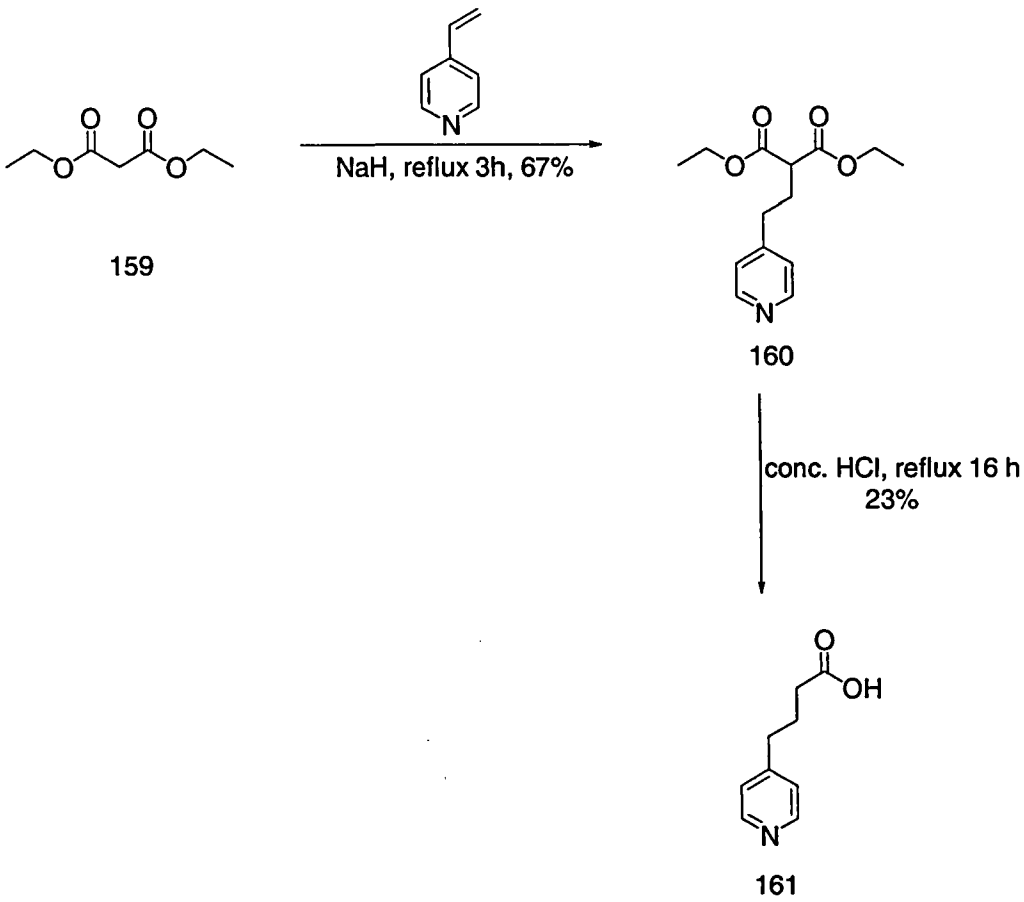


Figure 64

This was carried out using the conditions reported by Klein[151]. Sodium hydride was used to deprotonate the 1,3-dicarbonyl, diethyl malonate to give an enolate. Addition of 4-vinylpyridine would then encourage a Michael addition to occur to give the desired product, **160**. A yellow oily material was isolated in good yield, typically 67%. Analysis of the material using NMR spectroscopy showed the presence of the desired material, clearly showing the single proton, which resides between the two carbonyl groups at 3.46 ppm and the presence of signals due to the pyridine ring and the ethyl ester substituents. IR studies also showed the presence of carbonyl groups at 1744 cm^{-1}. The final stage of the synthesis of the acid was to carry out an ester hydrolysis and decarboxylation of the intermediate **160** to give the acid **161**. This was carried out using refluxing HCl.

A white solid was obtained in 23% yield, which was low. However, analysis showed the presence of the desired material, showing the presence of the –OH proton at 3.59 ppm. The reaction was deemed successful.

The reaction was repeated using identical conditions as stated above, but this time the intermediate was not isolated as this was not required. The material was used after aqueous extraction. A white solid was isolated from a brown sticky residue. This was clearly identified as NaCl. This was identified by ^{1}H NMR spectroscopy and flame test, which gave a yellow colour. The brown sticky material was analyzed using NMR and it was found that the desired product signals could be identified. However, the material was not pure, as a number of other peaks were seen between 1-4 ppm, which could not be identified. The material was triturated, using mixtures of EtOAc/ EtOH to try and remove these impurities. NMR studies failed to identify a clean product. The reaction was repeated to see if these results were consistent and this was found to be the case. It is not clear why the synthesis of the acid failed at the second stage, but one reason could be that decomposition was occurring of intermediate **160**, due to the use of the strong HCl acid and long refluxing conditions, which were using in the original synthesis of the compound.

It was decided to employ a different 1,3- dicarbonyl compound, di-*tert*-butyl malonate. *t*-Butyl esters are known to cleave more easily than ethyl esters, thus this approach would require less harsh conditions for this step. As previously, the first step of the synthesis was to carry out the synthesis of the Michael adduct di-(1,1-dimethylethyl) 2-[2-(pyridin-4yl)ethyl]propanedioate, **163**. ***See Figure 23.***

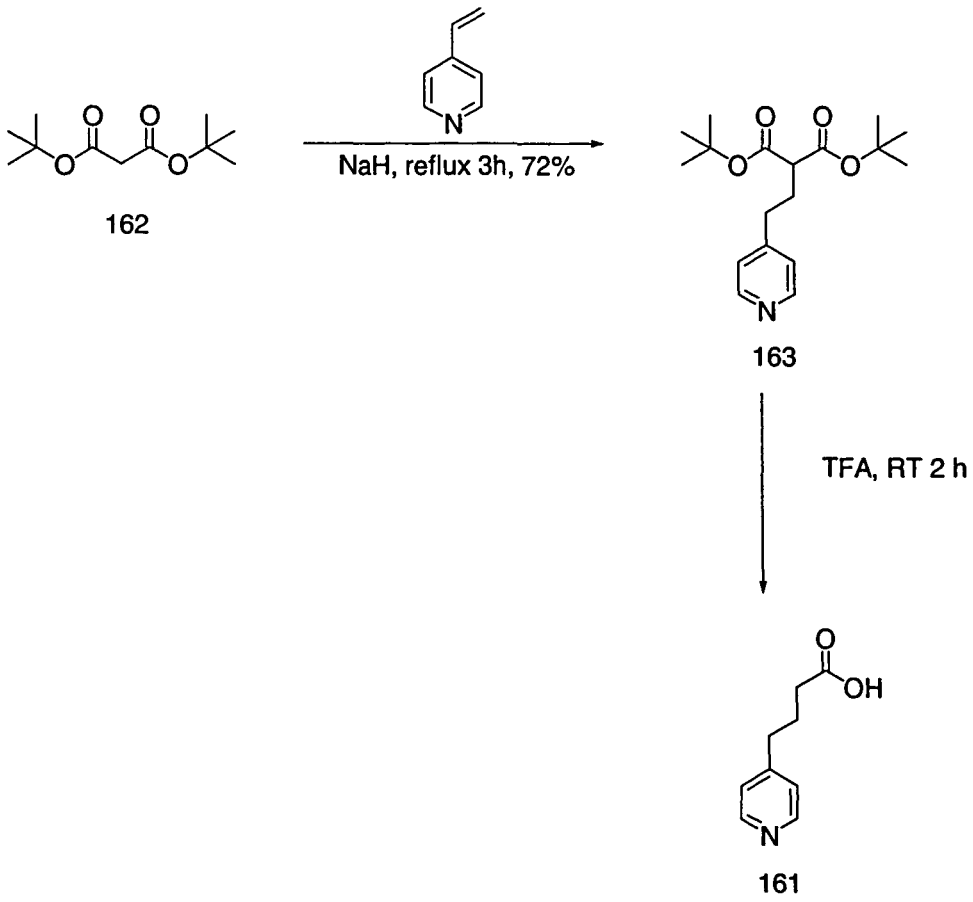


Figure 65

Sodium hydride was also used in this case to carry out the enolate formation. An orange oil was isolated in 72% yield, which was identified as the correct material. The *t*-butyl protons were found at 1.41 ppm in the ^{1}H NMR spectrum. The next step was to carry out the ester cleavage and decarboxylation. This was carried out using TFA in DCM, using short reaction times. A yellow oil was isolated, the weight of which was greater than the theoretical amount of product expected. The NMR spectrum showed positive evidence that the starting material was present. The *t*-butyl ester signals were still present in the spectrum. The reaction was attempted using a greater amount of TFA to drive the reaction to completion. The reaction was also left for a further three hours. A mixture of compounds was obtained, but signals at 1.92 and 2.44 ppm, which could correspond to the methylene groups, suggested that the desired material could be present. Attempts were made to purify this material further, but this was not successful.

It was decided to take compound **161** from the original reaction and try and couple this to the Rink amide resin. Two coupling reagents were investigated, DCCI and

PyBop. These were used with the acid mixture to couple onto the deprotected Rink amide resin. From both reactions, it was seen that the acid had not coupled onto the Rink resin. This could be due to there not being enough of compound **161** which could couple onto the acid, due to the presence of impurities.

It was decided next to investigate the use of the commercially available 3-(pyridin-3-yl)propionic acid. This was considered to be a good candidate, as it possessed both the pyridine and acid functionalities. ***See Figure 66.*** It was hoped that having the propionic acid chain attached at the 3-position of the pyridine ring would not hinder subsequent reactions at the pyridine nitrogen atom.

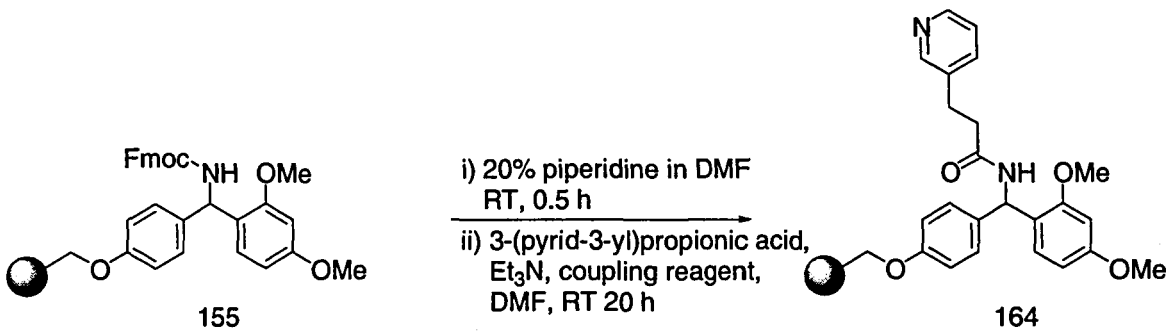
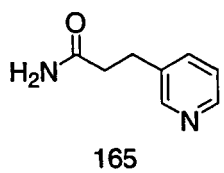


Figure 66

Both PyBop and PyBrop were used as the coupling reagents and it was found that PyBrop was the best, as it gave consistent results. After the amide coupling reaction was completed, TFA was used to cleave the resin to reveal the amide product, **165**. LC-MS studies showed the presence of the parent ion (MH^+) of mass 151. This was carried out on a few treated resin beads. This compound was also positively identified using ^1H and ^{13}C NMR. **See *Figure 67.***



165

Figure 67

The successful formation of a pyridine substituted resin, and the successful cleavage of the amide **165**, thus allowed an extensive study of alkylation reactions at the pyridine nitrogen, ***see Figure 68.*** ***Table 14*** shows a range of alkylating

reagents studied, including aliphatic, benzylic and α-halo carbonyl compounds. LC-MS was used to establish whether the parent ion was seen.

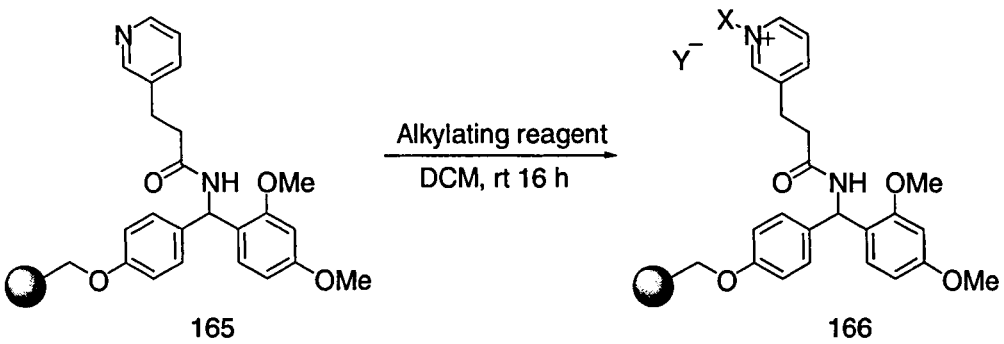


Figure 68

Reaction	Alkylating Reagent	Mass ion expected	Mass ion seen
68a	2-Nitrobenzyl bromide	286	√
68b	4-Nitrobenzyl bromide	286	√
86c	4-Methoxybenzyl chloride	271	√
68d	Allyl bromide	191	√
68e	Methyl iodide	165	√
68f	Ethyl bromoacetate	237	√
68g	Dodecyl bromide	320	√
68h	4-(Trifluoromethyl) benzyl bromide	309	√
68i	4-Fluorobenzyl bromide	259	√
68j	2-Bromoacetophenone	269	√
68k	Chloroacetone	207	√

Table 14

From the results reported above, it can be seen that the alkylation reactions attempted were successful. After cleavage to obtain the propanamide products, each reaction was initially analyzed using LC-MS to show the presence of the parent ion. The structure of these compounds was then confirmed using ^{1}H NMR spectroscopy, which exhibited signals fully consistent with the proposed structures. This can be illustrated with the results obtained from reaction **68a**,

3-[(2-nitrophenyl)methyl]pyridinium-3-yl}propanamide bromide, **166a**. Peaks at 2.50 and 3.02 ppm were present for the methylene peaks on the propanamide chain. **See Appendix 1** for ^{1}H NMR data. Pleasingly, the NMR spectra for each of the above compounds isolated were found to be clean, as no impurities were seen in the data collected. The alkylation study was repeated to ascertain the reproducibility of the alkylation reactions. The experiments were found to be reproducible. It is worth noting that these reactions were also attempted in solution phase, using pyridine to mimic the pyridine linker. In summary, the 'pre' linker method was found to be particularly useful, as both the alkylation and 'pre'-cleavage reactions were successful, thus allowing solid phase reactions to be followed.

Using resins **166J-K**, we studied cyclization reactions to build a range of fused ring systems. ***Table 15*** shows the alkylated resins and cyclization reagents used to attempt these reactions to build quinolines and benzopyrans.

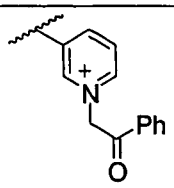
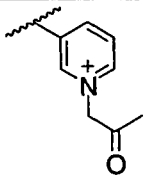
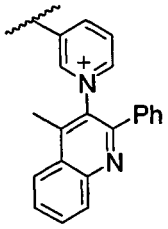
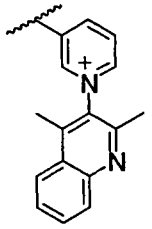
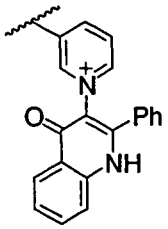
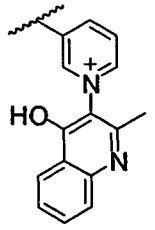
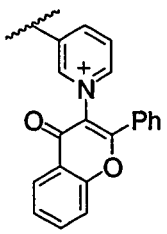
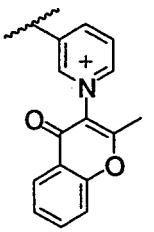
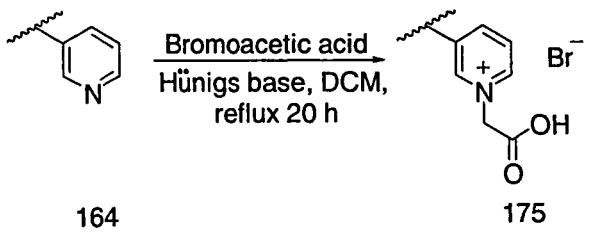
Resin studied	 166j	 166k
Cyclization reagents		
2-Aminoacetophenone	 167	 171
Anthranilic acid	 168	 172
Salicylic acid	 169	 173
Salicylaldehyde	170	174

Table 15

After cleavage at the 'pre' linker to release the amide product, LC-MS studies showed no evidence of any desired products. There was only evidence of the starting material, the alkylated pyridine compounds. In this instance, the reaction was carried out using THF at RT for 16 h. A repeat reaction was carried out with both the alkylated pyridine resins using DMF at RT for 16 h and again no desired parent ions were observed.

It was decided to approach this problem in a different way. Linker **164** was alkylated with bromoacetic acid. ***See Figure 69.***



164 175

Figure 69

The material cleaved for spectroscopic analysis was found to contain pyridinium bromide as well as the desired parent ion. This was corrected by addition of a larger quantity of DIPEA, as this would prevent the pyridine from being protonated by the bromoacetic acid. The alkylated resin was then treated with 2-aminoacetophenone, which it was hoped would couple onto the acid group via an amide coupling reaction in the presence of PyBrop. It was envisaged that in the presence of excess Et_3N, once this coupling had taken place, the acidic proton adjacent to the pyridinium nitrogen would be removed, causing a cyclization reaction to occur. **See *Figure 70.***

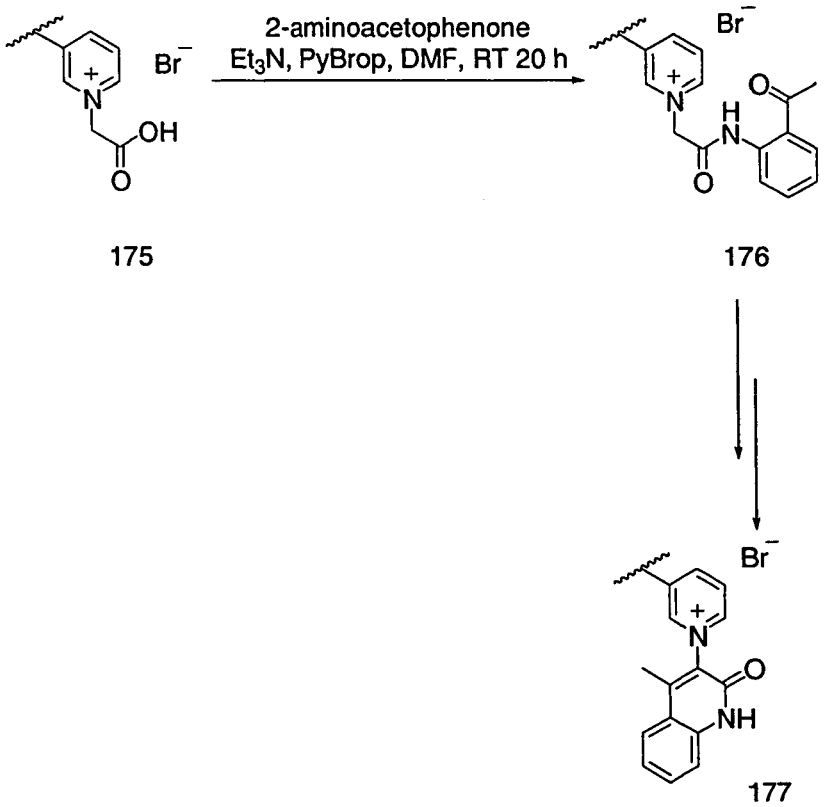


Figure 70

LC-MS studies showed the presence of three materials; i) pyridinium salt, ii) the un-cyclized product and iii) the cyclized product. The m/z values were seen at 185, 307 and 325 respectively. ***See Figure 71***

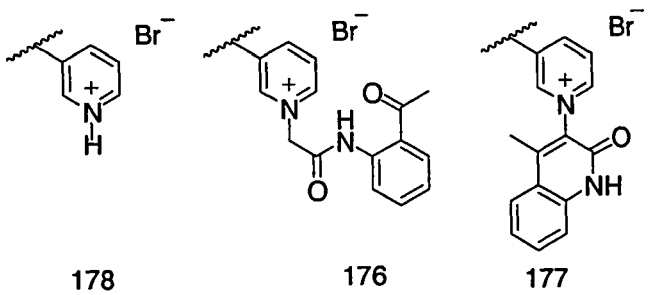


Figure 71

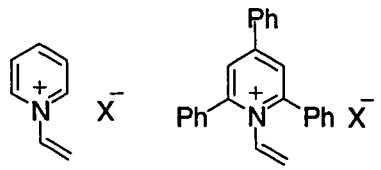
This was also confirmed by ^{1}H NMR spectroscopy, which showed the presence of three sets of pyridinium groups situated between 7-10 ppm. The methylene peaks could not be clearly identified at this point. There was not enough material at this point to try and separate the three compounds. This reaction will be investigated further.

In summary, we have shown that the use of the 'pre' linker gave successful results. We have shown the alkylations using a variety of reagents proved to give successful results on analysis using ^{1}H NMR spectroscopy and LC-MS. It was observed that cyclization reaction were successful, showing both the uncyclized and cyclized products. Future work will involve further investigation of these reactions, also looking at the cleavage of the amine products after alkylations and cyclization steps.

3 Vinyl Pyridinium Salts: Synthesis and Applications

3.1 Introduction

Vinylpyridinium salts have generated much interest due to their potential as use as monomers for polymerization in the synthesis of cationic quaternary polyelectrolytes. Several *N*-vinyl heterocycles such as *N*-vinylimidazoles[152], *N*-vinylcarbazoles and *N*-vinylpyrrolidones[153] are already in widespread use. Despite the potential practical importance of these vinylic salts, little work has been carried out on the chemistry of these types of compounds. ***See Figure 72.***



179 180

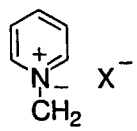
Figure 72

Coppola[154] carried out the earliest work on simple unsubstituted *N*-vinylpyridinium salts, in 1885. He reported the synthesis of the platinichloride salt, which was obtained from 1-(2-iodoethyl)pyridinium iodide and moist silver oxide, thus obtaining cation **179**. Schmidt[155] synthesized the above cation using 1-(2-bromoethyl)pyridinum bromide.

Duling and Price[156] further investigated this work in 1962. They were able to improve the overall yield of the vinylpyridinium salt. They were also able to prove the structure by IR and UV spectroscopy, and by carrying out various chemical reactions including hydrogenation of the *N*-vinylpyridinium perchlorate to furnish 1-ethylpiperidine. They studied the reactivity of **179** towards bromine and showed that no addition occurred across the double bond of the perchlorate. This was indicated by back titration with sodium thiosulphate solution. It was also observed that *N*-vinylpyridinum perchlorate polymerized with great readiness by free-radical initiation or ionizing radiation.

A study was carried out to see if polymerization could occur with other monomers. Due to the vinyl group on the *N*-vinylpyridinium cation being adjacent to the

positive charge of the pyridine nitrogen, the vinylic bond is electron deficient. Thus rapid polymerization with electron rich monomers, such as styrene is expected. In fact, research showed that *N*-vinylpyridinium cations co-polymerized poorly or not at all with electron rich polymers but well with electron poor monomers, such as methyl methacrylate and acrylonitrile.

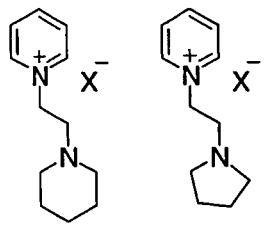


181

Figure 73

Katritzky[157] *et al.* carried out the synthesis of the vinylpyridinium salts at low temperatures to try to prevent polymerization. NaOH was utilized as the dehydrohalogenating reagent. Studies found that temperatures lower than 0 °C were needed for the dehydrohalogenation reaction to occur successfully as at 0 °C, polymerization of the product occurred readily.

It has been well established that the positive charge situated on the nitrogen of the pyridinium ring stabilizes an adjunct carboanion centre in pyridinium ylides such as **181**. These ylides can be prepared by deprotonation. Addition of nucleophiles by Michael addition to cations **179-180** involves the stabilized intermediate as reported by Duling and Price[156]. Katritzky *et al.* found that cation **179** and its triphenyl analogue **180** both undergo Michael additions using a variety of nitrogen, sulphur and carbon nucleophiles. Phillips[158] demonstrated an example of this. He showed that the addition of secondary amines such as piperidine and pyrrolidine to compound **179** led to rapid polymerization. However, addition of acetic acid to the methanolic solution of **179** prior to the addition of the amine, compounds **182** and **183** were formed as the *bis* (perchlorate) salts. ***See Figure 74.***



182 183

Figure 74

A review of the syntheses of several vinylpyridinium salts was published in 1984 by Katritzky[159]. This describes two different routes[156, 160] to synthesize the simple unsubstituted pyridinium cation. These methods were then applied to various substituted pyridines. ***See Figure 75.*** The first preparation involved the quaternization of pyridine, using 2-bromoethanol, followed by transformation of the hydroxyl group to a chloro group using $SOCl_2$[159, 160]. The second preparation involved the reaction between pyridine and 1,2-dibromoethane to give 1-(2-bromoethyl) pyridinum bromide[156]. Both these methods involved the use of sodium hydroxide to carry out the dehydrohalogenation reaction.

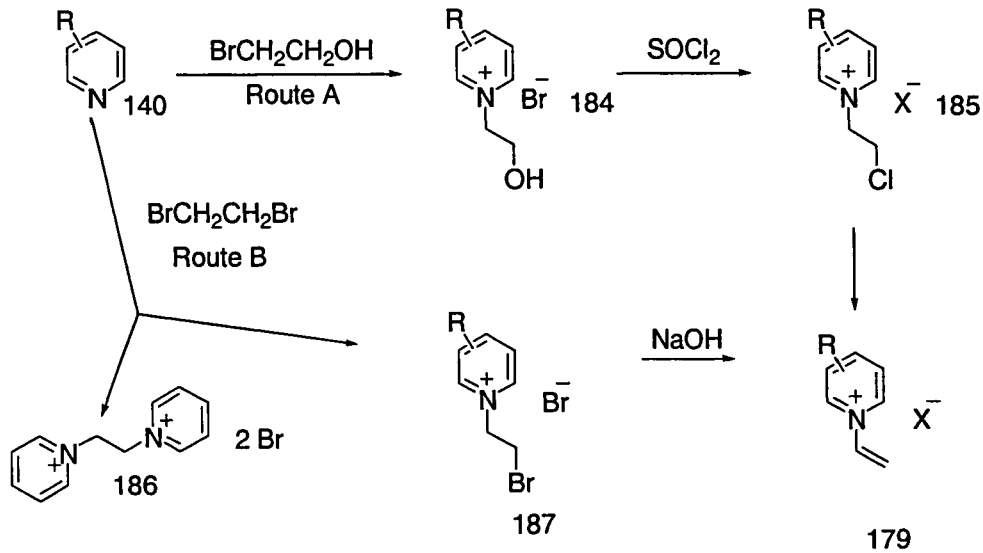
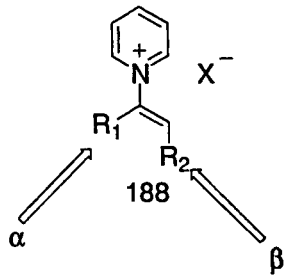


Figure 75

3.2 Synthesis of *N*-vinylpyridinium salts

The aim of this area of work was to synthesize various vinylpyridinium salts utilizing both routes A[160] and B[156]. From ***Figure 76***, it can be seen that

substitutions can occur either at the α or β position. This would allow a broad range of chemistry to be investigated. The aim of this project is to use the *N*-vinyl group or the dienyl groups for cycloaddition reactions to build rings onto the pyridinium ring, which again ultimately could be cleaved to reveal an amino group. ***See Figure 77.*** It was hoped that once reactions conditions were optimized in solution phase, the methods could then be transferred to solid phase.



Substitutions can occur at both these positions.

Figure 76

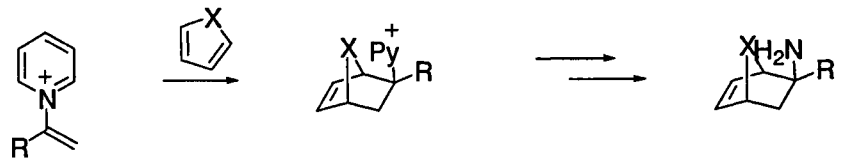


Figure 77

Our efforts started with the synthesis of a simple unsubstituted pyridinium bromide salt, **187**. ***See Figure 78.***

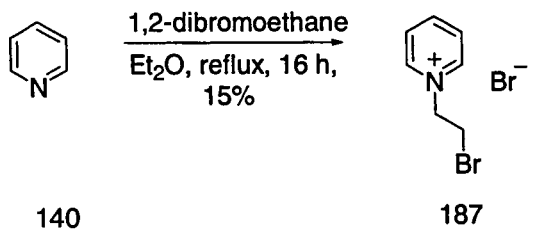
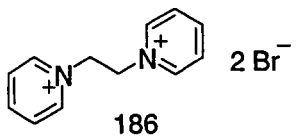


Figure 78

Equal amounts of pyridine and 1,2-dibromoethane were dissolved in Et_2O and refluxed for 16 h. This was chosen as the solvent to encourage the salt to precipitate out of solution. In fact, a whitish-pinkish salt was obtained in 15% yield. Analysis by ^1H NMR spectroscopy showed it to be the desired product, as two

triplets were present at 4.16 and 5.15 ppm, representing the methylene groups on the molecule. The formation of the correct product was confirmed by melting point analysis. The filtrate showed the presence of starting materials.

The reaction was carried out again. This time the mixture was refluxed for a further 32 h (48 h in total) to improve the yield. A salt was obtained in 48% yield. Analysis by ^{1}H NMR spectroscopy showed a *bis*-pyridinium compound **186** was formed. Compound **187** was present in 5% yield, however the two salts were found to be difficult to separate. ***See Figure 79.***



186

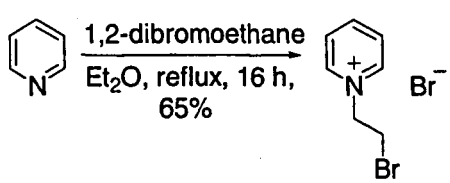
Figure 79

This was confirmed by ^{1}H NMR spectroscopy, which showed a singlet peak at 5.36 ppm corresponding to the two equivalent methylene groups situated adjacent to the pyridine nitrogens. We believe that one end of the 1,2-dibromoethane reacts with the pyridine molecule, the carbon atom adjacent to the pyridine molecule displays more cationic behaviour, i.e., it is more electrophilic. Thus it is likely that another pyridine molecule will attack the terminal carbon still bearing a bromine atom, thus forming the *bis*-pyridinium salt. To avoid this problem, we increased the proportion of 1,2-dibromoethane in the reaction, decreasing the chances of the *bis*-pyridinium salt being formed. Different solvents were also studied. ***Table 16*** shows the conditions studied for this reaction:

Reaction	Ratio of Pyridine/ $BrCH_2CH_2Br$ used	Solvent	Results
78a	1:1	PhMe	70% **186** isolated. 20% **187** isolated.
78b	1:1	DCM	48% **186** isolated. 5% **187** isolated.
78c	1:2	Et_2O	55% **186** isolated. 10% **187** isolated.
78d	1:5	Et_2O	35% **186** isolated. 5% **187** isolated.

Table 16

From these results it can be seen that the major product formed was compound **186**. Compound **187** was formed in low yields. This was confirmed using ^1H NMR, ^{13}C NMR and mass spectrometry.



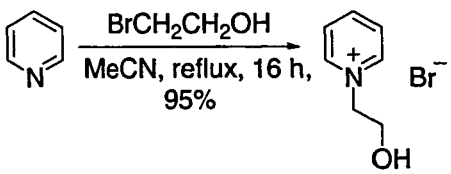
140 187

Figure 80

It was decided to attempt the reaction again but use a large excess of 1,2-dibromoethane to which the pyridine was added slowly. ***See Figure 80.*** The lower the amount of pyridine in the reaction mixture, the better the chances of the

desired salt forming and precipitating out of solution. 10 Equivalents of 1,2-bromoethane in Et_2O were used in the first instance. To this a solution of pyridine, also in Et_2O was added drop wise over 6 h. On completion of the reaction, a white solid was isolated in 65%. Analysis by ^1H NMR and ^{13}C NMR spectroscopy showed the desired material, which was confirmed by melting point analysis and elemental analysis. LC- MS analysis showed the presence of the pyridinium parent ion, seen at m/z values of 185 and 187, due to the bromine isotopes. The next step in the sequence was to study the synthesis of 1-(vinyl)pyridinium bromide, **179**.

The second synthetic route was also investigated, which would eventually lead to the synthesis of the unsubstituted vinylpyridinium salt. ***See Figure 81.***



140 184

Figure 81

Using the method of Crane and Fuoss[160], equimolar amounts of pyridine and 2-bromoethanol were refluxed in MeCN. This was carried out over a period of about 16 h. On completion of the reaction, drops of Et_2O were added to the MeCN mixture to promote precipitation. A white solid was obtained in 95% yield. ^1H NMR, ^{13}C NMR, IR and Mass spectroscopy confirmed this to be the correct material. Compared to the first method, which used 1,2-dibromoethane, this method was found to work well using equimolar amounts of reagents, as the hydroxyl moiety is a poor leaving group, thus preventing the formation of the *bis*-pyridinium salt. The next step was to convert the hydroxyl group to chlorine to introduce a good leaving group for the formation of the desired vinyl group. ***Figure 82 and 83*** shows the reaction and mechanism:

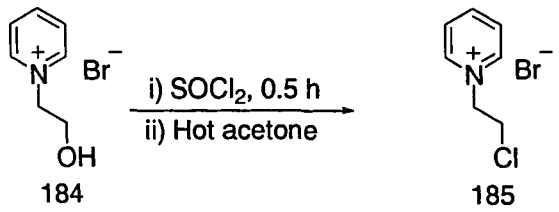


Figure 82

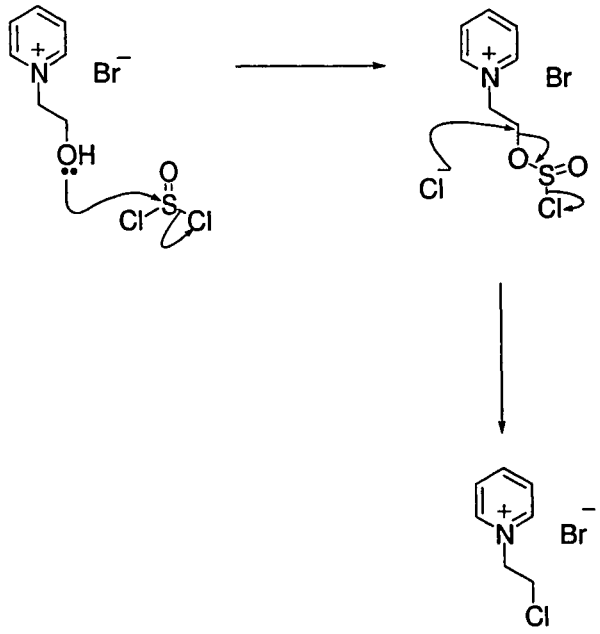
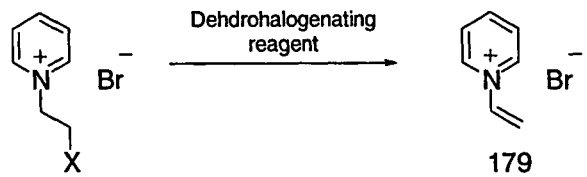


Figure 83

The mechanism is as follows: the lone pairs of hydroxyl group attack the nucleophilic sulphur of $SOCl_2$, causing a chloride group to leave. The other chloride group attached to the sulfur could attack carbon adjacent to the oxygen, causing SO_2 to be eliminated. Initial attempts at the reaction were carried out using the conditions as established by Katritzky[159]; an equimolar amount of neat $SOCl_2$ was added to compound **184** at 0 °C. After stirring the reaction mixture for 0.5 h, hot acetone was added to the mixture to encourage crystals to form. However on addition of the acetone to the mixture, an orange oily mixture was obtained. On analysis, this was shown to be a mixture and no evidence of the desired compound was found. Trituration of the oily material with Et_2O to promote precipitation was unsuccessful. The reaction was repeated using a large excess of $SOCl_2$, 500 equivalents to be exact. On addition of the hot acetone, yellow crystals were formed in 96% yield. On analysis with ^1H NMR spectroscopy, the desired material was found to have formed and this was confirmed using LC-MS.

This material was also found to be highly hygroscopic. Even though this reaction was successful on this occasion, the result could not be reproduced. Using an even bigger excess of $SOCl_2$ (> 1000 equivalents) also proved unsuccessful. Analysis of the material from these reactions showed the presence of a mixture of compounds. In comparison, the synthesis of compound **187** maintained reproducibility.

The next step in the sequence was to study the elimination reaction to form compound **179** using both the bromo- and chloro-ethyl pyridinium salts **187** and **185**. ***See Figure 84 and Table 17.***



X = Br, Cl

Figure 84

Reaction	X group	Dehyrdrohalogenating Reagent	Solvent Used	Temp/ °C	Result
84a	Br	NaOH (10 M)	MeOH/ EtOH	-10	Intractable material obtained. Complicated NMR spectrum.
84b	Br	NaOH (10 M)	MeOH/ EtOH	-15	Intractable material obtained. Complicated NMR spectrum.
84c	Br	*Solid-supported base	EtOH	-15	31% **187** recovered
84d	Cl	NaOH (10 M)	MeOH/ EtOH	- 10	Intractable material obtained. Complicated NMR spectrum.
84e	Cl	NaOH (10 M)	MeOH/ EtOH	- 15	Intractable material obtained. Complicated NMR spectrum.

*Solid- supported base: TBD-methyl polystyrene resin.

Table 17

From the table above, it can be seen that all reaction conditions, which were attempted gained no successful results. Apart from reaction **84c**, methods used

were similar to that of Katritzky's[157], where the use of 10M NaOH was demonstrated, using a solvent mixture of EtOH/ MeOH. The reactions were also carried out low temperatures to prevent the process of polymerization. Each reaction gave a brown intractable material, which was difficult to purify. NMR studies showed no evidence of any desired material, as no alkene proton peaks were present around 5-6 ppm, although pyridinium peaks were observed between 8-9 ppm. Reaction **84c** employed the use of a solid-supported base TBD-methyl polystyrene resin. It was hoped that the by-product of the base would be attached to the base, leaving the desired compound in solution. In this case, only starting material was observed by NMR analysis.

From the results obtained, it was found that the attempted synthesis of **179** was found to be extremely problematic. It is unclear as to why the formation of the final pyridinium salts was not possible using the methods studied and also the fact that Katritzky's results were not reproducible.

The next aspect of the work was to investigate alkylation of pyridine with groups having potential for conversion to dienyl substituents capable of undergoing cycloaddition reactions to construct rings on the pyridine ring. ***See Figure 85.***

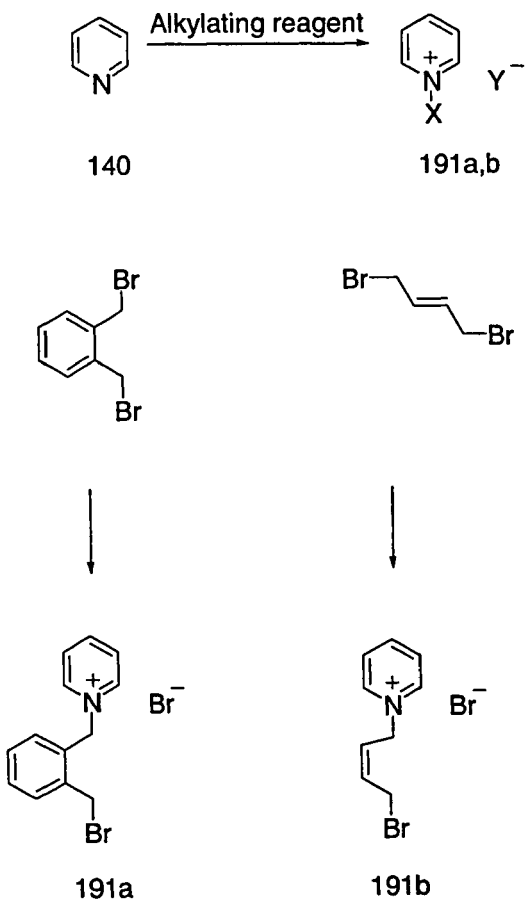


Figure 85

Two alkylating reagents were studied, xylylene dibromide[161] and 1,4-dibromo-2-butene[162]. These were both chosen due to the fact that an alkene bond could be set up in the molecule once dehydrohalogenation was carried out. ***Figure 86*** shows what the expected products would be before and after this step.

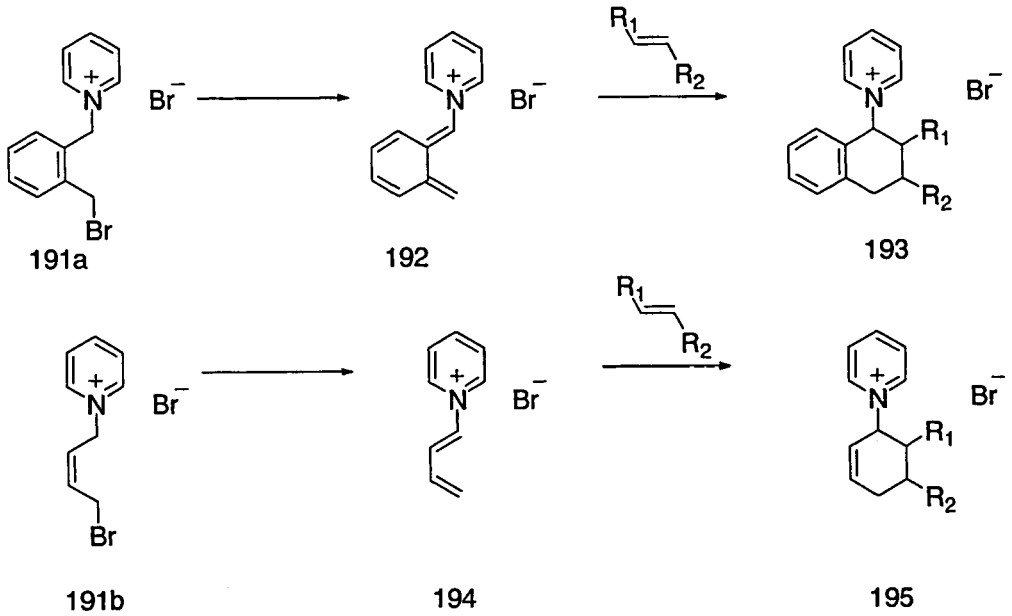


Figure 86

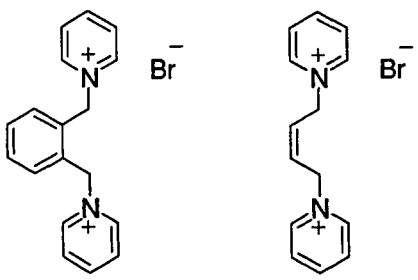
Dehydrohalogenation would allow a diene to be set up within both molecules. This would enable us to study a number of reactions such as Diels-Alder to synthesize fused ring compounds.

Pyridine was alkylated using these reagents under a number of reaction conditions. ***Table 18*** summarizes the reactions studied.

Reaction	Salt synthesized	Ratio of Pyridine/ Alkylating reagent Used	Time/ h	Temp/ °C	Result
86a	191a	1:1	8	RT	40% **196**
86b	191a	1:2	16	Reflux	61% **196**
86c	191a	2:1	16	Reflux	75% **196**
86d	191b	1:1	18	RT	80% **197**
86e	191b	1:2	16	Reflux	71% **197**
86f	191b	2:1	16	Reflux	76% **197**

Table 18

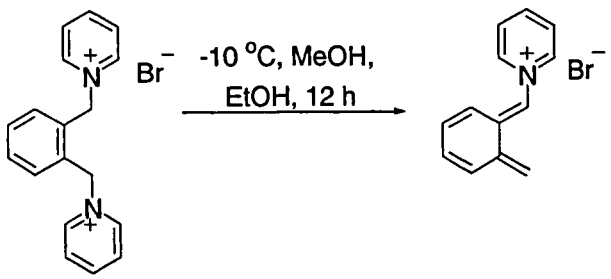
In each case, the *bis*-pyridinium salts were formed. This was the conclusion of the authors who had previously attempted to synthesize these salts. ***See Figure 87.*** It was hope that adjusting conditions, the desired compounds could be synthesized. Two further reactions were attempted, in which large excesses of each alkylating reagent was used. In both these cases also, no evidence was seen to suggest the desired material had been formed.



196 197

Figure 87

The synthesis of the vinyl pyridinium salt was attempted of the *bis*-salt, **196**, to see whether the pyridinium group could be eliminated to obtain the dienyl salt. This was carried out using conditions established by Katritzky[157]. ***See Figure 88.***

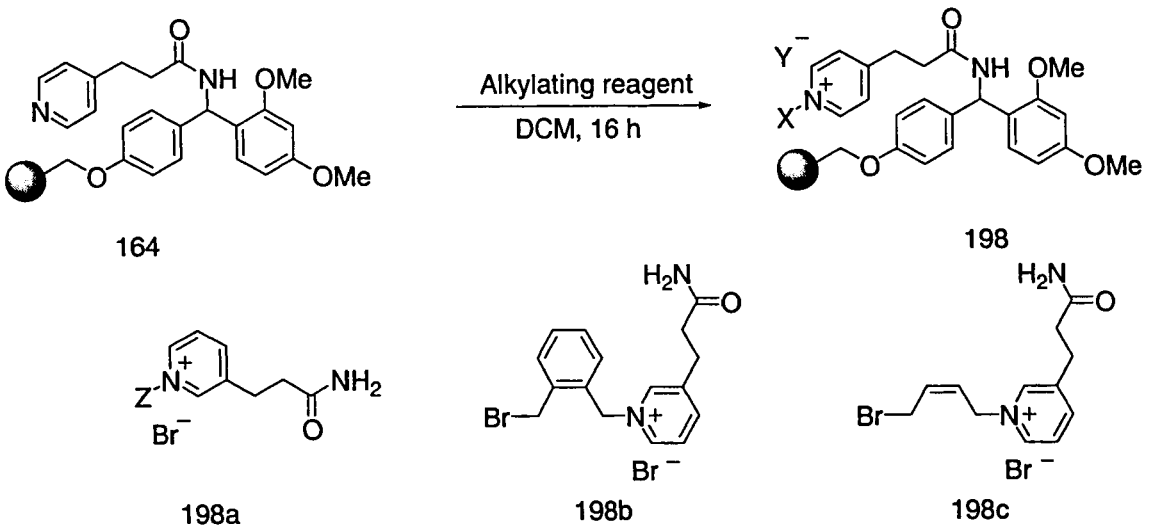


197 192

Figure 88

A black intractable oily material was isolated and analysis suggested that no vinyl pyridinium compound was present.

The final step in the investigation of these salts led us to attempt the alkylation reactions on our pyridine linker resin, **164**. It is known that alkylations have been successful using 1,2-dibromoethane on pyridine in solution phase, but could the application of 1,2-dibromoethane, xylylene dibromide and 1,4-dibromo-but-2-ene to alkylate the pyridine linker resin prove successful? It was considered that this should be an easier process, since the *bis*- salt should not form due to the pyridine molecule being attached to the resin, unless two pyridine groups were fortuitously held closely in space and in the correct orientation to both react with the dibromide molecule. ***See Figure 89.***

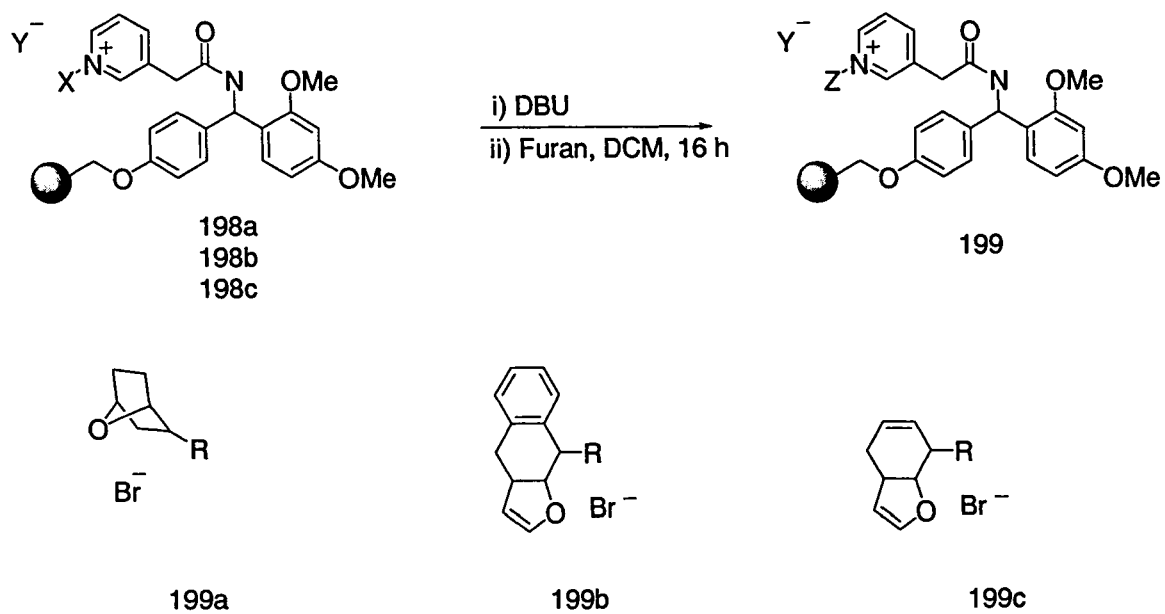


164 198

198a 198b 198c

Figure 89

On cleaving the analytical portion for analysis with TFA, LC-MS gave the m/z values for the compounds cleaved from the resin. It was decided to attempt to attempt the dehydrohalogenation reactions on each of these resins to synthesize the vinyl pyridinium salts. This was also combined with the next stage to carry out reaction across the vinyl bond. ***See Figure 90.***



198a
198b
198c

199

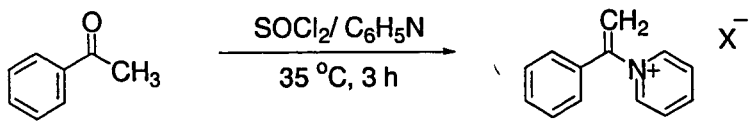
199a 199b 199c

Figure 90

DBU was used to carry out the dehydrohalogenation reaction and furan was used to study reactions across the double bond. Analysis by LC- MS found no evidence of the desired products. The reactions were repeated using large excesses of each reagent and again no evidence was seen of the desired material.

3.3 Synthesis of aryl-vinyl pyridinium salts

Another aspect of this area which was investigated was vinylpyridinium salts with substitutions at the α and β positions. Our research led into an investigation of arylvinylpyridinium salts. Relles[163] had reported the synthesis of 1-(1-arylvinyl)pyridinium salts. This was carried out using pyridine, acetophenone and $SOCl_2$. A drawback of this synthesis was that pyridine derivatives could not be used for the synthesis of these salts, as certain functional groups are sensitive to $SOCl_2$. These groups include NH_2, OH and CO_2R. ***See Figure 91.***

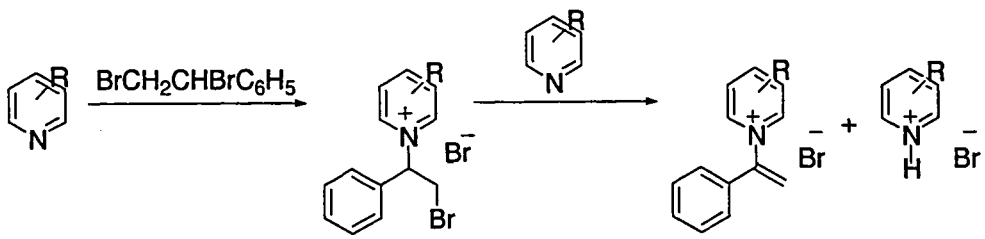


200 201

201a X = Cl
201b X = BF_4
201c X = I

Figure 91

In 1999 Eicher-Lorka[164] *et al*, ***see Figure 92*** reported a new efficient synthesis, which would allow the use of pyridine derivatives. It was based on the reaction of 1,2- dibromo-1-phenylethane with pyridine derivatives. The pyridine derivatives also acted as the dehydrohalogenating reagent. They found that electron-donating groups on the pyridinium ring accelerated the reaction rate, whilst electron-withdrawing groups caused a reduction in the rate.



140 202 203 204

R = H, *p*-CH_3, *m*-CH_3, *p*-$CH_2C_6H_5$, *m*-$CH_2C_6H_5$, *p*-COC_6H_5

Figure 92

Our efforts led us to the study of the synthesis of 1-(1-phenylvinyl)pyridinium salt. This began with the synthesis of the starting material, 1,2-dibromo-1-phenylethane, using the method of Singleton and Kochi[165]. ***See Figure 93.***

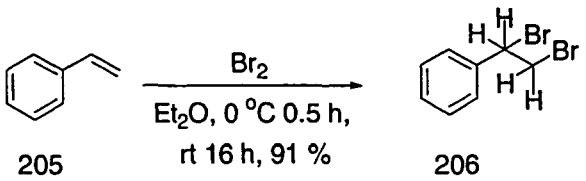


Figure 93

Compound **206** was synthesized in excellent yield, typically >90%. This was used in the next reaction to attempt the synthesis of compound **203**. ***Figure 94*** and ***Table 19*** shows the reaction scheme and the conditions studied.

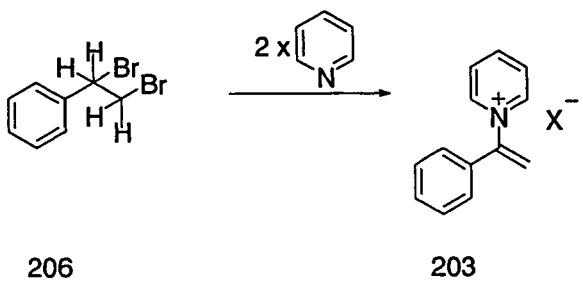


Figure 94

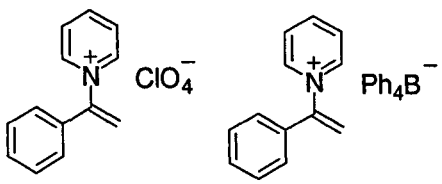
Reaction	Solvent	Temp/ °C	Time/ h	Yield/ %
94a	MeCN	Reflux	6	Mixture obtained
94b	Pyridine (100 eq.)	Reflux	6	10: 1 **204** and **203b**
94c	Pyridine (100 eq.)	Reflux, RT	1.5 h, 12 h	61- 76 **203a** and **203b**

Table 19

Various reaction conditions were studied. We found that the original conditions, refluxing the starting materials in MeCN used to synthesize the arylpyridinium salts were unsuccessful. It is not clear why. Reactions **94b** and **94c** showed the

presence of two products, the desired product **203** and the pyridinium bromide salt, **204**.

Products **204** and **203** were obtained in a 10:1 ratio. In these cases, the desired material was formed as the minor product. The reaction conditions used in 94c were found to give yields between 61-76%. It is also worth mentioning that pyridine was not used to carry out the dehydrohalogenation reaction as in the three previous attempts. The reaction was carried out in pyridine, which acted as the solvent and reaction material. On completion of this step, excess pyridine was removed and poly(4-vinyl)pyridine was used as the dehydrohalogenating reagent. The intermediate **202** was not isolated in any of the reactions carried out. As two salts are formed in the reaction, this would ensure that the pyridinium bromide would form on the resin pyridine molecules. This could then be separated easily by filtration and ion-exchange of the bromide salt would prove to be an easier process. The yields given in reaction **94c** were salts isolated as chlorate using perchloric acid and tetraphenylborate salts using sodium tetraphenylborate, ***Figure 95***, as the bromide salt was found to be difficult to isolate from the by-products. This was encountered in reaction **93a**, in which NMR studies showed the presence on the desired product, but it was found to be difficult to isolate. Eventually, we decide to use tetraphenylborate salts in our further reactions as chlorate salts have been reported to be explosive, thus would not be suitable.



203a 203b

Figure 95

We investigated the structure of compound **203b** further. Single crystal X-ray diffraction showed the phenyl ring is co-planar with the double bond and the pyridinium ring is twisted out of plane. The dihedral angle is found to be 113°. ***Figure 96*** shows the structure of the salt and the relative positions of the cation and anion.

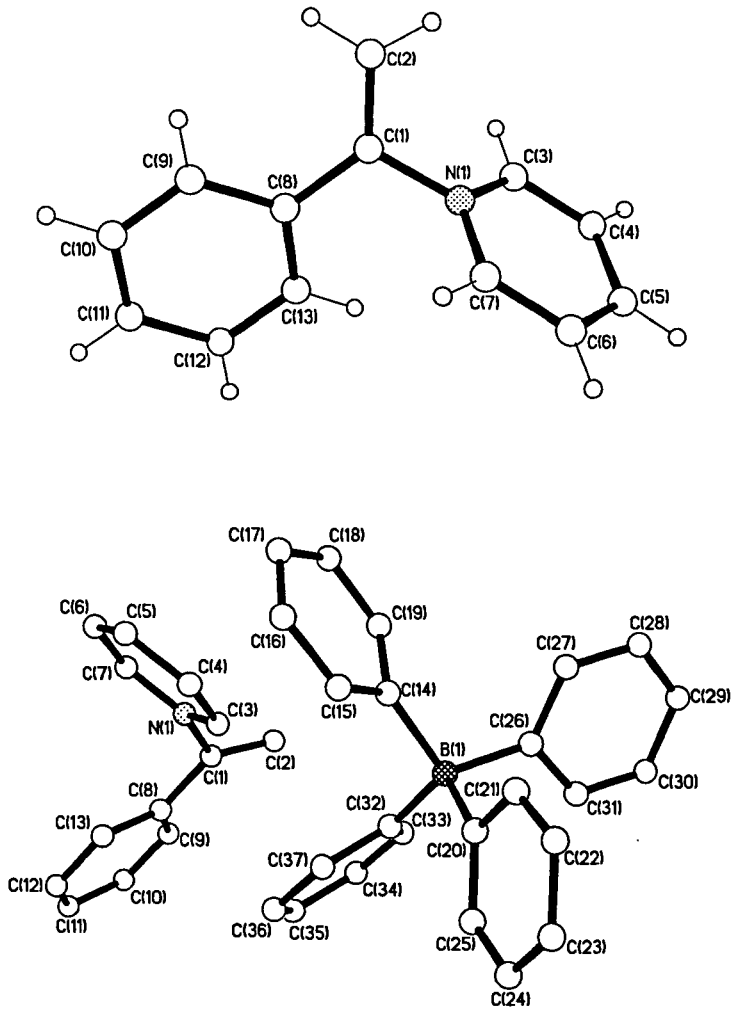
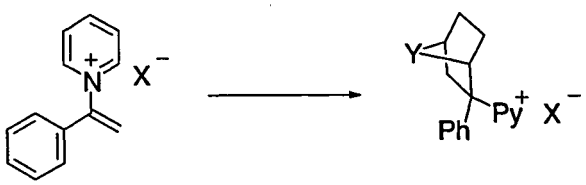


Figure 96

The next step was to study the reactions of the vinyl bond in compound **203b**. It was hoped that it would undergo cycloaddition reactions, namely Diels-Alder, with a variety of dienes to construct rings on the pyridinium ring. This was approached in two ways, using traditional chemistry and the use of microwave chemistry.

Our initial attempts began with the use of traditional Diels-Alder chemistry. We studied the use of three different compounds, furan, thiophene and 1-methyl pyrrole, which would act as dienes, whereas compound **203b** would act as a dienophile to form bridge-head ring structures via a Diels-Alder reaction. ***See Figure 97***. ***Table 20*** shows the reaction conditions used. It can be seen that no success was gained from the conditions studied. In each case, only starting material was isolated. Analysis was carried out using LC-MS and in each reaction

studied, aliquots were taken to carry out analysis during each experiment. It is not clear as to why these reactions were unsuccessful, but it could be due to steric hindrance owing to the two bulky ring groups on the molecule.



203a/ b

Figure 97

Reaction	Salt used	Diene used	Temp/ °C	Time/ h	Solvent	Yield
97a	ClO_4^-	Furan (10 eq.)	RT	16	MeOH	71% **203a** recovered
97b	ClO_4^-	Thiophene (10 eq.)	RT	16	MeOH	73% **203a** recovered
97c	Ph_4B^-	Furan (1 eq.)	RT	20	DCM	90% **203b** recovered
97d	Ph_4B^-	Furan (1 eq.)	RT	20	2:1 DCM: MeCN	95% **203b** recovered
97e	Ph_4B^-	Furan	RT	5 days	-	90% **203b** recovered
97f	Ph_4B^-	1-Methyl pyrrole	90	24	MeCN	75 % **203b** recovered

Table 20

We decided to employ the use of microwave irradiation to try to promote these cyclizations. ***See Table 21*** for the conditions studied.

Reaction	Solvent	Pressure/ bar	Temp/ °C	Result
97g	-	7-12	100-120	85% **203b** recovered
97h	DCM	7-12	100-120	71% **203b** recovered
97i	NMP	7-12	180	90% **203b** recovered

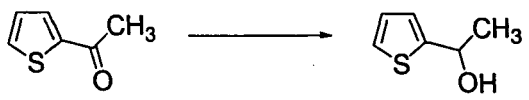
Table 21

Using NMR spectroscopy and LC-MS studies, it was observed that no desired product was formed. It was hoped that the use of these extreme temperatures and pressures would push the reactions to completion, but this was not the case. Again, the bulkiness of the two ring groups may have prevented any reaction from happening, thus decreasing the size of the α-substituent may help to complete this stage of the synthetic sequence.

The synthesis of aryl-vinylpyridinium salts has been successfully demonstrated and the salts identified. We have investigated cycloaddition reactions, particularly Diels-Alder reactions on the vinyl substituent. At present we have shown that the reactions attempted did not furnish successful results.

It has been decided to look at another aromatic substituent thiophene, which could be situated at the α-position. This would provide an interesting group of bicyclic compounds, which could be eventually cleaved from the pyridinium ring to release amine compounds.

The synthesis of the intermediate 2-vinylthiophene was the starting point for this investigation. This compound is not commercially available, so we devised a synthetic route. We started with the commercially available 2-acetylthiophene. The carbonyl group was reduced to the hydroxyl group, using a number of different reaction conditions to see which would be the most suitable. ***See Figure 98.***



200 205

Figure 98

Reaction	Reducing agent	Solvent	Temp/ °C	Time/ h	Yield/ %
98a	$NaBH_4$	MeOH	RT	2	90% **200**
98b	$NaBH_4$	MeOH	RT	48	78% **205**
98c	$NaBH_4$	MeOH	RT	72	88% **205**
98d	$LiAlH_4$	THF	RT	12	72% **205**

Table 22

The desired alcohol was obtained using either $NaBH_4$ or $LiAlH_4$. Compound **205** was obtained in excellent yields using both these reducing agents, although reaction **98a**, which employed the use of $NaBH_4$ recovered 90% starting material. This could be due to short reaction time used. This was confirmed with the subsequent reactions, which used longer reaction times. Yields of 78 and 88% were obtained. Analysis was carried out using NMR and mass spectroscopy studies. This method was found to be simpler than reported in literature, where the conversion of **200** was carried via a Grignard reaction[166]. The next step was to synthesize 2-vinylthiophene via a dehydration process. ***See Figure 99.***

205 206

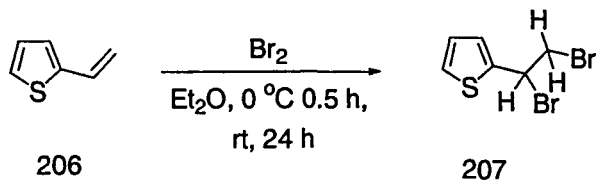
Figure 99

Reaction	Dehydration Reagent	Solvent	Temp/ °C	Time/ min.	Yield/ %
99a	TFA	DCM	0	3	> 100
99b	$BF_3.Et_2O$	THF	0	3	-
99c	Alumina	-	250-300	30	45% **206**

Table 23

A number of reaction conditions were investigated. Reaction **99a** was carried out using TFA as the dehydrating reagent. A solid was isolated and analyzed using ^1H NMR spectroscopy. The spectrum exhibited broad peaks at 1.56-1.72 ppm. This seem to suggest that polymerization of the vinyl thiophene compound has taken place. The melting point of the solid was found to be >350 °C, which is consistent with polymeric materials. The use of the Lewis acid $BF_3.Et_2O$ also gave a polymeric material. The method, which was found to be successful, was the use of alumina as the dehydrating reagent. Compound **205** was adsorbed onto a large amount of alumina. This was then heated to 250-350 °C and an oily liquid was collected by distillation, which was found to be desired material. The compound was isolated in 45% yield.

The next stage was the synthesis of 2-(1,2-dibromoethyl)thiophene, **207**. See ***Figure 100.***



206 207

Figure 100

This was attempted using the same conditions used to synthesize 1,2-dibromo-1-phenylethane. Bromine was added to compound **206**, using Et_2O as the reaction solvent. Analysis showed that the desired material had not been synthesized. The vinyl peaks of compound **206** had disappeared, however there was no evidence of the bromo compound. Further reaction conditions were investigated, whereby the reaction mixture was heated in Et_2O and again, no successful results were observed. In this case, a black intractable material was obtained, which

could not be positively identified. As the desired dibromoethyl thiophene could not be obtained, this prevented the further investigation into the reaction with pyridine.

4 Conclusion

4.1 Summary and Future work

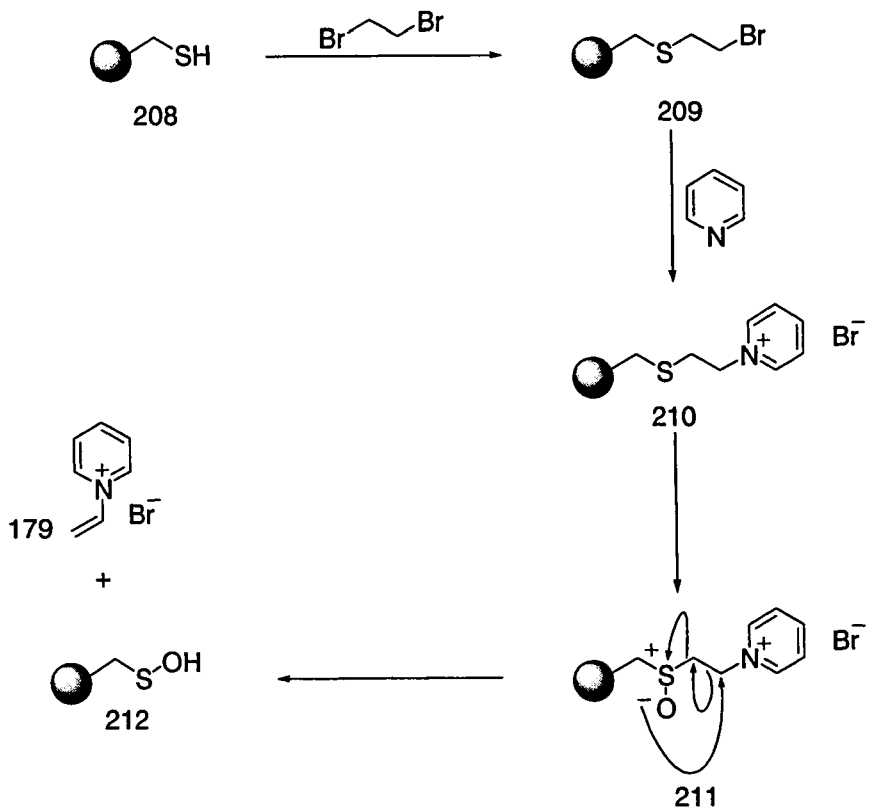
We have demonstrated the use of pyridine as a potential linker on which solid phase reactions can be carried out. The attachment of vinyl pyridine to Merrifield resins forming compounds **137** and **139** was successful. We demonstrated that simple alkylation reactions, benzylic halides and α-halocarbonyl compounds could be carried out easily. With these alkylated resins, we studied cyclization reactions, where these initial adducts were used to build heterocyclic ring structures such as quinolines by utilizing the acidity of the methylene group adjacent to the pyridinium nitrogen atom. These types of reactions were also studied in solution phase and it was demonstrated that these reactions were successful. The solid phase reactions showed little signs of success. Analysis of the Merrifield resins was found to be troublesome, this being a distinct disadvantage of conventional solid phase chemistry.

The use of Fmoc Rink amide resin was found to be better, as this allowed a method of analyzing the resin during a reaction sequence. The use of the 'pre' linker resin was found to be an effective way of analyzing the resin. This was clearly demonstrated by the alkylation of this solid support using several aliphatic, benzylic and α-halo carbonyl compounds. We investigated cyclization reactions on the Fmoc Rink amide resin. LC-MS studies showed the presence of a quinoline derivative formed in a condensation reaction, together with an uncyclized intermediate. A more thorough investigation needs to be carried out, whereby cyclization reagents to build a range of ring structures on the resin are investigated.

A variety of amine nucleophiles were studied to cleave open the pyridinium ring to allow the release of amino substituted products into solution. Dimethylamine was found to be a suitable reagent in initial studies. This compound also had the advantage due to the fact that it is highly volatile, thus the excess reagent could be removed from the solution easily. These reactions should be studied further.

Our efforts into the synthesis of vinyl pyridinium salts saw the successful synthesis of a phenyl vinyl pyridinium adduct, and single crystal X-ray diffraction showed the solid state conformation of the molecule. Diels-Alder reactions were investigated on the vinyl bond and at present, no successful cycloadditions were obtained. Further investigation of this would be desirable, whereby different substituents could be investigated at the α- positions, i.e., alkyl substituents.

The use of a solid supported pyridiniumyl ethyl sulfoxide to form vinyl pyridinium salts through an elimination process, which would release the product into solution has been considered. ***Figure 101*** shows the mechanism of this process.



5 Experimental

Solvent purification:

All the reactions herein were carried out in one of the following solvents, which were dried or purified in the following procedures.

Acetonitrile	Purchased from Aldrich in an anhydrous sure seal bottle.
Dichloromethane	For general use, CH_2Cl_2 was distilled over phosphorus pentoxide or calcium hydride for anhydrous solvent.
Diethyl ether	Purchased from Fisher Scientific and used without further purification for general use.
Dimethylformamide	Purchased from Aldrich in an anhydrous sure seal bottle.
Ethyl acetate	Distilled over calcium hydride for general use.
Light Petroleum	For general use, the solvent was distilled over fused calcium chloride, collecting the fraction boiling below 60 °C.
Methanol	Purchased from Fisher Scientific and used without further purification for general use.
Tetrahydrofuran	Distilled over sodium and benzophenone.

Analysis of the compounds herein was made using a number of the following instruments and the procedures indicated below.

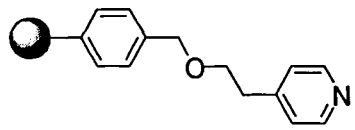
Melting points were taken on a Sheet Scientific SMP 3 melting point machine, and are uncorrected. Elemental analysis was carried out on a Perkin Elmer Elemental Analyser 2400 CHN machine. High-resolution mass spectrometry was carried out on a Jeol SX 102 machine, used for both electron ionisation (EI) and fast atom bombardment (FAB) ionisation techniques. Data was recorded to ± 3ppm. For FAB mass spectrometry, a matrix of 1,3-nitrobenzyl alcohol (NOBA) or octadecane was used to dissolve the compounds under investigation, prior to ionization. LC-MS analysis was carried out on a Platform LC-MS, ES machine. Nuclear magnetic resonance spectroscopy was performed using either a Bruker AC250 or Bruker DPX400 instrument. ^{1}H NMR spectroscopy was carried out using a field of 250.13 MHz and 400.13 MHz respectively. ^{13}C NMR was calibrated to the signals

of tetramethylsilane (TMS). NMR data are reported in ppm (δ). Deuterated solvents are as stated. Where possible signals are shown denoting their multiplicity, singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad signal (bs), etc. The size of the coupling constants (*J*) are displayed in Hertz (Hz). Coupling constants are quoted to 1 d.p. with an error of ± 0.5 Hz. In a number of cases dd signals are reported as apparent triplets, due to low resolution. Fourier Transform Infra Red spectroscopy was recorded using a Perkin Elmer 1600 series FTIR spectrometer and recorded in cm^{-1} (v).

All solid phase experiments were carried out using Alltech fritted tubes, using a flat bed shaker for shaking and a vacuum box for filtration, unless stated. The treated resins were washing using Procedure A, unless stated.

Procedure A: The treated resin was washed using the reaction solvent (3 x 10 ml) and Et_2O (3 x 10 ml), using one portion of each after the other, creating a 'sponge' effect.

Synthesis of Pyridine linker resin (137)

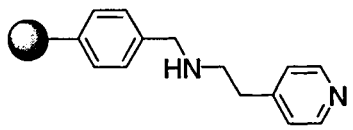


To hydroxymethylpolystyrene (100-200 mesh), 1% DVB resin (1.0 g; 0.82 mmol) was added anhydrous THF (5.0 ml). 20 s was allowed for the resin to swell. A further portion of THF (2.0 ml) was added. To the swelled resin was added LDA (2.0 M solution in heptane), (0.22 ml; 1.6 mmol). The resin was shaken at RT for 0.5 h. After this was completed, the excess reagent was removed by suction filtration and the resin was washed using anhydrous THF (3 x 2.0 ml). To the resin was added a portion of anhydrous THF (5 ml). 4-Vinylpyridine (0.44 ml; 4.1 mmol) was added to the resin and the mixture was shaken at RT for 0.5 h. After the reaction was completed, the excess reagent was removed under suction and the resin was washed thoroughly with portions of anhydrous THF (3 x 2.0 ml). The addition of both reagents was repeated a further two times. The treated resin was dried under vacuum for 0.5 h. Analysis was carried out using methanolic cobalt(II) chloride solution.

Loading calculated to be 0.29 mmol/g according to N content, N, 0.04%

Cobalt(II) chloride test (1.0 M): On addition of a few drops of methanolic cobalt(II) chloride solution to the treated resin, (0.5mg), the beads turned a blue colour. The reaction was deemed successful.

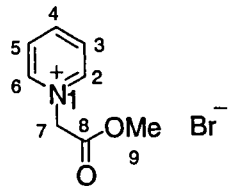
Synthesis of Pyridine Linker Resin (139)



To aminomethyl resin (0.50 g; 0.45 mmol) was added DCM (5.0 ml). 20 s were allowed for the resin to swell. A further portion of DCM (2.0 ml) was added to the resin. 4-Vinylpyridine (0.24 ml; 2.3 mmol) and glacial acetic acid (0.14 ml; 2.3 mmol) were added to the reaction mixture. The reaction mixture was refluxed for 4 h. Once this was completed, the excess reagents were removed under suction filtration. The resin was washed using washing **Procedure A**. After drying the resin under vacuum for 0.5 h, the treated resin was initially analyzed using methanolic cobalt(II) chloride solution.

Cobalt(II) chloride test: On addition of a few drops of methanolic cobalt(II) chloride solution to the treated resin, (0.5mg), the beads turned a blue colour. The reaction was deemed successful.

Synthesis of 1-methoxycarbonylmethylpyridinium bromide[139] (141a)



To pyridine (1.6 ml; 20.0 mmol) was added PhMe (10.0 ml). To this was added methyl bromoacetate (1.7 ml; 20.0 mmol). The reaction mixture was refluxed for 0.5 h. A precipitate was formed during this time. Once the reaction was completed, the reaction mixture was cooled and the solid was filtered under suction. Recrystallization was carried out using hot C_2H_5OH (2.0 ml) and scratching caused crystals to form. The crystals were filtered and dried under vacuum for 1 h to yield white crystals (3.58 g; 77%)

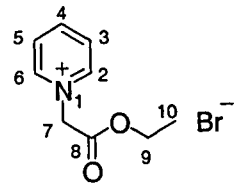
(**m.p:** 133-135 °C; lit. value[139]: 135-137 °C).

(Found m/z 185.99. $C_8H_{10}NO_2$ requires M^+ 185.99).

δ_H (250 MHz; $CDCl_3$): 3.35 (3H, s, H-9), 5.74 (2H, s, H-7), 8.29 (2H, apparent t, apparent *J* 6.7, H-3, 5), 8.80 (1H, t, *J* 7.5, H-4), 9.10 (2H, d, *J* 5.8, H-2, 6).

IR (Nujol) v/ cm-1: 1748 (-C=O).

Synthesis of 1-ethoxycarbonylmethylpyridinium bromide[140] (141b)



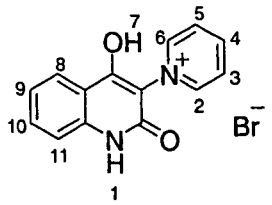
To a solution of pyridine (3.2 ml; 40.0 mmol) in PhMe (20.0 ml) was added methyl bromoacetate (4.4 ml; 40.0 mmol). The reaction mixture was refluxed for 0.5 h. A precipitate was formed during this time. Once the reaction was completed, the reaction mixture was cooled and the solid was filtered under suction. Recrystallization was carried out using hot EtOH (2.0 ml) and trituration caused crystals to form. The crystals were filtered and dried under vacuum for 1 h to yield white crystals (7.54 g; 77%)

(**m.p:** 136-138 °C; lit. value[140]: 136-138 °C)

δ_H (250 MHz; $CDCl_3$): 1.28 (3H, t, *J* 7.2, H-10), 4.25 (2H, q, *J* 7.2, H-9), 6.32 (2H, s, H-7), 8.09 (2H, apparent t, apparent *J* 7.6, H-3, 5), 8.54 (1H, t, *J* 7.6, H-4), 9.50 (2H, d, *J* 5.8, H-2, 6).

IR (Nujol) ν/ cm-1: 1756 (-C=O)

Synthesis of 1-(4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)pyridinium bromide[141] (143)



Compound **141a** (0.76 g; 3.0 mmol) was dissolved in MeCN (30.0 ml). Once the solid had dissolved, Et_3N (0.91 ml; 9.0 mmol) and isatoic anhydride (1.63 g; 9.0 mmol) were added and the reaction mixture was refluxed for 1 h. During this time, a precipitate formed in the solution. Once the reaction was completed, the solid was filtered under suction and the solid was washed with portions of diethyl ether (3 x 5.0 ml). On drying under vacuum, a yellow solid was isolated, (0.94 g; 99%).

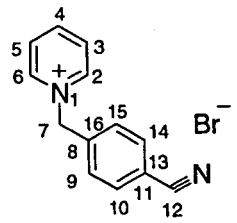
(**m.p:** 233-235 °C; lit. value[141]: 230-232 °C).

(Found m/z 238.99. $C_{11}H_9N_2O_2$ requires M^+ 239.25).

δ_H (250 MHz; $CDCl_3$): 7.04 (1H, apparent t, apparent *J* 7.4, H-9), 7.17 (1H, d, *J* 8.3, H-8), 7.26 (1H, apparent t, apparent *J* 5.1 H-10), 7.76 (1H, d, *J* 7.4, H-11), 8.07 (2H, apparent t, apparent *J* 6.9, H-3, 5), 8.47 (1H, t, *J* 5.4, H-4), 8.96 (2H, d, *J* 6.0, H-2, 6), 10.56 (1H, s, -NH).

IR (Nujol) v/ cm^{-1}: 3448 (-OH).

Synthesis of 1-[(4-cyanophenyl)methyl]pyridinium bromide[142] (144a)



To pyridine (0.40 ml; 5.0 mmol) was added PhMe (15.0 ml). To this was added 4-cyanobenzyl bromide (0.98 g; 5.0 mmol). The reaction mixture was refluxed for 0.5 h. A precipitate was formed during this time. Once the reaction was completed, the reaction mixture was cooled and the solid was filtered under suction and washed using portions of Et_2O (3 x 5.0 ml). After drying under vacuum for 1 h, a white solid was isolated (2.25 g; 82%).

(**m.p:** 136-138 °C; lit. value[142]: 138-140 °C)

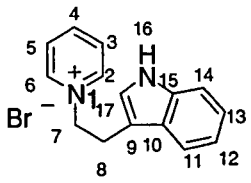
(Found: C, 56.6; H, 4.2; N, 10.5. $C_{13}H_{11}N_2Br$ requires C, 56.8; H, 4.0; N, 10.2 %)

δ_H (250 MHz; DMSO): 6.02 (2H, s, H-7), 7.73 (2H, d, *J* 8.1, H-10, 14), 7.96 (2H, d, *J* 8.1, H-9, 15), 8.23 (2H, apparent t, apparent *J* 7.6, H-3, 5), 8.68 (1H, t, *J* 7.9, H-4), 9.27 (2H, d, *J* 5.8, H-2, 6).

δ_C (100 MHz; DMSO): 62.09, 111.92, 118.20, 128.50, 129.63 132.95, 139.28, 145.03, 146.22.

IR (Nujol) ν/ cm^{-1}: 2230 (-CN).

Synthesis of 1-[2-(indol-3-yl)ethyl]pyridinium bromide[143] (144b)

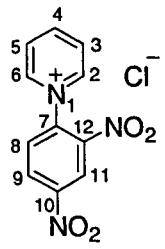


To pyridine (0.81 µml; 1.0 mmol) was added Et_2O (5.0 ml). To this was added 3-(2-bromoethyl)indole (0.22 g; 1.0 mmol). The reaction mixture was refluxed for 0.5 h. A precipitate was formed during this time. Once the reaction was completed, the reaction mixture was cooled and the solid was filtered under suction and washed using portions of Et_2O (3 x 5.0 ml). After drying under vacuum for 1 h, a yellow solid was isolated (0.24g; 80%).

δ_H (250 MHz; CD_3CN): 3.42 (2H, t, *J* 6.6 H-8), 4.83 (2H, t, *J* 6.6, H-7), 6.94 (1H, s, H-16), 7.03 (1H, t, *J* 7.9, H-13), 7.14 (1H, t, *J* 7.9, H-12), 7.43 (2H, m, H-11, 14), 7.86 (2H, apparent t, apparent *J* 6.9, H-3, 5), 8.39 (1H, t, *J* 7.9, H-4), 8.48 (2H, d, *J* 5.6, H-2, 6).

δ_C (100 MHz; CD_3CN): 27.3 (C-8), 62.5 (C-7), 107.2 (C-9), 111.7, 116.8, 119.3, 121.9, 123.8, 126.0, 127.6, 136.3, 144.1 (C-2, 6), 145.0 (C-4).

Synthesis of 1-(2,4-dinitrophenyl)pyridinium chloride (144d)



To pyridine (0.81; 10.0 mmol) in DCM (10 ml) was added 1-chloro-2,4-dinitrobenzene (2.0 g; 10.0 mmol). The reaction mixture was refluxed for 16 h, during which time a red solid precipitated out of solution. Once the reaction was complete, the solid was filtered under vacuum and washed with portions of Et_2O (3 x 5.0 ml) and after drying under vacuum for 1 h, a red solid was isolated, (0.31 g; 11%).

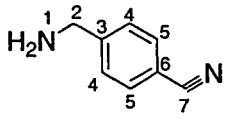
(Found: C, 46.7; H, 2.7; N, 14.7. $C_{11}H_8N_3O_4Cl$ requires C, 46.9; H, 2.9; N, 14.9 %)

(Found m/z 246.0513. $C_{11}H_8N_3O_4$ requires M^+ 246.0515); m/z: 185 (M+, 100 %).

δ_H (250 MHz; DMSO): 8.45-8.56 (3H, m, H-8, 9, 11), 8.99 (2H, apparent t, apparent *J* 7.4, H-3, 5), 9.12, (1H, t, *J* 8.0, H-4), 9.55 (2H, d, *J* 5.8, H-2, 6).

δ_C (100 MHz; DMSO): 121.28, 127.93, 130.10, 131.93, 138.64, 143.00, 146.02, 148.72, 148.96 (C-11).

Cleavage to 4-(aminomethyl)benzonitrile (147)



Compound **144a** (0.26 g; 1.0 mmol) was dissolved in EtOH (10.0 ml). Whilst stirring, $H_2NNH_2.H_2O$ (0.15 ml; 5.0 mmol) was added. The reaction mixture was refluxed for 4 h. After the reaction was completed, the solvent was removed under vacuum. The residue was extracted with Et_2O (3 x 50.0 ml). After drying with magnesium sulphate, the organic layer was reduced to isolate an orange oil, (0.06 g; 46 %).

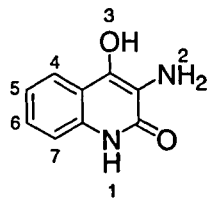
(Found m/z 132.17. $C_8H_8N_2$ requires M^+ 132.17).

δ_H (250 MHz; $CDCl_3$): 3.94 (2H, s, NH_2), 5.29 (2H, s, H-2), 7.43 (2H, d, *J* 8.0, H-4,), 7.61 (2H, d, *J* 8.0, H-5).

δ_C (100 MHz; $CDCl_3$): 45.95, 110.65, 118.95, 127.74, 132.36, 135.82.

IR (Nujol) v/ cm^{-1}: 2226 (-CN)

Synthesis of 3-amino-4-hydroxy-1*H*-quinolin-2-one[149] (149)



To compound **143** (0.31 g; 1.0 mmol) was added EtOH (15.0 ml). Whilst stirring, hydrazine hydrate (0.10 ml; 2.0 mmol) was added. The reaction mixture was refluxed for 4 h. All the starting material had dissolved and the reaction mixture turned a yellow colour. After the reaction was completed, the solvent and excess cleavage reagent was removed under suction filtration, to isolate a yellow solid, (0.09 g; 50 %).

(**m.p:** 117-119 °C; lit. value[149]: 114-116 °C).

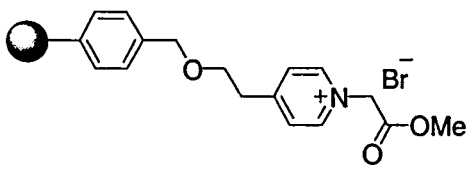
(Found m/z 176.50. $C_9H_8N_2O_2$ requires M^+ 176.22).

δ_H (250 MHz; DMSO): 4.37 (2H, s, NH_2), 6.48 (1H, apparent t, apparent *J* 6.1, H-5), 6.68 (1H, d, *J* 8.1, H-4), 7.12 (1H, apparent t, apparent *J* 7.6, H-6), 7.41 (1H, d, *J* 7.8, H-7), 9.46 (1H, s, H-1), no signal was observed for –OH peak.

δ_C (100 MHz; DMSO): 104.71, 121.15, 123.01, 126.92, 128.17, 135.77, 141.89, 164.01.

IR (Nujol) v/ cm^{-1}: 3440 (-OH)

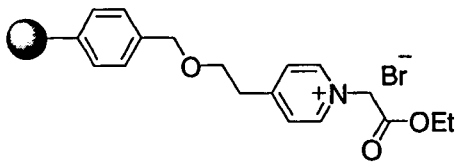
Alkylation of pyridine linker 137 with methyl bromoacetate (150a)



To resin **137** (0.25 g; 0.21 mmol) was added PhMe (10 ml). 20 s was allowed for the resin to swell. To the resin was added methyl bromoacetate (0.40 ml; 4.2 mmol). The reaction mixture was heated under reflux for 2 h. During this time, the resin turned a brown colour. After the reaction mixture was completed, the excess reagents were removed under suction. The resin was washed using **Procedure A**. After drying the resin for 1 h, the resin was analyzed using silver(I) nitrate solution.

Silver(I) nitrate test (1.0 M): On addition of a few drops of silver(I) nitrate solution to a few of the treated resin beads, which were suspended in a MeCN (1.0 ml), a cloudy precipitate formed in solution. The reaction was deemed successful.

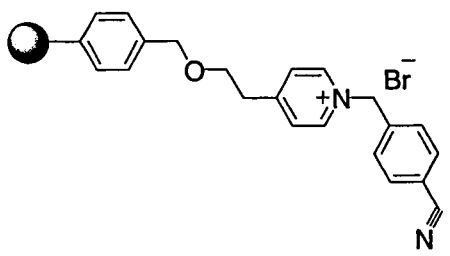
Alkylation of pyridine linker 137 with ethyl bromoacetate (150b)



To resin **137** (0.25 g; 0.21 mmol) was added PhMe (10.0 ml). 20 s was allowed for the resin to swell. To the resin was added ethyl bromoacetate (0.46 ml; 4.2 mmol). The reaction mixture was heated under reflux for 2 h. During this time, the resin turned a brown colour. After the reaction mixture was completed, the excess reagents were removed under suction. The resin was washed using **Procedure A**. After drying the resin for 1 h, the resin was analyzed using silver(I) nitrate solution.

Silver(I) nitrate test: On addition of a few drops of silver(I) nitrate solution to a few of the treated resin beads, which were suspended in a MeCN (1.0 ml), a cloudy precipitate formed in solution. The reaction was deemed successful.

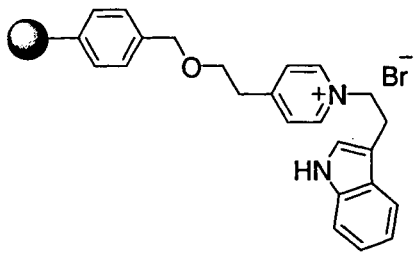
Alkylation of pyridine linker 137 with 4-cyanobenzyl bromide (150c)



To resin **137** (0.25 g; 0.21 mmol) was added THF (10.0 ml). 20 s was allowed for the resin to swell. To the resin was added 4-cyanobenzyl bromide (0.21 g; 1.1 mmol). The reaction mixture was heated under reflux for 3 h. During this time, the resin turned a brown colour. After the reaction mixture was completed, the excess reagents were removed under suction. The resin was washed using **Procedure A**. After drying the resin for 1 h, the resin was analyzed using silver(I) nitrate solution.

Silver(I) nitrate test: On addition of a few drops of silver(I) nitrate solution to a few of the treated resin beads, which were suspended in a MeCN (1 ml), a cloudy precipitate formed in solution. The reaction was deemed successful.

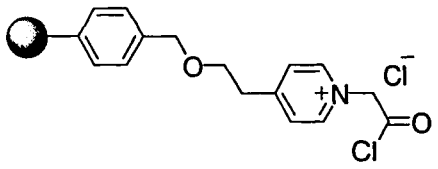
Alkylation of pyridine linker 137 with 3-(2-bromoethyl)indole (150d)



To resin **137** (0.25 g; 0.21 mmol) was added THF (10.0 ml). 20 s was allowed for the resin to swell. To the resin was added 3-(2-bromoethyl)indole (0.24 g; 1.1 mmol). The reaction mixture was heated under reflux for 3 h. During this time, the resin turned a brown colour. After the reaction mixture was completed, the excess reagents were removed under suction. The resin was washed using **Procedure A.** After drying the resin for 1 h, the resin was analyzed using silver(I) nitrate solution.

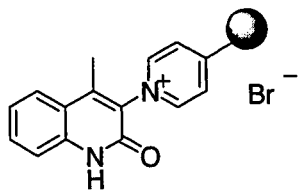
Silver(I) nitrate test: On addition of a few drops of silver(I) nitrate solution to a few of the treated resin beads, which were suspended in a MeCN (1 ml), a cloudy precipitate formed in solution. The reaction was deemed successful.

Alkylation of pyridine linker 137 with chloroacetyl chloride (150e)



To resin **137** (1.0 g; 0.82 mmol) was added anhydrous DCM (10.0 ml). 20 s was allowed for the resin to swell. To the resin was added chloroacetyl chloride (0.46 ml; 4.1 mmol). The reaction mixture was stirred at RT for 0.5 h. During this time, the resin turned a brown colour. After the reaction mixture was completed, the excess reagents were removed under suction. The resin was washed using procedure A. After drying the resin for 1 h under vacuum, the resin was utilized in the next reaction, due to its instability.

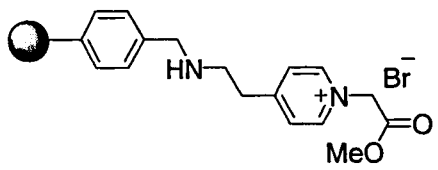
Reaction of compound 150e with 2-aminoacetophenone (151)



To resin **150e** (0.10 g; 0.08 mmol) was added anhydrous THF (10.0 ml). 20 sec was allowed for the resin to swell. To the resin was added DBU (0.24 ml; 1.6 mmol). The reaction mixture was stirred at RT for 15 min. After this time, the excess DBU was removed under suction and another portion of THF (10.0 ml) was added. To the resin was then added 2-aminoacetophenone (0.22 ml; 1.6 mmol). The reaction mixture was stirred at RT for 3 h. Once this was completed, the excess reagent was removed under suction and the resin was washed using portions of THF (3 x 5.0 ml). The resin was dried under vacuum for 1 h.

It was not possible to carry out any colour tests with the treated resin. Compound 151 was carried through to the next reaction.

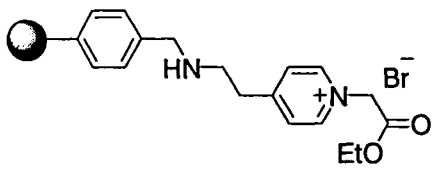
Alkylation of pyridine linker 139 with methyl bromoacetate (150f)



To resin **139** (0.50 g; 0.79 mmol) was added PhMe (10.0 ml). 20 s was allowed for the resin to swell. To the resin was added methyl bromoacetate (0.16 ml; 1.58 mmol). The reaction mixture was refluxed for 2 h. During this time, the resin turned a brown colour. After the reaction mixture was completed, the excess reagents were removed under suction. The resin was washed using **Procedure A**. After drying the resin for 1 h under vacuum, the resin was analyzed using silver(I) nitrate solution.

Silver(I) nitrate test: On addition of a few drops of silver(I) nitrate solution to a few of the treated resin beads, which were suspended in a MeCN (1.0 ml), a cloudy precipitate formed in solution. The reaction was deemed successful.

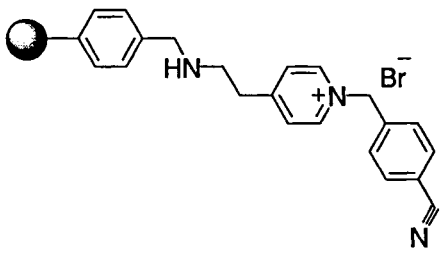
Reaction of pyridine linker 139 with ethyl bromoacetate (150g)



To resin **139** (0.50 g; 0.79 mmol) was added PhMe (10.0 ml). 20 s was allowed for the resin to swell. To the resin was added ethyl bromoacetate (0.17 ml; 1.58 mmol). The reaction mixture was heated under reflux for 2 h. During this time, the resin turned a brown colour. After the reaction mixture was completed, the excess reagents were removed under suction. The resin was washed using **Procedure A**. After drying the resin for 1 h under vacuum, the resin was analyzed using silver(I) nitrate solution.

Silver(I) nitrate test: On addition of a few drops of silver(I) nitrate solution to a few of the treated resin beads, which were suspended in a MeCN (1.0 ml), a cloudy precipitate formed in solution. The reaction was deemed successful.

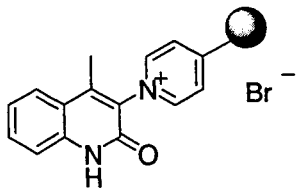
Alkylation of pyridine linker 139 with 4-cyanobenzyl bromide (150h)



To resin **139** (0.50 g; 0.79 mmol) was added THF (10.0 ml). 20 s was allowed for the resin to swell. To the resin was added 4-cyanobenzyl bromide (1.54 g; 7.9 mmol). The reaction mixture was heated under reflux for 3 h. During this time, the resin turned a brown colour. After the reaction mixture was completed, the excess reagents were removed under suction. The resin was washed using **Procedure A**. After drying the resin for 1 h under vacuum, the resin was analysed using silver(I) nitrate solution.

Silver(I) nitrate test: On addition of a few drops of silver(I) nitrate solution to a few of the treated resin beads, which were suspended in a MeCN (1.0 ml), a cloudy precipitate formed in solution. The reaction was deemed successful.

Reaction of compound 150a/b with 2-aminoacetophenone (1) (151a)



To resin **150a/b** (0.10 g; 0.08 mmol) was added anhydrous THF (10.0 ml). 20 s was allowed for the resin to swell. To the resin was added DBU (0.24 ml; 1.6 mmol). The reaction mixture was stirred at RT for 15 min. After this time, the excess DBU was removed under suction and another portion of THF (10.0 ml) was added. To the resin was then added 2-aminoacetophenone (0.22 ml; 1.6 mmol). The reaction mixture was stirred at RT for 2h. Once this was completed, the excess reagent was removed under suction and the resin was washed using portions of THF (3 x 5.0 ml). The resin was dried under vacuum for 1 h.

Reaction of compound 150a/b with 2-aminoacetophenone (2) (151b)

To resin **150a/b** (0.10 g; 0.08 mmol) was added anhydrous THF (10.0 ml). 20 s were allowed for the resin to swell. To the resin was added Et_3N (0.28 ml; 2.0 mmol). The reaction mixture was stirred at RT for 15 min. After this time, the excess Et_3N was removed under suction and another portion of THF (10.0 ml) was added. To the resin was then added 2-aminoacetophenone (0.22 ml; 1.6 mmol). The reaction mixture was stirred at 80 °C for 3 h. Once this was completed, the excess reagent was removed under suction and the resin was washed using portions of THF (3 x 5.0 ml). The resin was dried under vacuum for 1 h.

Reaction of compound 150a/b with 2-aminoacetophenone (3) (151c)

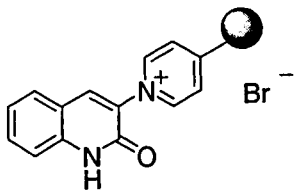
To resin **150a/b** (0.10 g; 0.08 mmol) was added C_6H_5N (20.0 ml). 2-Aminoacetophenone (0.22 ml; 1.6 mmol) was added to the resin. The reaction mixture was heated to 100 °C for 1.5 h. Once this was completed, the excess reagent was removed under suction and the resin was washed using portions of THF (3 x 5.0 ml). The resin was dried under vacuum for 1 h.

Reaction of compound 150a/b with 2-aminoacetophenone (4) (151d)

To resin **150a/b** (0.10 g; 0.08 mmol) was added C_6H_5N (20.0 ml). 2-Aminoacetophenone (0.22 ml; 1.6 mmol) was added to the resin. The reaction mixture was heated to 100 °C for 12 h. Once this was completed, the excess reagent was removed under suction and the resin was washed using portions of THF (3 x 5.0 ml). The resin was dried under vacuum for 1 h.

It was not possible to carry out any colour tests with the treated resins. The resins from each reaction were carried through to the next reaction.

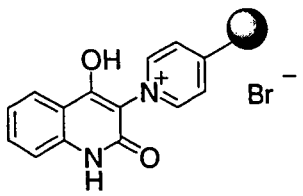
Reaction of pyridine linker 150a/b with 2-aminobenzaldehyde (152)



To resin **150a/b** (0.10 g; 0.08 mmol) was added anhydrous THF (10.0 ml). 20 s was allowed for the resin to swell. To the resin was added DBU (0.24 ml; 1.6 mmol). The reaction mixture was stirred at RT for 15 min. After this time, the excess DBU was removed under suction and another portion of THF (10.0 ml) was added. To the resin was then added 2- aminobenzaldehyde (0.50 g; 1.6 mmol). The reaction mixture was stirred at RT for 2 h. After this time, the excess reagents were removed under vacuum. The resin was washed with portions of THF (3 x 5.0 ml). The resin was dried under vacuum for 1 h.

It was not possible to carry out any colour tests with the treated resin. Compound 152 was carried through to the next reaction.

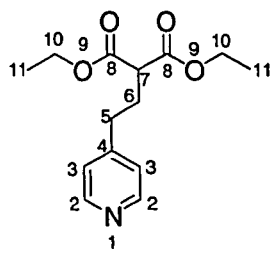
Reaction of resin 150a with isatoic anhydride (153)



To resin **150a** (0.10 g; 0.08 mmol) was added anhydrous THF (10.0 ml). 20 s was allowed for the resin to swell. To the resin was added DBU (0.24 ml; 1.6 mmol). The reaction mixture was stirred at RT for 15 min. After this time, the excess DBU was removed under suction and another portion of THF (10 ml) was added. To the resin was then added isatoic anhydride (0.26 g; 1.6 mmol). The reaction mixture was stirred at RT for 2 h. After this time, the excess reagents were removed under vacuum. The resin was washed with portions of THF (3 x 5.0 ml). The resin was dried under vacuum for 1 h.

It was not possible to carry out any colour tests with the treated resin. Compound 153 was carried through to the next reaction.

Synthesis of diethyl 2-[2-(pyridin-4-yl)ethyl]propanedioate[151] (160)

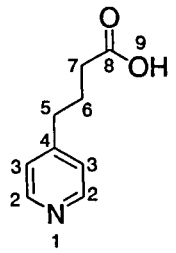


To sodium hydride, 60% dispersion in oil, (0.48 g; 12.0 mmol) was added anhydrous DMF (15.0 ml). To this was added diethyl malonate (1.5 ml; 10.0 mmol). The mixture was left to stir at RT for 0.5 h. After this time, whilst stirring, 4-vinylpyridine (1.1 ml; 10.0 mmol) was added. The reaction mixture was heated to 100 °C for 3 h. Initial analysis was carried out using TLC and this showed no evidence of the formation of a new product. The reaction mixture was heated for a further 9 h at the same temperature. After this was completed, the reaction mixture was cooled to RT and the solvent was removed under vacuum. Water (10.0 ml) was added to the oily material and the mixture was extracted with portions of Et_2O (3 x 25.0 ml). After drying the organic layers over magnesium sulphate, the solution was filtered and the solvent was removed under vacuum to give a yellow oil, (1.78g; 67%).

δ_H (250 MHz; DMSO): 1.19 (6H, t, *J* 7.0, H-11), 2.12 (4H, q, *J* 7.0, H-10), 2.63 (2H, t, *J* 8.3, H-5), 3.46 (1H, t, *J* 8.3 H-7), 4.13 (2H, q, *J* 8.3, H-6), 7.21 (2H, d, *J* 5.0, H-3), 8.47 (2H, d, *J* 5.0, H-2)

IR (Thin film) ν/ cm^{-1}: 1057 (C-O), 1726, 1744 (C=O).

Synthesis of 4-(pyridin-4-yl)butyric acid[151] (161)

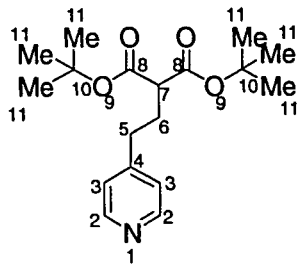


To compound **160** (1.78 g; 6.7 mmol) was added 32% conc. HCl (50.0 ml). The reaction mixture was refluxed for 16 h. Once the reaction was completed, the excess acid was removed under vacuum, to leave a brown residue. This was dissolved in hot MeOH (20.0 ml) and any solid, which had formed was filtered under vacuum. The filtrate was stripped of solvent and trituration was carried out using C_2H_5OH (5.0 ml) to give a white solid, (0.25 g; 23 %).

δ_H (250 MHz; DMSO): 1.91 (2H, apparent quintet, *J* 7.1,H-6), 2.42 (2H, t, *J* 7.5, H-5), 2.91 (2H, t, *J* 7.5, H-7), 3.59 (1H, s, OH), 7.95 (2H, d, *J* 5.5, H-3), 8.83 (2H, t, *J* 5.5 H-2)

IR (Nujol) v/ cm^{-1}: 3441 (-OH)

Synthesis of di-(1,1-dimethylethyl) 2-[2-(pyridin-4yl)ethyl] propanedioate(163)

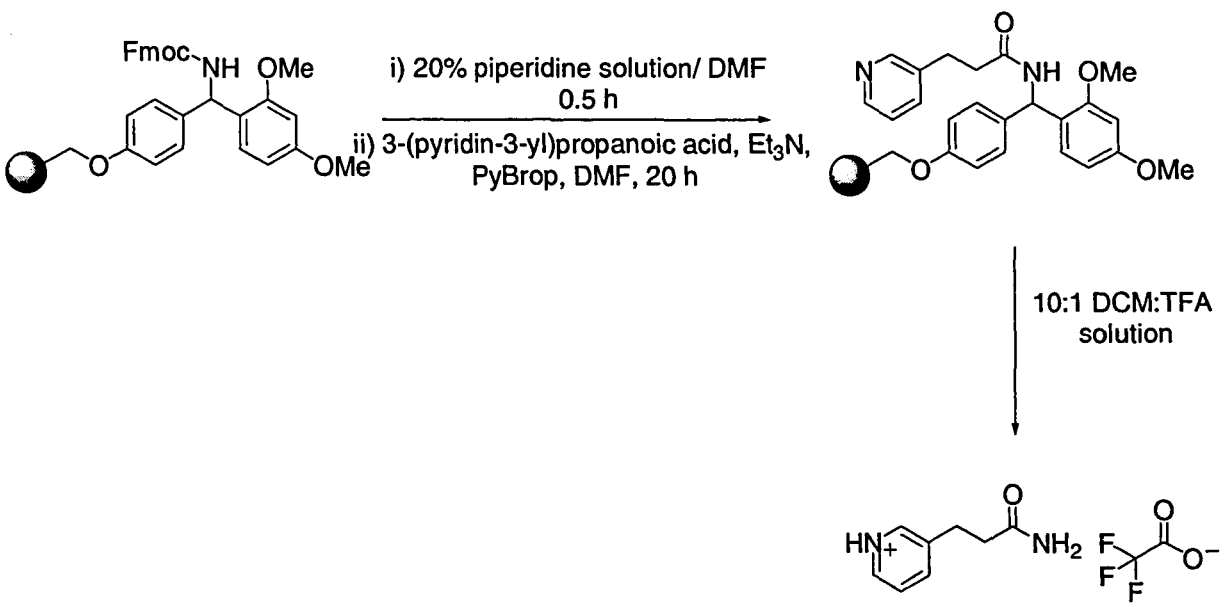


To sodium hydride, 60% dispersion in oil, (0.48 g; 12.0 mmol) was added anhydrous DMF (15.0 ml), under inert conditions. To this was added di- *tert* butyl malonate (2.2 ml; 10.0 mmol). The mixture was left to stir at RT for 0.5 h. After this time, whilst stirring, 4-vinylpyridine (1.1 ml; 10.0 mmol) was added. The reaction mixture was heated to 80 °C for 4 h. After this was completed, the reaction mixture was cooled to RT and the solvent was removed under vacuum. Water (10.0 ml) was added to the oily material and the residue was extracted with Et_2O (3 x 25.0 ml). After drying the organic layers over magnesium sulphate, the extract was filtered and the solvent was removed under vacuum to give an orange oil, (2.10 g; 72%).

δ_H (250 MHz; DMSO): 1.41 (18H, s, H-11), 1.98 (2H, apparent q, apparent *J* 7.4, H-6), 2.59 (2H, t, *J* 7.2, H-5), 3.21 (1H, t, *J* 7.0, H-7) 7.24 (2H, t, *J* 6.9, H-3), 8.47 (2H, t, *J* 6.9, H-2).

The intermediate was analyzed using ^1H NMR only as this was carried through to the next stage to synthesize compound 161.

Synthesis of Pyridine Linker Resin (164)

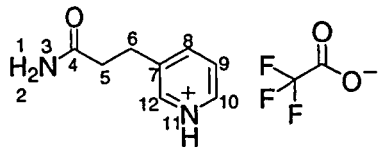


To Rink amide resin (1.0 g; 0.47 mmol) in DMF (5.0 ml) was added 20% piperidine solution in DMF (5.0 ml). The reaction mixture was shaken at RT for 0.5 h. After this time, the excess reagents were removed under suction filtration. The resin was washed using the **Procedure A**. The resin was dried under vacuum for 0.5 h. Analysis to confirm the removal of the Fmoc protecting group was carried out using the TNBSA test.

TNBSA Test: On addition of a few drops of TNBSA to a few of the resin beads in methanol, the resin beads turned red in colour. This indicated a positive result.

To the dried beads was added DMF (2.0 ml). To this, was added a mixture of PyBroP® (0.83 g; 1.8 mmol), Et_3N (0.25 ml; 1.8 mmol) and 3-(pyridin-3-yl)propanoic acid (0.27 g; 1.8 mmol) in DMF (5.0 ml). The reaction mixture was shaken at RT for 20 h. After this time, the excess reagents were removed under suction filtration. The resin was washed using **Procedure A**. After the resin beads were dried under vacuum for 0.5 h, a few of the resin beads were removed from the tube and to this was added a few drops of 10:1 DCM: TFA solution. This caused the resin beads to turn a red colour. After 0.25 h, the resin beads were filtered from the solution. The filtrate was analyzed by LC-MS.

3-(2-Aminocarbonylethyl)pyridinium trifluoroethanoate (165)



(Found m/z 150.0791. $C_8H_{10}N_2O$ requires M^+ 150.0790); m/z: 150 (MH^+, 72%),

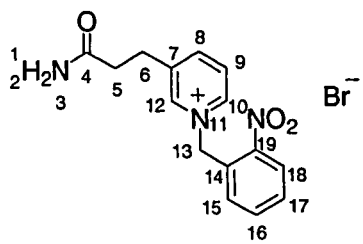
δ_H (400 MHz; DMSO): 2.48 (2H, t, *J* 7.4, H-6), 2.97 (2H, t, *J* 7.4, H-5), 6.82 (1H, s, NH, disappears on D_2O shake), 7.34 (1H, s, NH, disappears on D_2O shake), 7.82 (1H, dd, *J* 5.6, 8.0, H-9), 8.31 (1H, d, *J* 8.0, H-8), 8.70 (1H, d, *J* 5.6, H-10), 8.77 (1H, s, H-12).

δ_C (100 MHz; DMSO): 27.52 (C-5), 35.18(C-6), 125.78, 140.25, 141.60, 143.28, 143.55, 172.70 (C-12).

General procedure (1) for the alkylations of pyridine linker resin.

To pyridine linker resin **164** (0.10 g; 0.06 mmol), which was swelled in DCM (5.0 ml) was added the alkylating reagent (0.60 mmol), dissolved in DCM (2.0 ml.) The reaction mixture was shaken at RT for 20 h. Once the reactions were completed, the excess reagents were removed under suction. The resin was washed using **Procedure A**. After the resin beads were dried under suction filtration for 0.5 h, a few of the resin beads were removed from the tube and to this was added a few drops of 10:1 DCM: TFA solution. This caused the resin beads to turn a red colour. After 0.25 h, the resin beads were filtered from the solution, which was initially analyzed by LC-MS:

3-(2-Aminocarbonylethyl)-1-(2-nitrophenylmethyl)pyridinium bromide (166a)

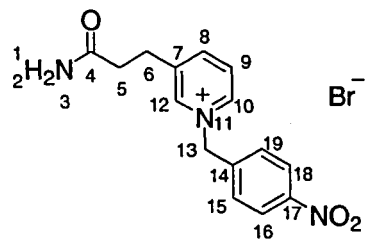


(Found m/z 286.1188. $C_{15}H_{16}N_3O_3$ requires M^+ 286.1191); m/z: 286 (M^+, 4%), 72 (27), 150 (52), 136 (49).

δ_H (250 MHz; DMSO): 2.50 (2H, t, *J* 7.4, H-6), 3.02 (2H, t, *J* 7.4, H-5), 6.20 (2H, s, H-13), 6.87 (1H, s, -NH), 7.39 (1H, s, -NH), 7.70-7.84 (3H, m, H-15-17), 8.16 (1H, dd, *J* 6.0, 8.1, H-9), 8.26 (1H, dd, *J* 1.5, 7.9, H-18), 8.59 (1H, d, *J* 8.1, H-8), 8.93 (1H, d, *J* 6.0, H-10), 9.06 (1H, s, H-12).

δ_C (100 MHz; DMSO): 27.51 (C-5), 34.64 (C-6), 60.45, 125.57, 127.80, 129.04, 130.15, 130.46, 134.89, 142.75, 143.05, 144.96, 146.18, 146.26, 172.42 (C-12).

3-(2-Aminocarbonylethyl)-1-(4-nitrophenylmethyl)pyridinium bromide (166b)

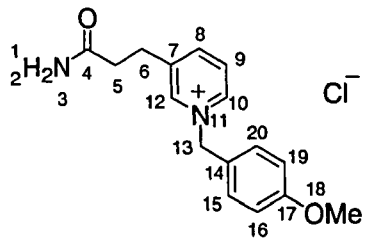


(Found m/z 286.23. $C_{15}H_{16}N_3O_3$ requires M^+ 286.28); m/z: 286 (M^+, 10%), 150 (50).

δ_H (250 MHz; DMSO): 2.53 (2H, t, *J* 7.2, H-6), 3.02 (2H, t, *J* 7.2, H-5), 6.00 (2H, s, H-13), 6.87 (1H, s, -NH), 7.38 (1H, s, -NH), 7.75 (2H, d, J 8.4, H-15,19), 8.12 (1H, dd, *J* 6.5, 8.2, H-9), 8.27 (2H, d, *J* 8.4, H-16, 18), 8.53 (1H, d, *J* 8.2, H-8), 9.08 (1H, d, *J* 6.5, H-10), 9.22 (1H, s, H-12).

δ_C (100 MHz; DMSO): Carbon NMR data were not obtained due to insufficient material available for analysis.

3-(2-Aminocarbonylethyl)-1-(4-methoxyphenylmethyl)pyridinium chloride (166c)

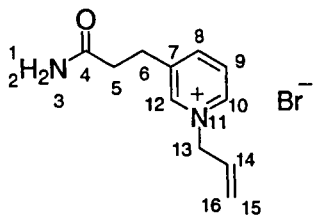


(Found m/z 271.1443. $C_{16}H_{19}N_2O_2$ requires M^+ 271.1447); m/z: 271 (M^+, 22%), 72 (10), 95 (13), 150 (70), 199 (1).

δ_H (250 MHz; DMSO): 2.52 (2H, t, *J* 7.4, H-6), 3.01 (2H, t, *J* 7.4, H-5), 5.72 (2H, s, H-13), 6.88 (1H, s, -NH), 6.99 (1H, s, -NH), 6.99 (2H, d, J 8.8, H-15, 20), 7.50 (2H, d, *J* 8.8, H-16, 19), 8.07 (1H, dd, *J* 6.2, 8.1, H-9), 8.47 (1H, d, *J* 8.1, H-8), 9.00 (1H, d, *J* 6.2, H-10), 9.17 (1H, s, H-12).

δ_C (100 MHz; DMSO): 27.45 (C-5), 34.62 (C-6), 55.21, 62.95, 114.52, 126.12, 141.99, 142.80, 144.04, 145.49, 157.69, 158.05, 159.96, 172.40 (C-12).

3-(2-Aminocarbonylethyl)-1-(prop-2-enyl)pyridinium bromide (166d)

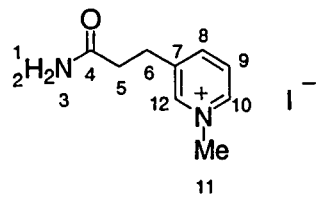


(Found m/z 191.1183. $C_{11}H_{13}N_2O$ requires M^+ 191.1184); m/z: 191 (M^+, 48%), 146 (38) (C-12).

δ_H (250 MHz; DMSO): 2.52 (2H, t, *J* 7.2, H-6), 3.01 (2H, t, *J* 7.2, H-5), 5.23 (2H, d, *J* 6.2, H-13), 5.43 (1H, dd, *J* 1.0, 8.0, H-15), 5.38 (1H, dd, *J* 1.0, 13.9, H-16), 6.08-6.21 (1H, m, H-14), 6.88 (1H, s, *J* 8.9, -NH), 7.39 (1H, s, -NH), 8.08 (1H, dd, *J* 6.2, 8.1, H-9), 8.51 (1H, d, *J* 8.1, H-8), 8.89 (1H, d, *J* 6.2, H-10), 8.99 (1H, s, H-12).

δ_C (100 MHz; DMSO): 27.43 (C-5), 34.61 (C-6), 62.28, 121.71, 127.59, 131.56, 142.32, 142.51, 144.25, 145.62, 172.42 (C-12).

3-(2-Aminocarbonylethyl)-1-methylpyridinium iodide (166e)

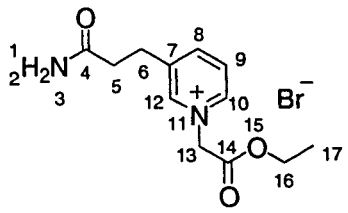


(Found m/z 165.1030. $C_9H_{13}N_2O$ requires M^+ 165.1028); m/z: 165 (M^+, 89%), 57 (1), 72 (3), 150 (19).

δ_H (250 MHz; DMSO): 2.50 (2H, t, *J* 7.4, H-6), 2.98 (2H, t, *J* 7.4, H-5), 4.30 (3H, s, H-11), 6.87 (1H, s, NH), 7.36 (1H, s, NH), 8.01- 8.06 (1H, dd, *J* 6.1, 8.3, H-9), 8.43 (1H, d, *J* 8.3, H-8), 8.81 (1H, d, *J* 6.1, H-10), 8.92 (1H, s, H-12)

δ_C (100 MHz; DMSO): 27.35, 34.67, 37.13, 47.73, 54.86, 127.08, 141.97, 143.08, 172,39 (C-12).

3-(2-Aminocarbonylethyl)-1-ethoxycarbonylmethylpyridinium bromide (166f)

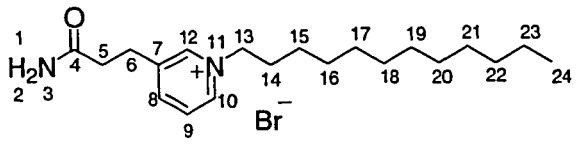


(Found m/z 237.27. $C_{12}H_{17}N_2O_3$ requires M^+ 237.27); m/z: 237 (M^+, 100%).

δ_H (250 MHz; DMSO): 1.25 (3H, t, *J* 7.1, H-17), 2.51 (2H, t, *J* 7.4, H-6), 3.01 (2H, t, *J* 7.4, H-5), 4.18- 4.27 (2H, q, *J* 7.1, H-16), 5.61 (2H, s, H-13), 6.88 (1H, s, NH), 7.39 (1H, s, NH), 8.13- 8.18 (1H, dd, *J* 6.0, 8.1, H-9), 8.58 (1H, d, *J* 8.1, H-8), 8.88 (1H, d, *J* 6.0, H-10), 8.98 (1H, s, H-12).

δ_C (100 MHz; DMSO): 13.88 (C-5), 27.39 (C-6), 33.22, 60.16, 62.29, 127.20, 142.09, 143.88, 145.59, 146.45, 166.27, 172.29 (C-12).

3-(2-Aminocarbonylethyl)-1-dodecylpyridinium bromide (166g)

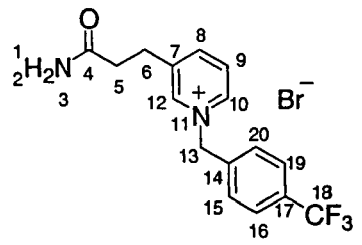


(Found m/z 319.2747. $C_{20}H_{35}N_2O$ requires M^+ 319.2749); m/z: 319 (M^+, 4%), 72 (7), 150 (83).

δ_H (250 MHz; DMSO): 0.84 (3H, t, *J* 6.4, H-24), 1.23 (18H, bs, H-15 to 23), 1.77 (2H, apparent quin, apparent *J* 6.8, H-14), 2.49 (2H, t, *J* 7.6, H-6), 2.98 (2H, t, *J* 7.6, H-5), 3.50 (2H, t, *J* 6.8, H-13), 6.85 (1H, s, NH), 7.36 (1H, s, NH), 7.91- 7.96 (1H, dd, *J* 5.5, 8.1, H-9), 8.41 (1H, d, *J* 8.1, H-8), 8.74 (1H, d, *J* 5.5, H-10), 8.78 (1H, s, H-12).

δ_C (100 MHz; DMSO): 13.90 (C-5), 22.05 (C-6), 27.42, 27.46, 28.87, 28.94, 30.62, 31.24, 32.19, 35.01, 38.82, 107.90, 126.29, 140.49, 140.97, 142.36, 144.86, 158.12, 172.60, 206.48 (C-12).

3-(2-Aminocarbonylethyl)-1-(4-trifluoromethylphenylmethyl)pyridinium bromide (166h)

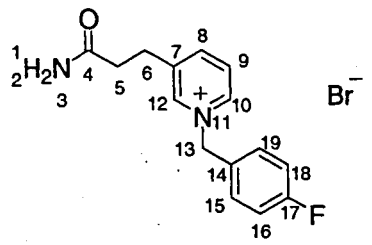


(Found m/z 309.1217. $C_{16}H_{16}N_2OF_3$ requires M^+ 309.1215); m/z: 309 (M^+, 6%), 72 (2), 150 (5).

δ_H (250 MHz; DMSO): 2.49 (2H, t, *J* 7.3, H-6), 3.01 (2H, t, *J* 7.3, H-5), 5.93 (2H, s, H-13), 6.88 (1H, s, NH), 7.39 (1H, s, NH), 7.71 (2H, d, *J* 8.2, H-15, 20), 7.81 (2H, d, *J* 8.2, H-16, 19), 8.08- 8.14 (1H, dd, *J* 6.0, 8.2, H-9), 8.53 (1H, d, *J* 8.2, H-8), 9.05 (1H, d, *J* 6.0, H-10), 9.22 (1H, s, H-12).

δ_C (100 MHz; DMSO): 27.07 (C-5), 34.60 (C-6), 48.53, 55.98, 62.38, 125.25, 127.95, 129.75, 142.39, 142.56, 144.63, 145.89, 158.27, (1C, q, $^1J_{CF}$ 36, C-18) 172.45 (C-12).

3-(2-Aminocarbonylethyl)-1-(4-fluorophenylmethyl)pyridinium bromide (166i)

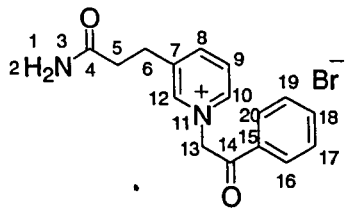


(Found m/z 259.12. $C_{15}H_{16}N_3OF$ requires M^+ 259.12); m/z: 286 (M^+, 65%), 150 (70).

δ_H (250 MHz; DMSO): 2.53 (2H, t, *J* 7.2, H-6), 3.01 (2H, t, *J* 7.2, H-5), 5.82 (2H, s, H-13), 7.71- 7.50 (4H, H-15, 16, 18, 19), 8.06 (1H, dd, *J* 6.1, 8.2, H-9), 8.49 (1H, d, *J* 8.2, H-8), 9.03 (1H, d, *J* 6.1, H-10), 9.21 (1H, s, H-12).

δ_C (100 MHz; DMSO): Carbon data were not obtained due to insufficient material available for analysis.

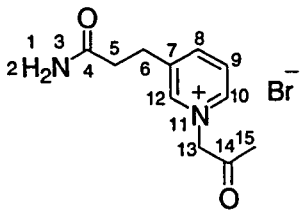
Synthesis of 3-(2-Aminocarbonylethyl)-1-(2-oxo-2-phenylmethyl)pyridinium bromide (166I)



(Found m/z 269.30. $C_{16}H_{17}N_2O_2$ requires M^+ 269.29).

δ_H (250 MHz; DMSO): 2.54 (2H, t, *J* 7.3, H-6), 3.06 (2H, t, *J* 7.3, H-5), 6.47 (2H, s, H-13), 6.92 (1H, s, NH), 7.46 (1H, s, NH), 7.51- 8.08 (5H, m, H-16- 20), 8.16- 8.21 (1H, dd, *J* 6.0, 8.1, H-9), 8.61 (1H, d, *J* 8.1, H-8), 8.53, 8.86 (1H, d, *J* 6.0, H-10), 8.97 (1H, s, H-12).

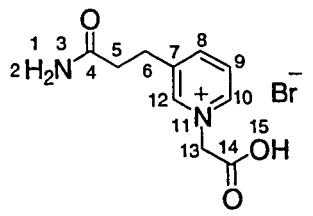
Synthesis of 3-(2-Aminocarbonylethyl)-1-(2-oxopropyl)pyridinium bromide (166J)



(Found m/z 206.94. $C_{11}H_{15}N_2O_2$ requires M^+ 207.15).

No other data were obtained on these compounds.

Alkylation of pyridine linker 164 with bromoacetic acid to form (175)



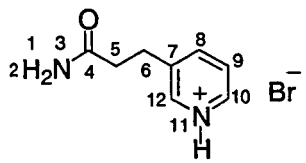
To pyridine linker **164** (0.10 g; 0.04 mmol) was added anhydrous DMF (5.0 ml). 20 s was allowed for the resin to swell. To the resin was added DIPEA (0.28 ml; 1.6 mmol) and bromoacetic acid (0.11 g; 0.80 mmol). The reaction was stirred at RT for 20 h. After this was completed, the excess reagents were removed under suction. The resin was washed using **Procedure A**. The treated resin was initially analyzed using LC-MS spectroscopy.

(Found m/z 209.03. $C_{10}H_{13}N_2O_3$ requires M^+ 209.05).

Coupling of 2-aminoacetophenone to compound 175

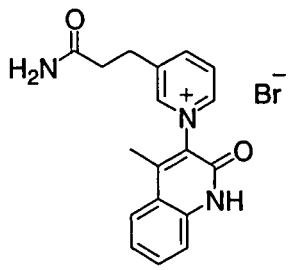
To compound **175** (0.10 g; 0.04 mmol) in DMF (5.0 ml) was added a solution of Et_3N (0.22 ml; 1.6 mmol), PyBrop (0.74 g; 1.6 mmol) and 2-aminoacetophenone (0.19 ml; 1.6 mmol) in DMF (5.0 ml). The reaction mixture was stirred at RT for 20 h. After this time, the excess reagents were removed under suction. After drying under vacuum for 1 h, the TFA treated resin was initially analyzed using LC-MS spectroscopy. 3 products were identified:

Compound 178



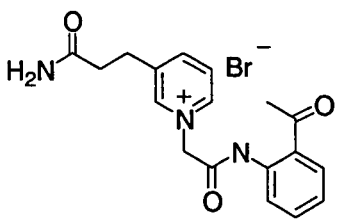
(Found m/z 150.93. $C_8H_{11}N_2O$ requires M^+ 150.93).

Compound 177



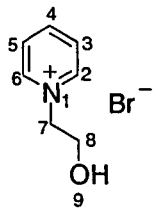
(Found m/z 307.86. $C_{18}H_{17}N_3O_2$ requires M^+ 307.88).

Compound 176



(Found m/z 325.95. $C_{18}H_{20}N_3O_3$ requires M^+ 325.95).

Synthesis of 1-(2-hydroxyethyl)pyridinium bromide[159, 160] (184)



To pyridine (0.30 ml; 5.0 mmol) in MeCN (5.0 ml) was added 2-bromoethanol (0.35 ml; 5.0 mmol). The reaction mixture was refluxed for 16 h. Once this was completed, the reaction mixture was cooled to RT and Et_2O was added to promote the formation of the solid. The solid was filtered under suction and washed with portions of Et_2O (3 x 5.0 ml) and after drying under vacuum for 1 h a white solid was isolated, (95%).

(**m.p:** 110-112 °C; lit. value[160]: 108-110 °C).

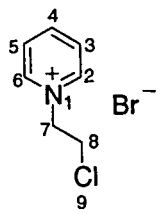
(Found m/z 123.0682. C_7H_9NO requires M^+ 123.0684); m/z: 123 (MH^+, 23%), 79 (100), 107 (5).

δ_H (250 MHz; DMSO): 3.85 (2H, t, *J* 5.0, H-7), 4.73 (2H, t, *J* 5.0, H-8), 8.17 (2H, apparent t, apparent *J* 6.9, H-3, 5), 8.64 (1H, t, *J* 7.7, H-4), 9.08 (2H, d, *J* 6.5, H-2, 6).

δ_C (100 MHz; DMSO): 58.62, 63.86, 126.32 (C-3, 5), 143.78 (C-4), 144.44 (C-2, 6).

IR (Nujol) v/ cm^{-1}: 3445 (-OH).

Synthesis of 1-(2-chloroethyl)pyridinium bromide[159] (185)

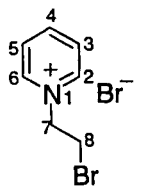


To compound **184** (0.47 g; 2.2 mmol) was added $SOCl_2$ (1.5 ml) drop-wise. This caused the solution to turn yellow. The reaction mixture was stirred at RT for 0.5 h. After this time, the excess $SOCl_2$ was removed under vacuum, leaving a yellow residue. To this residue was added hot acetone (5 ml). This caused a solid to precipitate of solution. The solid was filtered off and dried under vacuum for 1 h to leave yellow crystals, which were observed to be hygroscopic (96%).

(**m.p:** This compound was found to very hygroscopic, thus it was not possible to obtain melting point data).

δ_H (250 MHz; DMSO)[160]: 4.25 (2H, t, *J* 5.2, H-7), 5.14 (2H, t, *J* 5.2, H-8), 8.17 (2H, apparent t, apparent *J* 6.9, H-3, 5), 8.75 (1H, t, *J* 7.8, H-4), 9.27 (2H, d, *J* 6.7, H-2, 6).

Synthesis of 1-(2-bromoethyl)pyridinium bromide[156] (187)



To a solution of 1,2-dibromoethane (4.3 ml; 50.0 mmol) in Et_2O (10.0 ml) was added a solution of pyridine (0.40 ml; 5.0 mmol) in Et_2O (5.0 mmol) drop-wise. The reaction mixture was refluxed for 16 h. A white solid was formed in the reaction mixture. After cooling to RT, the solid was filtered under vacuum and washed with portions of cold Et_2O (3 x 5.0 ml). The solid was dried under vacuum for a further 0.5 h to give a white solid (65%).

(**m.p:** 128-130 °C; lit. value[156]: 126-128 °C)

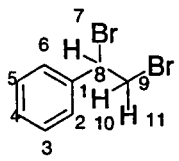
(Found: C, 31.6; H, 3.6; N, 5.1. C_7H_9NBr requires C, 31.5; H, 3.4; N, 5.3%)

(Found m/z 185.9922. C_7H_9NBr requires M^+ 185.9918); m/z: 185 (M+, 2%), 106 (100)

δ_H (250 MHz; DMSO): 4.15 (2H, t, *J* 5.9, H-8), 5.13 (2H, t, *J* 5.9, H-7), 8.25 (2H, apparent t, apparent *J* 7.1, H-3, 5), 8.71 (1H, t, *J* 7.8, H-4), 9.22 (2H, t, *J* 5.8, H-2, 6)

δ_C (100 MHz; DMSO): 31.80 (C-8), 60.79 (C-7), 127.83 (C-3, 5), 145.06 (C-4), 146.35 (C-2, 6)

Synthesis of 1,2-dibromo-1-phenylethane[165] (206)



Styrene (5.7.0 ml; 50.0 mmol) in Et_2O was cooled to 0 °C. To this was added drop-wise bromine (2.6 ml; 50 mmol). The reaction mixture was warmed to RT and stirred for 16 h. During this time, a precipitate came out of solution. Once this was completed, the solid was filtered under vacuum and washed with portions of cold Et_2O (3 x 10.0 ml). After drying under vacuum, a solid was isolated, (12.0 g; 91 %).

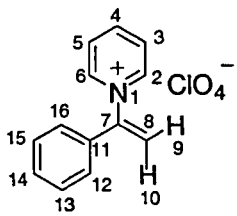
(**m.p:** 72-73 °C; lit. value[165]: 72-73 °C)

(Found: C, 36.6; H, 2.9. $C_9H_8Br_2$ requires C, 36.4; H, 3.1%)

δ_H (250 MHz; DMSO): 3.70- 4.12 (2H, m, H-10, 11), 5.13 (1H, dd, *J* 5.5, 10.3, H-7), 7.25 (5H, m, H-2- 6).

δ_C (100 MHz; DMSO): 35.43 (C-9), 51.30 (C-8), 128.07, 129.26, 129.58, 139.03 (C-1).

Synthesis of 1-(1-phenylethenyl)pyridinium perchlorate[164] (203a)



Compound **206** (4.0 g; 15.0 mmol) was dissolved in pyridine (12.1 ml; 0.15 mol). The reaction mixture was refluxed for 1.5 h, cooled to RT and stirred for a further 12 h. Once this was completed, the excess pyridine was removed under vacuum, leaving a brown material. The material was dissolved in MeOH (15.0 ml). To the reaction mixture was added poly(4-vinyl)pyridine (10.0 g). The reaction mixture was stirred at RT for 12 h. The resin was then filtered under vacuum and washed with MeOH (3 x 10.0 ml). The solvent was removed from the reaction mixture under vacuum, to leave a brown residue. Portions of Et_2O (3 x 10.0 ml) were swirled with the material and decanted to remove residual traces of pyridine. The brown residue was dissolved in MeOH (10.0 ml). Perchloric acid (5.0 ml) was added drop-wise to the mixture. This was left to stir at RT for 2 h, during which time needles began to precipitate out of solution. The solid were filtered under suction and washed with portions of Et_2O (2 x 5.0 ml) to give brown-coloured needles (2.61 g; 61%).

(m.p: 130- 131 °C; lit. value[164]: 129-130 °C)

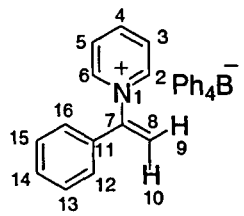
(Found: C, 55.8; H, 4.1; N, 4.9. $C_{13}H_{12}NO_4Cl$ requires C, 55.5; H, 4.3; N, 4.9 %)

(Found m/z 182.0966. $C_{13}H_{12}N$ requires M^+ 182.0970; m/z: 185 (M+, 44 %)

δ_H (250 MHz; DMSO): 6.04 (1H, d, *J* 2.4, H-9), 6.44 (1H, d, *J* 2.4, H-10), 7.34-7.53 (5H, m, H-12- 16), 8.29 (2H, apparent t, apparent *J* 6.8, H-3, 5), 8.82 (1H, t, *J* 7.0, H-4), 9.16 (2H, d, *J* 6.2, H-2, 6).

δ_C (100 MHz; DMSO): 117.05, 126.61, 128.75, 129.63, 130.95, 133.68, 145.36, 147.90, 148.65.

Synthesis of 1-(1-phenylethenyl)pyridinium tetraphenylborate[164] (203b)



Compound **206** (4.0 g; 15.0 mmol) was dissolved in pyridine (12.1 ml; 0.15 mol). The reaction mixture was refluxed for 1.5 h, cooled to RT and stirred for a further 12 h. Once this was completed, the excess pyridine was removed under vacuum, leaving a brown residue. The residue was dissolved in MeOH (15.0 ml). To the reaction mixture was added poly(4-vinyl)pyridine (10.0 g). The reaction mixture was stirred at RT for 12 h. The resin was then filtered under vacuum and washed with portions of MeOH (3 x 10.0 ml). The solvent was removed from the reaction mixture under vacuum, to leave a brown residue. Portions of Et_2O (3 x 10.0 ml) were swirled in the residue and decanted to remove residual traces of pyridine. The brown residue was dissolved in MeOH (10.0 ml). Sodium tetraphenylborate (5.1 g; 15.0 mmol) was added drop-wise to the mixture. This was left to stir at RT for 2 h, during which time a solid precipitated out of solution. The solid was filtered and under suction and washed with portions of Et_2O (2 x 5.0 ml) to give a brown solid (76%).

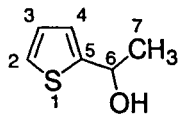
(Found: C, 88.3; H, 6.2; N, 2.7. $C_{37}H_{32}NB$ requires C, 88.6; H, 6.4; N, 2.8%)

(Found m/z 182.0970. $C_{13}H_{12}NB$ requires M^+ 182.0969); m/z: 185 (M+, 79%)

δ_H (250 MHz; DMSO): 5.95 (1H, d, *J* 2.3 H-9), 6.44 (1H, d, *J* 2.3 H-10), 6.77- 7.20 (20H, m, Ph_4B), 7.33- 7.49 (5H, m, H-12, 16), 8.21 (2H, apparent t, apparent *J* 7.2, H-3, 5), 8.72 (1H, t, *J* 8.0, H-4), 9.07 (2H, d, *J* 6.8, H-2, 6).

δ_C (400 MHz; DMSO): 31.02, 116.99, 121.95, 125.72, 126.58, 128.70, 129.64, 130.99, 133.01, 135.85, 145.23, 147.04, 148.62.

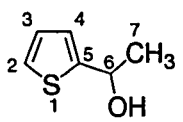
Synthesis of 1-(2-thienyl)ethanol[163] (1) (205)



To 2-acetylthiophene (2.2 ml; 20.0 mmol) in MeOH (15.0 ml) was added in small portions, $NaBH_4$ (0.83 g; 22.0 mmol). This addition caused effervescence. The reaction mixture was stirred at RT for 72 h. The solvent was removed under vacuum and the residue was extracted using portions of EtOAc (3 x 15.0 ml) and water (3 x 10 ml). After drying over magnesium sulphate, the solvent was removed under vacuum, leaving a colourless liquid, (4.49 g; 88%).

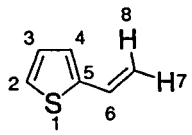
δ_H (250 MHz; $CDCl_3$): 1.53 (3H, d, *J* 6.6, H-7), 5.04 (1H, q, *J* 6.6, H-6), 6.90 (2H, m, H-3, 4), 7.17 (1H, d, *J* 7.2, H-2).

Synthesis of 1-(2-thienyl)ethanol[163] (2) (205)



To 2-acetyl thiophene (2.2 ml; 20.0 mmol) in THF (15.0 ml) was added in small portions, $LiAlH_4$ (0.84 g; 22.0 mmol). This addition caused initial effervescence. The reaction mixture was stirred at RT for 12 h. The solvent was removed under vacuum. The residue was extracted using portions of EtOAc (3 x 15.0 ml). After drying over magnesium sulphate, the solvent was removed under vacuum, leaving a colourless liquid, (1.83 g; 72%). ^1H NMR data corresponded to those reported for Method 1.

Synthesis of 2-vinylthiophene[163] (206)



To alumina (10.0 g) was added 1-(2-thienyl)ethanol, **205** (1.3 g; 10.0 mmol). The reaction mixture was heated to 250-300 °C in a distillation apparatus. The mixture was heated over 0.5 h and during this time an oily liquid distilled over into the collecting vessel, (0.50g; 45%).

δ_H (250 MHz; $CDCl_3$): 5.10 (1H, d, *J* 10.9, H-7), 5.55 (1H, d, *J* 17.3, H-8), 6.81 (1H, dd, *J* 10.9, 17.3, H-6), 6.90-6.94 (2H, m, H-3, 4), 7.10-7.12 (1H, m, H-2).

6 References

1 Furka, A., Sebestyen, F., Asgedom, M., Dibo, G., *Abstr. 14th. Int. Congr. Biochem. Prague. Czechoslovakia*, 5, 47, **(1988)**.

2 Baldwin, J.E., Adlington, R. M., O'Neil, I. A., Russell, A.T., Smith, M. L., *J. Chem. Soc; Chem. Commun.*, 41, **(1996)**.

3 Lee, J. G., Lee, J. A., Sohn, S. Y., *Synth. Commun.*, 26, 543, **(1996)**.

4 Trost, B. M., Warner, R. W., *J. Am. Chem. Soc.*, 105, 5940, **(1983)**.

5 Swali, V., Wells, N. G. J., Langley, J., Bradley, M., *J. Org. Chem.*, 62, 4902, **(1997)**.

6 Sande, A. R., Jagadale, M. H., Mane, R. B., Salunkhe, M. M., *Tetrahedron Lett.*, 25, 3501, **(1984)**.

7 Firouzabade, H., Tamani, B., *Synth. Commun.*, 21, 2275, **(1991)**.

8 Merrifield, R. B., *J. Am. Chem. Soc.*, 85, 2149, **(1963)**.

9 Bodansky, M., *Nature*, 175, 685, **(1955)**.

10 Letsinger, R. L., Hamilton, S. B., *J. Am. Chem. Soc.*, 81, 3009, **(1959)**.

11 Letsinger, R. L., Kornet, M. J., *J. Am. Chem. Soc.*, 85, 45, **(1963)**.

12 Letsinger, R. L., Kornet. M. J., Mahadevan, V., Jering, D. M., *J. Am. Chem. Soc.*, 86, 5163, **(1964)**.

13 a) Leznoff, C. C., Wang, J. Y., *Can. J. Chem.*, 50, 2892, **(1972)**; b) Leznoff, C. C., *Acc. Res. Chem.*, 11, 327, **(1978)**.

14 Fréchet, J. M. J., *Tetrahedron*, 37, 663, **(1981)**.

15 Camps, F., Castells, M. J., Ferrando, J., Font, J., *Tetrahedron Lett.*, 12, 1713, **(1971)**.

16 Patchornik, A., Kraus, M. A., *J. Am. Chem. Soc.*, 92, 7587, **(1970)**.

17 a) Crowley, J. I., Rapoport, H., *J. Am. Chem. Soc.*, 92, 6363, **(1970)**; b) Crowley, J. I., Rapoport, H., *Acc. Chem. Res.*, 9, 135, **(1976)**.

18 Camps, F., Cartells, J., *An. Quim.*, 70, 848, **(1974)**.

19 Houghten, R. A., *Proc. Natl. Acad. Sci. USA*, 82, 5131, **(1985)**.

20 Frank, R., Heikens, W., Heistberg- Moutis, G., Brocker, H., *Nucl. Acid Res.*, 11, 4365, **(1983)**.

21 Geysen, H, M., Meloen, R. H., Barteling, S. J., *Proc. Natl. Acad. Sci. USA.*, 81, 3988, **(1984)**.

22 Terrett, N. K., *"Combinatorial Chemistry"*, Oxford Uni. Press, p15, **(1998)**.

23 Lam, K. S., Salmon, S. E., Hersh, E. M., Hruby, V. J., Karzmierski, W. M., Knapp, R. J., *Nature*, 354, 82, **(1991)**.

24 Gravert, D. J., Janda, K. D., *Chem. Rev.*, 97, 489, **(1997)**.

25 Mutter. M., Hagenmaier, H., Bayer, E., *Angew. Chem., Int. Ed. Engl.*, 10, 811, **(1971)**.

26 Bayer, E., Mutter, M., *Nature*, 237, 512, **(1972)**.

27 Determann, H., *Arch. Pharm.*, 303, 117, **(1970)**.

28 Shemyakin, M. M., Ovchinnikov, Y. A., Kinyushkin, A. A., *Tetrahedron Lett.*, 6, 2323 **(1965)**.

29 Andreatta, R. H., Rink, H., *Helv. Chim. Acta*, 56, 1205, **(1973)**.

30 Narita, M., *Bull. Chem. Soc. Jpn.*, 51, 1477, **(1978)**.

31 Narita, M., Itsuno, S., Hirata, M., Kusano, K., *Bull. Chem. Soc. Jpn.*, 53, 1028, **(1980)**.

32 Andreatta, R. H., Rink, H., *Helv. Chim. Acta*, 56, 120, **(1973)**.

33 Gallop, M. A., Barrett, R. W., Dower, W. J., Foder, S. P. A., Gordon, E. M., *J. Med. Chem.*, 37, 1385, **(1994)**.

34 a) Studer, A., Hadida, S., Ferritto, R., Kim, S. Y., Jeger, P., Wipf, P., Curran, D. P., *Science*, 275, 823, **(1997)**; b) Curran, D. P., *Angew. Chem., Int. Ed. Engl.*, 37, 1230 **(1998)**; c) Curran, D. P., *Angew. Chem., Int. Ed. Engl.*, 37, 1174, **(1998)**.

35 a) Kim, R. M., Manna, M., Hutchins, S. M., Griffin, P. R., Yates, N. A., Bernick, A. M., *Proc. Natl. Acad. Sci. USA*, 93, 10012, **(1996)**; b) Hovestd, N. J., Ford, A., Jastrzebsk, J. T. B. H., Van Koten, G., *J. Org. Chem.*, 65, 5338, **(2000)**.

36 Bosanac, T., Yang, J., Wilcox, C. S., *Angew. Chem., Int. Ed. Engl.*, 40, 1875, **(2001)**.

37 Budaveri, S., Heckelman, P.E., Kinneary, J. F., O' Neil, M. J., Smith, A., *Merck Index. 12th ed.*, Merck, Whitehouse Station, N. I., 1505, **(1996)**.

38 Fletcher, K. A., McHale, M. E. R., Coym, K. S., Acree, W. E. Jr., *Can. J. Chem.*, 75, 258, **(1997)**.

39 Bosanac, T., Wicox, C. S., *Tetrahedron Lett.*, 42, 4309, **(2001)**.

40 Kitchner, J. A., *"Ion-exchange resins"*, Methus & Co., Ltd., London, 1- 3, 39.

41 Kitchner, J. A., *"Ion-exchange resins"*, Methus & Co., Ltd., London, 5.

42 Kitchner, J. A., *"Ion-exchange resins"*, Methus & Co., Ltd., London, 11.

43 a) Svec, F., Fréchet, J. M. J., *Science*, 273, 205, **(1996)**; b) McCollum, C., Andrus, A., *Tetrahedron Lett.*, 32, 4069, **(1991)**.

44 Seidi, J., Malinsty, J., Dusek, K., Heitz, W., *Adv. Poly. Sci.*, 5, 113, **(1967)**.

45 Millar, J. R., Smith., D. G., Marr, W. E., Kresman, T. R. E., *J. Chem. Soc.*, 18, **(1963)**.

46 Vairo, A. R., Janda, K. D., *J. Comb. Chem.*, 2, 579, **(2000)**.

47 Balakrishan, T., Ford, *J., Appl. Poly.* Sci., 27, 133, **(1982)**.

48 Rana, S., White, P., Bradley, M., *J. Comb. Chem.*, 3, 9, **(2001)**.

49 Akelah, A., Moet, A., *Funtionalized Polymers and their applications*, London, **(1990)**.

50 Horenstein, X., *US Patent N.O., 2524627*, **(1950)**.

51 MacDonald, A. A., Dewitt, S. H., Ghosh, S., Hogan, E. M., Kieras, L., Czarnik, A. W., Ramage, R., *Mol. Diversity*, 1, 183, **(1983)**.

52 Bayer. E., *Angew. Chem., Int. Ed. Engl.*, 30, 113, **(1991)**.

53 Park, B. D., Lee, H. I., Ryoo, S. J., Lee, Y. S., *Tetrahedron Lett.*, 38, 591, **(1997)**.

54 Santini, R., Griffith, M. C., Qi, M., *Tetrahedron Lett.*, 39, 8951, **(1998)**.

55 Porco, J. A., Deegan, T., Devonport, W., Gooding, O. W., Heisler, K., Labadie, J. W., Newcomb, B., Nguyen, C., Eikeren, P. V., Wong, J., Wright, P., *Mol. Diversity.*, 2, 197 **(1997)**.

56 Adams, J. H., Cook., R. H., Hudson, D., Jammalamadaka, H., Lyttle, M. H., Songster, M. F., *J. Org. Chem.*, 63, 3706, **(1998)**.

57 Gooding, O. W., Baudart, S., Deegan, T. L., Heisler, K, Labadue, J. W., Newcomb, W. S., Porco, J. A. Jr., Eikeren, P. V., *J. Comb. Chem.*, 1113 **(1999)**.

58 Atherton, E., Brown, E., Sheppard, R. C., *J. Chem. Soc., Chem. Commun.*, 1151, **(1981)**.

59 Meldal, M., *Tetrahedron Lett.*, 33, 3077, **(1992)**.

60 Renil, M., Meldal., *Tetrahedron Lett.*, 36, 4647, **(1995)**.

61 Meldal, M., Auzanneau, F. I., Hindsgaul, O., Palcic, M. M., *J. Chem. Soc., Chem. Commun.*,1849, **(1994)**.

62 Meldal, M., Auzanneau., F. I., Hindsgaul, O., Palcic, M. M., *J. Chem. Soc., Chem. Commun.*, 1949, **(1994)**.

63 Stahl, G. L., Walter, R., Smith, C. W., *Pept. Prot. Res.*, 13, 109, **(1979)**.

64 Atherton, E., Clive, D. L. J., Sheppard, R. C., *J. Am. Chem. Soc.*, 97, 6584, **(1975)**.

65 Smith, C. W., Stahl., G. L., Watter, R., *Pept. Prot, Res.*, 13, 109, **(1979)**.

66 Mutter, M., Bayer, E., *"In the Peptide"*, Academic, New York, Vol. 2, 285 **(1979)**.

67 Han, H., Janda, K. D., *J. Am. Chem. Soc.*, 118, 2539, **(1996)**.

68 Köster, H., *Tetrahedron Lett.*, 1535, **(1972)**.

69 Determann, H., Lampert, K., *Mitt. Dtsh. Pharmaz. Ges.*, 40, 117, **(1970)**.

70 Kontchev, A. B., Parquette, J. R., *Tetrahedron Lett.*, 40, 8049, **(1999)**.

71 Arnauld, T., Barrett., A. G. M., Cramp, S. M., Roberts, R. S., Zécri, F. J., *Org. Lett.*, 2, 2663, **(2000)**.

72 Geckeler, K. E., *Adv. Polymer. Sci.*, 121, 31, **(1995)**.

73 Nicolaou, K. C., Hanko, R., Hartwig, W., *"Handbook of Combinatorial Chemistry"*, Wiley-VCH, Germany, **(2000)**.

74 Mutter, M., Bayer, E., *Angew. Chem.*, 86, 101, **(1974)**.

75 Harris, J. M., *"Poly(ethyleneglycol)chemistry; Biothechnical and Biomedical applications"*, Harris, J. M., Ed; Plenum Press: New York, 2, **(1992)**.

76 Hagenmaier, H., *Z. Physiol. Chem.*, 356, 777, **(1975)**.

77 Weber, U., *Z. Physiol. Chem.*, 356, 701, **(1975)**.

78 Bayer, E., Holbach., *Angew. Chem., Int. Ed. Engl.*, 16, 117, **(1977)**.

79 Mutter, H., Mutter, M., Bayer, E., *Z. Naturforsch*, 343, 874, **(1979)**.

80 Anzinger, A., Mutter, M., *Polymer. Bull.*, 6, 595, **(1982)**.

81 Bayer, E., *Angew. Chem., Int. Ed. Engl.*, 30, 113, **(1991)**.

82 Jjoeng, F. S., Hodges, R. S., *Tetrahedron Lett.*, 20, 1273, **(1979)**.

83 Zhu, J., Hegedus, L. S., *J. Org. Chem.*, 60, 5831, **(1995)**.

84 Wentworth, P. Jr., Janda, K. D., *J. Chem. Soc., Chem. Commun.*, 1917, **(1999)**.

85 a) Cramer, F., Helbig, R., Hettler, H., Scheiy, K. H., *Angew. Chem., Int. Ed. Engl.*, 5, 601, **(1966)**; b) Hayatsu, H., Kharama, H. G., *J. Am. Chem. Soc.*, 89, 3880, **(1967)**.

86 Cole, E. R., Crank, G., Sheikh, A., *Tetrahedron Lett.*, 14, 2987, **(1973)**.

87 Kandil, A. A., Chan, N., *Synlett*, 555, **(1992)**.

88 Hodosi, G., Krepinsky, J. J., *Synlett*, 159, **(1996)**.

89 Maclean, D., Baldwin, J. J., Ivanov, V. T., Kato, Y., Shaw, A., Scheinder, P., Gordon, E. M., *Pure. Appl. Chem.*, 71, 2349, **(1999)**.

90 James, I., *Tetrahedron*, 55, 4855, **(1999)**.

91 Guillier, F., Orain, D., Bradley, M., *Chem. Rev.*, 100, 2091, **(2000)**.

92 Merrifield, R. B., *Biochemistry*, 3, 1385, **(1964)**.

93 Lenard, J., Robinson, A. B., *J. Am. Chem. Soc.*, 89, 181, **(1967)**.

94 Sakakibara, S., Shimonishi, Y., *Bull. Chem. Soc. Jpn.*, 38, 1412, **(1965)**.

95 Burdick, D. J., Struble, M. E., Burnier, J. P., *Tetrahedron Lett.*, 34, 2589, **(1993)**.

96 Wang, S, S., *J. Am. Chem. Soc.*, 95, 1328, **(1973)**.

97 Mergler, M., Nyfeler, R., Tanner, R., Gosteli, J., Grogg, P., *Tetrahedron Lett.*, 29, 4005, **(1988)**.

98 Mergler, M., Nyfeler, R., Tanner, R., Gosteli, J., Grogg, P., *Tetrahedron Lett.*, 29, 4009, **(1988)**.

99 Sheppard, R. C., Williams, B. J., *J. Chem. Soc., Chem. Commun.*, 587, **(1982)**.

100 Rink, H., *Tetrahedron Lett.*, 28, 3787, **(1987)**.

101 Orlowski, R. C., Walter, R., Winkler, D., *J. Org. Chem.*, 41, 3701, **(1976)**.

102 Brown, D. S., Revill, J. M., Shule, R. E., *Tetrahedron Lett.*, 39, 8533, **(1998)**.

103 Morphy, J. R., Rankovic, Z., Rees, D. C., *Tetrahedron Lett.*, 37, 3209, **(1996)**.

104 Swistok, J., Tiley, J. W., Dahno, W., Wagner, R., Mullkerins, K., *Tetrahedron Lett.*, 30, 5045, **(1989)**.

105 Yedidia, V., Leznoff, C. C., *Can. J. Chem.*, 58, 1144, **(1980)**.

106 Chamoin, S., Houldsworth, S., Snieckus, V., *Tetrahedron Lett.*, 39, 4175, **(1998)**.

107 Fancelli, D., Fangola, M. C., Severino, D., Bedeschi, A., *Tetrahedron Lett.*, 38, 231, **(1997)**.

108 Waldmann, H., *Angew. Chem., Int. Ed. Engl.*, 37, 1143, **(1998)**.

109 Böhm, G., Dowden, J., Rice, D. C., Burgess, I., Pilard, J. F., Guilbert, B., Haxton, R., Hunter, R. C., Turner, N. J., Flitsch, S. L., *Tetrahedron Lett.*, 39, 3819, **(1998)**.

110 Rich, D. H., Gurwara, S. K., *J. Chem. Soc. Chem. Commun.*, 610, **(1973)**.

111 Rich, D. H., Gurwara, S. K., *J. Am. Chem. Soc.*, 97, 1575, **(1975)**.

112 Ajayaghosh, A., Pillai, V. N. R., *Tetrahedron. Lett.*, 29, 6661, **(1988)**.

113 Ajayaghosh, A., Pillai, V. N. R., *Tetrahedron. Lett.*, 36, 777, **(1995)**.

114 Zehavi, U., Patchornik, A., *J. Am. Chem. Soc.*, 95, 5673, **(1973)**.

115 Sheenan, J. C., Umezawa, K., *J. Org. Chem.*, 38, 3774, **(1973)**.

116 Wang, S. S., *J. Org. Chem.*, 41, 3258, **(1976)**.

117 Rock, R. S., Chan, S. I., *J. Org. Chem.*, 61, 1526, **(1996)**.

118 Routledge, A., Abell, C., Balasubramanian, S., *Tetrahedron Lett.*, 38, 1227, **(1997)**.

119 Goldman, Y. E., Hibberd, M. G., Moray, J. A., Trentham, D. R., *Nature*, 701, **(1982)**.

120 Lee, H. B., Balasubramanian, S., *J. Org. Chem.*, 64, 3454, **(1999)**.

121 a) Schalatter, J. M., Mazur, R. H., *Tetrahedron Lett.*, 18, 2851, **(1977)**; b) Jones, D. A., *Tetrahedron Lett.*, 18, 2853, **(1977)**.

122 Khan, S. A., Sivanandaiah, K. M., *Synthesis*, 750, **(1978)**.

123 Virgilio, A. A., Schûrer, S. C., Ellman, J. A., *Tetrahedron Lett.*, 37, 6961, **(1996)**.

124 Sourers, A. J., Virgilo, A. A., Rosenquist, A., Feniuk, W., Ellman, J. A., *J. Am. Chem. Soc.*, 121, 1817, **(1999)**.

125 Ruhland, T., Andersen, K., Pedersen, H., *J. Org. Chem.*, 63, 9204, **(1998)**.

126 Nicolaou, K. C., Pastor, J., Barluenga, S., Winssinger, N., *J. Chem. Soc., Chem. Commum.*, 1947, **(1998)**.

127 Kobayashi, S., Hachiya, I., Yasuda, M., *Tetrahedron Lett.*, 37, 5569, **(1996)**.

128 Kobayashi, S., Hachiya, I., Suzuki, S., Moriwaki, M., *Tetrahedron Lett.*, 37, 2809, **(1996)**.

129 Kurth, M. J., Ahlberg-Randall, L. A., Chen, C., Melander, C., Bryan-Miller, R., *J. Org. Chem.*, 59, 5862, **(1994)**.

130 Tietze, L. F., Hippe, T., Steinmetz, A., *J. Chem. Soc., Chem. Commun.*, 793, **(1998)**.

131 Zheng, A., Shan, D., Wang, B., *J. Org. Chem.*, 64, 159, **(1999)**.

132 Deegan, T. L., Gooding, O. W., Baudart, S., Porco, J. Jr., *Tetrahedron Lett.*, 38, 4973, **(1997)**.

133 Kobayashi, S., Akiyama, R., *Tetrahedron Lett.*, 39, 9211, **(1998)**.

134 Kobayashi, S., Aoki, Y., *Tetrahedron Lett.*, 39, 7345, **(1998)**.

135 Fréchet, J. M., Schuerch, C. J., *J. Am. Chem. Soc.*, 93, 492, **(1971)**.

136 Sylvain, C., Wagner, A., Mioskowski, C., *Tetrahedron Lett.*, 38, 1043, **(1997)**.

137 Fruchart, J. S., Gras-Masse, H., Melnyk, O., *Tetrahedron Lett.*, 40, 6225, **(1999)**.

138 Phillips, A. R., *J. Am. Chem. Soc.*, 78, 4441, **(1956)**.

139 Zhu, S., Qin, C., Wang, Y., Chu, Q., *J. Fluorine. Chem.*, 2, 183, **(1999)**.

140 Bergmann., *J. Chem. Soc.*, 2564, **(1953)**.

141 Kappe, T., Hariri, M., Pongratz, E., *Monatsch. Chem.*, 112, 1211, **(1981)**.

142 Kröhnke, F., Vogt, I., *Chem. Ber.*, 85, 368, (1952).

143 Hanhinen, P., Putkonen, T., Lounasmaa, M., *Heterocycles*, 51, 785, **(1999)**.

144 Katritzky, A. R., Watson, C. H., Dega-Szafran, Z., Eyler, J. R., *J. Am. Chem. Soc.*, 112, 2471, **(1990)**.

145 Eda, M., Kurth, M. J., Nantz, M. H., *J. Org. Chem.*, 65, 5131, **(2000)**.

146 Hesek, J. A., Wilson, R. C., *Anal. Chem.*, 46, 1160, **(1974)**.

147 Wan, J. K. S., Wolf, K., Heyding, R. D., *"Catalysis on the Energy Scene"*, (Eds., Kaliaguine, S., Mahay, K)., Elsevier Science Publishers, Amsterdam, 561, **(1984)**.

148 Gedye, R., Smith, F., Westaway, K., Ali, H., Baldisera, L., Laberge, L., Rousell, J., *Tetrahedron Lett.*, 2, 279, **(1986)**.

149 Ukrainets, I. V., Taran, S. G., Sidorenko, L. V., Gorokhova., Ogirenko, A. A., Turov, A. V., Fillmonova, N. I., *Chem. Heterocycl. Compd.*, 32, 960, **(1996)**.

150 Geysen, H. M., Wagner, C. D., Wagner, W. M., Markworth, C. J., *Chem. Biol.*, 3, 679, **(1996)**.

151 Klein, S. I., Molino, B. F., Czekaj, M., Gardner, C. J., Chu, V., Brown, K., Sabatin, R. D., Boswick, J. S., Kasiewski, C., Bentley, R., Windisch, V., Perrone, M., Dunwidde, C. T., Leadley, R., *J. Med. Chem.*, 41, 1492, **(1998)**.

152 Salamone, J. C., Taylor, P., Snider, B., Israel, S. C. J., *Polym. Sci., Polym. Chem. Ed.*, 13, 161, **(1975)**.

153 Bawn, C. E. H., *"Molecular Behaviour and the Development of Polymeric Materials"*., Ledwith, A., North, A. M., Ed.; Wiley: New York, **(1975)**.

154 Coppola, F., *Gazz. Chim. Ital.*, 15, 333, **(1885)**.

155 Schimdt, E., *Arch. Pharm. (Weinheim. Ger.).*, 251, 206, **(1913)**.

156 Duling, I. N., Pice, C. C., *J. Am. Chem. Soc.*, 84, 578, **(1962)**.

157 Katritzky, A. R., Rubio, O., *J. Am. Chem. Soc.*, 105, 4017, **(1983)**.

158 Ratts, K. W., Howe, R. K., Phillips, W. G., *J. Am. Chem. Soc.*, 91, 6115, **(1969)**.

159 Katritzky, A. R., Makrosz, M. J., *Heterocycles*, 22, 505, **(1984)**.

160 Crane, F. E., Fuoss, R. M., *Anal. Chem.*, 1651, **(1954)**.

161 Eliel, E. L., Goldkamp, A. H., Carosino, L. E., Eberhardt, M., *J. Org. Chem.*, 26, 5190, **(1961)**.

162 Belluci, G., Berti, G., Bianchini, R., Ingrosso, G., *J. Org. Chem.*, 46, 2315, **(1981)**.

163 Relles, H., *J. Org. Chem.*, 38, 1570, **(1973)**.

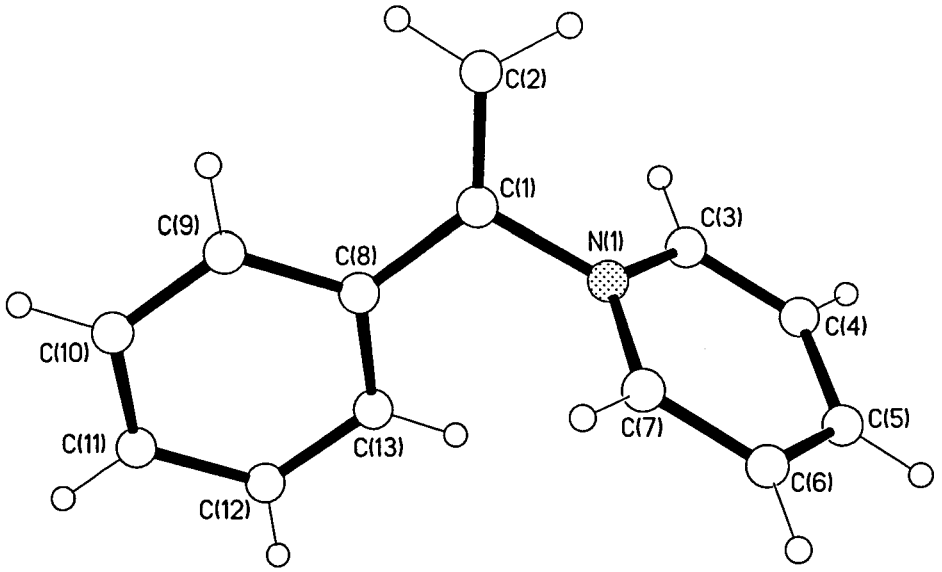
164 Eicher-Lorka, O., Kupetis, G. K., Rastenyté, L., Matijoška, A., *Synthesis*, 2131, **(1999)**.

165 Singleton, D. M., Kochi, J. K., *J. Am. Chem. Soc.*, 89, 6547, **(1967)**.

166 Abarca, B., Ballesteros, R., Enriquez, E., Jones, G., *Tetrahedron*, 41, 2435, **(1985)**.

APPENDIX (I)

Gw14 pictures – only resize via the corners!



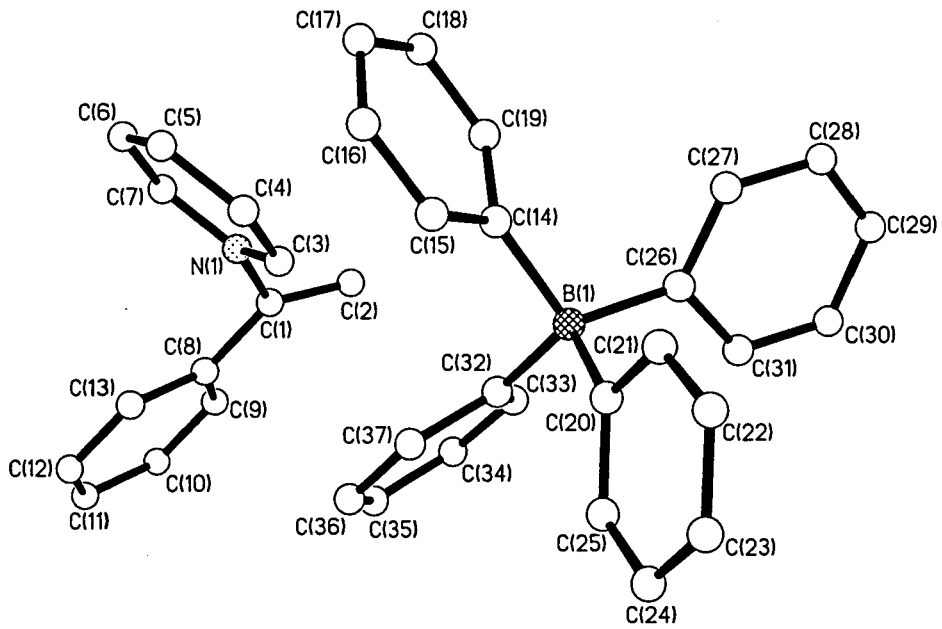


Table 1. Crystal data and structure refinement for gw14.

Identification code	gw14	
Chemical formula	$C_{37}H_{32}BN$	
Formula weight	501.45	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	monoclinic, $P2_1/n$	
Unit cell parameters	a = 9.3035(11) Å	α = 90°
	b = 16.749(2) Å	β = 90.924(2)°
	c = 17.984(2) Å	γ = 90°
Cell volume	2802.1(6) $Å^3$	
Z	4	
Calculated density	1.189 g/cm^3	
Absorption coefficient μ	0.067 mm^{-1}	
F(000)	1064	
Crystal colour and size	colourless, 0.30 × 0.07 × 0.04 mm^3	
Reflections for cell refinement	2502 (θ range 2.43 to 26.66°)	
Data collection method	Bruker SMART 1000 CCD diffractometer	
	ω rotation with narrow frames	
θ range for data collection	1.66 to 25.00°	
Index ranges	h −11 to 11, k −19 to 19, l −21 to 21	
Completeness to θ = 25.00°	100.0 %	
Intensity decay	0%	
Reflections collected	20124	
Independent reflections	4925 (R_{int} = 0.0736)	
Reflections with $F^2>2\sigma$	2862	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.980 and 0.997	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0000, 2.1865	
Data / restraints / parameters	4925 / 0 / 353	
Final R indices [$F^2>2\sigma$]	R1 = 0.0534, wR2 = 0.1135	
R indices (all data)	R1 = 0.1160, wR2 = 0.1550	
Goodness-of-fit on F^2	1.042	
Extinction coefficient	0.0093(10)	
Largest and mean shift/su	0.000 and 0.000	
Largest diff. peak and hole	0.196 and −0.242 e $Å^{-3}$	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for gw14. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
N(1)	−0.0097(3)	0.38562(14)	0.21072(13)	0.0341(6)
C(1)	0.1162(3)	0.37199(19)	0.25913(16)	0.0363(7)
C(2)	0.1666(4)	0.2985(2)	0.2638(2)	0.0563(10)
C(3)	0.0034(3)	0.37953(18)	0.13651(16)	0.0381(8)
C(4)	−0.1114(3)	0.39658(19)	0.09019(17)	0.0406(8)
C(5)	−0.2403(3)	0.41928(18)	0.12053(17)	0.0396(8)
C(6)	−0.2521(3)	0.4240(2)	0.19673(17)	0.0437(8)
C(7)	−0.1350(3)	0.40703(19)	0.24168(17)	0.0420(8)
C(8)	0.1712(3)	0.44457(19)	0.29639(16)	0.0359(7)
C(9)	0.2602(3)	0.4375(2)	0.35955(17)	0.0463(9)
C(10)	0.3110(3)	0.5049(3)	0.39605(19)	0.0570(10)
C(11)	0.2742(4)	0.5801(3)	0.3708(2)	0.0576(10)
C(12)	0.1865(4)	0.5880(2)	0.3082(2)	0.0540(9)
C(13)	0.1349(4)	0.52053(19)	0.27144(18)	0.0441(8)
B(1)	0.1914(4)	0.2649(2)	−0.07674(18)	0.0312(8)
C(14)	0.0166(3)	0.27442(17)	−0.06955(15)	0.0313(7)
C(15)	−0.0652(3)	0.32970(17)	−0.11043(16)	0.0352(7)
C(16)	−0.2121(3)	0.34001(19)	−0.10173(17)	0.0400(8)
C(17)	−0.2856(3)	0.29405(18)	−0.05088(17)	0.0391(8)
C(18)	−0.2096(3)	0.23861(18)	−0.00913(17)	0.0400(8)
C(19)	−0.0626(3)	0.22944(17)	−0.01769(16)	0.0343(7)
C(20)	0.2457(3)	0.29735(17)	−0.15839(16)	0.0326(7)
C(21)	0.1787(3)	0.26973(19)	−0.22414(16)	0.0418(8)
C(22)	0.2272(4)	0.28878(19)	−0.29451(17)	0.0471(9)
C(23)	0.3463(4)	0.33711(18)	−0.30249(17)	0.0430(8)
C(24)	0.4153(3)	0.36607(19)	−0.23905(17)	0.0422(8)
C(25)	0.3651(3)	0.34646(17)	−0.16878(17)	0.0373(7)
C(26)	0.2396(3)	0.17054(17)	−0.07597(14)	0.0300(7)
C(27)	0.1459(3)	0.10847(17)	−0.09732(16)	0.0342(7)
C(28)	0.1879(3)	0.02903(18)	−0.10189(17)	0.0395(8)
C(29)	0.3275(3)	0.00752(19)	−0.08400(17)	0.0421(8)
C(30)	0.4240(3)	0.06634(18)	−0.06329(16)	0.0375(8)
C(31)	0.3811(3)	0.14533(18)	−0.06056(15)	0.0336(7)
C(32)	0.2617(3)	0.31833(17)	−0.00878(15)	0.0318(7)
C(33)	0.3333(3)	0.28880(19)	0.05456(15)	0.0360(7)
C(34)	0.3868(3)	0.3381(2)	0.11101(17)	0.0430(8)
C(35)	0.3709(3)	0.4200(2)	0.10611(18)	0.0453(8)
C(36)	0.3007(4)	0.4520(2)	0.04436(17)	0.0448(8)
C(37)	0.2475(3)	0.40159(18)	−0.01081(17)	0.0383(8)

Table 3. Bond lengths [Å] and angles [°] for gw14.

N(1)–C(3)	1.346(4)	N(1)–C(7)	1.348(4)
N(1)–C(1)	1.466(4)	C(1)–C(2)	1.319(4)
C(1)–C(8)	1.476(4)	C(3)–C(4)	1.374(4)
C(4)–C(5)	1.379(4)	C(5)–C(6)	1.379(4)
C(6)–C(7)	1.375(4)	C(8)–C(13)	1.389(4)
C(8)–C(9)	1.400(4)	C(9)–C(10)	1.385(5)
C(10)–C(11)	1.380(5)	C(11)–C(12)	1.386(5)
C(12)–C(13)	1.391(4)	B(1)–C(14)	1.642(4)
B(1)–C(32)	1.642(4)	B(1)–C(26)	1.643(4)
B(1)–C(20)	1.653(4)	C(14)–C(15)	1.400(4)
C(14)–C(19)	1.415(4)	C(15)–C(16)	1.388(4)
C(16)–C(17)	1.384(4)	C(17)–C(18)	1.382(4)
C(18)–C(19)	1.387(4)	C(20)–C(25)	1.397(4)
C(20)–C(21)	1.406(4)	C(21)–C(22)	1.387(4)
C(22)–C(23)	1.382(4)	C(23)–C(24)	1.387(4)
C(24)–C(25)	1.394(4)	C(26)–C(31)	1.406(4)
C(26)–C(27)	1.406(4)	C(27)–C(28)	1.390(4)
C(28)–C(29)	1.381(4)	C(29)–C(30)	1.380(4)
C(30)–C(31)	1.383(4)	C(32)–C(33)	1.401(4)
C(32)–C(37)	1.401(4)	C(33)–C(34)	1.395(4)
C(34)–C(35)	1.382(5)	C(35)–C(36)	1.387(4)
C(36)–C(37)	1.388(4)		

C(3)–N(1)–C(7)	121.5(3)	C(3)–N(1)–C(1)	119.5(2)
C(7)–N(1)–C(1)	118.9(2)	C(2)–C(1)–N(1)	117.6(3)
C(2)–C(1)–C(8)	128.3(3)	N(1)–C(1)–C(8)	114.2(3)
N(1)–C(3)–C(4)	120.2(3)	C(3)–C(4)–C(5)	119.3(3)
C(6)–C(5)–C(4)	119.5(3)	C(7)–C(6)–C(5)	119.8(3)
N(1)–C(7)–C(6)	119.6(3)	C(13)–C(8)–C(9)	118.5(3)
C(13)–C(8)–C(1)	121.8(3)	C(9)–C(8)–C(1)	119.7(3)
C(10)–C(9)–C(8)	120.6(3)	C(11)–C(10)–C(9)	120.5(3)
C(10)–C(11)–C(12)	119.6(3)	C(11)–C(12)–C(13)	120.2(4)
C(8)–C(13)–C(12)	120.7(3)	C(14)–B(1)–C(32)	105.8(2)
C(14)–B(1)–C(26)	111.3(2)	C(32)–B(1)–C(26)	114.4(2)
C(14)–B(1)–C(20)	110.8(2)	C(32)–B(1)–C(20)	111.0(2)
C(26)–B(1)–C(20)	103.7(2)	C(15)–C(14)–C(19)	114.5(3)
C(15)–C(14)–B(1)	123.6(3)	C(19)–C(14)–B(1)	121.8(3)
C(16)–C(15)–C(14)	123.4(3)	C(17)–C(16)–C(15)	120.2(3)
C(18)–C(17)–C(16)	118.6(3)	C(17)–C(18)–C(19)	120.7(3)
C(18)–C(19)–C(14)	122.6(3)	C(25)–C(20)–C(21)	115.1(3)
C(25)–C(20)–B(1)	124.6(3)	C(21)–C(20)–B(1)	120.1(3)
C(22)–C(21)–C(20)	123.0(3)	C(23)–C(22)–C(21)	120.2(3)
C(22)–C(23)–C(24)	118.7(3)	C(23)–C(24)–C(25)	120.4(3)
C(24)–C(25)–C(20)	122.6(3)	C(31)–C(26)–C(27)	113.9(3)
C(31)–C(26)–B(1)	123.0(3)	C(27)–C(26)–B(1)	122.8(3)
C(28)–C(27)–C(26)	123.4(3)	C(29)–C(28)–C(27)	120.0(3)
C(30)–C(29)–C(28)	118.8(3)	C(29)–C(30)–C(31)	120.3(3)
C(30)–C(31)–C(26)	123.4(3)	C(33)–C(32)–C(37)	114.6(3)
C(33)–C(32)–B(1)	126.3(3)	C(37)–C(32)–B(1)	119.1(3)
C(34)–C(33)–C(32)	122.8(3)	C(35)–C(34)–C(33)	120.3(3)
C(34)–C(35)–C(36)	118.9(3)	C(35)–C(36)–C(37)	119.7(3)
C(36)–C(37)–C(32)	123.7(3)		

Table 4. Anisotropic displacement parameters ($Å^2$) for gw14. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ...+ 2hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	0.0378(15)	0.0363(14)	0.0283(14)	0.0022(11)	0.0024(11)	−0.0024(11)
C(1)	0.0341(17)	0.0436(19)	0.0312(17)	0.0067(14)	0.0004(13)	0.0003(14)
C(2)	0.064(2)	0.041(2)	0.064(2)	0.0122(18)	−0.0056(19)	0.0028(18)
C(3)	0.0410(19)	0.0409(18)	0.0327(18)	−0.0049(14)	0.0051(14)	−0.0012(15)
C(4)	0.046(2)	0.048(2)	0.0285(17)	−0.0041(15)	−0.0007(15)	−0.0064(16)
C(5)	0.0388(18)	0.0468(19)	0.0330(18)	0.0035(15)	−0.0034(14)	−0.0036(15)
C(6)	0.0368(19)	0.058(2)	0.0363(19)	0.0006(16)	0.0039(15)	−0.0002(16)
C(7)	0.0397(19)	0.054(2)	0.0325(18)	0.0014(15)	0.0053(15)	−0.0003(16)
C(8)	0.0319(17)	0.0483(19)	0.0276(16)	0.0017(14)	0.0026(13)	−0.0027(14)
C(9)	0.0333(18)	0.070(2)	0.0360(19)	0.0074(17)	−0.0017(15)	0.0013(17)
C(10)	0.0311(19)	0.101(3)	0.039(2)	−0.012(2)	0.0007(15)	−0.005(2)
C(11)	0.040(2)	0.075(3)	0.058(2)	−0.026(2)	0.0054(18)	−0.0060(19)
C(12)	0.053(2)	0.051(2)	0.058(2)	−0.0102(18)	−0.0006(19)	−0.0063(18)
C(13)	0.049(2)	0.045(2)	0.0383(19)	0.0009(16)	−0.0056(15)	−0.0045(16)
B(1)	0.0351(19)	0.0304(18)	0.0282(18)	0.0007(14)	−0.0012(14)	0.0004(15)
C(14)	0.0389(17)	0.0313(16)	0.0238(15)	−0.0050(13)	−0.0006(13)	0.0022(13)
C(15)	0.0411(18)	0.0335(17)	0.0308(16)	0.0004(14)	−0.0007(14)	−0.0010(14)
C(16)	0.048(2)	0.0386(18)	0.0337(18)	−0.0054(15)	−0.0070(15)	0.0054(15)
C(17)	0.0346(17)	0.0421(19)	0.0403(18)	−0.0095(15)	−0.0037(14)	0.0021(15)
C(18)	0.046(2)	0.0400(19)	0.0343(17)	−0.0023(14)	0.0048(15)	−0.0026(15)
C(19)	0.0371(18)	0.0353(17)	0.0306(16)	−0.0006(13)	0.0013(13)	0.0038(14)
C(20)	0.0358(17)	0.0303(16)	0.0316(17)	0.0013(13)	0.0006(13)	0.0023(13)
C(21)	0.050(2)	0.0445(19)	0.0314(17)	−0.0014(15)	0.0026(15)	−0.0077(16)
C(22)	0.066(2)	0.044(2)	0.0311(18)	0.0017(15)	0.0029(16)	−0.0022(18)
C(23)	0.061(2)	0.0392(19)	0.0288(17)	0.0051(15)	0.0136(16)	0.0043(17)
C(24)	0.045(2)	0.0400(19)	0.0420(19)	0.0035(15)	0.0104(16)	−0.0011(15)
C(25)	0.0407(18)	0.0380(18)	0.0334(17)	0.0021(14)	0.0037(14)	0.0010(14)
C(26)	0.0322(16)	0.0356(17)	0.0223(15)	0.0010(13)	0.0034(12)	−0.0013(13)
C(27)	0.0335(17)	0.0336(17)	0.0356(17)	−0.0019(14)	0.0034(13)	0.0023(13)
C(28)	0.0415(19)	0.0348(18)	0.0424(19)	−0.0020(14)	0.0090(15)	−0.0022(14)
C(29)	0.047(2)	0.0347(18)	0.0445(19)	0.0031(15)	0.0091(16)	0.0060(15)
C(30)	0.0358(18)	0.046(2)	0.0306(17)	0.0059(14)	0.0037(14)	0.0065(15)
C(31)	0.0368(17)	0.0377(18)	0.0263(16)	0.0029(13)	0.0030(13)	0.0022(14)
C(32)	0.0304(16)	0.0368(17)	0.0282(16)	0.0010(13)	0.0044(13)	−0.0002(13)
C(33)	0.0376(18)	0.0406(18)	0.0299(17)	0.0007(14)	0.0016(14)	−0.0017(14)
C(34)	0.0386(19)	0.058(2)	0.0322(18)	−0.0040(16)	−0.0032(14)	0.0026(16)
C(35)	0.046(2)	0.051(2)	0.0392(19)	−0.0122(16)	−0.0006(16)	−0.0074(16)
C(36)	0.059(2)	0.0366(18)	0.0393(19)	−0.0043(15)	0.0038(16)	−0.0026(16)
C(37)	0.048(2)	0.0361(18)	0.0302(17)	−0.0028(14)	−0.0014(14)	−0.0014(15)

Table 5. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for gw14.

	x	y	z	U
H(2A)	0.1214	0.2567	0.2363	0.068
H(2B)	0.2480	0.2873	0.2946	0.068
H(3)	0.0924	0.3634	0.1161	0.046
H(4)	−0.1021	0.3928	0.0378	0.049
H(5)	−0.3204	0.4316	0.0892	0.047
H(6)	−0.3408	0.4389	0.2181	0.052
H(7)	−0.1424	0.4104	0.2942	0.050
H(9)	0.2859	0.3861	0.3776	0.056
H(10)	0.3715	0.4994	0.4388	0.068
H(11)	0.3089	0.6262	0.3962	0.069
H(12)	0.1616	0.6397	0.2904	0.065
H(13)	0.0741	0.5265	0.2288	0.053
H(15)	−0.0178	0.3619	−0.1460	0.042
H(16)	−0.2623	0.3787	−0.1308	0.048
H(17)	−0.3861	0.3005	−0.0448	0.047
H(18)	−0.2585	0.2064	0.0258	0.048
H(19)	−0.0131	0.1915	0.0125	0.041
H(21)	0.0964	0.2365	−0.2202	0.050
H(22)	0.1783	0.2686	−0.3373	0.057
H(23)	0.3804	0.3502	−0.3505	0.052
H(24)	0.4972	0.3995	−0.2435	0.051
H(25)	0.4140	0.3673	−0.1263	0.045
H(27)	0.0489	0.1215	−0.1092	0.041
H(28)	0.1206	−0.0105	−0.1173	0.047
H(29)	0.3566	−0.0468	−0.0859	0.051
H(30)	0.5205	0.0525	−0.0509	0.045
H(31)	0.4508	0.1846	−0.0476	0.040
H(33)	0.3460	0.2327	0.0593	0.043
H(34)	0.4345	0.3153	0.1530	0.052
H(35)	0.4074	0.4538	0.1444	0.054
H(36)	0.2891	0.5082	0.0398	0.054
H(37)	0.1988	0.4248	−0.0523	0.046

Table 6. Torsion angles [°] for gw14.

C(3)–N(1)–C(1)–C(2)	–69.2(4)	C(7)–N(1)–C(1)–C(2)	113.3(3)
C(3)–N(1)–C(1)–C(8)	110.2(3)	C(7)–N(1)–C(1)–C(8)	–67.2(3)
C(7)–N(1)–C(3)–C(4)	1.1(4)	C(1)–N(1)–C(3)–C(4)	–176.3(3)
N(1)–C(3)–C(4)–C(5)	–0.5(5)	C(3)–C(4)–C(5)–C(6)	–0.4(5)
C(4)–C(5)–C(6)–C(7)	0.8(5)	C(3)–N(1)–C(7)–C(6)	–0.7(5)
C(1)–N(1)–C(7)–C(6)	176.7(3)	C(5)–C(6)–C(7)–N(1)	–0.3(5)
C(2)–C(1)–C(8)–C(13)	161.6(3)	N(1)–C(1)–C(8)–C(13)	–17.8(4)
C(2)–C(1)–C(8)–C(9)	–19.8(5)	N(1)–C(1)–C(8)–C(9)	160.8(3)
C(13)–C(8)–C(9)–C(10)	–0.2(4)	C(1)–C(8)–C(9)–C(10)	–178.9(3)
C(8)–C(9)–C(10)–C(11)	0.2(5)	C(9)–C(10)–C(11)–C(12)	–0.3(5)
C(10)–C(11)–C(12)–C(13)	0.5(5)	C(9)–C(8)–C(13)–C(12)	0.4(5)
C(1)–C(8)–C(13)–C(12)	179.0(3)	C(11)–C(12)–C(13)–C(8)	–0.5(5)
C(32)–B(1)–C(14)–C(15)	96.2(3)	C(26)–B(1)–C(14)–C(15)	–139.0(3)
C(20)–B(1)–C(14)–C(15)	–24.2(4)	C(32)–B(1)–C(14)–C(19)	–80.3(3)
C(26)–B(1)–C(14)–C(19)	44.5(3)	C(20)–B(1)–C(14)–C(19)	159.4(2)
C(19)–C(14)–C(15)–C(16)	–0.3(4)	B(1)–C(14)–C(15)–C(16)	–177.0(3)
C(14)–C(15)–C(16)–C(17)	–0.4(4)	C(15)–C(16)–C(17)–C(18)	0.4(4)
C(16)–C(17)–C(18)–C(19)	0.3(4)	C(17)–C(18)–C(19)–C(14)	–1.1(4)
C(15)–C(14)–C(19)–C(18)	1.0(4)	B(1)–C(14)–C(19)–C(18)	177.8(3)
C(14)–B(1)–C(20)–C(25)	134.8(3)	C(32)–B(1)–C(20)–C(25)	17.6(4)
C(26)–B(1)–C(20)–C(25)	–105.6(3)	C(14)–B(1)–C(20)–C(21)	–51.2(4)
C(32)–B(1)–C(20)–C(21)	–168.4(3)	C(26)–B(1)–C(20)–C(21)	68.3(3)
C(25)–C(20)–C(21)–C(22)	0.6(5)	B(1)–C(20)–C(21)–C(22)	–174.0(3)
C(20)–C(21)–C(22)–C(23)	–0.1(5)	C(21)–C(22)–C(23)–C(24)	–0.2(5)
C(22)–C(23)–C(24)–C(25)	0.2(5)	C(23)–C(24)–C(25)–C(20)	0.3(5)
C(21)–C(20)–C(25)–C(24)	–0.7(4)	B(1)–C(20)–C(25)–C(24)	173.6(3)
C(14)–B(1)–C(26)–C(31)	–161.7(2)	C(32)–B(1)–C(26)–C(31)	–41.9(4)
C(20)–B(1)–C(26)–C(31)	79.1(3)	C(14)–B(1)–C(26)–C(27)	24.3(4)
C(32)–B(1)–C(26)–C(27)	144.1(3)	C(20)–B(1)–C(26)–C(27)	–94.9(3)
C(31)–C(26)–C(27)–C(28)	0.9(4)	B(1)–C(26)–C(27)–C(28)	175.4(3)
C(26)–C(27)–C(28)–C(29)	0.9(5)	C(27)–C(28)–C(29)–C(30)	–1.4(4)
C(28)–C(29)–C(30)–C(31)	0.1(4)	C(29)–C(30)–C(31)–C(26)	1.9(4)
C(27)–C(26)–C(31)–C(30)	–2.3(4)	B(1)–C(26)–C(31)–C(30)	–176.8(3)
C(14)–B(1)–C(32)–C(33)	110.3(3)	C(26)–B(1)–C(32)–C(33)	–12.6(4)
C(20)–B(1)–C(32)–C(33)	–129.5(3)	C(14)–B(1)–C(32)–C(37)	–67.6(3)
C(26)–B(1)–C(32)–C(37)	169.5(3)	C(20)–B(1)–C(32)–C(37)	52.6(3)
C(37)–C(32)–C(33)–C(34)	–0.2(4)	B(1)–C(32)–C(33)–C(34)	–178.2(3)
C(32)–C(33)–C(34)–C(35)	–0.2(5)	C(33)–C(34)–C(35)–C(36)	0.2(5)
C(34)–C(35)–C(36)–C(37)	0.3(5)	C(35)–C(36)–C(37)–C(32)	–0.8(5)
C(33)–C(32)–C(37)–C(36)	0.7(4)	B(1)–C(32)–C(37)–C(36)	178.9(3)