SYNTHETIC APPROACHES TOWARDS HETEROCYCLIC ANALOGUES OF VIRANTMYCIN

A Thesis

Submitted Towards the

Degree of

Doctor of Philosophy

by

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Finally, to my husband Jeff, thankyou for all your love, support and encouragement over the past four wonderful years. A special thanks also to my parents and my brother and sister for their support throughout the course of my education.

Statement

This work contains no material which had been accepted for the award of any other degree or diploma in any university of other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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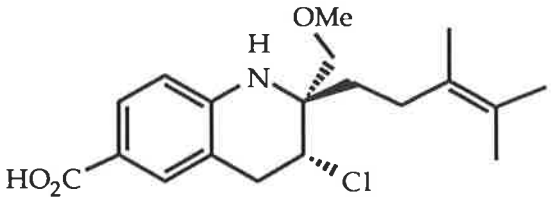
11-11-1993

Abstract

This thesis describes approaches towards the synthesis of heterocyclic analogues of virantmycin (4). The strategies employed were designed to enable variation of the heteroaromatic ring system, and in particular to encompass those common to nucleoside type systems such as substituted pyrimidines. In addition the methodologies were intended to provide a range of side chains and ultimately to achieve the synthesis of chiral derivatives of these analogues in future work.



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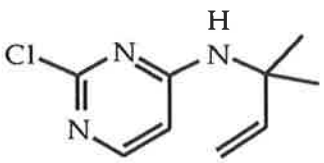
Chapter 2 describes the synthesis of the pyrimidine coupled derivative (32) as a precursor to a pyrimidine analogue of virantmycin. The amino-Claisen rearrangement of (32) to the *o*-allylaminopyrimidine (33), under both acidic and thermal conditions suitable for the corresponding benzenoid system, could not be effected.



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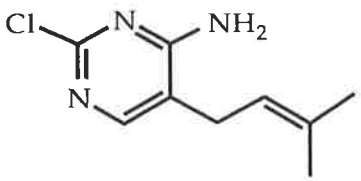
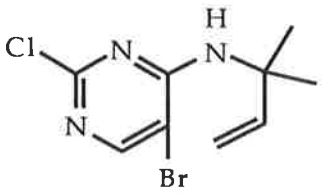


(33)

An alternative approach, outlined in chapter 3, involved the examination of electrophilically induced and palladium catalysed cyclisations to obtain pyrimidine analogues of virantmycin. Bromination of uracil, followed by

chlorination to form 5-bromo-2,4-dichloropyrimidine (39) and substitution of the C4 chloro moiety in (39) by 1,1-dimethylpropargylamine afforded the pyrimidine (37). Cyclisation of (37) using palladium catalysis gave the dihydropyrrolo[2,3-d]pyrimidine system (45). Conversely, (37) could be cyclised electrophilically, by addition of phenylselenenyl bromide across the alkene, followed by treatment with *n*-butyllithium, to afford the selenide (64). The selenide underwent oxidation followed by *syn*-elimination, resulting in the formation of the dihydropyrido[2,3-d]pyrimidine system (44). The structure of the intermediate selenide (64) was assigned from an extensive nmr study and by reduction of the seleno moiety to the corresponding hydrocarbon derivative (29).



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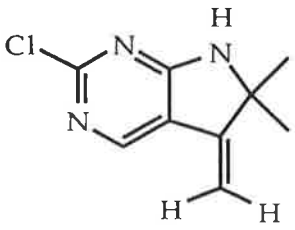

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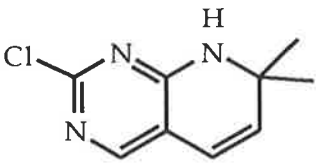

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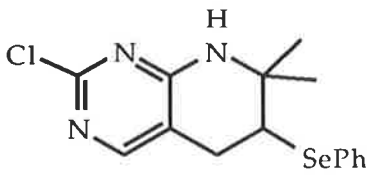

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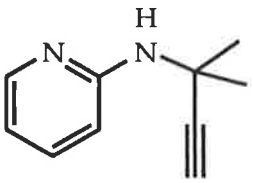
(29)

Chapter 4 reports on an investigation into the synthesis of precursors to pyridyl analogues of virantmycin. The first part of this chapter discusses attempts to form the coupled pyridine derivative (79). A copper catalysed, S_N1 type, substitution of a tertiary chloride using a aromatic amine was examined

for the aminopyridine system, utilising an approach that has been established for the corresponding benzenoid system. The coupling could not be achieved due to complications caused by coordination between the aminopyridine system and the copper, hence preventing catalysis of the reaction. An alternative approach involving nucleophilic substitution of the pyridine ring by amines proved unsuitable due to the lower reactivity of the pyridine system towards nucleophilic attack. The second part of this chapter outlines the use of benzotriazole chemistry in the attempted formation of the pyridine derivative (79). The benzotriazole chemistry proved suitable only for the formation of mono substituted pyridine derivatives such as (115). These compounds could not be further elaborated to obtain the disubstituted derivative (79).



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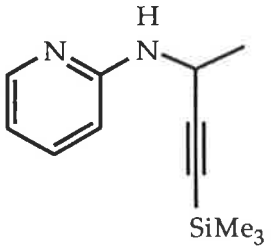

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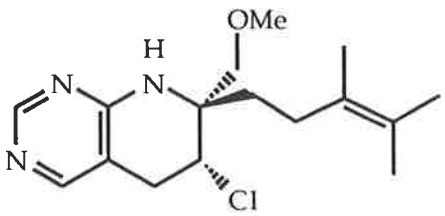
Chapter 5 discusses briefly the methodologies that could be investigated in the future, including the synthesis of a chiral amine which will enable heterocyclic analogues of virantmycin such as (16), with the desired side chains, to be obtained.



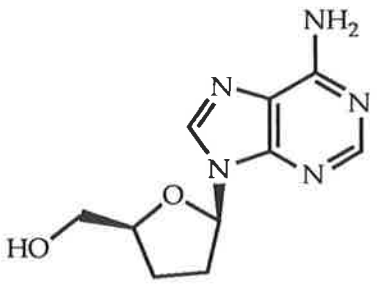
(16)

Chapter 1 *General Introduction*

Part 1 : Background

One of the major areas of current chemical research is the investigation into the syntheses of new and improved biologically active compounds. This is particularly extensive in the area of AIDS research[1,2,3,4,5] and the race to find a cure or vaccine for the AIDS virus.

Some compounds in the nucleoside class of drugs have been shown to inhibit the *in vitro* replication of the human immunodeficiency virus[4,5] and other RNA and DNA viruses. Common to this class of compound is the incorporation of a sugar based -O-C-N- linkage as shown in dideoxyadenosine (1) and zidovudine (2).



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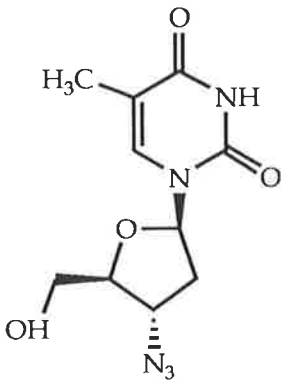


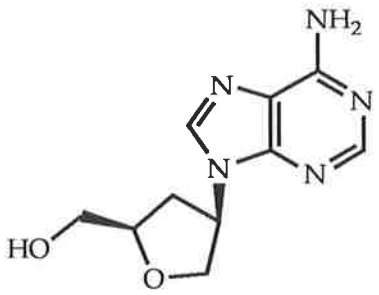
(2)

Dideoxyadenosine (ddA), zidovudine (AZT) and others in this class have been shown[3] to inhibit viral replication of the HIV reverse transcriptase rather than eradicate the virus. Consequently it is likely that this type of drug must be taken continuously if the therapeutic effect is to be maintained.

The most convenient method of continual dosage is via oral administration which exposes the drug to a pH range of 1-2 in the human stomach. The therapeutic uses of these compounds are then limited by their rapid degradation via acid catalysed hydrolysis of the glycosidic bond.[3]

In addition, recent studies[6] have raised doubts as to the effectiveness of zidovudine (AZT) in the treatment of the AIDS virus, indicating that while the administration of the drug may initially slow the progression of the disease, in the long term the virus will develop as quickly as in those not administered the drug.

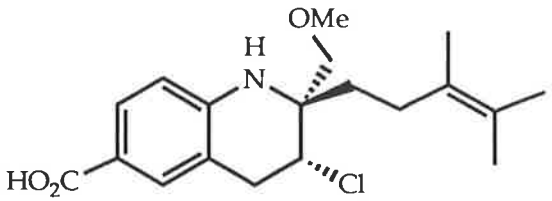
As a consequence research into the synthesis of acid-stable antiviral compounds is prevalent. It has been shown[2] that the sugar based linkage was not essential for biological activity to be observed since iso-ddA (3) was found to exhibit anti-HIV activity in the same range as that observed for ddA. Unlike ddA, however, iso-ddA is stable[2] in both acidic and basic media.



(3)

Another compound found to exhibit biological activity against some RNA and DNA viruses is virantmycin[7,8,9] (4), which has been isolated from the fermentation broth of *Streptomyces nitrosporeus*. It is a potent antibiotic which also possesses weak antifungal activity and in addition has been

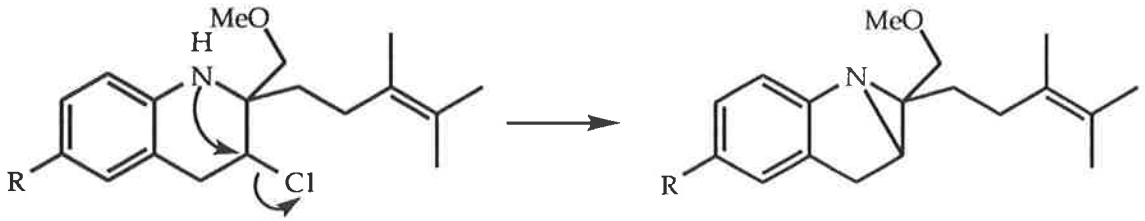
shown[10] to have significant *in vitro* activity against herpes simplex types 1 & 2.



(4)

It should be noted[7] that virantmycin inhibits the growth of both RNA and DNA viruses which differ from each other in their growth mechanism. This raises the question as to whether the mechanism of action of the drug is the same for both types of virus.

The mode of action of virantmycin is not known, although an aziridine species (5) (*Scheme* 1), which has been obtained chemically,[9] may be the reactive component.

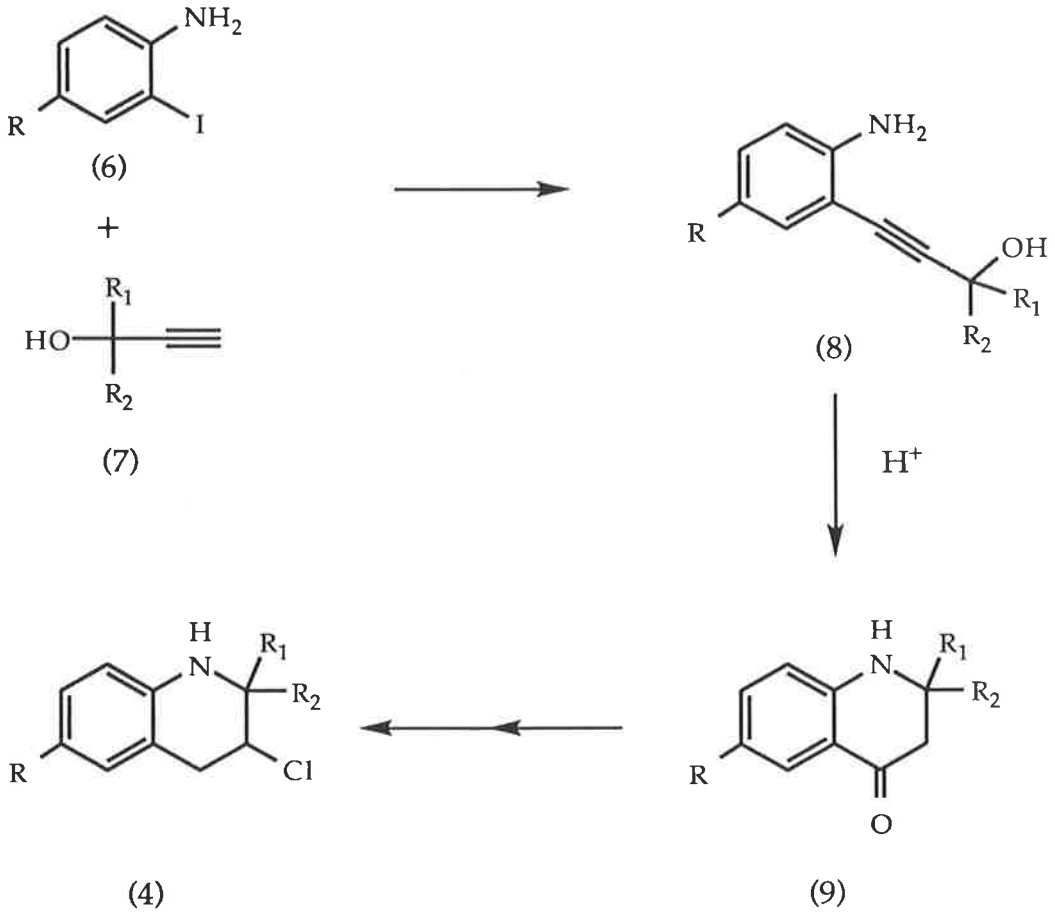


(4) (5)

Scheme 1

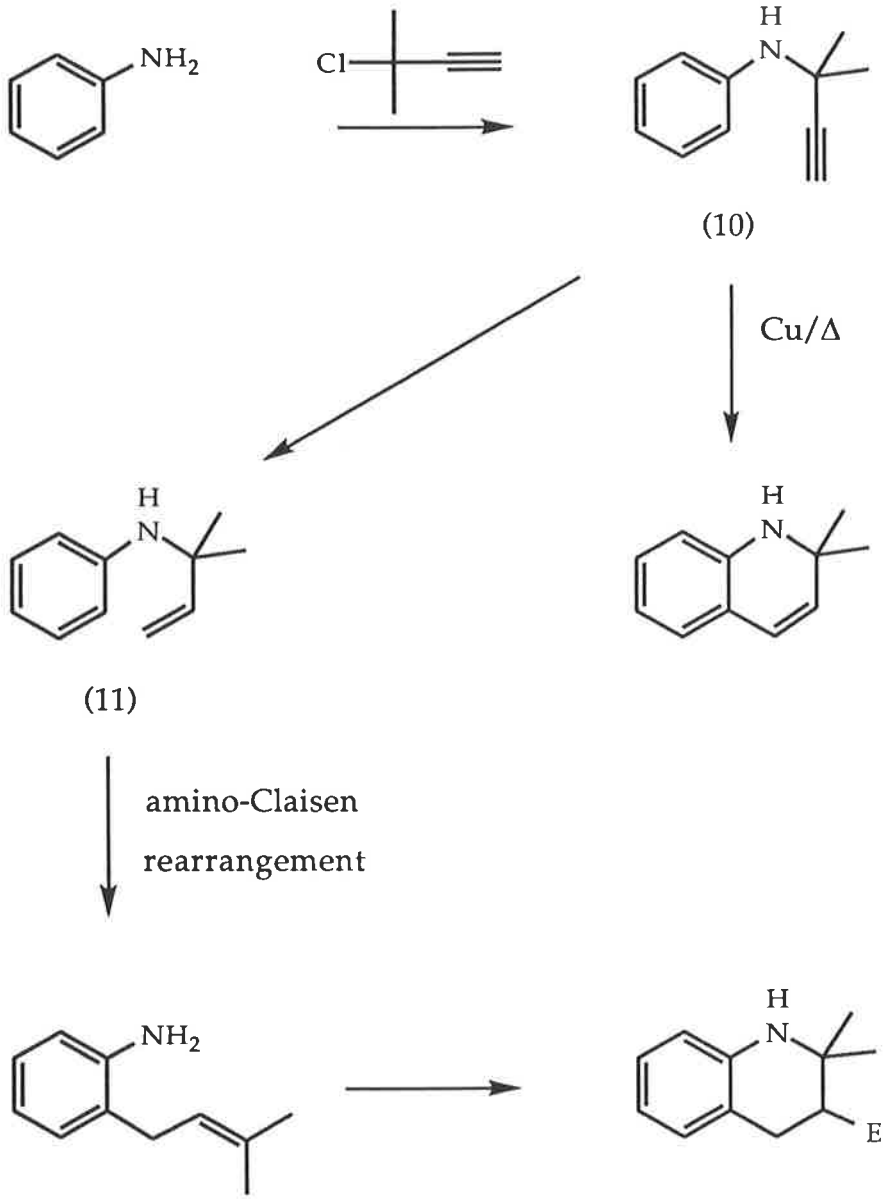
Several synthetic routes to virantmycin have been reported.[10,11] These, however, were not stereoselective and involved a large number of steps. Each approach employed an initial palladium catalysed coupling[12] between an *ortho*-haloaniline (6) and an acetylenic alcohol (7) to form the amino-alcohol (8), as depicted in scheme 2. Cyclisation of the amino-alcohol (8) can be

achieved using a Meyer-Schuster rearrangement[13] to afford the bicyclic ketone (9). Manipulation of the tetrahydroquinolone (9) to virantmycin has been achieved in several literature reports.[10,11]



Scheme 2

An alternative methodology which is currently being investigated in our laboratories involves the synthesis of the tetrahydroquinoline nucleus of virantmycin via the key intermediates of the allylamine (11) or alkynylamine (10). In the case of the allylamine an amino-Claisen rearrangement[14] followed by an electrophilically induced cyclisation[15] can be used to form the tetrahydroquinoline system, while cyclisation of the alkynylamine can be induced by copper catalysis[16] (*Scheme* 3).



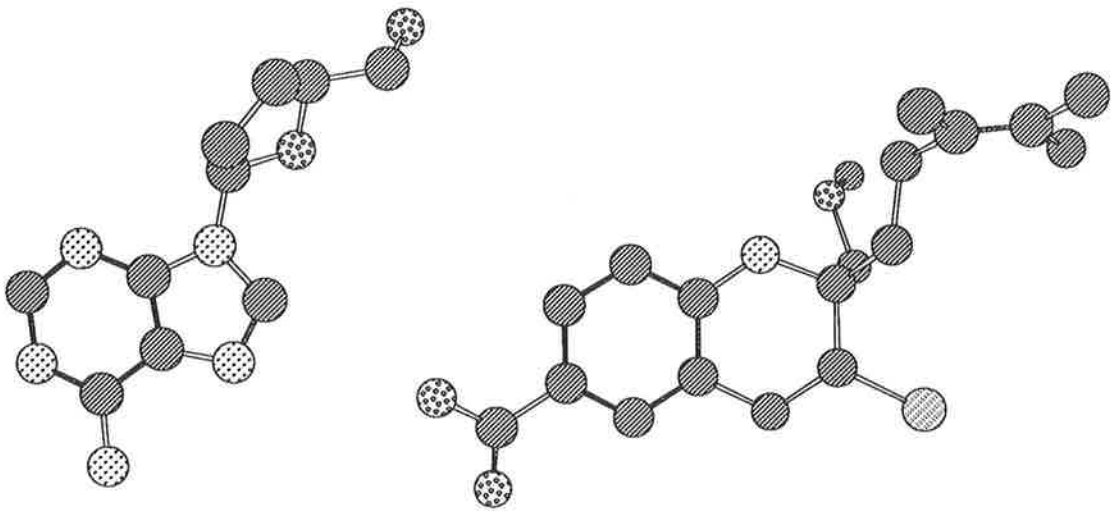
Scheme 3

A major drawback with these approaches to virantmycin is that at least one step in the reaction sequence proceeds via an S_N1 type transition state or an allene intermediate at the tertiary carbon centre. As a consequence this may prevent any stereochemical control at this position, which would be required for the synthesis of a single enantiomer of virantmycin.

Part 2 : Structural Analysis of Virantmycin and Analogues with Nucleosides

Virantmycin has been a major focus of research in our laboratories for some time. More recently attention has been centred on the possibility of extending the chemistry developed for virantmycin to the synthesis of analogues. Another area of particular interest to us was a structural comparison of virantmycin and its analogues with the nucleoside based drugs which exhibit activity towards RNA and DNA viruses.

Virantmycin and dideoxyadenosine may have more structural similarities than would first appear to be the case. The electron rich centres of the carboxylic acid, as the carboxylate anion, and the side chain alkene of virantmycin could possibly be equated to the electron rich amino and hydroxyl centres of the nucleoside respectively. Furthermore the nitrogen of the tetrahydropyridine ring and the methoxyl oxygen of virantmycin may be in a similar spatial position to the aminal nitrogen and oxygen of the nucleoside (*Fig* 1).

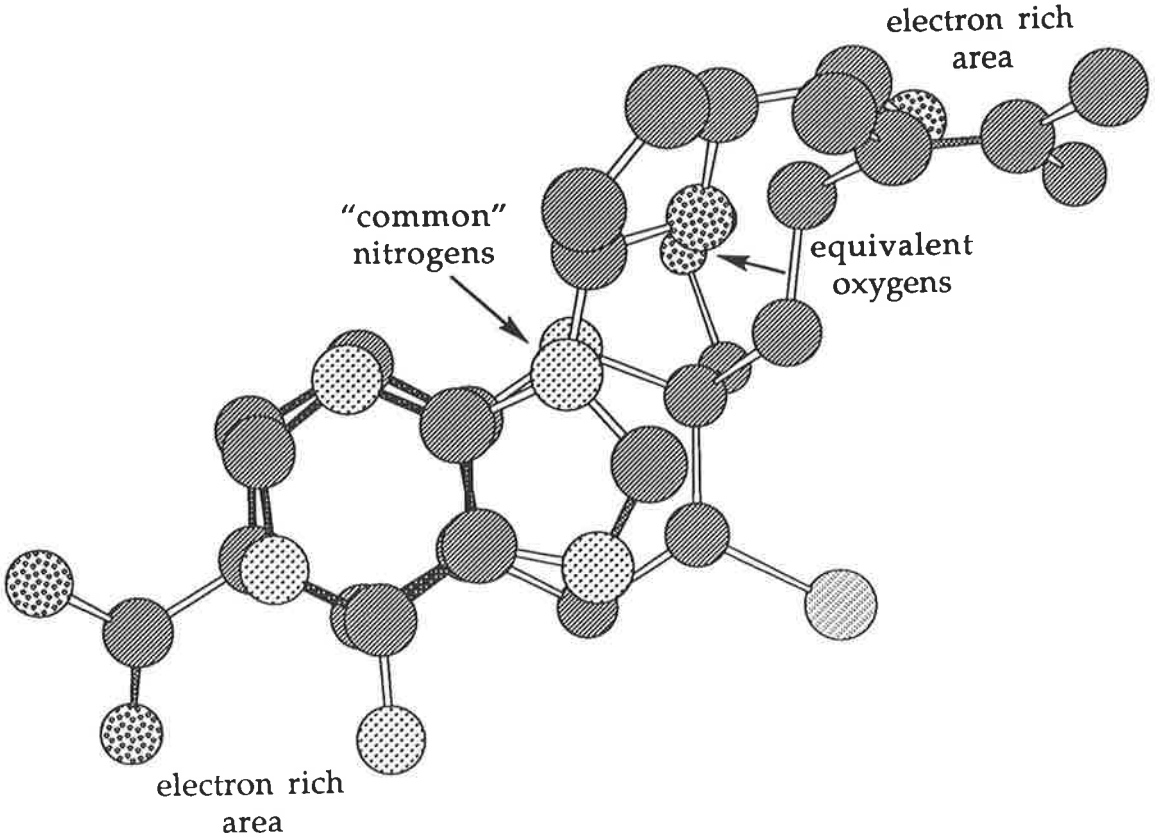


ddA Virantmycin

Conformers of Least Energy

Figure 1

Molecular modelling studies, carried out in our preliminary investigations to compare virantmycin with ddA and other nucleosides, have shown that the two compounds do have structural similarities and, in particular, have indicated that the spatial arrangements of the oxygens of the ether moiety in virantmycin and of the sugar based moiety of the dideoxynucleosides could be comparable. If this were the case, the methoxy oxygen of virantmycin may be mimicking the oxygen of the glycosidic bond in the nucleosides. This may enable the ether oxygen of virantmycin to bind to the same receptor sites as the nucleosides and then allow the drug to undergo reaction with the virus to achieve inhibition. Binding to the active sites would also be aided by the electron rich sites of virantmycin which appear to be closely related spatially to the electron rich sites of ddA, as outlined earlier.



Overlay of Virantmycin and Dideoxyadenosine.

Figure 2

By superimposing the structures obtained from the molecular modelling studies of the conformer of least energy, it appeared possible that the orientation of the oxygen from the ether moiety in one conformer of virantmycin may be considered to be in the same spatial arrangement as the oxygen of the glycoside moiety of the nucleoside (*Fig* 2).

If this were the case, derivatives with a virantmycin type skeleton could conceivably have a great advantage over the nucleoside based drugs. The glycosidic linkages present in the latter would no longer be incorporated into the molecule thus preventing degradation via hydrolysis and possibly prolonging the effectiveness of the drug.

To this end, it was of interest to design a series of analogues that incorporated features from both the virantmycin and nucleoside drug systems. It was envisaged that an interesting form of these derivatives would be nitrogen analogues of the virantmycin skeleton, whereby the benzenoid ring had been altered to a nitrogen containing heterocyclic ring system. Modification of the ring so as to incorporate the nitrogen atom in a position either *ortho, para* or both to the carbon bearing the nitrogen of the second ring (*Fig* 3) could then be utilised for comparison with the heterocyclic ring of the nucleoside systems.

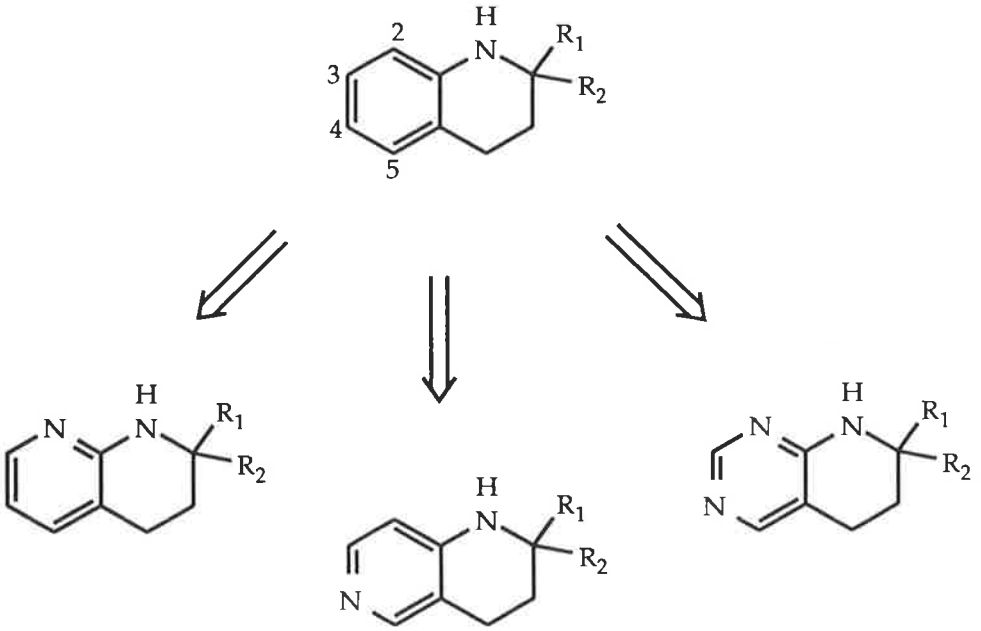
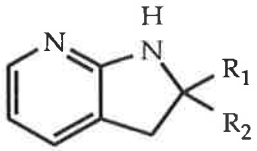


Figure 3

The synthesis of these compounds should enable variation of the heteroaromatic ring to encompass those common to the nucleoside type systems, eg. cytosine and substituted pyrimidines, as well as the simple pyridine systems.

Thus, the development of a general synthetic procedure which will enable incorporation of any desired heteroaromatic ring, fused to a five (12) or six (13) membered nitrogen containing ring was of interest. In addition the ability to vary the R_1 and R_2 substituents to ultimately include those of virantmycin, was also desired.



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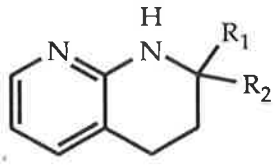
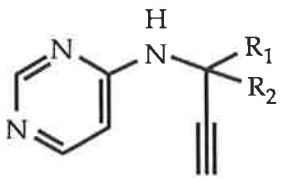


(13)

Consequently there were several major areas of investigation for this project. Firstly, it was necessary to establish a general synthetic pathway to the initial target of the coupled derivative in both the pyrimidine (14) and pyridine systems (15).



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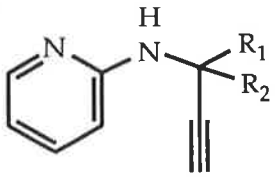


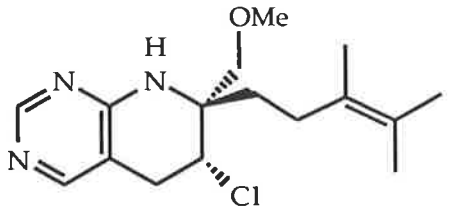
(15)

Secondly, an examination will be carried out on the cyclisation methods of the coupled derivatives. These approaches should enable selective formation of either the five or six membered bicyclic derivatives of the pyrimidine and pyridine systems. The study will involve the use of palladium catalysed couplings and electrophilically induced cyclisations.

Another focus of this work was to determine the generality of the amino-Claisen rearrangement by examining whether the acid catalysed rearrangement, as established for the benzenoid system, could be achieved for the heteroaromatic systems.

It was also of interest to investigate the methodologies already established for our approaches to the virantmycin system and to determine the applicability of these routes to heterocyclic analogues of virantmycin.

Finally, it was also necessary to establish a synthesis of the bicyclic compound which allowed for stereochemical control at the tertiary carbon, to obtain optically pure derivatives. This should eventually facilitate formation of heterocyclic analogues of virantmycin such as (16), containing the desired substituents attached to the chiral carbon.



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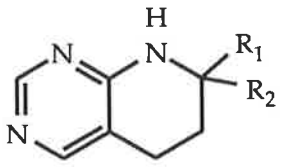
Chapter 2.1 *Synthesis of Pyrimidine Analogues*

Introduction

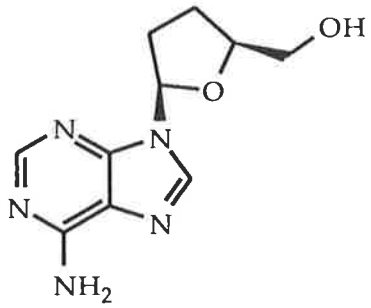
Preliminary investigations towards the formation of pyrimidine analogues of virantmycin involved the synthesis of an analogue with the basic skeleton (17). The pyrimidine system was studied initially because of the diverse chemistry that can be performed with these compounds compared to other heterocycles.



(17)

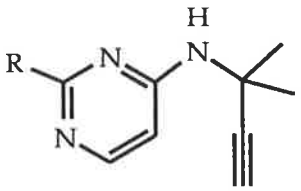
Firstly, the two, four and six positions of the pyrimidine ring are susceptible towards nucleophilic attack due to the additive electron withdrawing effects of both nitrogens.[17] Secondly, the five position is capable of undergoing electrophilic substitution, particularly when electron donating groups are attached to the ring.[17]

Further advantages in the investigation of the pyrimidine derivatives arises from the similarity of these virantmycin analogues (17) with the nucleoside systems (eg. dideoxyadenosine (1)) due to the common heterocyclic ring system and particularly the spatial arrangement of their respective ether and sugar oxygens as discussed in chapter one.



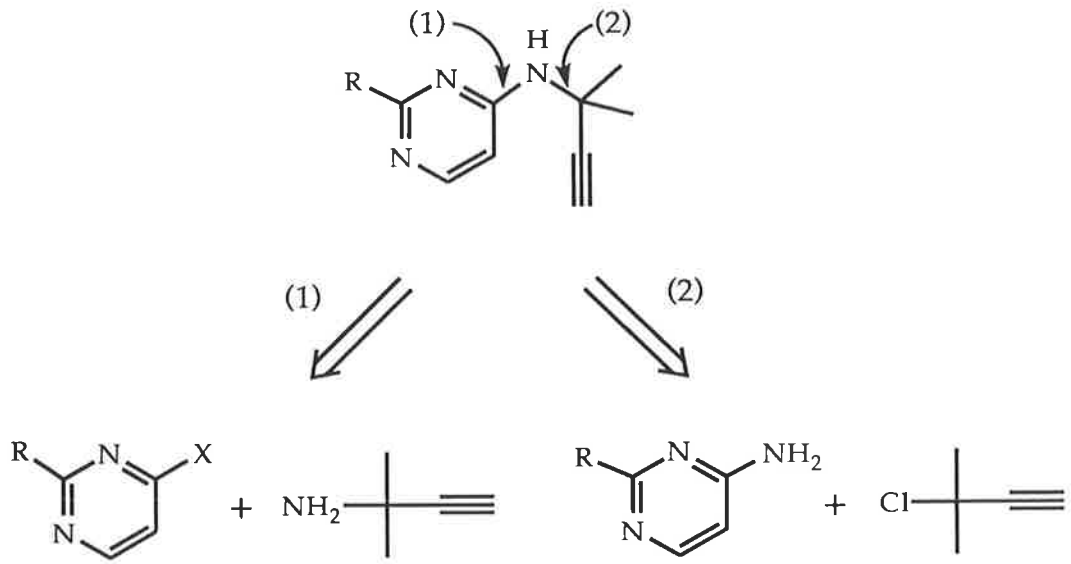
(1)

Consequently initial work was centred on the optimisation of a route to the dimethyl substituted compound of type (18). The dimethyl derivative was chosen as the model compound for the methodology studies as it enabled the use of readily available starting materials and afforded the structurally simplest form of the analogues.



(18)

Two synthetic routes were apparent by which the coupled product could be obtained.



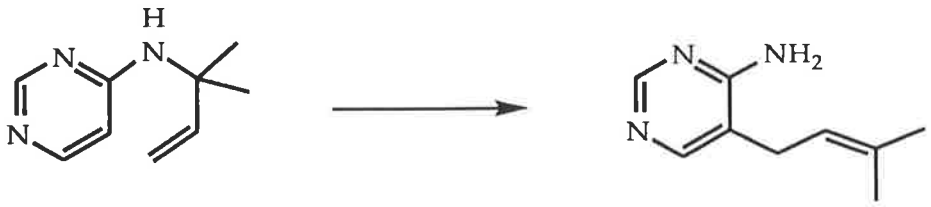
Scheme 4

The first method (*Scheme* 4: route 1) involved the formation of the Ar-N bond, by displacement of a leaving group (eg. halogen) by a suitable amine. The second (*Scheme* 4: route 2), required the formation of the bond between the nitrogen and the tertiary carbon centre. It was of interest to establish whether this approach could utilise the copper catalysed substitution of a tertiary chloride, by an aromatic amine, which has been established for benzenoid systems.[16,18]

Due to the reactivity of the pyrimidine ring towards nucleophilic attack at the two, four and six positions, the first method seemed more applicable. Although the second approach was successful for the aniline system, the same was not true for the heterocyclic, 2-aminopyridine system[19] as will be discussed later (See Chpt 4.1).

Having obtained the coupled pyrimidine (18), conversion to the cyclised derivative could be achieved by cyclisation to the C5 ring position utilising the ring's susceptibility to electrophilic attack at that position. Alternatively,

reduction of the coupled product to the N-allyl derivative (19) could enable the amino-Claisen rearrangement (*Scheme* 5) of this system to be investigated and compared with that of the corresponding aniline system.[14]



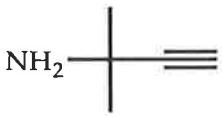
(19) (20)

Scheme 5

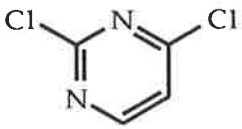
This chapter therefore encompasses two main areas, the synthesis of the coupled pyrimidine and subsequent reactions towards the cyclised product.

Results and Discussion

The initial route investigated followed the approach outlined in *Scheme* 1: route 1, whereby the formation of the Ar-N bond is achieved by the displacement of a halogen using a propargylamine. Both of the starting materials, 1,1-dimethylpropargylamine (21) and 2,4-dichloropyrimidine (22) were available commercially.

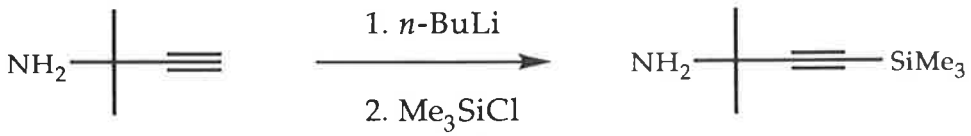


(21)



(22)

It was anticipated that displacement of the 4-chloro group of the pyrimidine ring may require amide anion formation to effect substitution. In the presence of the free alkyne, competing deprotonation and subsequent reaction with the pyrimidine system may occur between the amide and acetylide ions. To avoid this possibility, the alkyne was protected as its trimethylsilyl derivative (*Scheme* 6) by treatment of the alkyne with 1.1 equivalents of *n*-butyllithium. The lithium acetylide salt formed *in situ* was then reacted with trimethylsilyl chloride to yield the protected alkyne (23) in 84% yield.

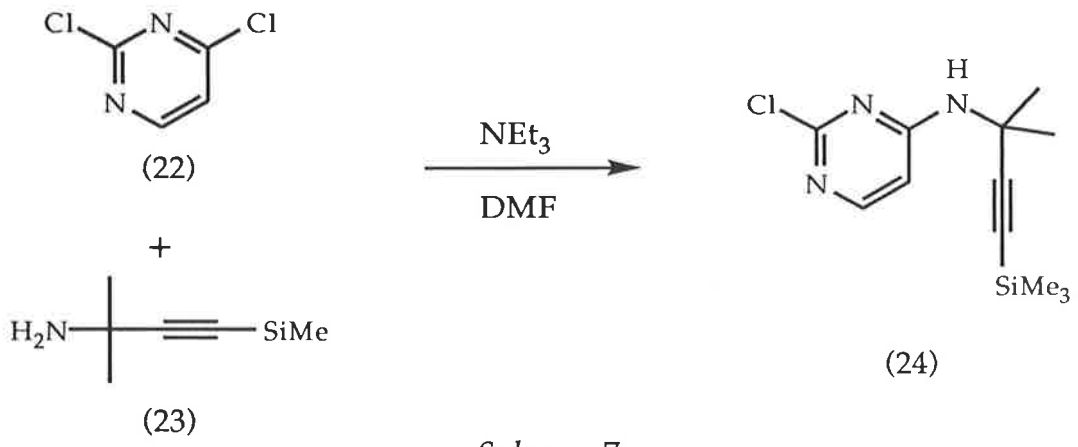


(21) (23)

Scheme 6

The proton nmr spectrum of the product showed three singlets at δ 1.95, 1.42 and 0.18. The peak at δ 1.95 was not observed after exchange with deuterium oxide and thus corresponded to the amine protons, while the signals at δ 1.42 and 0.18 were due to the geminal methyl groups and the trimethylsilyl group respectively. The peak observed in the starting material due to the acetylenic proton at δ 2.45 was no longer present in the proton nmr spectrum of the product. The expected molecular ion was observed at 155 m/z in the mass spectrum of the product, while the infrared spectrum did not show the alkyne C≡C-H stretch, observed at 3200 cm^{-1} for the amine (21).

The coupling of the protected alkynylamine (23) with 2,4-dichloropyrimidine (22) (*Scheme* 7) was accomplished using a standard procedure[20] for the displacement of chloropyrimidines by amines, in which the two were heated with triethylamine in dimethylformamide. Dimethylformamide was required as the solvent due to the poor solubility of the pyrimidine in other solvents. The product (24) was isolated from the reaction mixture as a viscous yellow oil.

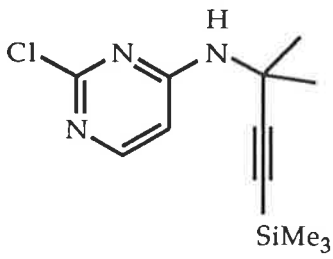


Scheme 7

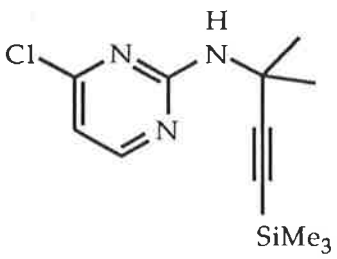
The use of 2,4-dichloropyrimidine (22) in this reaction meant that there were two possible sites for reaction. Literature data[21,22] suggested that the four position was the more reactive site and consequently that the 4-amino derivative (24) would be the major isomer.

Analysis of the oil using thin layer chromatography (tlc) showed one broad spot that resulted from two smaller spots which were partially overlapped. Neither of these spots coincided with that of the starting material.

The proton nmr spectrum of the oil revealed two sets of doublets for each of the aromatic protons. The two signals for the proton at C6 were observed at δ 8.13 and 7.99 while for the C5 proton two doublets resonated at δ 6.82 and 6.29. For each proton, the peak observed at the lower chemical shift was the predominating signal, favoured by a ratio of 9:1 over the corresponding higher chemical shift signal. Again neither set of peaks corresponded to those of the starting pyrimidine, while mass spectrometry showed a molecular ion at 267 m/z confirming that the coupling had taken place and that the two products were the two possible regioisomers (24) and (25) arising from nucleophilic displacement of either the 4 or the 2-chloro group of the pyrimidine ring.



(24)



(25)

The two regioisomers were separated from other minor impurities by flash chromatography. The mixture of isomeric pyrimidines then solidified and were further purified by fractional recrystallisation, enabling the separation of the major component.

The proton nmr spectrum of the major component, isolated as large colourless prisms, showed two doublets at δ 8.13 and 6.82 corresponding to the C6 and C5 protons respectively. Three singlets were also observed at δ 5.42, 1.62 and 0.15.

The first was a broad singlet which exchanged with deuterium oxide and was attributed to the NH, while the other signals corresponded to the geminal methyls and the trimethylsilyl moiety respectively.

An X-ray crystal structure (*Fig* 4, *Appendix* 1) was obtained for the major regioisomer which confirmed that the product, isolated in overall 79% yield, was the 4-amino substituted derivative (24).

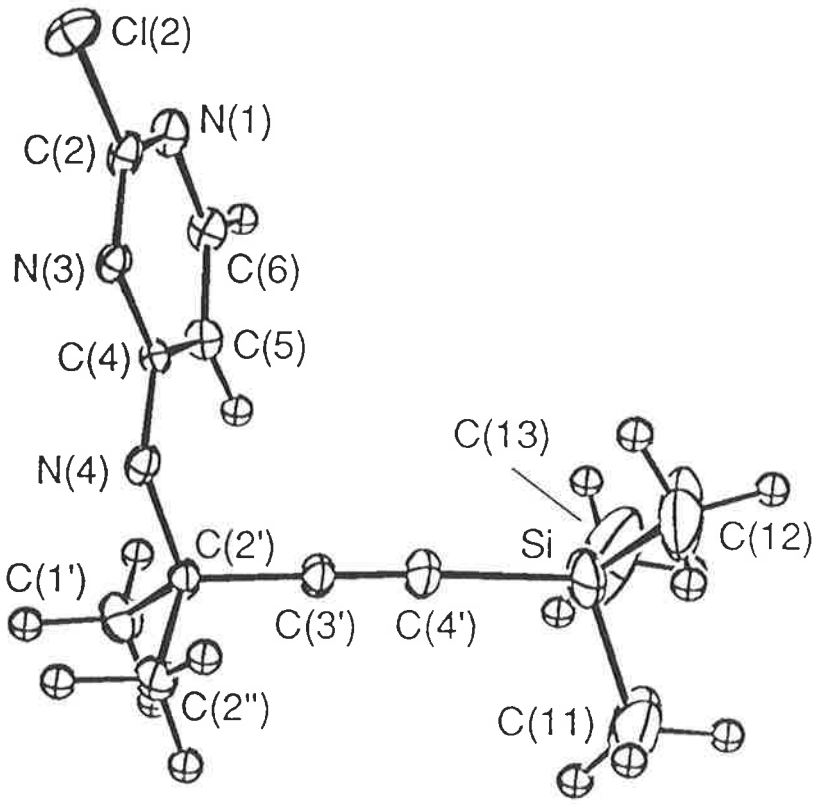
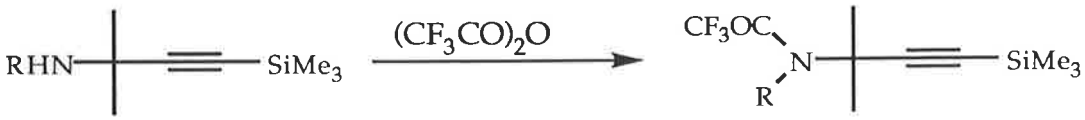


Figure 4

The minor regioisomer (25) could not be obtained in pure form but the proton nmr of (25) was assigned with the use of subtraction nmr. This showed two doublets resonating at δ 7.99 and 6.29 due to the C6 and C5 aromatic protons respectively and three singlets at δ 5.40, 1.46 and 0.12 corresponding to the amine NH, the geminal methyl protons and those of the trimethylsilyl moiety respectively.

Prior to employing fractional recrystallisation as the method for effective separation of the regioisomers it was thought that formation of a less polar derivative may facilitate chromatographic separation of the two compounds. The crude product obtained from the coupling reaction was converted to a mixture of trifluoroacetamides, using trifluoroacetic anhydride[23] (*Scheme* 8). Product analysis by tlc showed a separation of the two components and the isomeric trifluoroacetamides (26) and (27) were purified by flash chromatography.



R = -4-pyrimidyl (24)
-2-pyrimidyl (25)

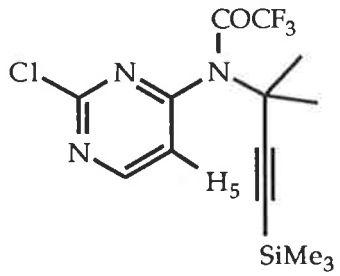
R = -4-pyrimidyl (26)
-2-pyrimidyl (27)

Scheme 8

The proton nmr spectrum of the major trifluoroacetamide (26) showed two doublets at δ 8.74 and 7.29 corresponding to the protons at C6 and C5 respectively. The spectrum showed no sign of the signal attributed to the NH in the starting material, while the peaks due to the geminal methyls and the trimethylsilyl moiety were shifted slightly downfield at δ 1.93 and 0.18

respectively. In addition the infrared spectrum of the material showed no sign of the peak at 3272 cm^{-1} due to the NH in the starting material but showed a signal at 1692 cm^{-1} corresponding to the amide carbonyl stretch.

The proton nmr spectrum of the major trifluoroacetamide derivative also suggested that substitution had occurred at the C4 position. The large downfield shift of the C5 aromatic proton (δ 7.29 compared to 6.82) indicated that the trifluoroacetamide group was close enough to deshield this proton. If the C2 derivative had been formed the protecting group would not have been expected to exert such a strong influence at the C5 position.

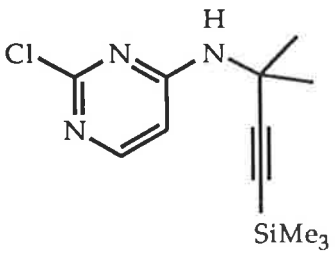


(26)

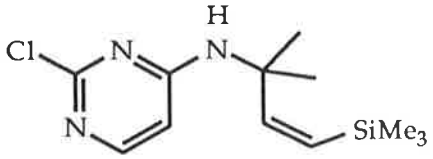
Verification that the 4-amino derivative (26) was the major component isolated from the formation of the isomeric trifluoroacetamides was achieved by conversion of the authentic amine (24) to the corresponding trifluoroacetamide. The proton nmr spectrum of this derivative was identical to that of the compound (26) isolated by chromatography.

Insufficient material was isolated to complete the purification of the minor trifluoroacetamide (27). Use of subtraction nmr showed two doublets for the minor isomer at δ 8.21 and 6.45 and two singlets at δ 1.53 and 0.15 as expected for the aromatic C6 and C5 protons, the geminal methyl protons and the trimethylsilyl group respectively.

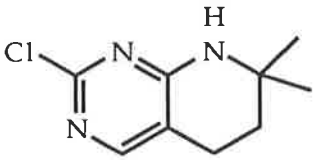
Reduction of the alkyne (24) to the alkene (28) was necessary to enable an investigation into the possible amino-Claisen rearrangements of the pyrimidine systems which would be followed by cyclisation to the bicyclic pyrimidine (29).



(24)



(28)



(29)

Triple bonds can be reduced by a number of methods, the most common being catalytic hydrogenation.[24,25] The ability to halt the reduction of the alkyne at the alkene stage depends on the catalyst employed and the comparative reactivities of each, to that catalyst.[26] The most effective method of achieving this reduction is using a Lindlar catalyst[27,28] which leads to the *cis* alkene. Other reagents which can also stop reduction at the alkene stage are diisobutylaluminium hydride,[29,30] (*cis*-alkene) a zinc-copper couple[31] or alkali metals in liquid ammonia (*trans*-alkene),[32] although this method cannot be employed for terminal alkynes since the acetylide ion is formed under these conditions.[32] Diimide[33,34] is another reagent which enables reduction to the alkene.

Catalytic reductions were first attempted on (24) using a Lindlar catalyst to obtain the *cis*-vinylsilane. The proton nmr spectrum of the crude product

showed no sign of the alkene protons expected for the desired product (28) and was identical to that of the starting material. It has been shown that steric influences are an important factor in catalytic hydrogenations where the substrate must be adsorbed onto the catalyst surface.[35] In this case it appeared that the bulk of the trimethylsilyl moiety hindered adsorption onto the catalyst thus preventing hydrogen transfer from the catalyst to the substrate.

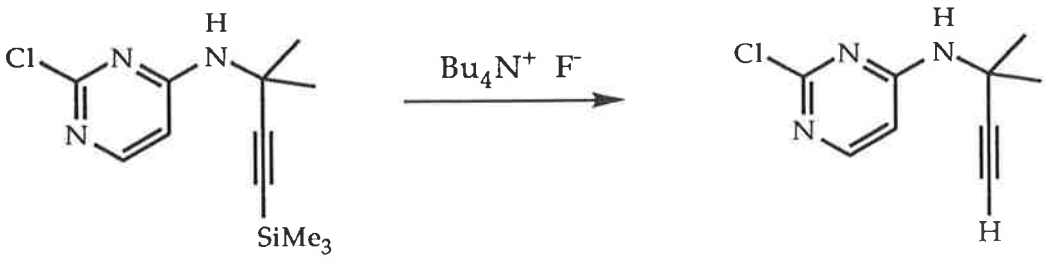
Reduction of trimethylsilyl protected alkynes has been achieved with the use of diisobutylaluminium hydride[36] (dibal) to afford the *cis* isomer.

The reduction was attempted by addition of 2.1 equivalents of dibal to a cooled solution of the alkyne (24). The excess dibal was required to react initially with the acidic NH proton followed by reduction of the alkyne. The proton nmr spectrum of the crude product showed that only a poor recovery of starting material had been obtained. This may indicate a coordination of the aluminium to the aminopyrimidine system, either rendering the reagent unreactive, or causing the product to be highly water soluble.

The dibal reduction was repeated on the trifluoroacetamide derivative (26) in an attempt to prevent coordination and promote reduction of the alkyne. However, only greater amounts of starting material were recovered.

The protected alkyne was converted to the free alkyne using tetrabutylammonium fluoride[37] (*Scheme* 9) in order to investigate the catalytic reduction of (30). The deprotected alkyne was obtained as a yellow oil which was purified by chromatography and then crystallised on standing. Further purification by recrystallisation afforded the free alkyne (30) as colourless needles. The proton nmr spectrum of this product showed the expected aromatic doublets, resonating at δ 8.11 and 6.75. A broad singlet at δ 5.42, which exchanged with deuterium oxide, was attributed to the NH and a singlet at

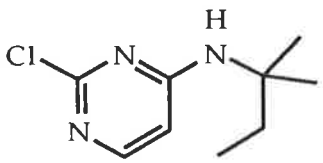
δ 1.63 corresponded to the geminal methyl groups. The acetylenic proton was observed as a singlet at δ 2.43 and the signal due to the trimethylsilyl group was no longer present at δ 0.15. The mass spectrum gave an ion at 194/196 m/z for the ion [M^+-H].



(24) (30)

Scheme 9

Hydrogenation of the free alkyne to the alkene was attempted using a Lindlar catalyst, but afforded only the fully reduced material (31).



(31)

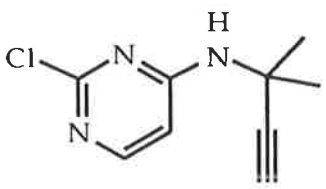
The proton nmr spectrum of (31) showed two doublets in the aromatic region at δ 7.91 and 6.33, a broad singlet at δ 5.77 exchangeable with deuterium oxide (NH) and a singlet at δ 1.38 due to the geminal methyl groups. Two new signals were observed at δ 1.82 (quartet) and 0.87 (triplet). Both sets of peaks showed identical coupling constants (J 5 Hz) and when either was irradiated the other collapsed to a singlet. There was no indication of any resonances between δ 4-6 as would have been expected for any alkene protons, while the absence of a signal near δ 2.4 (C≡C-H) indicated that the starting material had

been totally consumed.

The formation of the alkane suggested that the catalyst may require further poisoning with quinoline. However, this may then prove difficult to separate from the product and consequently was not pursued.

Reduction of the alkyne (30) was next attempted using diimide.[34,38,39] Dipotassium azodicarboxylate, formed by basic hydrolysis of azodicarbonamide, was used as the source of diimide, which is generated by reaction of the dicarboxylate with acid.[38]

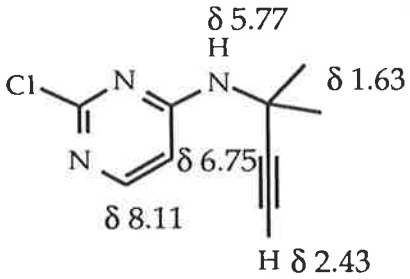
A major problem associated with this method of reduction is the large excess of the diimide source required for completion of the reaction. This is due to disproportionation of the dicarboxylate anion.[40] To partly overcome this problem, the acid required for conversion of the dicarboxylate to diimide, is added slowly to the solution, thus preventing a build up of excess diimide in the mixture capable of causing over reduction. This, in conjunction with careful monitoring of the solution by chromatography to enable termination of the reaction when the alkene has been formed in its highest concentration, should help to prevent over reduction. In the case of the free amine (30), however, the reaction could not be monitored by thin layer chromatography since the R_f values of the alkyne, alkene and alkane were coincident. Only the colour of the spots varied when visualised using vanillin in concentrated sulfuric acid and ethanol.



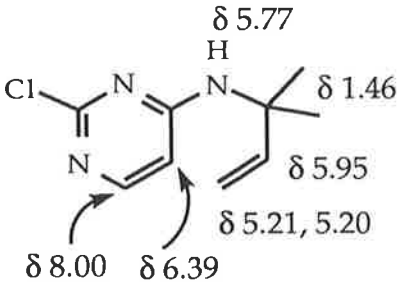
(30)

The proton nmr spectrum obtained on each attempt at reduction using diimide showed identical signals, in slightly varying ratios. In the aromatic region three sets of doublets were observed for both the C6 and C5 protons. For H6, the signals resonated at δ 8.11, 8.00 and 7.91, while for H5 the three doublets were observed at δ 6.75, 6.39 and 6.33. A broad doublet of doublets and two overlapping doublets occurred at δ 5.95, 5.21 and 5.20 respectively and were attributed to the vinyl protons of the alkene (32). There appeared to be no visible geminal coupling between the two terminal vinylic protons and consequently irradiation of the peak at δ 5.95 resulted in the collapse of both doublets to a coincident singlet. Due to the overlap of the doublets at δ 5.21 and 5.20, it was difficult to irradiate one and not the other, however, the signal at δ 5.95 was altered to a singlet, upon simultaneous irradiation of both doublets. A broad singlet at δ 5.77 which exchanged with deuterium oxide was attributed to the NH moieties of the three compounds. A quartet and a triplet were evident at δ 1.82 and 0.87 respectively,with irradiation of either set of signals resulting in the collapse of the other to a singlet. The presence of the starting alkyne was indicated by a singlet resonating at δ 2.43 and a further three singlets at δ 1.63, 1.46 and 1.38 also indicated the existence of the three distinct geminal methyl groups of the alkyne (30), the alkene (32) and the alkane (31) respectively, within the same product mixture. The mass spectrum showed a complex series of molecular ions at 194/196 m/z corresponding to the alkyne [M^+-H], 197/199 m/z due to the alkene [M^+] and 199/201 m/z for the alkane [M^+]. Thus all evidence suggested the formation of the three compounds from the diimide reduction. The average ratio of alkyne to alkene to alkane, determined by proton nmr spectroscopy was 3 : 4 : 6.

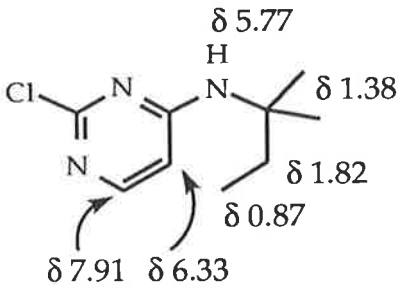
Comparison of the proton nmr spectrum of the product mixture acquired from the diimide reduction with those of the authentic alkyne (30) and alkane (31) samples enabled assignment of the chemical shift data as shown below:



(30)



(32)



(31)

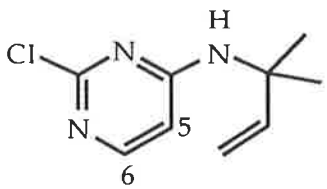
At no stage was the alkene (32) obtained in sufficient amount to warrant attempts at separation by high performance liquid chromatography. Consequently this procedure was not investigated.

Due to the successful separation of the two regioisomers (24) and (25) using the formation of a less polar derivative, the mixture of alkyne, alkene and alkane was converted to a mixture of trifluoroacetamides, in the usual manner, in an effort to effect separation. On this occasion, however, only one product spot with a higher R_f value was observed by tlc analysis, and hence no separation of the trifluoroacetamides was possible.

Reduction of the alkyne to the alkene was still considered most readily

achievable with the use of a Lindlar catalyst. Accordingly, the reaction was repeated using a fresh batch of catalyst. This, in conjunction with careful monitoring of the reaction by removal of aliquots from the reaction mixture at regular intervals and analysis of these by proton nmr spectroscopy, enabled the termination of the reaction at the alkene stage.

The proton nmr spectrum of the material, separated from impurities by flash chromatography and recrystallisation, showed two doublets for the C6 and C5 protons resonating at δ 8.00 and 6.39 respectively. A doublet of doublets was observed at δ 5.95 due to the internal vinylic proton, and a broad singlet which exchanged with deuterium oxide was observed at δ 5.51 due to the NH proton. Two overlapping doublets resonated at δ 5.21 and 5.20 corresponding to the two terminal vinylic protons but no visible geminal coupling was observed between the protons. A singlet at δ 1.46 was attributed to the geminal methyl protons. Neither the starting alkyne nor the fully reduced material were detectable by proton nmr spectroscopy. The mass spectrum of the product gave a molecular ion at 197/199 mass units, while the infrared spectrum showed no sign of the usual alkyne triple bond stretch at 2160 cm^{-1}, instead showing a C=C stretch at 1620 cm^{-1}. Thus all spectroscopic data indicated the formation of the desired alkene (32).



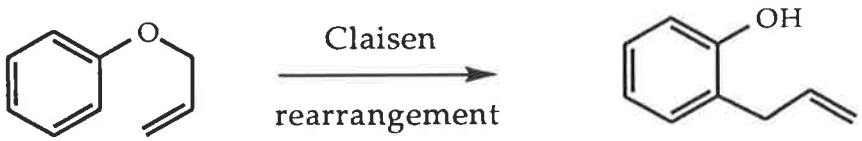
(32)

Having obtained the alkene (32) it was then possible to investigate the amino-Claisen rearrangement of the N-allyl aminopyrimidine.

Chapter 2.2 *Ammonium-Claisen Rearrangements*

Introduction

The Claisen rearrangement (*Scheme* 10), whereby allyl aryl ethers rearrange to *o*-allylphenols can be effected under either thermal or acidic conditions.[41,42] Interestingly, in both cases, the rate of rearrangement is increased as more of the rearranged product is formed.[42] This is attributed to the formation of the phenolic species which results in increased acid catalysis.

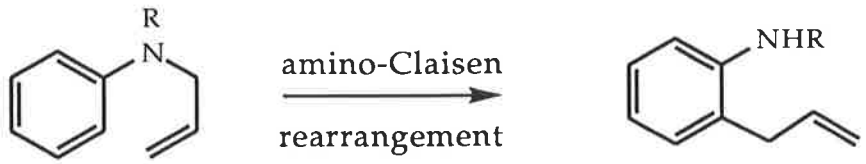


Scheme 10

As a consequence, numerous studies of solvent effects[42,43,44,45] on the rate of rearrangements have been carried out. The effect of solvents on the rearrangement has been found to be insignificant for most solvents other than hydroxylic or phenolic solvents.[45] This was attributed to either hydrogen bonding of the solvent with the ethereal oxygen or the inherent polar character of the solvent.[44] Of these polar solvents, trifluoroacetic acid was found to achieve a rate enhancement of 300 fold.[42]

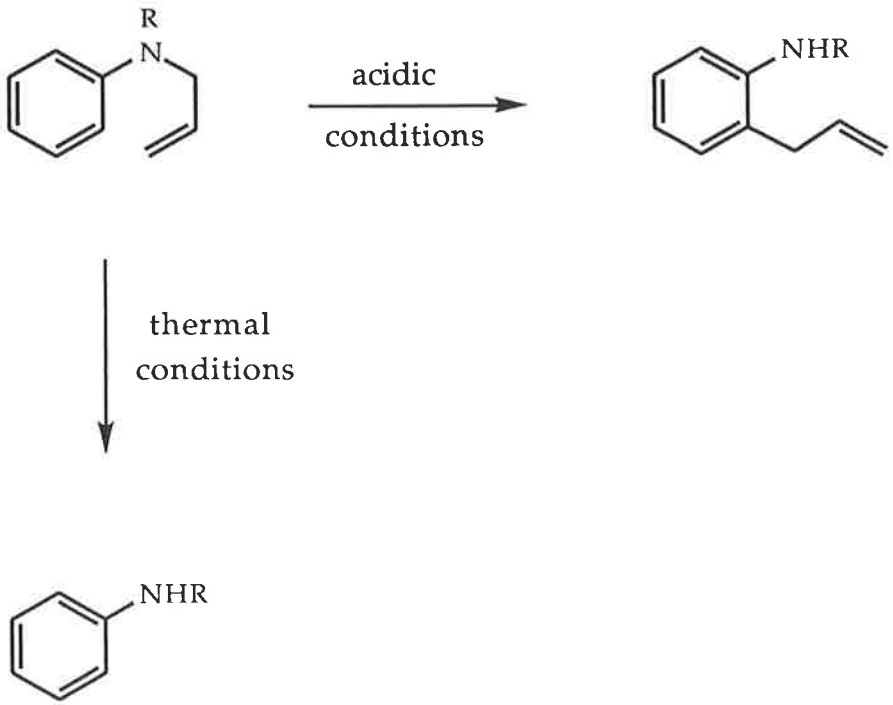
The sensitivity of the rearrangement to this acid catalysis suggested that the use of acidic media to effect the desired reaction was important. In the case of compounds which may otherwise undergo decomposition under thermal conditions, implementation of acid catalysis would enable reactions to be conducted at much lower temperatures.[42]

A modification of the Claisen rearrangement, the amino-Claisen rearrangement,[14,41] can be achieved for the corresponding N-allylamines (*Scheme* 11).



Scheme 11

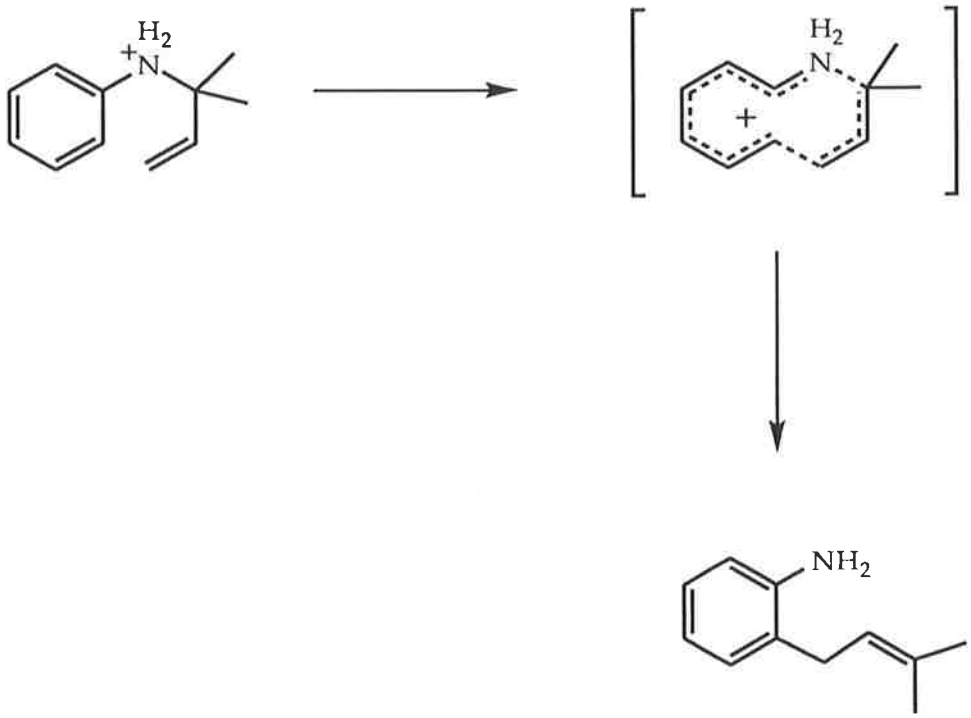
The main difference in this series is that pyrolysis of the N-allylaniline affords, as its major product, aniline itself rather than the expected *o*-allylaniline.[14,41] However, when conducted under acidic conditions, enabling reduction of the reaction temperature, the desired rearranged product was obtained almost exclusively (*Scheme* 12).[14]



Scheme 12

Similar results[14,47] were observed for the corresponding N-(1,1-dimethylallyl)aniline analogue, although some of the rearranged product was obtained from the pyrolysis reaction of this species.[14]

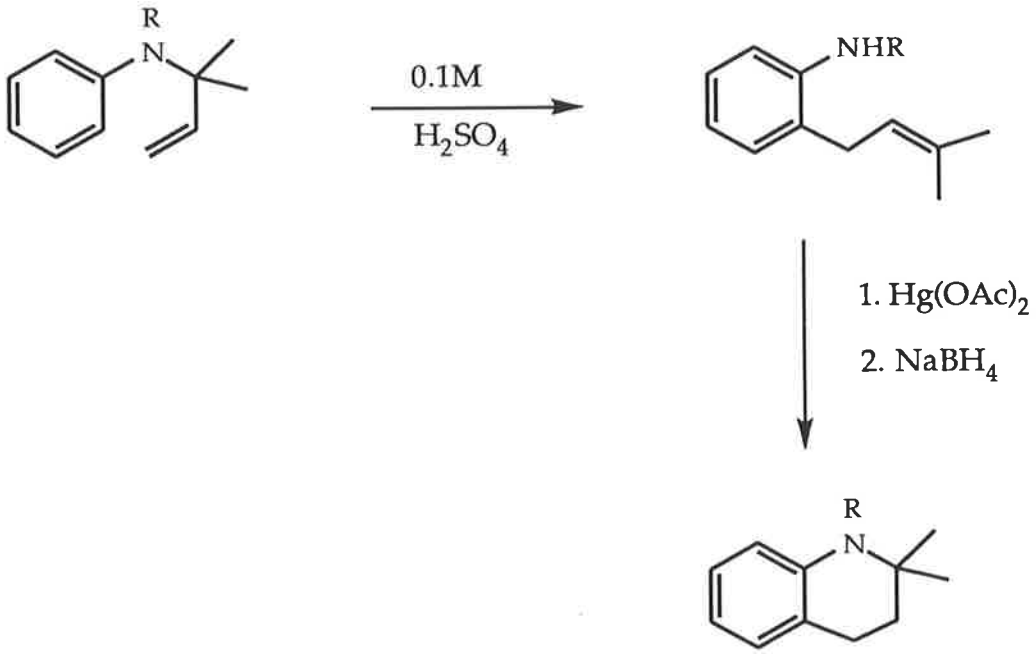
It has been shown that the essential driving force behind the pericyclic [3,3] sigmatropic rearrangement is the delocalisation of the positive charge in the transition state (*Scheme* 13) effectively lowering the free energy barrier of the reaction.[14]



Scheme 13

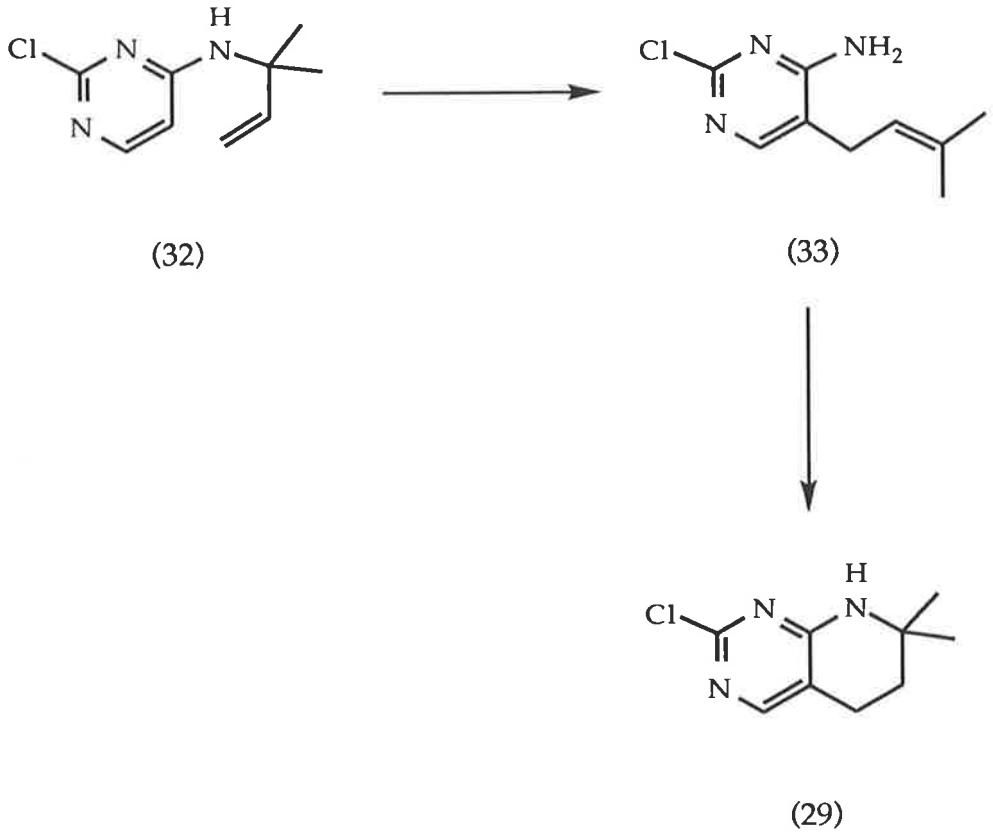
Recent investigations[15,47] in our laboratories have explored the possibility of the synthesis of a tetrahydroquinoline nucleus, utilising the amino-Claisen rearrangement of N-(1,1-dimethylallyl)aniline as a key step in the sequence. Subsequent electrophilically induced cyclisations of the *o*-allylaniline

derivatives, such as reaction with mercuric acetate followed by sodium borohydride[15] enabled formation of the second ring (*Scheme* 14).



Scheme 14

If the N-(1,1-dimethylallyl) derivative (32) was able to undergo an amino-Claisen rearrangement it may then be possible to cyclise the product (33) to afford the bicyclic pyrimidine system (29) (*Scheme* 15).



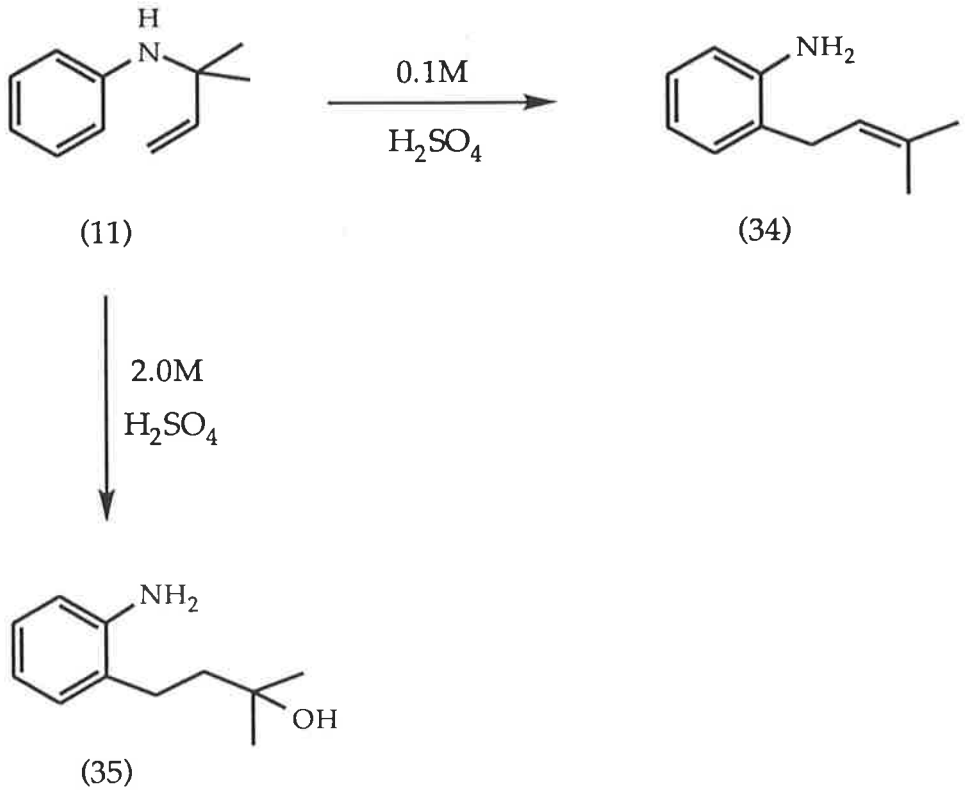
Scheme 15

Consequently the aim of this study was to investigate the extension of the amino-Claisen rearrangement to heteroaromatic rings such as the pyrimidyl system.

Results and Discussion

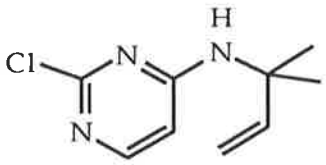
There have been three principle methods utilised for the amino-Claisen rearrangements of allylaniline systems. Two require the use of acidic media while the third is a thermal reaction.

For the aniline system (11),[14] the desired rearranged material (34) was obtained exclusively using 0.1M sulfuric acid in an aqueous ethanolic solution. However if the molarity of the sulfuric acid solution was increased, the yield of the rearranged alkene (34) was decreased as the hydrated product (35) became more prominent[14,47] (*Scheme* 16).

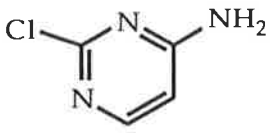


Scheme 16

Reaction of the N-(1,1-dimethylallyl)aminopyrimidine (32) in 0.1M sulfuric acid gave no organic material after a standard work up. Concentration of the aqueous layer, after neutralisation, afforded large colourless needles.



(32)



(36)

The proton nmr spectrum of this material in d_6-dimethyl sulfoxide revealed two doublets at δ 8.21 and 6.93, corresponding to H6 and H5 of a pyrimidine ring, respectively and a broad singlet at δ 5.90 attributed to an amine moiety. The mass spectrum gave a molecular ion at 129 m/z and the compound had a melting point of 217-219°C. The data pointed to the formation of 4-amino-2-chloropyrimidine[22,46] (36), suggesting that only cleavage of the N-C bond had occurred. This was not entirely unexpected as most amino-Claisen rearrangements result in the isolation of some of the cleaved product.[14]

The isolation of 4-amino-2-chloropyrimidine (36) was confirmed by treatment of the commercially available 2,4-dichloropyrimidine (22) with ammonia, following a literature preparation,[22] to obtain the aminopyrimidine (36) as colourless needles. This compound had identical spectroscopic and physical data to that of the compound isolated from the aqueous layer of the previous reaction and matched that of the literature.[46]

The amino-Claisen rearrangement of the aniline system was shown to give improved yields when an organic solvent system, rather than an aqueous acidic media, was used.[47] Thus, when N-(1,1-dimethylallyl)aniline was reacted

with a catalytic amount of *p*-toluenesulfonic acid in acetonitrile, a 91% yield of the rearranged product was obtained.[47]

This procedure was carried out on the pyrimidine system (32) and during the course of the reaction a white solid precipitated from the solution. Proton nmr spectroscopic analysis of the solid again showed two doublets in the aromatic region at δ 8.21 and 6.93, while the mass spectrum gave a molecular ion at 129 m/z corresponding to the isolation of 4-amino-2-chloropyrimidine as observed in the previous case. Concentration of the remaining organic solution afforded only a small amount of starting material.

From these results it was clear that under the conditions employed, the bond between the nitrogen and the tertiary carbon centre of the pyrimidine ring was being cleaved but rearrangement was not occurring.

Due to the inability to effect rearrangement under acidic conditions, the reaction was conducted under thermal conditions as N-(1,1-dimethylallyl)aniline can be rearranged[14] under these conditions to obtain some of the desired *o*-allyl aniline. Thermolysis of (32) at 200-210°C for 15-30 min. resulted in decomposition to an intractable black tar. This suggested that the thermal conditions were inappropriate for effecting the amino-Claisen rearrangement of the pyrimidine ring system.

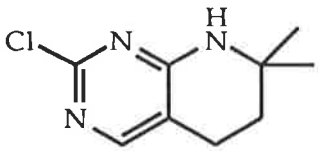
It has been observed that, in the Claisen rearrangement of allylaryl ethers to *o*-allyl phenols, employment of trifluoroacetic acid[43] as the solvent, increased the rate of reaction by 300 fold. The pyrimidine (32) was reacted with trifluoroacetic acid at both room temperature and at 50°C. However, on both occasions, the proton nmr spectroscopic analysis of the residue isolated indicated only the recovery of starting material.

In conclusion, it has been demonstrated that, for the pyrimidine system examined, the amino-Claisen rearrangement cannot be effected by the conditions that were employed for the aniline system. Hence this approach was not a viable method for the synthesis of the bicyclic pyrimidine systems.

Chapter 3 *Palladium Catalysed and Electrophilically Induced Cyclisation Reactions*

Introduction

An alternative methodology for the synthesis of the bicyclic pyrimidine system (29) could utilise either an electrophilically induced cyclisation or palladium catalysed coupling reaction.



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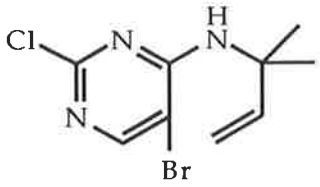
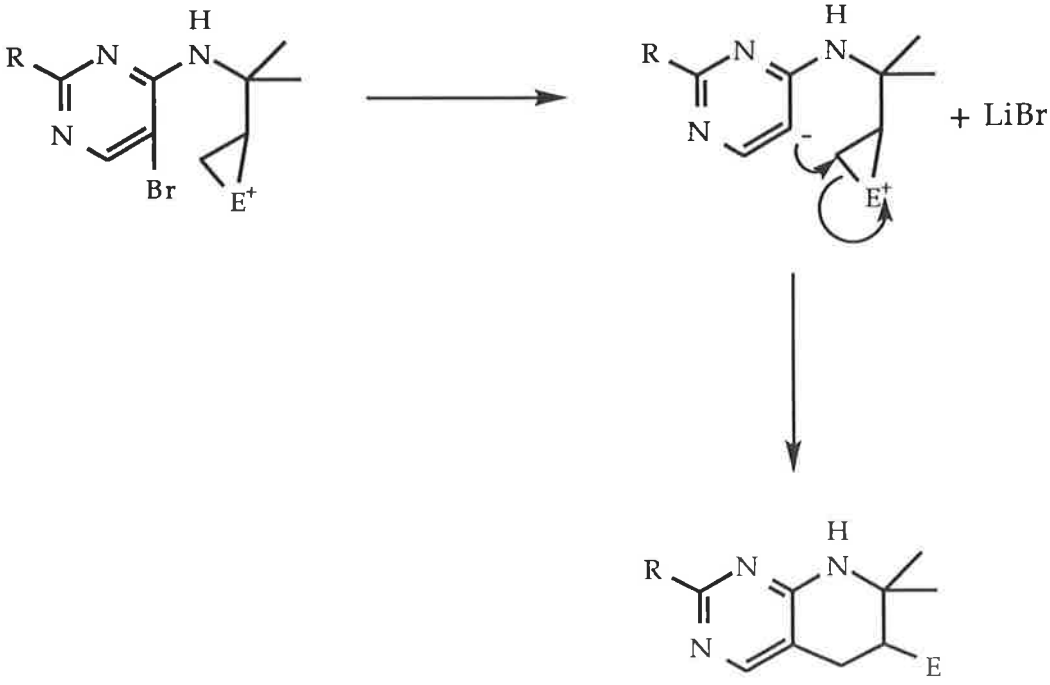


(37)

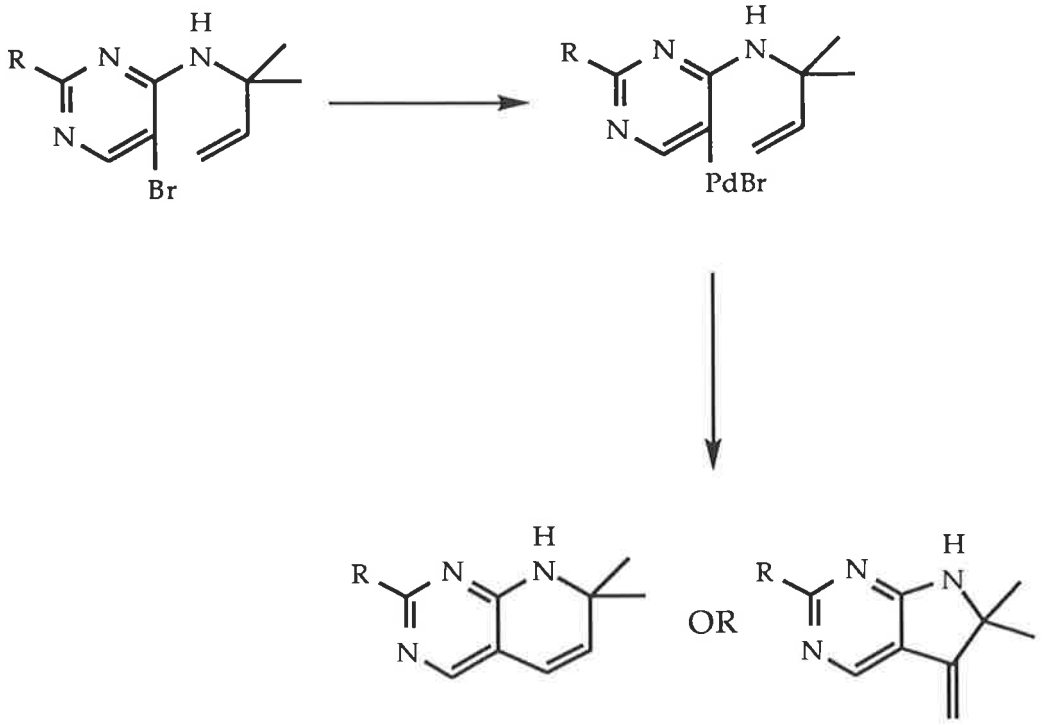
These approaches would both require the incorporation of a halogen into the C5 position of the pyrimidine ring as shown in (37).



Scheme 17

An electrophilically induced cyclisation could, in principle, be achieved by a lithium/halogen exchange[48] at the C5 ring position (*Scheme* 17), followed by attack of the heteroaryllithium species on an electrophilic moiety obtained by manipulation of the double bond.

Palladium catalysed coupling[49,50,51] could be effected by formation of an "arylpalladium" reagent which could then undergo addition to the olefin, as depicted in scheme 18, to give either of the two possible products.



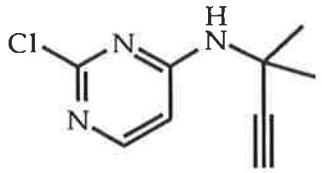
Scheme 18

The synthesis of the C5 brominated pyrimidine (37) will be outlined in this chapter and this will be followed by a discussion of the attempted cyclisations to the bicyclic pyrimidine ring system (29).

Results and Discussion

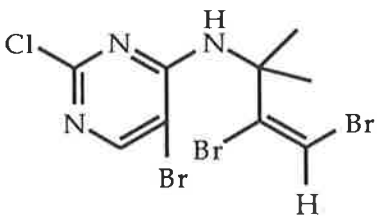
Part 1 : Synthesis of 5-Bromopyrimidyl Derivatives

Bromination of pyrimidine systems occurs readily at the C5 position, under mild conditions, when electron donating groups are attached to the ring.[52] Consequently it may be possible to obtain the C5 brominated derivative by the bromination of the coupled alkyne (30) previously synthesised (Chpt 2.1).



(30)

Bromination of the pyrimidine derivative (30) was also expected to result in addition of the halogen across the triple bond.[53] However, this vinylic halide species should then be sufficiently unreactive towards halogenation to enable the pyrimidine ring to undergo bromination at the C5 position to obtain the tribromide derivative (38). This derivative was considered especially useful for the palladium catalysed coupling reactions.



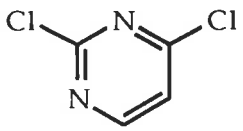
(38)

When the pyrimidine derivative (30) was treated with three equivalents of bromine in acetic acid, tlc analysis indicated that a complex mixture of products

had formed, only one of which could be isolated by chromatography. Proton nmr spectroscopy of this fraction showed that bromination had not occurred at the C5 ring position or at the alkyne and that only crude starting material had been isolated. Evidence for this included a singlet at δ 2.43 corresponding to the acetylenic proton and a doublet which resonated at δ 6.75 indicative of the C5 proton of the pyrimidine ring.

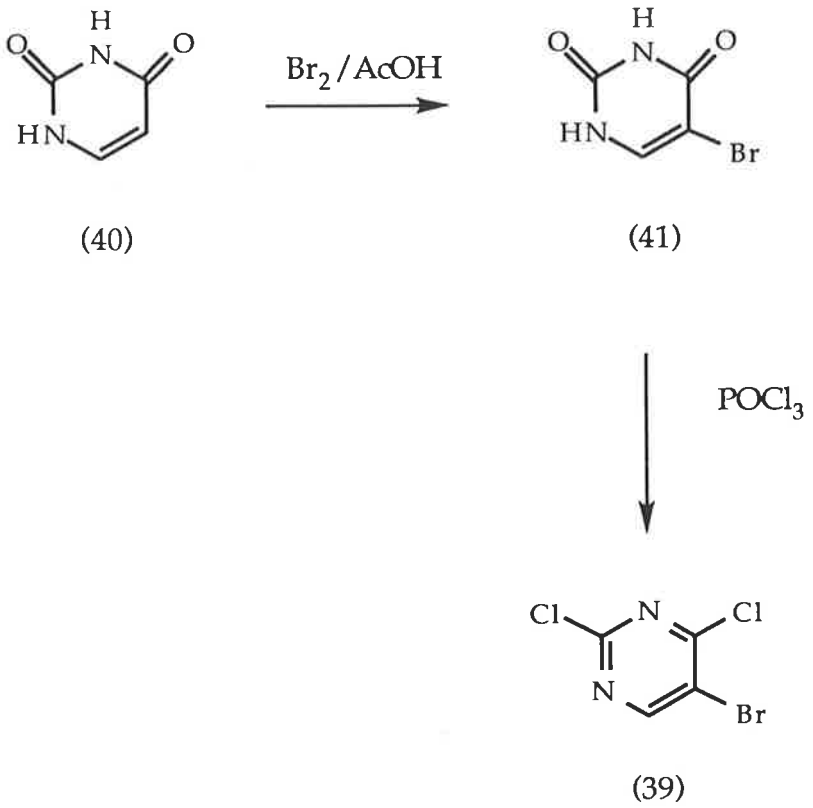
In the presence of a large excess of bromine, some addition to the alkyne was observed. This was indicated by the absence of the signal at δ 2.43 in the proton nmr spectrum of the crude material and the observation of a broad singlet at δ 6.56 for the olefinic proton. The signal due to the NH was not observed. Again no product could be isolated by flash chromatography.

These results showed that the formation of the C5 bromide (37) would require bromination of the ring to be carried out prior to coupling with the propargylamine. Bromination could not be achieved by direct reaction of the original pyrimidine ring (22) with bromine as it lacked the required electron donating groups to facilitate C5 substitution.[52]



(22)

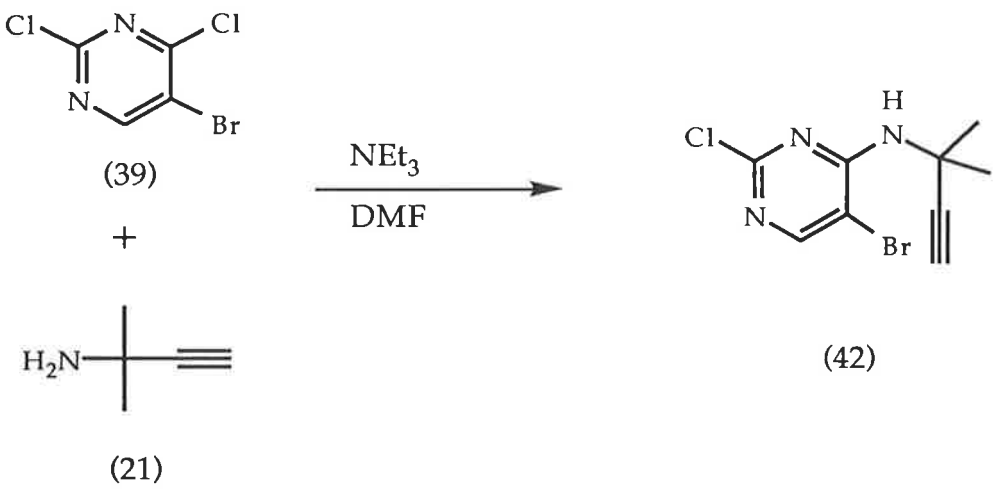
The desired 5-bromo-2,4-dichloropyrimidine (39) was synthesised using a literature procedure[54] as depicted in scheme 19.



Scheme 19

Uracil (40) was readily brominated using bromine in acetic acid to afford 5-bromouracil (41) in quantitative yields. Reaction of (41) with phosphorus oxychloride gave 5-bromo-2,4-dichloropyrimidine (39) as a colourless liquid. The spectroscopic data of the liquid were identical to that reported in the literature.[55]

There were two possible sites for reaction of a nucleophile with (39). As previously indicated, literature data[21,22] supported substitution at the C4 chloro group rather than the chlorine in the C2 position. The C5-bromine was expected to be inert to nucleophilic attack.



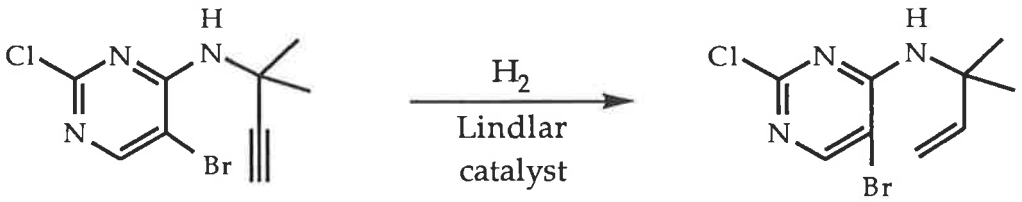
Scheme 20

Coupling of the propargylamine (21) with 5-bromo-2,4-dichloropyrimidine (39) was accomplished following the standard conditions[20] in which the two were heated with triethylamine in dimethylformamide (*Scheme* 20). The product obtained had a lower R_f than that of the starting pyrimidine by silica tlc analysis, consistent with the introduction of an amine moiety. The proton nmr spectrum of the product showed two sets of signals for each proton, corresponding to the formation of the two possible regioisomers (42) and (43). Each set of peaks occurred in a ratio of approximately 15:1 and by analogy with previous coupling reactions the major isomer was assigned as the 4-amino derivative (42).

The two isomers were purified by chromatography to yield a solid from which the major isomer was obtained by fractional crystallisation.

The proton nmr spectrum of the major regioisomer revealed one singlet in the aromatic region of the spectrum resonating at δ 8.17 due to the C6 proton. Three other singlets were observed for the product at δ 5.61, 2.39 and 1.80 corresponding to the amine (exchanged with deuterium oxide), the acetylenic proton and the geminal dimethyl groups respectively. The mass spectrum confirmed the presence of a chlorine and a bromine in the molecule and all spectroscopic data was consistent with that of the coupled product (42). The molecular formula was confirmed by high resolution mass spectrometry and microanalysis.

Reduction of the alkyne (42) was carried out in the presence of a Lindlar catalyst under an atmosphere of hydrogen (*Scheme* 21), and the reaction was stopped when the starting alkyne could no longer be detected by proton nmr spectroscopic analysis. Chromatography of the residue afforded a colourless oil which solidified on standing and was further purified by recrystallisation.



(42) (37)

Scheme 21

The proton nmr spectrum of the solid showed a singlet in the aromatic region at δ 8.11 due to the C6 proton. A doublet of doublets was observed at δ 6.12 corresponding to the vinylic methine proton. A broad singlet at δ 5.56 which exchanged with deuterium oxide was attributed to the NH, while two doublets were observed at δ 5.18 and 5.12 corresponding to the two terminal vinylic protons which exhibited no geminal coupling. The singlet due to the geminal

methyl groups resonated at δ 1.60. The mass spectrum gave a molecular ion at 275/277/279 m/z as expected for the alkene (37).

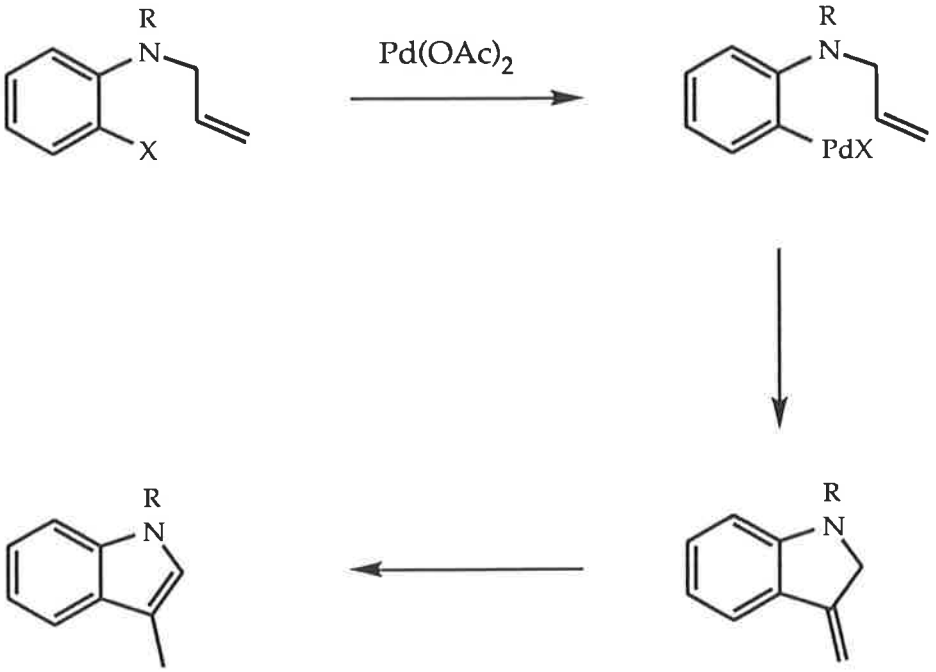
Having obtained the target molecule which now incorporated both a heteroaryl halide and an olefin, it was then possible to investigate cyclisations to form the second ring using either palladium catalysis or electrophiles.

Results and Discussion

Part 2 : Cyclisation Reactions

Initially, cyclisations of the bromoalkene (37) using palladium catalysis were examined to achieve formation of the second ring. There are several examples of palladium catalysed couplings that could be employed for the purpose of cyclisation, the most common of these being the Heck reaction.[49]

The Heck reaction involves the arylation of olefins by reaction of the olefin with an "arylpalladium" reagent, generated *in situ* by palladium insertion into an aryl halide bond. Arylation of the alkene usually occurs at the least hindered, or terminal end of the alkene. However, when the coupling is intramolecular, that is, both the aryl halide and olefinic groups are incorporated into the one molecule, the regiochemistry is less predictable and alkylation does not always occur at the less substituted position.[56] Consequently in such systems, either 1,5 *exo* cyclisation to the five membered ring or 1,6 *endo* cyclisation to the six membered ring may result. In many cases of 1,5 *exo* cyclisation, the *exo* olefin undergoes a double bond shift leading to an aromatic system (*Scheme* 22), making this process highly favoured compared to the formation of the 1,6 *endo* cyclised product where no such aromatisation can occur.

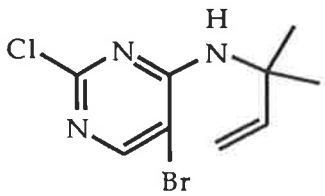


Second ring aromatised

1,5-exo cyclised product

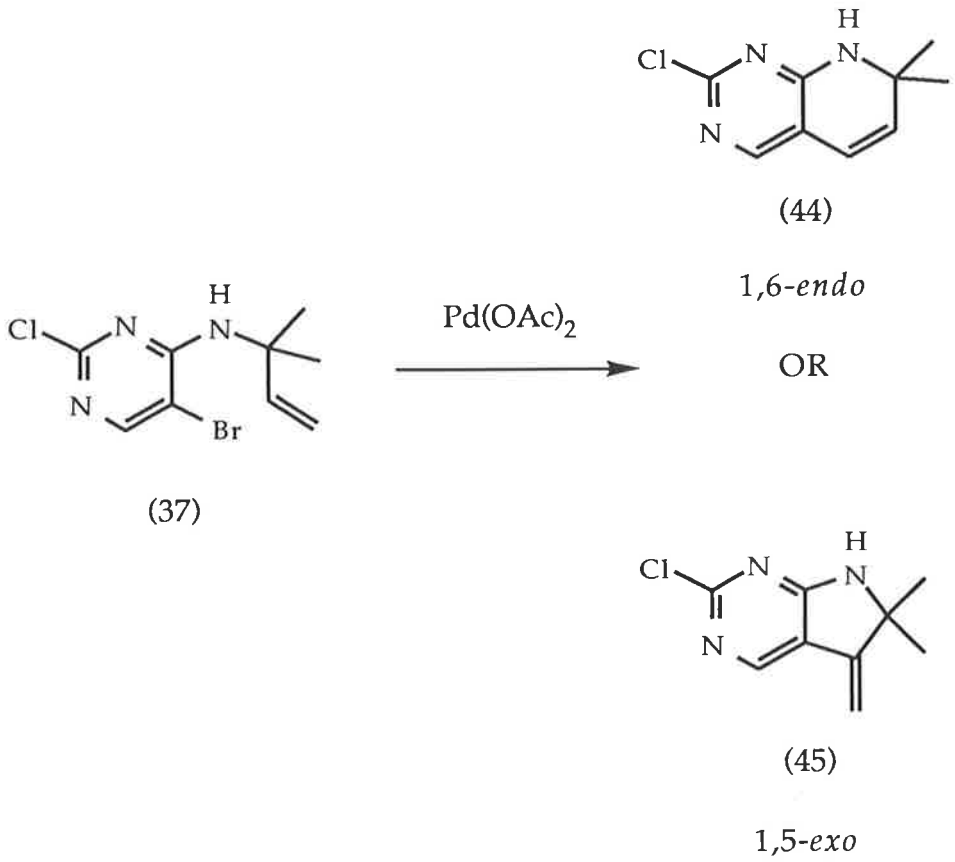
Scheme 22

Since the product arising from 1,5 cyclisation of (37) can not undergo aromatisation of the second ring due to the presence of the tertiary carbon centre it was expected that 1,5 *exo* cyclisation would not be so highly favoured and thus 1,6 *endo* cyclisation may be enhanced.



(37)

The Heck reaction was carried out following a literature procedure[57] whereby the alkene (37) was heated in a sealed tube in the presence of palladium acetate, tri-*o*-tolylphosphine and triethylamine (*Scheme* 23).



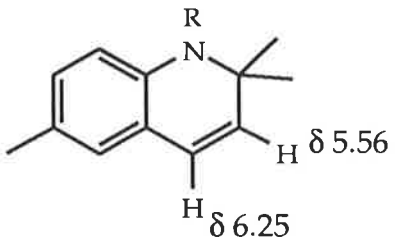
Scheme 23

The proton nmr spectrum of the crude material isolated after work up, showed that a large percentage of tri-*o*-tolylphosphine remained. Dry column chromatography with hexane as the eluting solvent removed the tri-*o*-tolylphosphine from the product.

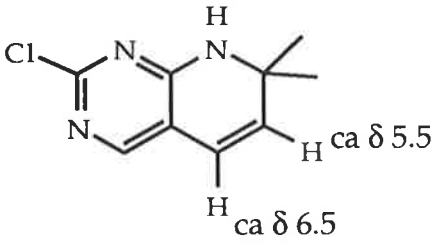
The material recovered after chromatography was analysised by proton nmr spectroscopy to show a singlet at δ 8.09 which corresponded to the aromatic C6 proton. A broad singlet at δ 6.65, which exchanged with deuterium oxide and a singlet at δ 1.44 were attributed to the NH and the geminal methyl groups

respectively. Two singlets were also observed at δ 5.54 and 5.13 resulting from two geminal alkene protons experiencing negligible geminal coupling. The ^{13}C nmr spectrum of the product showed the presence of two olefinic carbons at δ 137.6 and 115.4 ppm while the ^{13}C DEPT nmr spectrum of the product showed that the two olefinic carbons were a quaternary and a secondary carbon respectively. The mass spectrum showed a molecular ion at 195/197 m/z, confirming that cyclisation had taken place.

Comparison of the expected proton nmr spectrum of product (44) resulting from 1,6 *endo* cyclisation, with the proton nmr spectrum of compound[58] (46) showed that two doublets resonating at approximately δ 6.5 and 5.5 for the olefinic protons should be observed. Both doublets would be expected to show coupling in the range of 7-12 Hz due to their *cis* orientation. The ^{13}C DEPT nmr spectrum of (44) would have been expected to show that the olefinic carbons were both tertiary.

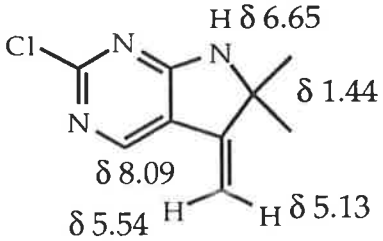


(46)



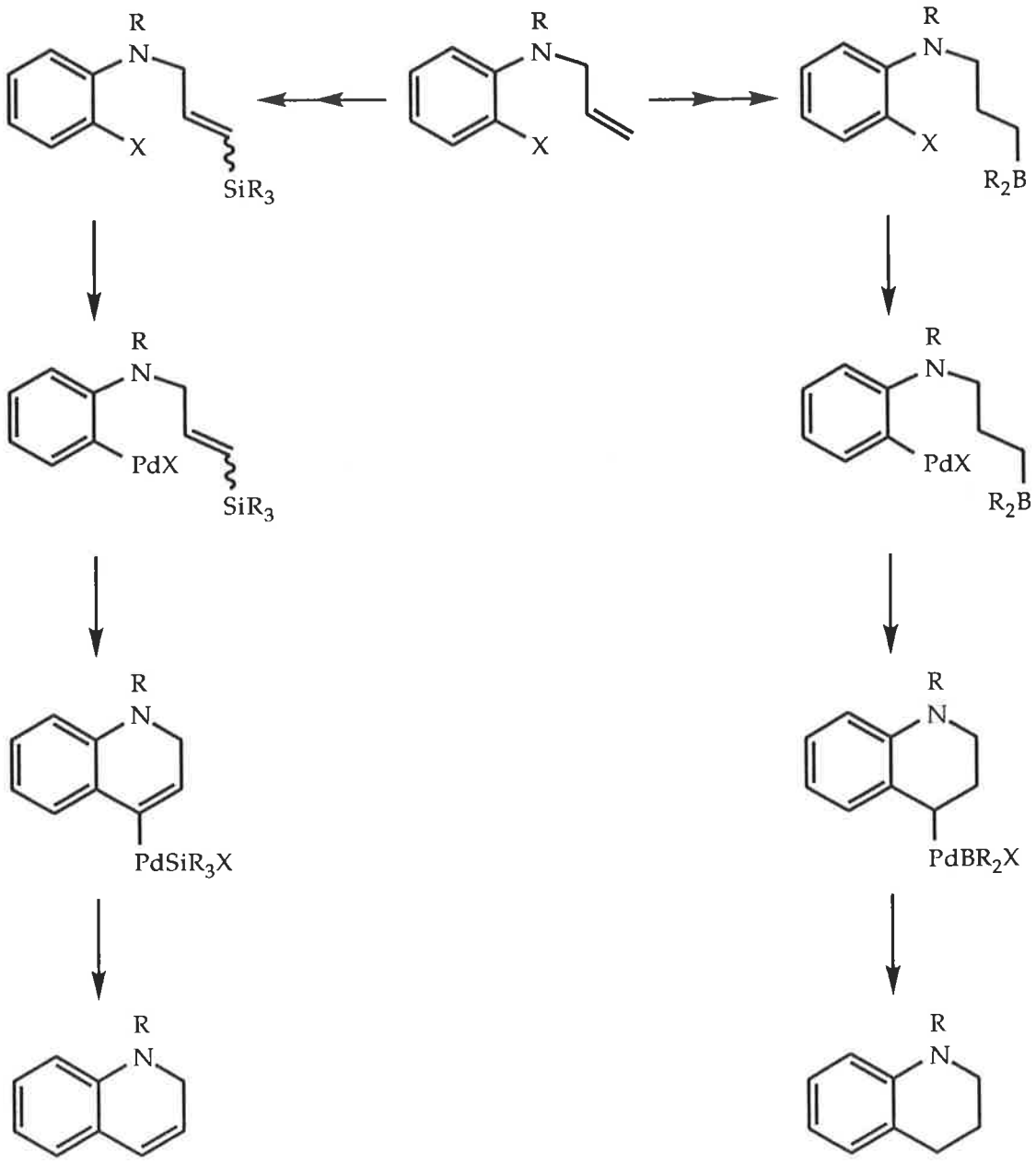
(44)

Therefore from the data obtained it was clear that 1,5 *exo* cyclisation to the five membered ring (45) had occurred.



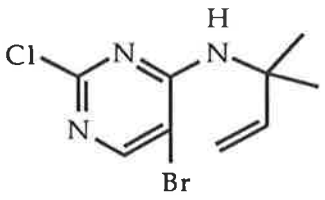
(45)

The formation of the five membered ring system in the Heck reaction led to an investigation to determine whether alternative forms of palladium catalysed couplings could lead to the six membered ring. Intramolecular cross coupling reactions can be utilised to ensure exclusive formation of a specific ring size.[50,51] This is achieved by insertion of an arylpalladium species between an appropriately positioned alkylborane[50] or vinylsilane[51] bond which has been set up to produce the desired ring size (*Scheme* 24).



Scheme 24

The alkylborane and the vinylsilane could possibly be obtained from the coupled alkene (37) and alkyne (47) respectively. Formation of either species should then enable the use of the palladium catalysed cross coupling reaction to afford the six membered ring system.



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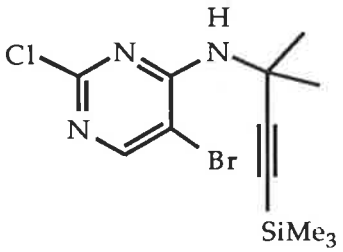
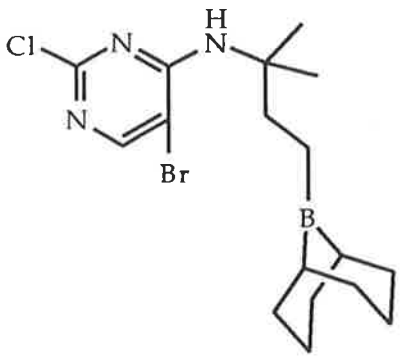


(47)

Synthesis of the alkylborane (48) was attempted by the addition of 9-borabicyclo[3.3.1]nonane (9-BBN), to the alkene (37). It was anticipated that the borane reagent would complex to the amine or the nitrogens of the heteroaromatic ring system and to counteract this, three to four equivalents of the borane were used for the reaction. After several hours the mixture was treated with the palladium catalyst and sodium hydroxide to effect the cyclisation.



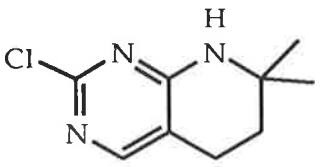
(48)

The proton nmr spectrum of the material isolated indicated that only starting

alkene had been recovered. This suggested that the formation of the alkylborane had been unsuccessful as the work up procedure should have afforded the corresponding alcohol, had the borane formed.

Repetition of the borane reaction and proton nmr spectroscopic analysis of the mixture prior to addition of the catalyst, again revealed the presence of only starting alkene, confirming that the borane was not forming.

The procedure outlined above to obtain the desired 1,6-*endo* cyclisation would give rise to the non functionalised tetrahydropyridine ring derivative (29). The absence of any functionality in this ring would prevent transformations to the C6 chloro derivative (49) as would be required for virantmycin analogues. Use of the vinylborane instead of the alkylborane was considered impractical since borane addition to the alkyne would afford the *trans* isomer resulting in the incorrect geometry[59] for the vinylborane to undergo the cross coupling reaction. Thus due to the problems encountered with the formation of the alkylborane this avenue was not pursued.



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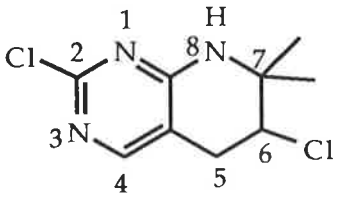
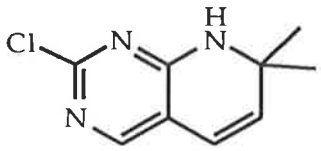


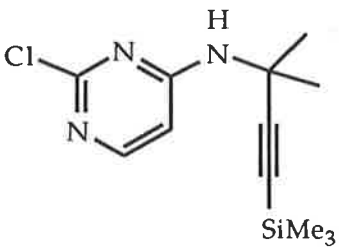
(49)

The alternative cross coupling reaction, employing the *cis*-vinylsilane,[51] would afford the more useful six membered *endo* cyclic alkene (44) which could then be manipulated to obtain the C6 chloro derivative (49).

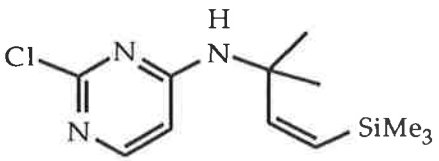


(44)

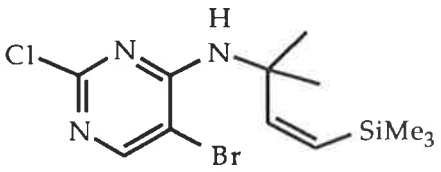
Formation of the vinylsilane (50) could be achieved by reduction of the corresponding silylalkyne using excess diisobutylaluminium hydride.[38] This approach had, however, been attempted previously for conversion of the silylalkyne (24) to the corresponding alkene (28) without success. As a result this procedure was deemed of little benefit and was not pursued. The possibility of employing a Lindlar reduction to obtain the vinylsilane was not investigated due to difficulties previously encountered with this reaction. The bulky silyl substituent hindered adsorption onto the catalyst preventing hydrogen transfer from the catalyst to the substrate[35] (Chapter 2.1).



(24)



(28)

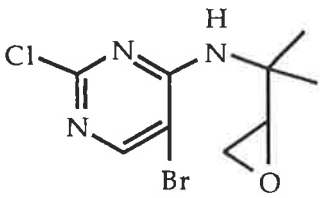


(50)

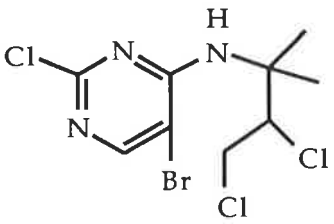
The inability to form the derivatives necessary for the palladium catalysed cross coupling reactions led to an investigation of alternative approaches to cyclisation.

Electrophilically induced cyclisations from the C5 position of the pyrimidine ring was an attractive approach due to the ease with which the C5 carbon can be converted to the corresponding anion.[48] It has been observed that a metal/halogen exchange[48] at the C5 ring position can be achieved and it is therefore possible that this species may then undergo reaction with an electrophile to afford the C5 substituted pyrimidine. Thus if an electrophilic moiety could be incorporated into the side chain of the coupled pyrimidine (37), cyclisation may be facilitated in this manner.

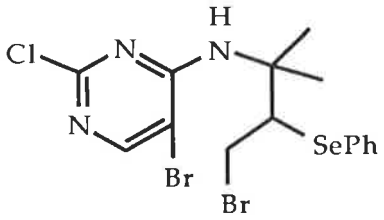
Suitable electrophilic species for this purpose would be an epoxide (51), 1,2-dichloride (52) or a β-haloselenide (53). Each of these derivatives should be obtainable from the corresponding olefinic moiety of the coupled pyrimidine (37) and each should react with an anion formed at the C5 ring position. It would then remain to determine whether 1,5-*exo* or 1,6-*endo* cyclisation had occurred.



(51)



(52)

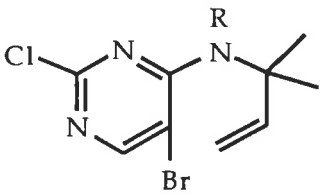


(53)

The mode of attack by the 'aryllithium' species onto the epoxide derivative (51) would have been expected to occur at the least hindered or least

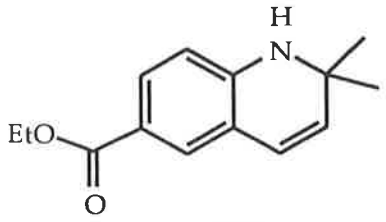
substituted position of the epoxide,[60] under basic conditions leading to 1,6-cyclisation. Similarly for the 1,2-dichloride (52), attack may be expected to occur preferentially at the terminal position to displace the primary halide[61] rather than the secondary, neopentyl type halide.[61] Alternatively, the mode of cyclisation for the β-haloselenide (53) will be determined by control of the addition of the selenium reagent across the olefin. Markovnikov addition would promote the 1,5 cyclisation while formation of the anti-Markovnikov adduct would result in the desired 1,6 cyclisation.

It was considered necessary to protect the free secondary amine as the electrophilic reagent could react at this position. Initial attempts to protect the amine as the trifluoroacetamide (54) under the standard conditions[23] resulted in only the recovery of starting materials. Attempts to form the acetamide (55), the ethyl carbamate (56), the *tert*-butyl carbamate (57) and the methanesulfonamide (58) were also unsuccessful, leading to the recovery of starting materials.



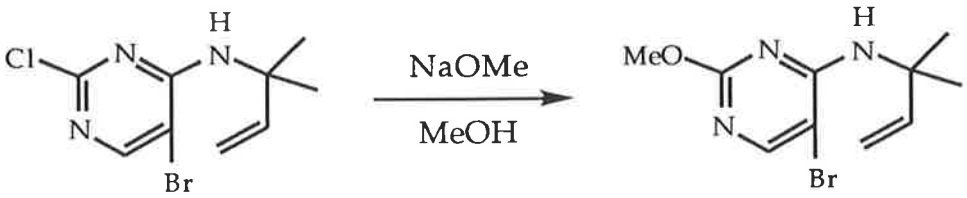
R = -$COCF_3$ (54)
-$COCH_3$ (55)
-OCOEt (56)
-OCO^tBu (57)
-SO_2Me (58)

It had been previously observed for the benzenoid analogues,[58] that electron withdrawing groups attached to the aromatic ring greatly reduce the reactivity of the amine. For example, compound (59) could not be converted to its N-protected derivative.



(59)

To counteract the lack of reactivity of the amine moiety in (37), the chlorine at C2 was replaced by a methoxy group in order to increase the electron density of the ring. This was accomplished by treatment of the alkene (37) with sodium methoxide (*Scheme* 25).



(37) (60)

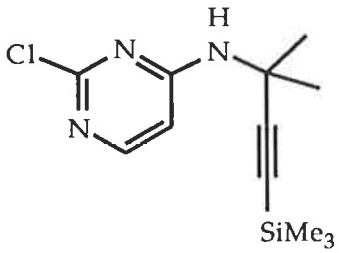
Scheme 25

Examination of the proton nmr spectrum of the new product showed that it had similar resonances to that of the starting alkene (37) except for a new peak at δ 3.87 corresponding to the methoxy group. The mass spectrum showed the expected molecular ion at 271/273 m/z for the methoxy derivative (60).

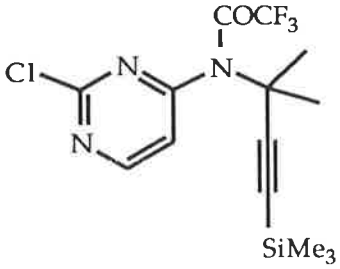
When protection was attempted on the more electron rich system (60) the trifluoroacetamide, acetamide and methanesulfonamide again could not be formed.

Since earlier work (Chapter 2) had shown that the amine (24) could be protected as its trifluoroacetamide (26) it appeared that the inductively electron

withdrawing ability and the steric demands associated with the bromine in the C5 position may be the major problem. The electron withdrawing ability of the bromine may lower the electron density at the amine nitrogen while the presence of the bromine at the C5 position of the ring may force the side chain into a position which increases the hinderance of the amine.

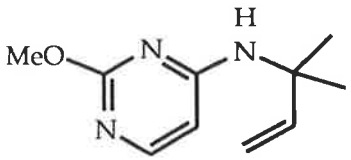


(24)



(26)

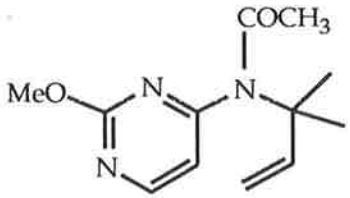
The bromine in the C5 position in (60) was removed by metal/halogen exchange with *n*-butyllithium followed by protic work up to afford the 2-methoxy derivative (61). The proton nmr spectrum of the product showed the expected resonances for the amino side chain but now two doublets resonating at δ 7.94 and 6.08 were observed, attributable to the aromatic protons at C6 and C5 respectively. The mass spectrum showed the expected molecular ion at 193 m/z for the debrominated methoxy derivative (61).



(61)

The amine (61) was then protected as the acetamide (62). The proton nmr spectrum of the product gave a similar spectrum to that of the starting amine (61) apart from a new singlet at δ 2.09 corresponding to the acetyl group and the absence of the broad signal at δ 5.26 for the amine NH. A molecular ion

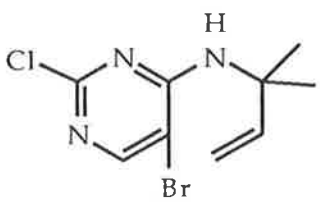
was observed at 235 m/z in the mass spectrum as expected for (62). In addition the infrared spectrum showed a carbonyl stretch at 1688 cm^{-1} which was consistent with the presence of an amide functionality. This information suggested that the problem of protection was due to the high electron withdrawing ability of the ring caused by the two halogens and/or the steric effects caused by the presence of the bulky bromine atom.



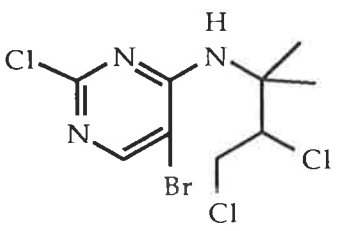
(62)

Unfortunately this result meant that electrophilic reactions at the C5 ring position could not be carried out on the amino protected derivative (62), since a halogen was necessary for lithiation to occur at that position. However, as the amine function proved unreactive, it was unlikely that it would participate in a reaction with the electrophilic reagent and it was decided to carry out the electrophilic reactions on the free amine.

The obvious candidate for cyclisation was a 1,2-dihalide since successfully employing the 1,2-dichloride (52) would directly afford the six membered ring containing a chloride at the C6 position (cf virantmycin), circumventing the need to further manipulate other functionality to obtain this species.

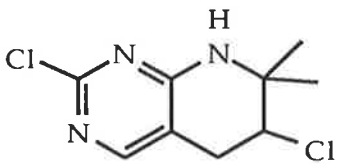


(37)



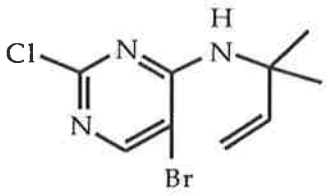
(52)

While this methodology would shorten the synthetic sequence required to obtain the chloride (49), the reaction was not investigated due to anticipated problems with the formation of the 'aryllithium' species in the presence of the 1,2-dihalide. The dihalide functionality may be prone to undergo many side reactions including elimination of hydrogen chloride to afford a vinyl halide which is of little synthetic use in this work. Hence alternative electrophilic species were examined.

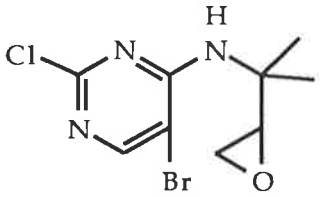


(49)

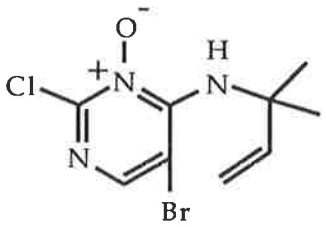
Attention was focussed on the formation of the epoxide[62] (51). This was attempted by the action of *m*-chloroperbenzoic acid on the alkene (37), however the reaction proved to be complicated, with little material being recovered upon work up of the reaction. The small amount of compound obtained was analysed by proton nmr spectroscopy to reveal that only reduced amounts of starting alkene had been isolated. These complications may have resulted from the formation of a water soluble N-oxide species[63] such as (63). The proton nmr spectrum of the reaction mixture prior to work up showed no sign of the epoxide with only the starting alkene being observed. Due to the recovery of only starting material (37), the lithiation reaction could not be attempted.



(37)



(51)



(63)

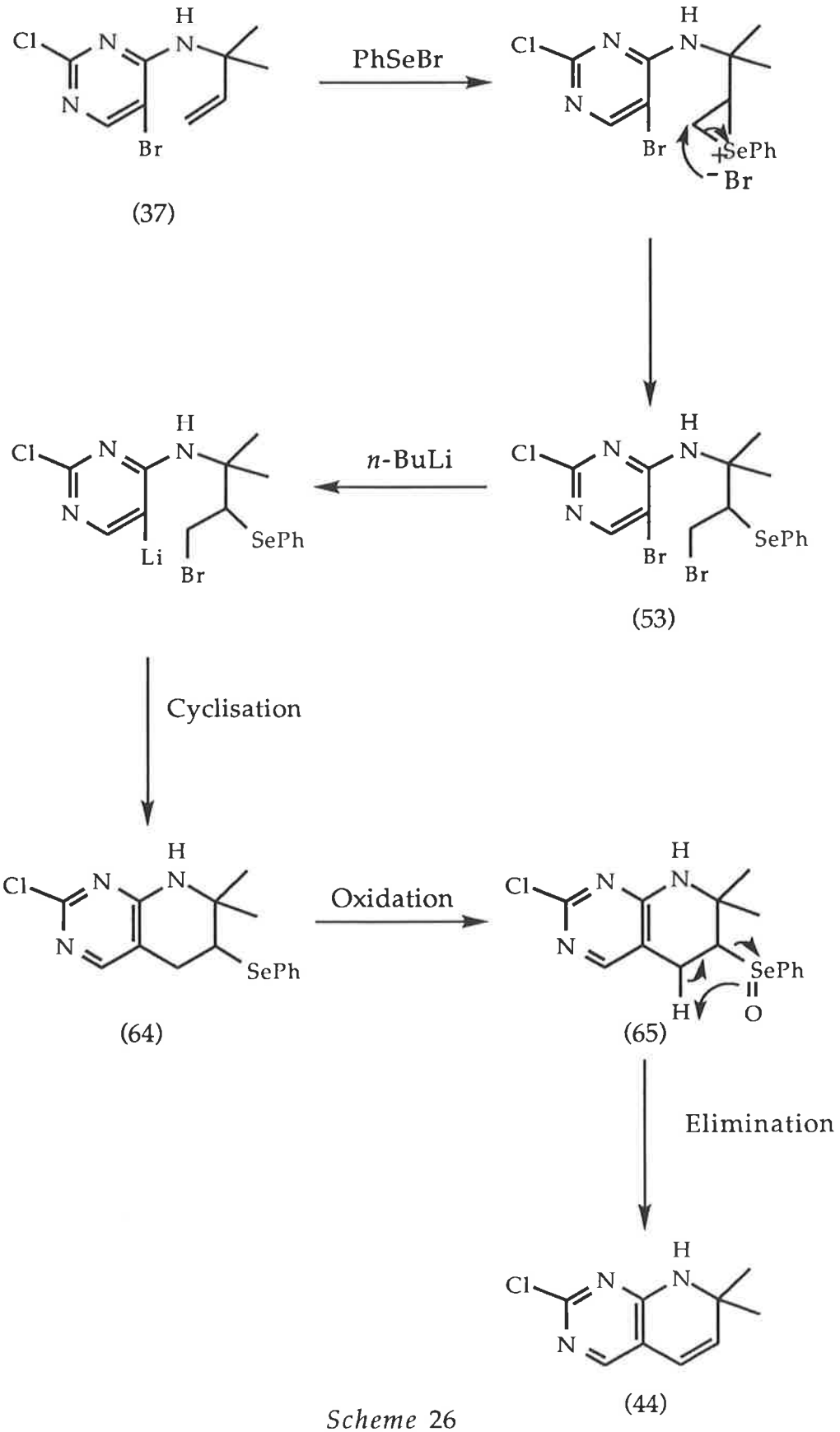
An alternative procedure for the formation of an epoxide is via a bromohydrin[64] formed by treatment of an alkene with N-bromosuccinimide and water. This reaction, when applied to (37) led only to the recovery of the starting alkene as indicated by proton nmr spectroscopy.

Attempted epoxidation using hydrogen peroxide resulted in the isolation of only reduced amounts of starting material, again possibly due to the formation of a water soluble N-oxide derivative.

Due to the difficulties encountered with epoxidation of the alkene, the use of the selenide as the electrophilic species was investigated.

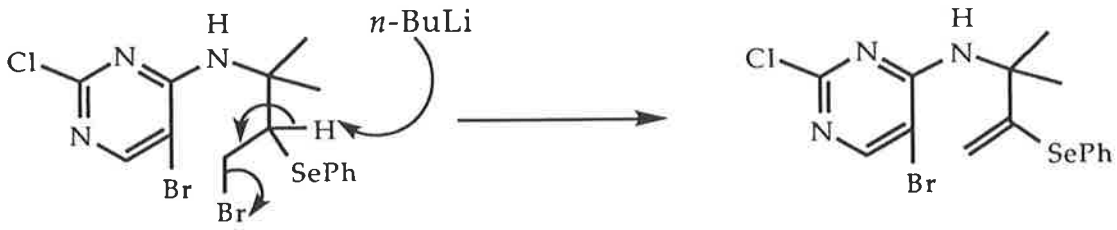
Organoselenium reagents such as phenylselenenyl chloride and phenylselenenyl bromide are powerful electrophilic species.[65] They readily undergo addition to double bonds[66] to afford the β-substituted selenides and, when subjected to oxidation and subsequent selenoxide *syn*-elimination, form alkenes.[67,68]

If addition of a phenylselenenyl halide across the olefinic moiety of the coupled pyrimidine (37) occurred to give the anti-Markovnikov product (53), then cyclisation to the six membered ring selenide (64), via the 'aryllithium' species, may be achieved. Oxidation of the selenide to the selenoxide (65) followed by elimination should then afford the 1,6-*endo* cyclic alkene (44) as depicted in scheme 26.


PhSeBr
n-BuLi
Cyclisation
Oxidation
Elimination
(37)
(53)
(64)
(65)
(44)

Scheme 26

As in the lithiation of the 1,2-dihalide, a consideration in this reaction must be the possible elimination of hydrogen bromide from the selenide species (53) due to the acidity of the proton α to the selenium moiety. This would result in the formation of the vinylselenide species (66), as detailed in scheme 27, which would be useless for the purpose of cyclisation. On this occasion, however, it was considered that due to the bulky substituents surrounding the α carbon, access of the base to the α proton would be limited, and lithiation of the aromatic ring would be favoured.



(53) (66)

Scheme 27

From related work carried out in our group it has been shown[47] that the anti-Markovnikov addition, required for 1,6-*endo* cyclisation, was achieved more readily with the use of phenylselenenyl bromide rather than the chloride. This was attributed to the larger size of the bromide ion which makes attack at the more substituted carbon less favourable.

Following a literature procedure,[69] in which the organoselenium reagent was added to a double bond in the presence of a pyrimidine type system, the alkene (37) in dichloromethane was treated with phenylselenenyl bromide at -78°C. After reaction of the selenium reagent, indicated by a colour change of the solution from deep red to yellow, *n*-butyllithium was added at -78°C and the mixture was allowed to warm to room temperature to effect the metal/halogen exchange and induce cyclisation. However, the proton nmr

spectrum of the crude material gave no indication that cyclisation had occurred. Chromatography of this crude mixture enabled separation of any products from the diphenyl diselenide by-product or unreacted phenylselenenyl bromide. The proton nmr spectrum of the purified material showed two products, that of the starting alkene (37) and some of the alkene (32) debrominated at the C5 position by the metal/halogen exchange.

Variations[47,70] on this procedure involved the use of dry dichloromethane and the addition to the reaction of a base, usually potassium carbonate, and a small amount of silica gel. Silica gel has been employed in these reactions to promote cyclisation.[47,70] The reaction was repeated using these conditions and upon consumption of the selenium reagent the mixture was filtered and the solvent removed as it was anticipated that the use of dichloromethane as solvent in the proceeding reaction with *n*-butyllithium would cause difficulties due to carbene formation.[71] Unfortunately the residue was insoluble in any of the solvents traditionally employed in reactions with *n*-butyllithium (eg. diethyl ether and tetrahydrofuran) and hence the halogen exchange reaction was performed using dry dichloromethane as the solvent, in order to keep the compound in solution. It was envisaged that the usually rapid acid/base reaction with the NH and the metal/halogen exchange at the C5 ring position may occur at an appreciably faster rate than carbene formation. Thus in a one-pot reaction phenylselenenyl bromide was added to a solution of the amine (37) in dichloromethane and, upon reaction of the selenium reagent, the mixture was treated with two equivalents of *n*-butyllithium at 0°C and allowed to warm to room temperature. The crude product was purified by chromatography to remove selenium by-products. Some inconsistencies were observed with the yields obtained in the reaction, which proved to be highly moisture sensitive. Ultimately it was found that the best results were achieved by drying of reagents and distillation of dried solvents immediately prior to reaction thus enabling consistent yields to be

obtained.

The proton nmr spectrum of the purified material showed two multiplets at δ 7.48 (2H) and 7.20 (3H) for the aromatic protons *ortho* to the selenium atom and for the aromatic protons *meta* and *para* to selenium respectively. A singlet resonating at δ 7.30 was attributed to the C6 proton of the pyrimidine ring, substantially further upfield than in the starting material consistent with the replacement of the adjacent bromine by a carbon. An ABX system was observed at δ 4.27, 3.21 and 3.08 (*Fig* 5) which could be attributed to the proton under selenium and the two non equivalent methylene benzylic protons for the 1,6 *endo* derivative (64). Alternatively, the signals could also correspond to the benzylic proton and the methylene protons under selenium for the 1,5 *exo* derivative (67). A broad singlet observed at δ 4.34 corresponded to the amine NH as it was no longer visible after deuterium oxide exchange. The geminal methyl groups, formerly coincident, were now observed as two distinct singlets at δ 1.46 and 1.24 suggesting that the two methyl groups were being held in different environments, which was expected due to the adjacent chiral centre. The mass spectrum showed a molecular ion at 353 m/z as expected for the formation of the cyclic selenide.

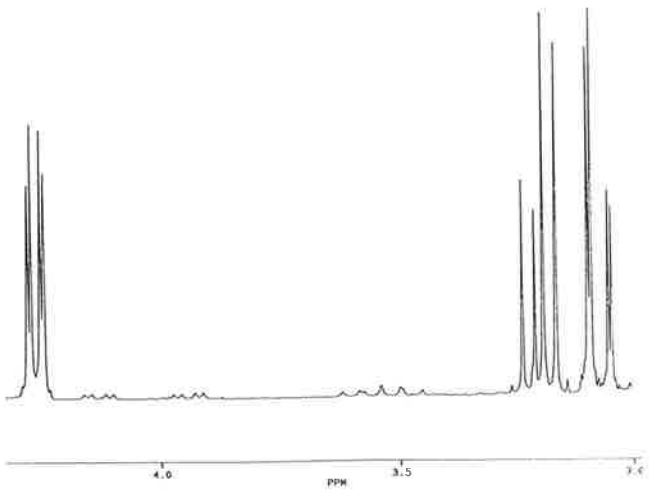
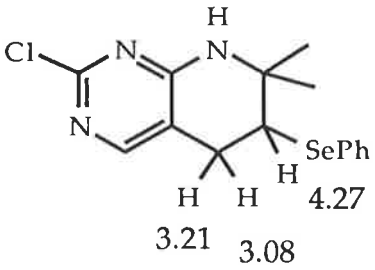
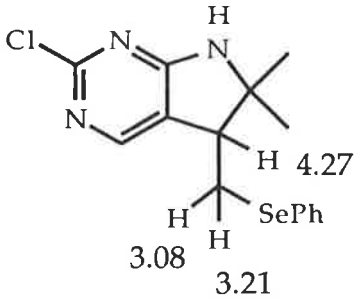


Figure 5

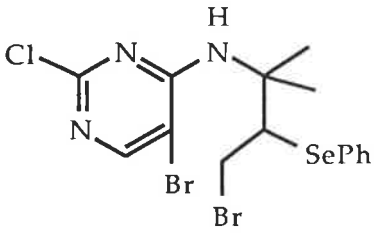


(64)

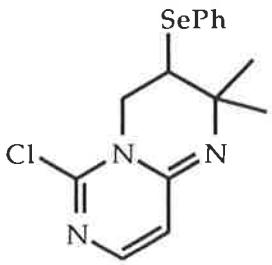


(67)

The cyclic selenide obtained could conceivably have one of three possible structures. Compound (64) would arise from the expected 1,6-*endo* cyclisation following anti-Markovnikov addition of phenylselenenyl bromide across the alkene. The 1,5-*exo* cyclic selenide (67) would have arisen from Markovnikov addition of the selenium reagent to the alkene. The structure (68) could have been formed by attack of the ring nitrogen on the acyclic species (53) prior to lithiation at C5. This last structure was ruled out by the presence of an NH in the proton nmr spectrum and the infrared spectrum. In addition, the presence of two doublets for the pyrimidyl C6 and C5 protons would have been expected for this compound, instead only a singlet was observed for the proton at C6.



(53)



(68)

On the basis of the spectroscopic data the 1,5-cyclic derivative could not be discounted, however the proton nmr spectrum was more consistent for that of the 1,6 derivative (64) due to the presence of only one proton at δ 4.27 which, on considering deshielding factors, may be expected for the proton adjacent to selenium. The proton nmr spectrum of the 1,5 derivative would have been

expected to show two protons in this region. Molecular modelling studies on the structure of the 1,6 cyclised derivative (64) (*Fig* 6) have indicated that the α proton under selenium could be expected to be observed further downfield than usual[70,72] (δ 3.0-3.5) due to the close proximity (approximately 3Å) of this proton to the aromatic ring attached to selenium. This proton appeared to be in the deshielding region of the aromatic ring which would explain the observation of the signal at δ 4.27.

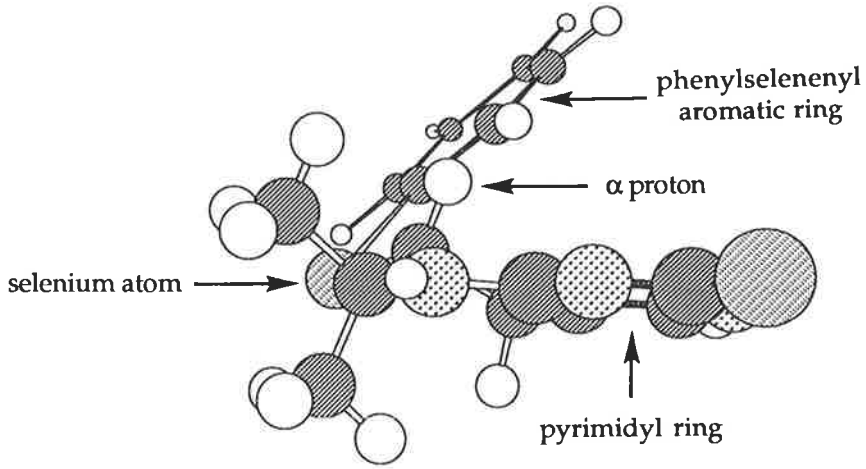
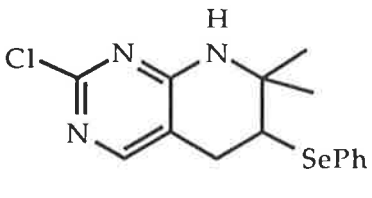


Figure 6

In addition, the proton nmr spectrum of the selenide showed a very similar pattern to that of the benzenoid C3 chloride derivative[58] (69) which showed an ABX system for the protons of interest at δ 4.15, 3.15, 3.01.



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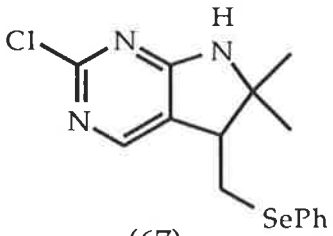

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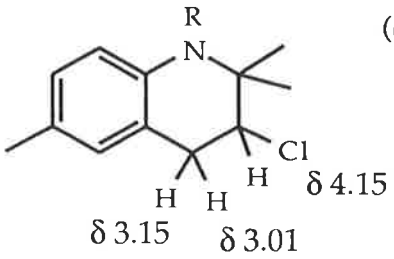
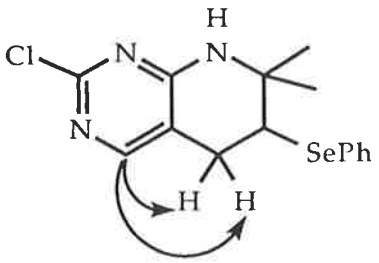
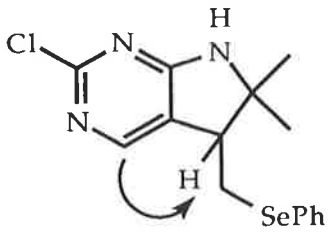


(69)

To establish the structure of the isolated compound as either the 1,5 or 1,6 derivative it was necessary to carry out an extensive nmr study to determine which of the signals in the proton and ^{13}C nmr spectra were adjacent to the selenium. The ^{13}C nmr spectrum showed two signals resonating at δ 27.5 and 70.7 which were assigned to the CH_2 and CH respectively by a ^{13}C DEPT nmr experiment. Hetcorr and COLOC 2D experiments were used in an attempt to establish long range correlations between the C6 pyrimidyl carbon and the proton or protons in the benzylic position (*Fig* 7). These, however, failed to provide the desired information to distinguish between the two possibilities as only short range couplings were observed.



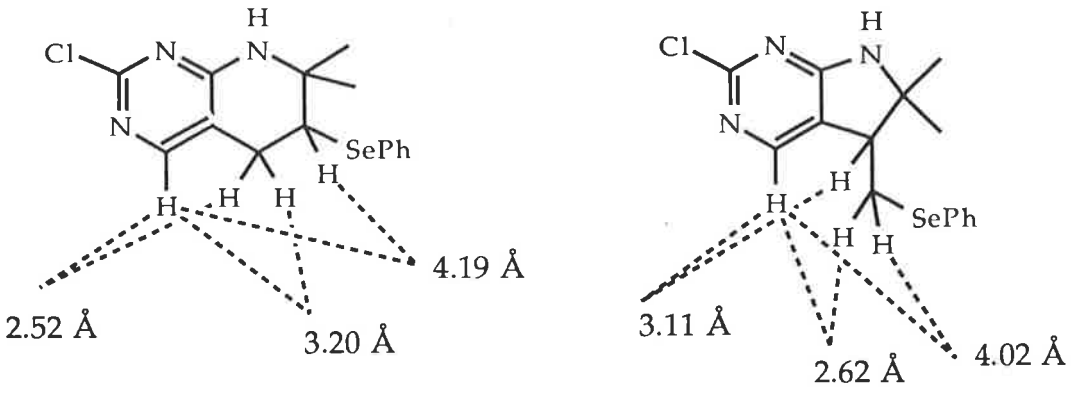
(64)



(67)

Figure 7

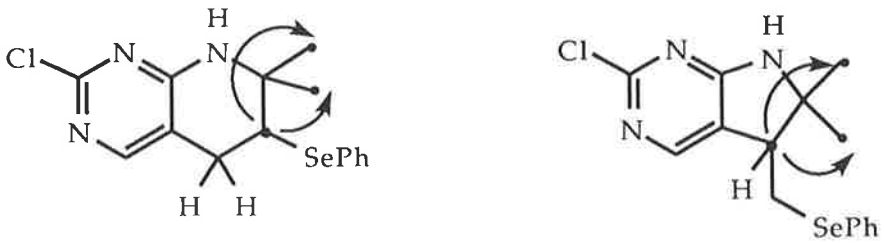
Nuclear Overhauser effect experiments to observe an nOe enhancement at the benzylic position upon irradiation of the C6 pyrimidyl proton also proved to be inconclusive. Since nOe enhancements are not observed over an interproton distance greater than 3Å, and the protons of interest were shown to be close to 3Å by the PC modelling program (*Fig* 8), the absence of enhancement for these was not unexpected. In each of the cases that the interproton distances were less than 3Å, the nOe enhancement was negligible and consequently the assignment of the selenide structure could not be achieved from this experiment.



(64) (67)

Figure 8

Coupled ^{13}C DEPT experiments at room temperature and at lower temperatures failed to reveal any useful data on the long range couplings within the molecule with which to determine the structure. The only correlations observed were between the CH and the geminal methyl carbons (*Fig* 9) which can exist in either (64) or (67) and therefore a distinction between the two was not possible.



(64) (67)

Figure 9

A ^{13}C nmr experiment was carried out to observe the selenium satellites of the carbon adjacent to the selenium atom. Selenium (^{77}Se) has a natural abundance of 7.6% which can be observed,[72] in the ^{13}C nmr spectrum, at 60-80 Hz either side of the carbon to which it is attached in an abundance of 3.8% for each satellite. The long range coupling[72] of the selenium to the carbon two

bonds removed is of the order of 5-15 Hz. The ^{13}C nmr spectrum of the selenium containing product showed satellites around the CH_2 carbon at δ 27.5 with a coupling constant of 36.4 Hz and an abundance of 3.0% each (*Fig* 10). Either side of the CH carbon were smaller satellites with couplings of 18 Hz, consistent with the second order coupling to the long range carbon. These results suggested that the 1,5 cyclised derivative (67) had been obtained, however, they were not conclusive due to the lower than expected coupling constant of 36.4 Hz for the satellites.

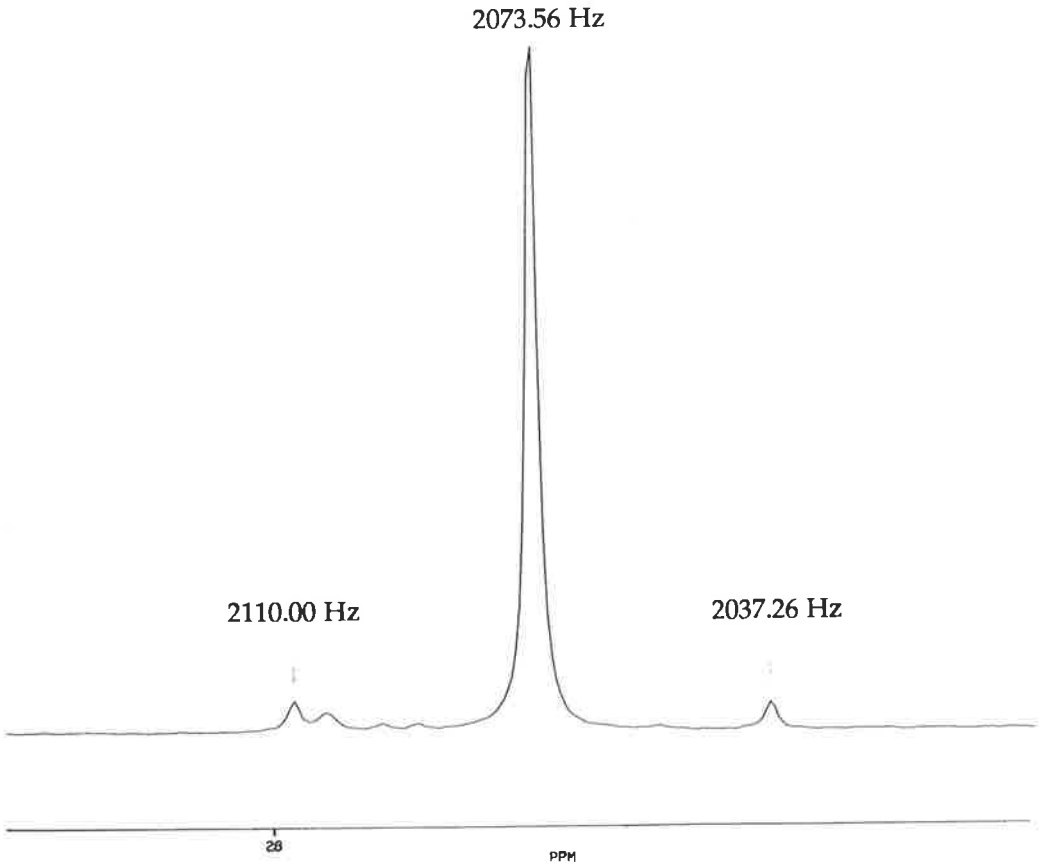
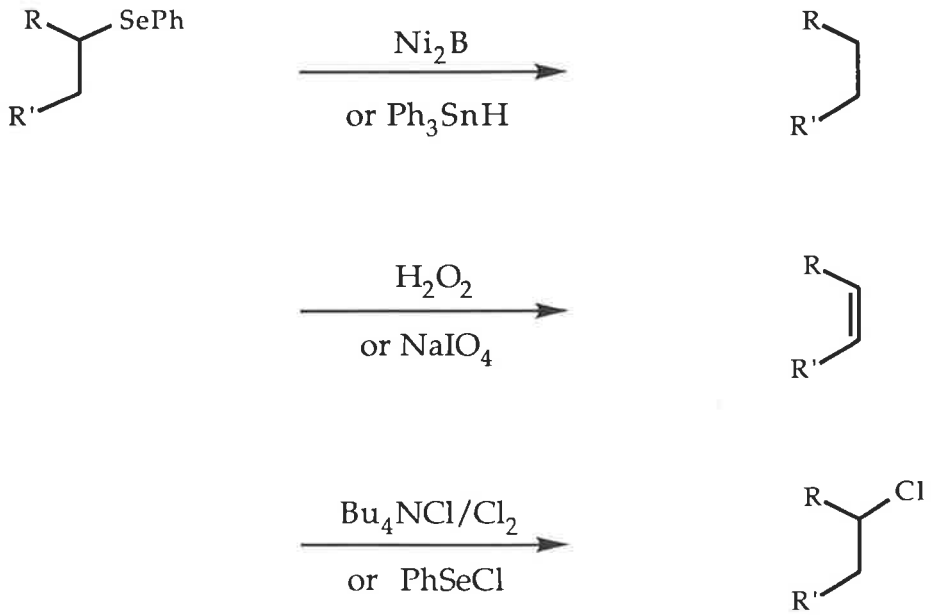


Figure 10

To obtain a decisive result a selenium-proton hetcorr 2D nmr experiment was carried out to establish which protons were attached to the carbon adjacent to

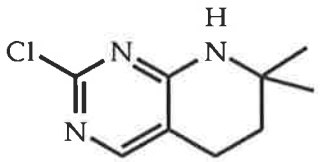
the selenium atom. This experiment, although not conclusive, contradicted the satellites experiment by showing a correlation between the CH proton and the selenium thus suggesting that the 1,6-cyclised derivative (64) had been obtained. However, due to problems with the hardware of the nmr spectrometer these results could not be repeated and consequently no decisive solution could be obtained. Thus, due to the difficulties encountered with the nmr programs and the subsequent inconsistencies in nmr spectroscopic data, the structure was deduced by chemical means.

The phenylseleno moiety can undergo a variety of functional group modifications. These include reduction to the hydrocarbon with triphenyltin hydride[73] or nickel boride[74] and oxidation with hydrogen peroxide[67] or sodium periodate[68] to the selenoxide followed by *syn*-elimination to form the alkene. The selenium can also be displaced by chlorine using tetrabutylammonium chloride and chlorine[70] or phenylselenenyl chloride[47,70] as shown in scheme 28.

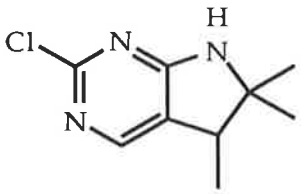


Scheme 28

Reduction of the seleno moiety to the corresponding methylene group would be expected to provide unambiguous identification of the structure. The proton nmr spectrum of the reduced 1,6 cyclic derivative (29) would be expected to show two triplets due to the methylene protons at C5 and C6 of the tetrahydropyridine ring as observed for the corresponding benzenoid derivative.[15] The 1,5-derivative (70) could be distinguished from (29), as its proton nmr spectrum should show a doublet and a quartet for the protons of interest. Reduction of the selenide was attempted following literature conditions established for both the triphenyltin hydride[73] and nickel boride[74] reductions however neither were successful. In the case of the triphenyltin hydride reduction, the low solubility of the selenide in the solvents employed for this reaction may have been a contributing factor, while for the nickel boride reduction the possible formation of a complex between the metal and the pyrimidine ring may have prevented reduction from occurring.



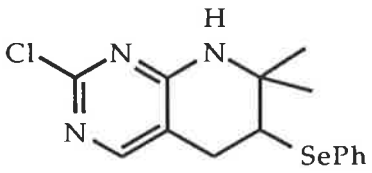
(29)



(70)

It has also been shown that selenides can undergo a metal/selenium exchange with *n*-butyllithium.[75] This was attempted in an effort to reduce the selenide moiety to the corresponding hydrocarbon. *n*-Butyllithium was added to the selenide at room temperature and after anion formation the reaction was quenched with water. The proton nmr spectrum of the product, purified by dry column chromatography, showed no sign of starting material. Two triplets, resonating at δ 3.58 and 2.85, were observed, corresponding to the two methylene groups of the reduced material, as expected for the 1,6 cyclised product (29). Also indicative of the removal of the bulky selenium group was

the presence of a coincident singlet at δ 1.29 for the geminal methyl groups which were formerly observed as two singlets in the selenide due to the bulky phenylselenium substituent forcing the methyl groups into different environments. The observation of the two triplets in the proton nmr spectrum of the product enabled the assignment of the reduced material as compound (29). This then confirmed the structure of the cyclic selenide as the 1,6 cyclised derivative (64).



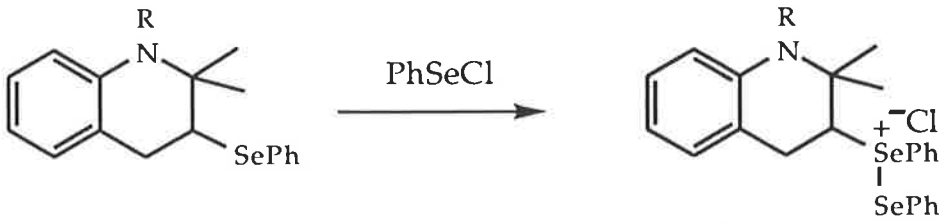
(64)

The formation of the reduction product (29) from the metal/selenium exchange on the selenide indicated that some of the nmr data obtained from the selenide was misleading. In particular the results from the reduction showed that the outcome of the selenium satellites experiment was inconsistent with the majority of evidence that supported the formation of the six membered derivative (64). The unusually low coupling constant for the selenium satellites may suggest that, in fact, it was not the satellites that were detected, implying that the experiment was not permitting the observation of the selenium satellites. This could also be due to the problems observed with the hardware of the nmr spectrometer.

Having established that the 1,6 cyclised selenide (64) had been obtained, manipulation of the selenide to the corresponding chloride was investigated.

Work conducted within our research group has shown that displacement of primary and secondary seleno moieties can be achieved by oxidation of the

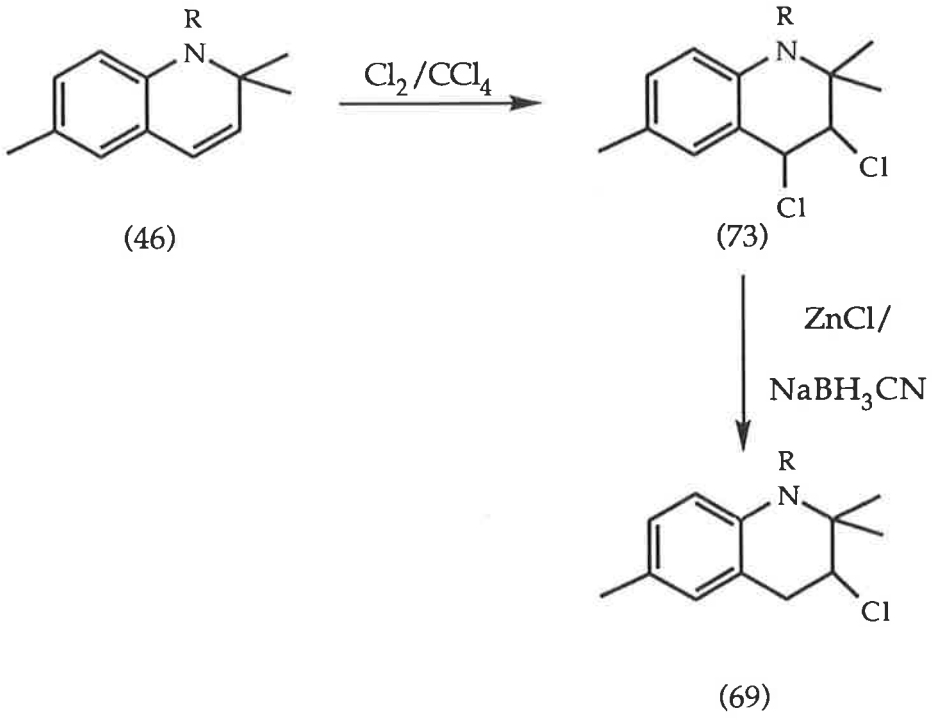
selenide with tetrabutylammonium chloride or phenylselenenyl chloride[47,70] followed by treatment with a suitable chloride source. However, when the tetrahydroquinoline nucleus (71) was treated with phenylselenenyl chloride,[47] the reaction proved to be ineffective. This was possibly due to the neopentyl type nature of the selenide. Instead the oxidation product (72), which had not undergone substitution with chloride, was isolated[47] (*Scheme* 29). Hence this method was not suitable for conversion of the pyrimidyl selenide system (64) to the chloride.



(71) (72)

Scheme 29

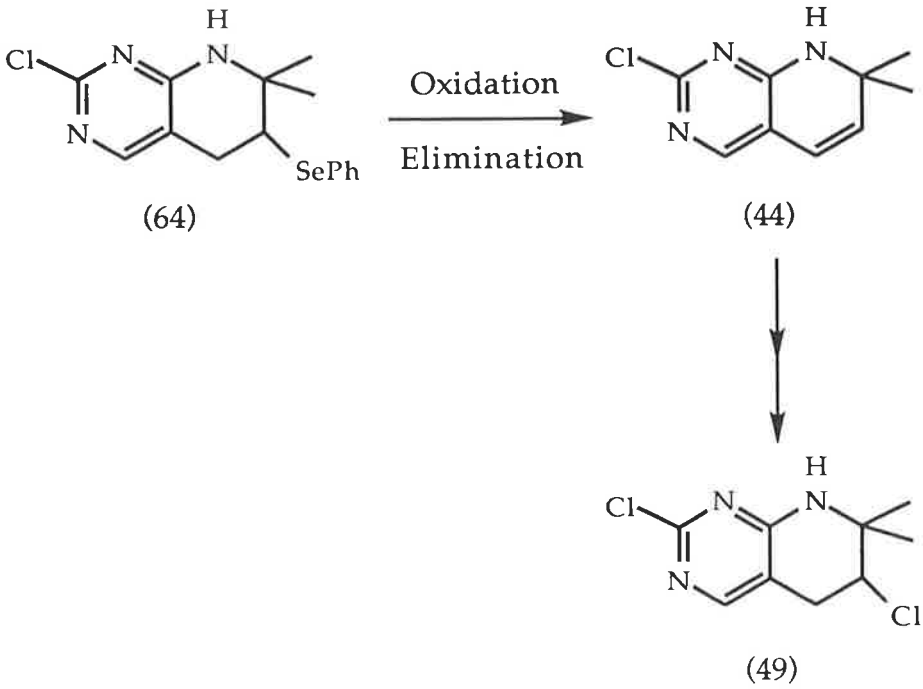
It has been established within our research group[58] that the dihydroquinoline (46) can be converted to compound (69) following the sequence outlined in scheme 30. Addition of chlorine across the double bond affords the dihalide (73) which can then be mono-dechlorinated at the benzylic position using a zinc modified cyanoborohydride[76] to obtain the C3 mono-chloride (69).



(46) (73) (69)

Scheme 30

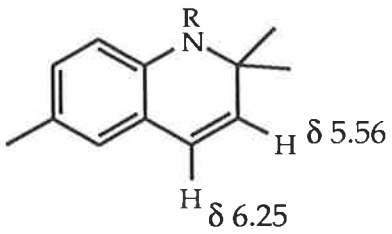
Thus if the pyrimidyl selenide (64) underwent the oxidation and elimination (*Scheme* 31) to form the alkene (44), application of the above transformations on this alkene may afford the desired mono-chloride derivative (49).



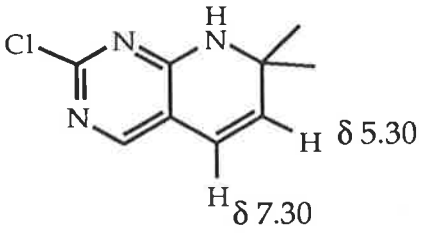
(64) (44) (49)

Scheme 31

The oxidation/elimination procedure was first attempted using sodium periodate[68] in an aqueous methanol solution. The proton nmr spectrum of the product in d_6-acetone, isolated in poor yield, showed a singlet at δ 7.55 corresponding to the C6 aromatic proton of the pyrimidine ring. Two doublets resonating at δ 7.04 and 5.22 were attributed to the olefinic protons. Both showed a coupling constant of 8 Hz, consistent with the expected *cis* orientation. This proton nmr data was consistent with that expected for the 1,6-*endo* cyclic alkene (44) when compared to the data for the benzenoid analogue[58] (46).



(46)

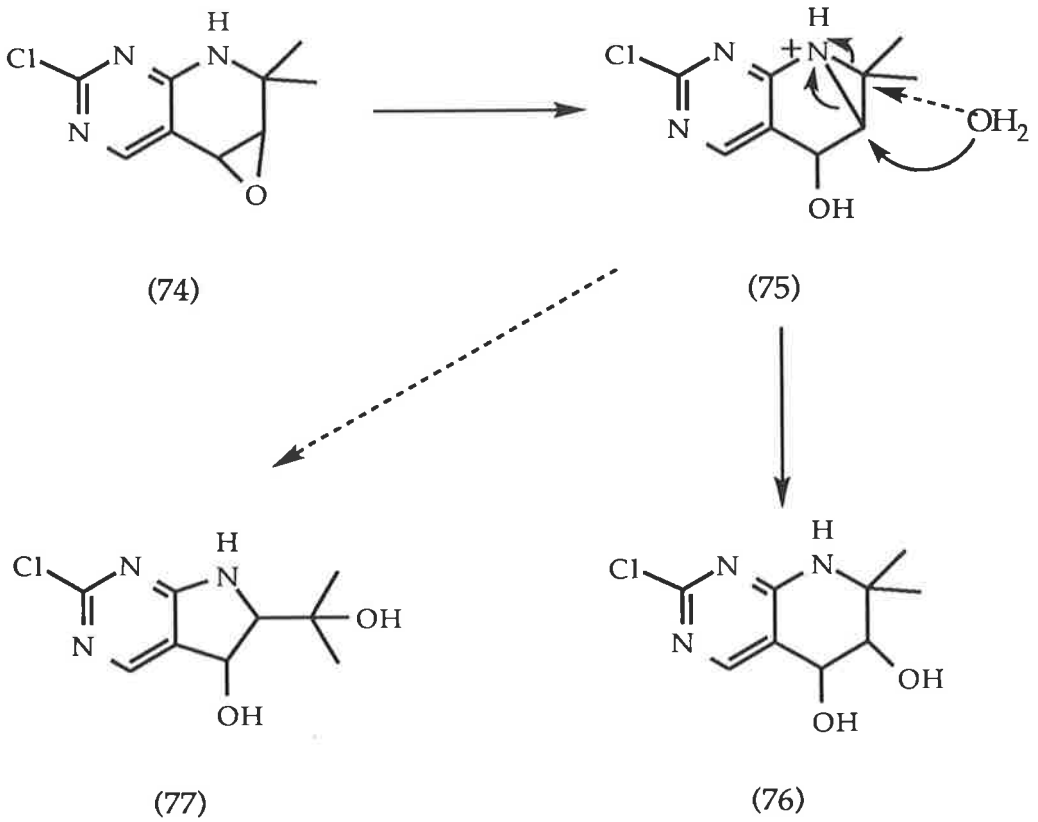


(44)

Unfortunately the loss of the large phenylseleno moiety and poor yields in the overall reaction hindered further elaboration of the alkene to obtain the C6 chloride (49). In addition the reaction proved to be difficult to reproduce consistently and thus alternative methods for the oxidation of the selenide (64) were investigated.

Hydrogen peroxide has been shown to be a more effective oxidising agent in some cases[67] and was also investigated. However, when this reaction was carried out none of the desired product was isolated, with only minor amounts of phenylselenium containing by-products being observed by proton nmr spectroscopy. The low recovery of material from the attempted oxidation suggested the majority of the product was water soluble and was retained in the aqueous layer upon work up.

A proton nmr study was carried out, in aqueous hydrogen peroxide and deuterochloroform, to determine the rate at which the reaction was occurring and the rate that the starting materials and/or products were being taken up into the aqueous layer. The first proton nmr spectrum, taken after 2 min, revealed that only minor amounts of starting material were present in the organic phase thus indicating that the reaction was almost instantaneous. There was no sign of the expected product, suggesting that any compounds formed were highly water soluble. As shown previously with the attempted epoxide formation from compound (37), the N-oxide may be produced in the reaction with hydrogen peroxide resulting in a low recovery of organic soluble material. The use of a large excess of hydrogen peroxide could also lead to the formation of the epoxide (74), from the alkene (44). The epoxide (74) could then be opened by the ring nitrogen to give the reactive aziridinium species (75), as observed in the virantmycin system,[9] which may then be readily opened to form water soluble diols (76) and (77) (*Scheme* 32). Alternatively the oxidation may have produced a selenoxide or selenone which was water soluble.

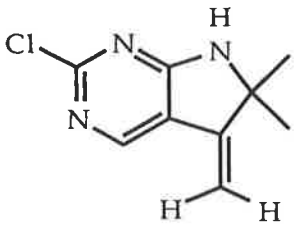


Scheme 32

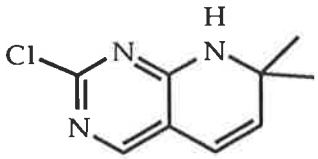
The oxidation/elimination was repeated using the alternative oxidising agent, *m*-chloroperbenzoic acid, but on this occasion only starting selenide (64) was recovered indicating no reaction had taken place.

In summary, the work outlined in this chapter has therefore shown that both the 1,5 and 1,6 cyclised pyrimidine derivatives can be obtained exclusively. The 1,5-*exo* derivative (45) was obtained by utilisation of the palladium catalysed Heck reaction[57] in moderate yields, while the 1,6-*endo* alkene (44) could be obtained from the selenide (64), albeit in low yields, by employing sodium periodate[68] as the oxidising agent. Due to the poor yields and lack of reproducibility of the latter reaction, other oxidising agents were also examined. These reagents, however, proved to be unsatisfactory and consequently the oxidation and elimination procedure to form the 1,6-*endo*

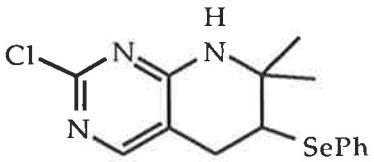
alkene (44) will require further attention. Time constraints prevented any further elaboration of this work being part of the current study. This work will, however, be continued by others within our research group to determine the most effective method for conversion of the selenide (64) to the alkene (44). Having obtained the alkene (44), an examination of the dichlorination/mono dechlorination of the *endo* alkene to obtain the C6 mono chloride (49) in the heteroaromatic system, can be carried out.



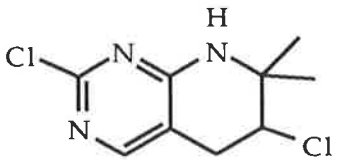
(45)



(44)



(64)



(49)

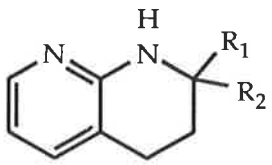
The ability of the selenide (64) to undergo a metal/selenium exchange[75] indicates that the chloride (49) could be produced directly from the selenide by quenching the anion with an appropriate electrophile. Consequently this approach will also be examined and if successful will be extended to other selenides. A major advantage in the implementation of this methodology is that it enables a relatively short synthetic sequence to be employed in the synthesis of nitrogen analogues of virantmycin.

Chapter 4.1 *Synthesis of Pyridine Analogues*

Introduction

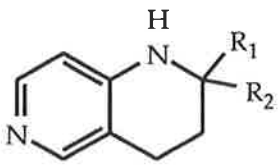
Concurrent with the synthesis of pyrimidyl analogues of virantmycin, the synthesis of pyridyl analogues was also investigated.

To enable a comparison of the pyridine analogues of virantmycin with the nucleosides, the pyridine nitrogen was required in either the 2- or 4- position with respect to the carbon bearing the nitrogen of the second ring as shown with derivatives (13) and (78).



(13)

1,8-naphthridine derivative



(78)

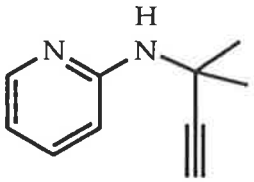
1,6-naphthridine derivative

It was also of interest to investigate the chemistry that was required to obtain the pyridine analogues and compare it with the methods already established for the benzenoid and pyrimidine systems.

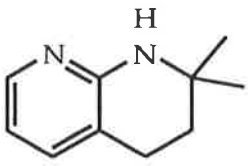
The two, four and six positions of the pyridine ring are electron deficient and are therefore subject to nucleophilic attack,[77] but to a lesser extent than that of the pyrimidine system. Alternatively, the three and five positions are susceptible towards electrophilic attack,[77] although less so than benzene.

Due to this difference in reactivity of the pyridine ring compared to both the benzenoid and pyrimidyl systems, it may be expected that the chemistry required to effect the same transformations would also vary.

The 2-pyridyl analogue was chosen as the target compound for the pyridine system, and the work in this area was focussed on the synthesis of compound (79) as a precursor to cyclisation leading to the formation of the desired target (80).

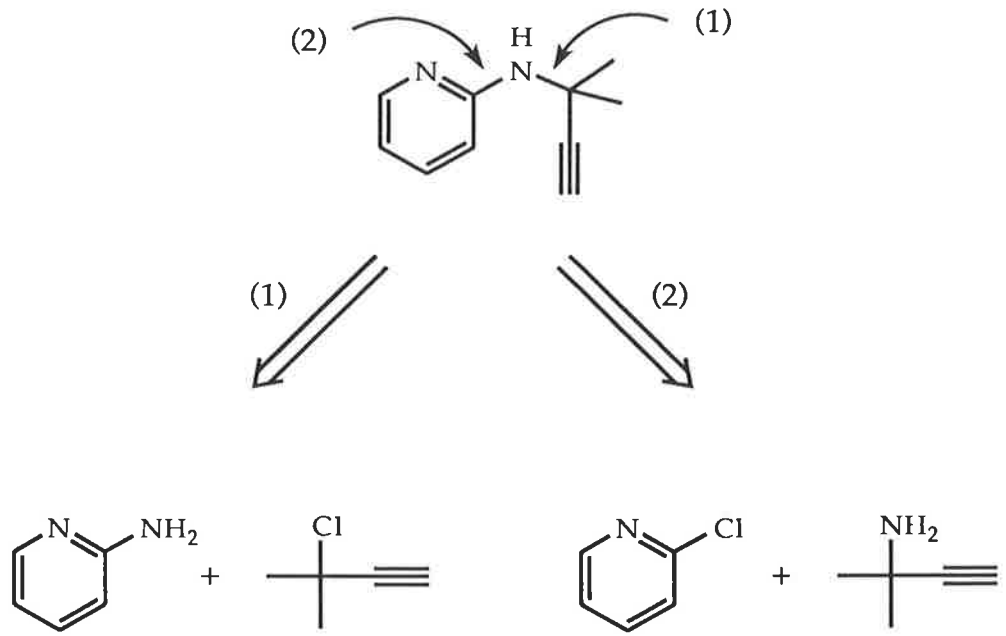


(79)



(80)

A retrosynthetic analysis suggested that there were two possible synthetic approaches to the alkynyl aminopyridine (79).



Scheme 33

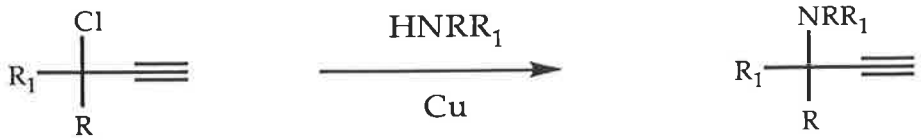
The first approach (*Scheme* 33 : route 1) involved the formation of a bond between the nitrogen and the tertiary carbon centre. This approach would utilise the copper catalysed coupling of an arylamine and a tertiary halide, as established for the aniline system.[18] The alternative method (*Scheme* 33 : route 2) would involve the displacement[78] of an aryl halide with a suitable amine. This method was expected to prove more difficult than for the corresponding pyrimidine system due to the lower reactivity of halopyridines towards nucleophiles.[77]

The work described in this chapter outlines approaches towards the synthesis of the coupled product (79).

Results and Discussion

The initial focus of this study involved an examination of the copper catalysed coupling of 2-aminopyridine and 3-chloro-3-methylbut-1-yne (*Scheme* 33 : route 1).

Hennion and coworkers[16,18] have developed a methodology for the synthesis of secondary and tertiary propargylamines. This procedure involved the reaction of secondary and tertiary propargyl halides with primary and secondary amines, in the presence of a catalytic amount of copper (*Scheme* 34).

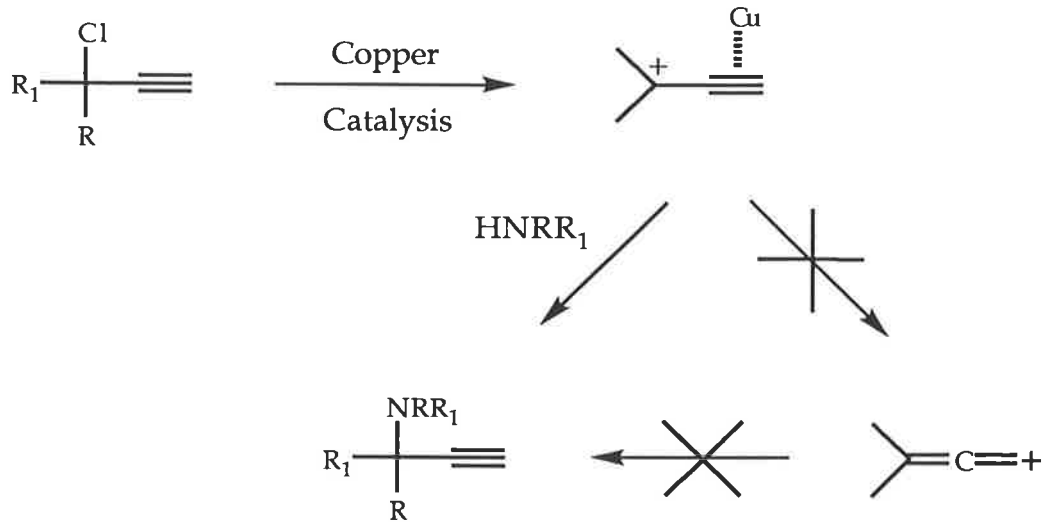


R = -H, -alkyl

R_1 = -alkyl

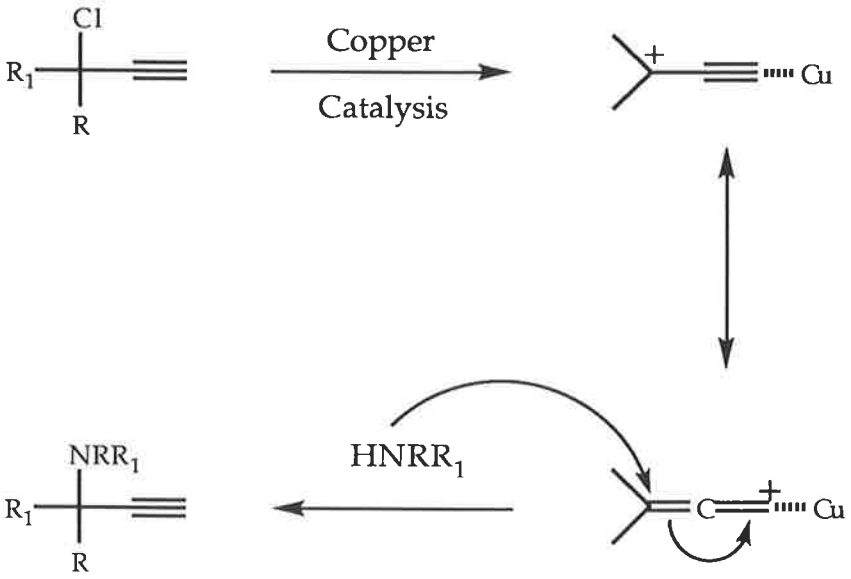
Scheme 34

The role played by copper in this reaction has not been fully identified and conflicting reports about its use have resulted. One suggestion[16] is that the copper coordinates to the alkyne thus preventing isomerisation of the alkyne to the allene. This then enables direct reaction at the tertiary cationic centre as depicted in scheme 35.



Scheme 35

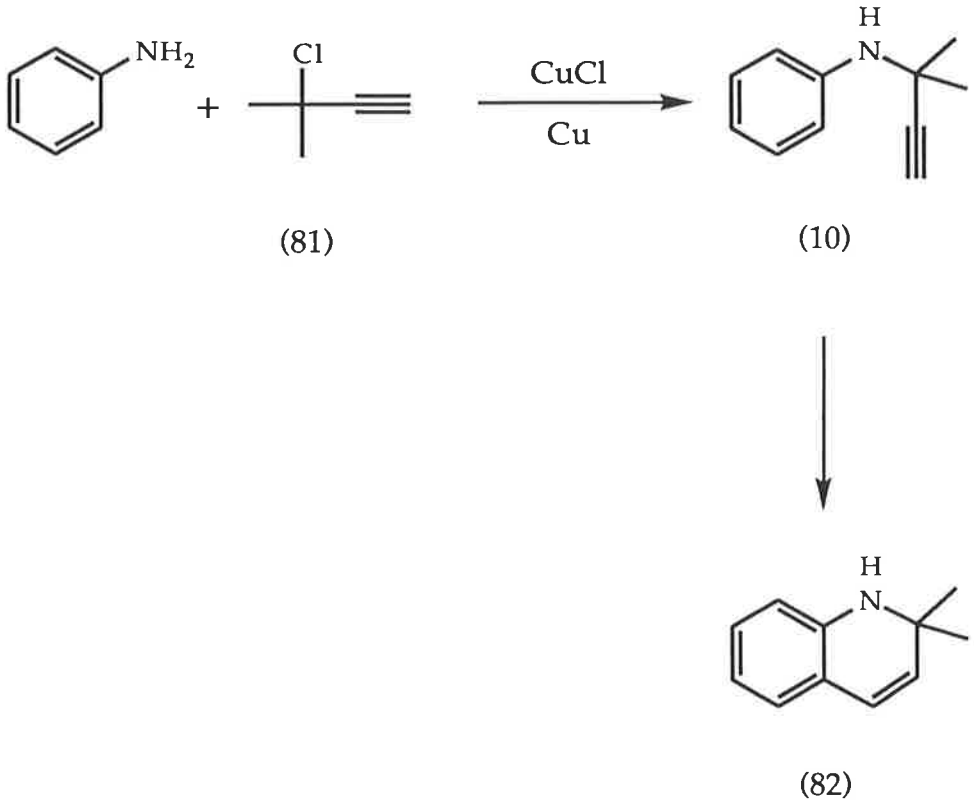
Alternatively, other reports[79,80] suggest that the copper, in conjunction with cuprous salts, promotes the formation of an allene which is the reactive species that undergoes attack by the amine (*Scheme* 36).



Scheme 36

Hennion[16] was able to employ this copper catalysed coupling methodology in a reaction between aniline and the tertiary chloride (81), to afford the coupled

arylpropargylamine (10). Some cyclisation of the coupled derivative to the corresponding dihydroquinoline (82) was observed,[16,81] however no mechanism explaining this observation was offered (*Scheme* 37).

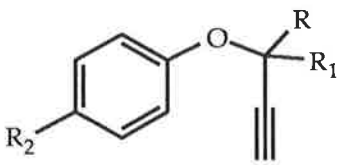


(81) (10) (82)

Scheme 37

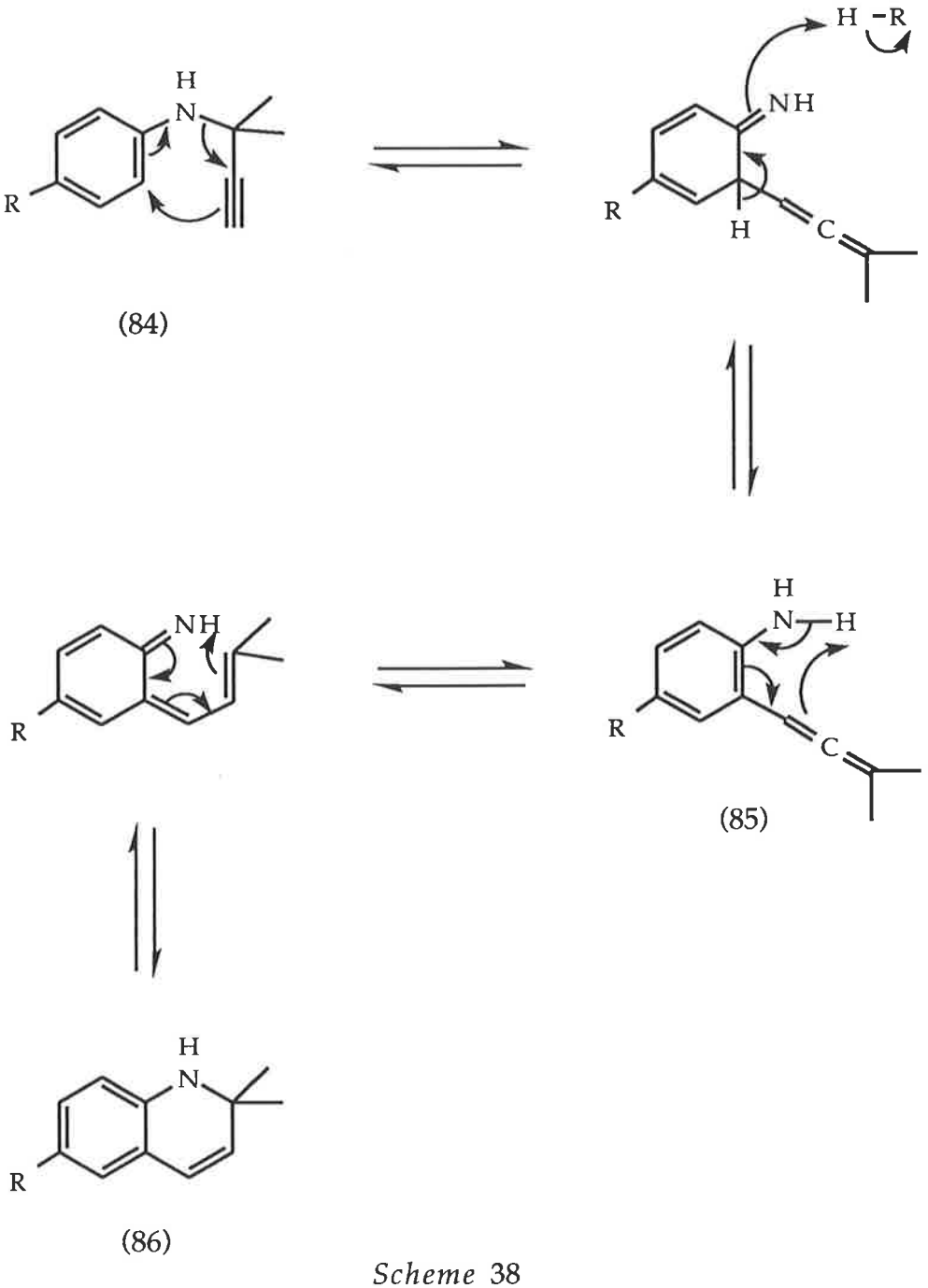
An investigation into the cyclisation of the coupled aniline (10) to the dihydroquinoline (82) has been carried out within our research group.[58,82] This study has suggested that the cyclisation occurs under thermal reaction conditions requiring copper catalysis. Thus the cyclised product obtained by Hennion et. al.[16] may have resulted from the purification, by distillation, of the crude alkynylamine (10) where traces of copper may have been present.

Iwai and Ide[83] found that for the corresponding oxygen analogues (83) the cyclisation involved electrophilic attack by the triple bond on to the aromatic ring.



(83)

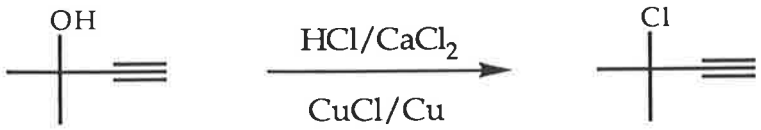
From this and further work carried out in our research group[58] a mechanism of cyclisation of the aniline derivative (84) was proposed[58] (Scheme 38).



Scheme 38

The first step involves an electrocyclic process which affords the allene (85) after aromatisation of the ring. A 1,5 hydrogen shift, followed by electrocyclisation, leads to the formation of the dihydroquinoline (86). The role played by copper has not been established but it may be required for stabilisation of the allene intermediate.

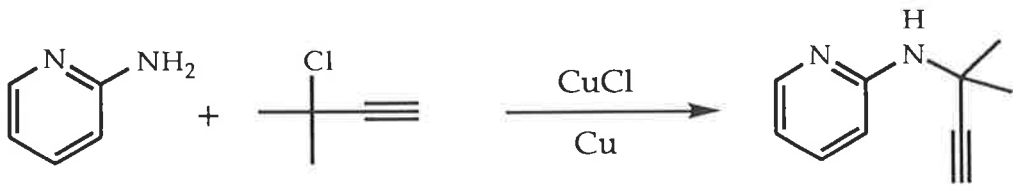
For the purpose of obtaining the coupled pyridyl derivative (79) it was necessary to first synthesise the tertiary chloride (81). This was achieved following a literature procedure,[84] by treatment of the commercially available acetylenic alcohol (87) with concentrated hydrochloric acid, in the presence of calcium chloride, cuprous chloride and a catalytic amount of copper bronze powder. This gave the chloride (81) in good yields with the expected physical and spectroscopic data[84] (*Scheme* 39).



(87) (81)

Scheme 39

Reaction of 2-aminopyridine with the tertiary chloride (*Scheme* 40), in the presence of cuprous chloride and copper bronze, was carried out using a two phase system of either diethyl ether or tetrahydrofuran in water to effect solubility of all the reagents. During the course of the reaction a dark precipitate was deposited, which was found to be highly insoluble in a variety of solvents. Upon work up of the remaining solution a yellow solid was isolated.



(81) (79)

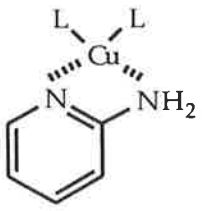
Scheme 40

The proton nmr spectrum of the yellow solid was identical to that of 2-aminopyridine, showing only aromatic resonances between δ 8.1 - 6.5 along with a broad singlet at δ 5.5 which exchanged with deuterium oxide (NH) and integrated for two protons.

The percentage of starting material recovered was found to be inversely proportional to the amount of copper catalyst employed in the reaction. Increasing the amount of catalyst did not improve the outcome of the reaction instead causing an increase in the amount of insoluble precipitate deposited and a decrease in the amount of starting material recovered.

The copper coupling reaction for the aniline system was found[16] to be dependent on both the copper bronze and the cuprous chloride as no reaction occurred when only one of these reagents was employed.[58]

From this information it was concluded that no reaction was occurring due to the formation of a complex[19] such as (88) between the nitrogens of 2-aminopyridine and the copper. Complexation of a catalytic amount of the copper prevented catalysis of the reaction while additional copper caused an increase in the amount of aminopyridine-copper complex that was precipitated. In the absence of copper no reaction occurred.



(88)

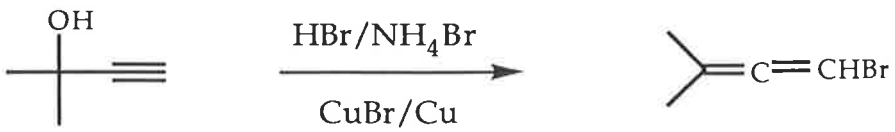
The report by Hennion[16] suggested that 4-aminopyridine also underwent the copper catalysed coupling reaction, however no details were provided. Since

either the 2- or 4-aminopyridyl systems were considered a suitable target, the copper catalysed coupling was attempted on 4-aminopyridine under the same conditions used for the 2-aminopyridine reaction with the tertiary chloride.

A dark solid precipitated from the solution which, while being slightly more soluble that its 2-aminopyridine counterpart, was still quite insoluble.

To confirm that the solid isolated was that of the starting aminopyridine complexed to the copper, a dilute solution of the complex in water was treated with the copper complexing reagent ethylenediaminetetraacetic acid (EDTA). Gradually a thin layer of organic material was formed on the surface of the solution and the mixture was extracted to remove the organic component. The proton nmr spectrum of the product isolated was identical to that of an authentic sample of 4-aminopyridine.

Due to the possibility that the reactive species in the coupling reactions of tertiary halides with amines may be an allene,[79,80] formed by the rearrangement of the tertiary carbocation, it was decided to prepare a 1-haloallene (89) and investigate its reactivity. This may enable the reaction to be carried out in the absence of copper.



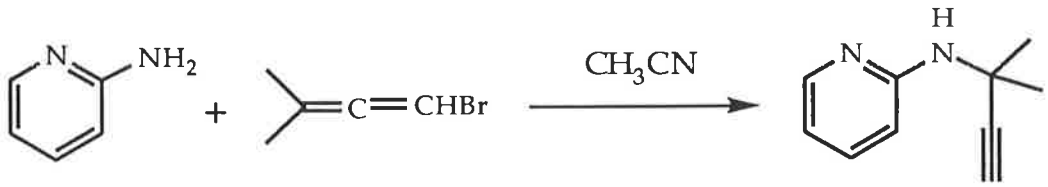
(87) (89)

Scheme 41

The bromoallene (89) was synthesised, using a literature procedure,[79] by treatment of 2-methylbut-3-yne-2-ol (87) with cuprous bromide, copper bronze

powder, ammonium bromide and concentrated hydrobromic acid (*Scheme* 41). The infrared spectrum of the product isolated showed no hydroxyl or alkyne (C-H or C≡C) stretches while a peak at 1960 cm^{-1}, diagnostic for allenes, was observed. The proton nmr spectrum of the product showed a doublet at δ 1.85 for the geminal methyl protons, which were coupled through the 1,2-diene system, to the terminal allenic proton. The allenic proton was visible as a mutiplet at δ 5.85. All physical and spectroscopic data were consistent with the formation of the allene (89) and matched that of the literature.[79]

The coupling[80] of 2-aminopyridine and the 1-bromoallene was attempted by addition of the allene to a solution of 2-aminopyridine in acetonitrile (*Scheme* 42). However, work up of the mixture led to the recovery of starting materials.



(89) (79)

Scheme 42

The reaction was repeated using copper catalysis. Addition of the allene to an acetonitrile solution of the amine and cuprous bromide resulted in precipitation of a rust coloured solid. This suggested that by the time the allene was added, the aminopyridine had already complexed with the copper thus preventing reaction.

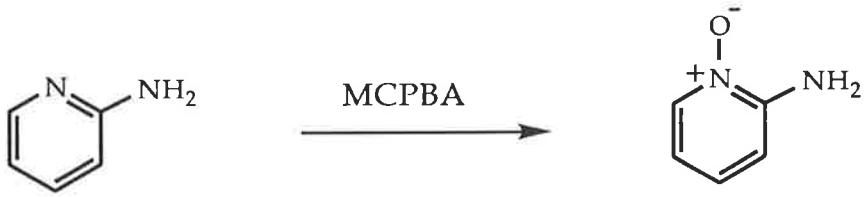
No difference was observed with a reverse reaction when the cuprous bromide was added gradually to a solution of 2-aminopyridine and the allene in acetonitrile. On addition of the cuprous bromide a blue solution was

immediately formed along with the rust precipitate and only starting materials were recovered from the organic phase.

Similarly, the reaction between the allene (89) and 4-aminopyridine resulted in the recovery of starting materials.

In an effort to prevent the coordination of the catalyst to the pyridine moiety, the corresponding N-oxide was investigated in the expectation that it would reduce or prevent formation of a copper complex.

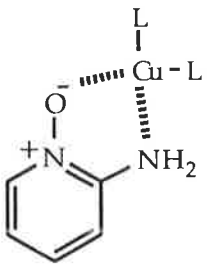
2-Aminopyridine-N-oxide (90) was synthesised by the action of *m*-chloroperbenzoic acid on 2-aminopyridine (*Scheme* 43) following a standard literature procedure.[63]



(90)

Scheme 43

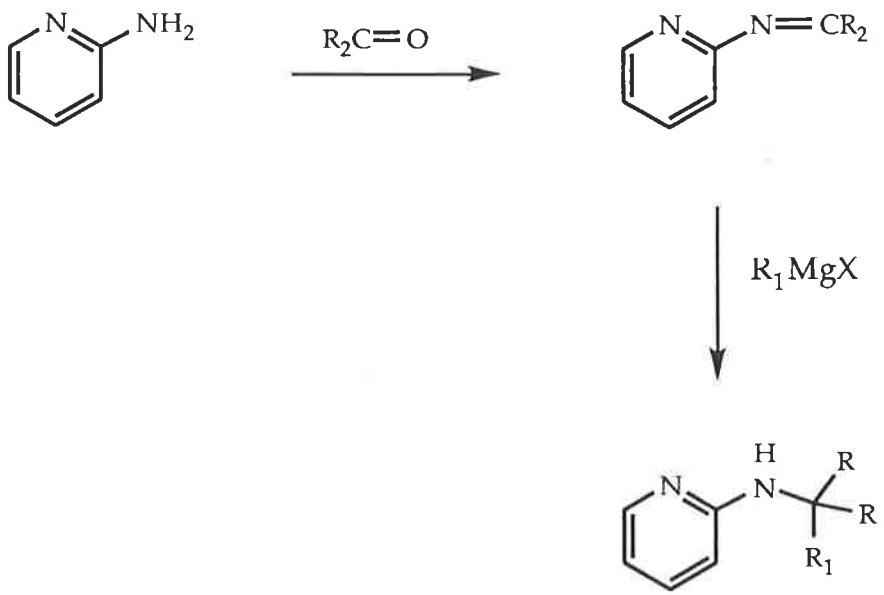
The N-oxide was then subjected to the original coupling conditions, with the tertiary acetylenic chloride (81). Unfortunately, precipitation of a complex[85] such as (91) occurred thus preventing the desired reaction.



(91)

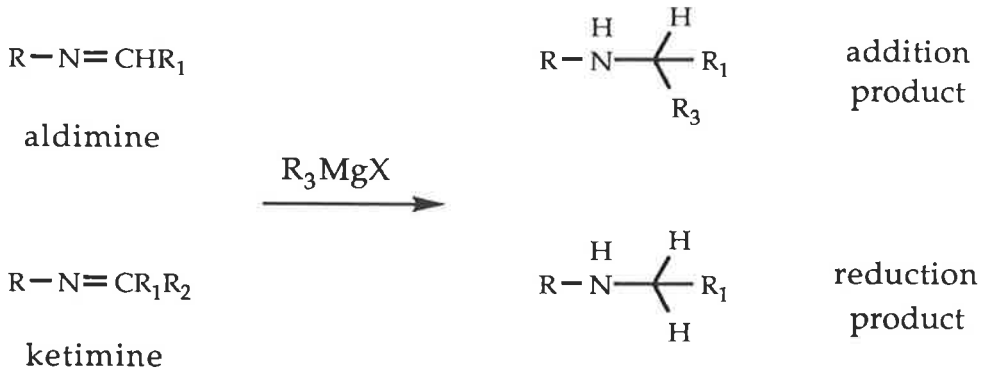
At this point it was decided to investigate other approaches for the formation of the coupled derivative (79) due to the problems encountered with coordination between the substrate and the catalyst.

An alternative course of action for the formation of a bond between the nitrogen and the tertiary carbon is outlined in scheme 44. Addition of a Grignard reagent to an imine should give rise to the desired tertiary centre.



Scheme 44

It has been shown[86] that, under normal circumstances, addition of a Grignard reagent to an aldimine results in the expected addition product. However, attempts to add Grignard reagents to ketimines generally results in reduction products[86] (*Scheme* 45).



Scheme 45

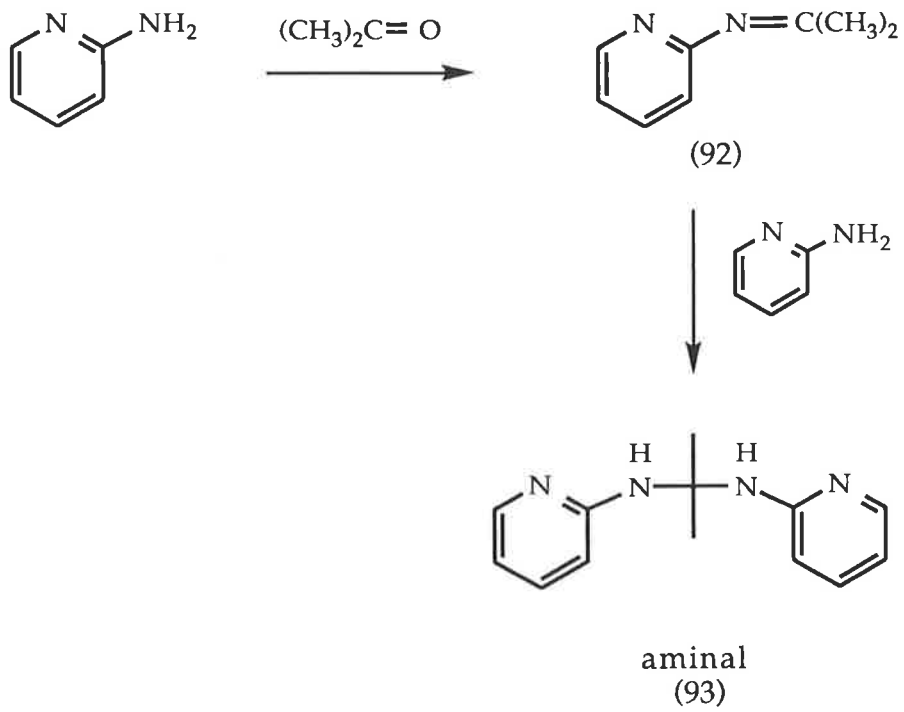
In this work, the use of an aldimine would be of little benefit, since it would only lead to the production of a secondary carbon centre adjacent to the nitrogen.

A literature report has shown[87] that Grignard reagents could be successfully added to ketimines when the reagent was complexed with cerium(III) salts prior to reaction with the imine. It was conceivable that this methodology would enable the formation of the desired tertiary centre adjacent to the nitrogen in the product (Scheme 46).

Scheme 46

It was envisaged that the reaction of 2-aminopyridine with acetone would afford the desired imine (92). However a literature report[88] suggested that although the imine was readily obtained from 3-aminopyridine, the imine of

2-aminopyridine could not be isolated. Instead the authors suggested[88] that while the imine itself was readily formed, it was more reactive towards the 2-aminopyridine than was acetone. Thus immediately upon imine formation, coupling with a second equivalent of 2-aminopyridine occurred, resulting in production of an aminal (93) (*Scheme* 47).



Scheme 47

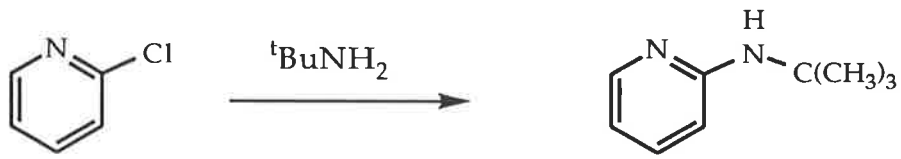
Due to the anticipated problem of aminal formation[88] this methodology was not investigated further and attention was turned to the alternative route involving displacement of a heteroaryl halide with a suitable amine[78] (*Scheme* 33 : route 2). This route has the advantage that it may allow for future stereochemical control at the tertiary carbon centre (Chapter 5). The formation of a bond between the nitrogen and the tertiary carbon (*Scheme* 33 : route 1) requires direct reaction at that centre. Assuming that this reaction proceeds via either an S_N1 like transition state or an allene intermediate, the stereochemical integrity of any optically active amine would be lost under the

reaction conditions. Thus nucleophilic attack of a chiral amine on the ring may overcome this loss of chirality.

Nucleophilic attack[77] occurs preferentially on the pyridine ring at the two or six positions over the four position and therefore for this study, 2-chloro and 2-bromopyridine were used.

A series of model reactions were employed to determine the optimum reaction conditions, whereby *tert*-butylamine was used as a substitute for the propargylamine.

The first investigation was to determine whether the use of the amine, or the corresponding amide ion, was more productive in obtaining the substituted derivative. To this end, 2-chloropyridine was refluxed in excess *tert*-butylamine (*Scheme* 48), to determine the reactivity of the free amine. Analysis of the reaction mixture by tlc indicated some unchanged 2-chloropyridine remained but also showed the formation of a new product. These were separated by flash chromatography to give the product (94) in 20% yield.



(94)

Scheme 48

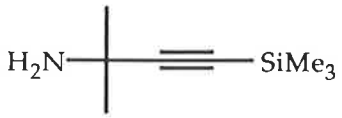
Proton nmr spectroscopic analysis of the product revealed a doublet at δ 8.09, two doublet of doublets at δ 7.45 and 6.67 and another doublet at δ 6.53. These signals corresponded to the protons at C6, C4, C5 and C3 of the pyridine ring respectively. Two singlets were also observed at δ 4.71 and 1.26 due to the NH

and ^{t}butyl moieties respectively. All the data obtained corresponded to those reported in the literature,[89,90] indicating that the coupled derivative (94) had been isolated, albeit in low yields.

The reactivity of the amide ion was then investigated by reacting sodium hydride with the amine in a tetrahydrofuran solution to form the amide anion to which the 2-chloropyridine was then added. Monitoring of the reaction by tlc analysis showed the formation of a new product with an identical R_f value to that formed in the previous reaction. This product was isolated by chromatography in a 53% yield and was identical to that previously obtained, indicating that prior anion formation resulted in a more effective substitution of the pyridine ring.

The above reaction, employing anion formation, was repeated using 2-bromopyridine to determine which of the halides was the better leaving group. The results were found to be very similar, with the latter reaction recording a slightly improved yield of 60%.

For the substitution of 2-bromopyridine with the propargylamine, the use of the previously synthesised protected propargylamine (23) would be required to prevent formation of the acetylide ion.



(23)

The protected propargylamine was treated with sodium hydride and then 2-bromopyridine was added to the solution. Analysis of the reaction mixture by

tlc showed no indication of product formation and upon work up of the solution each of the starting materials were recovered.

The substitution was repeated, without anion formation, by reaction of an excess of the free amine (21) with 2-bromopyridine but again no reaction occurred. The same result was also obtained using 2-chloropyridine.

The conditions utilised for the successful coupling[20] of the pyrimidine system (Chapter 2.1) were then employed, whereby the propargylamine (21), the halopyridine and triethylamine were heated in dimethylformamide. However, yet again, only starting materials were recovered after chromatography.

As an alternative, the amine moiety was protected to allow formation of the corresponding amide anion which could then attack the heteroaromatic ring.

The protecting group chosen was an acetamide (95) formed by treatment of the amine (21) with acetyl chloride (*Scheme* 49). The product obtained had data that were identical to those observed in the literature.[91]

(21) (95)

Scheme 49

Reaction of the acetamide anion, formed by sodium hydride treatment of the protected amine (95), with 2-bromopyridine resulted only in the recovery of starting materials.

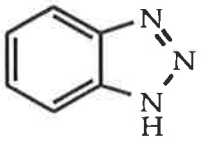
Failure of the acetamide anion to displace the 2-chloro group of the pyridine system was shown to be a direct result of the lower reactivity of the pyridine ring, as the substitution by the amide anion of (95) was successfully carried out on the corresponding pyrimidine system (22).

In conclusion, the conditions investigated for nucleophilic attack of the propargylamine on the pyridine ring were found to be ineffective, while the approach involving copper catalysis was unsuitable due to coordination between the metal and the aminopyridine substrate. As a result alternative procedures to obtain the coupled pyridine system were sought.

Chapter 4.2 *Benzotriazole Chemistry*

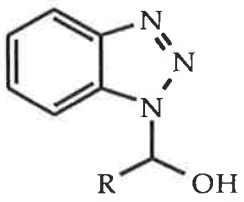
Introduction

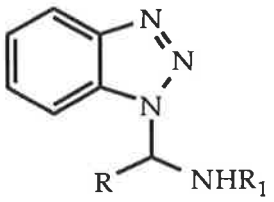
An entirely different approach to the formation of the bond between the nitrogen and the propargylic side chain involved the use of benzotriazole (96) chemistry.[90]



(96)

Katritzky and coworkers have demonstrated that benzotriazole (Bt) readily formed adducts (97) with aldehydes[92] and in the presence of both aldehydes and amines afforded adducts[90] of the form (98).

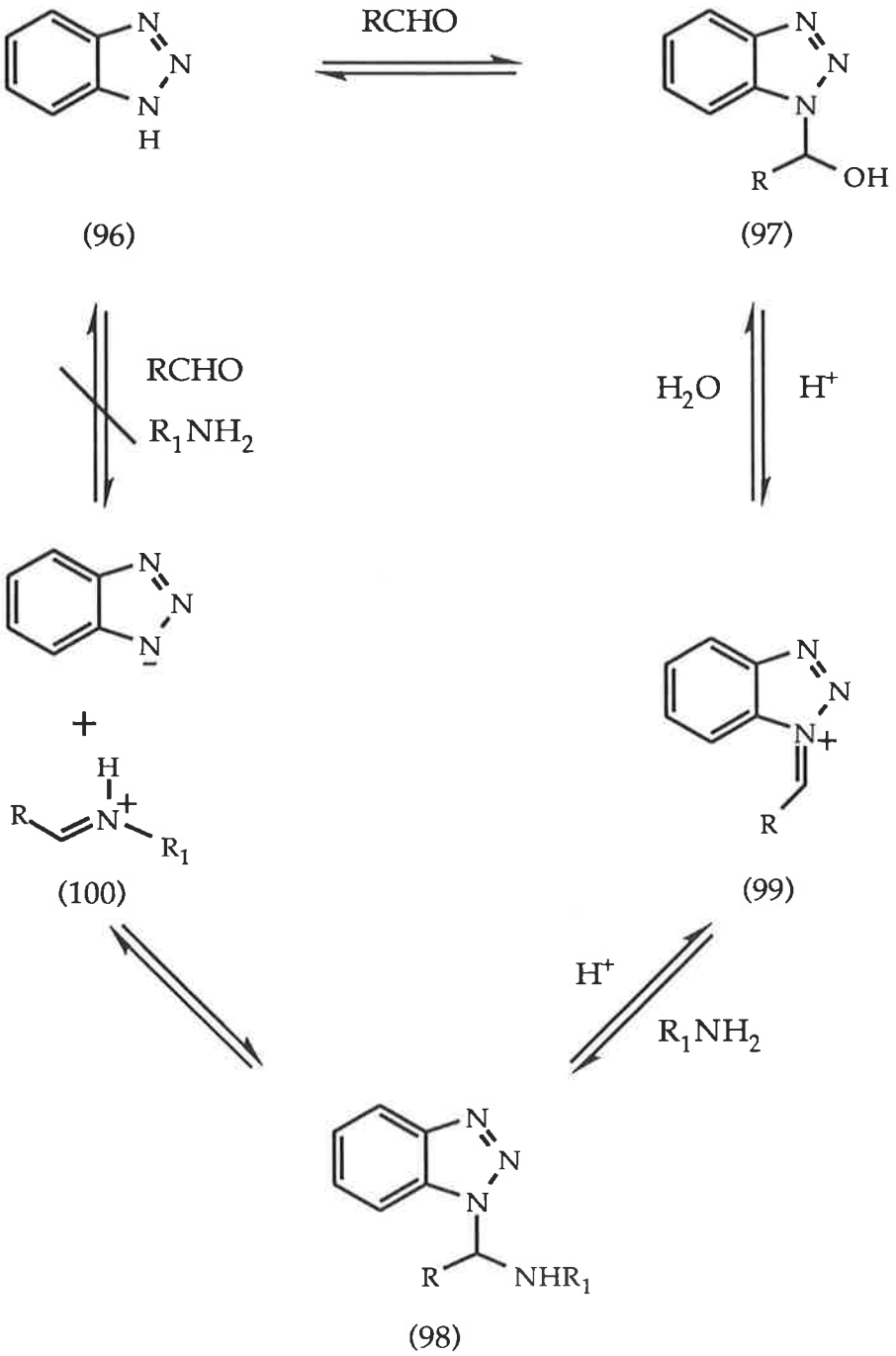




(97) (98)

Katritzky suggested[92] the reaction follows the mechanism depicted in scheme 50 involving a rapid reaction between the benzotriazole and an aliphatic aldehyde, leading to the establishment of an equilibrium between the starting materials and the adduct (97). Under the acidic conditions of the reaction an equilibrium is then set up with the adduct (97) and the corresponding iminium ion (99). The iminium ion is then capable of acting as an electrophile

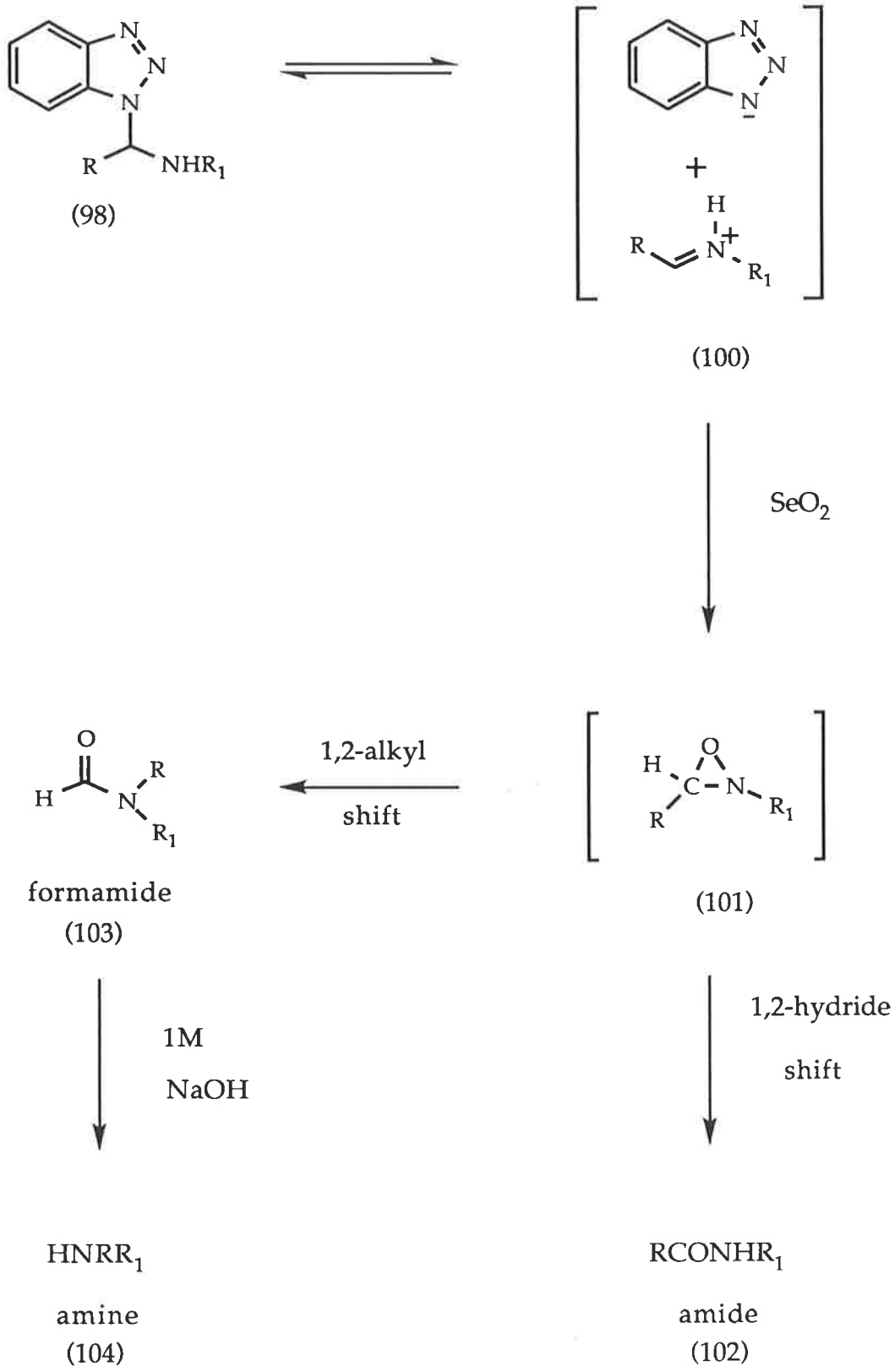
in a reaction with an amine to form the adduct (98) which can undergo an ionic dissociation to (100).



Scheme 50

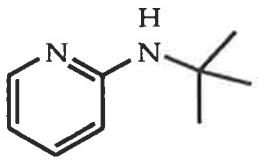
The ionic species (100) can be oxidised by selenium dioxide to form an oxaziridine ring system (101) (*Scheme* 51). Relief of ring strain then promotes the cleavage of the N-O bond rather than the C-O bond particularly when an aryl group is attached to the nitrogen of the three membered ring since the aryl group is better able to stabilise the developing charge.[90] This ring cleavage is accompanied by a rearrangement involving a 1,2 shift of either the hydrogen, resulting in amide (102) production, or migration of an alkyl group to afford the formamide (103).

The ratio of amide to formamide produced in the rearrangement is dependent on the nature of the R group. Migratory aptitude increases as the bulk of the substituent increases, hence in the majority of cases the migration of the alkyl group will be favoured and consequently the formamide will predominate. These amides can then be easily separated by chromatography and, after isolation, the formamide can be hydrolysed to the free amine (104).


(98)
(100)
SeO_2
1,2-alkyl
shift
formamide
(103)
(101)
1,2-hydride
shift
1M
NaOH
$HNRR_1$
amine
(104)
$RCONHR_1$
amide
(102)

Scheme 51

Utilising the benzotriazole chemistry outlined,[90] Katritzky and coworkers synthesised N-(1,1-dimethylethyl)-2-aminopyridine (94). This type of compound was of interest to us due to the presence of a tertiary carbon centre directly adjacent to the amine nitrogen, which represents one of the features of our target molecules.

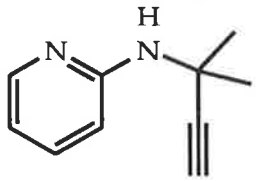


(94)

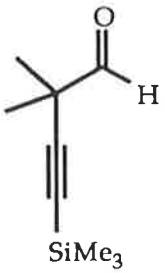
Hence this section will involve the application of benzotriazole chemistry in the synthesis of the coupled pyridine derivatives.

Results and Discussion

Katritzky's methodology was investigated as a possible synthetic route to (79) by reaction of the aldehyde (105) and 2-aminopyridine in the presence of benzotriazole.

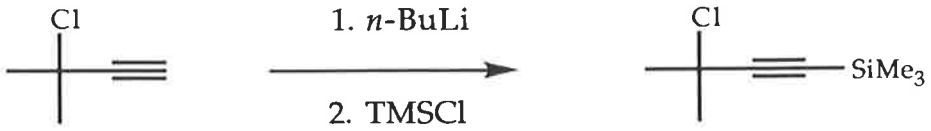


(79)



(105)

The aldehyde (105), required for this approach, was synthesised from the chloroalkyne (81) via a Grignard reaction.[93] Protection of the chloroalkyne (81) as its trimethylsilyl derivative (106) (*Scheme* 52) was necessary as any formation of a Grignard reagent in the presence of a terminal alkyne would result in a reaction between the Grignard reagent and the acetylenic proton to give the corresponding acetylide anion.



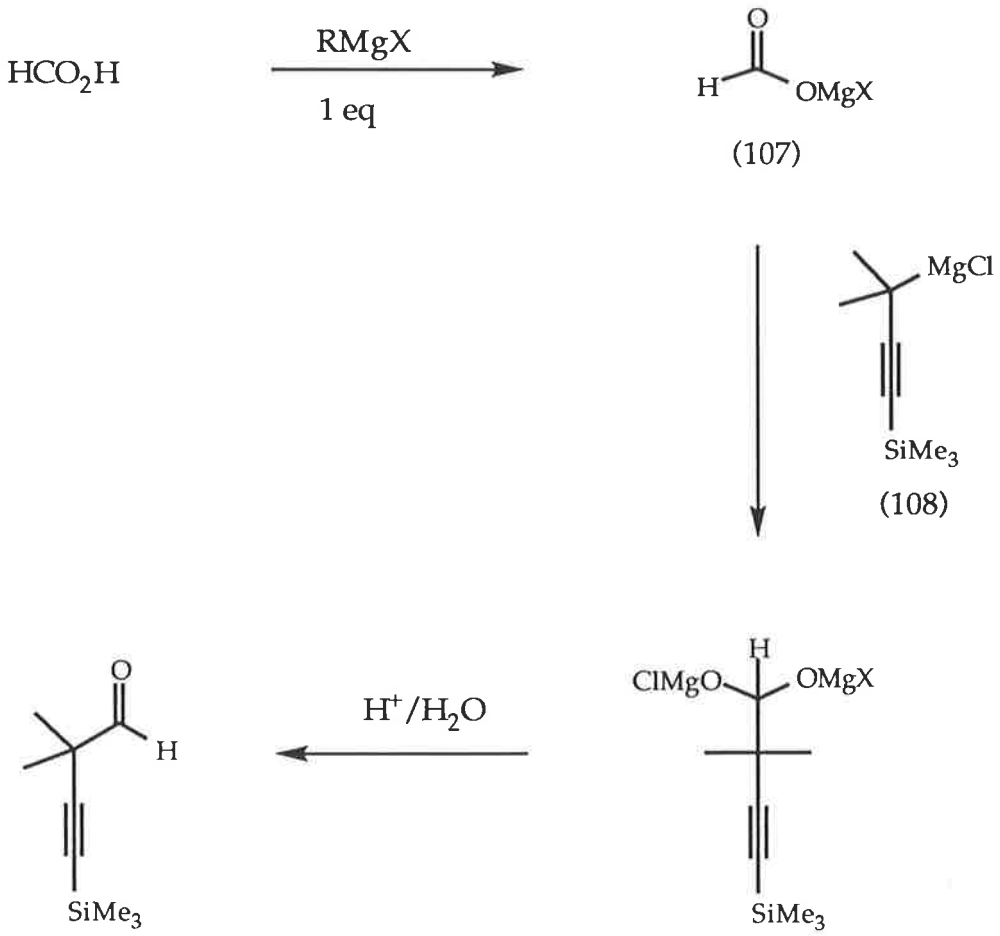
(81) (106)

Scheme 52

Protection was achieved by the reaction of *n*-butyllithium with the chloroalkyne (81) and quenching of the product with trimethylsilyl chloride. The protected derivative (106) was obtained in good yield and was purified by

distillation. The spectroscopic and physical data obtained for the protected alkyne (106) were identical to that found in the literature.[94]

Reaction[93] of the magnesium salt of formic acid (107) with the Grignard reagent (108), formed from the chloroalkyne (106), followed by acidic hydrolysis, gave the aldehyde (105) as depicted in scheme 53.

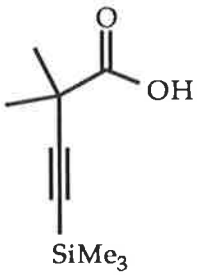


Scheme 53

The aldehyde (105) was obtained as an oily solid, which gave a positive Tollens test indicating the presence of an aldehyde. The proton nmr spectrum of the crude product revealed three singlets at δ 8.1, 1.35 and 0.2 in a ratio of 1 : 6 : 9

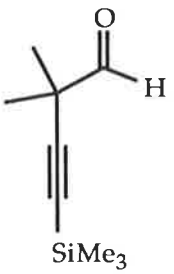
corresponding to the aldehydic proton, the geminal methyl groups and the trimethylsilyl moiety respectively. The infrared spectrum showed a carbonyl stretch at 1724 cm^{-1}.

The aldehyde (105) was found to undergo rapid oxidation to the corresponding carboxylic acid (109) upon exposure to air. Similarly, rapid oxidation occurred upon chromatography and the attempted distillation of the material resulted in decomposition to an intractable black tar.

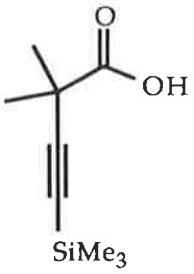


(109)

Recrystallisation of the oily solid obtained from the Grignard reaction yielded a yellow solid with a melting point of 131-134°C which gave a negative Tollens test. The proton nmr spectrum of the yellow solid showed the expected singlets at δ 0.2 for the methyl groups of the trimethylsilyl moiety and at δ 1.40 for the geminal methyls. A new signal was observed at δ 9.3 which was no longer visible after exchange with deuterium oxide, suggesting that it corresponded to a carboxylic acid. The infrared spectrum of the material showed both a carbonyl and a broad alcohol stretch at 1715 and 2900-3300 cm^{-1} respectively, while the mass spectrum revealed a small molecular ion at 184 mass units with a base peak at 140 mass units due to $[M^+-CO_2]$. This evidence showed that the carboxylic acid (109) had been isolated from the recrystallisation and not the purified aldehyde (105).



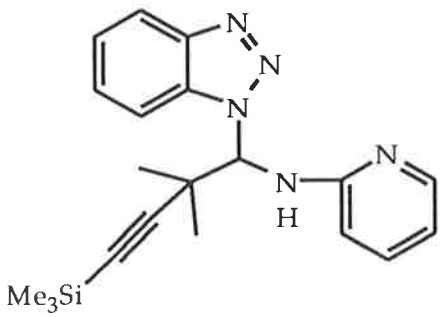
(105)



(109)

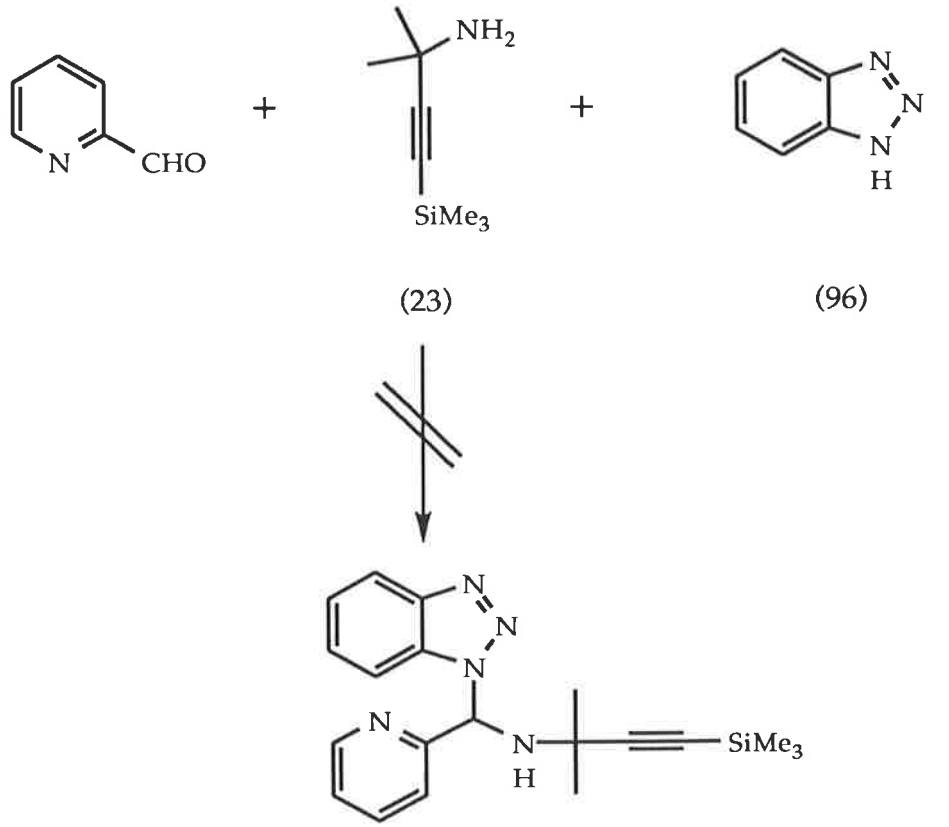
These results were confirmed by the reaction of the Grignard reagent (108) with solid carbon dioxide which gave the carboxylic acid (109) directly. The data obtained for this compound was identical to that obtained for the recrystallised material.

Benzotriazole adduct formation was attempted by the reaction of 2-aminopyridine and benzotriazole with the crude aldehyde (105). However, none of the expected adduct (110) was formed and separation of the residue by chromatography yielded crude 2-aminopyridine and benzotriazole. The carboxylic acid (109) was also recovered instead of the aldehyde (105). The literature indicated[92] that the success of adduct formation was greatly dependent on the purity of the starting aldehyde. The inability to purify the aldehyde prevented adduct formation and as a consequence this method of reaction was not pursued further.



(110)

To avoid having to synthesise the aldehyde, the benzotriazole adduct formation was repeated, reversing the substituents by using 2-pyridinecarboxaldehyde and the propargylamine (23) in an effort to obtain the adduct (111) (*Scheme* 54).



Scheme 54

The literature suggested[90] that when aliphatic amines were used, the reaction was not as successful. This was due to the presence of the aryl group attached to the carbon which encourages the cleavage of the C-O bond of the oxaziridine ring (*Fig* 11) during oxidation of the adduct, rather than the desired N-O bond cleavage, due to the greater stabilisation of the developing positive charge by the aryl group. The same report[90] also indicated that initial adduct formation was less probable when aliphatic amines were employed. This was found to be

the case as the only isolable products from the attempted adduct formation were starting materials.

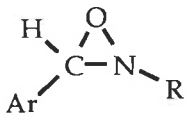
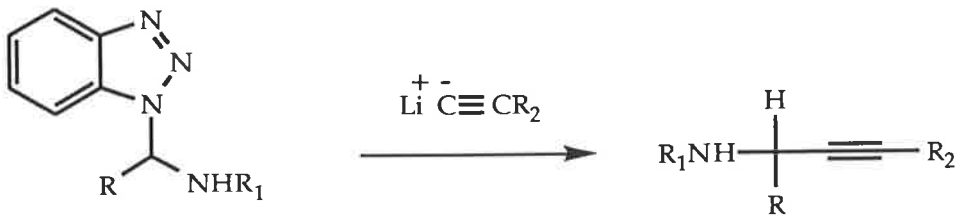


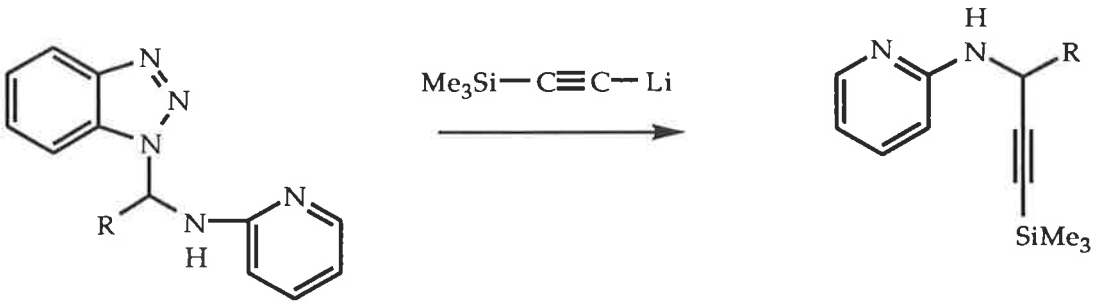
Figure 11

Further work by Katritzky in the area of benzotriazole chemistry, established a versatile method for the formation of propargylamines.[95,96] The initial benzotriazole adduct was reacted with lithium acetylides, to displace the benzotriazole anion to afford the corresponding propargylamine (*Scheme* 55).



Scheme 55

Utilising the literature method[90,92] for benzotriazole adduct formation discussed previously in this chapter, adducts (112) and (113) were synthesised. It was envisaged that attack of a lithium acetylide species on the benzotriazole adduct would then afford the corresponding propargylamine (*Scheme* 56).



R = -C(CH$_3$)$_3$ (112)

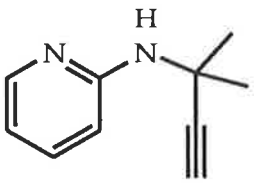
-CH$_3$ (113)

R = -C(CH$_3$)$_3$ (114)

-CH$_3$ (115)

Scheme 56

It should be noted that the propargylamine derivatives (114) and (115) are mono-substituted at the carbon centre α to the acetylene. Further substitution at this α carbon would be required in order to obtain the di-substituted α centre present in the target molecule (79).

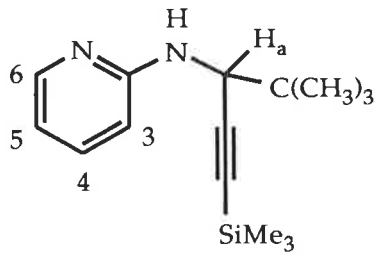


(79)

Both (112) and (113) were added to separate solutions of lithium trimethylsilyl acetylide, freshly prepared by addition of *n*-butyllithium to trimethylsilyl acetylene.

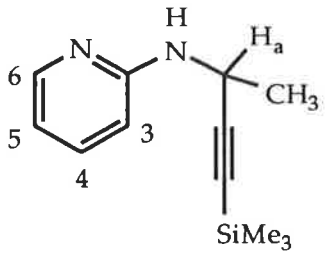
The product derived from (112) was a colourless solid whose proton nmr spectrum showed a doublet of doublets at δ 8.10 for the proton at C6 coupled to

the *ortho* and *meta* protons. A triplet of doublets resonated at δ 7.42 for H4 as a result of being coupled to two different *ortho* protons and one *meta* proton. The signal for H5 appeared at δ 6.59 as a doublet of doublets due to two *ortho* proton couplings, while H3 resonated at δ 6.47 as a doublet resulting from coupling to one *ortho* proton. Two doublets were observed at δ 4.53 and 4.41. The first doublet was removed by deuterium oxide exchange, and hence was attributed to the amine NH, while the second collapsed to a singlet indicating that the two protons, H_a and NH, were coupled. Two singlets at δ 1.06 and 0.13 represented the tertiary butyl and the trimethylsilyl groups respectively. The infrared showed the expected absorbances at 3306 cm^{-1} for the NH stretch and 2160 cm^{-1} for the alkyne while the mass spectrum gave a molecular ion at 260 m/z which was consistent with the structure (114).



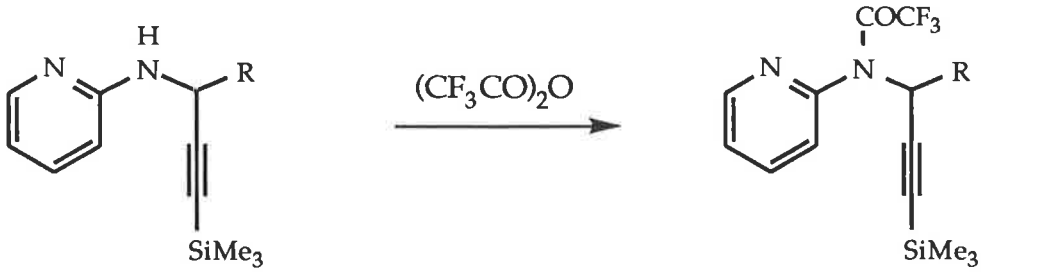
(114)

The proton nmr spectrum of the product obtained from the reaction of (113) showed a similar pattern in the aromatic region to that of (114). Again a doublet was observed for the amine NH at δ 4.72 and this peak was not visible upon deuterium oxide exchange. A doublet of quartets at δ 4.59 which collapsed to a quartet with deuterium oxide exchange corresponded to H_a which was in turn coupled to the doublet at δ 1.46 of the adjacent methyl group. Infrared and mass spectra also confirmed the structure of this product as (115).



(115)

Having obtained the mono-substituted derivatives (114) and (115) it was of interest to establish whether the di-substituted compounds could be obtained by further substitution at the α carbon to the acetylene. It was hoped that this could be achieved with the use of a base to remove the proton from the α carbon, followed by alkylation of the anion.[97] For this purpose it was necessary to remove the acidic amine proton by converting the material to the corresponding trifluoroacetamide. This conversion was achieved by reaction of both mono-substituted compounds (114) and (115) with trifluoroacetic anhydride[23] (*Scheme* 57).

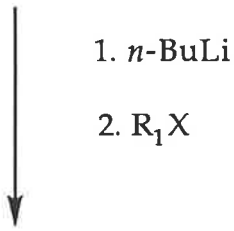


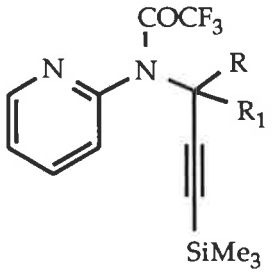
R = -C(CH$_3$)$_3$ (114)

-CH$_3$ (115)

R = -C(CH$_3$)$_3$ (116)

-CH$_3$ (117)





R = -C(CH$_3$)$_3$ (118)

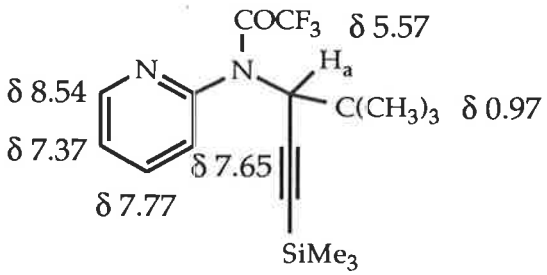
-CH$_3$ (119)

R$_1$ = -CH$_3$

Scheme 57

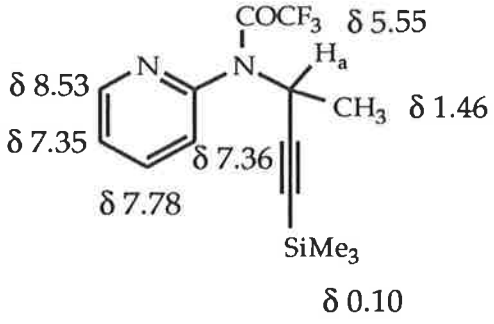
The proton nmr spectrum of the trifluoroacetamide, isolated from reaction of (114) with trifluoroacetic anhydride, showed a similar splitting pattern to that

of the starting material in the aromatic region, with resonances being slightly further downfield due to the incorporation of the electron withdrawing trifluoroacetamide moiety into the molecule. The signal observed at δ 4.53 due to the amine in the starting material was no longer present, while the doublet that resonated at δ 4.41 for H_a in the starting material now resonated as a singlet at δ 5.57 in the product. The tertiary butyl and the trimethylsilyl groups were observed as singlets at δ 0.97 and δ 0.15 respectively. The infrared spectrum of the product showed a carbonyl group at 1706 cm^{-1} but no absorption above 3100 cm^{-1}. The mass spectrum showed a molecular ion at 356 m/z as expected for (116).



(116)

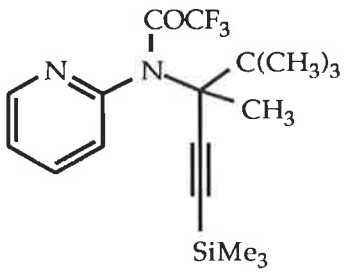
A similar trend towards the downfield shift of resonances was experienced by protons in the proton nmr spectrum of the yellow oil obtained from reaction of (115) with trifluoroacetic anhydride. The only other significant variations from the starting material were the absence of resonances at δ 4.72 observed for the starting amine NH and the collapse of the doublet of quartets at δ 4.59 in the starting material to a quartet at δ 5.55 as it was no longer coupled to an adjacent NH and was further deshielded by the trifluoroacetamide group. The infrared spectrum showed a carbonyl group at 1708 cm^{-1} and the mass spectrum showed a molecular ion at 314 m/z as expected for the trifluoroacetamide (117).



(117)

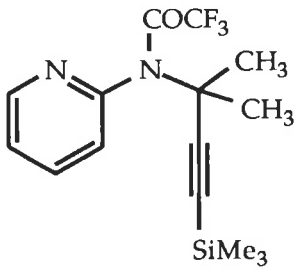
Alkylation[97] was attempted initially on the protected tertiary butyl derivative (116) to determine whether the bulk of the substituent already present would be a significant factor in these reactions.

The reaction of *n*-butyllithium with a cooled solution of the protected *tert*-butyl derivative (116), followed by addition of iodomethane gave a yellow oil after work up. All the spectroscopic data obtained indicated that only crude starting material, not the desired di-substituted derivative (118), had been recovered. Failure of the substrate to methylate could be due to the bulk of the *tert*-butyl group either hindering reaction of the methylating agent with the anion or by preventing the anion from forming by blocking the approach of the base. Alternatively, this problem may be due to the α proton not being acidic enough for removal by the base.



(118)

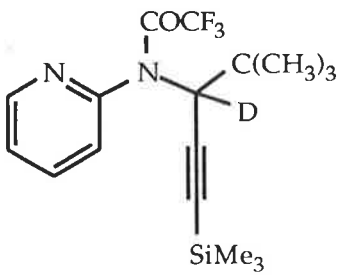
Alkylation of (117) was then attempted since the methyl substituent should be less likely to hinder approach by either the base or the methylating agent to enable formation of the derivative (119).



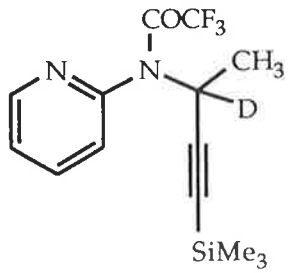
(119)

The spectroscopic data of the product isolated from the reaction of (117) with *n*-butyllithium, followed by iodomethane, was identical to that of the starting material.

In order to determine if anion formation had been achieved, base was added to both protected derivatives. Each reaction was then quenched with deuterium oxide in an attempt to form derivatives deuterated at the α carbon (120) and (121). The proton nmr spectra of the products isolated from both reactions gave no indication that deuterium had been incorporated at the α carbon, thus suggesting that the α proton was not sufficiently acidic to be abstracted by the *n*-butyllithium under the reaction conditions employed.

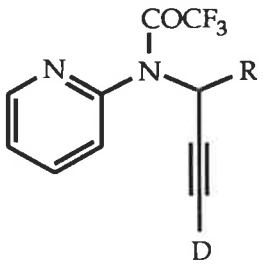


(120)



(121)

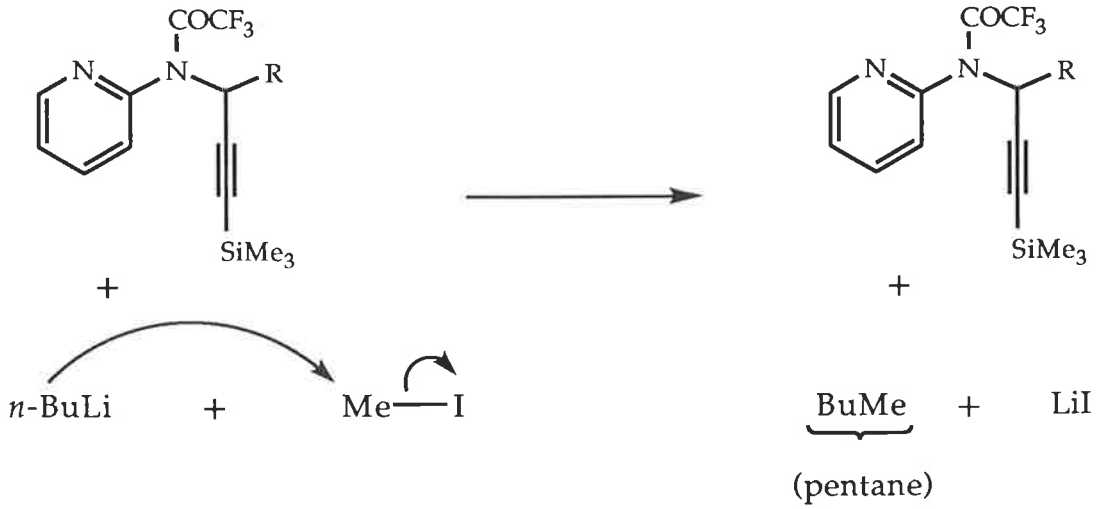
When iodomethane was used as alkylating reagent, only decreased amounts of starting materials were recovered. However, when the mixture was quenched with deuterium oxide, the desilylated derivatives (122) and (123), with deuterium incorporation at the terminal acetylenic position, were obtained.



R = -$C(CH_3)_3$ (122)

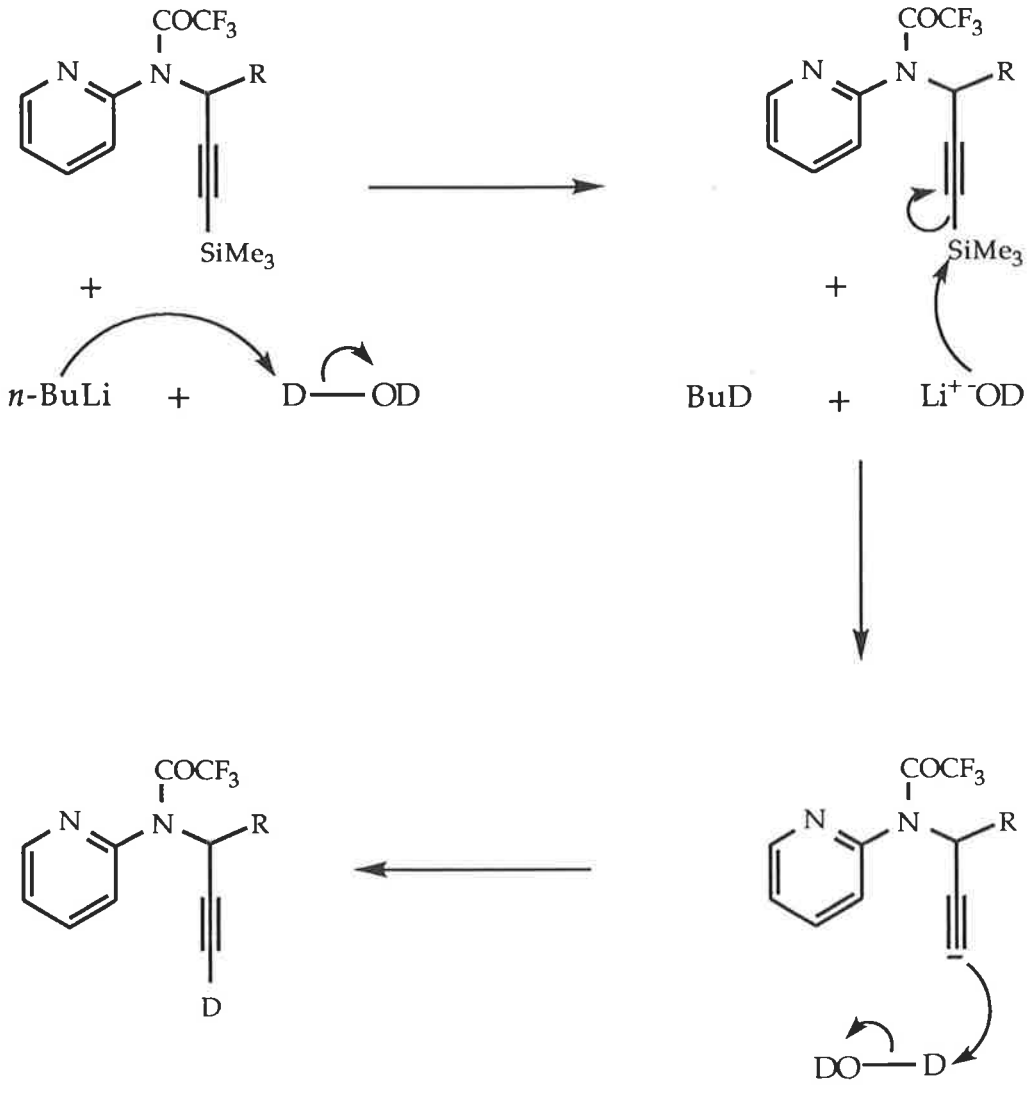
-CH_3 (123)

A plausible explanation accounting for this observation could be that in the first example the iodomethane reacts with the unreacted *n*-butyllithium, to form pentane and lithium iodide. During work up, the lithium salt is extracted into the aqueous layer while the pentane would be later removed under reduced pressure leaving behind only the starting material (*Scheme* 58).



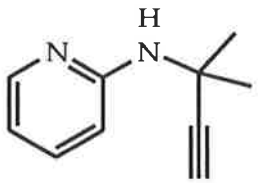
Scheme 58

It may be possible that in the second case, addition of excess deuterium oxide to the solution of the protected amine and unreacted *n*-butyllithium results in the formation of deuterated butane and lithium deuteroxide, the latter could then be capable of attacking the silyl group. The acetylide anion may then abstract a deuterium from the deuterium oxide solution, giving rise to the deuterated acetylene (*Scheme* 59).



Scheme 59

Due to the inability of the base to abstract the α proton this synthetic route would not afford the desired di-substituted derivative (79). Consequently this route was not pursued further.

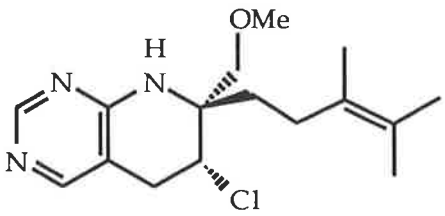


(79)

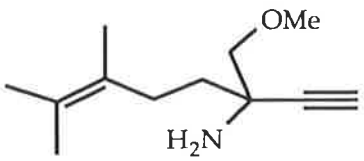
In conclusion, a methodology for the formation of the mono-substituted pyridine derivative has been established. However, this approach was not able to be further elaborated to obtain a general synthetic route for the formation of the desired di-substituted pyridine coupled derivative, possibly due to the α proton not being sufficiently acidic enough for abstraction by the base. Other problems encountered in the formation of the coupled pyridine derivatives were due to the relative lack of reactivity of the pyridine ring towards nucleophilic attack compared to the pyrimidine system. The greater ability of the pyridine ring to complex to metals compared with benzenoid ring systems also made the use of the copper catalysed couplings reactions impractical. Thus for the synthesis of heterocyclic analogues of virantmycin, the pyrimidine system proved a more suitable substrate for investigation.

Chapter 5 *Future Investigations*

Ongoing research efforts in these laboratories will involve the synthesis of the heterocyclic analogue of virantmycin (16) with the desired side chains following the methodologies outlined in this thesis. To undertake this work it would first be necessary to synthesise the corresponding propargylamine (124) with which to carry out these transformations.



(16)

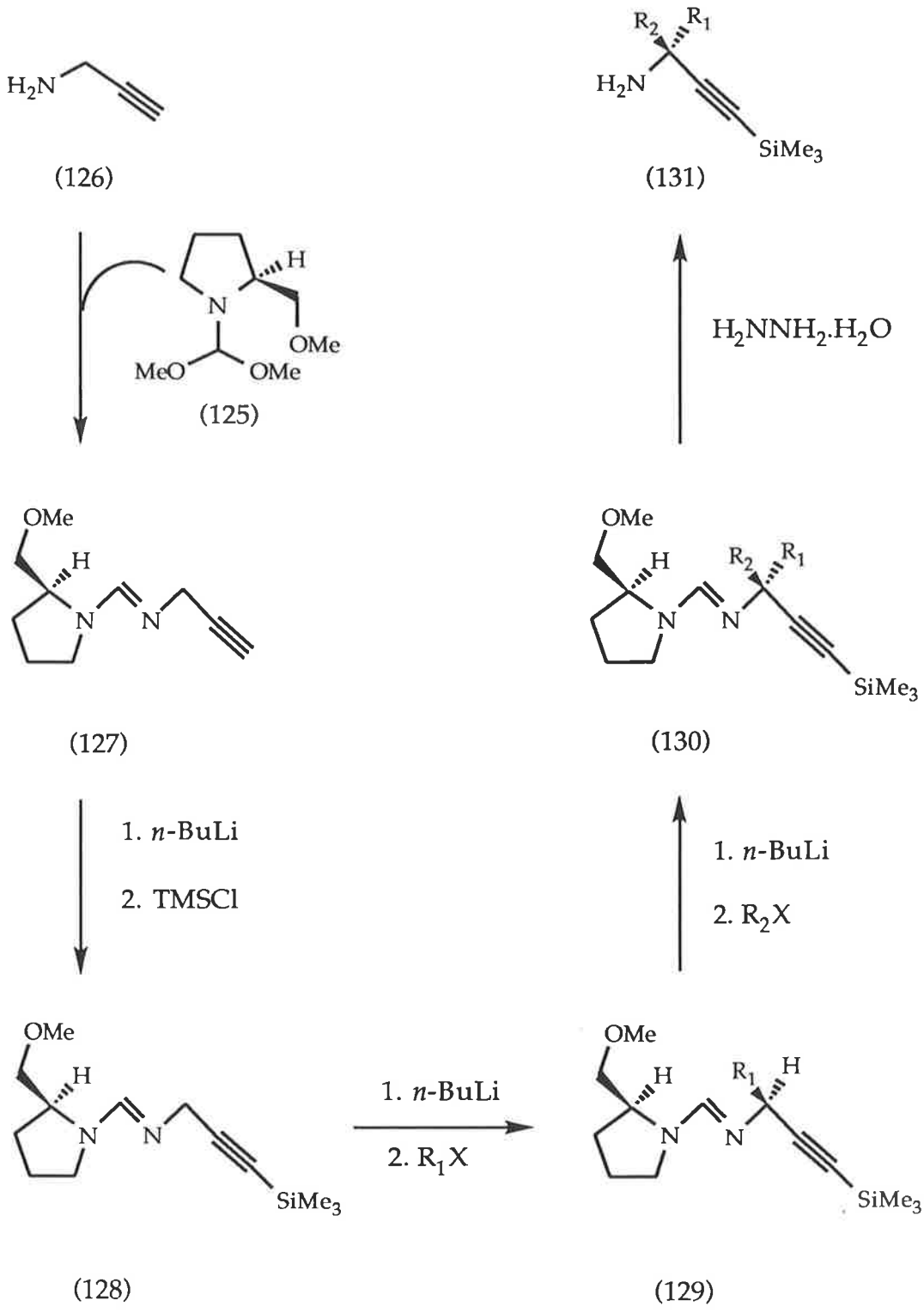


(124)

There are a number of methods that may be suitable for the synthesis of propargylamines. The most general method for the conversion of chlorides to the corresponding amines is by the action of sodamide in liquid ammonia[98] on the chloride. However, this may not be suitable for the formation of tertiary amines from tertiary chlorides as elimination would be favoured in this instance. Alternatively, a Ritter reaction[91] could be employed whereby the acetylenic alcohol is treated with concentrated sulfuric acid in the presence of a nitrile. This results in the formation of the corresponding amide which upon hydrolysis should afford the amine. For this purpose, the formation of a formamide, from reaction with hydrogen cyanide, may be the most effective derivative to obtain, as formamides are more readily hydrolysed than other amides.[86]

A major draw back with either of these approaches is that, although suitable for the formation of the racemic amines, neither would be effective for the synthesis of a chiral amine as required for the virantmycin analogue (16).

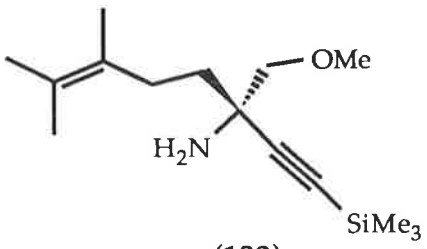
Kolb and Barth[99] have developed a useful asymmetric synthesis of α-amino acids which proceeds via the propargylamine derivative. In this procedure (S)-1-(dimethoxymethyl)-2-(methoxymethyl)pyrrolidine (125) is employed as a chiral agent. Propargylamine (126) is converted to the amidine (127) by reaction with the chiral reagent (125). The amidine is in turn treated with *n*-butyllithium to achieve hydrogen/lithium exchange of the acetylenic functionality, followed by reaction with trimethylsilyl chloride to afford the protected derivative (128). The action of *n*-butyllithium on (128) results in stereoselective metallation at the carbon α to the alkyne and addition of an electrophile to this mixture results in the formation of the mono-substituted amidine (129). The completely alkylated derivative (130) is obtained by repetition of the metallation and alkylation procedures. Hydrolysis of the amidine function then affords the protected propargylamine (131) as depicted in scheme 60.



Scheme 60

The authors[99] claimed that only the enantiomerically pure derivatives were obtained by this procedure indicating that the reaction did not proceed via an

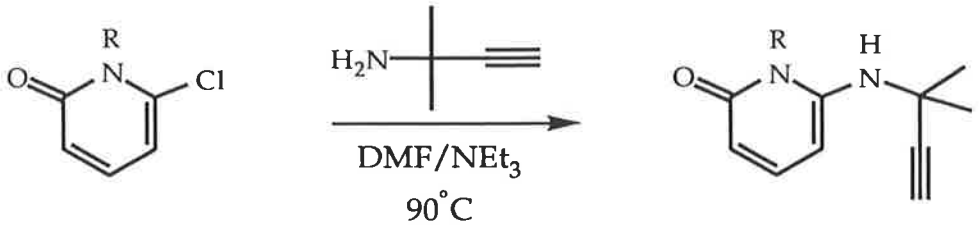
allene intermediate. Thus for future investigations this methodology could be employed to obtain the chiral propargylamine (132) to enable the synthesis of a single enantiomer of the virantmycin heterocyclic analogue. By employing the synthetic route outlined in chapter 3 of this thesis, the chiral centre, once formed, does not undergo further reaction. Thus chiral purity would be retained at the tertiary carbon centre throughout the synthesis.



(132)

Formation of the tetrahydropyridine ring system via selenide formation in the presence of the virantmycin side chains will require additional investigation due to the incorporation of the more electron-rich side chain double bond. However, due to this alkene being tetra-substituted, it may be expected to react less rapidly towards the bulky selenium electrophile, due to steric factors, than the alkene involved in cyclisation.

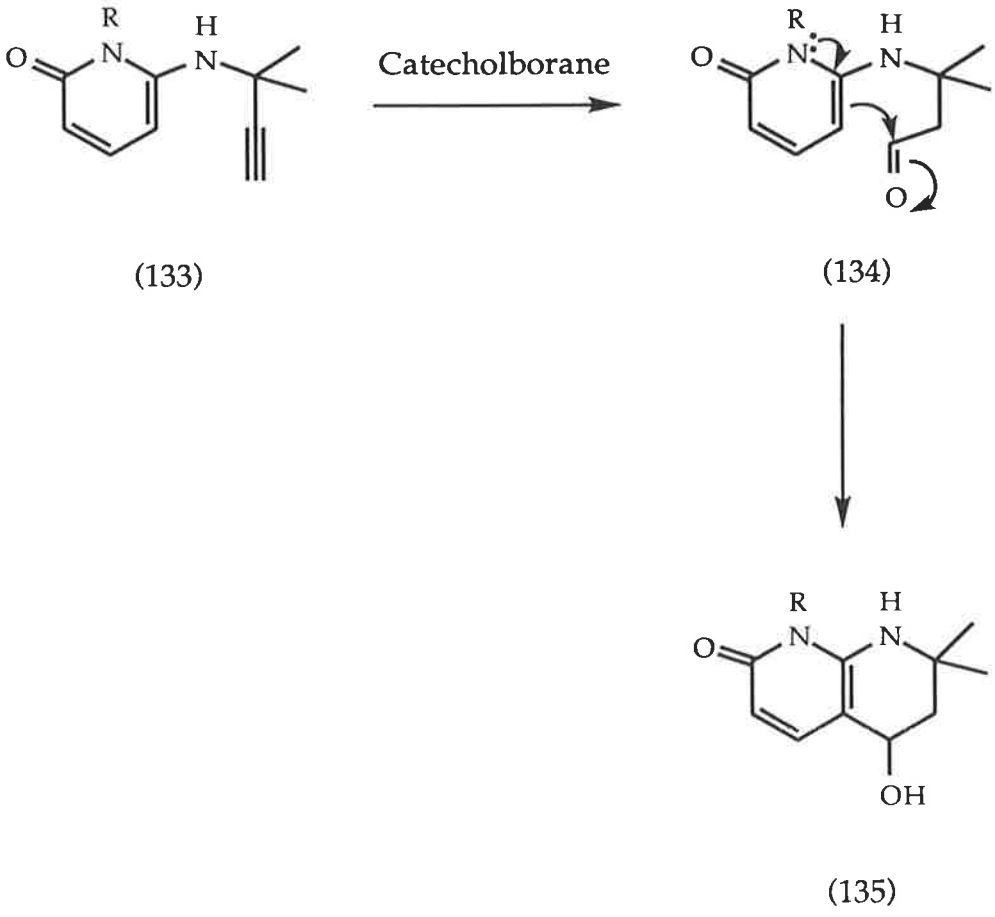
The implementation of alternative approaches to the coupling and cyclisations of these derivatives are also underway. It is of interest to obtain a method by which both the pyridine and pyrimidine derivative could be synthesised by a common route. Due to the lack of reactivity of the pyridine system towards nucleophilic attack, future studies may use more reactive pyridine systems, such as a pyridone, which should be more prone to attack by a nucleophile, while pyrimidones could also be used in these reactions. Coupling of these heteroaromatic systems to the propargylamines should be obtainable by a similar reaction to that used for the coupled pyrimidine derivatives[20] (*Scheme* 61).



(133)

Scheme 61

Cyclisation of the resulting coupled compound (133) could possibly be achieved by conversion of the alkyne to the corresponding aldehyde (134) from reaction with a hindered borane[100] (eg; catecholborane), followed by an acid or base catalysed cyclisation to the alcohol[101] (135) as depicted in scheme 62.



(133) (134)

(135)

Scheme 62

Consequently it is envisaged that future application of the methodologies outlined above should result in the obtainment of a range of interesting heterocyclic analogues of virantmycin. These derivatives may then undergo a comparison with virantmycin and some nucleosides, investigating the relative spatial arrangements of the ether and glycosidic oxygens as well as comparing the respective biological activities of the compounds.

Experimental

General

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

Microanalyses were performed by the Canadian Microanalytical Service Ltd., New Westminster, Canada or by the Chemical and Microanalytical Service Pty. Ltd., Melbourne, Australia.

Analytical thin layer chromatography (t.l.c.) was performed using Merck Kieselgel $60F_{254}$ silica on aluminium backing plates. T.l.c. plates were visualised using an ultra violet lamp (254 nm). Flash chromatography[102] refers to nitrogen-pressure driven rapid chromatography using Amicon Matrix Silica, (pore diameter 60Å) or Merck Kieselgel 60 (230-400 mesh ASTM). Dry column chromatography[103] was carried out using Merck Kieselgel HF_{254} silica. All chromatography was carried out using silica.

Infrared spectra were recorded on a Jasco A-102 spectrometer or on a Hitachi 270-30 spectrometer using the 1603 cm^{-1} band of polystyrene as a reference.

Proton nuclear magnetic resonance (^1H nmr) spectra were recorded on a Bruker ACP300 spectrometer operating at 300 MHz or a Varian T60 spectrometer operating 60 MHz. Unless otherwise indicated, ^1H nmr spectra were recorded on the ACP300 nmr spectrometer. Spectra were recorded in the solvents indicated using tetramethylsilane as an internal standard. Chemical shifts are quoted as δ in parts per million downfield from the internal standard and coupling constants (J) are given in Hertz (Hz). Multiplicities are abbreviated to: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad.

Carbon nuclear magnetic resonance (^{13}C nmr) spectra were recorded on either a Bruker CXP300 or Bruker ACP300 spectrometer operating at 75.5 MHz. The chemical shifts are reported as δ in parts per million relative to the residual undeuterated solvent. Some spectra were assigned using the DEPT sequence, and the multiplicities of the resonances in these spectra are abbreviated as follows : q, quartet (CH_3); t, triplet (CH_2); d, doublet (CH); s, singlet (C).

Electron impact mass spectra (EIMS) and high resolution mass spectra were recorded on a AEI MS-30 double focussing mass spectrometer operating at 70 eV. Only the major fragments are given with their assignments and their relative abundances shown in brackets.

All solvents were distilled prior to use. Anhydrous diethyl ether and tetrahydrofuran were obtained by distillation from sodium benzophenone ketyl. Drying and other purification of organic solvents and reagents was accomplished by standard laboratory procedures.[104,105]

Experimental

Chapter 2

1,1-Dimethyl-3-trimethylsilyl-2-propynylamine (**23**).

The propargylamine (**21**) (1.0 g, 12.05 mmol) was dissolved in tetrahydrofuran (15 ml) and the solution was cooled to -78°C. *n*-Butyllithium (6.62 ml, 13.25 mmol, 2.0 M) was added slowly to the cooled solution and the reaction mixture was stirred at this temperature for 30 min. The solution was quenched with chlorotrimethylsilane (1.44 g, 13.25 mmol) and the mixture allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with water (5 ml), extracted with dichloromethane (3 x 15 ml) and the combined organic layers were washed with saturated sodium hydrogen carbonate solution (15 ml). The organic extracts were dried (Na_2SO_4), the solvent was removed and the residue distilled to afford the *title compound* (**23**) as a colourless liquid (1.56 g, 84%), b.p. 67-69°C/24 mm. (High resolution mass spectrum : 155.1147, $C_8H_{17}NSi$ requires M^+ : 155.1130). ν_{max} (film) : 3370, 3300 (NH), 2160 cm^{-1} (C≡C). ^1H nmr δ ($CDCl_3$) : 1.95, bs, 2H (NH_2); 1.42, s, 6H ($C(CH_3)_2$); 0.18, s, 9H ($Si(CH_3)_3$). EIMS *m/z* : 155 (M^+, 5%), 140 (M^+-CH_3, 100%).

2-Chloro-4-(1,1-dimethyl-3-trimethylsilyl-2-propyn-1-ylamino)pyrimidine (**24**)

and

4-Chloro-2-(1,1-dimethyl-3-trimethylsilyl-2-propyn-1-ylamino)pyrimidine (**25**).

2,4-Dichloropyrimidine (**22**) (0.123 g, 0.823 mmol), the trimethylsilyl protected propargylamine (**23**) (0.153 g, 0.99 mmol), and triethylamine (0.10 g, 0.99 mmol) were heated in dimethylformamide (5 ml) at 90°C for 5 h. The solution

was cooled and the solvent removed under reduced pressure. The residue was dissolved in dichloromethane (10 ml), washed with sodium hydroxide solution (2 x 10ml, 1M), dried (Na_2SO_4) and the solvent removed. The yellow oil obtained was chromatographed (methanol/dichloromethane : 2/98) to afford a yellow solid which contained the two regioisomers (**24**) and (**25**) in a ratio of 9:1. The solid was fractionally recrystallised from ethanol/water to afford the *major isomer* (**24**) as colourless prisms (0.174 g, 79%), m.p. 89-90°C. (Found : C, 54.3%; H, 6.6%; N, 15.9%; $C_{12}H_{18}ClN_3Si$ requires : C, 53.8%; H, 6.7%; N, 15.7%. High resolution mass spectrum : 267.0966, $C_{12}H_{18}{}^{35}ClN_3Si$ requires M^+ : 267.0959). ν_{max} (nujol) : 3272 (NH), 2164 (C≡C), 1674 (C=N), 1600 cm^{-1} (C=C). ^1H nmr δ ($CDCl_3$) : 8.13, d, J 6 Hz, 1H (**H**6); 6.82, d, J 6 Hz, 1H (**H**5); 5.42, bs, 1H (**NH**); 1.62, s, 6H ($C(CH_3)_2$); 0.15, s, 9H ($Si(CH_3)_3$). ^{13}C nmr δ ($CDCl_3$) : 162.4 (**C**4); 160.1 (**C**2); 156.9 (**C**6); 106.2 (**C**≡CSiMe$_3$); 103.1 (**C**5); 88.1 (C≡**C**SiMe$_3$); 47.9 ($C(CH_3)_2$); 29.6 ($C(CH_3)_2$); 0.3 ($Si(CH_3)_3$). EIMS *m/z* : 267/269 (M^+, 70%), 252/254 (M^+-CH_3, 100%), 232 (M^+-Cl, 40%). The mother liquor contained both the major and minor regioisomers and from this, the proton nmr spectroscopic data for the *minor regioisomer*, (**25**) was assigned. ^1H nmr δ ($CDCl_3$) : 7.99, d, J 6 Hz, 1H (**H**6); 6.29, d, J 6 Hz, 1H (**H**5); 5.40, bs, 1H (NH); 1.46, s, 6H ($C(CH_3)_2$); 0.12, s, 9H ($Si(CH_3)_3$).

1,1,1-Trifluoro-N-(1,1-dimethyl-3-trimethylsilyl-2-propynyl)-N-(2-chloro-4-pyrimidyl)acetamide (**26**) *and* *1,1,1-Trifluoro-N-(1,1-dimethyl-3-trimethylsilyl-2-propynyl)-N-(4-chloro-2-pyrimidyl)acetamide* (**27**)

Trifluoroacetic anhydride (0.03 g, 0.14 mmol) was added slowly to a solution of the mixture of regioisomers (**24**) and (**25**) (0.024 g, 0.09 mmol), and triethylamine (0.01 g, 0.10 mmol) in dry dichloromethane (5 ml) at 0°C under

an atmosphere of nitrogen. The solution was allowed to warm to room temperature and stirred for 2 h. The mixture was washed with saturated sodium hydrogen carbonate (2 x 5 ml), dried (Na_2SO_4), and the solvent removed under reduced pressure to afford the isomeric trifluoroacetamides as a yellow oil. The major component was obtained by flash chromatography (hexane/dichloromethane : 30/70) to afford the *major isomer* (**26**) as a colourless oil (0.019 g, 58%). Purity was determined by tlc analysis and ^1H nmr spectroscopy. (High resolution mass spectrum : 363.0769, $C_{14}H_{17}{}^{35}ClF_3N_3OSi$ requires M^+ : 363.0782). ν_{max} (CH_2Cl_2) : 3410, 3300 (NH, two bands), 1692 cm^{-1} (C=O). ^1H nmr δ ($CDCl_3$) : 8.74, d, J 5 Hz, 1H (**H6**); 7.29, d, J 5 Hz, 1H (**H5**); 1.93, s, 6H ($C(CH_3)_2$); 0.18, s, 9H ($Si(CH_3)_3$). EIMS *m/z* : 363/365 (M^+, 17%), 328 (M^+-Cl, 13%), 294/296 (M^+-CF_3, 100%), 266/268 (M^+-$COCF_3$, 12%). The *minor regioisomer* (**27**), could not be purified and its proton nmr spectroscopic data was assigned by subtraction from that of the mixture of trifluoroacetamides. ^1H nmr δ ($CDCl_3$) : 8.21, d, J 5 Hz, 1H (**H6**); 6.45, d, J 5 Hz, 1H (**H5**); 1.53, s, 6H ($C(CH_3)_2$); 0.15, s, 9H ($Si(CH_3)_3$).

2-Chloro-4-(1,1-dimethyl-2-propyn-1-ylamino)pyrimidine (**30**).

Tetrabutylammonium fluoride (0.43 ml, 0.43 mmol, 1 M) was added to a solution of the pyrimidine (**24**) (0.108 g, 0.40 mmol) in dry tetrahydrofuran (10 ml) and the mixture stirred at room temperature overnight. The solution was diluted with dichloromethane (10 ml), washed with water and the aqueous phase backwashed with dichloromethane (2 x 10 ml). The combined organic phases were dried (Na_2SO_4) and the solvent was removed to give a yellow solid which was recrystallised from ethanol/water to yield the *title compound* (**30**) as colourless needles (0.061 g, 77%), m.p. 90-91°C. (Found : C, 55.0%; H, 5.2%; N, 21.8%; $C_9H_{10}ClN_3$ requires : C, 55.2%; H, 5.2%; N, 21.5%. High

resolution mass spectrum : 194.0490, $C_9H_{10}{}^{35}ClN_3$ requires [M^+-H] : 194.0485). ν_{max} (CH_2Cl_2) : 3292 (NH), 3128 (C≡CH), 1651 (C=N), 1588, 1500 cm^{-1} (C=C). ^1H nmr δ ($CDCl_3$) : 8.11, d, J 6 Hz, 1H (**H**6); 6.75, d, J 6 Hz, 1H (**H**5); 5.42, bs, 1H (N**H**); 2.43, s, 1H (C≡C**H**); 1.63, s, 6H (C(CH_3)$_2$). ^{13}C nmr δ ($CDCl_3$) : 162.4 (**C**4); 160.5 (**C**2); 157.4 (**C**6); 103.1 (**C**5); 84.5 (**C**≡CH); 71.9 (C≡**C**H); 47.3 (**C**(CH_3)$_2$); 29.7 (C(**C**H_3)$_2$). EIMS *m/z* : 194/196 (M^+-H, 96%), 180/182 (M^+-CH_3, 100%), 160 (M^+-Cl, 38%).

2-Chloro-4-(1,1-dimethyl-2-propen-1-ylamino)pyrimidine (**32**).

A solution of the alkyne (**30**) (0.195 g, 1.0 mmol) in diethyl ether (10 ml) was stirred in the presence of a Lindlar catalyst (0.02 g, 10%) under an atmosphere of hydrogen (24 ml, 1.1 mmol hydrogen uptake) for 4 h at room temperature. The solution was filtered through celite and the solvent evaporated to afford a yellow solid which was recrystallised from ethanol/water to yield the *title compound* (**32**) as colourless needles (0.178 g, 90%), m.p. 84.5-85.5°C. (Found : C, 54.8%; H, 6.1%; N, 21.6%; $C_9H_{12}ClN_3$ requires : C, 54.7%; H, 6.1%; N, 21.2%. High resolution mass spectrum : 197.0735, $C_9H_{12}{}^{35}ClN_3$ requires M^+ : 197.0720). ν_{max} (CH_2Cl_2) : 3298 (NH), 1620 cm^{-1} (C=C). ^1H nmr δ ($CDCl_3$) : 8.00, d, J6 Hz, 1H (**H**6); 6.39, d, J 6 Hz, 1H (**H**5); 5.95, dd, J_{cis} 10 Hz, J_{trans} 17 Hz, 1H (C**H**=CH_2); 5.51, bs, 1H (N**H**); 5.21, d, J_{cis} 10 Hz, 1H (CH=C**H**$_2$); 5.20, J_{trans} 17 Hz, 1H (CH=C**H**$_2$); 1.46, s, 6H (C(CH_3)$_2$). ^{13}C nmr δ ($CDCl_3$) : 162.2 (**C**4); 158.6 (**C**2); 156.7 (**C**6); 142.1 (**C**H=CH_2); 113.4 (CH=**C**H_2); 103.1 (**C**5); 54.2 (**C**(CH_3)$_2$); 27.8 (C(**C**H_3)$_2$). EIMS *m/z*: 197/199 (M^+, 23%), 182/184 (M^+-CH_3, 100%), 162 (M^+-Cl, 14%).

Attempted Diimide Reduction of

2-Chloro-4-(1,1-dimethyl-2-propyn-1-ylamino)pyrimidine (**30**).

Dipotassium azodicarboxylate (0.995 g, 5.31 mmol) and 2-chloro-4-(1,1-dimethyl-2-propyn-1-ylamino)pyrimidine (**30**) (0.2 g, 1.03 mmol) were stirred in methanol (10 ml) at room temperature, and to the suspension was added acetic acid (0.25 g, 4.17 mmol) in methanol (2 ml) over a period of 1 h. The mixture was stirred for a further 30 min, the solution was diluted with water (10 ml) and extracted with dichloromethane (15 ml). The organic extracts were dried (Na_2SO_4) and the solvent removed to afford a mixture of products; the starting alkyne (**30**), the alkene (**32**) and the alkane (**31**) in a ratio of 3:4:6 as determined by proton nmr spectroscopy. Alkyne (**30**) : ^{1}H nmr δ ($CDCl_3$) : 8.11, d, J 6 Hz, 1H (**H**6); 6.75, d, J 6 Hz, 1H (**H**5); 5.77, bs, 1H (**NH**); 2.43, s, 1H (C≡**CH**); 1.63, s, 6H (C(**CH**$_3$)$_2$). Alkene (**32**) : ^{1}H nmr δ ($CDCl_3$) : 8.00, d, J 6 Hz, 1H (**H**6); 6.39, d, J 6 Hz, 1H (**H**5); 5.95, dd, J_{cis} 10 Hz, J_{trans} 17 Hz, 1H (**CH**=CH$_2$); 5.77, bs, 1H (**NH**); 5.21, d, J_{cis} 10 Hz, 1H (CH=**CH**$_2$); 5.20, J_{trans} 17 Hz, 1H (CH=**CH**$_2$); 1.46, s, 6H (C(**CH**$_3$)$_2$). Alkane (**31**) : ^{1}H nmr δ ($CDCl_3$) : 7.91, d, J 5 Hz, 1H (**H**6); 6.33, d, J 5 Hz, 1H (**H**5); 5.77, bs, 1H (**NH**); 1.82, q, J 7 Hz, 2H (**CH**$_3$**CH**$_2$); 1.38, s, 6H (C(**CH**$_3$)$_2$); 0.87, t, J 7 Hz, 3H (**CH**$_3$**CH**$_2$). The mass spectrum showed a mixture of molecular ions : 194/196 *m/z* [M$^+$-H] (**30**); 197/199 *m/z* [M$^+$] (**32**); 199/201 *m/z* [M$^+$] (**31**).

Attempted Reductions of

2-Chloro-4-(1,1-dimethyl-3-trimethylsilyl-2-propyn-1-ylamino)pyrimidine (**24**).

(i). *Lindlar Reduction.* - A solution of the silylalkyne (**24**) (0.267 g, 1.0 mmol) in diethyl ether (10 ml) was stirred in the presence of a Lindlar catalyst (0.027 g, 10%) under an atmosphere of hydrogen for 6 h at room temperature.

The solution was filtered through celite and the solvent evaporated to recover the *starting material* (**24**) as determined by tlc analysis and proton nmr spectroscopy, in quantitative yields (0.261 g, 98%).

(ii). *Diisobutylaluminium Hydride.* - Diisobutylaluminium hydride (0.43 g, 3.0 mmol) was added dropwise to a solution of the silylalkyne (**24**) (0.2 g, 0.75 mmol) in tetrahydrofuran (10 ml) at -78°C under an atmosphere of nitrogen. The reaction mixture was allowed to warm to room temperature slowly and stirred overnight. The mixture was again cooled to -78°C and methanol added followed by enough sulfuric acid (20%) to dissolve the precipitated aluminium methoxide. Diethyl ether was added and the aqueous layer was separated and extracted with more diethyl ether (2x10 ml). The combined organic layers were washed with water, saturated sodium hydrogen carbonate and water again until the washings were neutral. The solution was dried (Na_2SO_4) and the solvent removed to recover *starting material* (**24**) (0.069 g, 35%) as shown by a proton nmr spectrum that was identical to that of the starting alkyne. No further material could be recovered from the aqueous phase.

Attempted amino-Claisen Rearrangement of 2-Chloro-4-(1,1-dimethyl-2-propen-1-ylamino)pyrimidine (**32**).

(i). *With 0.1 M H_2SO_4* - 2-Chloro-4-(1,1-dimethyl-2-propyn-1-ylamino)pyrimidine (**32**) (0.050 g, 0.26 mmol) was heated at 75°C in the presence of sulfuric acid (0.1 M) for 8 h. The solution was extracted with diethyl ether (3 x 10 ml), the extracts were washed with water, dried (Na_2SO_4) and the solvent removed. No organic material was obtained from this

with diethyl ether (3 x 10 ml), the extracts were washed with water, dried (Na_2SO_4) and the solvent removed. No organic material was obtained from this extraction procedure. The acidic aqueous layer was neutralised with sodium hydroxide solution (10%) and was extracted with ethyl acetate (3 x 15 ml), but no organic material was obtained from this extraction. Concentration of the aqueous layer afforded, on standing, colourless needles (0.027 g, 82%) of *4-amino-2-chloropyrimidine* (**36**) m.p. 217-219°C {lit[46] m.p. 218-219°C}. EIMS *m/z*: 129/131 (M^+, 100%), 94 (M^+-Cl, 26%).

(ii). *With p-Toluenesulfonic Acid.* - A mixture of the alkene (**32**) (0.045 g, 0.23 mmol), p-toluenesulfonic acid (4.4 mg, 0.023 mmol), acetonitrile (5 ml) and water (1.5 ml) were refluxed at 100°C overnight. The solution was concentrated, dissolved in ethyl acetate (15 ml) and washed with sodium hydroxide solution (2 x 10 ml, 10%). The organic extracts were dried (Na_2SO_4) and the solvent removed. The starting alkene (**32**) was isolated from the organic extracts as a white solid (5.0 mg, 11%). The aqueous layer was neutralised and concentrated to afford *4-amino-2-chloropyrimidine* (**36**) as large colourless needles (0.022 g, 74%), as determined by comparison of the physical and spectroscopic data with that of the literature.[46]

(iii). *With Trifluoroacetic Anhydride (Room Temperature).* - The alkene (**32**) (0.040 g, 0.205 mmol) was dissolved in trifluoroacetic anhydride (10 ml) and the mixture stirred at room temperature overnight. The solvent was removed under reduced pressure, the residue dissolved in dichloromethane

(iv). *With Trifluoroacetic Anhydride (50°C).* - The above reaction was repeated at 50°C with the *starting material* (**32**) being recovered in quantitative yields (0.039g, 98%), as determined by ^{1}H nmr spectroscopy.

(v). *Under Thermal Conditions.* - The alkene (**32**) (0.03g, 0.15 mmol) was heated in a sealed tube in an oil bath set at 200-210°C for 30 min. This resulted in the formation of an intractable tar.

Experimental

Chapter 3

*Attempted Bromination of 2-Chloro-4-(1,1-dimethyl-2-propyn-1-ylamino)pyrimidine (**30**).*

Bromine (0.125 g, 0.78 mmol) in acetic acid (1 ml) was added dropwise to a solution of the alkyne (**30**) (0.05 g, 0.26 mmol) in acetic acid (5 ml) at 0°C and the reaction mixture was stirred for 5 min. at this temperature. The solvent was evaporated, the residue dissolved in dichloromethane and washed with sodium hydroxide solution (2 x 5 ml, 1M). The organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure. Tlc analysis (dichloromethane) indicated that a complex mixture of products had been formed. Flash column chromatography of the crude material enabled the isolation of a fraction which was predominantly the *starting material* (**30**) as indicated by proton nmr spectroscopy, with some broadening of the signals observed. Other fractions proved intractable. When a large excess of bromine was employed and the length of reaction time was increased, some bromination of the alkyne was observed by proton nmr spectroscopy of the crude material. ^{1}H nmr δ ($CDCl_3$) : 8.11, bd, J 6 Hz, 1H (H6); 6.75, bd, J 6 Hz, 1H (H5); 6.56, bs, 1H (BrHC=CBr); 1.63, bs, 6H ($C(CH_3)_2$). However no pure material could be isolated by flash chromatography.

*5-Bromouracil (**41**).*

Bromine (6.0 ml, 0.12 mmol) in acetic acid (60 ml) was added slowly, with stirring, to a suspension of uracil (12.0 g, 0.1 mmol) in acetic acid (60 ml) at room temperature. After 12 h the solid was collected and recrystallised from

water to afford the *title compound* (**41**) as colourless needles (20.2 g, 99%), m.p. 299-300°C {lit[106] m.p. 300°C}. ^{1}H nmr δ (d_6-DMSO) : 11.50, bs, 1H (**NH**); 11.22, bs, 1H (**NH**); 7.91, s, 1H (**H6**). EIMS *m/z* : 190/192 (M^+, 94%), 147/149 (M^+-NHCO, 100%), 111 (M^+-Br, 22%).

5-Bromo-2,4-dichloropyrimidine (**39**).

Phosphorous oxychloride (40.14 g, 262.0 mmol) was added slowly to a suspension of 5-bromouracil (5.0 g, 26.2 mmol) in N,N-dimethylaniline (0.95 g, 7.9 mmol) and the mixture was refluxed for 20 h during which time the suspension dissolved. The mixture was cooled, poured slowly onto ice and the solution extracted with diethyl ether (3 x 20 ml). The combined organic extracts were washed with saturated sodium hydrogen carbonate solution (2 x 30 ml), dried (Na_2SO_4), the solvent evaporated and the residue distilled to afford the *title compound* (**39**) as a colourless liquid (5.1 g, 85%), b.p. 112-113°C/12 mm {lit[55] b.p. 112-113°C/12 mm}. ^{1}H nmr δ ($CDCl_3$) : 8.72, s, 1H (**H6**). ^{13}C nmr δ ($CDCl_3$) : 161.4 (**C4**); 161.3 (**C6**); 159.9 (**C2**); 118.7 (**C5**). EIMS *m/z* : 226/228/230/232 (M^+, 100%), 190/192/194 (M^+-Cl, 52%).

5-Bromo-2-chloro-4-(1,1-dimethyl-2-propyn-1-ylamino)pyrimidine (**42**).

and

5-Bromo-4-chloro-2-(1,1-dimethyl-2-propyn-1-ylamino)pyrimidine (**43**).

5-Bromo-2,4-dichloropyrimidine (**39**) (0.572 g, 2.5 mmol), 1,1-dimethylpropargylamine (**21**) (0.32 g, 3.8 mmol) and triethylamine (0.38 g, 3.8 mmol) were heated in dimethylformamide (10 ml) at 90°C for 5 h. The

solution was cooled and the solvent removed under reduced pressure. The residue was dissolved in dichloromethane (20 ml), washed with sodium hydroxide solution (2 x 15 ml, 1M), dried (Na_2SO_4) and the solvent removed. The yellow oil obtained was chromatographed (dichloromethane) to give a pale yellow solid which contained the two regioisomers (**42**) and (**43**) in a ratio of 15:1. The crystalline material was purified by fractional recrystallisation from ethanol/water to afford the *major isomer* (**42**) as colourless needles (0.523 g, 76%), m.p. 81-81.5°C. (Found : C, 39.5%; H, 3.4%; N, 15.4%; $C_9H_9BrClN_3$ requires : C, 39.4%; H, 3.3%; N, 15.3%. High resolution mass spectrum : 272.9679, $C_9H_9{}^{79}Br^{35}ClN_3$ requires M^+ : 272.9670). ν_{max} (nujol) : 3420, 3216 (NH), 2158 (C≡C), 1640 (C=N), 1600 cm^{-1} (C=C). ^1H nmr δ ($CDCl_3$) : 8.17, s, 1H (**H**6); 5.61, bs, 1H (**NH**); 2.39, s, 1H (C≡**CH**); 1.80, s, 6H ($C(CH_3)_2$). ^{13}C nmr δ ($CDCl_3$) : 158.6 (**C**4); 158.3 (**C**2); 156.6 (**C**6); 103.5 (**C**5); 86.0 (**C**≡CH); 70.2 (C≡**C**H); 49.4 ($\mathbf{C}(CH_3)_2$); 28.9 ($C(\mathbf{C}H_3)_2$). EIMS *m/z* : 273/275/277 (M^+, 100%), 258/260/262 (M^+-CH_3, 92%). The mother liquor contained the minor regioisomer and a small amount of the major product. From this the proton nmr spectroscopic data for the *minor regioisomer* (**43**) was assigned. ^1H nmr δ ($CDCl_3$) : 8.38, s, 1H (**H**6); 5.48, bs, 1H (**NH**); 2.31, s, 1H (C≡**CH**); 1.72, s, 6H ($C(CH_3)_2$).

5-Bromo-2-chloro-4-(1,1-dimethyl-2-propen-1-ylamino)pyrimidine (37).

A solution of the alkyne (**42**) (0.58 g, 2.12 mmol) in diethyl ether (15 ml) was stirred in the presence of a Lindlar catalyst (0.06 g, 10%) under an atmosphere of hydrogen (49 ml, 1.1 mmol hydrogen uptake) for 5 h at room temperature. The solution was filtered through celite and the solvent evaporated to afford a yellow oil that crystallised on standing. The solid was recrystallised from ethanol/water to yield the *title compound* (**37**) as colourless needles (0.53 g, 91%), m.p. 57-58°C. (Found : C, 39.0%; H, 4.0%; N, 15.2%; $C_9H_{11}BrClN_3$ requires

: C, 39.1%; H, 4.0%; N, 15.2%). ν_{max} (nujol) : 3316 (NH), 1582 cm^{-1} (C=C). ^1H nmr δ ($CDCl_3$) : 8.11, s, 1H (**H6**); 6.12, dd, J_{cis} 10 Hz, J_{trans} 17 Hz, 1H (**CH**=CH_2); 5.56, bs, 1H (**NH**); 5.18, d, J_{trans} 17 Hz, 1H (CH=**CH**$_2$); 5.12, d, J_{cis} 10 Hz, 1H (CH=**CH**$_2$); 1.60, s, 6H (C(**CH**$_3$)$_2$). ^{13}C nmr δ ($CDCl_3$) : 158.5 (**C4**); 156.6 (**C2**); 156.2 (**C6**); 142.7 (**CH**=CH_2); 112.9 (CH=**CH**$_2$); 103.5 (**C5**); 56.1 (**C**(CH$_3$)$_2$); 26.8 (C(**CH**$_3$)$_2$). EIMS *m/z*: 275/277/279 (M^+, 38%), 260/262/264 (M^+-CH_3, 100%).

2-Chloro-6,6-dimethyl-5-methylidene-5,6-dihydropyrrolo[2,3-d]pyrimidine (45).

The alkene (**37**) (0.0205 g, 0.075 mmol), triethylamine (0.22 g, 2.2 mmol) palladium acetate (2.0 mg, 0.0075 mmol) and tri-*o*-tolylphosphine (5.0 mg, 0.015 mmol), were combined in a heavy walled pyrex tube which was sealed. The mixture was warmed until the palladium acetate had dissolved (60°C), the temperature was then increased to 100°C and stirring maintained at this temperature for 16 h. The solution was diluted with water, extracted with diethyl ether (3 x 15 ml), dried (Na_2SO_4) and the solvent removed. The reaction mixture was purified using dry column chromatography (hexane/dichloromethane) to afford the *title compound* (**45**) as a colourless oil (0.01 g, 70%). (Found : C, 55.4%; H, 5.1%; N, 21.2%; $C_9H_{10}ClN_3$ requires : C, 55.3%; H, 5.2%; N, 21.5%). ν_{max} (CH_2Cl_2) : 3270 (NH), 1622 cm^{-1} (C=C). ^1H nmr δ ($CDCl_3$) : 8.09, s, 1H (**H6**); 6.65, bs, 1H (**NH**); 5.54, s, 1H (C=C**H**$_a$H$_b$); 5.13, s, 1H (C=CH$_a$**H**$_b$); 1.44, s, 6H (C(**CH**$_3$)$_2$). ^{13}C nmr δ ($CDCl_3$) : 149.1, s (**C4**); 147.3, d (**C6**); 145.1, s (**C2**); 137.6, s (**C**=CH$_2$); 115.4, t (C=**CH**$_2$); 106.2, s (**C5**); 57.3, s (**C**(CH$_3$)$_2$); 28.1, q (C(**CH**$_3$)$_2$). EIMS *m/z* : 195/197 (M^+, 42%), 180/182 (M^+-CH_3, 100%).

Attempted Cross Coupling Reaction of
5-Bromo-2-chloro-4-(1,1-dimethyl-2-propen-1-ylamino)pyrimidine (37)
With Alkylborane.

9-Borabicyclo[3.3.1]nonane (0.31 ml, 0.152 mmol, 0.5 M) was added to a solution of the alkene (**37**) (0.02 g, 0.073 mmol) in dry tetrahydrofuran (1 ml) at 0°C and the mixture allowed to warm slowly to room temperature and stir for 5 h. [1,1'-Bis(diphenylphosphino)ferrocene]palladium(II) chloride (1.1 mg, 1.46×10^{-3} mmol) and aqueous sodium hydroxide (0.075 ml, 0.25 mmol, 3M) were added to the solution and the mixture refluxed for a further 14 h. The solution was cooled to room temperature, 30% hydrogen peroxide solution (20% excess) was added and stirring continued for 1 h. The reaction mixture was extracted with dichloromethane (3 x 5 ml), the organic extracts were washed with brine (2 x 5 ml), dried over sodium sulfate and the solvent removed to yield the *starting material* (**37**) (0.016 g, 80%) as determined by tlc analysis and proton nmr spectroscopy.

Attempted Protection of
5-Bromo-2-chloro-4-(1,1-dimethyl-2-propen-1-ylamino)pyrimidine (37).

(i). *Trifluoroacetamide.* - Trifluoroacetic anhydride (0.043 g, 0.203 mmol) was added slowly to a solution of the amine (**37**) (0.051 g, 0.185 mmol) and triethylamine (0.019 g, 0.185 mmol) in dichloromethane (5 ml) at 0°C under an atmosphere of nitrogen. The mixture was warmed to room temperature and stirring continued for 30 min. The mixture was washed with saturated sodium hydrogen carbonate solution (2 x 5 ml), dried (Na_2SO_4) and the solvent

removed under reduced pressure to recover the *starting material* (**37**) (0.048 g, 94%), as indicated by the proton nmr spectrum of the residue.

(ii). *Acetamide.* - A solution of the amine (**37**) (0.051 g, 0.185 mmol) in pyridine (5 ml) and dichloromethane (5 ml) was cooled to 0°C and to the solution was added acetyl chloride (0.022 g, 0.28 mmol) dropwise under an atmosphere of nitrogen. The mixture was stirred at room temperature for 3 h, was quenched with water (10 ml) and the organic layer separated and washed with hydrochloric acid (3 x 10 ml, 5%). The organic layer was dried (Na_2SO_4) and the solvent removed to afford a solid (0.046 g, 90%) whose proton nmr spectrum was identical to that of the *starting material* (**37**).

(iii). *Ethyl carbamate.* - To an emulsified mixture of the amine (**37**) (0.051 g, 0.185 mmol) in water (2 ml) at 0°C was cautiously added ethyl chloroformate (5.3 mg, 0.05 mmol). The mixture was stirred vigorously for 10 min., then a solution of sodium hydroxide (8.8 mg, 0.22 mmol) in water (1 ml) was added followed immediately by more ethyl chloroformate (5.3 mg, 0.05 mmol). The mixture was stirred at 0°C for a further 2 h and then extracted with dichloromethane (3 x 5 ml). The organic extracts were dried (Na_2SO_4) and the solvent removed to give the *starting material* (**37**) (0.035 g, 69%) as indicated by tlc analysis and proton nmr spectroscopy.

(iv). *^{t}Butyl carbamate.* - The amine (**37**) (0.048 g, 0.175 mmol) and triethylamine (0.027 g, 0.26 mmol) were dissolved in dichloromethane (10 ml)

and to the solution was added BOC-ON (0.047 g, 0.192 mmol) portionwise under an atmosphere of nitrogen. The mixture was stirred at room temperature for 48 h, then washed with aqueous sodium hydroxide solution (2 x 10 ml, 20%), the organic phase separated, dried with sodium sulfate and the solvent evaporated. The compound isolated showed an identical proton nmr spectrum to that of the *starting material* (**37**) (0.41 g, 85%).

(v). *Methanesulfonamide*. - Methanesulfonyl chloride (0.38 g, 0.34 mmol) was added to a solution of the amine (**37**) (0.084 g, 0.30 mmol) in dry pyridine (2 ml) at 0°C under an atmosphere of nitrogen. The mixture was stirred at room temperature for 48 h, diluted with dichloromethane and washed with dilute hydrochloric acid (3 x 10 ml, 1M) and saturated sodium hydrogen carbonate solution (2 x 10 ml). The organic phase was dried (Na_2SO_4) and the solvent evaporated to give the *starting material* (**37**) (0.62 g, 74%) as indicated by proton nmr spectroscopy.

5-Bromo-2-methoxy-4-(1,1-dimethyl-2-propen-1-ylamino)pyrimidine (***60***).

Sodium (8.50 mg, 0.37 mmol) was added to dry methanol (10 ml) and the solution stirred at room temperature until the sodium was dissolved (5 min). The amine (**37**) (0.102 g, 0.37 mmol) in dry methanol (5 ml) was added to the methoxide solution and the reaction mixture was refluxed for 2 h. The solvent was removed, the residue was dissolved in dichloromethane (10 ml) and washed with water (2 x 5 ml). The organic phase was separated, dried (Na_2SO_4) and the solvent evaporated to give a pale yellow oil which was purified by flash chromatography (ethyl acetate/dichloromethane : 5/95) to afford the *title*

compound (**60**) as a colourless oil (0.093 g, 93%). (High resolution mass spectrum : 271.0327, $C_{10}H_{14}{}^{79}BrN_3O$ requires M^+ : 271.0320). ν_{max} (CH_2Cl_2) : 3298 (NH), 1609 cm^{-1} (C=C). ^1H nmr δ ($CDCl_3$) : 8.04, s, 1H (**H6**); 6.11, dd, J_{cis} 10 Hz, J_{trans} 17 Hz, 1H (**CH**=CH_2); 5.41, bs, 1H (**NH**); 5.15, d, J_{trans} 17 Hz, 1H (CH=**CH$_2$**); 5.08, d, J_{cis} 10 Hz, 1H (CH=**CH$_2$**); 3.87, s, 3H (**OCH$_3$**); 1.59, s, 6H (**C(CH$_3$)$_2$**). EIMS *m/z* : 271/273 (M^+, 70%), 256/258 (M^+-CH_3, 100%).

Attempted Protection of

5-Bromo-2-methoxy-4-(1,1-dimethyl-2-propen-1-ylamino)pyrimidine (**60**).

Protection of the methoxy amine (**60**) as the trifluoroacetamide, acetamide and methane sulfonamide were attempted in the same manner as for the chloro derivative (**37**) with each reaction resulting in the recovery of the *starting material* (**60**).

2-Methoxy-4-(1,1-dimethyl-2-propen-1-ylamino)pyrimidine (**61**).

n-Butyllithium (0.186 ml, 0.47 mmol, 2.5M) was added to a solution of the methoxyamine (**60**) (0.060 g, 0.22 mmol) in dry tetrahydrofuran (5 ml) at -78°C. The mixture was allowed to warm slowly to room temperature and was stirred overnight. The solution was quenched with water, extracted with dichloromethane (3 x 10 ml), the aqueous phase was saturated with sodium chloride and further extracted with dichloromethane (2 x 5 ml). The combined organic extracts were dried (Na_2SO_4) and the solvent removed to afford a yellow oil which was purified by chromatography (ethyl acetate/dichloromethane : 5/95) to yield the *title compound* (**61**) as a colourless

oil (0.040 g, 94%). (High resolution mass spectrum : 193.1227, $C_{10}H_{15}N_3O$ requires M^+ : 193.1215). ν_{max} (CH_2Cl_2) : 3294 (NH), 1612 cm^{-1} (C=C). ^1H nmr δ ($CDCl_3$) : 7.94, d, J 6 Hz, 1H (**H6**); 6.08, d, J 6 Hz, 1H (**H5**); 5.99, dd, J_{cis} 11 Hz, J_{trans} 17 Hz, 1H (CH=CH_2); 5.26, bs, 1H (**NH**); 5.17, d, J_{trans} 17 Hz, 1H (CH=CH_2); 5.13, d, J_{cis} 11 Hz, 1H (CH=CH_2); 3.88, s, 3H (OCH_3); 1.47, s, 6H ($C(CH_3)_2$). EIMS *m/z* : 193 (M^+, 40%), 178 (M^+-CH_3, 100%).

N-(1,1-dimethyl-2-propenyl)-N-(2-methoxy-4-pyrimidyl)acetamide (**62**).

A solution of the amine (**61**) (0.048 g, 0.25 mmol) in pyridine (5 ml) and dichloromethane (5 ml) was cooled to 0°C and to the solution was added acetyl chloride (0.029 g, 0.38 mmol) dropwise under an atmosphere of nitrogen. The mixture was stirred at room temperature for 3 h, quenched with water (10 ml), the organic phase was separated and was washed with hydrochloric acid (3 x 10 ml, 5%). The organic layer was dried (Na_2SO_4) and the solvent removed to afford a yellow oil which was purified by chromatography (ethyl acetate/dichloromethane : 2/98) to yield the *title compound* (**62**) as a colourless oil (0.045 g, 77%). (High resolution mass spectrum : 235.1329, $C_{12}H_{17}N_3O_2$ requires M^+ : 235.1321). ν_{max} (CH_2Cl_2) : 1688 (C=O), 1607 cm^{-1} (C=C). ^1H nmr δ ($CDCl_3$) : 8.10, d, J 6 Hz, 1H (**H6**); 6.23, d, J 6 Hz, 1H (**H5**); 5.99, dd, J_{cis} 11 Hz, J_{trans} 17 Hz, 1H (CH=CH_2); 5.17, d, J_{trans} 17 Hz, 1H (CH=CH_2); 5.13, d, J_{cis} 11 Hz, 1H (CH=CH_2); 3.88, s, 3H (OCH_3); 2.09, s, 3H ($COCH_3$); 1.47, s, 6H ($C(CH_3)_2$). EIMS *m/z* : 235 (M^+, 15%), 220 (M^+-CH_3, 100%), 192 (M^+-$COCH_3$, 67%).

Attempted Epoxidation of

5-Bromo-2-chloro-4-(1,1-dimethyl-2-propen-1-ylamino)pyrimidine (37).

(i). *m-Chloroperbenzoic acid.* - *m*-Chloroperbenzoic acid (0.13 g, 0.62 mmol, 85%) was added to a solution of the alkene (**37**) (0.17 g, 0.62 mmol) in dry dichloromethane (5 ml) under an atmosphere of nitrogen. The reaction mixture was stirred at room temperature for 6 h, washed in succession with saturated sodium hydrogen carbonate solution (2 x 10 ml) and water (10 ml), dried (Na_2SO_4) and the solvent evaporated. The proton nmr spectrum of the residue (0.082 g, 48%) indicated that the *starting material* (**37**) had been isolated.

(ii). *Via bromohydrin.* - A solution of the alkene (**37**) (0.05 g, 0.18 mmol) in water (0.01 g, 0.51 mmol) and dimethyl sulfoxide (0.2 ml) was stirred at room temperature until the alkene had dissolved (5 min.). N-bromosuccinimide (0.065 g, 0.36 mmol) was added in portions and the mixture allowed to stir at room temperature for a further 2 h. The mixture was poured into ice-water and the aqueous solution was extracted with diethyl ether (3 x 5 ml). The ethereal extracts were combined, washed successively with water (2 x 5 ml) and brine solution (2 x 5 ml), dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The proton nmr spectrum of the residue (0.039 g, 78%) showed that the *starting material* (**37**) had been recovered.

*2-Chloro-7,7-dimethyl-6-phenylselenenyl-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidine (**64**).*

Phenylselenenyl bromide (0.373 g, 1.58 mmol) in dry dichloromethane (5 ml), was added to a mixture of the amine (**37**) (0.402 g, 1.51 mmol), anhydrous potassium carbonate (2.08 g, 15.1 mmol) and dry silica gel (0.40 g, Merck 60, 230-400 mesh) in dry dichloromethane (15 ml), dropwise over 15 min. The reaction mixture was stirred at room temperature for 36 h in the dark. The solution was cooled to 0°C and *n*-butyllithium (1.3 ml, 3.02 mmol, 2.5M) was added. The mixture was warmed to room temperature and stirred in the dark for a further 12h. The reaction mixture was filtered through celite and the residue washed with dichloromethane (3 x 25 ml). The filtrate was washed with water (2 x 20 ml) followed by saturated sodium hydrogen carbonate solution (2 x 20 ml), dried (Na_2SO_4) and the solvent removed to afford a yellow oil. The oil was purified by performing sequential flash column chromatography. The first column (methanol/dichloromethane : 5/95) removed any selenium by-products while a final purification using chloroform/acetone (98:2) yielded the *title compound* (**64**) as a pale yellow oil (0.315 g, 66%). (High resolution mass spectrum : 353.0198, $C_{15}H_{16}{}^{35}ClN_3{}^{77}Se$ requires M^+ : 353.0187). ν_{max} (CH_2Cl_2) : 3275 (NH), 1600, 1500 cm^{-1} (C=C, aromatic). ^1H nmr δ ($CDCl_3$) : 7.48, m, 2H (*o*-$C_6\mathbf{H}_5Se$); 7.30, s, 1H (**H6**); 7.20, m, 3H (*m*-,*p*-$C_6\mathbf{H}_5Se$); 4.34, bs, 1H (**NH**); 4.27, dd, J_{ax} 2 Hz, J_{bx} 8 Hz, 1H ($CH_xCH_aH_b$); 3.21, dd, J_{ba} 13 Hz, J_{bx} 8 Hz, 1H ($CH_xCH_aH_b$); 3.08, dd, J_{ab} 13 Hz, J_{ax} 2 Hz, 1H ($CH_xCH_aH_b$); 1.46, s, 3H ($C(CH_3)$); 1.24, s, 3H ($C(CH_3)$). ^{13}C nmr δ ($CDCl_3$) : 149.5, s (**C4**); 147.9, d (**C6**); 145.5, s (**C2**); 134.3, d, 129.1, d, 128.6, s, 128.1, d (C_6H_5Se); 105.3, s (**C5**); 70.7, d ($CHCH_2$); 67.3, s ($C(CH_3)_2$); 30.5, q ($C(CH_3)$); 27.5, t ($CHCH_2$); 22.7, q ($C(CH_3)$). EIMS *m/z* : 351/353/355/357 (M^+, 65%), 276/278/280/282 (M^+-Ph, 100%).

*Reduction of 2-Chloro-7,7-dimethyl-6-phenylselenenyl-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidine (**64**).*

(i). *Triphenyltin hydride.* - The selenide (**64**) (0.07 g, 0.20 mmol) was weighed into a dry flask, toluene (2 ml) added, the flask flushed with nitrogen for a further 5 min and the system maintained at a slightly positive pressure of nitrogen. Triphenyltin hydride (0.35 g, 1.0 mmol) in toluene (2 ml), was injected into the flask which was then lowered into a preheated oil bath (120-125°C). The reaction mixture was heated for 12 h, the solution was cooled and the solvent evaporated. The residue was chromatographed (acetone/chloroform : 2/98) to afford the *starting material* (**64**) (0.041 g, 59%) as indicated by tlc analysis and proton nmr spectroscopy.

(ii). *Nickel boride.* - The selenide (**64**) (0.047 g, 0.13 mmol) and nickel chloride hexahydrate (0.095 g, 0.40 mmol) were dissolved in tetrahydrofuran/methanol (5 ml, (1:3)) at 0°C in a conical flask. Sodium borohydride (0.047 g, 1.24 mmol) was added to the stirred solution in portions and a fine black precipitate formed immediately. Stirring was continued at 0°C for a further 1 h at which point the solution was filtered through celite and washed with methanol and tetrahydrofuran. The solvent was evaporated and purified by chromatography (acetone/chloroform : 2/98) to give the *starting material* (**64**) (0.019 g, 40%), as shown by tlc analysis and proton nmr spectroscopy.

(iii). *n-Butyllithium.* - The selenide (**64**) (0.020 g, 0.06 mmol) was dissolved in tetrahydrofuran (2 ml), *n*-butyllithium (60 µl, 0.12 mmol, 2M) was added to the

solution at room temperature and the mixture stirred for 30 min. The reaction mixture was quenched with water and then stirred for a further 15 min. The solution was extracted with dichloromethane (3 x 10 ml), the aqueous phase saturated with sodium chloride and extracted with a further portion of dichloromethane (10 ml). The combined organic extracts were washed with saturated sodium hydrogen carbonate solution (2 x 10 ml), dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue was purified by dry column chromatography (dichloromethane/methanol) to afford the reduction product, *2-chloro-7,7-dimethyl-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidine* (**29**) as a pale yellow oil (6.0 mg, 54%). (High resolution mass spectrum : 197.0706, $C_9H_{12}{}^{35}ClN_3$ requires M^+ : 197.0720). ν_{max} (CH_2Cl_2) : 3266 cm^{-1} (NH). ^1H nmr δ ($CDCl_3$) : 7.36, s, 1H (H6); 5.44, bs, 1H (NH); 3.58, t, J 7 Hz, 2H (CH_2CH_2); 2.85, t, J 7 Hz, 2H (CH_2CH_2); 1.29, s, 6H ($C(CH_3)_2$). EIMS *m/z* : 197/199 (M^+, 28%), 182/184 (M^+-CH_3, 100%).

*2-Chloro-7,8-dihydro-7,7-dimethylpyrido[2,3-d]pyrimidine (**44**).*

(i). *Sodium periodate.* - An aqueous solution of sodium periodate (0.05 g, 0.22 mmol) in water (1 ml) was added dropwise to a solution of the selenide (**64**) (0.035 g, 0.1 mmol) in methanol (3.5 ml) and water (1.5 ml) at 0°C. The mixture was allowed to warm slowly to room temperature and was stirred overnight. The solution was filtered, the solid washed with methanol (2 x 3 ml) and the filtrate concentrated. The residue was extracted into dichloromethane (10 ml), washed with water (2 x 5 ml), dried (Na_2SO_4) and the solvent evaporated. The material was purified by flash chromatography (methanol/dichloromethane : 2/98) to afford the *title compound* (**44**) as a colourless oil (3.4 mg, 18%). (High resolution mass spectrum : 195.0571, $C_9H_{10}{}^{35}ClN_3$ requires M^+ : 195.0563). ν_{max} (CH_2Cl_2) : 3281 (NH), 1620 cm^{-1}

(C=C). ^{1}H nmr δ (d_6-acetone) : 7.55, s, 1H (**H6**); 7.04, d, J 8 Hz, 1H (**CH**=CH); 5.22, d, J 8 Hz, 1H (CH=**CH**); 2.93, bs, 1H (**NH**); 1.49, s, 6H ($C(CH_3)_2$). EIMS *m/z* : 195/197 (M^+, 76%), 180/182 (M^+-CH_3, 100%).

(ii). *Hydrogen peroxide.* - The selenide (**64**) (0.035 g, 0.1 mmol) was dissolved in tetrahydrofuran (5 ml) and the solution cooled to 0°C. The solution was then treated with 30% hydrogen peroxide (20% excess) and the temperature allowed to warm slowly to room temperature and was stirred for 6 h. The reaction mixture was diluted with water and extracted with dichloromethane (3 x 10 ml). The aqueous phase was saturated with sodium chloride and extracted with a further portion of dichloromethane (10 ml). The combined organic extracts were washed with saturated sodium hydrogen carbonate solution (2 x 10 ml), dried (Na_2SO_4) and the solvent evaporated to afford the *starting material* (**64**) in low yield (5.9 mg, 17%) as determined by proton nmr spectroscopy. Further saturation of the aqueous layer with sodium chloride followed by extraction with dichloromethane (3 x 10 ml) failed to afford any more organic soluble material.

Experimental

Chapter 4

3-Chloro-3-methylbut-1-yne (81).

2-Methylbut-3-yn-2-ol (4.21 g, 50.0 mmol) was added to a stirred mixture of calcium chloride (2.3 g, 25.0 mmol) cuprous chloride (2.0 g, 20 mmol) and concentrated hydrochloric acid (21.5 ml, 250.0 mmol), dropwise over a period of 15 min at 0°C. The mixture was stirred at this temperature for a further hour. The organic phase was separated, washed with cold concentrated hydrochloric acid (3 x 50 ml) and water (2 x 20 ml), dried (K_2CO_3) and the residue distilled distilled to afford the *title compound* (**81**) as a colourless liquid (4.14 g, 81%), b.p 73-76°C {lit[84] b.p. 73-76°C}. ν_{max} (film) : 3300 (C≡C-H), 2140 cm^{-1} (C≡C). ^1H nmr δ ($CDCl_3$) : 2.65, s, 1H (C≡C**H**); 1.85, s, 6H ($C(CH_3)_2$). EIMS *m/z* : 102/104 (M^+, 14%), 87/89 (M^+-CH_3, 100%).

2-Aminopyridine-N-oxide (90).

m-Chloroperbenzoic acid (0.2 g, 1.16 mmol) in acetone (2 ml) was added in one portion to a solution of 2-aminopyridine (0.1 g, 1.06 mmol) in acetone (2 ml) and the mixture was allowed to stir at room temperature for 30 min. Diethyl ether (2 ml) was added and hydrogen chloride gas was bubbled through the solution until it remained acidic. The solution was cooled, the solid filtered and washed with diethyl ether to obtain the hydrochloride salt. The free base was obtained by mixing the salt with solid potassium carbonate (0.513 g, 3.72 mmol) followed by a continuous extraction with hot chloroform to afford the *title compound* (**90**) as a solid (0.61 g, 52%), m.p. 157-162°C {lit[63] m.p. 157-162°C}. EIMS *m/z* : 110 (M^+, 28%), 94 (M^+-O, 100%).

Attempted Coupling of 3-Chloro-3-methylbut-1-yne (81).

(i). *With 2-aminopyridine.* - The chloride (**81**) (0.77 g, 7.5 mmol) in diethyl ether (2 ml) was added dropwise over 5 min to a stirred mixture of 2-aminopyridine (0.85 g, 9.0 mmol), triethylamine (1.22 g, 12.0 mmol), copper bronze powder (50 mg) cuprous chloride (50 mg), water (1 ml) and ether (4 ml). The mixture was stirred at room temperature for 24 h, washed with water (2 x 10 ml) and the aqueous layer extracted with diethyl ether (3 x 10 ml). The combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated to recover 2-aminopyridine as a yellow solid (0.43 g, 51%) as indicated by proton nmr spectroscopy.

(ii). *With 4-aminopyridine.* - The chloride (**81**) (0.77 g, 7.5 mmol) in tetrahydrofuran (2 ml) was added dropwise over 5 min to a stirred mixture of 4-aminopyridine (0.85 g, 9.0 mmol), triethylamine (1.22 g, 12.0 mmol), copper bronze powder (50 mg) cuprous chloride (50 mg) water (1 ml) and tetrahydrofuran (4 ml). The mixture was stirred at room temperature for 28 h, washed with water (2 x 10 ml) and the aqueous layer extracted with diethyl ether (3 x 10 ml). The combined ethereal extracts were dried (Na_2SO_4) and the solvent was evaporated to recover 4-aminopyridine as a pale yellow solid (0.35 g, 60%) as determined by proton nmr spectroscopy.

(iii). *2-aminopyridine-N-oxide.* - The chloride (**81**) (0.50 g, 4.9 mmol) in tetrahydrofuran (2 ml) was added dropwise over 5 min to a stirred mixture of 2-aminopyridine-N-oxide (0.65 g, 5.9 mmol), triethylamine (0.81 g, 7.8 mmol),

copper bronze powder (40 mg), cuprous chloride (40 mg), water (1 ml) and tetrahydrofuran (4 ml). The mixture was stirred at room temperature for 24 h, washed with water (2 x 10 ml) and the aqueous layer extracted with hot chloroform (3 x 10 ml). The combined extracts were dried (Na_2SO_4) and the solvent was evaporated to recover 2-aminopyridine-N-oxide (**90**) as an off white powder (0.18 g, 28%) as indicated by proton nmr spectroscopy.

1-Bromo-3-methylbuta-1,2-diene (89).

A mixture of 2-methylbut-3-yn-2-ol (2.5 g, 29.7 mmol), cuprous bromide (1.5 g, 10.4 mmol), ammonium bromide (0.99 g, 10.1 mmol), copper powder (0.07 g, 1.1 mmol) and hydrobromic acid (7.5 ml, 65.4 mmol) were stirred at room temperature for 24 h. The mixture was cooled in an ice bath, filtered and the residue washed with hexane. The filtrate was separated and washed with hydrobromic acid (48%) until the lower aqueous layer showed no violet colouration. The organic layer was dried (K_2CO_3) and fractionally distilled to afford the *title compound* (**89**) as a colourless liquid (2.3 g, 53%), b.p. 39-40°C/20 mm {lit[79] b.p 53-54°C/60 mm}. ν_{max} (film) : 1960 cm^{-1} (C=C=C). ^1H nmr δ ($CDCl_3$) : 5.85, m, J 2 Hz, 1H (C=C=CHBr); 1.85, d, J 2 Hz, 6H ($(CH_3)_2C$). EIMS *m/z* : 146/148(M^+, 72%), 131/133 (M^+-CH_3, 100%), 67 (M^+-Br, 18%).

Attempted Coupling of 1-Bromo-3-methylbuta-1,2-diene (89) and 2-Aminopyridine.

(i). *With Copper Catalysis.* - The allene (**89**) (0.30 g, 2.0 mmol) was slowly added to a solution of 2-aminopyridine (0.23 g, 2.4 mmol), triethylamine (0.83

g, 8.2 mmol) and cuprous bromide (0.01 g, 0.07 mmol) in anhydrous acetonitrile (2 ml) at 0°C under a nitrogen atmosphere. The solution was stirred at room temperature for 24 h and then poured into hydrochloric acid (10 ml, 1M). The aqueous layer was washed with diethyl ether (2 x 10 ml) and then neutralised by addition of potassium carbonate solution (10%). The product was then extracted from the aqueous layer with diethyl ether (4 x 15 ml), the organic extracts washed with water (2 x 10 ml), dried (Na_2SO_4) and the solvent evaporated. The residue was purified by chromatography to recover the two starting materials, *1-bromo-3-methylbuta-1,2-diene* (**89**) (0.037 g, 12%) and *2-aminopyridine* (0.092 g, 40%) as indicated by tlc analysis and proton nmr spectroscopy.

(ii). *Without Copper Catalysis*. - The allene (**89**) (0.32 g, 2.2 mmol) was slowly added to a solution of 2-aminopyridine (0.26 g, 2.6 mmol) and triethylamine (0.92 g, 9.0 mmol) in anhydrous acetonitrile (2 ml) at 0°C under a nitrogen atmosphere. The solution was stirred at room temperature for 24 h and then poured into hydrochloric acid (10 ml, 1M). The aqueous phase was washed with diethyl ether (2 x 10 ml) and then neutralised by addition of potassium carbonate solution (10%). The product was then extracted from the aqueous layer with diethyl ether (4 x 15 ml), the organic extracts washed with water (2 x 10 ml), dried (Na_2SO_4) and the solvent evaporated. The residue was purified by chromatography to recover the two starting materials, *1-bromo-3-methylbuta-1,2-diene* (**89**) (0.13 g, 41%) and *2-aminopyridine* (0.22 g, 85%) as indicated by tlc analysis and proton nmr spectroscopy.

2-(1,1-Dimethylethylamino)pyridine (94).

(i). *Neat.* - 2-Chloropyridine (0.1 g, 0.88 mmol) was refluxed in *tert*-butylamine (0.26 g, 3.5 mmol) for 38 h. The excess amine was removed under reduced pressure, the residue was dissolved in dichloromethane (15 ml), washed with sodium hydroxide solution (2 x 10 ml, 10%), the organic phase dried (Na_2SO_4) and the solvent evaporated. The solid was recrystallised from hexane to afford the *title compound* (**94**) as colourless needles (0.026 g, 20%), m.p. 52-53°C {lit[90] m.p. 52-53°C}. ν_{max} (nujol) : 3436 (NH), 1614 cm^{-1} (C=C). ^1H nmr δ ($CDCl_3$) : 8.09, d, J 5 Hz, 1H (**H6**); 7.45, dd, J 7, 8 Hz, 1H (**H4**); 6.67, dd, J 5, 7 Hz, 1H (**H5**); 6.53, d, J 8 Hz, 1H (**H3**); 4.71, bs, 1H (**NH**), 1.26, s, 9H ($C(CH_3)_3$). EIMS *m/z* : 150 (M^+, 93%), 97 (M^+-$C(CH_3)_3$, 100%).

(ii). *Prior Anion Formation.* - Sodium hydride (0.03 g,1.2 mmol) was added to a solution of *tert*-butylamine (0.08 g, 1.1 mmol) in tetrahydrofuran (5 ml) and the mixture stirred at room temperature for 30 min. 2-Chloropyridine (0.1 g, 0.88 mmol) in tetrahydrofuran (2 ml) was then added slowly to the solution and the reaction stirred at room temperature for a further 16 h. The reaction mixture was concentrated and the residue was dissolved in dichloromethane (15 ml). The solution was washed with sodium hydroxide solution (2 x 10 ml, 10%), the organic layer dried (Na_2SO_4) and the solvent evaporated. The solid was recrystallised from hexane to afford the *title compound* (**94**) as colourless needles (0.070 g, 53%), m.p. 52-53°C {lit[90] m.p. 52-53°C}. Spectroscopic data were identical to that quoted above.

*Attempted Coupling of 1,1-Dimethylpropargylamine (**21**) and 2-Bromopyridine.*

(i). *Neat.* - 2-Bromopyridine (0.14 g, 0.88 mmol) was refluxed in 1,1-dimethylpropargylamine (**21**) (0.29 g, 3.5 mmol) for 38 h. The reaction mixture was diluted with dichloromethane (15 ml) and washed with sodium hydroxide solution (2 x 10 ml, 10%). The organic phase was dried (Na_2SO_4) and the solvent was evaporated to recover *2-bromopyridine* (0.077, 55%) as indicated by proton nmr spectroscopy.

(ii). *DMF Solvent.* - A mixture of 2-bromopyridine (0.14 g, 0.88 mmol), 1,1-dimethylpropargylamine (**21**) (0.088 g, 1.1 mmol) and triethylamine (0.11 g, 1.1 mmol) were heated in dimethylformamide (5 ml) at 90°C for 5 h. The solution was cooled and the solvent removed under reduced pressure. The residue was dissolved in dichloromethane (10 ml), washed with sodium hydroxide solution (2 x 10 ml, 1M), dried (Na_2SO_4) and the solvent evaporated. The proton nmr spectrum and tlc analysis indicated that only *2-bromopyridine* (0.098 g, 70%) had been recovered.

*Attempted Coupling of 1,1-Dimethyl-3-trimethylsilyl-2-propynylamine (**23**) and 2-Bromopyridine.*

Sodium hydride (0.03 g,1.2 mmol) was added to a solution of 1,1-dimethyl-3-trimethylsilyl-2-propynylamine (**23**) (0.17 g, 1.1 mmol) in dry tetrahydrofuran (5 ml) and the mixture stirred at room temperature for 30 min. 2-Bromopyridine (0.14 g, 0.88 mmol) in tetrahydrofuran (2 ml) was then added

slowly to the solution and the reaction stirred at room temperature for a further 16 h. The reaction mixture was concentrated and the residue was dissolved in dichloromethane (10 ml). The solution was washed with aqueous sodium hydroxide (2 x 5 ml, 1M), the organic layer dried (Na_2SO_4) and the solvent evaporated. The residue was purified by flash chromatography to recover the two starting materials, *2-bromopyridine* (0.11 g, 79%) as a yellow liquid and *1,1-dimethyl-3-trimethylsilyl-2-propynylamine* (**23**) (0.12 g, 71%) as an orange oil as determined by tlc analysis and proton nmr spectroscopy.

N-(1,1-dimethyl-2-propynyl)acetamide (95).

A solution of the amine (**21**) (0.5 g, 6.0 mmol) in pyridine (5 ml) and dichloromethane (5 ml) was cooled to 0°C and to the solution was added acetyl chloride (0.71 g, 9.1 mmol) dropwise under an atmosphere of nitrogen. The reaction mixture stirred at room temperature for 2 h, was quenched with water (10 ml) and the organic layer separated and washed with hydrochloric acid (3 x 10 ml, 5%). The organic layer was dried (Na_2SO_4) and the solvent was evaporated. The solid obtained was recrystallised from ether/hexane to afford the *title compound* (**95**) as colourless needles (0.61 g, 81%), m.p.103-105°C {lit[91] m.p. 103-104.5°C}. ν_{max} (nujol) : 3272, 3064 (NH), 1650 cm^{-1} (C=O). ^1H nmr δ ($CDCl_3$) : 2.31, s, 1H (C≡CH); 1.95, s, 3H ($COCH_3$); 1.77, s, 6H ($C(CH_3)_2$). EIMS *m/z* : 125 (M^+, 100%), 110 (M^+-CH_3, 53%).

Attempted Coupling of N-(1,1-dimethyl-2-propynyl)acetamide (95) and 2-Bromopyridine.

Sodium hydride (0.042 g,1.76 mmol) was added to a solution of the amide (**95**) (0.2 g, 1.6 mmol) in anhydrous tetrahydrofuran (10 ml) and the mixture stirred at room temperature for 30 min. 2-Bromopyridine (0.21 g, 1.3 mmol) in tetrahydrofuran (2 ml) was then added slowly to the solution and the reaction stirred at room temperature for a further 16 h. The reaction mixture was concentrated and the residue was dissolved in dichloromethane (15 ml). The solution was washed with aqueous sodium hydroxide (2 x 10 ml, 10%), the organic layer dried (Na_2SO_4) and the solvent evaporated. Analysis of the crude mixture by tlc and proton nmr spectroscopy indicated that the two starting materials *2-bromopyridine* (0.15 g, 71%) and *N-(1,1-dimethyl-2-propynyl)acetamide* (**95**) (0.13 g, 65%) had been recovered.

3-Chloro-3-methyl-1-trimethylsilylbut-1-yne (106).

To a solution of the propargyl chloride (**81**) (0.50 g, 4.9 mmol) in tetrahydrofuran (10 ml) was added *n*-butyllithium (2.3 ml, 4.9 mmol, 2.1M) at -78°C slowly over 5 min. and the solution was stirred at this temperature for a further 30 min. Chlorotrimethylsilane (0.53 g, 4.9 mmol) was then added to the solution dropwise at -78°C over 5 min., the mixture allowed to warm to room temperature and stirring continued for 12 h. The solution was diluted with water (10 ml) and extracted with dichloromethane (3 x 10 ml). The combined organic extracts were washed with saturated sodium hydrogen carbonate solution (2 x 10 ml), dried (Na_2SO_4), the solvent evaporated and the residue distilled to afford the *title compound* (**106**) as a colourless liquid (0.85 g, 99%), b.p. 46-47°C/15 mm {lit[94] b.p. 32-35°C/5 mm}. ν_{max} (nujol) : 2164 cm^{-1} (C≡C). ^1H

nmr δ (60 MHz, $CDCl_3$) : 1.9, s, 6H ($C(CH_3)_2$); 0.3, s, 9H ($Si(CH_3)_3$). EIMS *m/z* : 174/176 (M^+, 15%), 159/161 (M^+-CH_3, 100%), 139 (M^+-Cl, 10%).

2,2-Dimethyl-4-trimethylsilylbut-3-ynal (105).

A dry flask was charged with magnesium turnings (0.068 g, 2.8 mmol) and iodine (1 crystal) and to the flask was added a few drops of a solution of the chloride (**106**) (0.41 g, 2.4 mmol) in dry tetrahydrofuran (10 ml) under a nitrogen atmosphere. Upon initiation of the reaction the remaining solution of the chloride (**106**) in tetrahydrofuran was added and the mixture heated on a water bath until the reaction was complete (2 h). In a separate flask, a solution of methylmagnesium iodide in tetrahydrofuran (3 ml, 3.9 mmol, 1.32M) was added dropwise over 15 min. at 0°C to a solution of formic acid (0.16 g, 3.5 mmol) under an atmosphere of nitrogen and the mixture was stirred for 30 min. The Grignard reagent, formed in the first flask, was then added to the second, at 0°C, using a transfer line. The resultant mixture was allowed to stir at room temperature for 1 h and was then decomposed with hydrochloric acid (10 ml, 1M). The solution was extracted with diethyl ether (4 x 15 ml), the organic extracts dried (Na_2SO_4) and the solvent evaporated to afford the crude *title compound* (**105**) as an oily solid (0.18 g, 46%) which gave a positive Tollens test. Spectroscopic data was taken of crude material. ν_{max} (CH_2Cl_2) : 2156 (C≡C), 1724 cm^{-1} (C=O). ^1H nmr δ (60 MHz, $CDCl_3$) : 8.1, s, 1H (O=C**H**); 1.35, s, 6H ($C(CH_3)_2$); 0.2, s, 9H ($Si(CH_3)_3$). Recrystallisation of the oily solid from ethanol yielded a yellow solid (0.088 g, 45%), m.p. 131-134°C. The spectroscopic data of the recrystallised material was different to that of the aldehyde and corresponded to that of the *carboxylic acid* (**109**). (High resolution mass spectrum : 184.0923, $C_9H_{16}O_2Si$ requires M^+ : 184.0919). ν_{max} (CH_2Cl_2) : 3300-2900 (broad OH), 1715 cm^{-1} (C=O, carboxylic acid). ^1H nmr δ (60 MHz, $CDCl_3$) :

9.3, bs, 1H (CO_2H); 1.40, s, 6H ($C(CH_3)_2$); 0.2, s, 9H ($Si(CH_3)_3$). EIMS *m/z* : 184 (M^+, 5%), 140 (M^+-CO_2, 100%).

*2,2-Dimethyl-4-trimethylsilylbut-3-ynoic acid (**109**).*

A portion of a solution of the chloride (**106**) (0.15 g, 0.86 mmol) in diethyl ether (5 ml) was added to a dry flask containing magnesium turnings (0.023 g, 0.95 mmol) and iodine (1 crystal). After initiation had occurred the remaining solution was added and the mixture stirred, with heating on a water bath until the reaction was completed (2 h). The Grignard reagent was cooled, poured onto a slurry of dry ice in diethyl ether and the mixture stirred vigorously until the dry ice had evaporated. Ice (5 g) and dilute hydrochloric acid (1.0 ml, 1M) were added, the organic phase separated and the aqueous phase washed with more diethyl ether (2 x 10 ml). The combined organic extracts were dried (Na_2SO_4) and the solvent evaporated. The solid was recrystallised from ethanol/water to yield the *title compound* (**109**) as a pale yellow solid (0.087 g, 55%), m.p. 132-133°C. All spectroscopic data were identical to that obtained previously for the *carboxylic acid* (**109**).

General Procedure for Benzotriazole Adduct Formation.

The aldehyde (1.0 mol equiv), the amine (1.0 mol equiv) and benzotriazole (1.0 mol equiv) were heated in ethanol (1.0 ml/mmol) under reflux for 4 h. The solvent was evaporated under reduced pressure and the residue triturated with diethyl ether and the remaining solid was recrystallised from ethanol.

Using this procedure, adduct formation was attempted :

(i). The residue from the reaction between the crude aldehyde (**105**), 2-aminopyridine and benzotriazole, was triturated with diethyl ether to obtain a small amount of solid (0.02 g, 33%), m.p. 98-99°C, which was shown to be benzotriazole by m.p and proton nmr spectroscopy. The diethyl ether solution obtained from the trituration of the residue contained the starting 2-*aminopyridine* and the *carboxylic acid* (**109**) as indicated by tlc analysis (methanol/dichloromethane : 2/98 - for the amine; ether/hexane : 5/95 - for the carboxylic acid) and proton nmr spectroscopy.

(ii). The residue from the reaction between 2-pyridinecarboxaldehyde, 1,1-dimethyl-3-trimethylsilyl-2-propynylamine (**23**) and benzotriazole was triturated with diethyl ether to isolate a small amount of solid (0.02 g, 33%), m.p. 98-99°C which was shown to be benzotriazole by m.p and proton nmr spectroscopy. The diethyl ether solution contained the *starting amine* (**23**) and *2-pyridinecarboxaldehyde* as determined by proton nmr spectroscopy.

*1-[2-(1,1-Dimethylprop-1-ylamino)pyridyl]benzo-1,2,3-triazole (**112**).*

(iii). Reaction of trimethylacetaldehyde, 2-aminopyridine, and benzotriazole afforded the *title compound* (**112**) as colourless prisms (2.37 g, 85%), m.p. 210-211°C {lit[90] m.p. 210-211°C}. EIMS *m/z* : 281 (M^+, 100%), 266 (M^+-CH_3, 48%).

*1-(2-Ethylaminopyridyl)benzo-1,2,3-triazole (**113**).*

(iv). Reaction of acetaldehyde, 2-aminopyridine and benzotriazole gave the *title compound* (**113**) as colourless prisms (1.91 g, 80%), m.p. 125-128°C {lit[92] m.p. 126-128°C}. EIMS *m/z* : 239 (M^+, 65%), 224 (M^+-CH_3, 100%).

General Procedure for the Preparation of Propargylic Amines.

n-Butyllithium (2.2 mol equiv) was added to a solution of trimethylsilyl acetylene (2.0 mol equiv) in tetrahydrofuran (20 ml) and the solution allowed to stir at room temperature for 2 h. The benzotriazole adduct (1.0 mol equiv) in tetrahydrofuran (10 ml) was then added to the mixture and stirring was continued for a further 2 h. The solution was quenched with water (0.1 g), the solvent removed under reduced pressure and the residue partitioned between diethyl ether and sodium hydroxide solution (1.0 M). The organic phase was separated, the aqueous layer further extracted with diethyl ether (2 x 10 ml) and the combined ethereal extracts were washed with water (2 x 10 ml), dried (Na_2SO_4) and the solvent evaporated.

By this method the following compounds were prepared:

*2-(2,2-Dimethyl-5-trimethylsilyl-4-pentyn-3-ylamino)pyridine (**114**).*

The residue isolated from the reaction of (**112**) was purified by recrystallisation from ethanol/water to afford the *title compound* (**114**) as colourless needles (0.132 g, 71%), m.p.100-102°C. (Found: C, 69.4%; H, 9.2%; N, 10.9%; $C_{15}H_{24}N_2Si$

requires : C, 69.2%; H, 9.3%; N, 10.7%. High resolution mass spectrum : 260.1715, $C_{15}H_{24}N_2Si$ requires M^+ : 260.1717). ν_{max} (nujol): 3306 (NH), 2160 cm^{-1} (C≡C). ^1H nmr δ ($CDCl_3$) : 8.10, dd, J 2, 5 Hz, 1H (**H**6); 7.42, td, J 2, 7, 8 Hz, 1H (**H**4); 6.59, dd, J 5, 7 Hz, 1H (**H**5); 6.47, d, J 8 Hz, 1H (**H**3); 4.53, d, J 9 Hz, 1H (N**H**); 4.41, d, J 9 Hz, 1H (NHC**H**); 1.06, s, 9H ($C(CH_3)_3$); 0.13, s, 9H ($Si(CH_3)_3$). ^{13}C nmr δ ($CDCl_3$) : 156.0 (**C**2); 147.9 (**C**6); 137.3 (**C**4); 113.4 (**C**5); 107.6 (**C**3); 90.1 (**C**≡CSiMe$_3$); 77.0 (C≡**C**SiMe$_3$); 53.6 (**C**H$(CH_3)_3$); 38.0 (**C**$(CH_3)_3$); 26.2 (C$(CH_3)_3$); 0.2 ($Si(CH_3)_3$). EIMS *m/z* : 260 (M^+, 30%), 245 (M^+-CH_3, 100%), 203 (M^+-^{t}Bu, 52%).

*2-(4-Trimethylsilyl-3-butyn-2-ylamino)pyridine (**115**).*

The material isolated from the reaction of (**113**) was purified by flash chromatography (ethyl acetate/dichloromethane : 10/90) to yield the *title compound* (**115**) as a yellow oil (0.15 g, 82%). (Found : C, 65.8%; H, 8.4%; N, 13.1%; $C_{12}H_{18}N_2Si$ requires : C, 66.0%; H, 8.3%; N, 12.8%. High resolution mass spectrum : 218.1247, $C_{12}H_{18}N_2Si$ requires M^+ : 218.1239). ν_{max} (film) : 3256 (NH), 2164 cm^{-1} (C≡C). ^1H nmr δ ($CDCl_3$) : 8.07, d, J 5 Hz, 1H (**H**6); 7.39, dd, J 6, 8 Hz, 1H (**H**4); 6.57, dd, J 5, 6 Hz, 1H (**H**5); 6.43, d, J 8 Hz, 1H (**H**3); 4.72, d, J 8 Hz, 1H (N**H**); 4.59, dq, J 7, 8 Hz, 1H (NHC**H**); 1.46, d, J 7 Hz, 3H (CH(CH_3)); 0.1, s, 9H ($Si(CH_3)_3$). ^{13}C nmr δ ($CDCl_3$) : 157.3 (**C**2); 147.9 (**C**6); 137.3 (**C**4); 113.4 (**C**5); 107.6 (**C**3); 85.9 (**C**≡CSiMe$_3$); 69.5 (C≡**C**SiMe$_3$); 39.8 (**C**HCH_3); 22.3 (CH**C**H$_3$); 0.5 ($Si(CH_3)_3$). EIMS *m/z* : 218 (M^+, 70%), 203 (M^+-CH_3, 100%).

General Procedure for the Preparation of Trifluoroacetamides.

Trifluoroacetic anhydride (1.2 mol equiv) was slowly added to a cooled solution of the amine (1.0 mol equiv) and triethylamine (1.0 mol equiv) in dichloromethane (10 ml) under an atmosphere of nitrogen and the mixture was stirred at room temperature for 30 min. The solution was then washed with saturated sodium hydrogen carbonate solution (2 x 15 ml), dried (Na_2SO_4) and the solvent evaporated to afford the trifluoroacetamide.

By this method the following compounds were prepared:

*1,1,1-Trifluoro-N-[3-(2,2-dimethyl-5-trimethylsilyl-4-pentynyl)]-N-2-pyridylacetamide (**116**).*

Purification of the material isolated from the reaction of (**114**) by flash chromatography (ethyl acetate/dichloromethane : 10/90) gave the *title compound* (**116**) as a pale yellow oil (0.082 g, 80%). (High resolution mass spectrum : 356.1537, $C_{17}H_{23}F_3N_2OSi$ requires M^+ : 356.1532). ν_{max} (CH_2Cl_2) : 2180 (C≡C), 1706 cm^{-1} (C=O). ^1H nmr δ ($CDCl_3$) : 8.54, dd, J 2, 5 Hz, 1H (**H**6); 7.77, dd, J 2, 8 Hz, 1H (**H**4); 7.65, d, J 8 Hz, 1H (**H**3); 7.37, dd, J 5, 8 Hz, 1H (**H**5); 5.57, s, 1H (NC**H**); 0.97, s, 9H ($C(CH_3)_3$); 0.15, s, 9H ($Si(CH_3)_3$). ^{13}C nmr δ ($CDCl_3$) : 199.7 (**C**=O); 154.2 (**C**2); 149.2 (**C**6); 137.7 (**C**4); 124.9 (**C**5); 124.1 (CF_3); 102.2 (**C**3); 88.6 (**C**≡CSiMe$_3$); 79.9 (C≡**C**SiMe$_3$); 54.1 (**C**H$C(CH_3)_3$); 44.3 ($C(CH_3)_3$); 25.6 ($C(CH_3)_3$); 0.2 ($Si(CH_3)_3$). EIMS *m/z* : 356 (M^+, 2%), 341 (M^+-CH_3, 5%), 299 (M^+-^{t}Bu, 47%), 259 (M^+-$COCF_3$, 5%), 203 (M^+-^{t}Bu,-$COCF_3$, 100%).

*1,1,1-Trifluoro-N-[2-(1-methyl-4-trimethylsilyl-3-butynyl)]-N-2-pyridylacetamide (**117**).*

Purification of the compound obtained from the reaction of (**115**) by flash chromatography (ethyl acetate/dichloromethane : 10/90) afforded the *title compound* (**117**) as a yellow oil (0.1 g, 65%). (High resolution mass spectrum : 314.1059, $C_{14}H_{17}F_3N_2OSi$ requires M^+ : 314.1062). ν_{max} (flim) : 2176 (C≡C), 1708 cm^{-1} (C=O). ^1H nmr δ ($CDCl_3$) : 8.53, dd, J 2, 5 Hz, 1H (**H6**); 7.78, dd, J 2, 8 Hz, 1H (**H4**); 7.36, dd, J 1, 8 Hz, 1H (**H3**); 7.35, td, J 1, 5, 8 Hz, 1H (**H5**); 5.55, q, J 7 Hz, 1H (NC**H**); 1.46, d, J 7 Hz, 3H (CHC**H**$_3$); 0.1, s, 9H (Si(C**H**$_3$)$_3$). ^{13}C nmr δ ($CDCl_3$) : 201.6 (**C**=O); 155.8 (**C2**); 149.0 (**C6**); 137.7 (**C4**); 124.8 (**C5**); 124.4 (**C**F$_3$); 102.2 (**C3**); 91.5 (**C**≡CSiMe$_3$); 87.9 (C≡**C**SiMe$_3$); 46.5 (**C**HCH$_3$); 20.2 (CH**C**H$_3$); 0.2 (Si(**C**H$_3$)$_3$). EIMS *m/z* : 314 (M^+, 18%), 299 (M^+-CH_3, 8%), 217 (M^+-$COCF_3$, 100%).

General Procedure for the Attempted Alkylation of Propargylamines.

n-Butyllithium (1.0 mol equiv) was added to the protected propargylamine (1.0 mol equiv) in tetrahydrofuran (10 ml/mmol) at -78°C and the solution was allowed to warm slowly to room temperature and stirred for 1 h. The mixture was cooled on an ice bath and to it was added methyl iodide (1.1 mol equiv) and the mixture was stirred at room temperature over night. The solution was quenched with water (5 ml) and the layers were separated. The aqueous phase was extracted with dichloromethane (3 x 10 ml), the combined organic extracts dried (Na_2SO_4) and the solvent was evaporated.

Using the procedure outlined, alkylation was attempted on compounds (**116**) and (**117**):

(i). The crude reaction mixture obtained from the attempted methylation of (**116**) was purified by flash chromatography (ethyl acetate/dichloromethane : 10/90) to afford the *starting material* (**116**) as a yellow oil (0.057 g, 80%) as determined by proton nmr spectroscopy.

(ii). The crude reaction mixture obtained from the attempted alkylation of (**117**) with methyl iodide, was purified by flash chromatography (ethyl acetate/dichloromethane : 10/90) to afford the *starting material* (**117**) as an orange oil (0.055 g, 73%) as indicated by proton nmr spectroscopy.

General Procedure for the Attempted Deuterium Incorporation at α Carbon.

n-Butyllithium (1.0 mol equiv) was added to the protected propargylamine (1.0 mol equiv) in tetrahydrofuran (10 ml/mmol) at -78°C and the solution was allowed to warm slowly to room temperature and stirred for 1 h. The mixture was cooled on an ice bath and to it was added deuterium oxide (3.0 mol equiv), the mixture was stirred at room temperature for 2 h and the layers were then separated. The aqueous phase was extracted with dichloromethane (3 x 10 ml), the combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated to obtain the crude material.

Using the method outlined, the deuterium incorporation of compounds (**116**) and (**117**) were attempted :

(i). The crude material isolated from the attempted deuterium incorporation of (**116**), was purified by flash chromatography (ethyl acetate/dichloromethane : 10/90) to afford *1,1,1-trifluoro-N-[3-(2,2-dimethyl-5-[^{2}H]-4-pentynyl)]-N-2-pyridylacetamide* (**122**) as an unstable yellow oil (0.017 g, 47%). ^{1}H nmr δ ($CDCl_3$) : 8.50, dd, J 2, 5 Hz, 1H (**H6**); 7.76, dd, J 2, 8 Hz, 1H (**H4**); 7.62, d, J 8 Hz, 1H (**H3**); 7.35, dd, J 5, 8 Hz, 1H (**H5**); 5.59, s, 1H (**NCH**); 0.95, s, 9H ($C(CH_3)_3$). EIMS *m/z* : 285 (M^+, 6%), 283, (M^+-D, 15%), 225 (M^+-D,-^{t}Bu, 52%), 186 (M^+-D,-$COCF_3$, 100%).

(ii). The crude material isolated from the attempted deuterium incorporation of (**117**), was purified by flash chromatography (ethyl acetate/dichloromethane : 10/90) to give *1,1,1-trifluoro-N-[2-(1-methyl-4-[^{2}H]-3-butynyl)]-N-2-pyridylacetamide* (**123**) as an unstable yellow oil (0.01 g, 32%). ^{1}H nmr δ ($CDCl_3$) : 8.47, dd, J 2, 5 Hz, 1H (**H6**); 7.70, dd, J 2, 8 Hz, 1H (**H4**); 7.32, dd, J 1, 8 Hz, 1H (**H3**); 7.30, td, J 1, 5, 8 Hz, 1H (**H5**); 5.51, q, J 7 Hz, 1H (**NCH**); 1.48, d, J 7 Hz, 3H (CH_3); EIMS *m/z* : 243 (M^+, 5%), 241 (M^+-D, 12%), 226 (M^+-D, -CH_3, 30%), 144 (M^+-D, -$COCF_3$, 100%).

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Appendix

Bond Angles (deg) for (**24**).

Atom	Atom	Atom	Angle	Atom	Atom	Atom	Angle
C11	Si	C4′	108.8 (6)	C12	Si	C4′	110.3 (6)
C12	Si	C11	100.9 (8)	C13	Si	C4′	110.7 (12)
C13	Si	C11	94.5 (18)	C13	Si	C12	128.3 (20)
C6	N1	C2	113.6 (6)	C4	N3	C2	116.3 (6)
C2′	N4	C4	126.2 (5)	N1	C2	C12	116.9 (6)
N3	C2	C12	114.7 (5)	N3	C2	N1	128.5 (7)
N4	C4	N3	114.1 (5)	C5	C4	N3	120.3 (6)
C5	C4	N4	125.5 (6)	C6	C5	C4	116.3 (7)
C5	C6	N1	124.9 (6)	C1′	C2′	N4	113.3 (6)
C2″	C2′	N4	106.1 (6)	C2‴	C2′	C1′	108.1 (6)
C3′	C2′	N4	110.9 (6)	C3′	C2′	C1′	110.8 (6)
C3′	C2′	C2″	107.3 (6)	C4′	C3′	C2′	178.7 (8)
C3′	C4′	Si	177.1 (9)				

Bond Distances (Å) for (**24**)

Atom	Atom	Distance	Atom	Atom	Distance
C2	Cl2	1.714 (8)	C4′	Si	1.834 (9)
C11	Si	1.752 (16)	C12	Si	1.883 (15)
C13	Si	1.874 (30)	C6	N1	1.342 (9)
C2	N1	1.316 (8)	C4	N3	1.349 (8)
C2	N3	1.338 (9)	C2′	N4	1.447 (8)
C4	N4	1.360 (7)	C6	C5	1.364 (10)
C5	C4	1.405 (8)	C2′	C2″	1.567 (9)
C2′	C1′	1.552 (9)	C4′	C3′	1.181 (9)
C3′	C2′	1.500 (9)			