STUDIES ON PYRIDINE *N*-OXIDES

A thesis submitted to the Board of the Faculty of Physical Sciences

in partial fulfilment of the requirements for the degree of

Doctor of Philosophy

by

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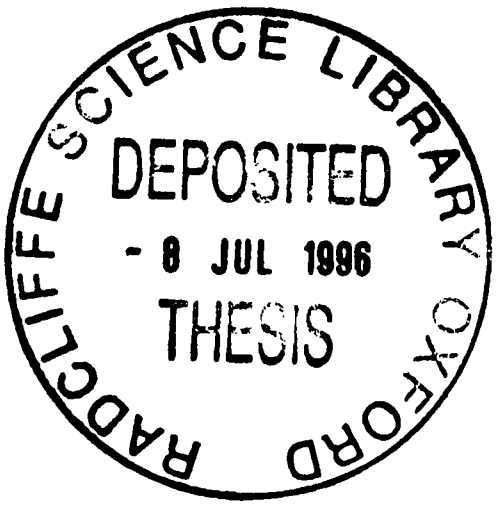
Michaelmas Term 1995



To Mum and Dad
and to Carl

Thanks for everything

Where there is much desire to learn,

there of necessity will be much arguing, much writing, many opinions;

for opinion in good men is but knowledge in the making.

John Milton.

ASLIB ABSTRACT

STUDIES ON PYRIDINE *N*-OXIDES

J. M. Knott **D. Phil.**

Linacre College, Oxford **Michaelmas Term 1995**

The work described herein is directed towards the Claisen rearrangements and [3+2] cycloaddition reaction of pyridine *N*-oxide systems. The pyridine *N*-oxide molecule is a very versatile and useful synthetic intermediate for the construction of more complex pyridines.

Chapter 1 contains a review of work carried out within the group towards Claisen rearrangement of benzene-type systems. The acid catalysed rearrangement of these systems affords a high degree of regioselectivity. A literature survey of the [3+2] cycloaddition reaction of both aliphatic nitrones and aromatic *N*-oxides with various dipolarophiles is also included. Access to many stereochemically pure products demonstrates that the [3+2] cycloaddition has become a very important ring-forming reaction.

Chapter 2 describes development of two Claisen rearrangement precursors and their subsequent attempted Claisen rearrangement is outlined.

Chapter 3 details the construction of a range of 3-substituted pyridine *N*-oxides. Their attempted intermolecular cycloaddition, by thermal means and at high pressure, with mono- and di-activated dipolarophiles is described.

Chapter 4 outlines attempts towards and the final synthesis of the ester cycloaddition precursors. Attempted intramolecular [3+2] cycloaddition of these substrates both thermally and under high pressure is summarised.

Chapter 5 describes approaches towards [3+2] cycloaddition precursors that contain mono- and di-activated dienophiles. The synthesis of a variety of 3-substituted pyridines is detailed.

ACKNOWLEDGEMENTS

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Last but not least, it remains for me to say a big thank you to Harriet and Ali for being the best and most supportive friends anyone could ever ask for, all my family especially Mum and Dad for always caring and for believing in me but most of all, Carl for his love and concern and for always understanding me.

ABBREVIATIONS

Ac	Acetyl
aq	aqueous
Ar	aryl
Bu	Butyl
cat.	catalytic quantity
C.I.	Chemical Ionisation
Δ	heat
DCM	Dichloromethane
DMAP	4-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulphoxide
EDG	Electron Donating Group
E.I.	Electron Impact
equiv.	equivalents
E.S.	Electrospray
Et	Ethyl
EWG	Electron Withdrawing Group
FMO	Frontier Molecular Orbital
Fu	Furyl
GC	Gas Chromatography
GCMS	Gas Chromatography Mass Spectrometry
hν	photochemical irradiation
HOMO	Highest Occupied Molecular Orbital
IMDAF	Intramolecular Diels-Alder Reaction of Furan
IR	Infrared
LDA	Lithium diisopropylamide
LUMO	Lowest Unoccupied Molecular Orbital
m	*meta*

m-CPBA	*meta*-Chloroperbenzoic acid
Me	Methyl
m.p.	melting point
n	*normal*
NBS	*N*-Bromosuccinimide
NHOMO	Next Highest Occupied Molecular Orbital
NLUMO	Next Lowest Unoccupied Molecular Orbital
NMR	Nuclear Magnetic Resonance
o	*ortho*
ox	oxidation
p	*para*
PCC	Pyridinium Chlorochromate
PDC	Pyridinium Dichromate
Ph	Phenyl
ppm	parts per million
Py	Pyridine
R_f	retention factor
red^n	reduction
r.t.	room temperature
S.M.	Starting Material
t	*tertiary*
TBAF	Tetra-*N*-butylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
Tf	Trifluoromethanesulphonate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
t.l.c.	thin layer chromatography
TMS	Trimethylsilyl
Ts	*p*-Toluenesulphonyl
UV	Ultraviolet

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CHAPTER 1
INTRODUCTION

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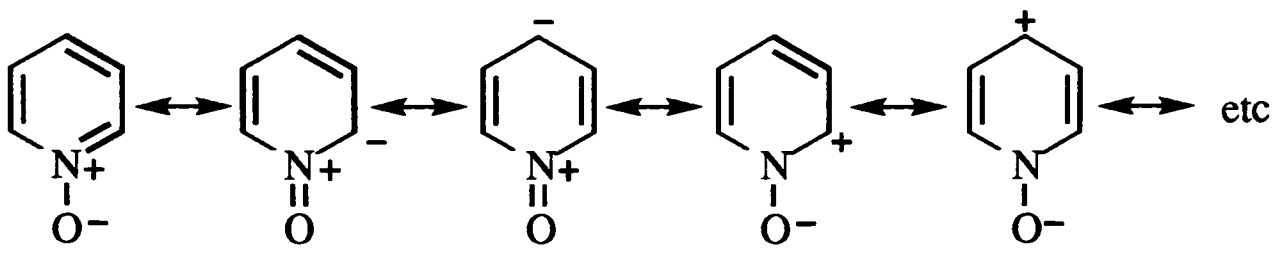
1.1 Introduction

The pyridine system is very important in both organic and pharmaceutical chemistry. Although there has been much research into this system, reactions aimed specifically at direct substitution of the parent hydrogen at the 2-position are rare. Since there are no simple methods for accessing these systems directly from pyridine itself, it is necessary to construct them either by synthesis of the pyridine ring from a precursor already bearing the appropriate substituent, or *via* an intermediate species. Most methods for construction of the pyridine ring involve the use of carbonyl compounds and the scope of the construction of substituted pyridines is limited by the availability of the appropriate starting materials. The pyridine *N*-oxide molecule (**1**), however, can provide a very versatile and useful synthetic intermediate for the construction of more complex pyridines by virtue of its ability to react in very different ways from simple pyridines.[1,2]

1.2 Introduction to Pyridine *N*-Oxide

The oxygen of pyridine *N*-oxide (**1**) is believed to release electrons mesomerically into the pyridine ring in a manner formally analogous to the electron release of the phenoxide anion. As a consequence, pyridine *N*-oxide exhibits very different physical and chemical properties from pyridine. Various canonical forms of pyridine *N*-oxide can be envisaged which can help explain the type of reactions it is capable of undergoing (**Figure 1**).



(1) **(1a)** **(1b)** **(1c)** **(1d)**

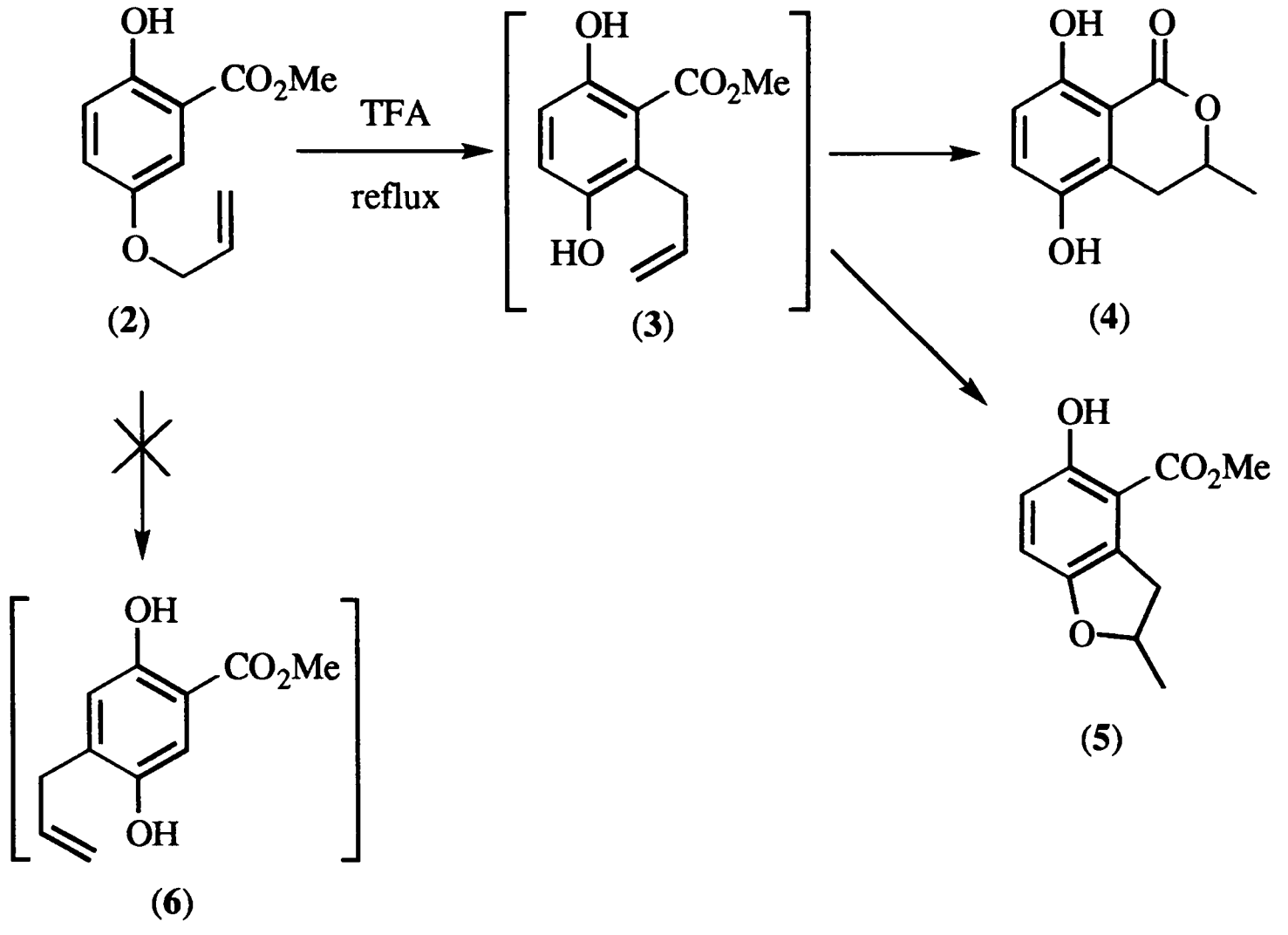
Figure 1

Considering the canonical forms (**1a**) and (**1b**), the *N*-oxide group can be seen to act as an electron donor whereas canonical forms (**1c**) and (**1d**) indicate that it can also act as an electron acceptor. Pyridine *N*-oxide (**1**) can therefore potentially react both by electrophilic and nucleophilic addition to the 2- and 4-positions.

This thesis will examine some reactions of pyridine *N*-oxide (**1**) in particular the [3+2] cycloaddition with preliminary studies on the Claisen type rearrangement and their applicability as methods for the synthesis of the desired 2-substituted pyridines.

1.3 Initial Studies on the Claisen Rearrangement

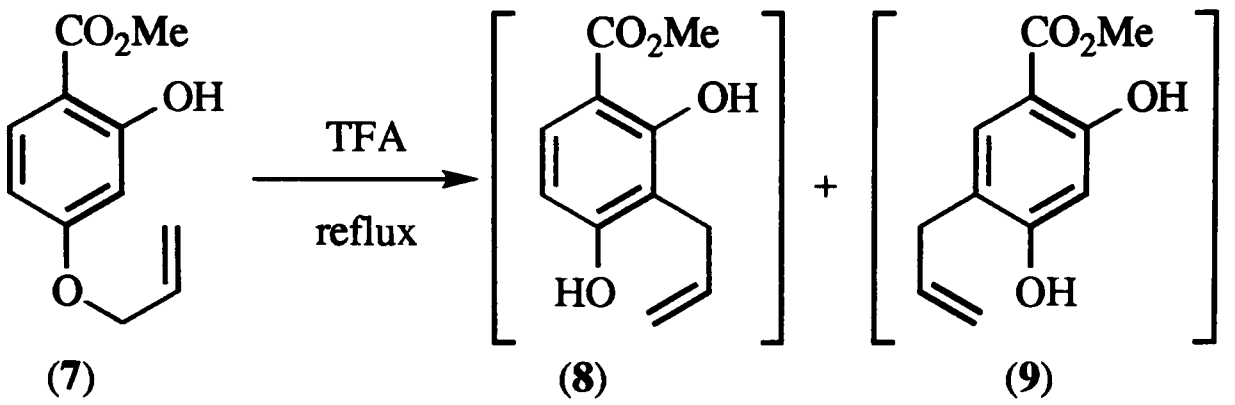
Initial studies were carried out on the applicability of regioselective Claisen rearrangements on a pyridine substrate with a view to the construction of novel 2-substituted pyridines. Work within the group has shown that for benzene-type systems, regiospecific rearrangement depended on the electrostatic influence of various groups attached to the ring.[3] Acid catalysed Claisen rearrangement on methyl 5-allyloxy-2-hydroxybenzoate (**2**) in refluxing TFA occurred with high regioselectivity giving rearrangement only to the sterically disfavoured *ortho*-position yielding the intermediate (**3**) which resulted in the products (**4**) and (**5**). No rearrangement to the intermediate (**6**) occurred with this substrate (**Scheme 1**).



Scheme 1

The orientation of the rearrangement was thought to be influenced by the group *meta* to the allyloxy substituent. In the above case, this was the ester group. It exerted an inductive electron withdrawing effect on the ring system and as a result, rearrangement occurred to the sterically most hindered site.

By exchanging the hydroxyl and ester groups, as in methyl 4-allyloxy-2-hydroxybenzoate (**7**), rearrangement resulted in a preference for the sterically least hindered adduct (**9**) of the two isomeric Claisen products. Therefore, the trifluoroacetic acid catalysed rearrangement of (**7**) resulted in 1.0 : 2.9 mixture of (**8**) to (**9**) (**Scheme 2**).[3]



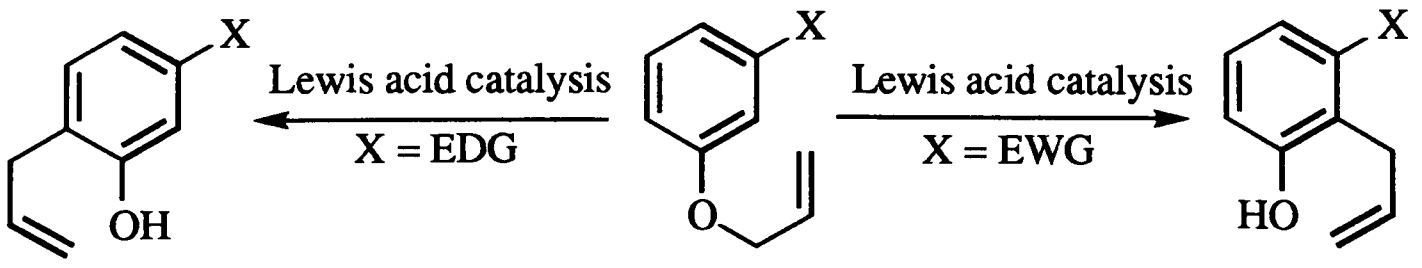
(7) **(8)** **(9)**

1.0 : 2.9

Scheme 2

In this instance, the *meta* group was hydroxyl which, although it exerted an inductive electron withdrawing effect, this was weaker than the electron donation due to the mesomeric contribution of electrons into the π-system. The overall effect was therefore electron donation.

When the *meta* group (X) of (**10**) was electron withdrawing (EWG), rearrangement was seen to occur preferentially to the sterically hindered *ortho*-position to yield (**11**), but when it was electron donating (EDG), rearrangement occurred to preferentially give the least hindered *ortho*-substituted product (**12**) (**Scheme 3**).

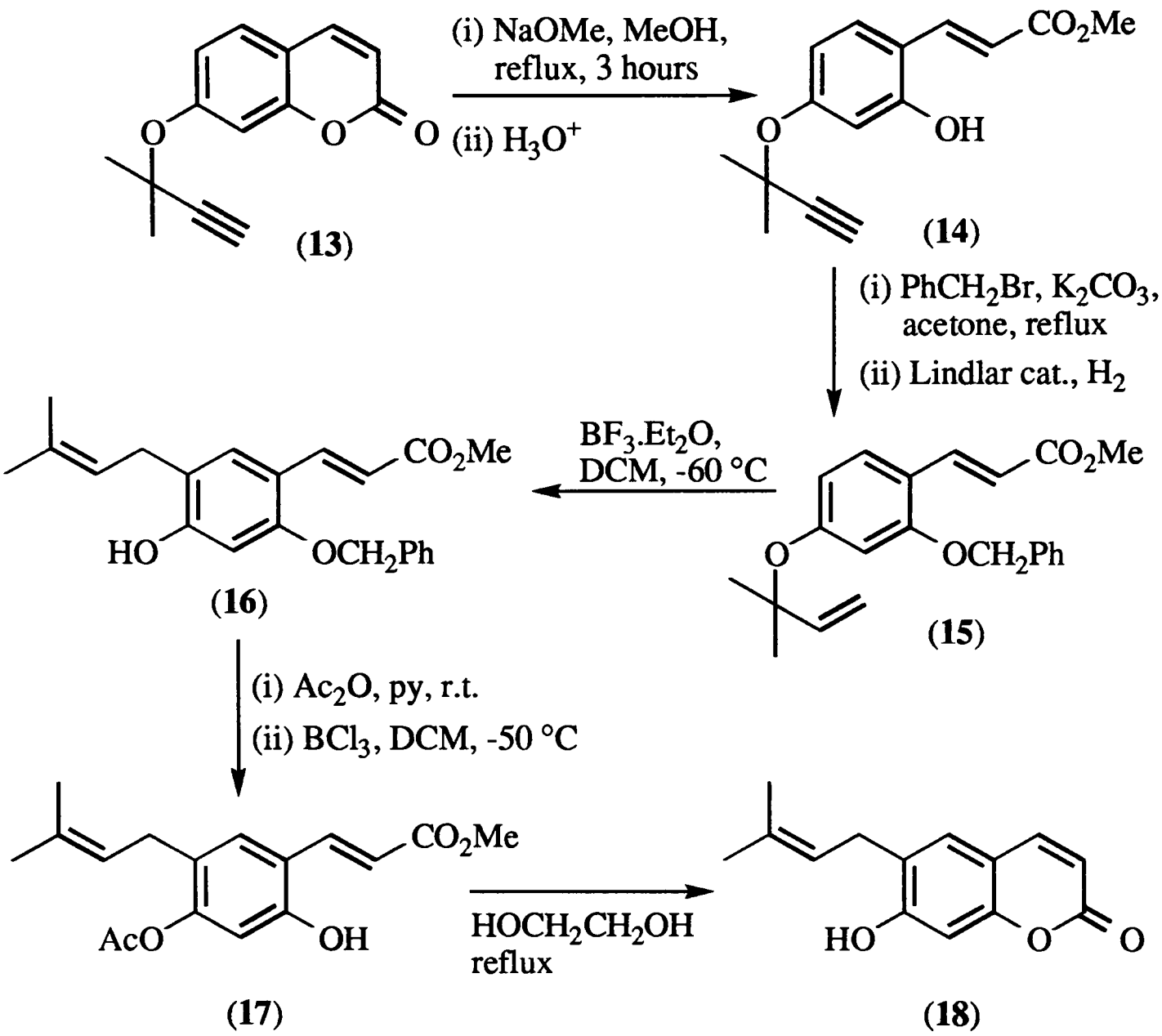


(12) **(10)** **(11)**

Scheme 3

Knowledge of the type of regioselectivity that could be achieved allowed this methodology to be developed by Harwood in the construction of a range of biologically interesting coumarins *via ortho*-Claisen rearrangements.[4] Synthesis of the linear coumarin intermediate demethylsuberosin (**18**) was accomplished after the

Lewis acid catalysed Claisen rearrangement of methyl 2'-benzyloxy-4'-(1,1-dimethylallyloxy)cinnamate (**15**) with boron trifluoride-etherate (**Scheme 4**).



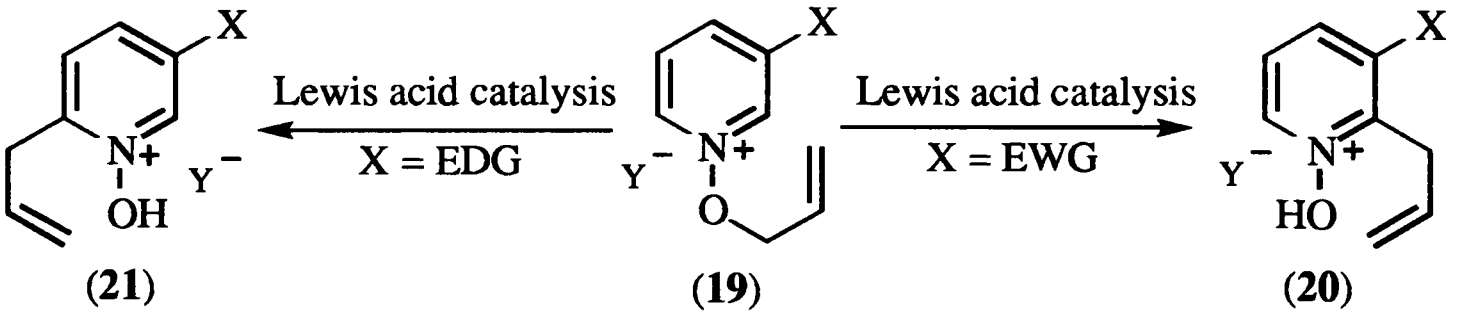
Scheme 4

Claisen rearrangement on 7-(1,1-dimethylallyloxy)coumarin would result in formation of the sterically hindered undesired adduct, hence it was necessary to change the electronics of the aromatic ring, which was achieved by lactone cleavage. This could not be carried out on the 7-(1,1-dimethylallyloxy)coumarin as it resulted in Claisen rearrangement to the wrong isomer before lactone cleavage. Starting with the propynylic ether (**13**) allowed lactone cleavage and after reduction of the triple bond, the desired Claisen rearrangement could occur, catalysed by boron trifluoride-etherate. It was, however, necessary to protect the hydroxyl function before reduction of the triple bond and this was achieved by formation of the benzyl ether (**15**). After

Claisen rearrangement, removal of the benzyl ether group was achieved with boron trichloride following acetylation of the new hydroxyl function, since attempted hydrogenolysis of the benzyl ether resulted in cyclisation of the *ortho*-hydroxyl group onto the prenyl side chain. Cyclisation to generate the coumarin was effected with concomitant deacetylation in refluxing ethylene glycol to yield the desired demethylsuberosin (**18**).

1.3.1 Initial Aim of Project

Initial investigation of the applicability of the Claisen rearrangement when applied to pyridine substrates would involve preparation of the allyloxy species (**19**). It was hoped that such pyridines would undergo Claisen rearrangement in a stereospecific manner to yield either (**20**) or (**21**) (**Scheme 5**).



(**21**) (**19**) (**20**)

Y^- = anion

Scheme 5

Unfortunately, preliminary studies, described in Chapter 2, did not prove to be very encouraging and a diversion was made to investigate the suitability of the [3+2] cycloaddition when applied to pyridine *N*-oxide substrates.

A review of some of the developments within the field of [3+2] cycloadditions of both aromatic and non-aromatic 1,3-dipoles will follow.

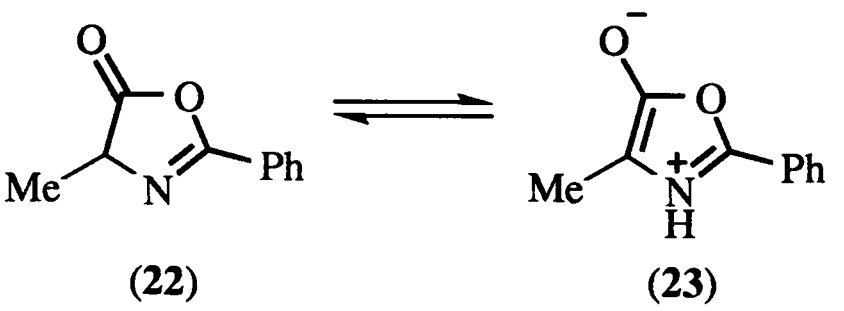
1.4 [3+2] Dipolar Cycloaddition Reactions with Non-Aromatic 1,3-Dipoles

1.4.1 Introduction

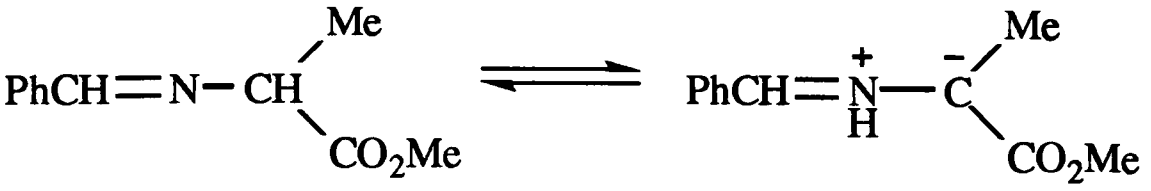
Since the general concept of the 1,3-dipolar cycloaddition was fully recognised by Huisgen in the early 1960's,[5] the [3+2] cycloaddition reaction has developed considerably over the last three decades.[6-9] In recent years it has become a very important ring-forming reaction and many stereochemically pure natural products have been synthesised.[10]

1.4.2 Examples of Dipoles Used

Early work of Huisgen, together with that of Grigg, demonstrated the wide range of dipoles that could be utilised in this reaction. Huisgen showed that oxazolines such as (**22**) that could undergo [3+2] cycloaddition *via* their mesoionic oxazolium tautomer (**23**)[11] and Grigg performed cycloadditions on imines such as (**24**) which were capable of undergoing [3+2] cycloaddition *via* their azomethine ylid tautomer (**25**) (**Figure 2**).[12]



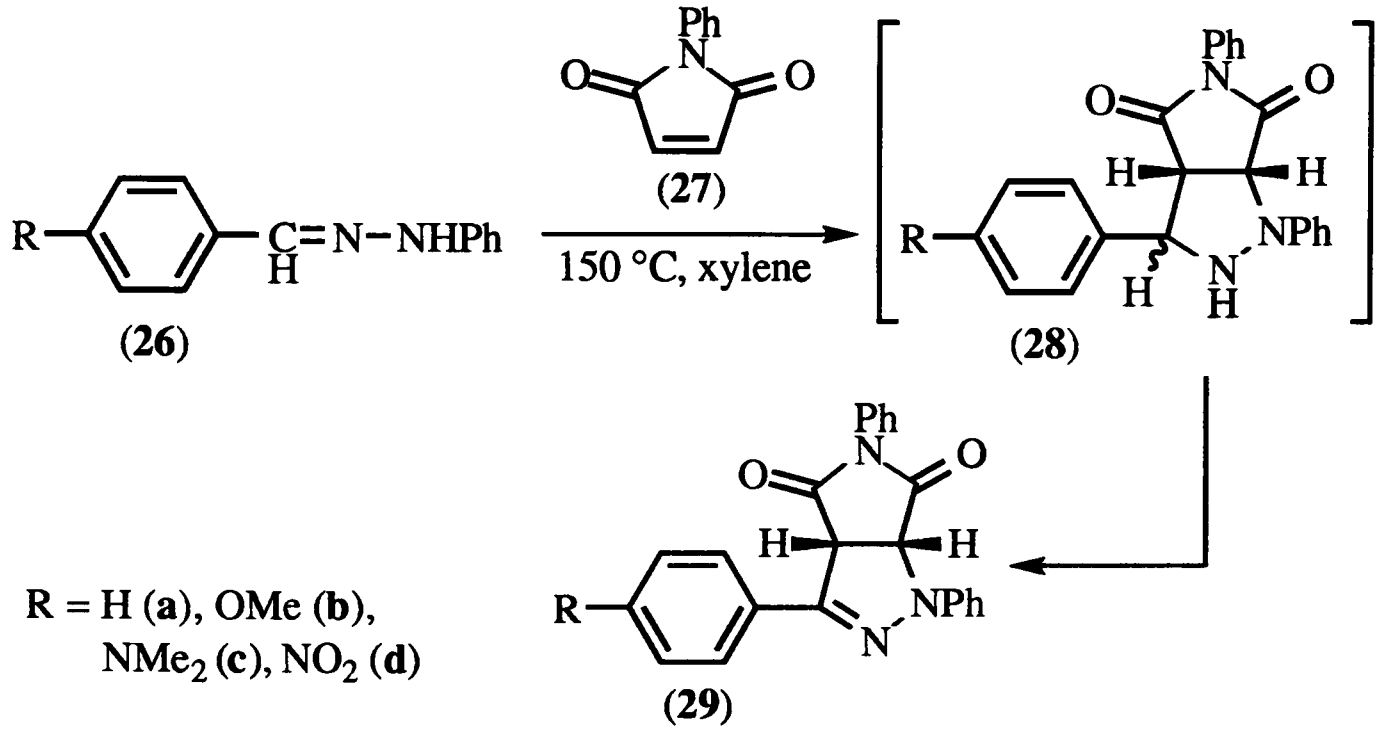
(**22**) (**23**)



(**24**) (**25**)

Figure 2

Grigg also showed that hydrazones (**26**) were capable of undergoing [3+2] cycloaddition with *N*-phenylmaleimide (**27**) to yield pyrazolidines (**28**) which then decomposed to pyrazolines (**29**) (**Scheme 6**).[13]

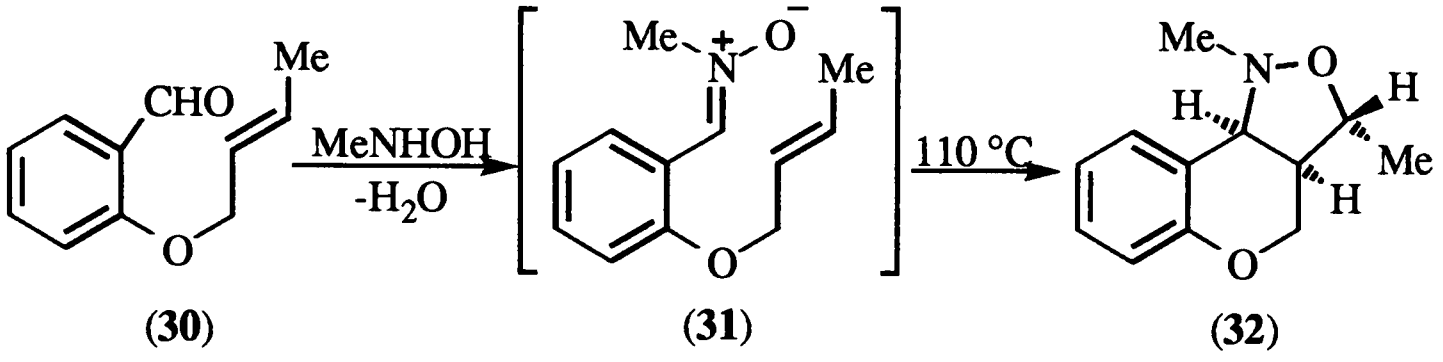


Scheme 6

1.4.3 [3+2] Dipolar Cycloadditions with Nitrones

Using [3+2] dipolar cycloadditions with nitrones, many stereochemically pure pyrrolidine natural products, for example, have been synthesised.[10]

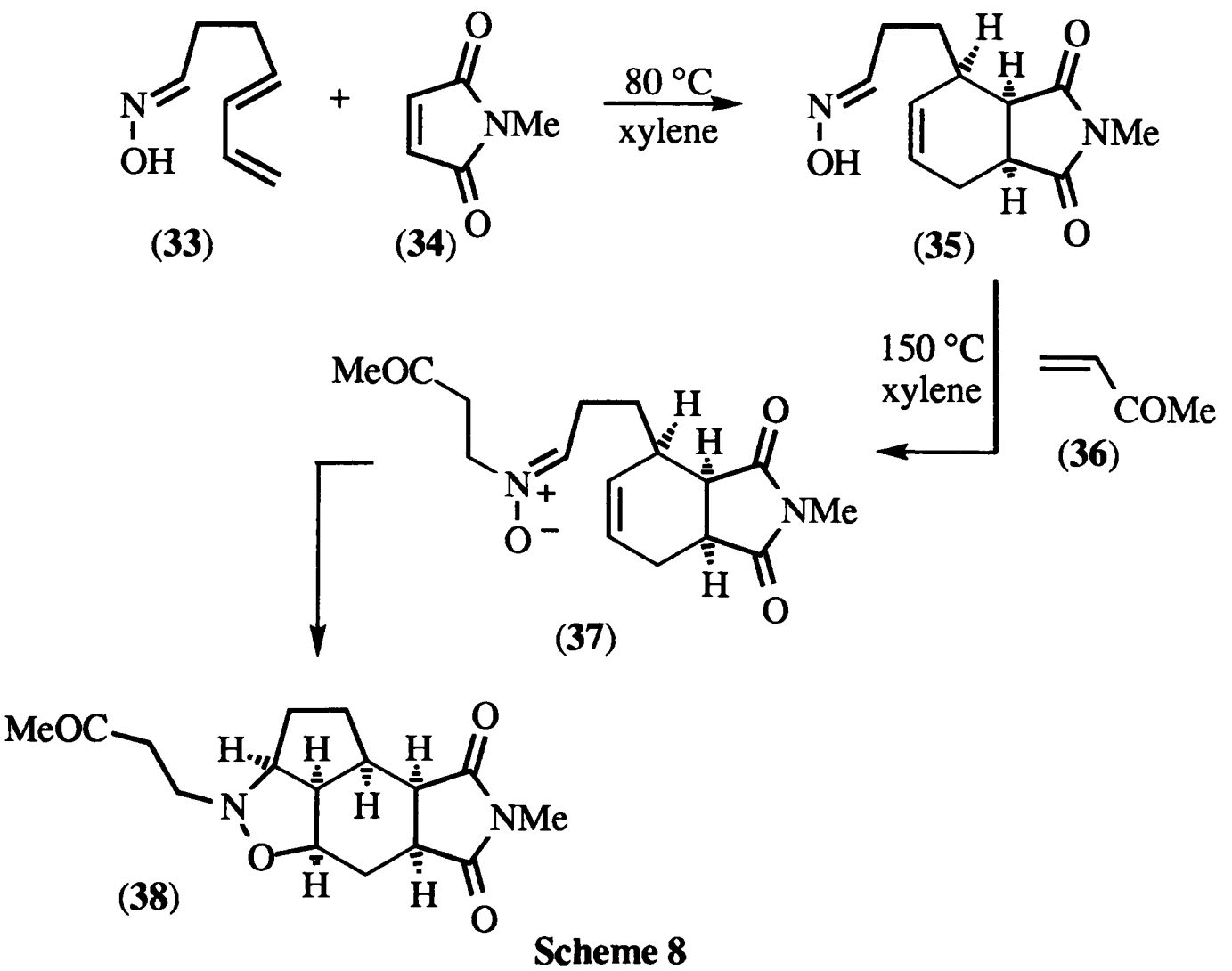
Oppolzer was responsible for a great deal of the early work on nitrone-olefin cycloadditions for the construction of heterocyclic ring systems. One example is the construction of the isoxazolidine (**32**) by intramolecular [3+2] cycloaddition of the nitrone (**31**). The nitrone (**31**) was formed by reaction of the aldehyde function of (**30**) with methylhydroxylamine and then underwent intramolecular cycloaddition onto the double bond to yield the product (**32**) (**Scheme 7**).[14]



(30) **(31)** **(32)**

Scheme 7

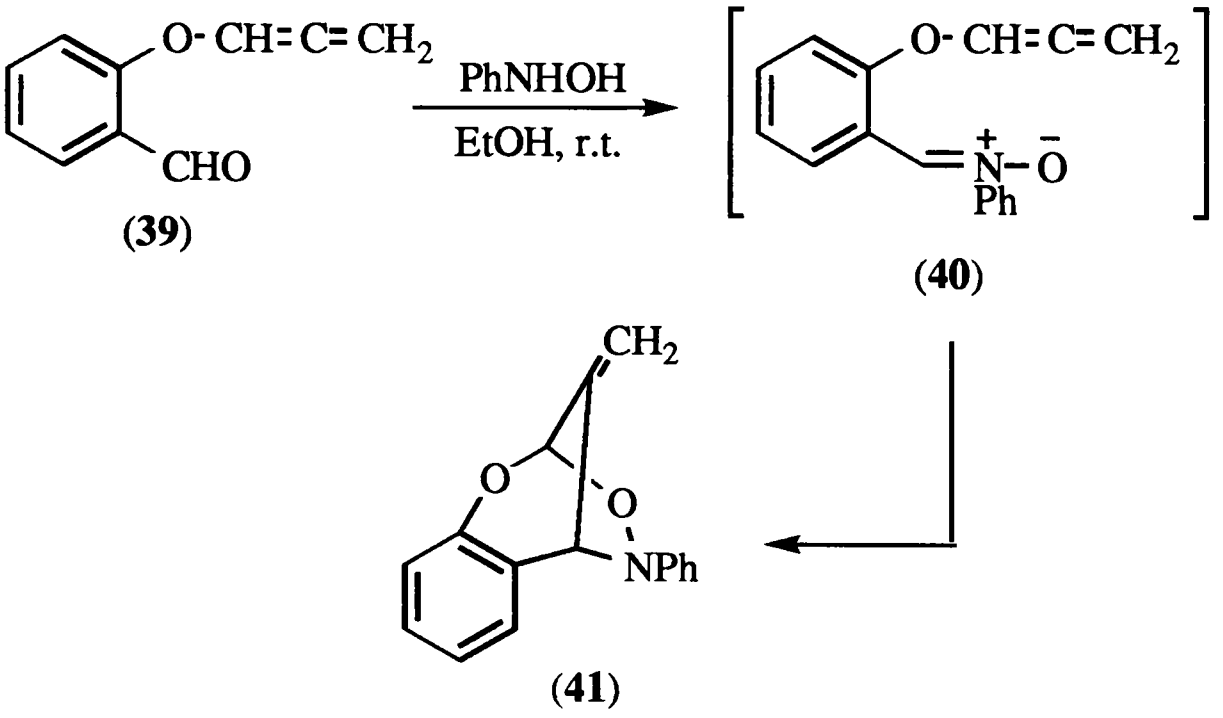
Since then, [3+2] nitrone cycloaddition reactions have been elegantly utilised by both Grigg and Padwa. Grigg's recent work centred upon this cycloaddition reaction in the synthesis of a number of 5-membered heterocycles.[15] The nitrone (**37**) was generated *in situ* by Michael addition of the nitrogen lone pair from the oxime to the electron deficient double bond of (**36**). He in fact used this [3+2] reaction as part of a tandem sequence involving a preliminary Diels-Alder reaction between the diene oxime (**33**) and *N*-methylmaleimide (**34**) in xylene at 80 °C, followed by addition to the Michael acceptor, methyl vinyl ketone (**36**) when the temperature was raised to 140 °C. The resultant nitrone intermediate (**37**) underwent subsequent intramolecular [3+2] cycloaddition yielding (**38**) in 60 % yield (**Scheme 8**).



(33) **(34)** **(35)** **(36)** **(37)** **(38)**

Scheme 8

Padwa recently demonstrated the scope of the [3+2] cycloaddition by effecting the intramolecular dipolar cycloaddition reaction between nitrones and both allenes and alkynes.[16] Allenes generally are unreactive as dipolarophiles but this was overcome by making the reaction occur in an intramolecular sense thus enhancing the reactivity. The stereoselectivity of attack at one position of the allene over the two possible sites should also have increased by virtue of the reaction occurring in an intramolecular manner. Intramolecular [3+2] cycloaddition reaction of the intermediate nitrone (**40**), formed from *o*-(1,2-propadienyloxy)benzaldehyde (**39**) and phenylhydroxylamine, was made to occur in ethanol at room temperature yielding only the bridged system dioxazabicyclo[3.2.1]octene (**41**) in 84 % yield. Lack of formation of the fused product was accounted for by the greater orbital overlap available and the minimisation of non-bonded interactions in construction of the bridged system (**Scheme 9**).

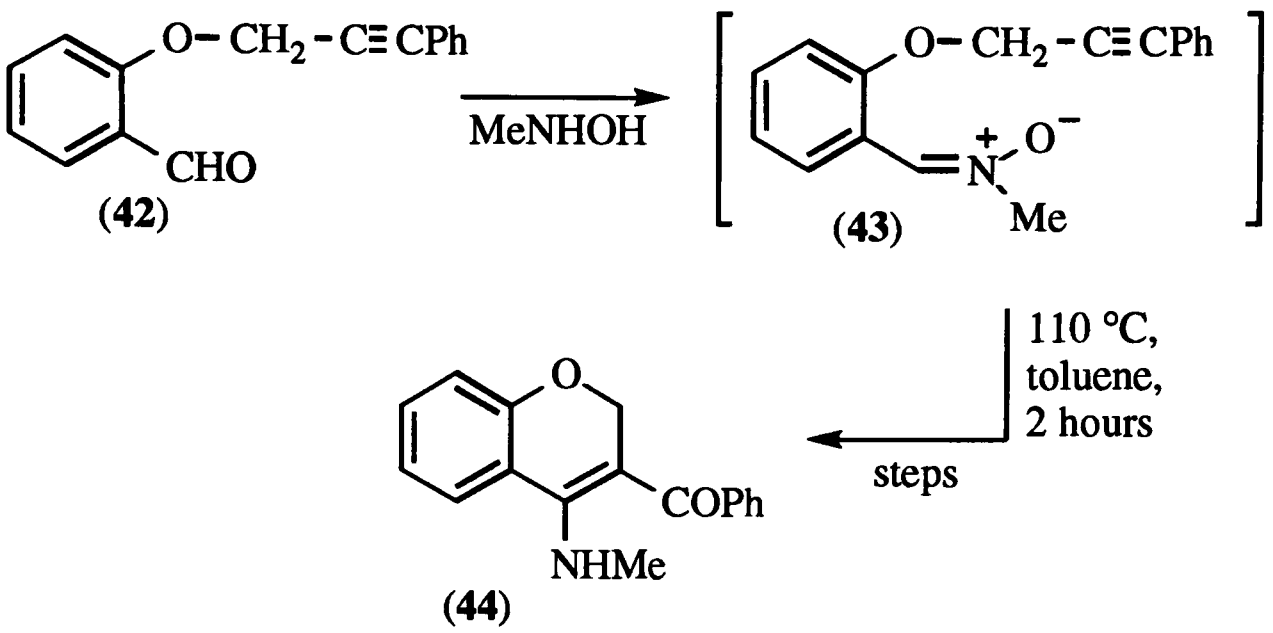


(**39**) (**40**) (**41**)

Scheme 9

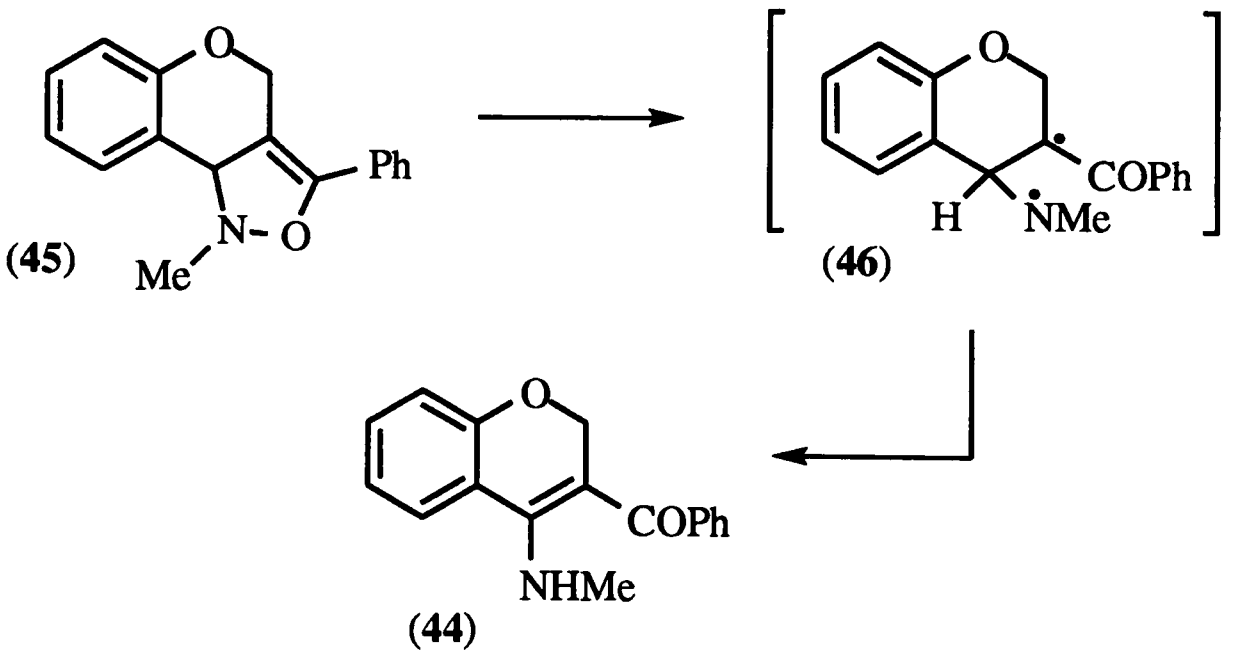
Padwa's investigation of nitrone-alkyne cycloaddition revealed a number of possible decompositions from the transient intermediate (**45**), formed by the cycloaddition reaction.[16] For the reaction of methylhydroxylamine with 2-(3-phenyl-2-propynyloxy)benzaldehyde (**42**), the nitrone (**43**) was formed and the cycloaddition

proceeded to yield 60 % of 3-benzoyl-4-*N*-methyl-amino-2*H*-1-benzopyran (**44**) as the final product (**Scheme 10**).



Scheme 10

Padwa proposed a possible radical decomposition of the 4-isoxazoline (**45**) which was the intermediate formed after cycloaddition. N-O bond cleavage produced the diradical (**46**) and subsequent [1,2]-hydrogen shift yielded the product (**44**) (**Scheme 11**). However, the isomerisation of (**45**) to (**44**) could also follow an acid catalysed pathway.

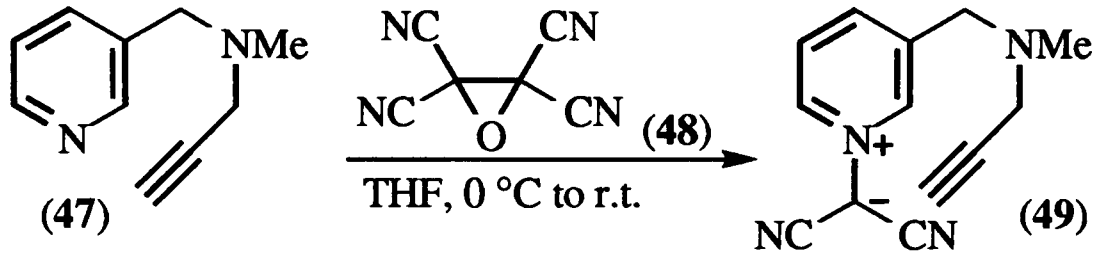


Scheme 11

1.5 [3+2] Dipolar Cycloaddition Reaction with Pyridinium Ylids

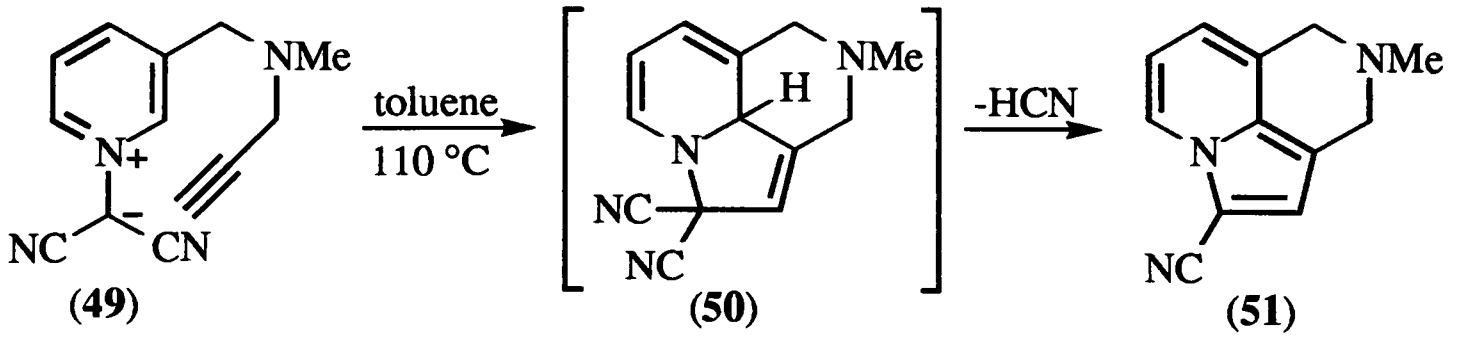
1.5.1 Pyridinium *N*-Dicyanomethylide

Since its first preparation by Linn in 1965,[17] pyridinium *N*-dicyanomethylide has been used in the synthesis of many indolizine derivatives in [3+2] cycloaddition reactions.[18-29] One example was the synthesis of a pyrido[hi]indolizine (**51**) by Noguchi.[30] A pyrido[hi]indolizine is basically an indolizine fused onto a piperidine ring. It was necessary to prepare the cycloaddition precursor, *N*-dicyanomethylide (**49**) which was achieved by reaction of the 3-substituted pyridine (**47**) with tetracyanoethylene oxide (**48**) in THF (**Scheme 12**).



Scheme 12

The dicyanomethylide (**49**) was subsequently heated in toluene to 110 °C for 2 hours under an inert atmosphere. Isolation of the primary cycloadduct (**50**) was not possible as it readily extruded a mole of hydrogen cyanide to yield the 2-cyano-8-methyl-8,9-dihydro-7*H*-pyrido[3,4,5-hi]indolizine (**51**) in 91% yield (**Scheme 13**).



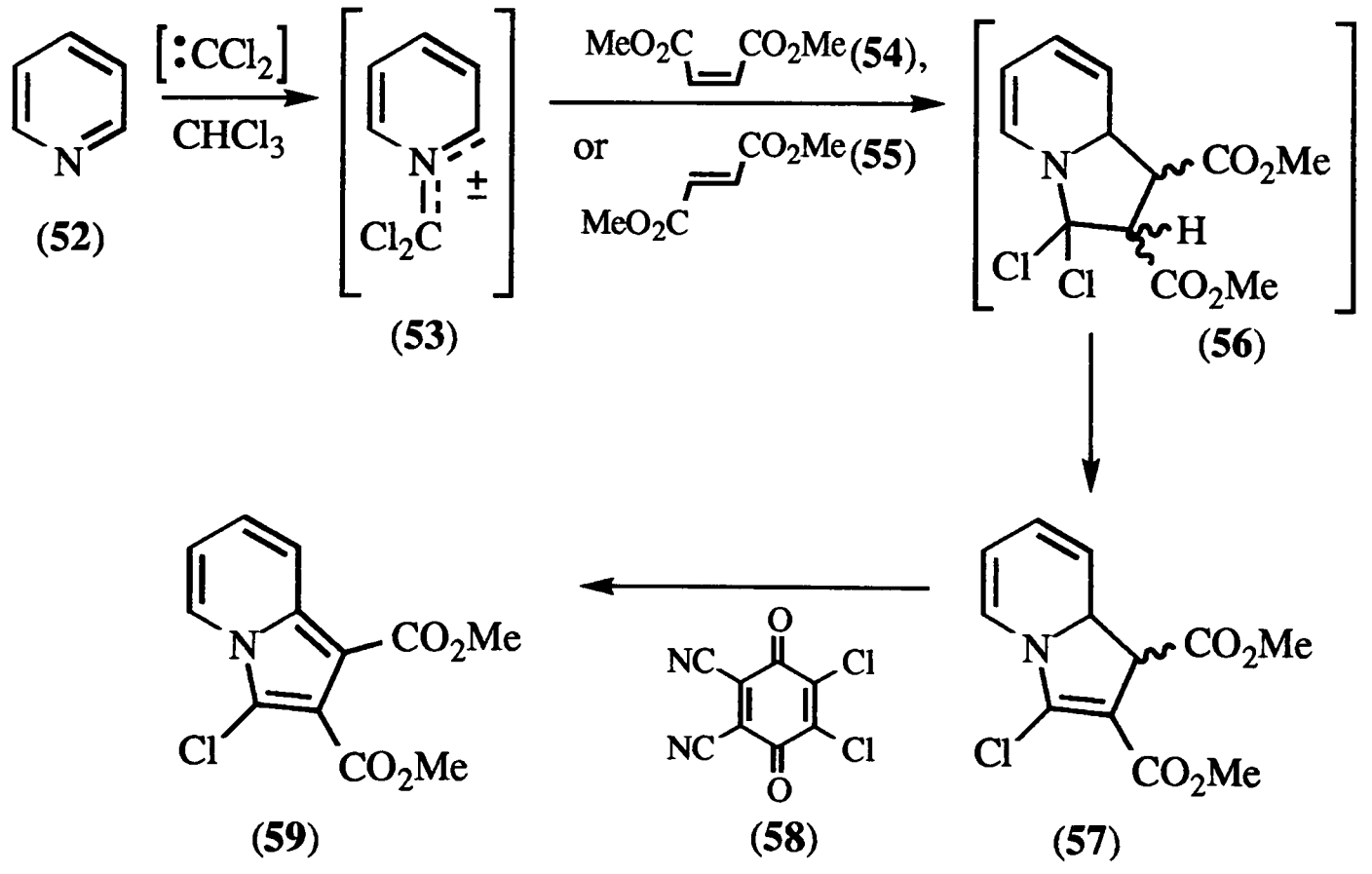
Scheme 13

The reactivity was enhanced by the intramolecular nature of the reaction and the extrusion of one mole of hydrogen cyanide and the pyridinium

N-dicyanomethylide unit added easily to the unactivated acetylenic bond. The reaction was not hindered by the attachment of a methyl group on the end of the triple bond and yielded the 1-alkylated pyrido[hi]indolizine product.

1.5.2 Cycloimmonium Ylids

When pyridine (**52**) was reacted with dichlorocarbene, which was formed by the thermal decomposition of sodium trichloroacetate in the presence of benzyltriethyl ammonium chloride in chloroform, the ylid (**53**) was generated. The ylid could undergo [3+2] cycloaddition with dimethyl maleate (**54**) and fumarate (**55**) to yield the primary cycloadducts (**56**). Subsequent dehydrochlorination gave the dihydroindolizines (**57**). Although a different stereoisomer resulted when maleate (**54**) was used rather than fumarate (**55**), conversion of (**57**) to the required substituted indolizine, which was achieved by oxidation with 2,3-dichloro-5,6-dicyanoquinone (**58**), gave the same product (**59**) (**Scheme 14**).[31]



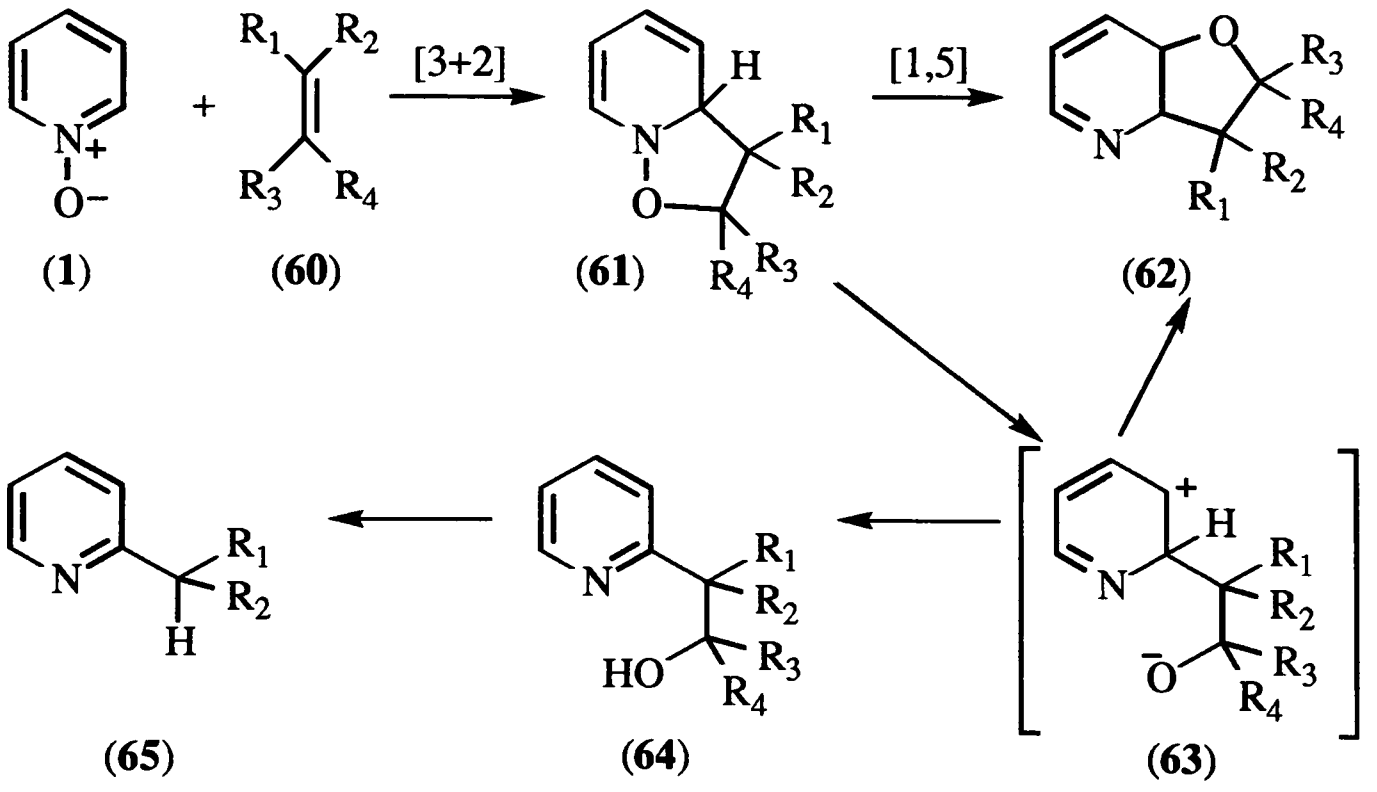
Scheme 14

1.6 [3+2] Dipolar Cycloaddition Reaction between Aromatic *N*-Oxides and Alkenes, Cumulenes and Heterocumulenes

1.6.1 General Characteristics of the [3+2] Dipolar Cycloaddition Reaction

As previously discussed, the higher reactivity of aromatic *N*-oxides, in comparison with the straightforward aromatic bases, with electrophilic and nucleophilic reagents secured these compounds as very important intermediates in the preparation of pyridine derivatives.[32] Hisano has been responsible for a great deal of work on [3+2] cycloadditions of pyridine *N*-oxides since the early 1970's and also conducted many empirical calculations in order to comprehend fully this fascinating and synthetically useful reaction.

It was helpful to consider first the theoretical [3+2] cycloaddition reaction between an *N*-oxide (**1**), pyridine in this case, with any alkene, cumulene or heterocumulene (**60**) (**Scheme 15**).

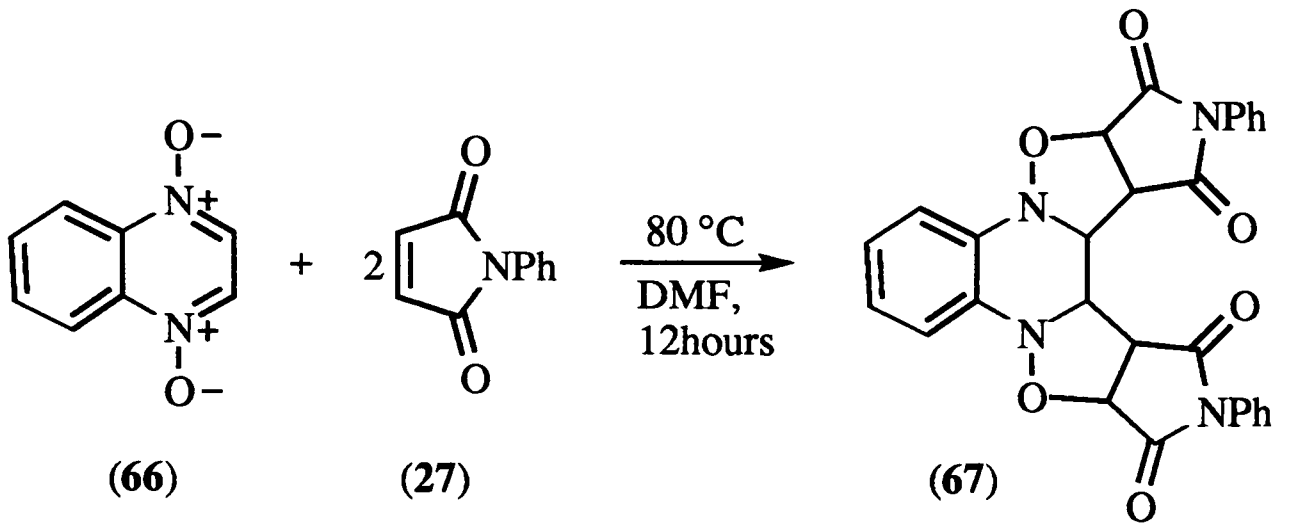


Scheme 15

As seen in Section 1.4.3, most [3+2] dipolar cycloaddition reactions of nitrones with dipolarophiles resulted in the formation of 5-membered isoxazolidine ring systems which tended to be rather stable. In contrast, inclusion of the 1,3-dipole in an aromatic system (pyridine as shown above) tended to make the initially formed primary cycloadduct (**61**) rather unstable to further rearrangement. For cycloaddition to occur, the aromatic system had to be destroyed which led to lower reactivity of the aromatic *N*-oxides compared with the aliphatic. However, once the reaction occurred, the primary cycloadduct (**61**) usually underwent secondary reaction to yield products in which the aromaticity of the heterocyclic ring was restored (**64**) and (**65**) as well as the 2,3-dihydropyridine (**62**). For this reason primary cycloadducts were rarely isolated although it was assumed that they were always formed in the [3+2] addition.

1.6.2 Isolation of Stable Primary Cycloadducts

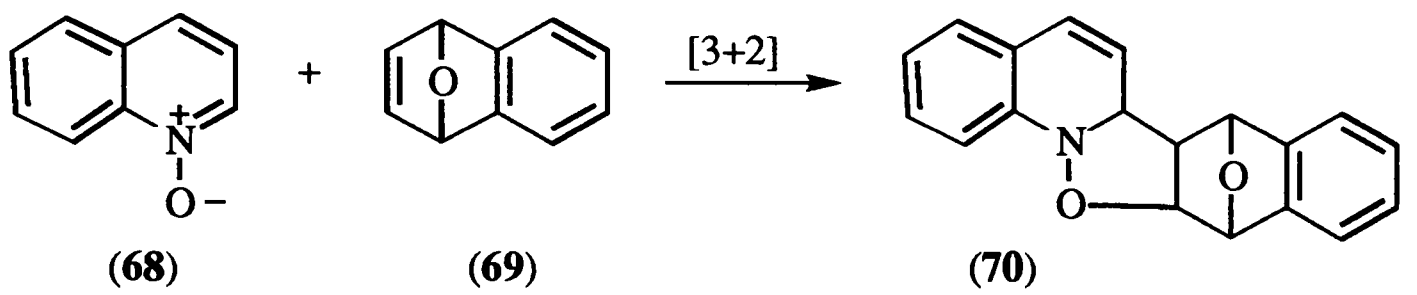
Isolation of primary cycloadducts had only been accomplished in a few cases. These seemed to be in cycloadditions when the 1,3-dipole was contained in a quinoxaline *N*-oxide (**66**) or quinoline *N*-oxide (**68**). It could be postulated that this was due to the lower aromatic stabilisation energy in these structures compared with pyridine *N*-oxide (**1**). The driving force for rearomatisation of these primary cycloadducts was therefore not as great and consequently they could be isolated. Such an example was found to occur in the cycloaddition of two molecules of *N*-phenylmaleimide (**27**) with quinoxaline *N*-oxide (**66**) to give the primary cycloadduct (**67**) (**Scheme 16**).[33]



(66) **(27)** **(67)**

Scheme 16

Wittig and Steinhoff also managed to isolate the primary cycloadduct (**70**) of the [3+2] dipolar cycloaddition reaction between quinoline *N*-oxide (**68**) with 1,4-epoxy-1,4-dihydronaphthalene (**69**) (**Scheme 17**).[34]



(68) **(69)** **(70)**

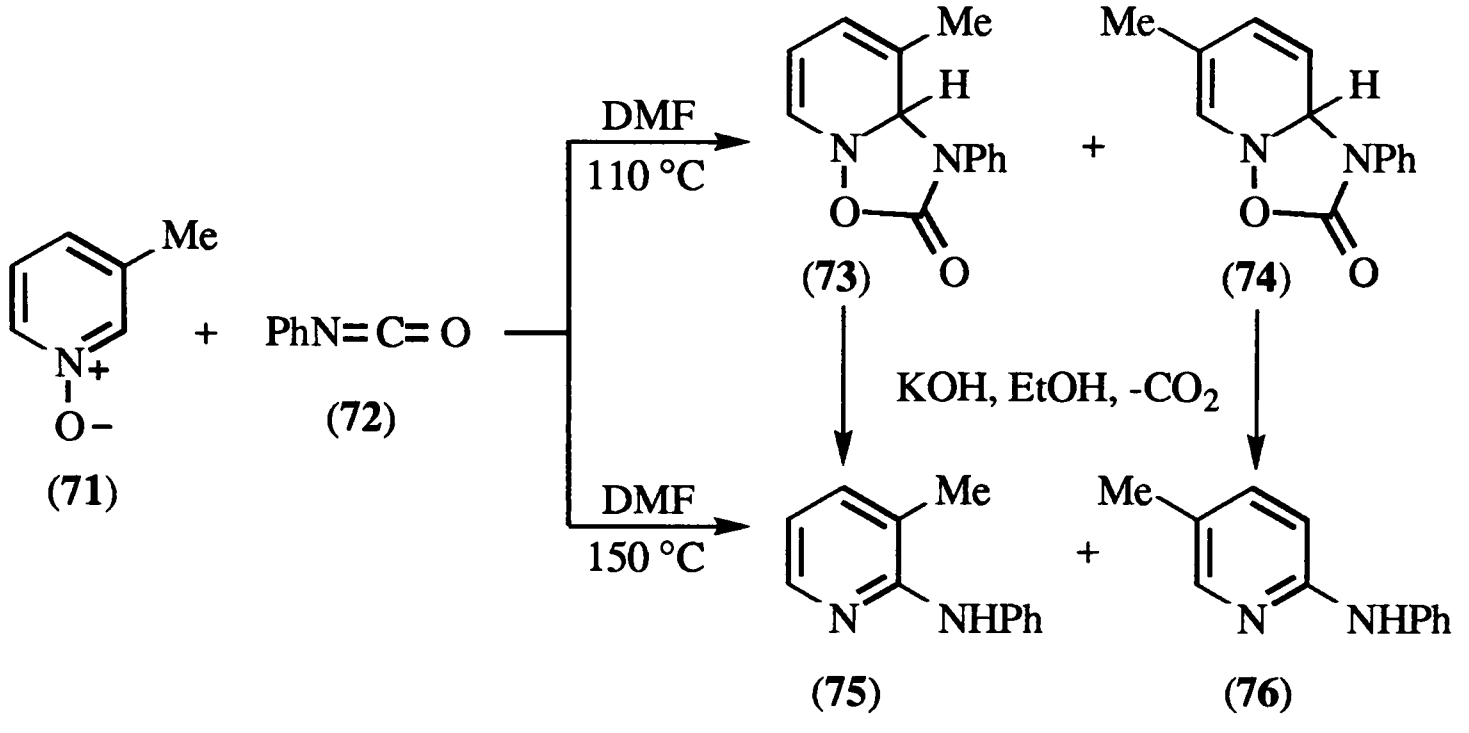
Scheme 17

This reaction raised another question involving more than the simple aromatic stabilisation energy. It was thought to proceed with inverse electron demand of both *N*-oxide substrate (**68**) and dipolarophile (**69**) which will be discussed in Section 1.6.3.4.

1.6.3 Hisano's Work on [3+2] Cycloaddition Reactions of Pyridine *N*-Oxides

Hisano's initial studies were carried out upon the [3+2] cycloaddition of 3-methylpyridine *N*-oxide (**71**) and phenyl isocyanate (**72**). At 150 °C in DMF, the products isolated were the 2-anilino derivatives (**75**) in 30 % yield and (**76**) in 24 % yield, but at the lower temperature of 110 °C, two products were isolated that were

initially assumed to be the primary cycloadducts, namely the 1,2-dihydropyridine species (**73**) in 34 % yield and (**74**) in 24 % yield. These products could be converted into the corresponding 2-anilino species (**75**) and (**76**) respectively, by refluxing in ethanolic potassium hydroxide (**Scheme 18**).[35]



Scheme 18

It was not until some 5 years later that Hisano realised that the products from the cycloaddition at 110 °C in DMF were in fact 2,3-dihydropyridines formed by a [1,5] rearrangement of the primary cycloadducts (**73**) and (**74**). So from the above reaction (**Scheme 18**), the products that resulted were (**77**) and (**78**) (**Figure 3**).[36]

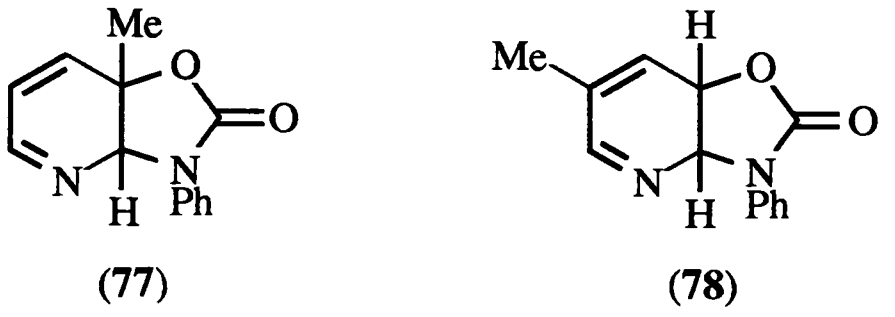


Figure 3

Both these products were found to be stable to heating in DMF to 150 °C with no expulsion of carbon dioxide.

Similar studies between the reaction of pyridine *N*-oxide (**1**) with phenyl isothiocyanate have been attempted by Huisgen who isolated only the 2-aminopyridine.[37] However, attempts by Hisano to make use of this dipolarophile with 3-methylpyridine *N*-oxide (**71**) in DMF at 110 °C for 7 hours resulted in deoxygenation to give 3-methylpyridine in 80 % yield.[35]

1.6.3.1 Solvent and Temperature Effects

Various studies followed these results to see how substitution of the pyridine ring in the *N*-oxide and phenyl group in the isocyanate affected the type of products isolated and the yields of these products, as well as the stereoselectivity of reaction. Reaction conditions, solvent and temperature dependence were also investigated.

The yield of the [3+2] cycloaddition reaction between 3-methylpyridine *N*-oxide (**71**) and phenyl isocyanate (**72**) was found to be largely solvent independent but very temperature dependent. Change of the solvent from DMF to DMSO and dioxan therefore, did not change the orientation of reaction and hardly affected the product yields (**Table 1**).[38]

Solvent§	**Reaction Temperature**	**Yield of (77)**	**Yield of (78)**
DMF	110 °C	34 %	24 %
DMSO	110 °C	25 %	16 %
dioxan	reflux	23 %	11 %

§ For reaction of 3-methylpyridine *N*-oxide (**71**) and phenyl isocyanate (**72**)

Table 1

The lower boiling solvents such as diethyl ether, benzene and chloroform at reflux, resulted in no cycloadducts being formed, the exception being benzene where a trace of each 2,3-dihydro derivative was found which indicated the temperature sensitivity of this reaction. The yields of 2,3-dihydro pyridines reached a maximum with two equivalents of phenyl isocyanate after 7 hours at 110 °C in DMF. Longer reaction times led to increased amounts of 2-anilino derivatives as indeed did the increase of temperature to 150 °C in DMSO where these products predominated.

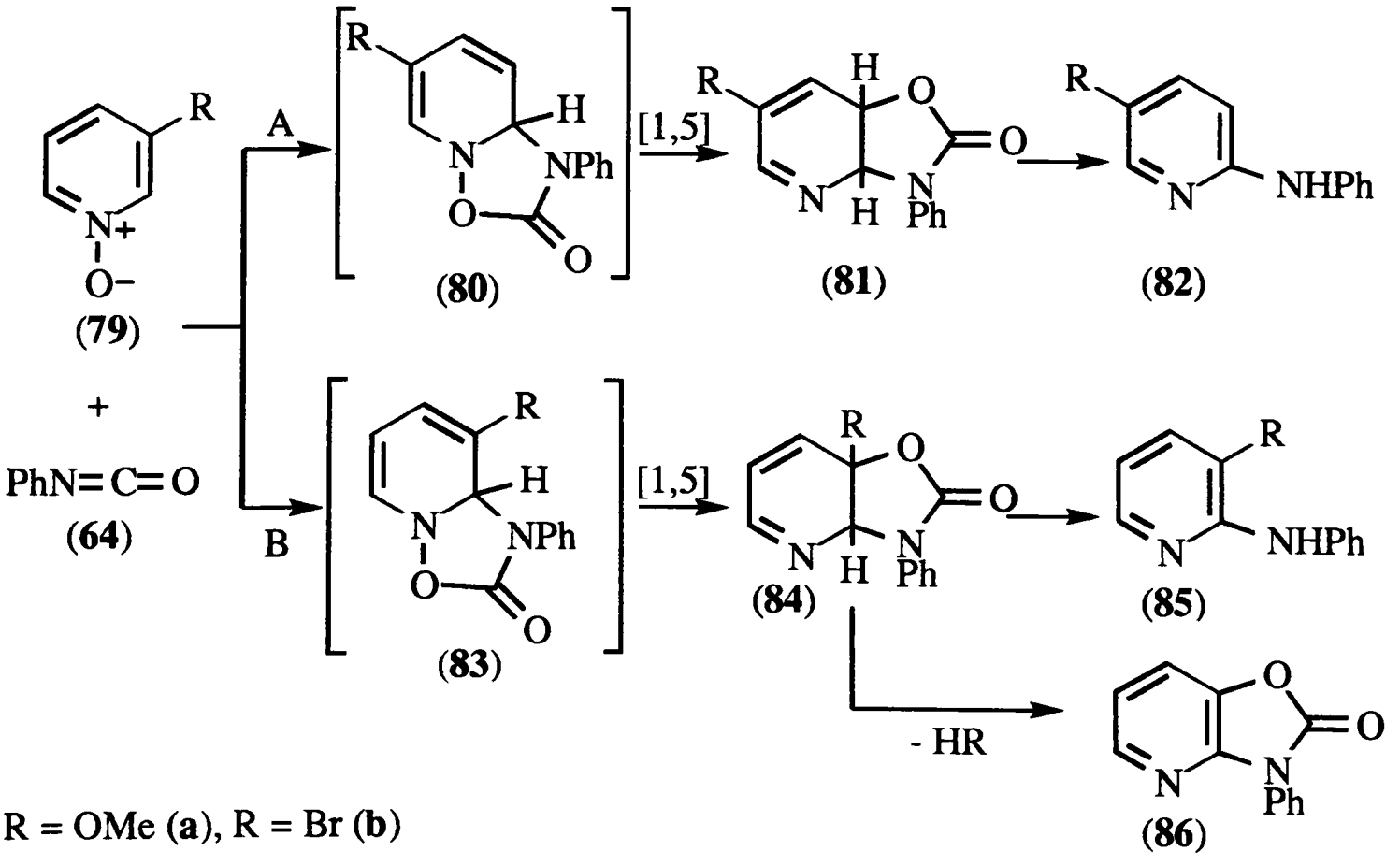
1.6.3.2 Charge Transfer Complexes in the [3+2] Dipolar Cycloaddition Reaction

Although there was very little solvent dependence on the yield of cycloaddition products, a large anomaly was found in the regioselectivity of these products when switching solvents. [39] The reaction between 3-methylpyridine *N*-oxide (**71**) and phenyl isocyanate (**72**) was used as the model. The ratio of products (**78**) and (**77**) (**Figure 3**, page 17) was found to be equal in sulfolane for example, but lay 3 : 1 in favour of the least sterically hindered product (**78**) in 3-methylpyridine as solvent. The ratio of products was not found to be in accord with the polarities of these solvents so another explanation was required. Invoking the possibility of a charge transfer complex could explain this irregularity and UV and NMR spectroscopic data suggested the presence of a charge transfer complex involving dipole and dipolarophile and possibly the solvent in the case of 3-methylpyridine. For example, the ^{1}H NMR spectrum of a mixture of 3-methylpyridine *N*-oxide (**71**) and phenyl isocyanate (**72**) showed a large shift up field in the methyl singlet of the *N*-oxide from δ 2.35 ppm in the parent *N*-oxide (**71**) to δ 2.13 ppm in the complex. The UV spectrum provided further evidence, revealing a maximum at 450 nm for the mixture of 3-methylpyridine *N*-oxide (**71**) and phenyl isocyanate (**72**) which was not equal to the sum of the spectra of the two individual molecules. This suggested that the complexes may have existed only in solution in equilibrium with their components.

1.6.3.3 Substitution of the Pyridine Ring

3-Cyanopyridine *N*-oxide was found to be completely ineffective as a 1,3-dipole as was 3-nitropyridine *N*-oxide and no cycloaddition was seen to occur in either case with a range of phenyl isocyanates under a variety of reaction conditions.[38]

An interesting result was achieved with 3-methoxy and 3-bromopyridine *N*-oxide (**79a** and **79b**). Of course, with unsymmetrical substitution of the pyridine ring, two possible 2,3-dihydropyridine products could result. As previously noted, with the unsymmetrical 3-methylpyridine *N*-oxide (**71**), the 2,3-dihydro species (**77** and **78**) were formed in fairly similar yields.[36] With 3-methoxypyridine *N*-oxide (**79a**), this was found not to be the case and the 3-methoxy substituted derivative (**83a**), produced by Route B, was preferentially formed over the 5-methoxy substituted product (**80a**) which was derived from Route A. A similar, although more pronounced effect, was encountered with 3-bromopyridine *N*-oxide (**79b**) (**Scheme 19** and **Table 2**).[40]



Scheme 19

Compound	R =	Reaction Conditions	Route§ A	Route§ B
(79a)	OMe	DMF / 110 °C	4 %	34 %
(79b)	Br	DMF / 110 °C	5 %	60 %

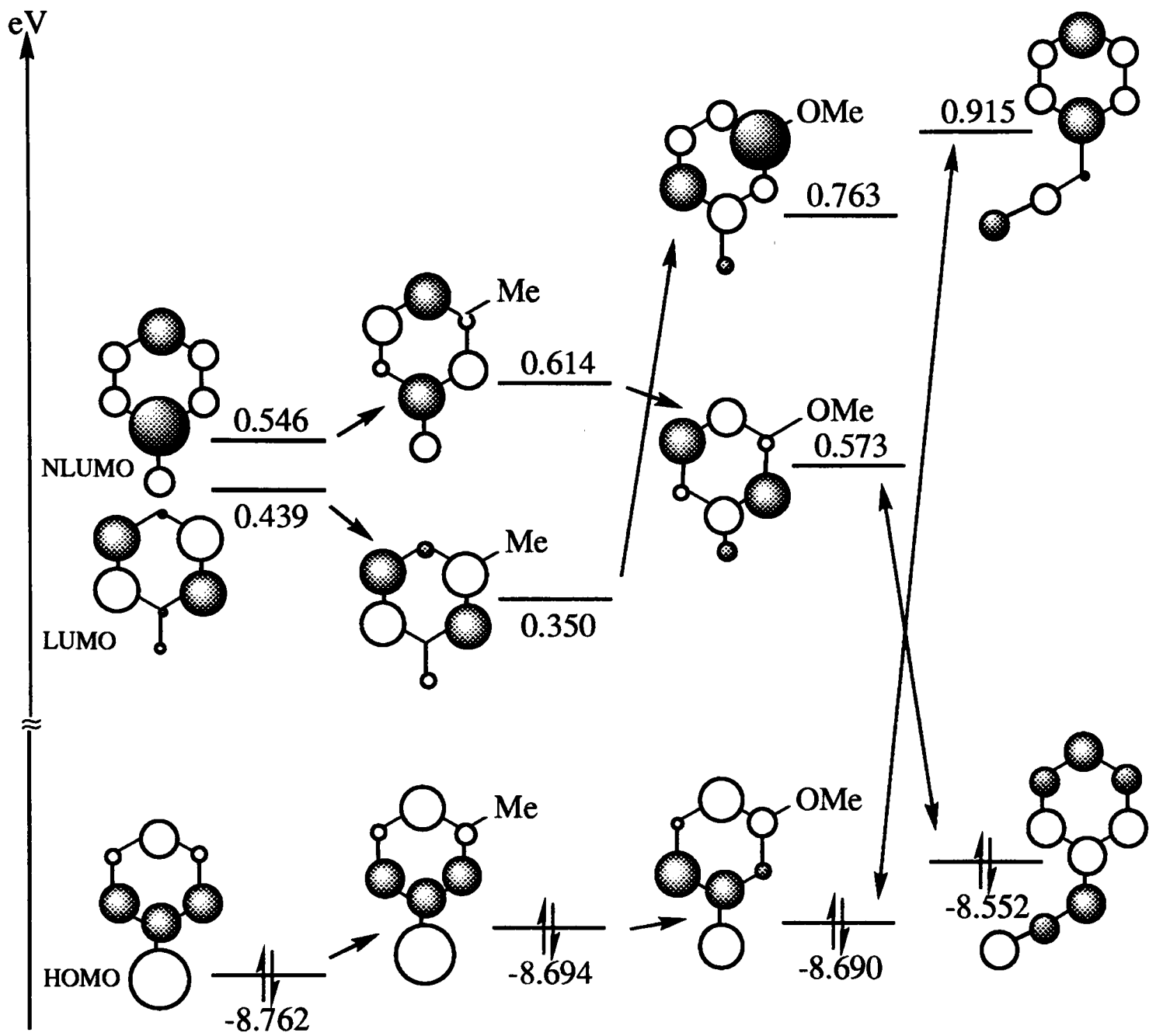
§ determined by gas chromatography

Table 2

To rationalise this result, it was necessary to look at a range of competing factors. For 3-substituted pyridine *N*-oxides there were two different sites for attack. If only the steric constraint of the reaction was considered, then the predominant product in all cases would have been the least sterically hindered adduct derived from attack at C_6 rather than C_2. Since the product ratio was obviously not in agreement with this rationale, it was fair to assume that there was very limited steric constraint. For this reason it was necessary to consider the energetic requirements of the [3+2] cycloaddition reaction.

1.6.3.4 Energy Requirements of the Cycloaddition Reaction

For cycloaddition to occur, the 1,3-dipole of the *N*-oxide must be complimentary in energy consideration to the dipolarophile. Since the electron density of the aromatic *N*-oxide is generally higher than that of the dipolarophile, cycloaddition has normally been shown to proceed *via* the 'usual bonding interaction' for this type of reaction.[40] Hence the HOMO of the *N*-oxide reacts with the LUMO of the dipolarophile in what is assumed to be a concerted process. Since the aromatic nature of the ring system is destroyed on cycloaddition, there needs to be a good HOMO-LUMO interaction between *N*-oxide and dipolarophile in order for the reaction to occur. Consequently, cycloaddition is thought to be facilitated by the presence of electron donating groups attached to the aromatic nucleus of the *N*-oxide which raise the energy of the HOMO and by electron withdrawing groups on the dipolarophile which lower the LUMO's energy thus improving the bonding interaction. It was therefore necessary to investigate the frontier molecular orbitals (FMOs) on both *N*-oxide and isocyanate. Since the frontier orbitals on the pyridine *N*-oxide moiety are higher in energy than those on the parent nitrone, pyridine *N*-oxide should behave as a good donor to general olefins. For isocyanic acid, the HOMO and LUMO are degenerate but attachment of an aryl group as in phenyl isocyanate results in the splitting of these orbitals. The FMO energy difference (i.e. HOMO - LUMO) of pyridine *N*-oxide lies between the FMO levels of phenyl isocyanate, which suggests that both interactions may determine the reactivity and therefore pyridine *N*-oxide could participate in a neutral-type cycloaddition (**Figure 4**).[40]



(1) **(71)** **(79a)** **(72)**

Figure 4

Using Hisano's calculated data for the HOMO's, LUMO's and NLUMO's of 3-methylpyridine *N*-oxide (**71**) and 3-methoxypyridine *N*-oxide (**79a**), it could be seen that the energy of the HOMO did not vary greatly on changing the substitution at the 3-position. This was due to the location of a node on C_3 and C_5 atoms. However, the LUMO was localised at the C_3 and C_5 atoms so replacement of the proton at C_3 by a mesomerically electron donating group greatly destabilised the LUMO and in fact in 3-methoxypyridine *N*-oxide (**79a**), caused a crossover with the NLUMO. The new LUMO now had a node at C_6 so formation of the cycloadduct at C_2 was very favourable. In this case, there also may have been a secondary orbital interaction, that made this approach more favourable (**Figure 5**).

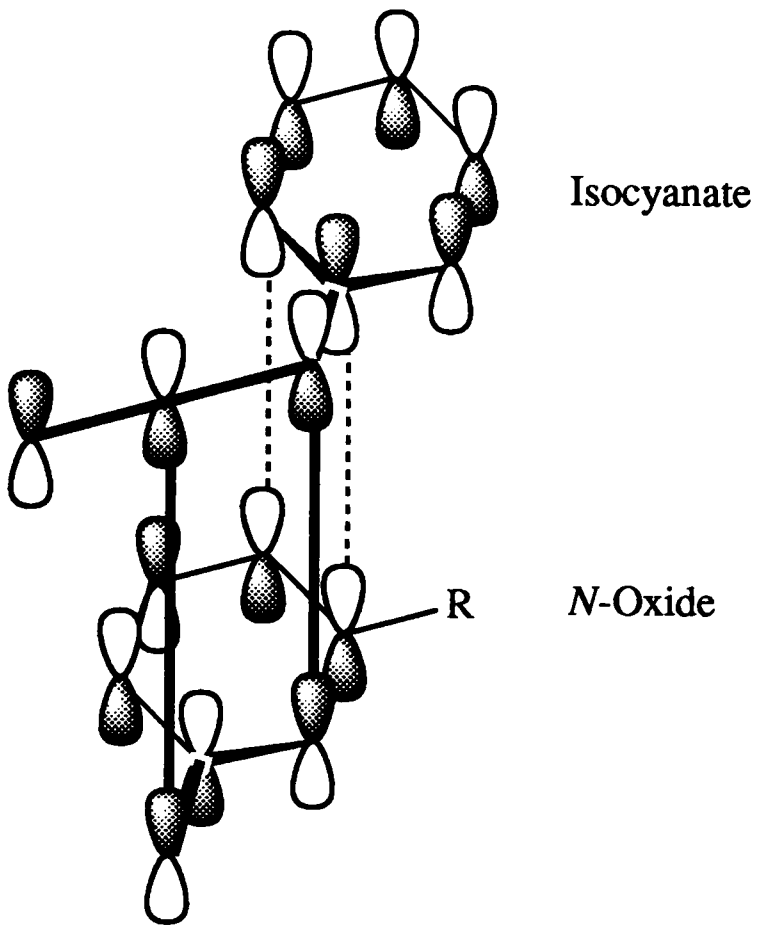


Figure 5

Hisano also reported a [3+2] cycloaddition reaction that he considered to proceed with inverse electron demand, namely the cycloaddition involving 3,5-dibromopyridine *N*-oxide (**87**) using Wittig and Steinhoff's dipolarophile 1,4-epoxy-1,4-dihydronaphthalene (**69**) (**Scheme 20**).[41] He considered this dipolarophile would be suitable as it would behave as an electron donor towards electron deficient pyridine *N*-oxides and has no additional orbitals that could be involved in secondary non-bonding interactions. Hisano calculated the theoretical energies of the HOMO and the NHOMO for the dipolarophile along with the LUMO and the NLUMO for the 1,3-dipole.

For 1,4-epoxy-1,4-dihydronaphthalene (**69**) he calculated a HOMO of -9.33 eV and a NHOMO of -10.08 eV resulting from the destabilising effect of through space interactions between bridge oxygen, alkene and aromatic π-systems. The calculation was also performed on 3,5-dibromopyridine *N*-oxide (**87**) placing its LUMO at -1.174 eV and NLUMO at -1.019 eV (**Figure 6**).

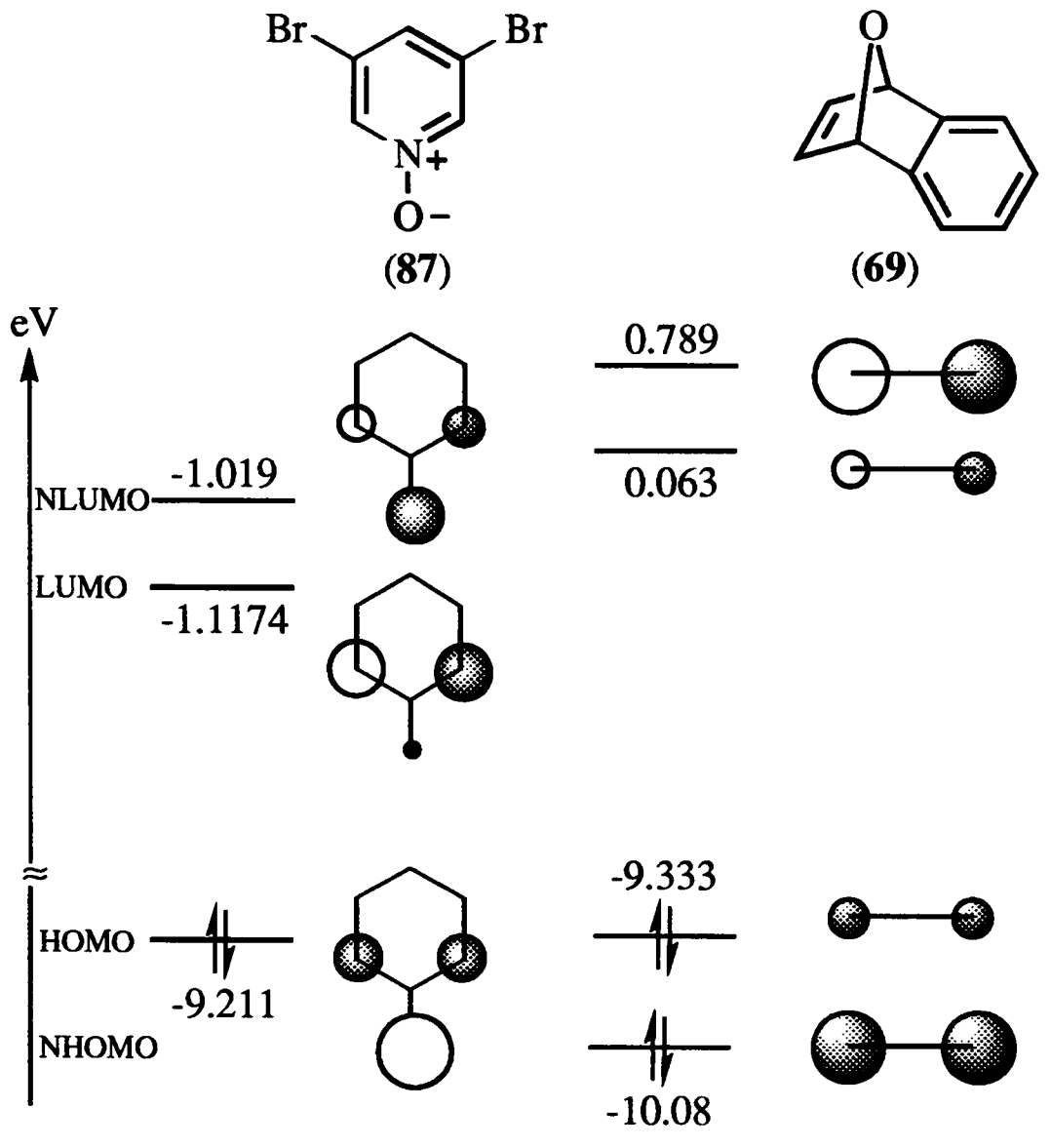
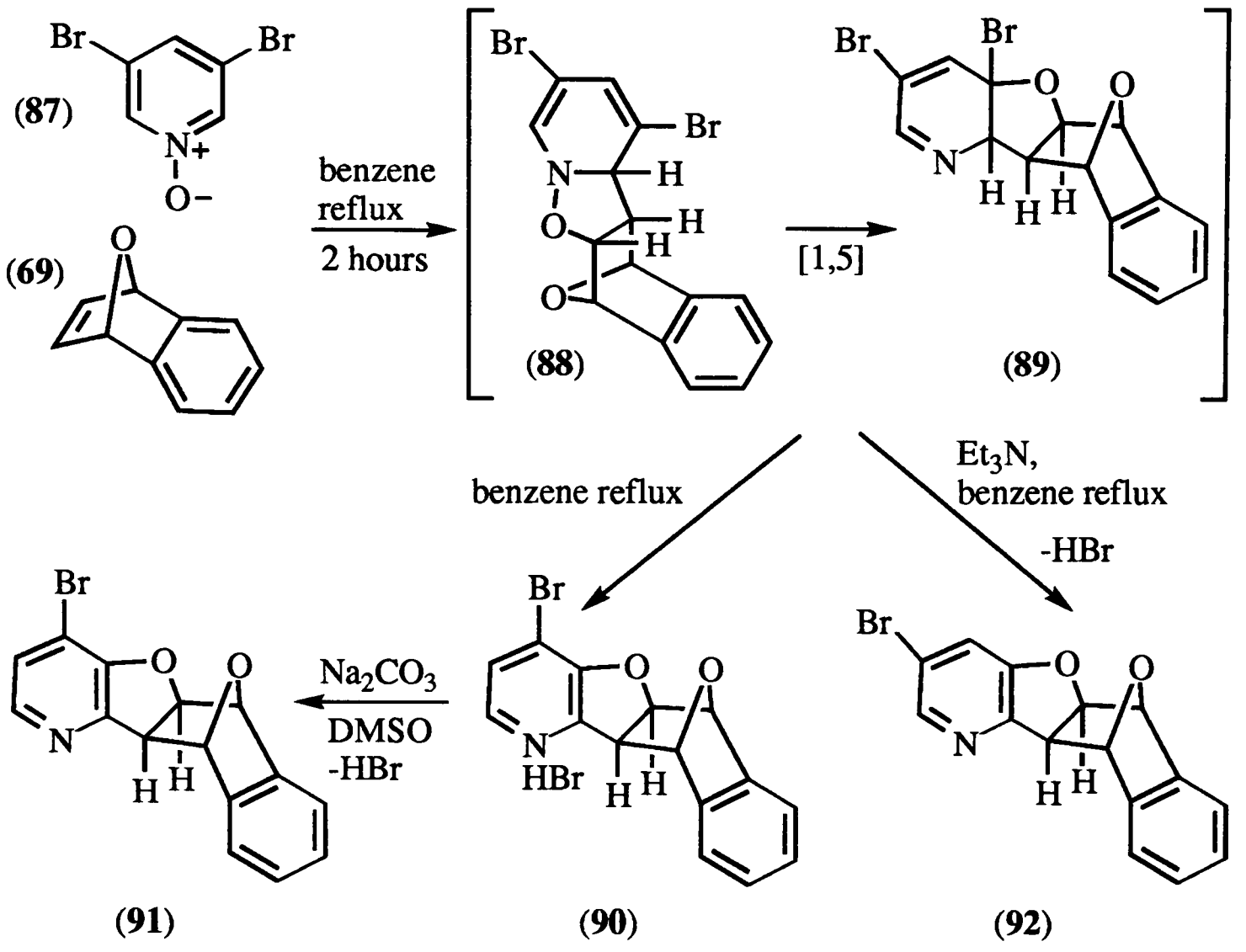


Figure 6

When the reaction was conducted, Hisano found he only isolated the [1,5]-rearranged product (**90**) as the hydrogen bromide salt, not the primary cycloadduct (**88**) or the straightforward [1,5]-rearranged product (**89**) (**Scheme 20**).



Scheme 20

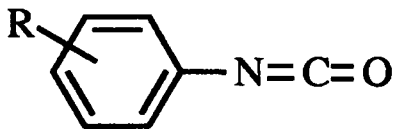
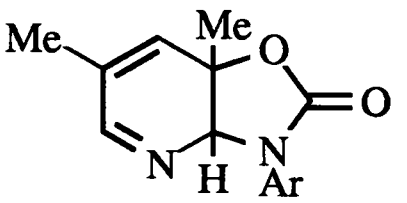
On closer inspection of the NMR spectrum of the product of cycloaddition, Hisano noticed that the α-proton of the aromatic ring had a typical *ortho* coupling constant of *J* 8 Hz suggesting that the bromide had undergone a [1,2]-shift yielding the *para* bromo-substituted pyridine (**90**). The 'free' pyridine (**91**) was liberated by treatment of the hydrogen bromide salt (**90**) with sodium carbonate in DMSO. Conducting the cycloaddition reaction in refluxing benzene in the presence of triethylamine yielded the 'free' *meta* bromo-substituted pyridine (**92**); this time the α-proton had a typical *meta* coupling constant of *J* 1.8 Hz.

FMOs, therefore, were presumed to control the stereochemistry of these reactions. However, these calculations could not account for the apparent unreactivity of 3-cyano and 3-nitropyridine *N*-oxides with varying phenyl isocyanates under differing conditions. Calculation of the FMOs for these substituted pyridines revealed a very low lying LUMO in both cases which would suggest inverse-type cycloaddition behaviour. Hisano therefore had to look for another explanation for this

unreactivity. He was able to account for these anomalous results by invoking what he called 'aromatic stabilisation energy'. In 3-cyano and 3-nitropyridine *N*-oxides, electron delocalisation was expected to be more extensive than in the parent 1,3-dipole since substitution by powerful acceptors caused effective donor-acceptor interaction between the π-systems. In contrast, in 3,5-dimethyl or 3-methoxypyridine *N*-oxides for example, this donor-acceptor interaction did not occur effectively which resulted in destabilisation of the cyclic three-system interaction. Localisation of the electron diminished the aromatic character of the pyridine *N*-oxide and allowed it to act as a reactive 1,3-dipole.[42]

1.6.3.5 Effects of Substitution on the Phenyl Isocyanate

Hisano also undertook a study of how the substitution of the phenyl ring of the isocyanate affected the types and ratios of products obtained in the reaction. For cycloaddition of 3,5-dimethylpyridine *N*-oxide (**104**) with *ortho*-, *meta*-, and *para*-chloro and methyl substituted phenyl isocyanates, the products obtained in every case were the 2,3-dihydro derivatives (**Table 3**).

Substitution of  (R =)	**Yield§ of** 
o-Me	20 %
m-Me	48 %
p-Me	50 %
o-Cl	23 %
m-Cl	48 %
p-Cl	52 %

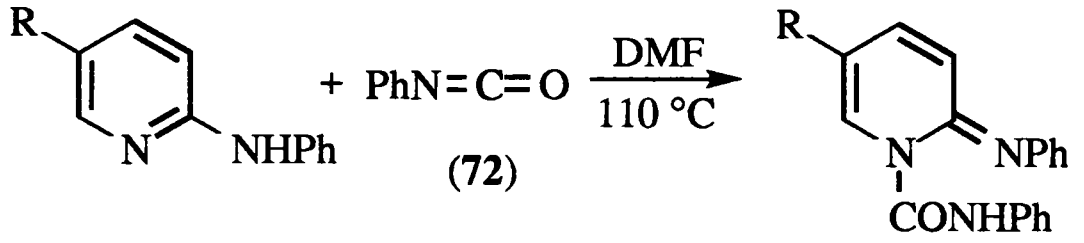
§ For reaction of the isocyanates with 3,5-dimethylpyridine *N*-oxide (**104**)

Table 3

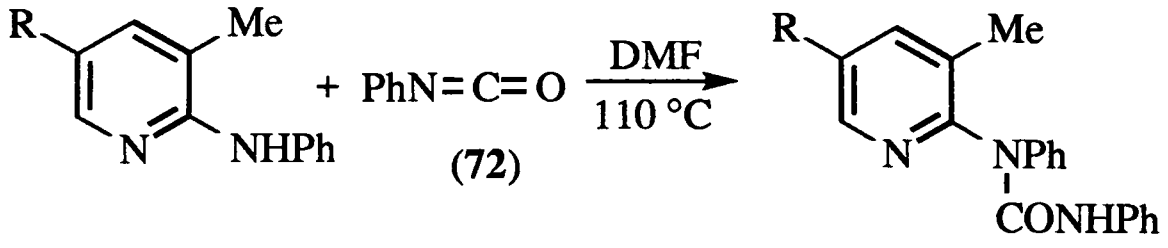
The yield was lowest for both *ortho*-substituted isocyanates, increased dramatically for the *meta*-substituted reagents to more than double and increased further, although only by a few percent, for the *para*-substituted compound. There was also no appreciable difference between methyl and chloro substitution noted. For strongly electron withdrawing groups such as nitro, the products tended to be the anilinopyridine but *p*-nitrophenyl isocyanate was unreactive.[36,43]

1.6.3.6 Products of 1 : 2 Cycloaddition Reactions

In the early 1980's, Hisano investigated the carbamation reactions of the 2-anilino derivatives with more phenyl isocyanate (**72**).[43,44] The substitution pattern on the pyridine ring dramatically affected the type of product isolated. 2-Anilino-5-methylpyridine (**76**) and 2-anilinopyridine (**93**) yielded the 1-phenylcarbamoyl-2-phenylimino-1,2-dihydropyridines (**94**) and (**95**) respectively, whereas 2-anilino-3,5-dimethylpyridine (**96**) and 2-anilino-3-methylpyridine (**75**) yielded the carbamation products (**97**) and (**98**), not the imino form (**Scheme 21**).



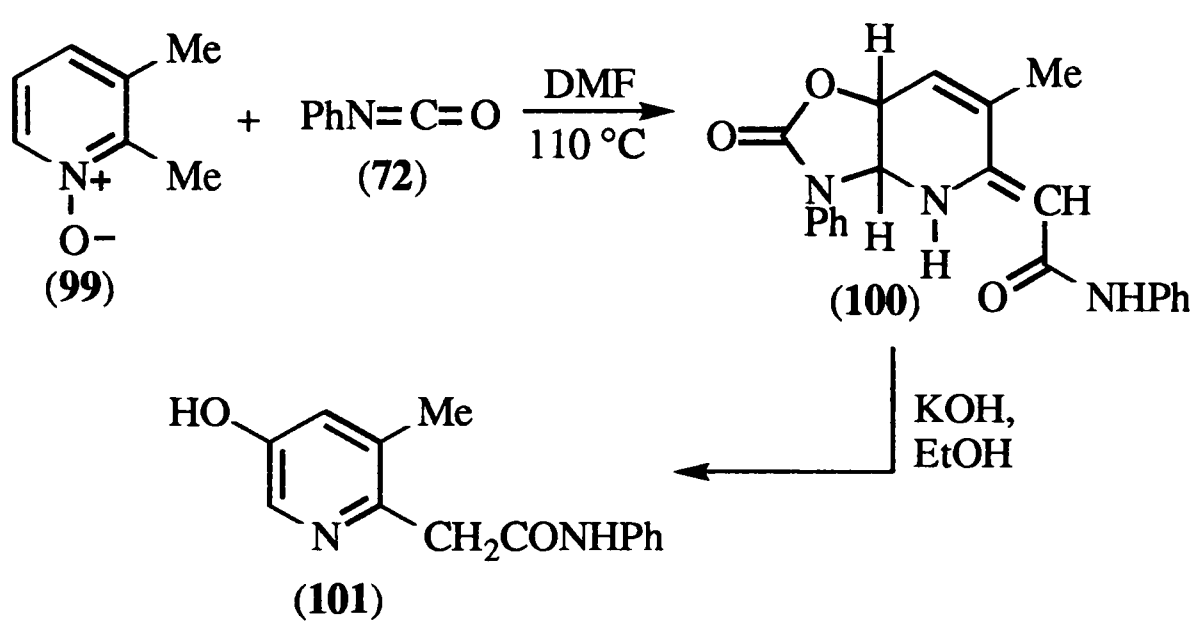
R = Me (**76**), H (**93**) R = Me (**94**), H (**95**)



R = Me (**96**), H (**75**) R = Me (**97**), H (**98**)

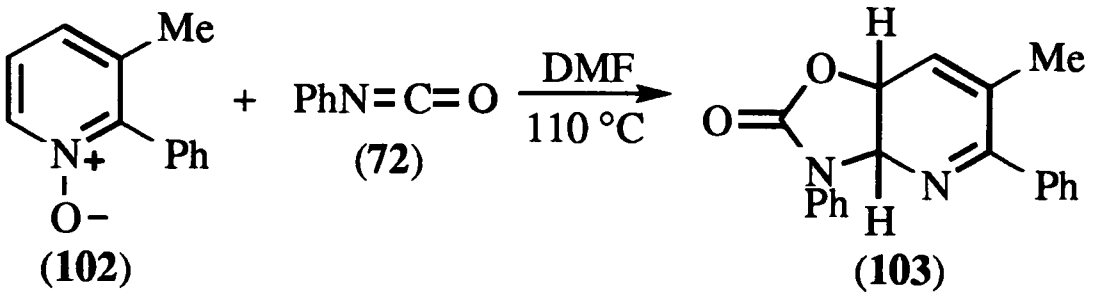
Scheme 21

An interesting case arose for the reaction of 2,3-dimethylpyridine *N*-oxide (**99**) with phenyl isocyanate (**72**) in DMF at 110 °C. Only the 1 : 2 cycloadduct as the carbamation product (**100**) was isolated even when the reaction was limited to only one equivalent of phenyl isocyanate (**72**) (although obviously in lower yield). Under no reaction conditions were any of the 1 : 1 cycloadducts isolated. Refluxing the product (**100**) in ethanolic potassium hydroxide, resulted in the loss of one mole of phenyl isocyanate (**72**) yielding 5-methyl-6-*N*-phenylcarbamoylmethyl-3-pyridinol (**101**).[45] Investigation of the stereochemistry of the carbamation product (**100**) revealed that the phenylcarbamoyl moiety had only *cis* conformation relative to the ring N-H, indicated by the existence of an intramolecular hydrogen bond between the hydrogen atom of N-H and the oxygen of the carbonyl group, which was evident in the IR spectrum of the product (**Scheme 22**).[46]



Scheme 22

However, reaction with 3-methyl-2-phenylpyridine *N*-oxide (**102**) and phenyl isocyanate (**72**) in DMF at 110 °C for 7 hours yielded only the 1 : 1 cycloadduct in the 2,3-dihydropyridine form (**103**) (**Scheme 23**).[45]



Scheme 23

These curious results were explained by invoking FMO theory and calculating the relevant energy levels of the substrates. It was noted that the introduction of an electron-donating group (e.g. methyl) at the 2-position of the pyridine ring caused a destabilisation of the FMO energy level because there was a node close to the C_3 atom but not at C_2 (**Figure 4**, page 23). For 2,3-dimethylpyridine *N*-oxide (**99**), this resulted in a rise of 0.3 eV of the HOMO, compared with that for unsubstituted pyridine *N*-oxide (**1**), which suggested that 2,3-dimethylpyridine *N*-oxide (**99**) would consequently show higher reactivity towards phenyl isocyanate (**72**) and may explain the existence of the 1 : 2 cycloadduct.[46]

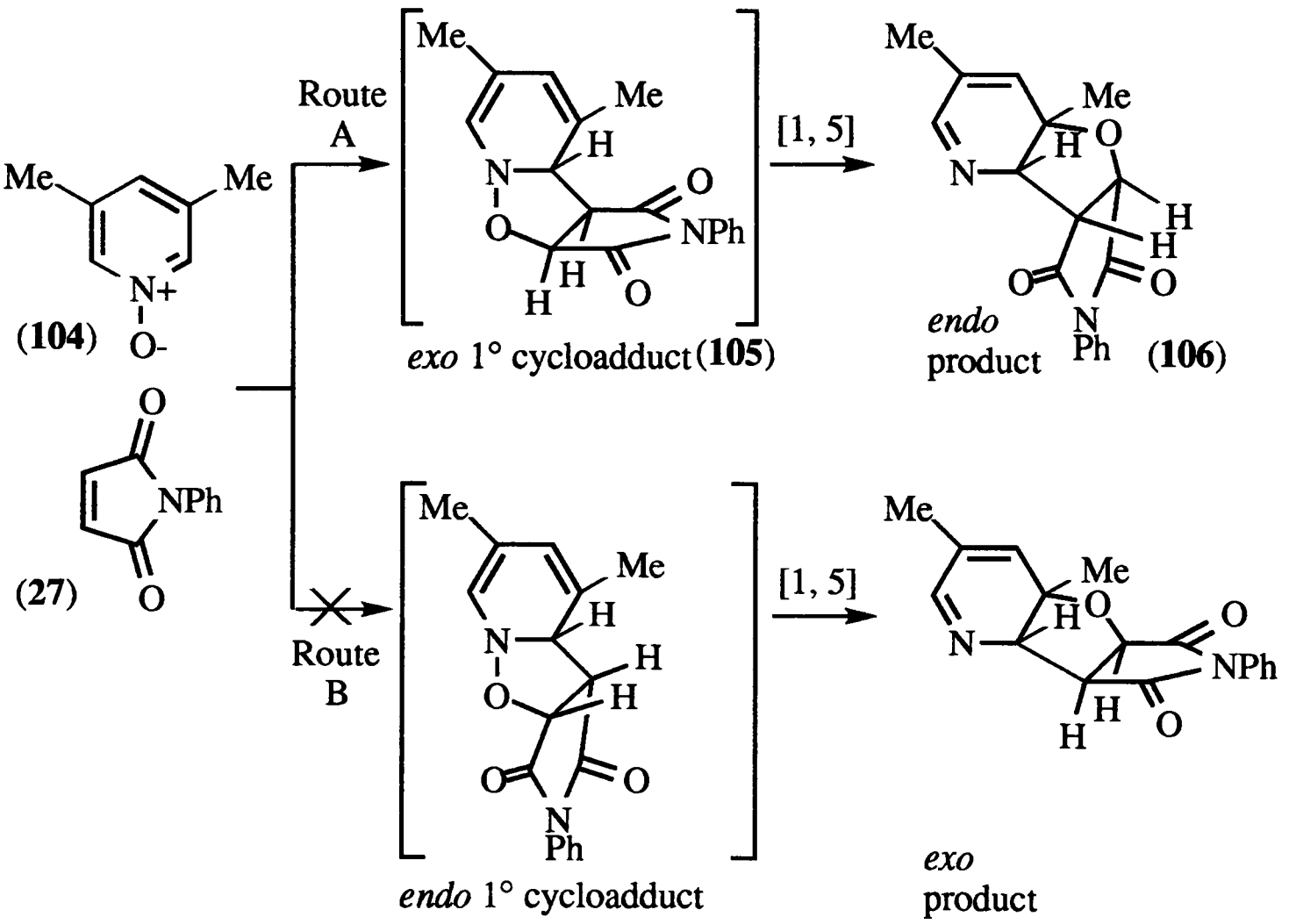
Huisgen proposed that the typical 1,3-dipolar cycloaddition reaction proceeded *via* a concerted mechanism showing only a small solvent effect on the rate of reaction (Section 1.6.3.1).[5] For the reactions above yielding the 1 : 2 cycloadducts, Hisano found that the yield was improved by the use of xylene rather than DMF and therefore suggested that these reactions proceeded by a non-ionic mechanism.[46]

1.6.3.7 Stereochemistry of the [3+2] Cycloaddition Reaction

The [3+2] cycloaddition between pyridine *N*-oxides and phenyl isocyanates has been shown to proceed by a concerted process on the basis of the observed stereoselectivity, lack of solvent dependence, low activation energy and strongly negative entropy[42] but so far, the stereochemical consequence of the dipolar cycloaddition reaction and determination of the nature of the transition states has not

been possible. Since phenyl isocyanates have a linear structure, both transition states from *exo*- and *endo*-addition yield the same product. However, using substituted maleimides as the dipolarophiles in the [3+2] cycloaddition reaction with pyridine *N*-oxides could allow investigation of the stereochemistry of the transition states due to the rigid nature of the products.

Hisano has shown the reaction between 3,5-dimethylpyridine *N*-oxide (**104**) and *N*-phenylmaleimide (**27**) to occur, yielding only *exo* primary cycloadduct (**105**), which then underwent the usual [1,5]-shift resulting in only *endo* product (**106**) (**Scheme 24**).[47]



Scheme 24

The small response of this reaction to a variation in ionising power of the solvent ruled out the existence of an intermediate or transition state with any appreciable degree of charge separation. Hisano proposed that the reaction was

occurring *via* the normal-type cycloaddition energetics involving the HOMO of the 1,3-dipole and the LUMO of the dipolarophile.

The observation of *exo*-cycloaddition in [3+2] cycloaddition reactions is very rare and indeed in the cycloaddition of *N*,α-diphenylnitrone with maleimides for example, *endo* cycloaddition is mainly observed.[48] For the above reaction (**Scheme 24**), the observation of only *exo* primary cycloadduct (**105**) resulting in *endo* product (**106**) can be accounted for purely on a steric basis. The *N*-phenyl ring of the maleimide (**27**) (which lies almost perpendicular to the imide ring) experiences steric repulsion by the *N*-oxide (**104**) in the *endo* transition state. However, the same result is achieved with *N*-methylmaleimide (**34**) which does not involve any unfavourable steric interactions (**Figure 7**). Evidence for this *endo* product came from a crystal structure of the adduct formed in the cycloaddition of 3,5-dimethylpyridine *N*-oxide (**104**) and *N*-butylmaleimide.[49]

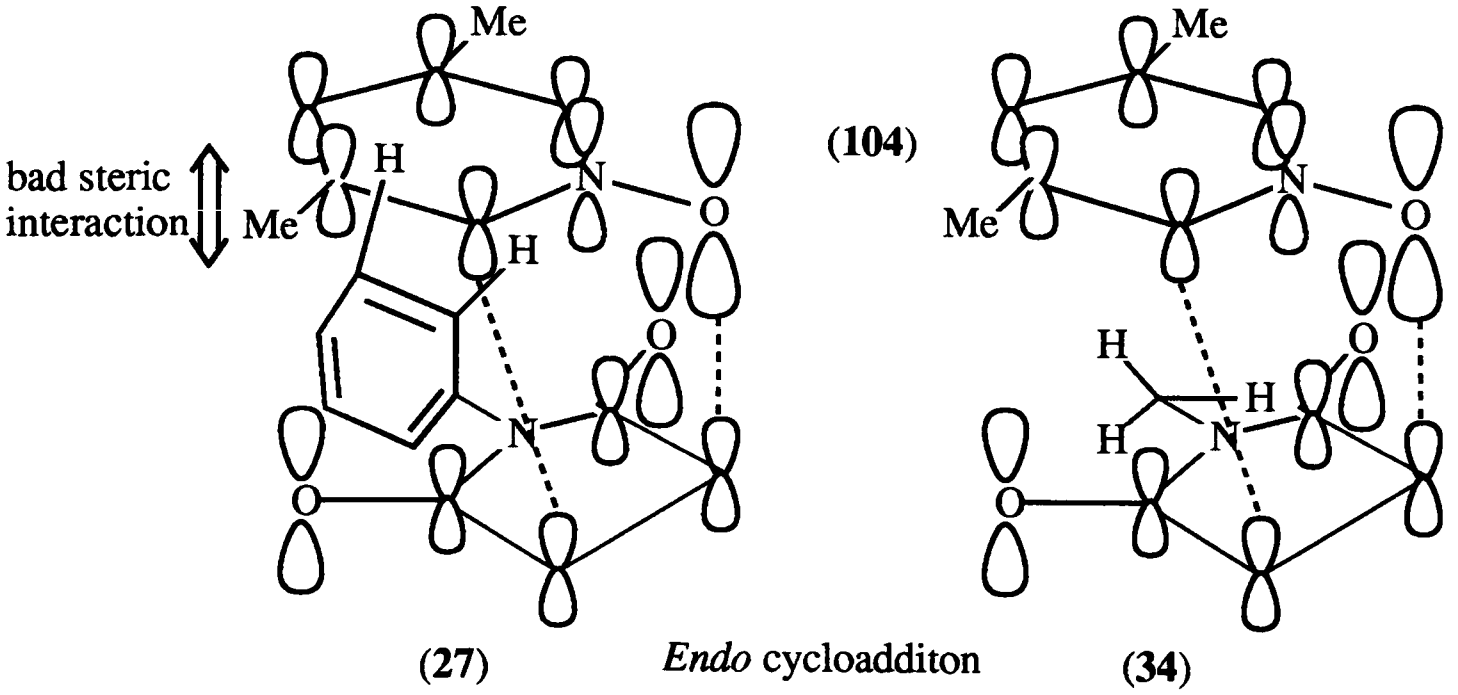
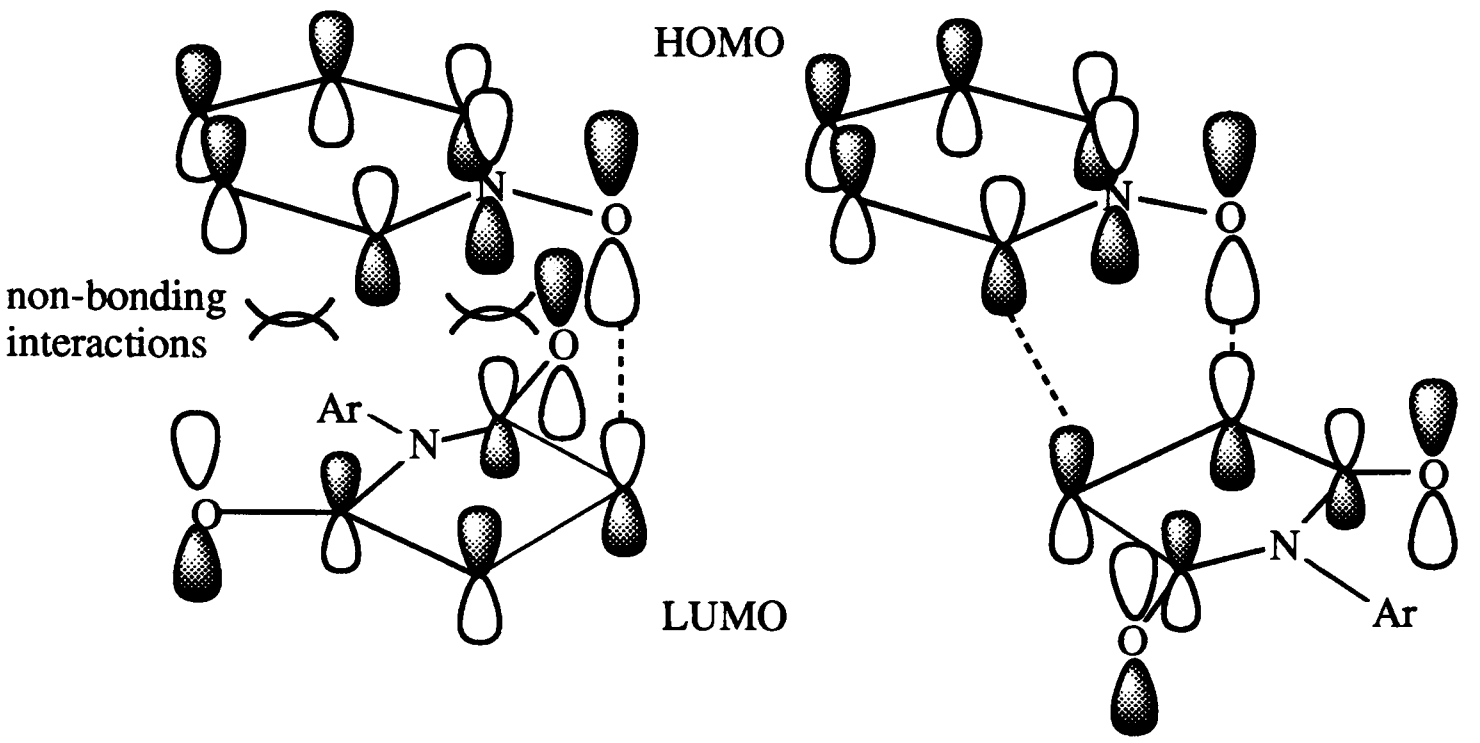


Figure 7

As the steric factor had been discounted, another alternative explanation lay with FMO theory. A closer inspection of the possible secondary orbital interactions in both *exo* and *endo* transition states revealed non-bonding interactions for the *endo* case that must have been the major factor determining the reaction path (**Figure 8**).

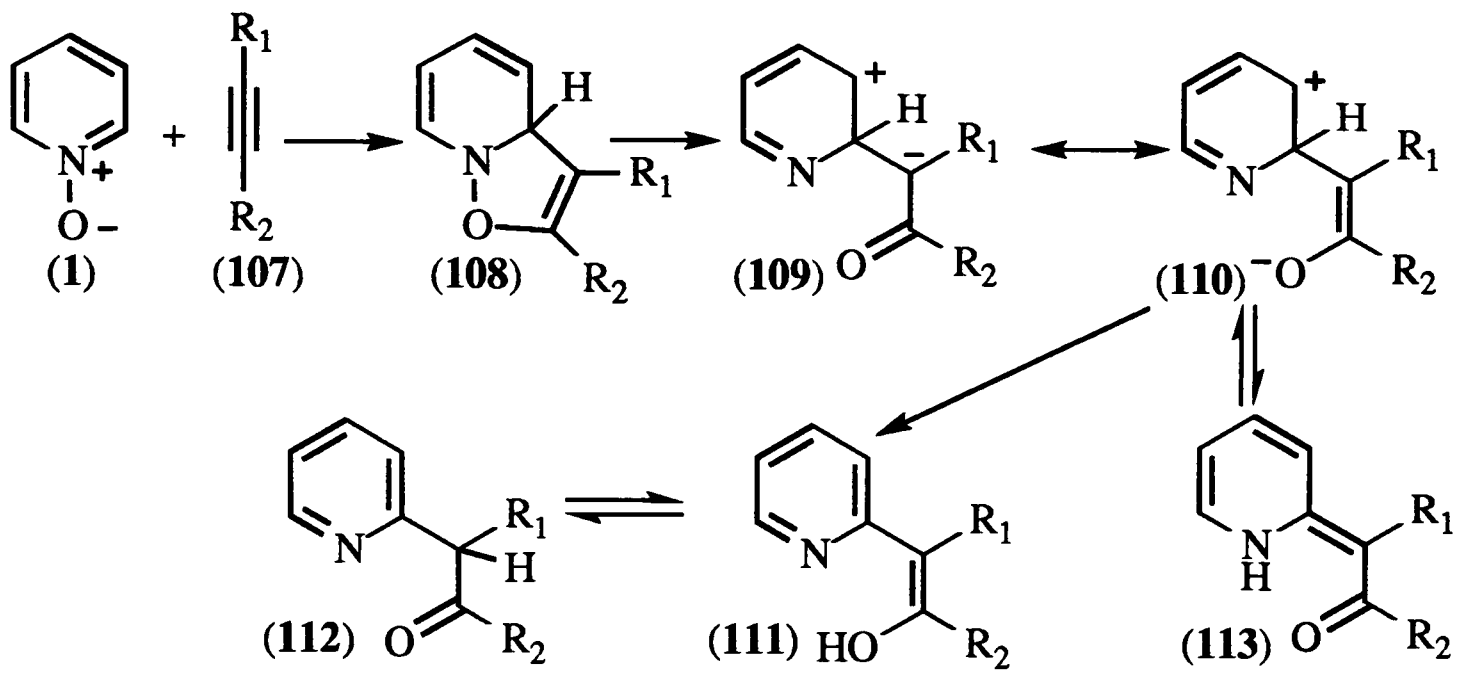


Endo transition state *Exo* transition state

Figure 8

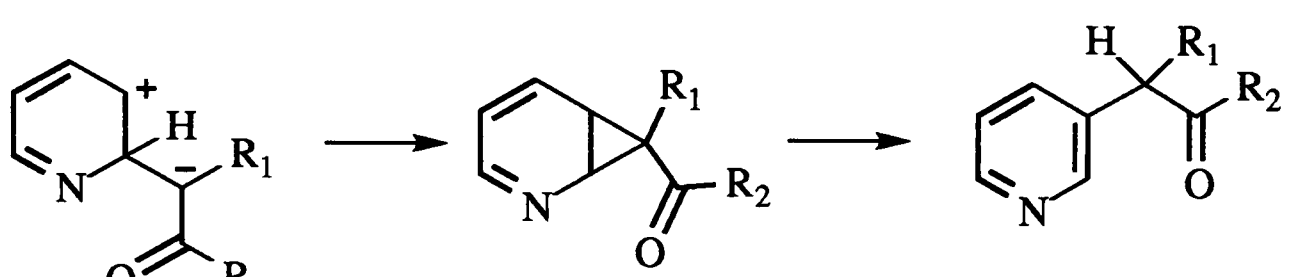
1.7 [3+2] Dipolar Cycloaddition Reaction between Aromatic *N*-Oxides and Alkynes

Pyridine *N*-oxides also have shown reactivity toward substituted acetylenes in the [3+2] cycloaddition reaction.[33] In this case, many more rearrangements of the primary cycloadducts were possible than for dipolarophiles containing a double bond. As well as the straightforward 2-substituted pyridines that could result, a whole host of other products could be envisaged. Considering the theoretical [3+2] cycloaddition reaction between an *N*-oxide (**1**), pyridine in this case, with any substituted alkyne (**107**), rearrangement of the primary cycloadduct (**108**) could give 2-substituted products (**111**), (**112**) and (**113**) (**Scheme 25**),



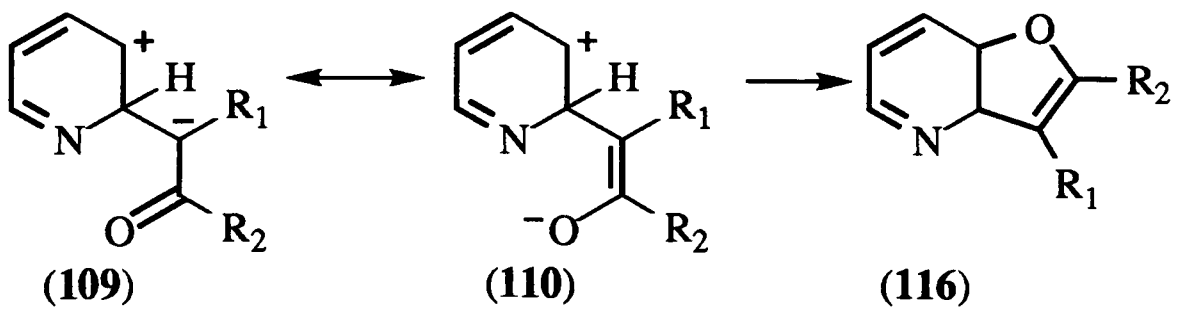
Scheme 25

as well as 3-substituted pyridines (**115**) (**Scheme 26**).



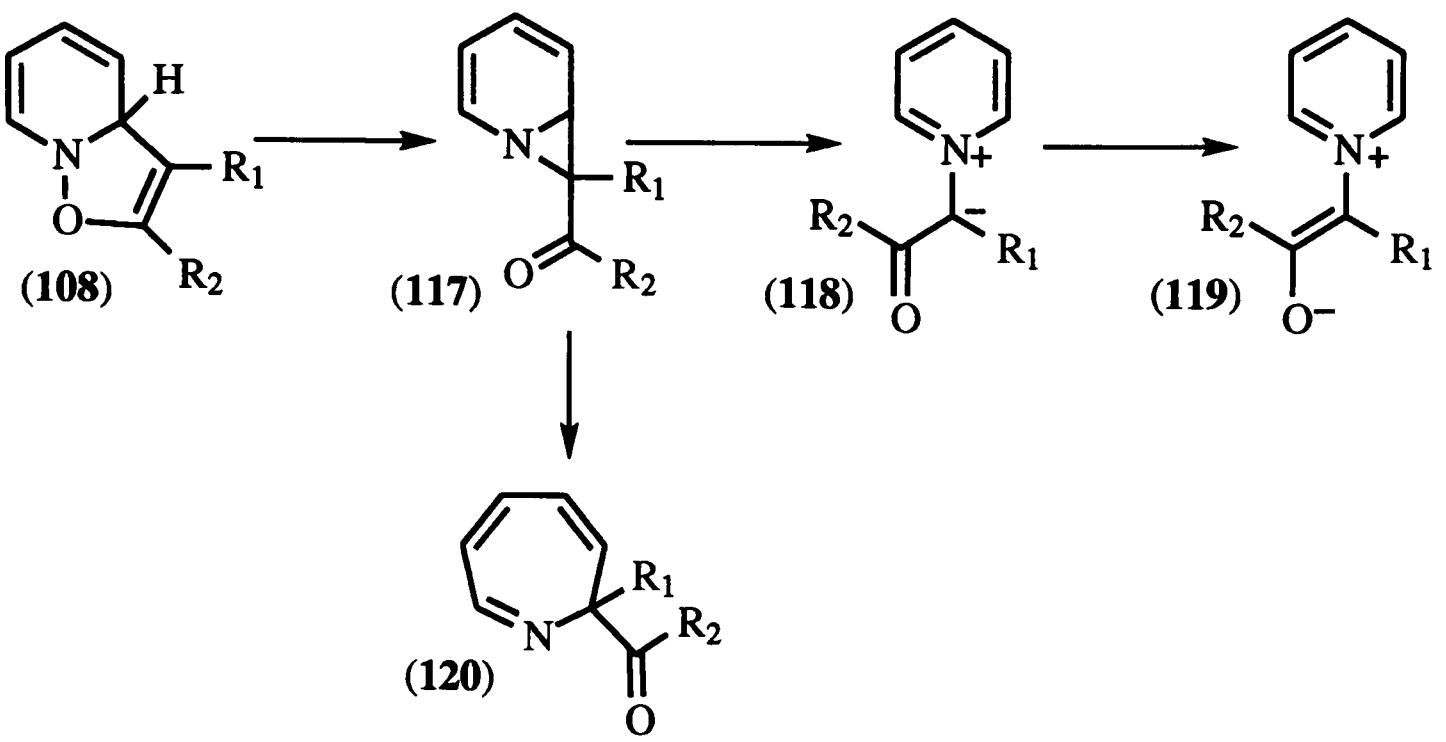
Scheme 26

Condensed systems, such as furo[2,3-*b*]pyridine (**116**) could also result (**Scheme 27**),



Scheme 27

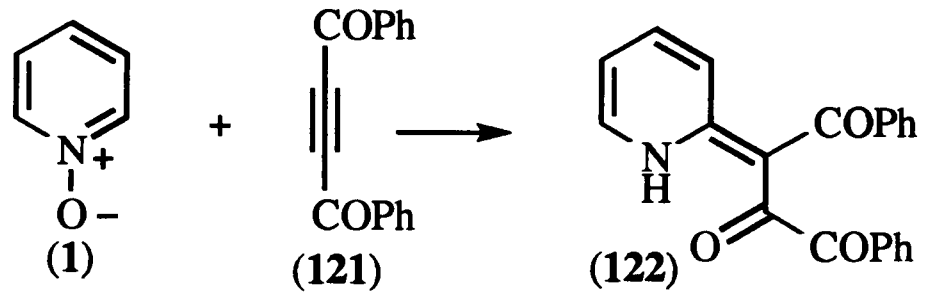
as could *N*-substituted pyridine products (**117**), (**118**) and (**119**) and azepine-type structures (**120**) (**Scheme 28**).



Scheme 28

1.7.1 Isolation of 2-Substituted Derivatives

Reaction of pyridine *N*-oxides (**1**) with the dibenzoylacetylene (**121**) has been shown to yield 2-substituted derivatives in the form of adduct (**122**) (**Scheme 29**). [33]

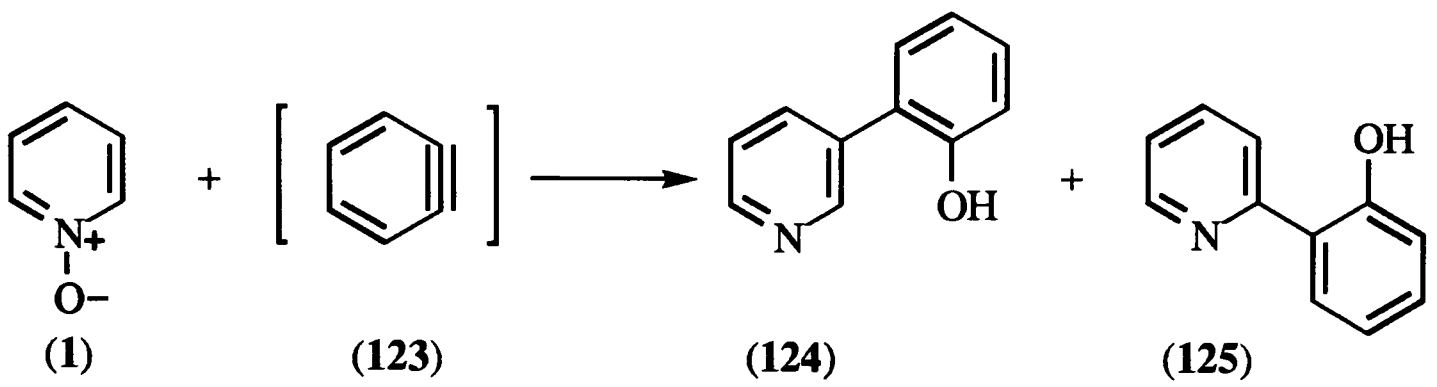


Scheme 29

1.7.2 Isolation of 3-Substituted Derivatives

The isolation of 3-substituted pyridines could only occur for acetylenic dipolarophiles in the [3+2] cycloaddition with pyridine *N*-oxides as there was no mechanism for the conversion to these products in the reaction with alkenes. It was proposed that this came about *via* cyclisation of the ylid structure (**109**) (**Scheme 26**).

to form a 3-membered ring (**114**) which could then collapse forming the 3-substituted pyridine (**115**). A good example came from cycloaddition between pyridine *N*-oxide (**1**) and the very reactive benzyne (**123**) (**Scheme 30**).[50]



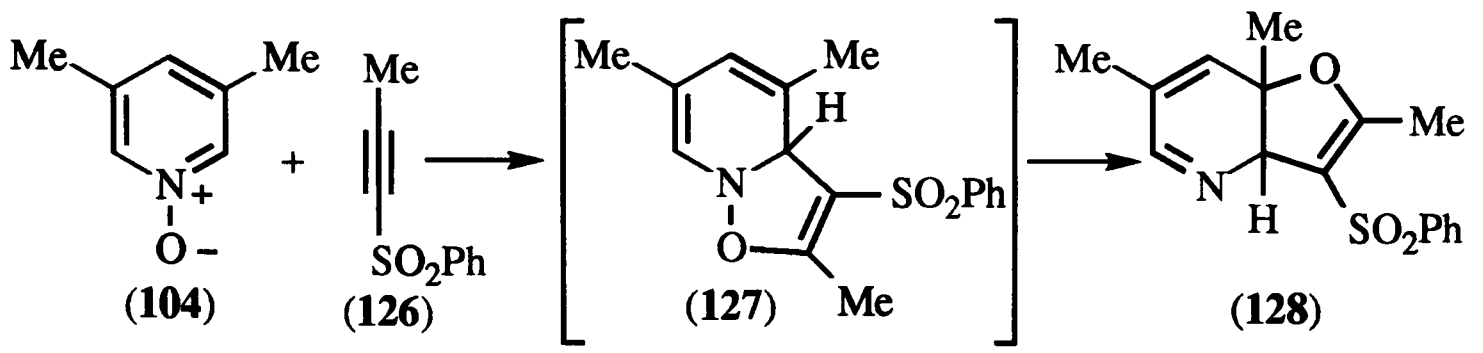
(**1**) (**123**) (**124**) (**125**)

Scheme 30

With pyridine *N*-oxide (**1**), both 2- (**125**) and 3-substituted (**124**) derivatives were formed in 6 % and 21 % yield respectively. However, with substituted pyridine *N*-oxides such as 2- and 4-cyano and 2- and 3-methyl (**71**), only the 3-substituted derivative, of the form of (**124**), was produced. The best yield of the 3-substituted product was achieved with 2-cyanopyridine *N*-oxide, i.e. in 36 %. For substituted pyridines, the only way to get the 2-substituted adduct, of the form of (**125**), was to block both the 3- and 5-positions, such as with 3,5-dimethylpyridine *N*-oxide (**104**), producing 2-(2-hydroxyphenyl)-3,5-dimethylpyridine in 54 % yield.

1.7.3 Isolation of the Condensed Furo[2,3-*b*]pyridine Systems

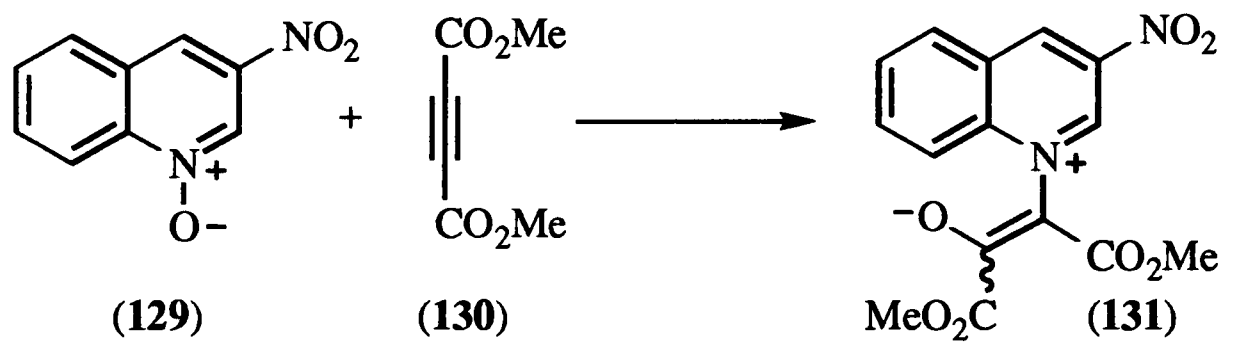
Hisano encountered products of this nature in the reaction of 3,5-dimethylpyridine *N*-oxide (**104**) with 1-phenylsulfonylpropyne (**126**). [3+2] Cycloaddition, with resultant [1,5]-sigmatropic rearrangement of the primary cycloadduct (**127**), resulted in the isolation of (**128**) in 41 % yield (**Scheme 31**).[51]



Scheme 31

1.7.4 Isolation of the *N*-Substituted Derivatives

This type of product is very rare with pyridine *N*-oxides but has been isolated from the reaction of 3-substituted quinoline *N*-oxides, such as (**129**), with dimethylacetylene dicarboxylate (**130**) (**Scheme 32**).[52]

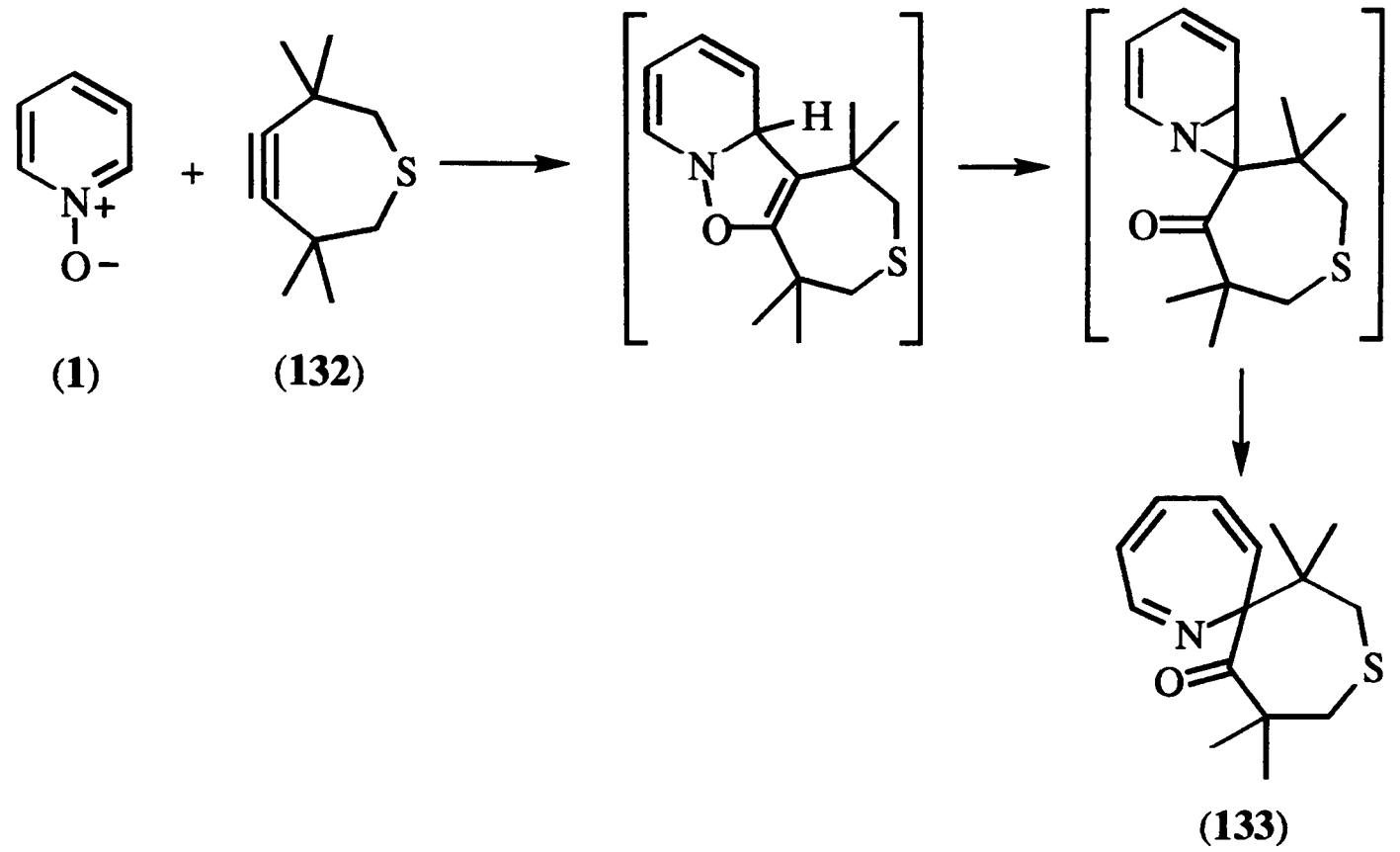


Scheme 32

Ease of formation of the *N*-ylid (**131**) was seen to correlate with the electronegativity of the 3-substituent on the *N*-oxide.

1.7.5 Isolation of the Azepine-type Product

This type of product tended only to be formed during cycloaddition involving addition to strained cycloalkynes. One example was the addition of 3,3,6,6-tetramethyl-1-thia-4-cycloheptyne (**132**) to pyridine *N*-oxide (**1**), over 24 hours at room temperature in chloroform, which afforded the azepine (**133**) in 70 % yield (**Scheme 33**).[53]



(1) **(132)** **(133)**

Scheme 33

1.8 Secondary Aim of Project

The aim was to further investigate the intermolecular [3+2] cycloaddition reaction of pyridine *N*-oxides with alkenes and to probe the applicability of the intramolecular reaction by tethering the dipolarophile onto the pyridine ring.

CHAPTER 2
RESULTS & DISCUSSION

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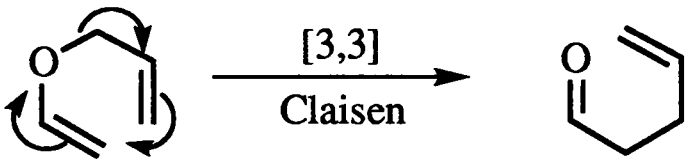
Introductory Studies on the Claisen-Type Rearrangement

2.1 Introduction

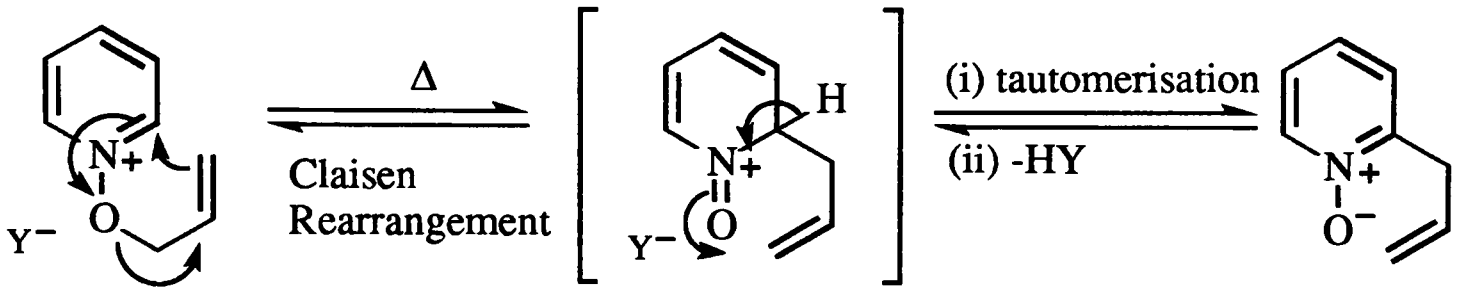
Pericyclic reactions are valuable tools in organic synthesis as they allow access to products with a high degree of stereospecificity. One such reaction is the Claisen rearrangement. This falls into the category of a sigmatropic rearrangement where there is a [3,3]-sigmatropic shift of an atom or group of atoms within a π-system (**Scheme 34**).



Scheme 34

The initial aim of this project was to examine the applicability of this aromatic rearrangement in a regioselective manner on unsymmetrically substituted heterocyclic substrates. In the 1980's, the Harwood group was widely involved in studies of regioselective aromatic rearrangements on benzene-type precursors as discussed in Section 1.3. It was hoped that similar reaction conditions could be used on analogous pyridine substrates to effect a regioselective Claisen-type rearrangement.

It firstly was necessary to synthesise pyridine *N*-oxide systems such as (**134**) that would be the precursors for the proposed aza-analogous Claisen rearrangement (**Scheme 35**).



(134) **(135)** **(136)**

Y^- = anion

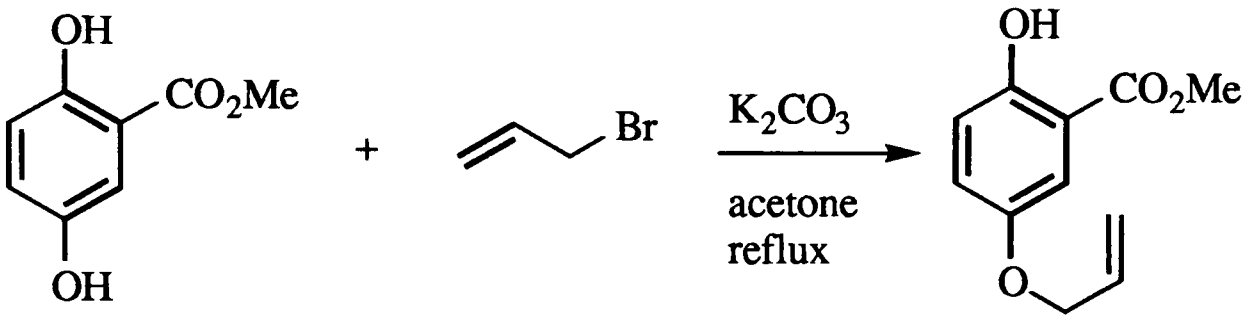
Scheme 35

In the Claisen rearrangement of the precursor (**134**), a [3,3]-sigmatropic shift would occur to give the intermediate (**135**), which should then undergo a rearomatisation process to yield the pyridine *N*-oxide (**136**), with loss of HY.

Since the aromatic nature of the pyridine ring would be destroyed during the rearrangement process, the driving force for the reaction would probably be rearomatisation of (**135**) by the tautomerisation shown above. It should be noted that the Claisen rearrangement also is reversible. In systems such as (**136**) a further [3,3]-shift can occur to yield the *para* substituted product, but this can be prevented by blocking this position with a *para* substituent.

2.2 Synthesis of the 1-(2-Allyloxypyridinium) Substrate

Synthesis of an 1-(2-allyloxypyridinium) substrate proved to be anything but trivial. Construction of this type of system had been easily achieved on benzene substrates and was used within the group, for example, in the construction of methyl 5-allyloxy-2-hydroxybenzoate (**2**) (**Scheme 36**).[3]

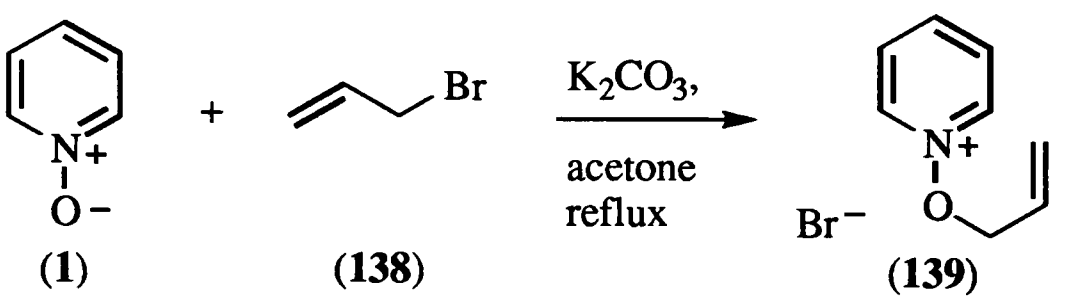


(137) **(138)** **(2)**

Scheme 36

Synthesis of (**2**) was achieved by refluxing methyl 2,5-dihydroxybenzoate (**137**) in acetone with potassium carbonate and two equivalents of allyl bromide (**138**).

Attempting the analogous reaction with pyridine *N*-oxide (**1**) instead of methyl 2,5-dihydroxybenzoate (**137**) was hoped to yield the desired 1-(2-allyloxypyridinium) salt (**139**), which presumably would be the bromide salt (**Scheme 37**).

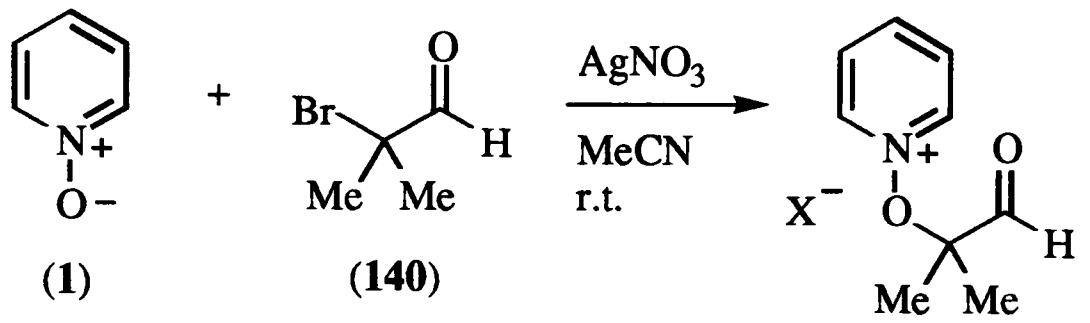


(1) **(138)** **(139)**

Scheme 37

However, when applied to pyridine *N*-oxide (**1**), these reaction conditions caused polymerisation of the allyl bromide (**138**). Stirring at room temperature gave no reaction. Omitting the potassium carbonate base, as there was strictly no longer a requirement for deprotonation of pyridine *N*-oxide (**1**), did not affect the outcome of either set of reaction conditions.

In 1991, Silwa reported the use of silver nitrate in similar reactions with pyridine *N*-oxide (**1**) and α-bromoaldehydes, such as (**140**), yielding *N*-alkoxypyridinium salts (**141**) (**Scheme 38**).[54]



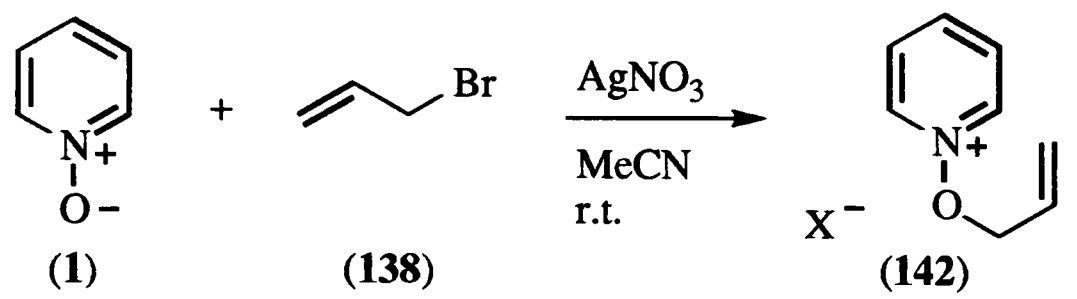
(1) **(140)** **(141)**

X^- = unknown anion

Scheme 38

However, Silwa made no reference to the nature of the anion of the pyridinium salt (**141**) and made no attempt to purify and characterise the product, except to comment that it was extremely hygroscopic and existed as the hemihydrate.

Similar reaction conditions were applied to the reaction of pyridine *N*-oxide (**1**) with four equivalents of allyl bromide (**138**) and one equivalent of silver nitrate. It was found that the precipitation of silver bromide in this reaction was successful in promoting the allylation reaction, yielding the desired adduct (**142**) as a pale pink hygroscopic salt (**Scheme 39**).



(1) **(138)** **(142)**

X^- = unknown anion

Scheme 39

The reaction was conducted in acetonitrile at room temperature and was seen to reach completion by the disappearance of the pyridine *N*-oxide starting material (**1**), as indicated by t.l.c. analysis in 4 : 1 ethyl acetate / glacial acetic acid.

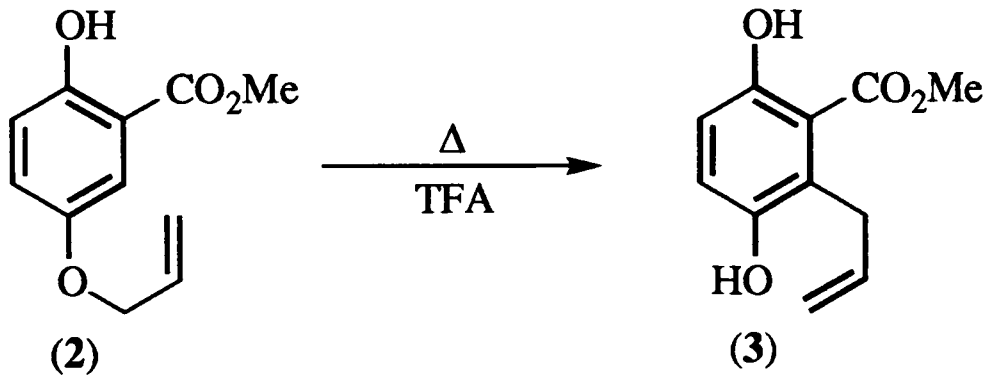
Proof of formation of the 1-(2-allyloxypyridinium) cation of (**142**) was obtained from mass spectrometric studies which showed a peak at 136 Daltons corresponding to the M^+ ion. The ^1H NMR spectrum showed a large shift in the aromatic resonances, from two multiplets at δ 8.31 and 7.42 ppm, representing two and three protons respectively, to δ 8.97 ppm as a double doublet with *J* 6.8 Hz and *J'* 1.1 Hz for the two *ortho* protons, δ 8.49 ppm as a doublet with *J* 7.8 Hz for the *para* proton and δ 8.06 ppm as a multiplet for the two *meta* protons in the pyridinium salt (**142**). The resonances for the allyl group were seen at δ 6.09 - 6.01 ppm as a multiplet corresponding to the vinylic CH, δ 5.41 ppm as a double doublet with a *cis* coupling constant of *J* 11.1 Hz and a *geminal* coupling constant of *J'* 1.0 Hz, δ 5.32 ppm as another double doublet with a *trans* coupling constant *J* 16.1 Hz and the same *geminal* coupling constant and at δ 5.03 ppm as a doublet for the saturated CH_2 with *J* 7.0 Hz. It was not unusual to see the *meta* coupling constant around the pyridine ring, typically of the value *J* 1 - 2 Hz, although it seemed mainly to be evident for the protons *ortho* to the nitrogen.

The anion was initially assumed to be nitrate but infra red analysis indicated the absence of the nitrate stretching frequency around 1 350 cm^{-1}. The microanalysis data also provided confirmation that a nitrate salt had not been obtained since the percentage of C, H and N totalled less than 30% and suggested the possibility of a complex anion such as $AgBr_2$ although this could not be confirmed by mass spectrometric analysis. It was also found that the salt was insoluble in most organic solvents and extremely hygroscopic. Due to its hygroscopy, (**142**) appeared to melt at 61 °C.

The Claisen rearrangement could now be attempted on this substrate (**142**).

2.3 Claisen Rearrangement of the 1-(2-Allyloxypyridinium) Salt

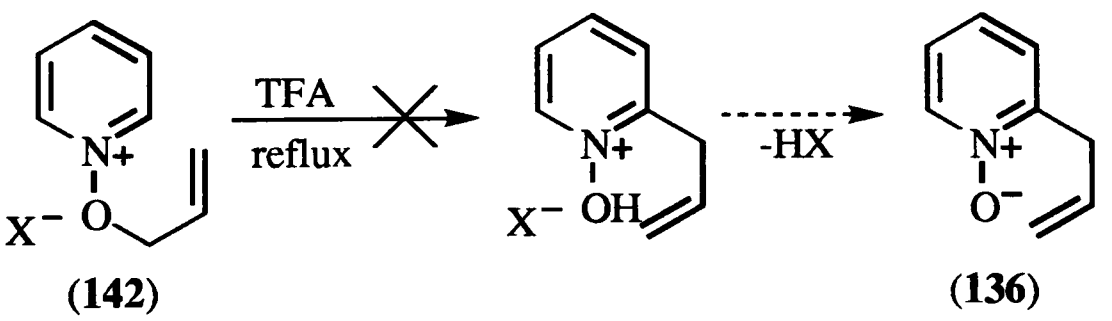
The Claisen rearrangement firstly was attempted by the method used by Harwood for the acid catalysed regiospecific rearrangement of methyl 5-allyloxy-2-hydroxybenzoate (**2**). This involved refluxing the substrate in trifluoroacetic acid, which gave rearrangement only to the most sterically hindered 2-position, yielding (**3**) (**Scheme 40**).[55]



(**2**) (**3**)

Scheme 40

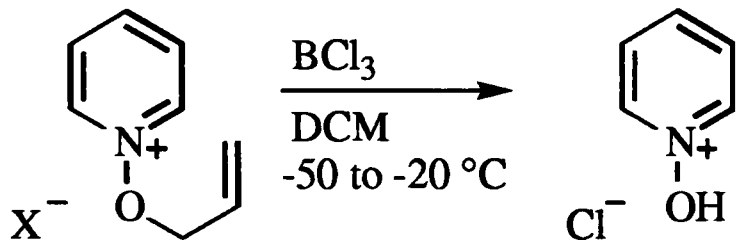
Carrying out this reaction on the 1-(2-allyloxypyridinium) salt (**142**) in refluxing TFA did not effect the Claisen rearrangement and starting material was recovered (**Scheme 41**).



(**142**) (**136**)

Scheme 41

Using the Lewis acid catalyst boron trichloride at room temperature in DCM, previously used within the group for Claisen rearrangements,[56] resulted in removal of the allyl chain from (**142**) yielding a white solid with data consistent with pyridine *N*-oxide hydrochloride (**143**) (**Scheme 42**).



(142) **(143)**

Scheme 42

In the mass spectrum, the M^+ ion of (**143**) was detected at 96 Daltons. A broad hydroxyl stretching absorption at 3 400 cm^{-1} was detected in the IR spectrum as well as an N-O stretching absorption at 1 197 cm^{-1}. In the ^1H NMR spectrum, three multiplets were detected, δ 8.85 - 8.84 ppm for the two *ortho* protons, δ 8.26 - 8.22 ppm for the *para* proton and δ 7.94 - 7.91 ppm for the *meta* protons as well as a broad singlet representing 1H at δ 3.55 ppm, presumed to be due to the hydroxyl group.

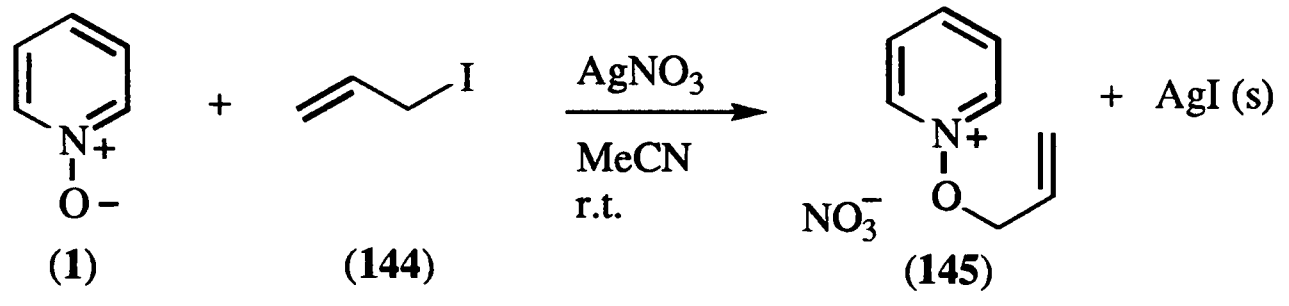
It is known, however, that boron trichloride is capable of forming complexes with pyridine itself, but there was no evidence to suggest this type of product had formed with the *N*-oxide.[57]

It was decided to try a non-catalysed Claisen rearrangement by heating (**142**) in the high boiling solvent *N,N*-diethylaniline. This caused degradation of the starting material resulting in the formation of a black tar.

Since it was considered that the insolubility of this 1-(2-allyloxypyridinium) salt (**142**) was due to complexation with a silver ion, attempts were made to form the required salt without the use of silver nitrate. For this purpose, it was proposed that a more reactive allyl species would be required.

2.4 Synthesis of 1-(2-Allyloxypyridinium) Nitrate

The more reactive allyl iodide (**144**) was chosen for attempted formation of the 1-(2-allyloxypyridinium) substrate. Carrying out the reaction in acetonitrile without silver nitrate present resulted in the formation of what appeared to be the desired product, probably as the iodide salt, but vast amounts of starting material pyridine *N*-oxide (**1**) still remained. However, inclusion of the silver nitrate was able to effect the desired reaction, forming 1-(2-allyloxypyridinium) nitrate (**145**) in 65 % yield (**Scheme 43**).



(**1**) (**144**) (**145**)

Scheme 43

The 1-(2-allyloxypyridinium) nitrate (**145**) was obtained as a yellow hygroscopic solid and appeared to melt below 50 °C, which may have been due to its dissolution in water.

Evidence for the cation of the product (**145**), was obtained from the mass spectrometric peak at 136 Daltons for the M^+ ion. In the ^1H NMR spectrum, the allyl resonates appeared as a 1H multiplet at δ 6.25 - 6.14 ppm for the vinylic CH, at δ 5.49 ppm as a 1H double doublet with *cis* and *geminal* coupling constants *J* 10.2 Hz and *J'* 1.0 Hz respectively, for the *cis* proton of the vinylic CH_2 group and the *trans* proton came at δ 5.46 ppm as a 1H double doublet with *trans* and *geminal* coupling constants *J* 15.9 Hz and *J'* 1.0 Hz respectively. The saturated CH_2 of the allyl group appeared as a 2H doublet at δ 5.18 ppm with *J* 7.1 Hz.

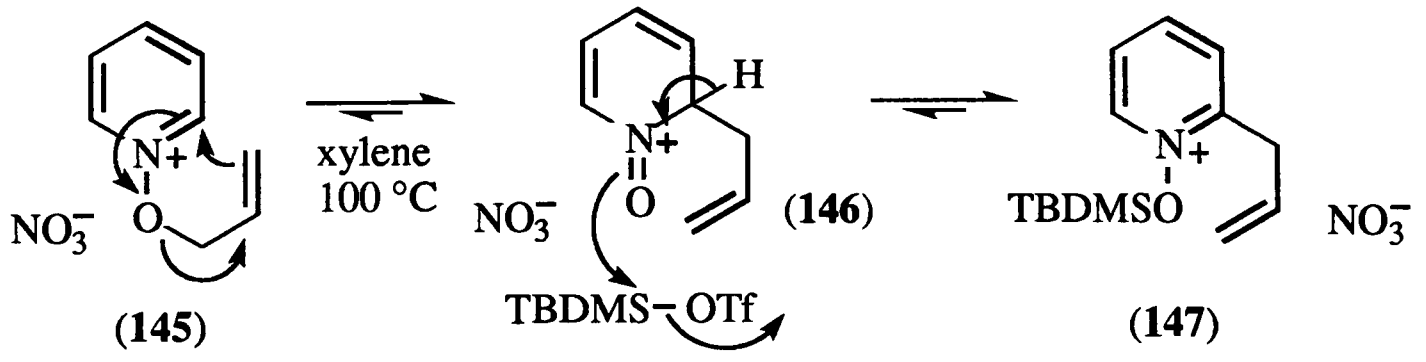
Evidence for the nitrate anion was seen in the IR spectrum by the very intense peak at 1 348 cm^{-1}.

2.5 Claisen Rearrangement of 1-(2-Allyloxypyridinium) Nitrate

Various attempts were made to effect the Claisen rearrangement on this substrate (**145**) as solubility in organic solvents was no longer a problem. The acid catalysed reaction was carried out by refluxing 1-(2-allyloxypyridinium) nitrate (**145**) in trifluoroacetic acid, but was found to cause some degradation of the starting material. Upon heating, there was evolution of a brown acidic gas, presumed to be nitrogen dioxide, but 38 % of the starting material (**145**) was recovered after work up.

Since the Claisen rearrangement was in effect reversible, if the second rearomatisation step cannot occur, then any rearranged intermediates may be reverting to starting material. For this reason, two attempts were made to try and drive forward the rearomatisation step in order to push over the equilibrium for the rearrangement in favour of the product.

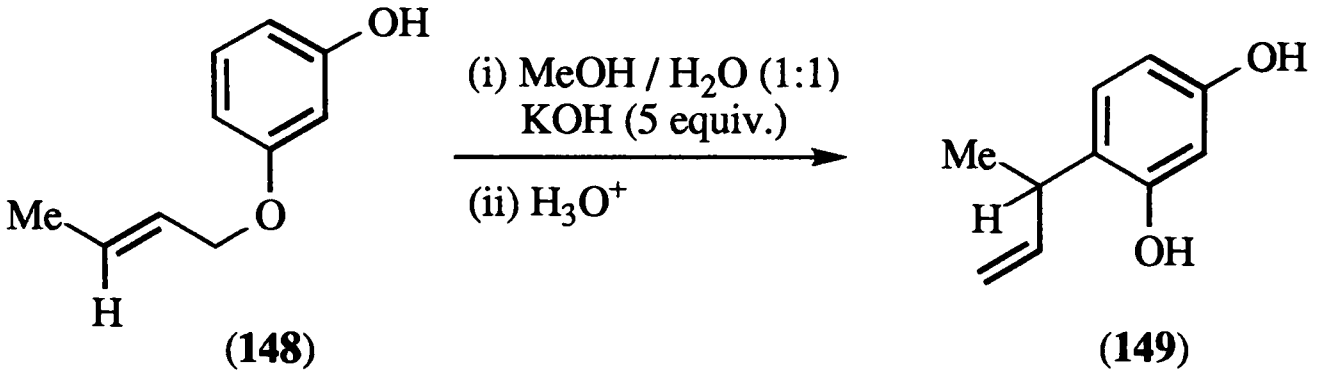
The first idea was to carry out the reaction in the presence of TBDMSOTf. It was hoped that the strong affinity of silicon for oxygen would allow the rearranged intermediate (**146**) to be trapped, giving the silyl protected *N*-oxide salt (**147**) (**Scheme 44**).[58]



Scheme 44

This unfortunately did not yield the desired product (**147**) and starting material was recovered.

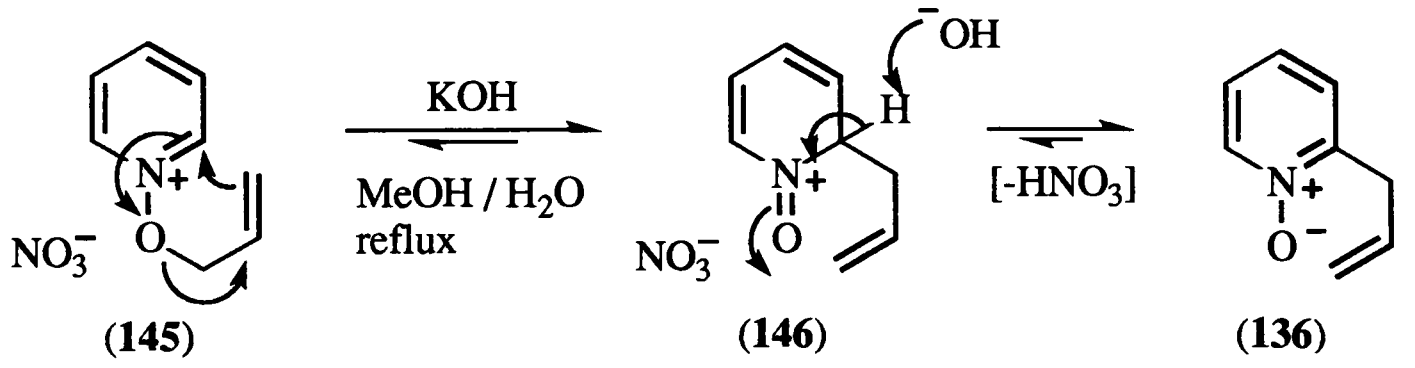
The last and final attempt to effect Claisen rearrangement was to use a base catalysed reaction, employed previously within the group to accomplish the Claisen rearrangement of systems such as (**148**), which gave the adduct (**149**) in a 62 % yield as the major product (**Scheme 45**).[59]



(**148**) (**149**)

Scheme 45

It was hoped that by carrying out the reaction in the presence of a base, proton removal at C_2 of (**146**) would be favoured, resulting in formation of the rearomatised product (**136**) (**Scheme 46**).



(**145**) (**146**) (**136**)

Scheme 46

This too proved fruitless and starting material was again recovered after work up of the reaction mixture.

2.6 Summary

Since it had proved impossible to effect the Claisen rearrangement on the 1-(2-allyloxypyridinium) salts, it was decided to abandon this approach and change the course of the investigation.

CHAPTER 3
RESULTS & DISCUSSION

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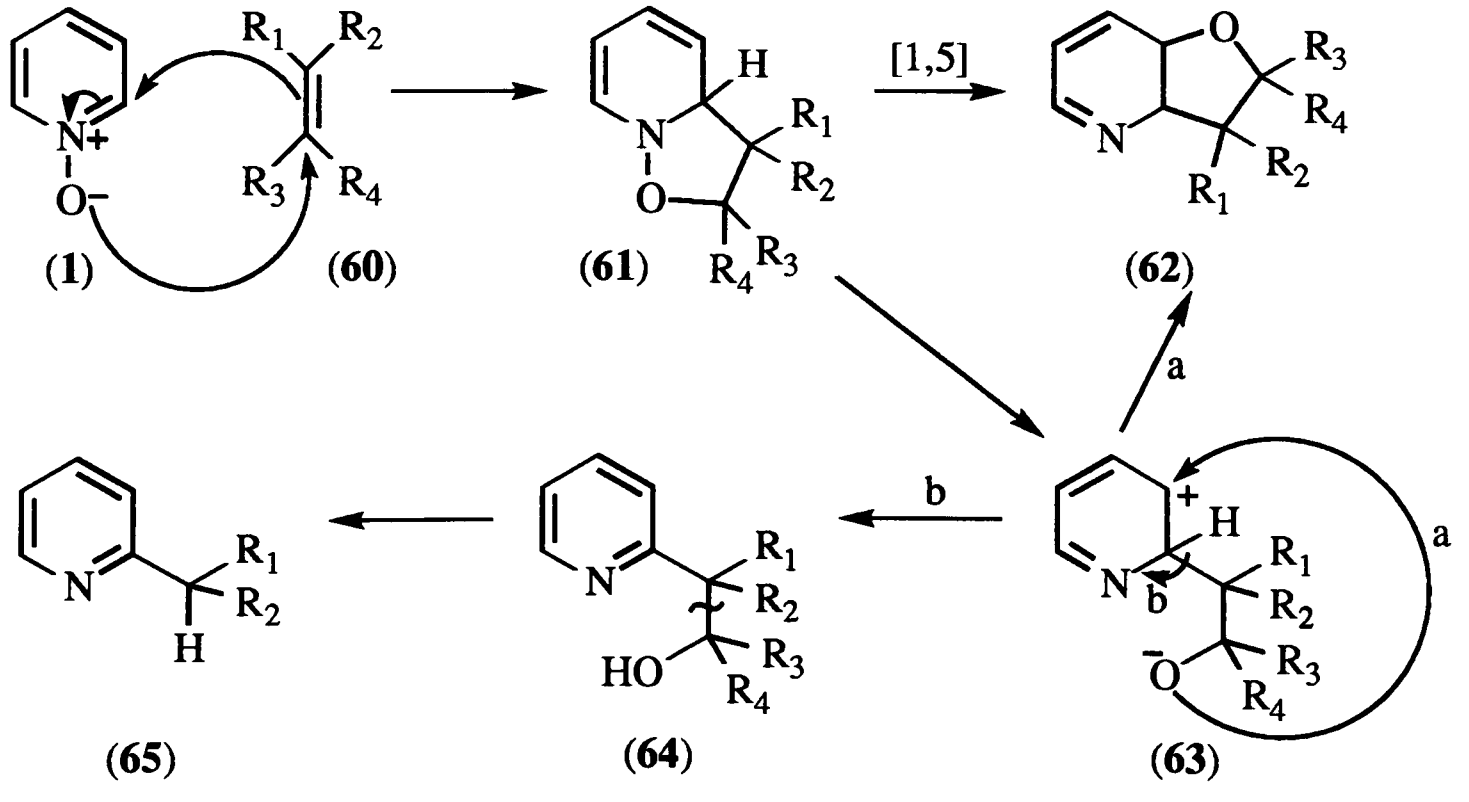
RESULTS & DISCUSSION

Investigation of the Intermolecular [3+2] Cycloaddition Reaction

3.1 Introduction

From the theoretical view point, the intermolecular [3+2] cycloaddition reaction proceeds by concerted nucleophilic addition of the oxygen lone pair of electrons to the dipolarophile (**60**), addition of the π-electrons of the dipolarophile (**60**) to the 2-position of the *N*-oxide (**1**) and the movement of π-electrons that form the aromatic nucleus to the positively charged nitrogen. This results in loss of aromatic stabilisation energy and forms the primary cycloadduct (**61**). As Hisano observed, this can undergo a [1,5]-shift to yield the 2,3-dihydropyridine species (**62**).[36] The primary cycloadduct (**61**) is also capable of undergoing another rearrangement, resulting in cleavage of the N-O bond, producing the ylid (**63**). This ylid can then either cyclise to give the 2,3-dihydropyridine (**62**) by pathway 'a' or rearomatise *via* pathway 'b' resulting in the alcohol (**64**). If subsequent C-C bond cleavage results, the 2-substituted pyridine (**65**) is the final product (**Scheme 47**).



Scheme 47

For the purpose of carrying out a study of the intermolecular cycloaddition reaction, various 3-substituted *N*-oxides were needed. A range of compounds bearing both electron donating and electron withdrawing substituents, as well as straightforward pyridine *N*-oxide (**1**) were required. These *N*-oxides would have differing HOMO and LUMO energy levels with respect to pyridine *N*-oxide (**1**).

3.2 Synthesis of the Pyridine *N*-Oxides

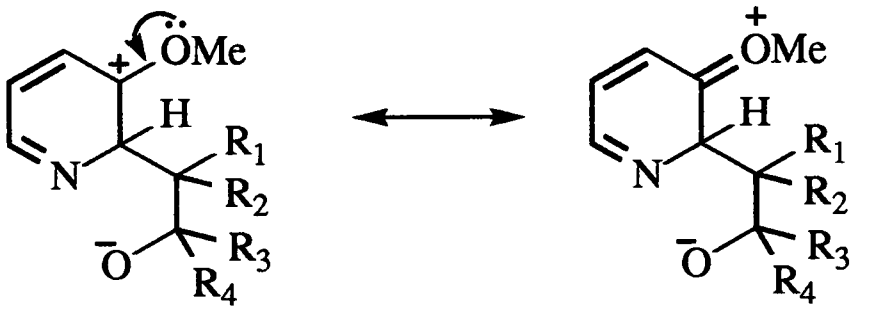
The *N*-oxides that were chosen were pyridine *N*-oxide (**1**) and 3-methylpyridine *N*-oxide (**71**) both of which were cheap and readily available, but it was necessary to synthesise the three other substituted pyridine *N*-oxides that were selected as starting materials for the [3+2] cycloaddition reaction. They were 3-chloropyridine *N*-oxide (**151**), 3-methoxypyridine *N*-oxide (**79a**) and methyl pyridine-3-carboxylate *N*-oxide (**152**).

Hisano found that the energy of the HOMO of the *N*-oxides varied slightly on changing the substitution at the 3-position.[40] Cycloaddition by the 'usual bonding interaction' was thought to be favoured by the presence of electron donating groups attached to the pyridine ring, which raised the energy of the HOMO, but attachment of an electron withdrawing group to the aromatic nucleus lowered the energy of the LUMO and cycloaddition may have occurred in an opposite sense to the 'usual bonding interaction'.

The location of a node on C_3 and C_5 atoms of the HOMO of the *N*-oxides meant that its destabilisation with electron donating groups was not very pronounced and in fact the HOMO energy level only increased slightly on going from pyridine *N*-oxide (**1**) to 3-methylpyridine *N*-oxide (**71**) and increased only slightly again for 3-methoxypyridine *N*-oxide (**79a**). The localisation of the LUMO of the *N*-oxide at C_3 and C_5 meant that 3-substitution markedly affected this energy level. For example,

replacement of the proton at C_3 by a mesomerically electron donating group greatly destabilised the LUMO and, in fact, Hisano observed that for 3-methoxypyridine *N*-oxide (**79a**), a crossover was observed with the NLUMO. The new LUMO had a node at C_6, so formation of the cycloadduct at C_2 was favourable.[40]

Although for 3-methoxypyridine *N*-oxide (**79a**), the oxygen atom adjacent to the nucleus exerted an electron withdrawing polar effect, this was outweighed by the mesomeric electron donation. The electron pair also could stabilise the intermediate (**150**) which had the positive charge on the carbon atom to which the substituent was attached (**Figure 9**).



(150)

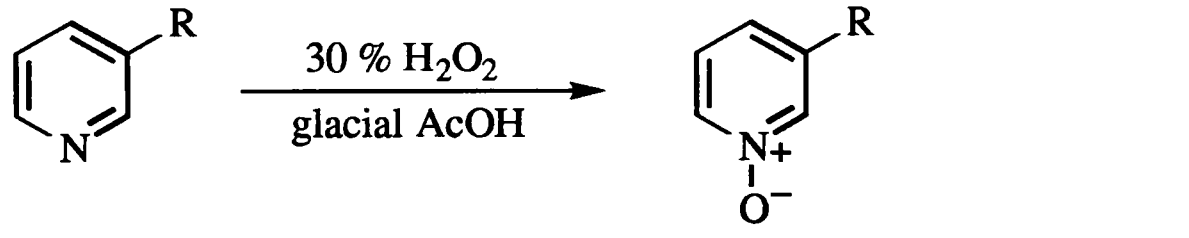
Figure 9

The destabilisation of the LUMO was not seen to occur with 3-methylpyridine *N*-oxide (**71**), although the HOMO was slightly destabilised compared with pyridine *N*-oxide (**1**). This substituent exerted an electron donating inductive (polar) effect on the pyridine nucleus and cycloaddition probably would occur *via* the 'usual bonding interaction'.

3-Chloropyridine *N*-oxide (**151**) also has an atom adjacent to the nucleus that carries an electron pair, thus the same stabilisation of (**63**) can in theory occur, but the overall effect is inductive electron withdrawal. This probably will disfavour cycloaddition by the 'usual bonding interaction'. Since the LUMO presumably will be greatly lowered in energy, it may play some part in the bonding interaction.

In methyl pyridine-3-carboxylate *N*-oxide (**152**), the ester substituent exerts a powerful electron withdrawing effect on the aromatic nucleus because the substituent has a positively polarised atom adjacent to the pyridine ring. Thus cycloaddition *via* the usual bonding interaction may again be disfavoured and the LUMO may be involved in the bonding interaction.

The synthesis of both 3-chloropyridine *N*-oxide (**151**) and methyl pyridine-3-carboxylate *N*-oxide (**152**) was accomplished by oxidation of the required pyridine compound with hydrogen peroxide in acetic acid (**Scheme 48**).[32]



R = Cl, CO_2Me R = Cl (**151**), CO_2Me (**152**)

Scheme 48

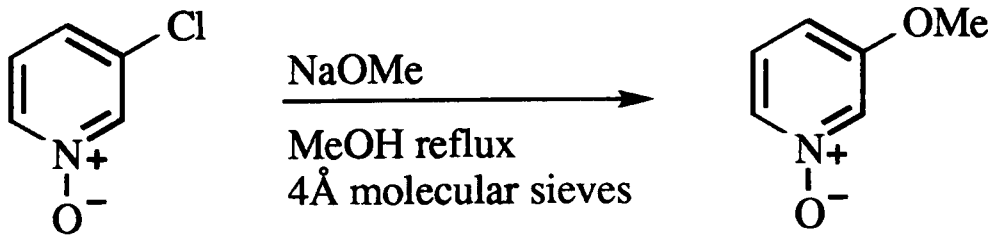
The yields of both reactions were high (> 80 %) and 3-chloropyridine *N*-oxide (**151**) and methyl pyridine-3-carboxylate *N*-oxide (**152**) were isolated as very hygroscopic solids.

Evidence for formation of the *N*-oxide of 3-Chloropyridine was seen in the mass spectrum by a gain of 16 Daltons. Both the parent MH^+ ions showing the two chloride isotopes were detected at 132 and 130 Daltons. The IR spectrum revealed formation of the *N*-oxide as the N-O absorption was detected at 1 247 cm^{-1}. In the ^1H NMR spectrum, there was a shift in the pyridine resonances from two 1H doublets at δ 8.58 and 8.49 ppm with coupling constants of *J* 1.9 Hz and *J* 4.8 Hz respectively and two 1H multiplets, δ 7.70 - 7.64 and 7.28 - 7.24 ppm in the starting material to a 1H triplet at δ 8.21 ppm with *J* 1.5 Hz, two 1H double triplets at δ 8.08 ppm with

J 6.3 Hz and *J'* 1.5 Hz and at δ 7.24 ppm with *J* 8.3 Hz and *J'* 1.5 Hz and a double doublet at δ 7.19 ppm with *J* 8.3 Hz and *J'* 6.3 Hz.

Similar evidence for formation of the methyl pyridine-3-carboxylate *N*-oxide (**152**) was found. Again the molecular ion peak for MH^+ was detected in the mass spectrum at 154 Daltons and in the IR spectrum, the N-O stretching absorption appeared at 1 238 cm^{-1}. The ^1H NMR spectrum revealed a change in the pyridine proton resonances from a doublet at δ 9.24 ppm with *J* 2.1 Hz, a double doublet at δ 8.78 ppm with *J* 4.8 Hz and *J'* 1.5 Hz, a *pseudo*-double triplet at δ 8.31 ppm with apparent *J* 7.9 Hz and *J'* 1.9 Hz and another double doublet at δ 7.40 ppm with *J* 7.9 Hz and *J'* 4.8 Hz in the starting material to a 1H singlet at δ 8.75 ppm, two 1H doublets at δ 8.32 and 7.83 ppm with *J* 6.4 Hz and *J* 8.0 Hz respectively and a 1H *pseudo*-triplet at δ 7.35 ppm with *J* 7.2 Hz in the *N*-oxide (**152**). The methyl 3H singlet moved only slightly from δ 3.97 ppm to δ 3.95 ppm.

3-Methoxypyridine was not readily available, so it could not be synthesised directly by oxidation with hydrogen peroxide. It was found however, that it could be constructed easily from the 3-chloropyridine *N*-oxide (**151**) with sodium methoxide in refluxing methanol in the presence of 4Å molecular sieves, in 46 % yield (**Scheme 49**).



(**151**) (**79a**)

Scheme 49

Again, confirmation that the desired reaction had occurred came from the detection of the MH^+ ion at 126 Daltons. The N-O stretching absorption was still

present in the IR spectrum and shifted only slightly to 1 245 cm^{-1}. In the ^{1}H NMR spectrum, there was an additional proton resonance at δ 3.85 ppm as a 3H singlet corresponding to the methoxy methyl group. This was confirmed by the ^{13}C NMR spectrum which had a new resonance at δ 56.10 ppm.

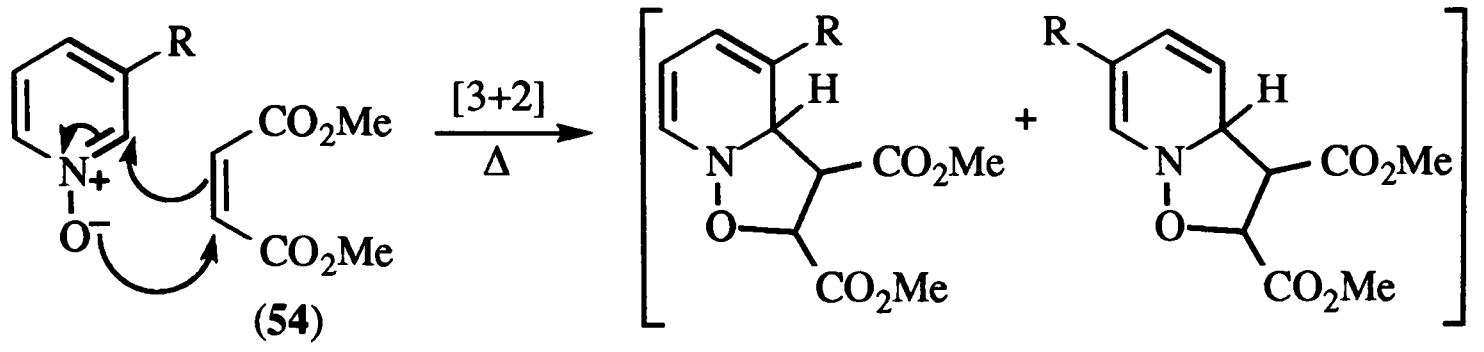
Intermolecular [3+2] cycloaddition reactions could now be attempted on the five *N*-oxides.

3.3 Thermal Intermolecular [3+2] Cycloaddition Reactions

For the intermolecular cycloaddition reaction, two alkene dipolarophiles were chosen in order to generate novel cycloadducts. They were methyl acrylate (**153**) and dimethyl maleate (**54**). Both have electron withdrawing groups in the form of esters, methyl acrylate (**153**) has one and dimethyl maleate (**54**), two. Dimethyl maleate (**54**) bearing two electron withdrawing groups would be expected to have a much lower LUMO energy level than methyl acrylate (**153**) and [3+2] cycloaddition would presumably be favoured by a 'usual bonding interaction' for this dipolarophile. Since there is not such a lowering in the LUMO's energy level for methyl acrylate (**153**), the bonding interaction may involve some participation by the HOMO.

There were potentially many secondary reactions that could follow the initial cycloaddition. The possible products depended upon the *N*-oxide and dipolarophile used.

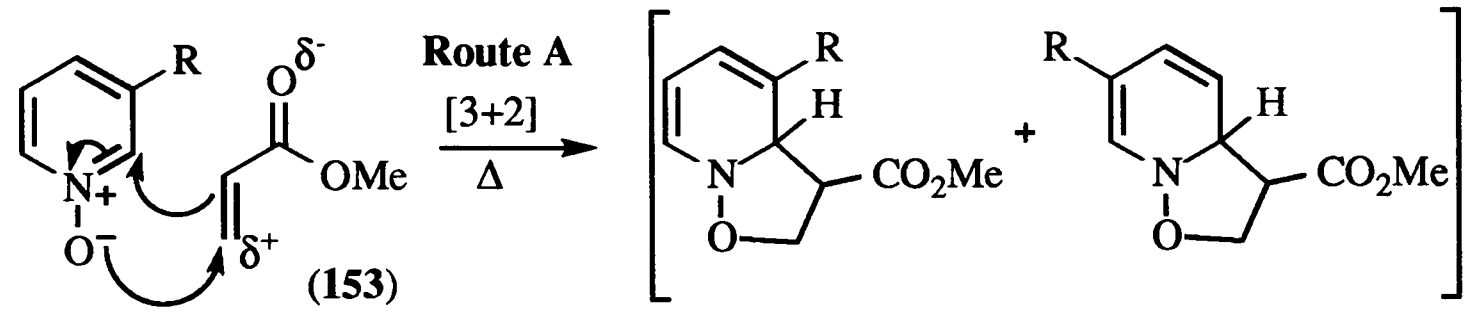
With all the pyridine *N*-oxides and dimethyl maleate (**54**) there were two possible primary cycloadducts (**Scheme 50**).



For the *N*-oxide, R = H (**1**), Me (**71**), Cl (**151**), OMe (**79a**), CO_2Me (**152**)

Scheme 50

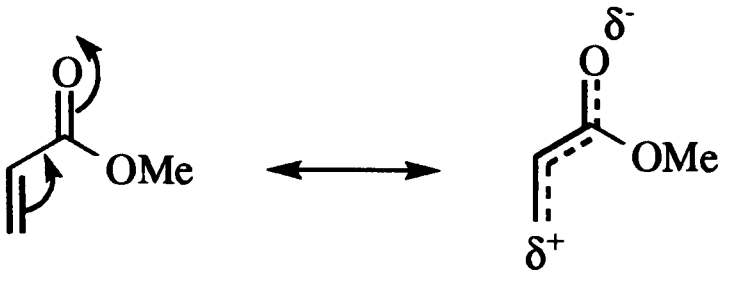
With methyl acrylate (**153**) as the dipolarophile, in theory, there were four possible primary cycloadducts (**Scheme 51**).



For the *N*-oxide, R = H (**1**), Me (**71**), Cl (**151**), OMe (**79a**), CO_2Me (**152**)

Scheme 51

However, the polarisation of the methyl acrylate (**153**) is such that one end of the double bond has a partial positive charge. This is due to the electron withdrawing effect of the ester group that polarises the electrons in the double bond (**Figure 10**).

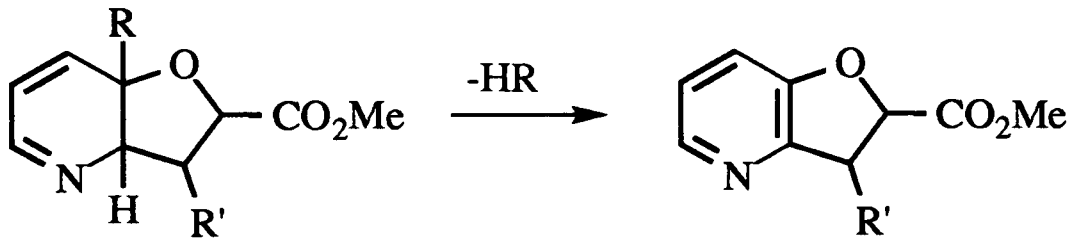


(153)

Figure 10

This would disfavour the [3+2] cycloaddition by Route B, so Route A was expected to predominate (**Scheme 51**).

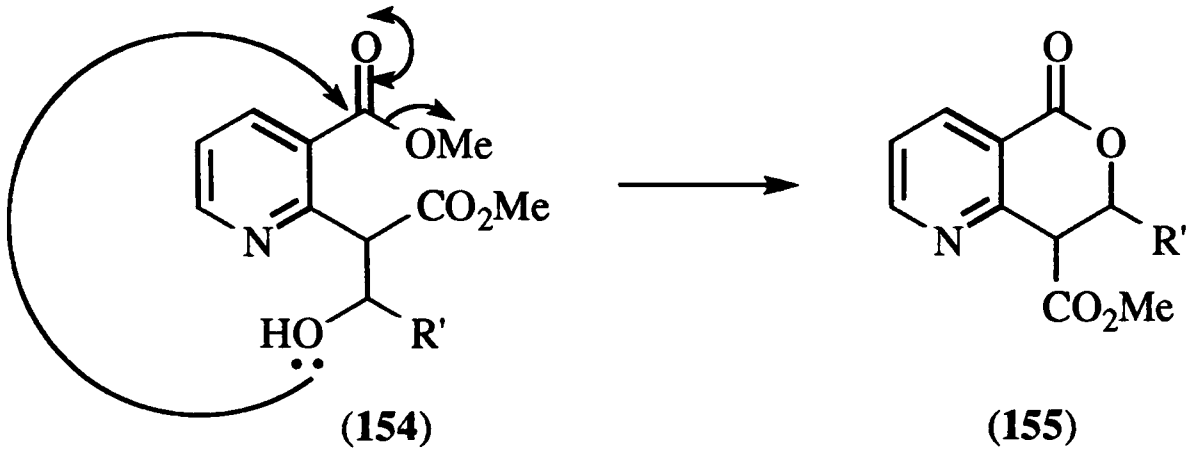
With both methyl acrylate (**153**) and methyl maleate (**54**), the primary cycloadducts formed, could undergo a [1,5]-shift to yield the 2,3-dihydropyridine products of the type of (**62**) (**Scheme 47**). For 3-chloropyridine *N*-oxide (**151**) and 3-methoxypyridine *N*-oxide (**79a**), the 2,3-dihydropyridines formed by cycloaddition to the sterically hindered site could rearomatise, with loss of hydrogen chloride and methanol, respectively (**Scheme 52**).



R = Cl, OMe
R' = H, CO_2Me

Scheme 52

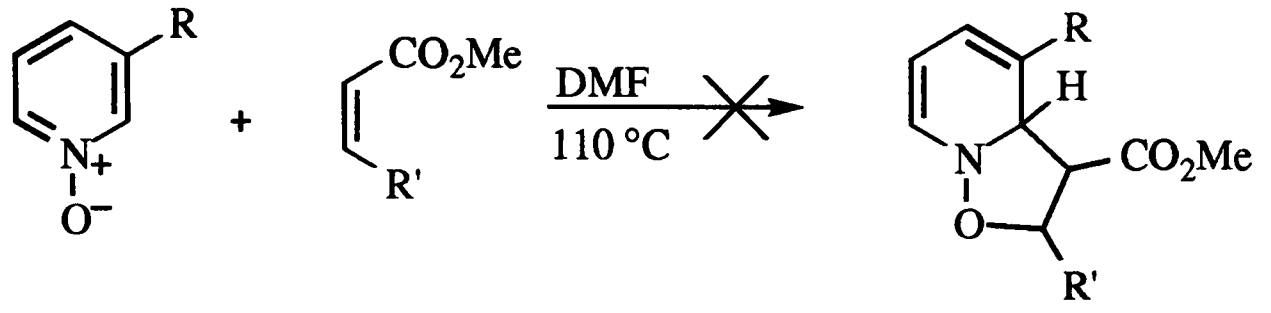
With methyl pyridine-3-carboxylate *N*-oxide (**152**), another possible product could result from rearrangement of the 'more sterically hindered' primary cycloadduct. Formation of the alcohol-type structure (**154**) and displacement of the methoxy group by the hydroxyl group would form the bicyclic product (**155**) (**Scheme 53**).



Scheme 53

Hisano found the relatively high boiling dipolar aprotic solvents, DMF and DMSO to be the most effective in which to conduct the intermolecular [3+2] cycloaddition reaction.[35,43] This may have been due to the absence of hydrogen-bonding between the *N*-oxide substrate and the solvent, which in water or methanol for example, would have resulted in an envelope of hydrogen-bonded solvent molecules around the dipole and could have been due also to efficient solubility of the *N*-oxide starting materials in these solvents. Thus in DMF or DMSO, the *N*-oxide dipole should be more reactive and consequently, cycloaddition more likely to occur.

As a result, the above intermolecular cycloadditions were attempted in DMF at 110 °C. The starting material *N*-oxides were dissolved in dry, distilled DMF, 1.5 equivalents of the appropriate dipolarophile added and the reaction mixture heated to 110 °C under an inert atmosphere of nitrogen. After stirring at this temperature for 24 hours, t.l.c. analysis eluting with 4 : 1 ethyl acetate / glacial acetic acid revealed that starting material *N*-oxide remained in all cases, with no evidence of any type of product material. The reactions were subsequently left at this temperature for 5 more days with periodic t.l.c. analysis. After this time, removal of the reaction solvent afforded complete recovery of the starting material *N*-oxides and the dimethyl maleate (**54**) was recovered from the reactions in which it was used. Unreacted methyl acrylate (**153**) was removed at the same time as the solvent (**Scheme 54**).

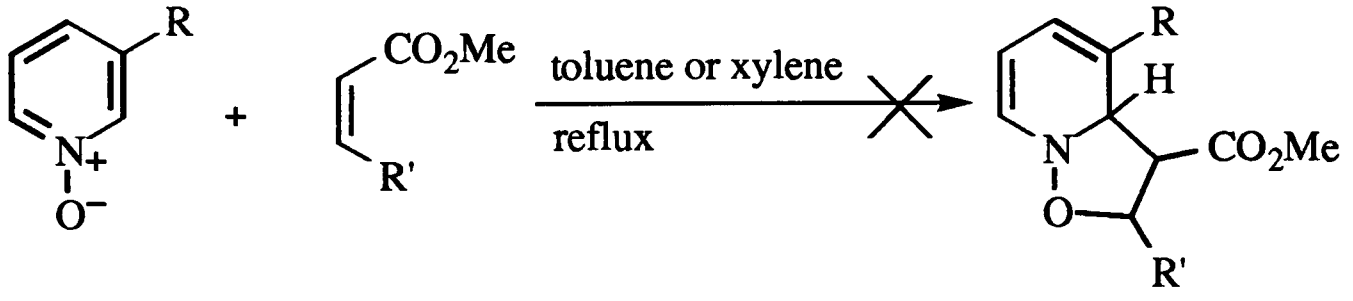


For the *N*-oxide, R = H (**1**), Me (**71**), Cl (**151**), OMe (**79a**), CO_2Me (**152**)
For the dipolarophile, R' = H (**153**), CO_2Me (**54**)

Scheme 54

It was proposed that the lack of reactivity could have been due to the insufficient input of energy into the reaction pathway, and to this end, the reactions were repeated with Hisano's other favoured solvent DMSO and at the higher temperature of 150 °C.[43] Unfortunately, after several days at this temperature, the results were the same, with complete recovery of the starting materials.

The [3+2] cycloaddition reactions of nitrones, carried out by both Grigg and Padwa, discussed in Chapter 1, tended to favour the aprotic solvents toluene and xylene. For this reason, all the cycloadditions were repeated in both toluene and xylene at reflux (**Scheme 55**).



For the *N*-oxide, R = H (**1**), Me (**71**), Cl (**151**), OMe (**79a**), CO_2Me (**152**)
For the dipolarophile, R' = H (**153**), CO_2Me (**54**)

Scheme 55

Unfortunately, the outcome of the reactions was not changed and the starting materials were recovered as before.

It was proposed that cycloaddition was prevented by the hygroscopic nature of the pyridine *N*-oxides, since hydration would lower the reactivity of the 1,3-dipole. For this reason, activated 4Å molecular sieves were used, as it was hoped that by removing water form the reaction mixture, cycloaddition would be aided. The position of the equilibrium of the first cycloaddition step may also be moved, favouring product formation, if subsequent reactions would occur more easily. For example, the use of molecular sieves may cause dehydration of the alcohol-type product (**65**) (**Scheme 47**).

The molecular sieves were firstly used in Soxhlet extractors, with both toluene and xylene as solvents, but the reactions failed to give any cycloaddition with any of the combinations of *N*-oxides and dipolarophiles. Starting materials, unfortunately, were also recovered when the sieves were added to the reaction mixture.

The results of all the attempted cycloadditions between the five pyridine *N*-oxides with methyl acrylate (**153**) and dimethyl maleate (**54**) are summarised in **Table 4.**

Reaction Conditions	**Cycloadditions Results**
DMF / 110 °C	S.M. recovered
DMSO / 150 °C	S.M. recovered
Toluene reflux	S.M. recovered
Xylene reflux	S.M. recovered
Toluene reflux / 4Å molecular sieves	S.M. recovered
Xylene reflux / 4Å molecular sieves	S.M. recovered

Table 4

Since the cycloadditions could not be effected by thermal means, an alternative reaction condition was sought.

3.4 High Pressure Mediated Cycloaddition Reactions

3.4.1 Theory

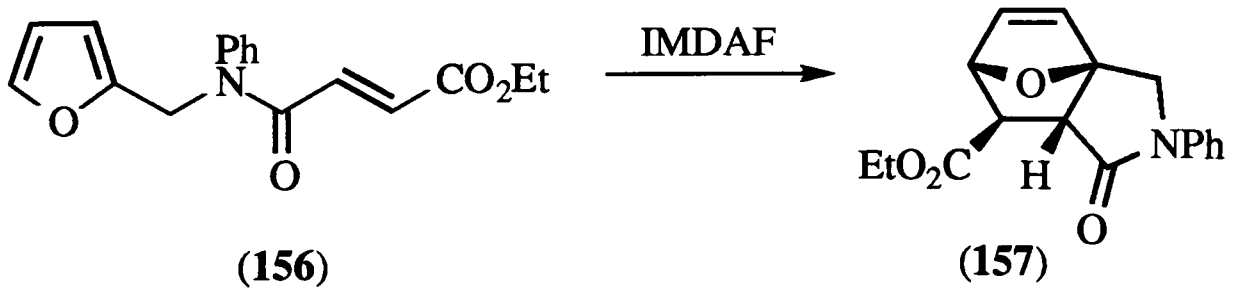
Reactions that have both negative activation volume ($\Delta V^{\ddagger}$) and a negative reaction volume (ΔV^{θ}) are favoured kinetically and thermodynamically by the application of high pressure (**Figure 11**).[60] Cycloaddition reactions necessarily fall in to the category of having both a negative activation volume and a negative reaction volume, since the two reacting entities have to come together, for reaction to occur, which will result in a decrease in the occupied volume.

$$\frac{\delta \ln k}{\delta P} = \frac{-\Delta V^{\ddagger}}{RT}$$ Negative Activation Volume $\Delta V^{\ddagger}$

$$\frac{\delta \ln K}{\delta P} = \frac{-\Delta V^{\theta}}{RT}$$ Negative Reaction Volume ΔV^{θ}

Figure 11

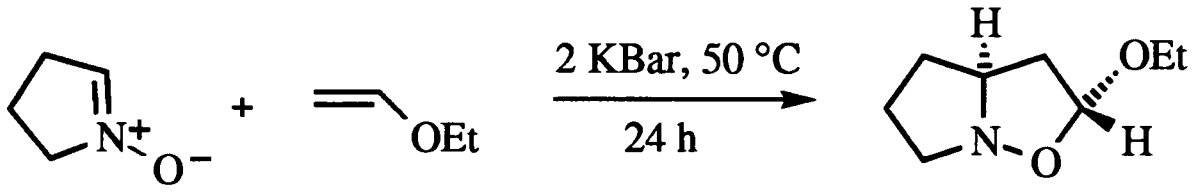
The change in activation volume of the IMDAF of (**156**) was measured by Isaacs.[61] The change, on conversion to the cycloadduct (**157**), was measured as $-25(\pm 2)cm^3mol^{-1}$ (**Scheme 56**). This was predictably lower in magnitude than typical intermolecular measurements (-30 to -40 cm^3mol^{-1}).[62]



(**156**) (**157**)

Scheme 56

Dicken had shown that the nitrone (**158**) could undergo intermolecular cycloaddition with the dipolarophile (**159**) at high pressure with slight warming to yield the cycloadduct (**160**) (**Scheme 57**).[63]



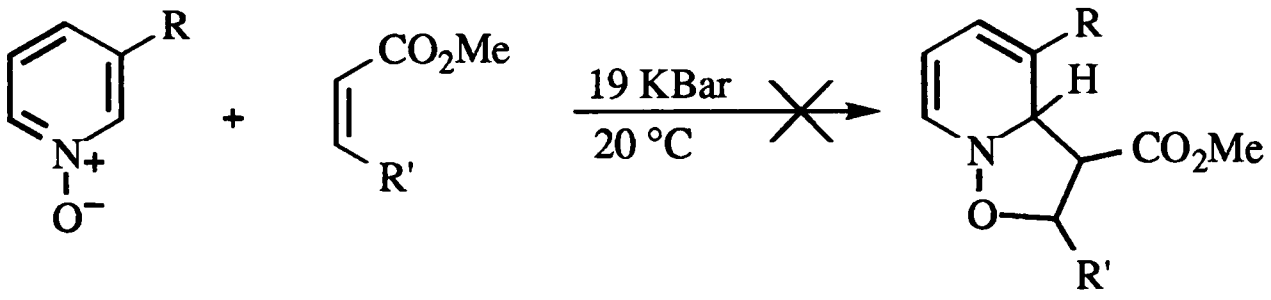
(158) **(159)** **(160)**

Scheme 57

Therefore, it was assumed that intermolecular cycloaddition of a pyridine *N*-oxide with the dipolarophiles could be made to occur at high pressure.

3.4.2 High Pressure Intermolecular [3+2] Cycloaddition Reactions

Each combination of the five *N*-oxides, with the dipolarophiles methyl acrylate (**153**) and dimethyl maleate (**54**), were dissolved in *ca.* 1-5 mL of freshly distilled DCM, put into individual Teflon® reaction pots and then subjected to 19 KBar pressure at 20 °C, in order to effect the intermolecular cycloaddition reaction. Unfortunately, after leaving the reaction for several days, no reaction was seen to occur in all cases and only the starting materials were recovered (**Scheme 58**).



For the *N*-oxide, R = H (**1**), Me (**71**), Cl (**151**), OMe (**79a**), CO_2Me (**152**)
For the dipolarophile, R' = H (**153**), CO_2Me (**54**)

Scheme 58

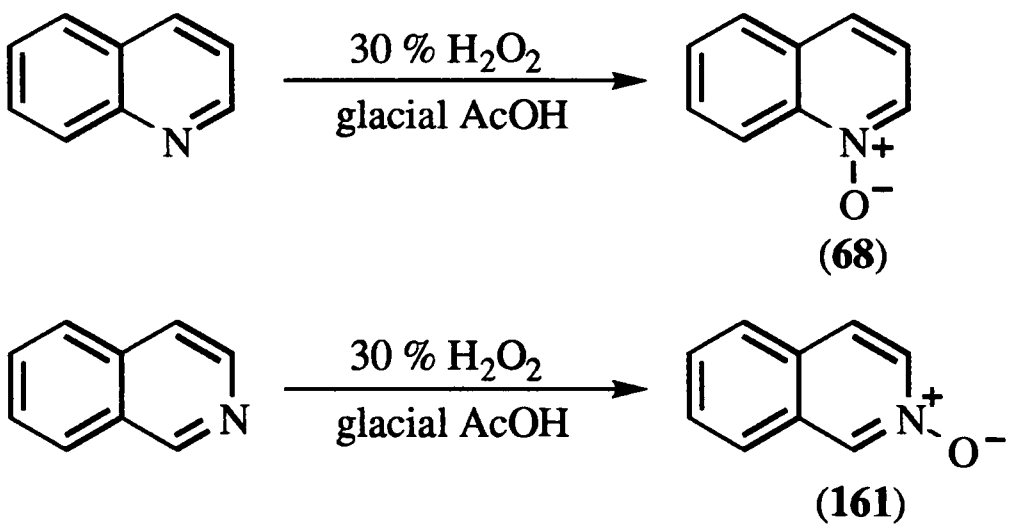
With the cycloadditions that utilised dimethyl maleate (**54**) as the dipolarophile, removal of the solvent, after the reaction had returned to ambient pressure afforded moderate amounts of the stereoisomer of dimethyl maleate (**54**), i.e. dimethyl fumarate (**55**). This presumably arose from isomerisation of the double bond, that was able to occur at high pressure.

The proposed failure of the intermolecular cycloaddition reactions of the various pyridine *N*-oxides was thought to be due to the large amount of aromatic stabilisation energy that would be lost on cycloaddition. This prompted the use of quinoline and isoquinoline *N*-oxides, (**68**) and (**161**). These *N*-oxides have a much lower aromatic stabilisation energy, which should make reaction more favourable.

3.5 Intermolecular [3+2] Cycloaddition Reactions with Quinoline and Isoquinoline *N*-Oxides

3.5.1 Synthesis of the *N*-Oxides

Both *N*-oxides were conveniently synthesised with 30 % hydrogen peroxide in glacial acetic acid using the conditions employed previously (**Scheme 59**).



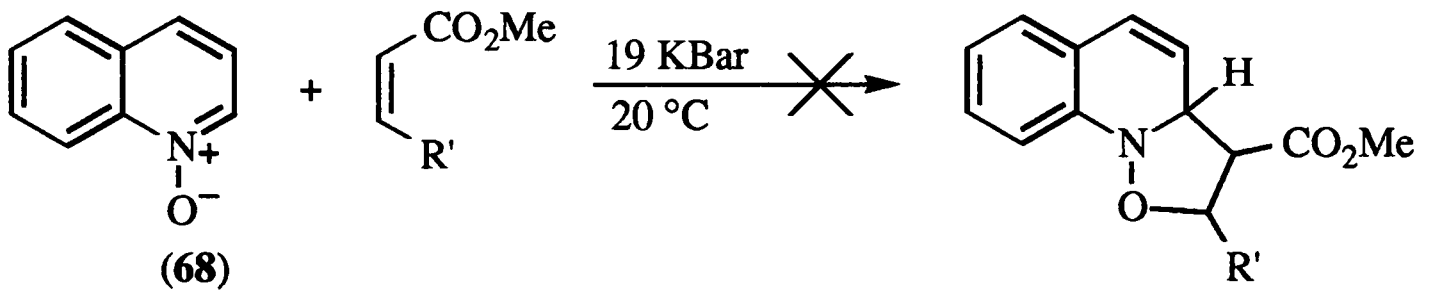
Scheme 59

Evidence for product formation in both cases came from the appearance of the molecular ion, MH^+, in the mass spectrum at 146 Daltons. In the IR spectra of both quinoline *N*-oxide (**68**) and isoquinoline *N*-oxide (**161**), there were strong N-O stretching absorptions at 1 228 and 1 253 cm^{-1}, respectively. Both *N*-oxides were isolated as crystalline solids, although quinoline *N*-oxide (**68**) appeared to be more hygroscopic than isoquinoline *N*-oxide (**161**), which meant that although a melting point of 99 °C could be obtained for isoquinoline *N*-oxide (**161**), quinoline *N*-oxide (**68**) appeared to melt at 60 °C, which was attributed to its dissolution in water. There was a large change in the ^1H NMR spectra of both compounds, upon oxidation, which

was clearly illustrated by the shift of the proton on C_1 in isoquinoline *N*-oxide (**161**), from δ 9.70 ppm in the starting material to 8.74 ppm.

3.5.2 High Pressure Cycloaddition Reactions

The cycloadditions of both quinoline and isoquinoline *N*-oxides (**68** and **161**) with methyl acrylate (**153**) and dimethyl maleate (**54**) were attempted at high pressure. For quinoline *N*-oxide (**68**), there was only one position to which cycloaddition could occur, but with isoquinoline *N*-oxide (**161**), there were two possible positions. Unfortunately, all four cycloaddition reactions proved unsuccessful, with starting materials recovered in all cases (**Scheme 60**). As before, the dimethyl maleate (**54**) reactions afforded some dimethyl fumarate (**55**).



Scheme 60

3.6 Summary

The [3+2] cycloaddition reactions had proved to be more difficult to effect than had been expected. It was decided to approach the cycloaddition in an intramolecular manner. By having the dipolarophile and *N*-oxide in the same molecule, the reactivity should increase, facilitating the reaction.

CHAPTER 4
RESULTS & DISCUSSION

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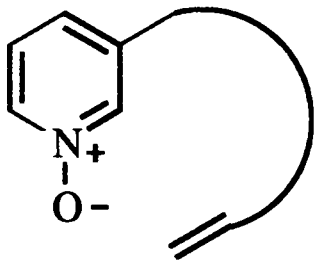
RESULTS & DISCUSSION

Investigation of the Intramolecular [3+2] Cycloaddition Reaction

4.1 Introduction

The study of the [3+2] cycloaddition reaction between pyridine *N*-oxides and a dipolarophile was expanded to include intramolecular reactions. It was hoped that the presence of an 'internal' dipolarophile should facilitate the reaction on the grounds of proximity of the reacting entities.

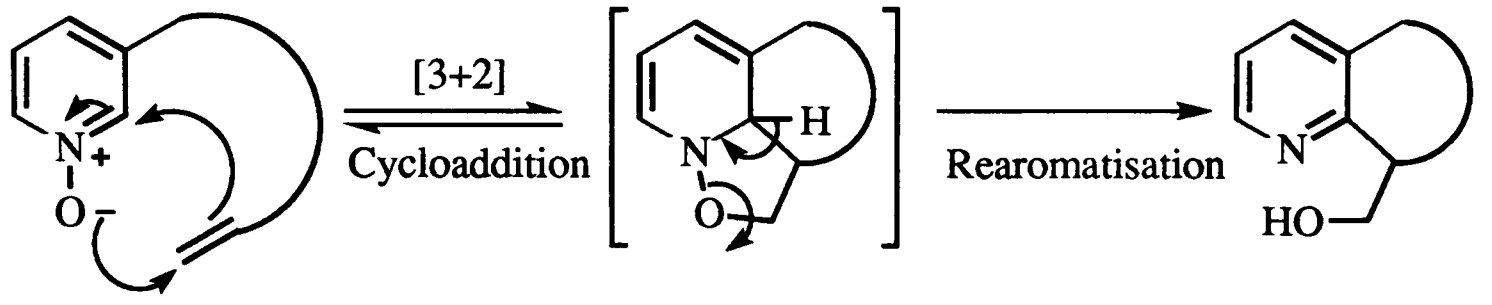
The aim was to produce novel target molecules containing the double bond tethered to the pyridine ring of the type as shown below (**162**) (**Figure 12**).



(**162**)

Figure 12

These types of substrates with the basic structure of (**162**) should be capable of undergoing [3+2] cycloaddition reactions in an intramolecular manner thereby forming polycyclic structures such as (**164**) (**Scheme 61**).

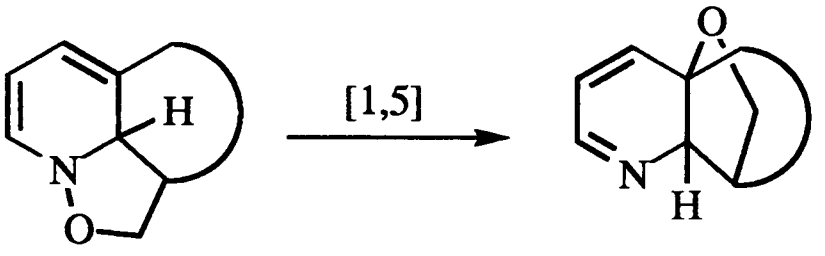


(162) **(163)** **(164)**

Scheme 61

The initial step of the [3+2] cycloaddition is presumed to occur *via* a concerted mechanism. This results in the intermediate (**163**), which is postulated to undergo N-O bond cleavage yielding the polycycle (**164**).

The possibility of a [1,5]-shift in the intermediate (**163**) would result in the 2,3-dihydro species (**165**) but formation of this type of species was ruled out, as it was assumed to be a high energy conformation (**Scheme 62**).



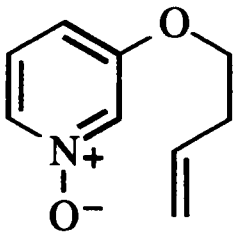
(163) **(165)**

Scheme 62

It seems likely that there may be a degree of out-of-plane twisting of the pyridine ring in this type of structure (**165**) although the four doubly bonded atoms (three carbons and one nitrogen) can all lie in a plane. It will subsequently be assumed that this type of product is not formed unless strong evidence for its existence is observed.

4.2 Construction of the Unactivated Cycloaddition Precursor

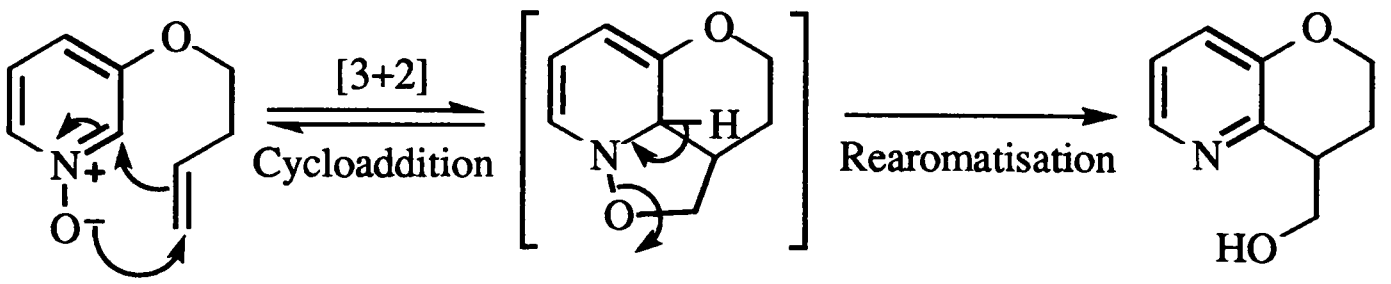
The first target molecule envisaged was 3-(3-butenyloxy)pyridine *N*-oxide (**166**), where the double bond is tethered to the pyridine ring by an alkyl chain with an oxygen atom as the linking unit (**Figure 13**).



(166)

Figure 13

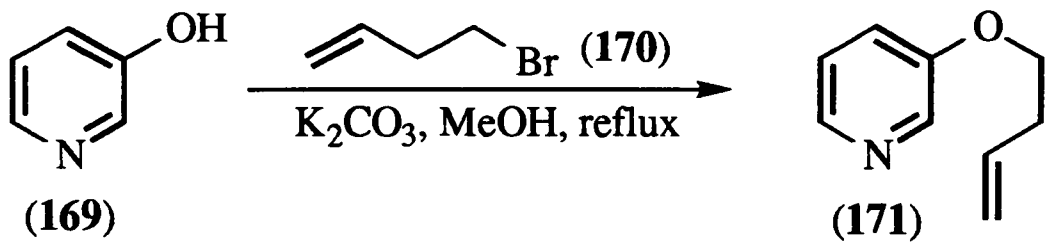
This should be capable of undergoing [3+2] cycloaddition in an intramolecular sense to yield the polycyclic intermediate (**167**) by forming a 6,6,5-ring system which presumably would rearomatise to yield the adduct (**168**) consisting of a 6-membered ring fused onto the pyridine nucleus (**Scheme 63**).



(166) **(167)** **(168)**

Scheme 63

Pyridine *N*-oxides are extremely hygroscopic and highly polar. As a consequence, the strategy adopted for forming this type of cycloaddition precursor was to construct the pyridine substrate first and then carry out the oxidation step to yield the *N*-oxide. To this end, synthesis of 3-(3-butenyloxy)pyridine (**171**) was the first step. This was accomplished by reaction of 3-hydroxypyridine (**169**) with 2 equivalents of 4-bromobut-1-ene (**170**) refluxing in methanol with potassium carbonate as the base for 17 hours (**Scheme 64**).



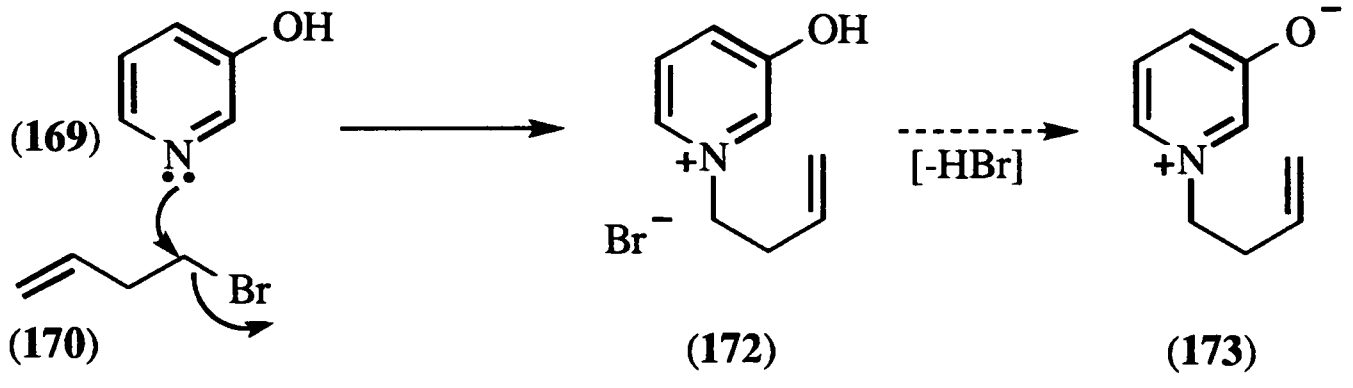
(169) **(171)**

Scheme 64

After work up, the crude reaction mixture was purified by column chromatography to yield the desired product (**171**) as a colourless oil in a rather disappointing 11 % yield. Evidence for the nature of the product came from the IR spectrum which showed the disappearance of the broad hydroxyl stretching frequency around 3 000 cm^{-1} present in the spectrum of the 3-hydroxypyridine (**169**) starting material. In the mass spectrum, the parent ion MH^+ was detected at 150 Daltons. The ^1H NMR spectrum also revealed resonances associated with the butenyl group in the product with a 1H multiplet from δ 5.94 - 5.86 ppm for the vinylic CH, a 1H double double doublet at δ 5.18 ppm for the *trans* vinylic proton with a *trans* coupling constant of *J* 17.2 Hz, a *geminal* coupling constant of *J'* 2.9 Hz and a long range four bond coupling of *J''* 1.5 Hz. The *cis* vinylic proton appeared at δ 5.13 ppm as another double double doublet with a *cis* coupling constant of *J* 10.3 Hz and with the same *geminal* and long range coupling constants. The two saturated CH_2 groups appeared as a triplet at δ 4.07 ppm showing a *vicinal* coupling of *J* 6.7 Hz for the one adjacent to the oxygen atom and a multiplet from δ 2.59 - 2.55 ppm for the other. The ^{13}C NMR spectrum also conveyed the identity of the product with resonances at δ 117.37 ppm for the vinylic CH_2 and at δ 67.52 ppm and δ 33.48 ppm for the two saturated CH_2 groups. It was not possible to assign unambiguously the ^{13}C NMR resonance for the vinylic CH, as it appeared in the same region as the pyridine resonances.

Various attempts were made to improve this yield. The use of 4 equivalents of 4-bromobut-1-ene (**170**) in the above reaction did not increase the amount of 3-(3-butenyloxy)pyridine (**171**) isolated.

In both reactions, there were vast amounts of insoluble material precipitated, which it was postulated was formed by reaction at the other nucleophilic centre in the 3-hydroxypyridine (**169**), i.e. the heterocyclic nitrogen, with 4-bromobut-1-ene (**170**). Nucleophilic displacement of the bromine by the nitrogen would form the 1-(3-butenyloxy)pyridinium bromide salt (**172**); subsequent loss of HBr forming (**173**) (**Scheme 65**).



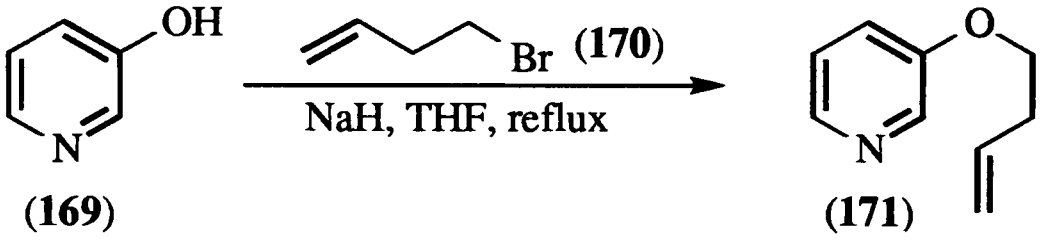
Scheme 65

It was not possible to isolate and subsequently purify either of these products (**172**) or (**173**) from the insoluble residue as it was found to be a mixture of inseparable adducts. The crude data could not be assigned to either adduct.

As a consequence, it was assumed that use of a stronger base would increase the amount of the desired product (**171**). If deprotonation of the hydroxyl group occurred efficiently, the oxide anion should be the most reactive centre and there would be more likelihood of the reaction occurring in the desired manner. Therefore the procedure was repeated with the more basic sodium methoxide in methanol. The reaction was carried out with the same 3-hydroxypyridine (**169**) with just over 1 equivalent of 4-bromobut-1-ene (**170**) and 1.3 equivalents of sodium methoxide. The sodium methoxide was generated *in situ* in the reaction mixture by the careful dissolution of a known amount of sodium in the reaction solvent methanol. The 3-hydroxypyridine (**169**) was allowed to deprotonate for 1 hour before the addition of the 4-bromobut-1-ene (**170**). On work up, the ^{1}H NMR spectrum of the product

obtained from the crude reaction mixture revealed that it consisted mainly of unreacted starting materials.

As a final attempt to improve the yield of this system, sodium hydride was employed as the base, this time the reaction was carried out in refluxing THF (**Scheme 66**).

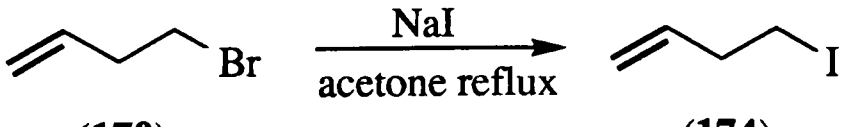


(169) **(171)**

Scheme 66

Again, the 3-hydroxypyridine (**169**) was allowed to deprotonate over 1 hour before the addition of the 4-bromobut-1-ene (**170**). On work up of the reaction mixture, a large quantity of insoluble material again was formed and purification of the crude organic soluble residue by column chromatography resulted in a 6 % yield of 3-(3-butenyloxy)pyridine (**171**) which gave spectroscopic data identical to that collected previously.

As with the allylation reaction in Chapter 2, attention was turned to the nature of the leaving group of 4-bromobut-1-ene (**170**). In order to facilitate nucleophilic displacement of the leaving group, iodide was used instead of bromide and 4-iodobut-1-ene (**174**) was synthesised in 63 % yield by the Finkelstein reaction from 4-bromobut-1-ene (**170**) by the standard method with 2 equivalents of sodium iodide in refluxing acetone (**Scheme 67**).[64]

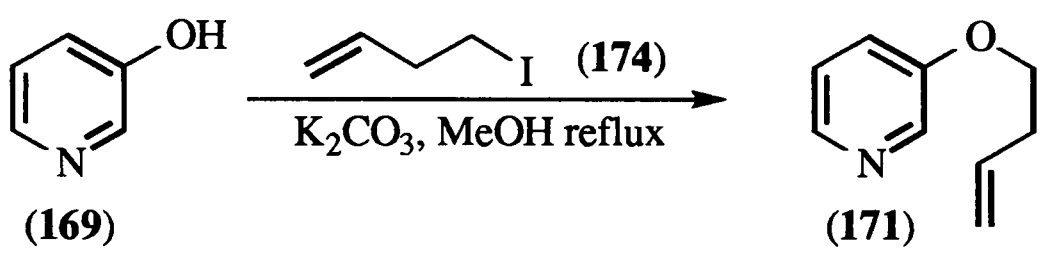


(170) **(174)**

Scheme 67

Interconversion of the leaving group was confirmed by mass spectrometric data showing the parent MH^+ ion at 182 Daltons and the shift of the proton resonance in the ^1H NMR spectrum for the saturated CH_2 adjacent to the halide. In the bromide (**170**) it existed as a triplet with *J* 7.0 Hz at δ 3.42 ppm whereas in the iodide (**174**) it was the same triplet with essentially the same coupling constant, within experimental error, of *J* 7.2 Hz but shifted up field to δ 3.19 ppm.

Reaction of the 4-iodobut-1-ene (**174**) with 3-hydroxypyridine (**169**) was carried out using the optimised reaction conditions employed previously, i.e. potassium carbonate in methanol at reflux. Unfortunately the yield of 3-(3-butenyloxy)pyridine (**171**) was not improved, the desired material being obtained in a very discouraging 10 % yield (**Scheme 68**).

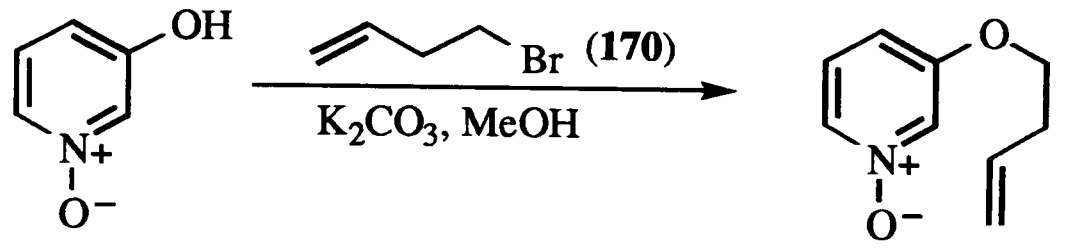


(**169**) (**171**)

Scheme 68

It was by now apparent that the problem lay with the competing reaction of nucleophilic displacement of the leaving group by the pyridine nitrogen (**Scheme 65**).

To circumvent the possible problem of reaction preferentially occurring at the nitrogen of the pyridine (**169**), attention was turned to 3-hydroxypyridine *N*-oxide (**175**) which now had the nitrogen blocked as nucleophilic attack by the oxygen atom of the *N*-oxide would not be a problem. The reaction was therefore carried out with 3-hydroxypyridine *N*-oxide (**175**) with 4-bromobut-1-ene (**170**) with potassium carbonate as the base (**Scheme 69**).

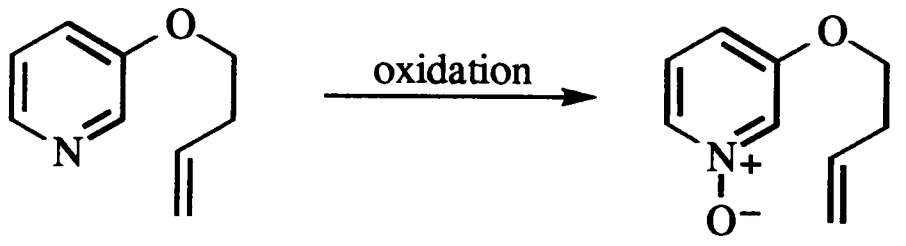


(175) **(166)**

Scheme 69

Carrying out the reaction at both room temperature and at refluxing did not effect the reaction with complete recovery of the starting material 3-hydroxypyridine *N*-oxide (**175**). Despite being successful in avoiding formation of the undesired insoluble products, of type (**172**) and (**173**) (**Scheme 65**), there was no formation of the required product (**166**) either. As before, transition to the more basic conditions provided by sodium hydride in refluxing THF was investigated in an attempt to isolate the adduct (**166**). Disappointingly, none of the desired product was found in the crude reaction mixture.

Since it had proved impossible to form the required cycloaddition precursor (**166**) directly from the *N*-oxide, an attempt was made to synthesise the 3-(3-butenyloxy)pyridine *N*-oxide (**166**) by oxidation of pyridine from the small amount of 3-(3-butenyloxy)pyridine (**171**) isolated previously (**Scheme 70**).



(171) **(166)**

Scheme 70

There are several methods for effecting the oxidation reaction of pyridines to their corresponding *N*-oxides. The most widely used methods tend to employ peracids, both as added reagents such as *m*-chloroperbenzoic acid which is one of the

most popular,[65] or prepared *in situ* from 30 - 90 % hydrogen peroxide and glacial acetic acid (discussed in Chapter 3).[32]

However, since the double bond in 3-(3-butenyloxy)pyridine (**171**) was fairly electron rich, care was needed to avoid epoxidation of the double bond. It was suspected that using hydrogen peroxide in glacial acetic acid would effect this transformation, rather than the requisite oxidation of the nitrogen atom.

In fact use of 30 % hydrogen peroxide in glacial acetic acid was found to cause degradation of the pyridine starting material (**171**) and for this reason a more mild oxidation reagent was sought.

Recently, there has been much effort put into the search for mild, safe and efficient oxidising agents. Kaczmarek has shown the urea / hydrogen peroxide adduct (UHP) to be an effective oxidising agent for *N*-heteroaromatic compounds.[66] The reagent is a white crystalline solid formed when urea is crystallised from aqueous hydrogen peroxide[67] and from the IR spectrum of the adduct, it is believed to be a complex formed by hydrogen-bonding between a urea hydrogen atom and a peroxide oxygen (**Figure 14**).[68]

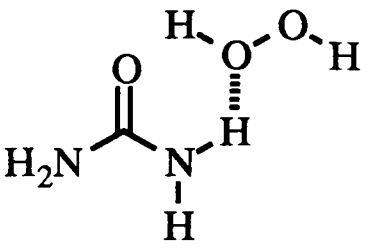
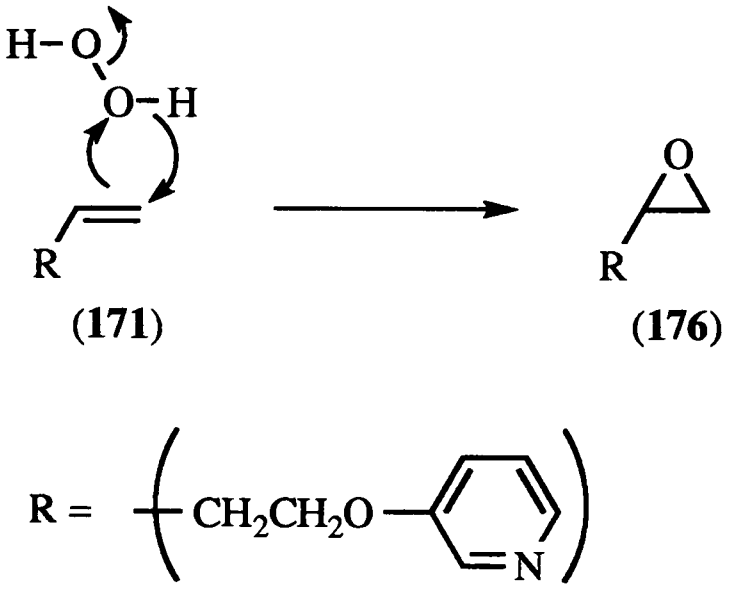


Figure 14

UHP is much safer than the usual reagents, very cheap and easy to prepare and also has a high proportion of hydrogen peroxide in the complex (36.2 %), which makes it a very desirable oxidising agent. The available oxygen content is about 90 % of the theoretical value.

However, attempted oxidation of the 3-(3-butenyloxy)pyridine (**171**) with the hydrogen peroxide from the UHP complex, resulted in formation of the epoxide (**176**) as a colourless oil (**Scheme 71**).



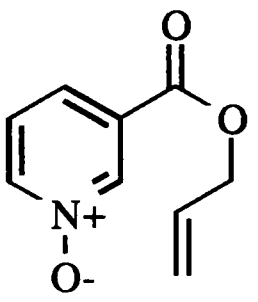
Scheme 71

Evidence for the formation of this product came mainly from the ^{1}H NMR spectrum showing loss of the vinyl proton resonances at δ 5.94 - 5.86 ppm which appeared as a 1H multiplet in the starting material along with the resonance at δ 5.18 ppm as a 1H double double doublet corresponding to the *trans* proton and at δ 5.13 ppm as another 1H double double doublet corresponding to the *cis* proton. These are replaced by a 1H multiplet at δ 3.17 - 3.09 ppm for the CH of the epoxide and a *pseudo*-triplet with *J* 4.6 Hz for both *geminal* and *vicinal* coupling constants at δ 2.85 ppm for the proton of the epoxide CH_2 group *trans* relative to the epoxide CH and as a double doublet with *geminal* coupling constant *J* 4.6 Hz and *vicinal* coupling constant of *J'* 2.7 Hz at δ 2.58 ppm for the proton of the epoxide CH_2 group *cis* relative to the epoxide CH. There was also an increase of 16 Daltons in the mass spectrum with a peak at 166 corresponding to the MH^+ ion of the epoxide (**176**). It would have been the same for the *N*-oxide (**166**) but the ^{1}H NMR spectrum discounted this. This result was not particularly surprising since the double bond was by far the most electron rich centre in the molecule.

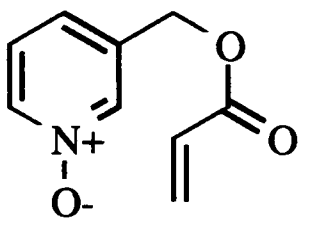
Due to the poor yields achieved for the allylation of the 3-hydroxypyridine (**169**), the difficulty experienced in selective oxidation of the resultant pyridine derivative (**171**) and the inability to synthesise the desired tethered moiety (**166**) directly from the *N*-oxide (**175**), attention was turned to the construction of pyridine substrates with less electron rich double bond tethers that can be formed by reaction of pyridine compounds with more reactive species.

4.3 Construction of the Ester Linked Cycloaddition Precursors

Two ester cycloaddition precursors were envisaged that could undergo [3+2] cycloaddition yielding a 6,6-fused ring system. They were 2-propenyl (3-pyridine) carboxylate *N*-oxide (**177**) which had an electron withdrawing group on the pyridine moiety and (3-pyridyl)methyl propenoate *N*-oxide (**178**) which had an electron withdrawing group on the dipolarophilic part of the molecule (**Figure 15**).



(**177**)



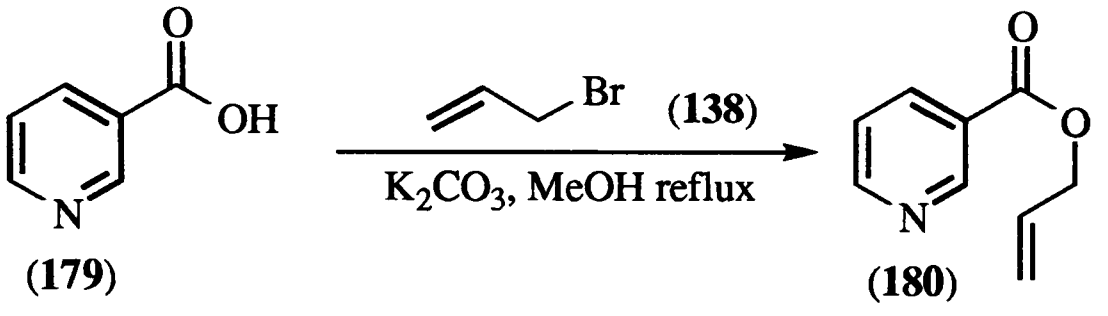
(**178**)

Figure 15

The same strategy of construction of the 3-substituted pyridine prior to oxidation to the *N*-oxide was applied.

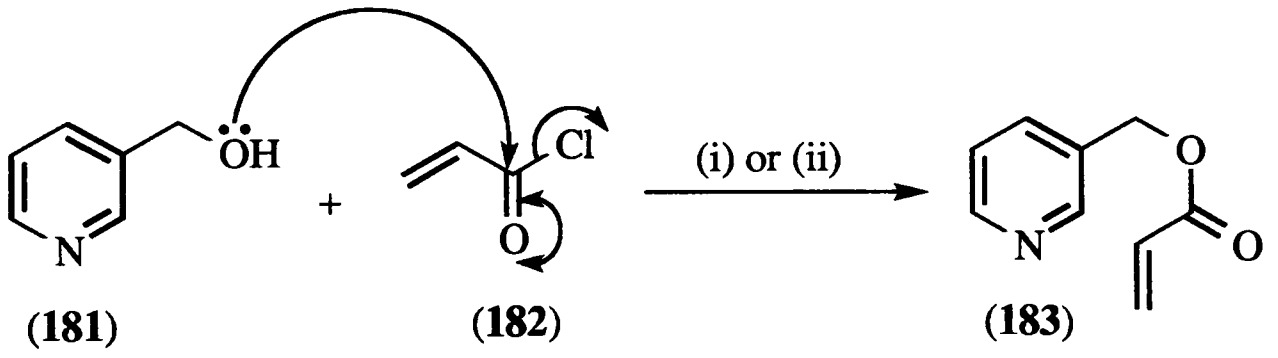
Synthesis of the substrate 2-propenyl (3-pyridine) carboxylate (**180**) was attempted using similar reaction conditions applied to construction of the 3-(3-butenyloxy)pyridine (**171**) compound. Refluxing the acid (**179**) in methanol with the more reactive allyl bromide (**138**) and potassium carbonate (**Scheme 72**) gave none of the desired compound (**180**), only a water soluble gummy orange solid, which

was presumed to consist of pyridinium salts formed by reaction at the heterocyclic nitrogen with allyl bromide (**138**). Purification of this residue proved impossible and the crude reaction mixture was unidentifiable due to the very poor quality of the ^1H NMR spectrum obtained from it.



Scheme 72

By now it was obvious that a change in tactics was required in order to construct the required pyridine cycloaddition precursors. Transfer to the more reactive acid chlorides could be made in the construction of the other cycloaddition precursor (**178**). Synthesis of the 3-substituted pyridine (**183**) was attempted by reaction of 3-pyridinemethanol (**181**) with acryloyl chloride (**182**) in DCM, both with and without potassium carbonate (**Scheme 73**).



(i) K_2CO_3, DCM, r.t. (ii) DCM, r.t.

Scheme 73

Both reactions resulted in the formation of a thick yellow precipitate and a yellow solution. The reaction carried out with potassium carbonate failed to give any of the desired product (**183**) but, in the absence of potassium carbonate, the reaction did result in a small amount of (**183**). Preparative t.l.c. on neutral alumina plates

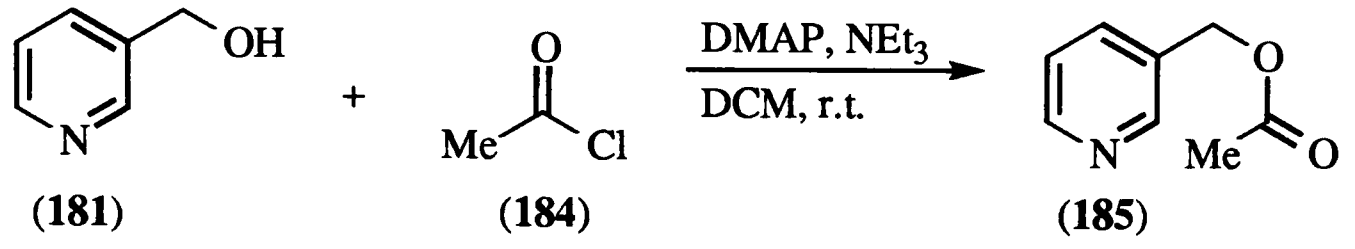
eluting with ethyl acetate afforded the pure (3-pyridyl)methyl propenoate (**183**) as a yellow oil in a yield of just over 1 %. In both cases, the gummy precipitates were assumed to contain a mixture of the salts formed, as before, by reaction at the nitrogen as well as potassium carbonate. Adequate purification of these salts could not be achieved.

Evidence for the product (**183**) was seen in the mass spectrum with a peak corresponding to the MH^+ ion at 164 Daltons. In the ^1H NMR spectrum, the vinyl proton resonances appeared at δ 6.44 ppm as a 1H double doublet with *trans* and *geminal* coupling constants, *J* 17.3 and *J'* 1.3 Hz respectively, for the *trans* proton, at δ 6.15 ppm as another 1H double doublet showing both *trans* and *cis* coupling constants, *J* 17.3 and *J'* 10.4 Hz respectively, for the vinylic CH and at δ 5.86 ppm as a 1H double doublet for the *cis* proton with *cis* and *geminal* coupling constants of *J* 10.4 and *J'* 1.3 Hz respectively. The ^{13}C NMR spectrum showed the carbonyl resonance at δ 165.73 ppm and the vinylic CH_2 resonance at δ 131.51 ppm. The vinylic could not be assigned unambiguously as it appeared in the same region of the spectrum as the pyridine CH resonances. The IR spectrum showed a strong carbonyl stretching frequency at 1 724 cm^{-1} and the vinylic stretching frequencies at 1 597 and 1 579 cm^{-1}.

In an attempt to improve the yield of this reaction, it was decided to change the reaction conditions slightly and use DMAP with triethylamine.[69,70]

Before attempting the reaction on these substrates, two test reactions were carried out. The acetylation of both 3-pyridinemethanol (**181**) and 3-pyridinemethanol *N*-oxide (**186**) was attempted to see if this reaction could be successfully applied to pyridine substrates, and more importantly, to see if it could be carried out on the *N*-oxide thus avoiding subsequent oxidation. To this end, the first reaction was conducted with 3-pyridinemethanol (**181**) and acetyl chloride (**184**), 0.1 equivalents

of DMAP and 1 equivalent of triethylamine in DCM at room temperature. After work up and purification of the crude product by flash chromatography, (3-pyridyl)methyl acetate (**185**) was obtained as a yellow oil in 79 % yield (**Scheme 74**).

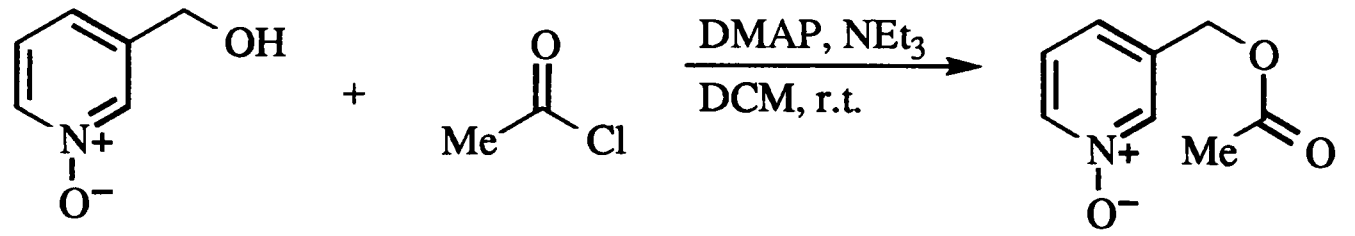


(181) **(184)** **(185)**

Scheme 74

Evidence for the product was seen in the mass spectrum with a peak corresponding to the M^+ ion at 151 Daltons. The appearance of the methyl singlet at δ 2.05 ppm for the ester methyl group in the ^1H NMR spectrum, the carbonyl resonance at δ 170.44 ppm in the ^{13}C NMR spectrum and the strong carbonyl stretching frequency in the IR spectrum at 1 746 cm^{-1}, supported product formation.

The reaction of 3-pyridinemethanol *N*-oxide (**186**) with acetyl chloride (**184**), 0.1 equivalents of DMAP and 1 equivalent of triethylamine in DCM at room temperature was unfortunately not as successful in forming the pure product (**187**) (**Scheme 75**).



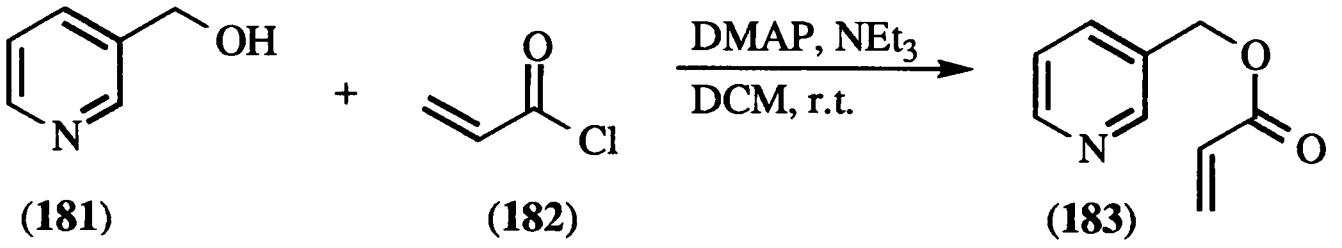
(186) **(184)** **(187)**

Scheme 75

Although the (3-pyridyl)methyl acetate *N*-oxide (**187**) was indeed formed, as seen in the ^1H NMR spectrum of the crude reaction mixture with the methyl singlet at δ 2.06 ppm for the ester methyl group, separation of the desired adduct (**187**) from the triethylamine hydrochloride side product proved impossible.

It was therefore obvious that the strategy for forming the cycloaddition precursors would have to proceed *via* the pyridine intermediate and would require subsequent oxidation to the *N*-oxide in order to form the cycloaddition precursor.

In order to synthesise the first ester cycloaddition precursor (**178**), the above reaction was carried out using 3-pyridinemethanol (**181**) and acryloyl chloride (**182**). This resulted in formation of the product (3-pyridyl)methyl propenoate (**183**) in 44 % yield (**Scheme 76**).

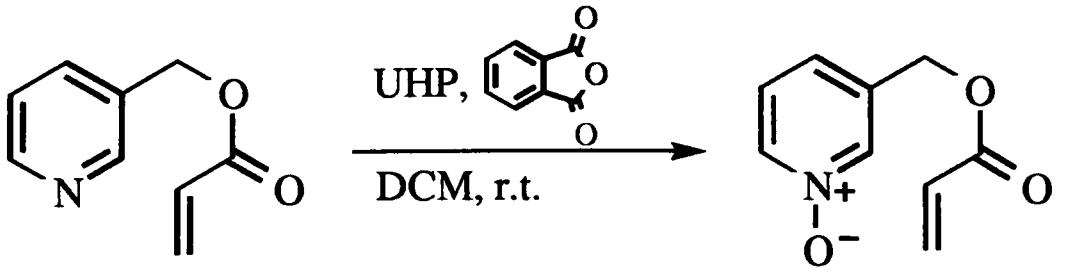


(181) **(182)** **(183)**

Scheme 76

The spectrometric data for this compound (**183**) agreed with that already obtained.

This product (**183**) has an electron deficient double bond, which should permit selective oxidation of the pyridine nitrogen to yield the *N*-oxide (**178**) rather than epoxidation of the double bond. This was carried out using the mild and safe reagent, UHP with phthalic anhydride according to the procedure of Kaczmarek (**Scheme 77**).[66]



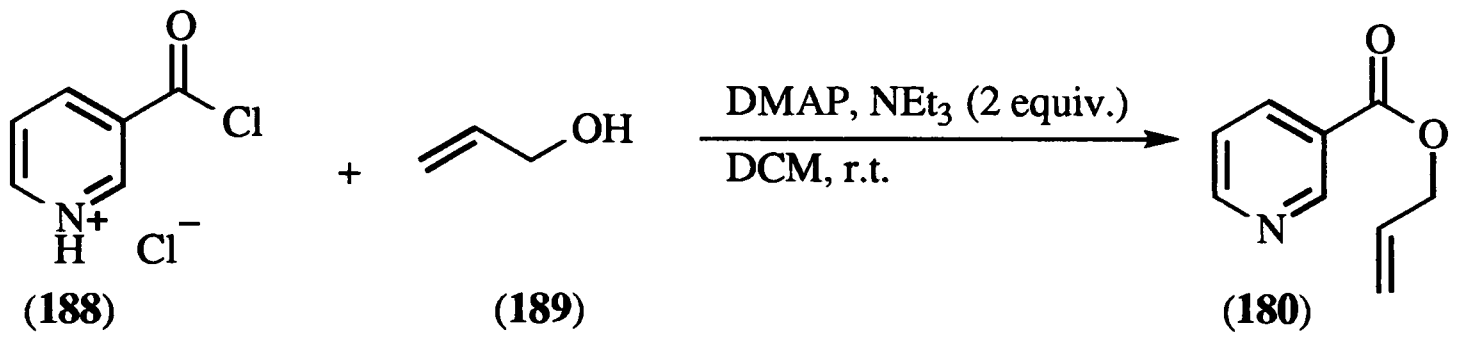
(183) **(178)**

Scheme 77

The (3-pyridyl)methyl propenoate *N*-oxide (**178**) was formed by the above reaction in 82 % yield as the only product. No epoxidation of the double bond was encountered. The product (**178**) was easily purified by recrystallisation from DCM resulting in a white crystalline hygroscopic solid. The hygroscopic nature of this compound meant that it appeared to melt below 50 °C, but this was attributed to its dissolution in water. Confirmation of the product was from the mass spectrum showing a peak at 180 Daltons corresponding to the MH^+ ion, the N-O stretching frequency in the IR spectrum at 1 280 cm^{-1} and the vast change in the pyridine proton resonances in the ^1H NMR spectrum. In (3-pyridyl)methyl propenoate (**183**) they were at δ 8.64 ppm as a 1H doublet with a coupling constant of *J* 2.2 Hz for the proton pyH_2, δ 8.57 ppm as a 1H double doublet with coupling constants of *J* 4.8 Hz and *J'* 1.6 Hz for pyH_6, δ 7.71 ppm as a 1H double triplet with *J* 7.9 Hz and *J'* 1.9 Hz for pyH_4 and at δ 7.29 ppm as a 1H double doublet with *J* 7.9 Hz and *J'* 4.8 Hz for pyH_5. This changed to δ 8.28 ppm as a 1H singlet for pyH_2, δ 8.17 ppm as a 1H double triplet with *J* 5.6 Hz, *J'* 1.8 Hz for pyH_6 and δ 7.30 - 7.27 ppm as a 2H multiplet for both pyH_4 and pyH_5 in (3-pyridyl)methyl propenoate *N*-oxide (**178**). The larger coupling constants in all cases were the *ortho* couplings round the ring but also seen were the much smaller *meta* couplings which were four bond couplings typically around 1 - 2 Hz. The coupling patterns also showed some anomalies, mainly the appearance of an apparent double triplet for pyH_4, but a double doublet for pyH_6 in (3-pyridyl)methyl propenoate (**183**) and pyH_6 as a double triplet in (3-pyridyl)methyl propenoate *N*-oxide (**178**). The pyH_2 protons also differed between the two compounds, as a doublet in the former and as a singlet in the latter. The ^{13}C NMR spectrum also revealed a shift of the pyridine carbon resonances. The only pyridine carbon it was possible to assign unambiguously was the one at the quaternary centre C_3, due to the situation of the vinylic CH resonance in the same region as the pyridine CH's. This resonance was shifted from δ 131.51 ppm in the pyridine (**183**) to δ 135.61 ppm in the *N*-oxide (**178**).

Encouraged by this success, analogous reactions were carried out in an attempt to construct 2-propenyl (3-pyridine) carboxylate (**180**) and its *N*-oxide 2-propenyl (3-pyridine) carboxylate *N*-oxide (**177**).

In order to synthesise the 3-substituted pyridine (**180**), the appropriate alcohol and acid chloride was required. For this reason, it was necessary to use the acid chloride of the pyridine compound and the alcohol of the allylic compound, and reverse the nature of the substrates used previously. The synthesis was accomplished by reaction of allyl alcohol (**189**) with the hydrochloride salt of 3-pyridinecarbonyl chloride (**188**) with 0.1 equivalents of DMAP, as before, but using 2 equivalents of triethylamine to 'trap' the extra equivalent of hydrogen chloride from the pyridine salt (**Scheme 78**).



(188) **(189)** **(180)**

Scheme 78

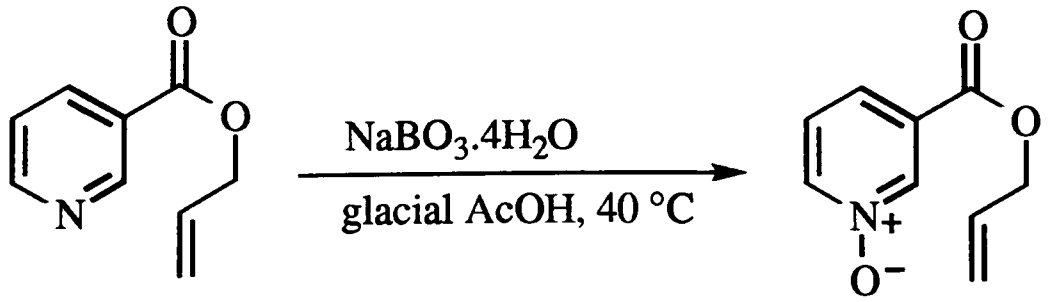
The reaction was carried out, as before, at room temperature in DCM and produced the desired compound 2-propenyl (3-pyridine) carboxylate (**180**) in an 88 % yield after purification by flash chromatography.

Again evidence for product formation came from the spectral information. In the mass spectrum, a peak corresponding to M^+ was detected at 163 Daltons. The ^1H NMR spectrum showed the allyl group at δ 6.07 - 6.02 ppm as a 1H multiplet for the vinylic CH proton, δ 5.43 ppm as a 1H double doublet corresponding to the *trans* vinylic proton with a *trans* coupling constant of *J* 17.2 Hz and *geminal* coupling constant of *J* 1.4 Hz, δ 5.32 ppm as a 1H double doublet corresponding to the

cis vinylic proton with a *cis* coupling constant of *J* 10.4 Hz and *geminal* coupling constant of *J* 1.4 Hz and δ 4.86 ppm as a 2H double triplet corresponding to the saturated CH_2 protons which had a *vicinal* coupling constant of *J* 5.7 Hz and a long range four bond coupling constant of *J* 1.4 Hz. In the ^{13}C NMR spectrum, the allyl group resonances appeared at δ 118.79 ppm for the vinylic CH_2 and at δ 65.92 ppm for the saturated CH_2. The resonance for the vinylic CH in the carbon spectrum could not be distinguished conclusively from the pyridine CH resonances.

Oxidation of the product (**180**) was then considered knowing that for this compound there was not such an electron deficient double bond as found with (3-pyridyl)methyl propenoate (**183**), thus the possibility of problematic epoxidation of the double bond was increased. At this time, the sodium perborate oxidation procedure of McKillop was investigated.[71] He reported that sodium perborate tetrahydrate in glacial acetic acid was a very cheap and effective oxidising agent and more importantly that 'olefins were only very slowly oxidised, if at all'. Sodium perborate had also recently been presented as capable of oxidising pyridine compounds to *N*-oxides in good yield in the presence of a double bond, albeit an electron deficient one.[72]

Accordingly, oxidation of 2-propenyl (3-pyridine) carboxylate (**180**) to the *N*-oxide (**177**) was attempted with the optimum amount of sodium perborate tetrahydrate, found to be 2.2 equivalents, in glacial acetic acid with stirring at 40 °C for 22 hours (**Scheme 79**).



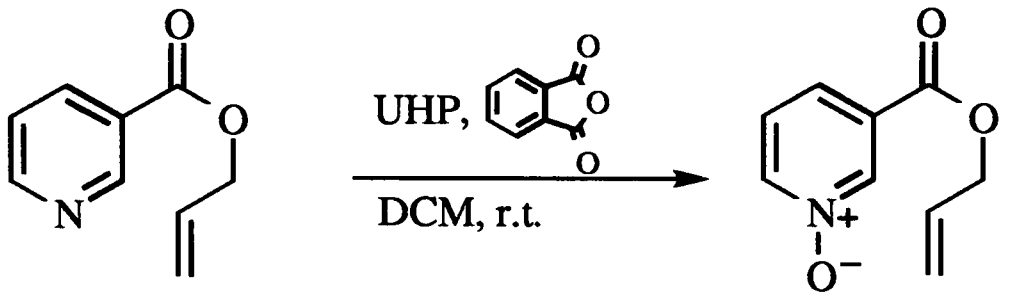
(180) **(177)**

Scheme 79

The required oxidation was seen to occur producing 2-propenyl (3-pyridine) carboxylate *N*-oxide (**180**) in an excellent 98 % yield. Again, the *N*-oxide (**177**) was a very hygroscopic solid, which meant that a valid melting point could not be obtained.

Indication that the oxidation had occurred came from the mass spectrum which showed the protonated molecular ion MH^+ at 180 Daltons and the IR spectrum which showed an N-O stretching frequency at 1 304 cm^{-1}. The ^1H NMR spectrum provided further evidence for the oxidation by comparison of the pyridine proton resonances of the *N*-oxide (**177**) with those for the unoxidised compound (**180**). Before oxidation they appeared as a 1H doublet at δ 9.25 ppm with a *meta* coupling *J* 1.6 Hz for pyH_2, a 1H double doublet at δ 8.78 ppm with an *ortho* coupling *J* 4.8 Hz and a *meta* coupling *J* 1.6 Hz for pyH_6, a 1H double triplet at δ 8.32 ppm with an *ortho* coupling *J* 7.9 Hz and a *meta* coupling *J* 2.0 Hz for pyH_4 and another 1H double doublet at δ 7.40 ppm with one *ortho* coupling of *J* 7.9 Hz and the other at *J* 4.8 Hz for pyH_5. After oxidation they changed quite dramatically to a 1H singlet at δ 8.83 ppm for pyH_2, a 1H multiplet from δ 8.39 to 8.38 ppm for pyH_6, a 1H double doublet at δ 7.91 ppm with an *ortho* coupling *J* 7.2 Hz and a *meta* coupling *J* 1.2 Hz for pyH_4 and another 1H double doublet at δ 7.41 ppm with one *ortho* coupling of *J* 7.2 Hz and the other at *J* 6.8 Hz for pyH_5. This change of the electron density around the pyridine ring by oxidation was also exemplified by the differences between the carbon resonances in the ^{13}C NMR spectrum. Since it was again not possible to assign unambiguously the carbon resonances corresponding to the pyridine CH carbons (due to the vinylic CH resonance occurring in the same spectral region), it was necessary to note the change of the quaternary ring carbon C_3. In the oxidised product (**177**) it appeared at δ 130.46 ppm, as it was more deshielded in the *N*-oxide (**177**) than in the pyridine compound (**180**), where it was seen at δ 126.05 ppm.

Satisfied with the advantages of oxidation of 2-propenyl (3-pyridine) carboxylate (**180**) by sodium perborate, it was decided to see if the UHP oxidation could oxidise (**180**) to the *N*-oxide without epoxidising the double bond. To this end, 1 equivalent of both UHP and phthalic anhydride were dissolved in dry DCM and stirred under nitrogen at room temperature before the addition of 0.9 equivalents of 2-propenyl (3-pyridine) carboxylate (**180**) (**Scheme 80**).



(180) **(177)**

Scheme 80

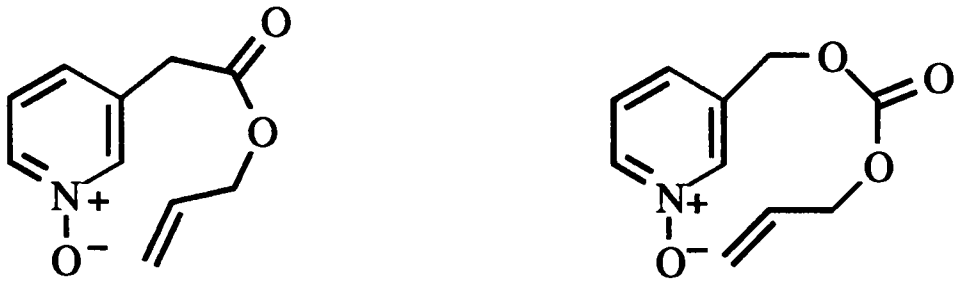
In fact, the oxidation did occur as desired producing the *N*-oxide (**177**) in 79 % yield, as the sole product with no suggestion of reaction with the double bond. The spectroscopic data obtained was identical to that found for the product of the sodium perborate oxidation.

Two cycloaddition precursors (**177** and **178**), that should have different electronic requirements in the [3+2] cycloaddition reaction, had been synthesised and upon cycloaddition should form a 6-membered ring fused onto the pyridine.

To further the study, synthesis of more cycloaddition precursors of this nature using the effective ester linking system were required prior to attempting the [3+2] addition.

Accordingly, two more cycloaddition precursors were envisaged that could result in the formation of 6,7- and 6,8-fused ring systems after cycloaddition, namely 2-propenyl (3-pyridyl)acetate *N*-oxide (**190**) and 2-propenyl (3-pyridyl)methyl

carbonate *N*-oxide (**191**) (**Figure 16**). These could be constructed using the methodology already developed, particularly since it has been discovered that oxidation of the pyridine ring of this type of system no longer presents any difficulty.



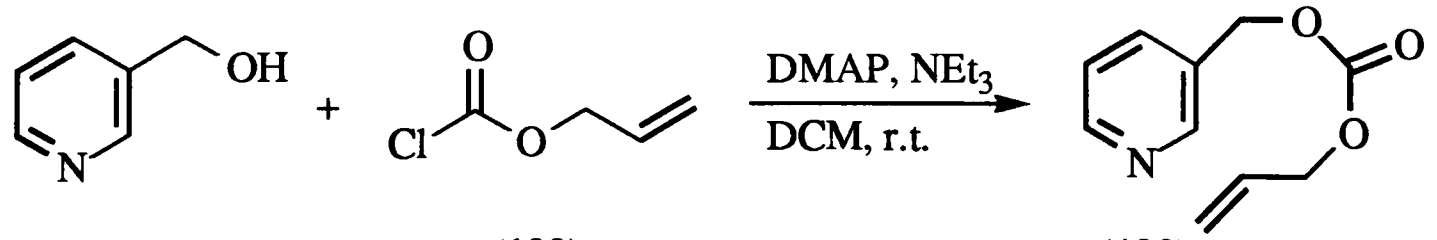
(190) **(191)**

Figure 16

Subsequent [3+2] cycloaddition of 2-propenyl (3-pyridyl)acetate *N*-oxide (**190**) would result in a 7-membered ring fused onto the pyridine ring and cycloaddition of 2-propenyl (3-pyridyl)methyl carbonate *N*-oxide (**191**) would result in a 8-membered ring fused onto the pyridine ring.

Construction of the cycloaddition precursor (**191**) was able to follow the synthetic pathway previously established using commercially available reagents, so it was more convenient to deal with its synthesis prior to that for (**190**).

2-Propenyl (3-pyridyl)methyl carbonate (**193**) was therefore constructed by reaction of 3-pyridinemethanol (**181**) with 1 equivalent of allyl chloroformate (**192**) in the presence of 0.1 equivalents of DMAP and 1.1 equivalents of triethylamine in dry DCM at room temperature under nitrogen (**Scheme 81**).

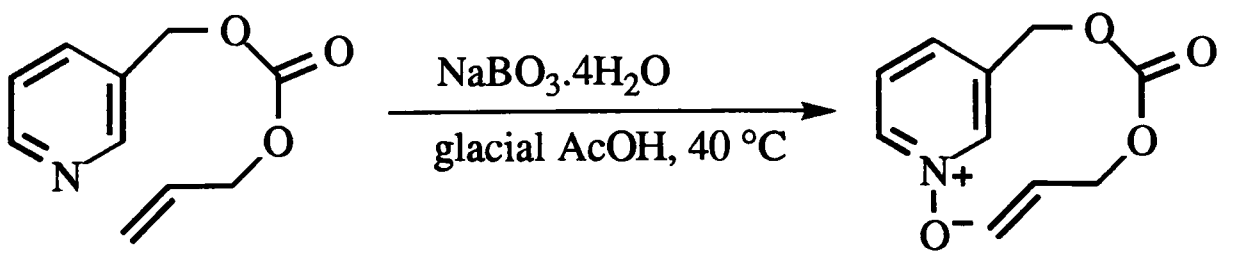


(181) **(192)** **(193)**

Scheme 81

After work up and subsequent purification by flash chromatography, 2-propenyl (3-pyridyl)methyl carbonate (**193**) was obtained in 87 % yield as a yellow oil. Proof of product structure was seen in the mass spectrum by the peak corresponding to the molecular ion M^+ at 193 Daltons. There was also a carbonyl resonance in the IR spectrum at 1 747 cm^{-1}, typical of the carbonate group. The ^1H NMR spectrum showed evidence of the allyl group with resonances at δ 6.01 - 5.85 ppm as a 1H multiplet corresponding to the vinylic CH group, δ 5.36 ppm as a 1H double double doublet with a *trans* coupling constant of *J* 17.3 Hz, *geminal* coupling of *J'* 2.7 Hz and a four bond coupling with *J"* 1.3 Hz for the *trans* vinylic proton, δ 5.28 ppm as a 1H double double doublet with a *cis* coupling constant of *J* 10.4 Hz, a *geminal* coupling of *J'* 2.7 Hz and a four bond coupling with *J"* 1.3 Hz for the *cis* vinylic proton and at δ 4.65 ppm as a 2H double triplet with a *vicinal* coupling constant of *J* 5.8 Hz and the four bond coupling of *J'* 1.3 Hz for the saturated CH_2 next to the vinyl group. The other saturated CH_2 next to the pyridine ring appeared as a 2H singlet at δ 5.19 ppm, compared with its position at δ 4.65 ppm as a 2H singlet in the starting material 3-pyridinemethanol (**181**).

Formation of *N*-oxide (**191**) was achieved by the higher yielding perborate oxidation. Correspondingly, the product (**193**) from the above reaction was dissolved in glacial acetic acid and warmed to 40 °C before the addition of 2.2 equivalents of sodium perborate (**Scheme 82**).



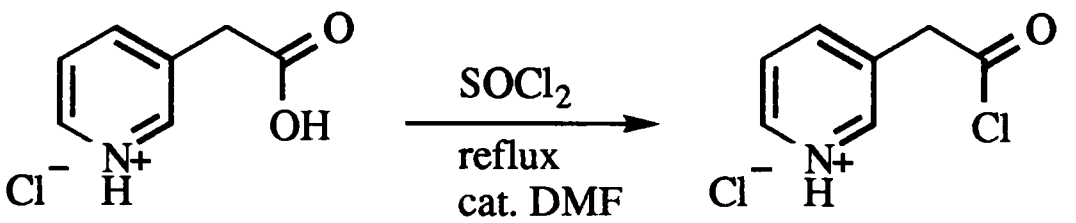
(193) **(191)**

Scheme 82

After subsequent work up, the product 2-propenyl (3-pyridyl)methyl carbonate *N*-oxide (**191**) was isolated in an 88 % yield as a beige crystalline hygroscopic solid revealing that pyridine compounds of this type are stable under these fairly adverse reaction conditions. The compound was seen to melt at a fairly low temperature (50 - 51 °C) that was attributed to its dissolution in water.

Spectroscopic data confirmed that the reaction had been successful. The mass spectrum showed a peak corresponding to the molecular ion M^+ at 209 Daltons and the IR spectrum revealed an N-O stretching frequency at 1 270 cm^{-1}. Again the ^1H NMR showed a change in the pyridine proton resonances on going from the pyridine to the *N*-oxide. In the pyridine (**193**) they appeared as a 1H doublet at δ 8.65 ppm with a *meta* coupling constant *J* 2.2 Hz for the proton at pyH_2, as a 1H double doublet at δ 8.60 ppm with an *ortho* coupling constant of *J* 4.8 Hz and a *meta* coupling constant of *J* 1.7 Hz for the proton at pyH_6, as a 1H multiplet from δ 7.76 - 7.72 ppm for pyH_4 and as a 1H double double doublet at δ 7.31 ppm with one *ortho* coupling constant of *J* 7.8 Hz, the other of *J* 4.8 Hz and a *meta* coupling constant of *J* 0.8 Hz for the proton at pyH_5. However, for the *N*-oxide (**191**) a large shift was noted, to a 1H singlet at δ 8.33 ppm for the proton pyH_2, a 1H multiplet at δ 8.23 - 8.22 ppm for pyH_6 and a 2H multiplet, δ 7.35 - 7.32 ppm, for pyH_5 and pyH_4.

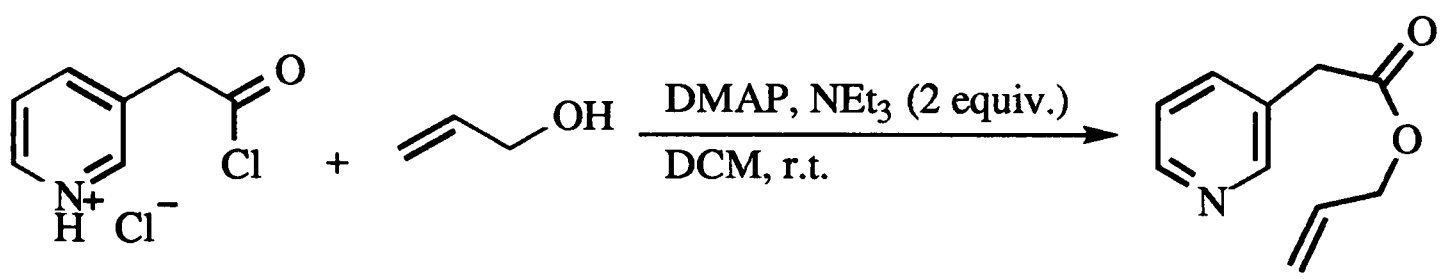
Construction of the other ester cycloaddition precursor 2-propenyl (3-pyridyl)acetate *N*-oxide (**190**) proved to be very problematic. In order to use the previously developed methodology, the starting materials required were allyl alcohol (**189**) and (3-pyridyl)methylcarbonyl chloride (**195**). The allyl alcohol (**189**) was readily available, but it was necessary to synthesise the (3-pyridyl)methylcarbonyl chloride (**195**) from the carboxylic acid, (3-pyridyl)acetic acid. This acid was commercially available as the hydrochloride salt (**194**) and conversion to the acid chloride as a hydrochloride salt (**195**) was attempted by refluxing in thionyl chloride with a catalytic amount of DMF for 1.5 hours (**Scheme 83**).



(194) **(195)**

Scheme 83

It was found impossible to isolate and characterise the acyl chloride (**195**) so, after the solvent was removed from the reaction mixture to yield a red oil, it was taken up in DCM and the next part of the reaction sequence was conducted. The solution of (**195**) in DCM was then added dropwise to a solution of allyl alcohol (**189**) containing a catalytic amount of DMAP and 2 equivalents of triethylamine since the acyl chloride (**195**) was presumed to be a hydrochloride salt (**Scheme 84**).



(195) **(189)** **(196)**

Scheme 84

After being allowed to stir overnight, subsequent work up and attempted purification of the resultant residue by flash chromatography gave none of the desired product (**196**).

It was assumed that it was the chlorination reaction that had been unsuccessful since successful reaction of an acid chloride with an alcohol in DCM with DMAP and triethylamine had been demonstrated with a variety of substrates.

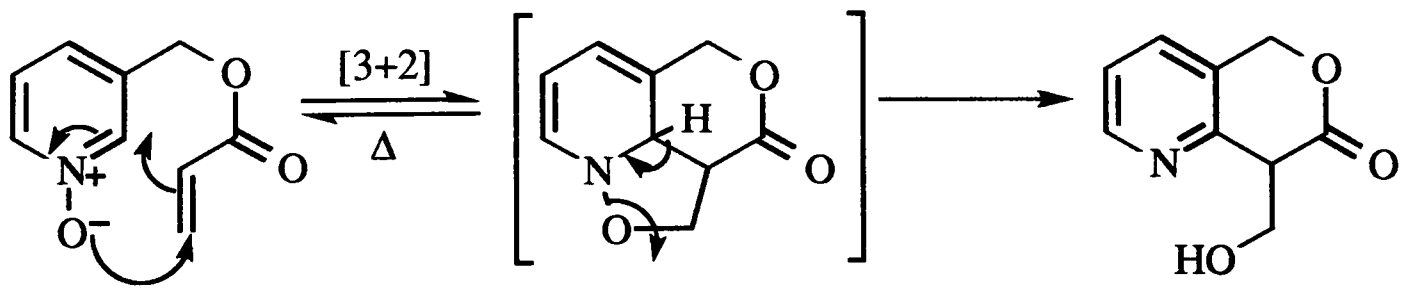
The reaction sequence was therefore repeated, this time leaving the chlorination reaction for a longer time period of 4 hours which resulted in formation a

green oil on this occasion, but the second step was carried out as before. Again purification of the resultant residue by flash chromatography gave none of the desired product (**196**) in any of the collected fractions, which on this occasion all had a pungent odour.

At this stage, it was decided to proceed with the three cycloaddition precursors already constructed, namely (3-pyridyl)methyl propenoate *N*-oxide (**178**), 2-propenyl (3-pyridine) carboxylate *N*-oxide (**177**) and 2-propenyl (3-pyridyl)methyl carbonate *N*-oxide (**191**) in order to attempt an intramolecular [3+2] cycloaddition reaction.

4.4 Thermal [3+2] Cycloaddition Reactions of the Ester Precursors

The first cycloaddition precursor considered was (3-pyridyl)methyl propenoate *N*-oxide (**178**). Intramolecular cycloaddition of the 1,3-dipole of the aromatic pyridine *N*-oxide unit onto the double bond tethered to the 3-position of the pyridine ring would be assumed to occur *via* the concerted mechanism forming the intermediate (**197**), losing the aromaticity of the pyridine nucleus. This intermediate could then undergo a rearomatisation step to yield the alcohol product (**198**), presumably driven by the gain in aromatic stabilisation energy (**Scheme 85**).



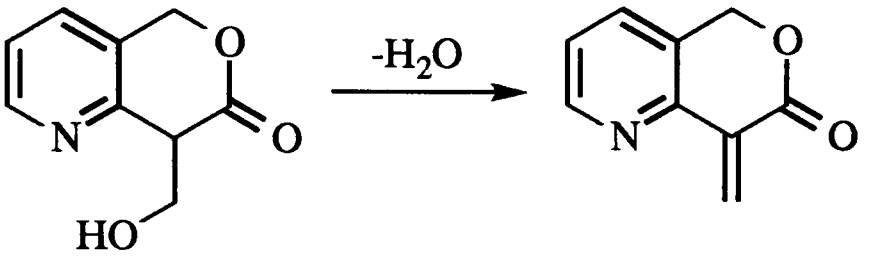
(178) **(197)** **(198)**

Scheme 85

It could be postulated that this cycloaddition would occur *via* the so called 'usual bonding interaction'[40] since the dipolarophile has an electron withdrawing substituent by virtue of it being part of the propenoate group. The bonding interaction

then may be between the HOMO of the *N*-oxide moiety and LUMO of the dipolarophile moiety.

The alcohol (**198**) was not the only possible product from this reaction since it could dehydrate losing one molar equivalent of water producing the product (**199**) generating an *exo*cyclic double bond that will be in conjugation with the carbonyl group and pyridine ring (**Scheme 86**).



(198) **(199)**

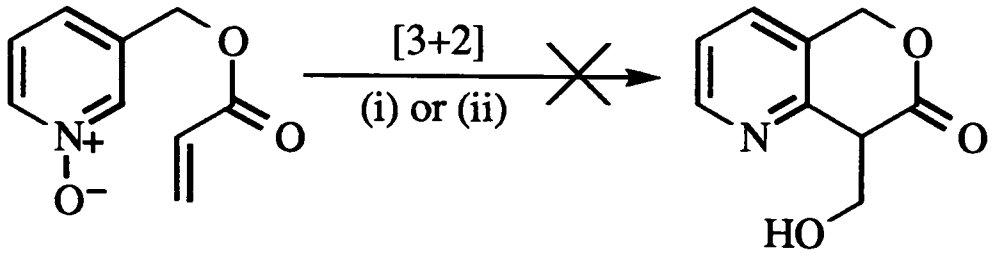
Scheme 86

Hisano favoured the relatively high boiling dipolar aprotic solvents, DMF and DMSO for carrying out the [3+2] cycloaddition reaction,[35,43] so the above intramolecular cycloaddition was attempted firstly in DMF at 110 °C. The starting material (3-pyridyl)methyl propenoate *N*-oxide (**178**) was dissolved in dry, distilled DMF and heated to 110 °C under an inert atmosphere of nitrogen. After stirring at this temperature for 18 hours, t.l.c. analysis eluting with 4 : 1 ethyl acetate / glacial acetic acid, revealed that the starting material (**178**) remained, with no evidence of any type of product material. The reaction was subsequently left at this temperature for another 5 days with periodic t.l.c. analysis. After this time, work up of the reaction afforded complete recovery of the starting material (**178**), confirmed by the ^{1}H NMR spectrum which remained unchanged with the vinylic protons still intact .

It was suspected that the lack of reactivity could have been due to the insufficient input of energy into the reaction pathway, so the reaction was repeated with DMSO at 150 °C. Unfortunately, after several days at this temperature the

starting material (3-pyridyl)methyl propenoate *N*-oxide (**178**) was completely recovered.

The intramolecular [3+2] cycloaddition reactions of Grigg and Padwa (Chapter 1) used toluene or xylene as the solvent. Therefore, cycloaddition of (3-pyridyl)methyl propenoate *N*-oxide (**178**) was attempted in both toluene and xylene at reflux (**Scheme 87**).



(178) **(198)**

(i) toluene reflux, (ii) xylene reflux

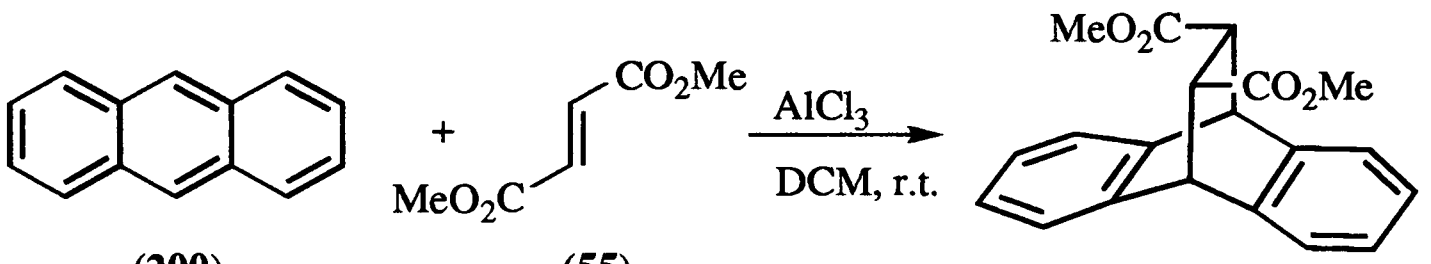
Scheme 87

Unfortunately, the outcome of the reaction was not changed and the starting material was recovered, with no suggestion of possible cycloaddition having occurred.

It was propounded that the cycloaddition was occurring but was not undergoing the rearomatisation step and was therefore reverting to the starting material (**178**), as the first step is indeed an equilibrium. In order to push the equilibrium in favour of product formation, it was necessary to ensure that the second, or subsequent steps for that matter, occurred faster than the reverse reaction. For this reason, activated 4Å molecular sieves were used, as it was hoped that by removing water from the reaction mixture, the dehydration step would be aided and the reaction forced to completion.

The molecular sieves were firstly used in Soxhlet extractors in the parallel reactions using both toluene and xylene as solvents, but to no avail, as starting material was still recovered. Adding the sieves to the reaction mixture also failed to give any reaction.

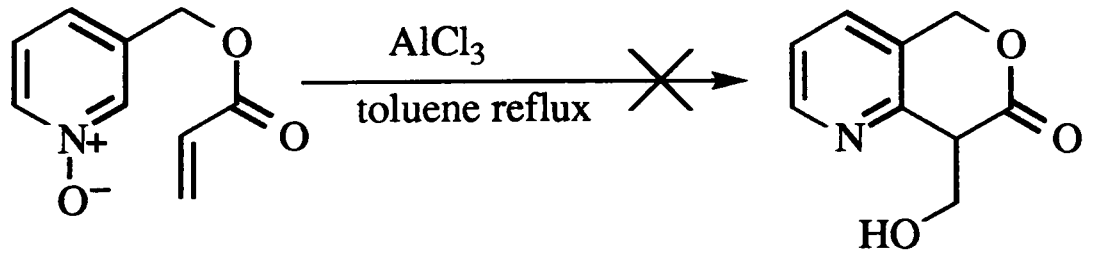
As a last resort, the Lewis acid catalysis, that had been successfully employed by Yates and Eaton in the Diels-Alder reaction, was attempted.[73] They found a drastically accelerated [4+2] cycloaddition rate between anthracene (**200**) and dimethyl fumarate (**55**), in the presence of aluminium chloride, at room temperature in DCM (**Scheme 88**). This was ascribed to conjugation of the Lewis acid to the dienophile carbonyls, which lowered the FMO energy levels.[74]



(**200**) (**55**)

Scheme 88

To this end, (3-pyridyl)methyl propenoate *N*-oxide (**178**) was dissolved in toluene and 1 molar equivalent of the Lewis acid, aluminium trichloride was added. The reaction mixture was then brought to reflux (**Scheme 89**).



(**178**) (**198**)

Scheme 89

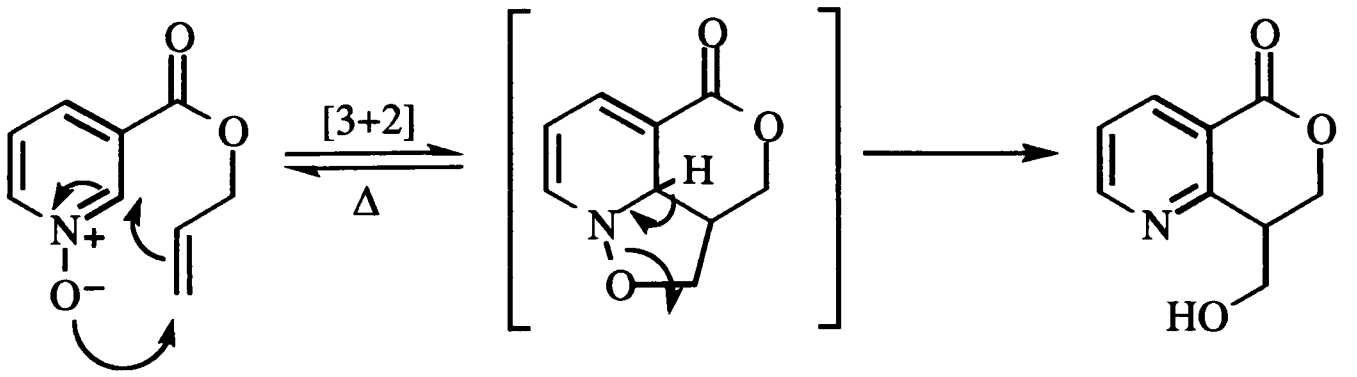
After refluxing at this temperature for a few hours, work up showed complete degradation of the starting material (**178**), with no assignable resonances in the ^{1}H NMR spectrum.

The results of the attempted cycloadditions of (3-pyridyl)methyl propenoate *N*-oxide (**178**) are summarised in **Table 5**.

Reaction Conditions	Cycloaddition Result
DMF / 110 °C	S.M. recovered
DMSO / 150 °C	S.M. recovered
Toluene reflux	S.M. recovered
Xylene reflux	S.M. recovered
Toluene reflux / 4Å molecular sieves	S.M. recovered
Xylene reflux / 4Å molecular sieves	S.M. recovered
Toluene reflux / $AlCl_3$	Degradation of S.M.

Table 5

Attention was now turned to the second cycloaddition precursor 2-propenyl (3-pyridine) carboxylate *N*-oxide (**177**). Again, intramolecular cycloaddition of the 1,3-dipole of the aromatic pyridine *N*-oxide unit with the double bond tethered to the 3-position of the pyridine ring would be assumed to occur *via* the concerted mechanism forming the intermediate (**201**) with loss of the aromatic nature of the pyridine ring. This intermediate could then undergo subsequent rearomatisation to yield the alcohol product (**202**), the reaction driven by a gain in aromatic stabilisation energy (**Scheme 90**).

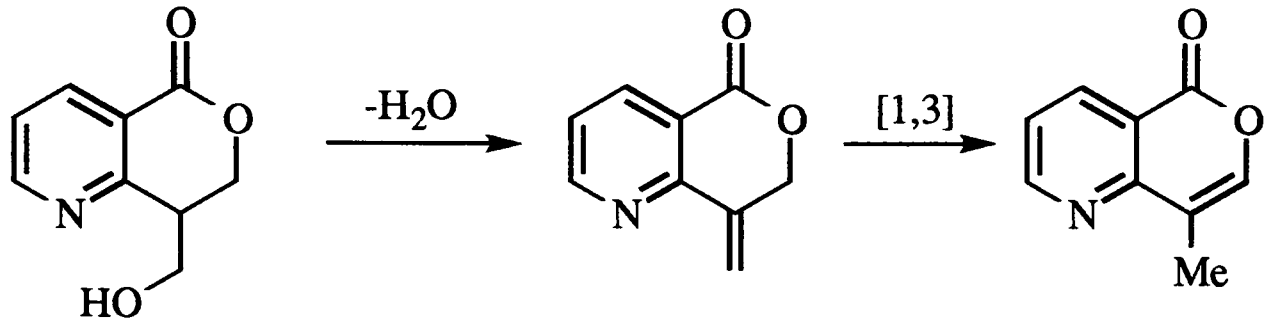


(177) **(201)** **(202)**

Scheme 90

In this case, it might be possible that the cycloaddition will occur in an opposite manner to the so called 'usual bonding interaction' since the pyridine *N*-oxide (**177**) now has an electron withdrawing substituent i.e. the ester group in the 3-position. The bonding interaction, therefore, may involve participation by the LUMO of the *N*-oxide moiety and HOMO of the dipolarophile moiety.

As before, the alcohol (**202**) is not the only possible product from this reaction since it could dehydrate producing the *exo*cyclic doubly bonded product (**203**), which in this case can undergo isomerisation to give an *endo*cyclic double bond (**204**) (**Scheme 91**).



(202) **(203)** **(204)**

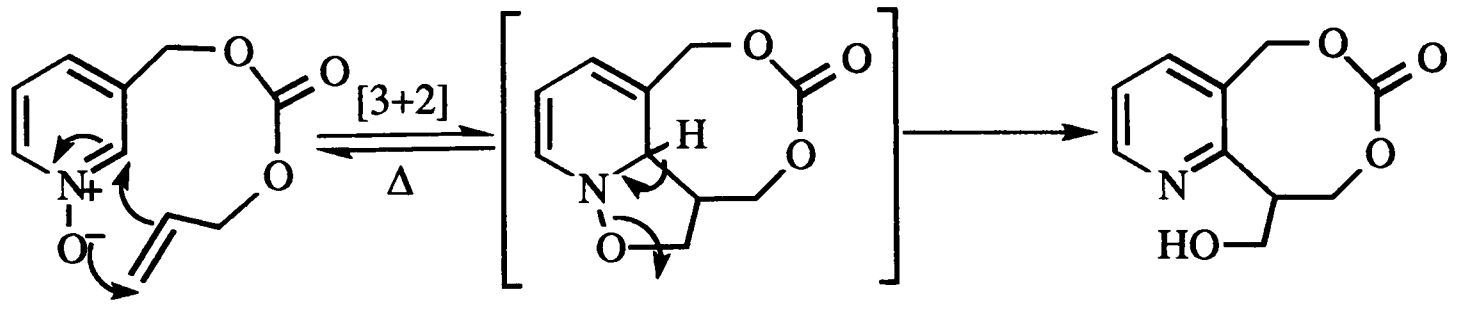
Scheme 91

Unfortunately all attempts to effect this [3+2] cycloaddition using all the reaction conditions employed previously were unsuccessful and are summarised in **Table 6**.

Reaction Conditions	Cycloaddition Result
DMF / 110 °C	S.M. recovered
DMSO / 150 °C	S.M. recovered
Toluene reflux	S.M. recovered
Xylene reflux	S.M. recovered
Toluene reflux / 4Å molecular sieves	S.M. recovered
Xylene reflux / 4Å molecular sieves	S.M. recovered
Toluene reflux / $AlCl_3$	Degradation of S.M.

Table 6

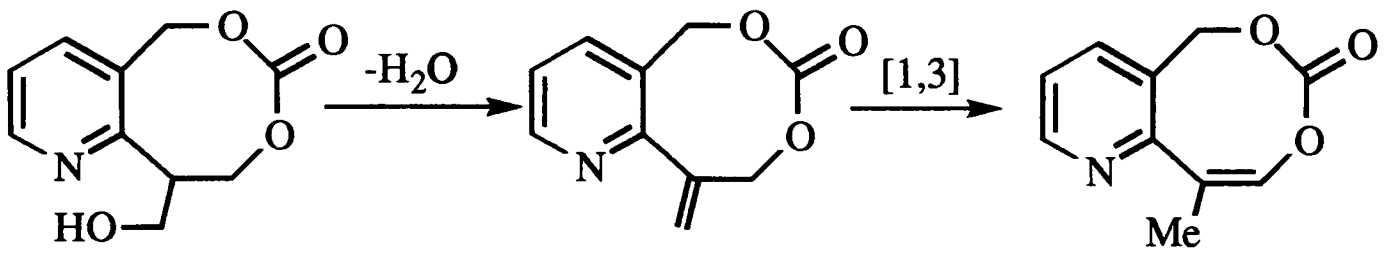
Finally, the [3+2] cycloaddition reaction of the precursor 2-propenyl (3-pyridyl)methyl carbonate *N*-oxide (**191**) was attempted, hoping that the increased tether length would make the cycloaddition reaction more favourable. Similarly, intramolecular cycloaddition *via* the concerted mechanism will result in the intermediate (**205**) which has an 8-membered ring fused onto the pyridine substrate. Rearomatisation of this intermediate will yield the alcohol product (**206**) (**Scheme 92**).



(191) **(205)** **(206)**

Scheme 92

As before, the alcohol (**206**) can dehydrate producing the product (**207**) possessing an *exo*cyclic double bond which can isomerise to give the *endo*cyclic doubly bonded product (**208**) (**Scheme 93**).



(206) **(207)** **(208)**

Scheme 93

Again, all attempts to effect this [3+2] cycloaddition using all the reaction conditions employed previously (**Table 7**), were unsuccessful.

Reaction Conditions	**Cycloaddition Result**
DMF / 110 °C	S.M. recovered
DMSO / 150 °C	S.M. recovered
Toluene reflux	S.M. recovered
Xylene reflux	S.M. recovered
Toluene reflux / 4Å molecular sieves	S.M. recovered
Xylene reflux / 4Å molecular sieves	S.M. recovered
Toluene reflux / $AlCl_3$	Degradation of S.M.

Table 7

There was still another option open to try in order to effect these intramolecular [3+2] cycloadditions, i.e. the high pressure mediated reaction. Although this was not successfully employed with the intermolecular reaction, causing the reaction to occur in an intramolecular sense should drastically increase its reactivity.[16]

4.5 High Pressure Mediated Cycloaddition Reactions of the Ester Precursors

Firstly, each of the ester cycloaddition precursors (3-pyridyl)methyl propenoate *N*-oxide (**178**), 2-propenyl (3-pyridine) carboxylate *N*-oxide (**177**) and 2-propenyl (3-pyridyl)methyl carbonate *N*-oxide (**191**) were dissolved in *ca.* 1-5 mL of freshly distilled DCM, put into individual Teflon® reaction pots and then subjected to 19 KBar pressure at 20 °C. Unfortunately, the desired reaction was not seen to occur with any of the precursors and starting material was recovered in all cases.

As a last resort, the high pressure reaction was repeated with an increase in temperature hoping that it would increase the reaction rate. Carrying out the reaction at elevated temperature meant that the high pressure machine could no longer work at its maximum pressure of 19 KBar, therefore these cycloadditions were attempted at 18 KBar pressure and 75 °C.

After 2 days under these conditions, work up of the three reactions and subsequent ^{1}H NMR analysis gave spectra not consistent with that expected for the product, in all cases the vinylic protons remained unchanged. However, the spectra were not in accord with the starting material *N*-oxides either. On closer inspection, it was realised that the product in each case was the pyridine compound, recovered in *ca.* 40 - 50 % yield for all three reactions. Hence the reaction at 18 KBar / 75 °C had not effected the cycloaddition but had resulted in cleavage of the N-O bond giving (3-pyridyl)methyl propenoate (**183**), 2-propenyl (3-pyridine) carboxylate (**180**) and 2-propenyl (3-pyridyl)methyl carbonate (**193**) respectively. This occurrence was thought to be due to a 'self-oxidation' process whereby one molecule of the pyridine *N*-oxide oxidised another molecule of *N*-oxide. This oxygen transfer was thought to have resulted in degradation of the oxidised molecule with recovery of the reduced pyridine substrate in < 50 % yield.

The high pressure [3+2] cycloaddition results are summarised in **Table 8**.

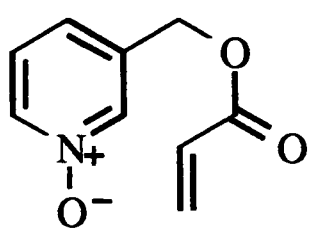
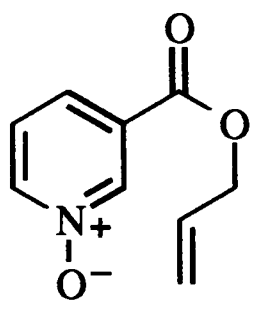
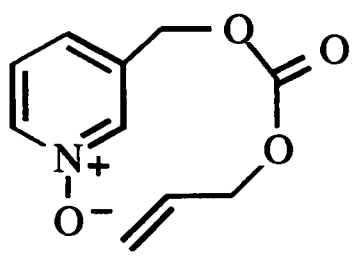
Ester Substrate	Reaction Conditions	Result
 **(178)**	19 KBar / 20 °C	No reaction (S.M. recovered)
	18 KBar / 75 °C	Cleavage of N-O Bond (39 % of **183**)
 **(177)**	19 KBar / 20 °C	No reaction (S.M. recovered)
	18 KBar / 75 °C	Cleavage of N-O Bond (47 % of **180**)
 **(191)**	19 KBar / 20 °C	No reaction (S.M. recovered)
	18 KBar / 75 °C	Cleavage of N-O Bond (49 % of **193**)

Table 8

4.6 Summary

So far, cycloadditions have been attempted with a range of ester precursors (**178**), (**177**) and (**191**) under a range of conditions (various thermal means and the application of high pressure) but the appropriate combination of precursor and reaction condition has yet to be established but it has also been demonstrated that both sodium perborate and UHP oxidations are safe and efficient methods for the conversion of pyridines to *N*-oxides in the presence of potentially sensitive groups.

The inertness of these adducts to cycloaddition was considered to be a consequence of the ester tether which was presumed to prefer a *trans* conformation which prevented the [3+2] addition. It was therefore necessary to construct precursors without this ester linkage in order to facilitate the cycloaddition reaction.

CHAPTER 5
RESULTS & DISCUSSION

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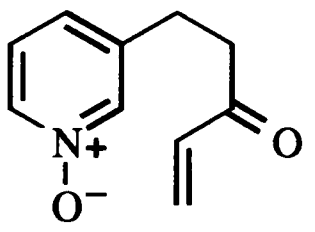
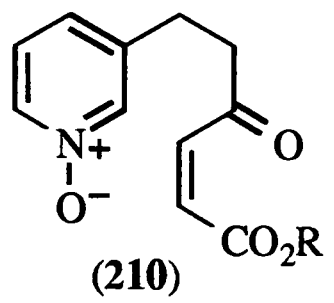
Investigation of the Intramolecular [3+2] Cycloaddition Reaction

5.1 Introduction

The aim was to construct intramolecular [3+2] cycloaddition precursors without the ester linkage, in order to facilitate the cycloaddition reaction. These types of substrates should be able to adopt a more favourable *cis*-type conformation and subsequent cycloaddition would be more likely to occur. Two cycloaddition precursors were envisaged; the mono-activated cycloaddition precursor (**209**) and the di-activated cycloaddition precursor (**210**) (**Figure 17**).



(**209**)



(**210**)

R = alkyl group

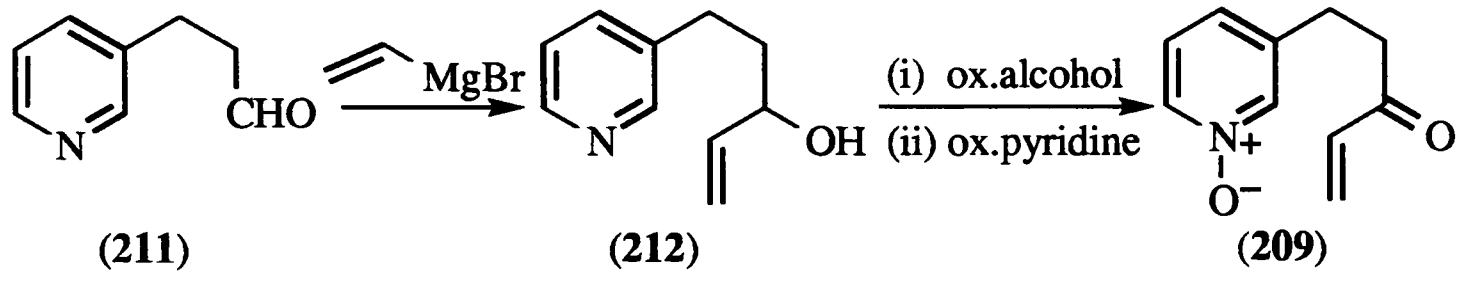
Figure 17

The mono-activated precursor (**209**) has one electron withdrawing group present on the dipolarophilic part of the molecule, which should lower the energy of the LUMO and make cycloaddition by the 'usual bonding interaction' more favourable. The energy of the dipolarophilic LUMO would be lowered further where two electron withdrawing groups as present, as in the di-activated cycloaddition precursor (**210**).

5.2 Synthesis of the Mono-Activated Cycloaddition Precursor

By analogy with the construction of the ester cycloaddition precursors synthesised in Chapter 4, it was decided firstly, to construct the appropriate 3-substituted pyridine compound and to effect oxidation to the *N*-oxide in the ultimate step of the reaction sequence.

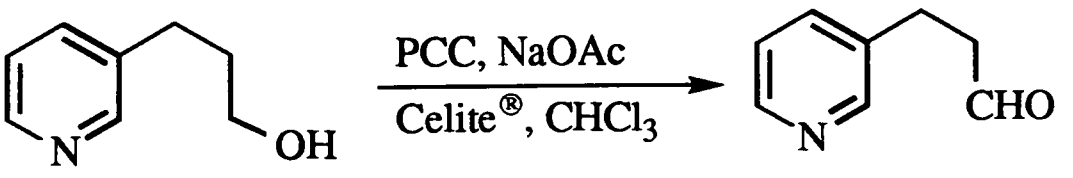
In order to construct this precursor (**209**), a route from the aldehyde 3-(3-pyridine)propanal (**211**) and addition of the Grignard vinyl magnesium bromide, followed by two oxidation steps, was envisaged (**Scheme 94**).



(211) **(212)** **(209)**

Scheme 94

Firstly, it was necessary to construct the 3-(3-pyridine)propanal (**211**). This was attempted by PCC oxidation of the alcohol 3-pyridinepropanol (**213**) in a buffered solution containing sodium acetate and Celite® in chloroform (**Scheme 95**).



(213) **(211)**

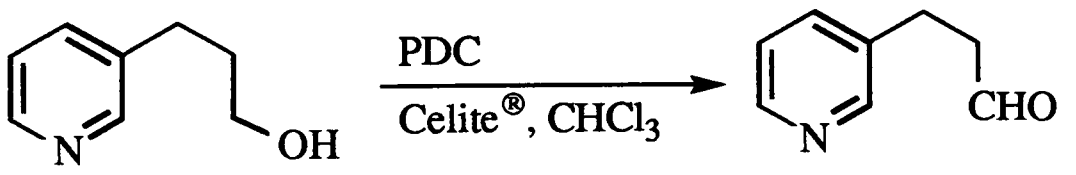
Scheme 95

The reaction was completed after 4 hours, seen by the disappearance of the starting material alcohol (**213**) and the observation of a less polar spot by t.l.c. analysis. Subsequent work up of the reaction and purification by flash chromatography gave the aldehyde (**211**) in a disappointing 12 % yield.

Evidence for the product (**211**) came from the ^{1}H NMR spectrum which revealed an aldehyde proton with a resonance at δ 9.84 ppm as a 1H singlet. There were only two CH_2 resonances, both appeared as triplets with *J* 7.3 Hz, at δ 2.96 ppm and at δ 2.82 ppm. This compared with two triplets, one with *J* 6.3 Hz at δ 3.68 ppm and the other with *J* 7.2 Hz at δ 2.73 ppm and a multiplet at δ 1.96 - 1.82 ppm for the three CH_2 groups in the starting material. The ^{13}C NMR spectrum also revealed a carbonyl carbon resonance at δ 200.39 ppm. In the mass spectrum of the product (**211**), a peak corresponding to the parent ion MH^+ at 136 Daltons was detected and the IR spectrum revealed no hydroxyl stretching absorption above 3 000 cm^{-1} but showed a carbonyl stretch at 1 723 cm^{-1}.

Various attempts were made to improve the yield of the 3-(3-pyridine)propanal (**211**), using DCM rather than chloroform, but the desired product was produced in an even poorer yield of 7 %.

Since no starting material was recovered in either case, it was assumed that either the PCC had resulted in some decomposition of the 3-pyridinepropanol (**213**) or that it was lost as the pyridinium salt, even though a sodium acetate buffer was used. For this reason, the milder, neutral PDC oxidising agent was employed (**Scheme 96**).

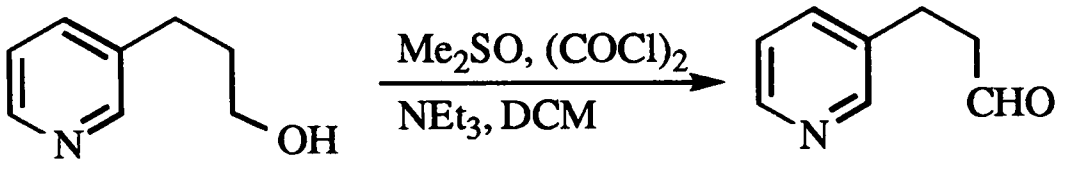


(213) **(211)**

Scheme 96

After work up, the desired product 3-(3-pyridine)propanal (**211**) was obtained in a very poor 7 % yield, with recovery of a large amount of pyridine. It was

suspected that, in fact, the 3-pyridinepropanol (**213**), or indeed the product (**211**), had exchanged with the pyridine ligands on the chromium metal in each case, so oxidation using a non-metallic substrate was required. To this end, the Swern oxidation using DMSO, oxalyl chloride and triethylamine was chosen (**Scheme 97**).[75]

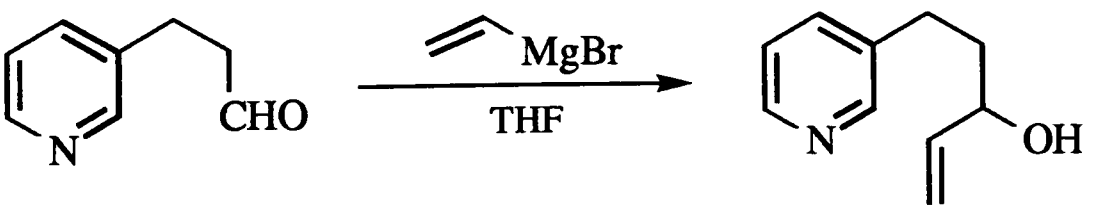


(213) **(211)**

Scheme 97

Fortunately, the reaction was successful and after work up and subsequent purification by flash chromatography, 3-(3-pyridine)propanal (**211**) was obtained in 97 % yield and gave spectrometric data consistent with that previously noted for this compound.

The next step was the nucleophilic addition of the Grignard reagent vinyl magnesium bromide to the aldehyde (**211**) (**Scheme 98**).



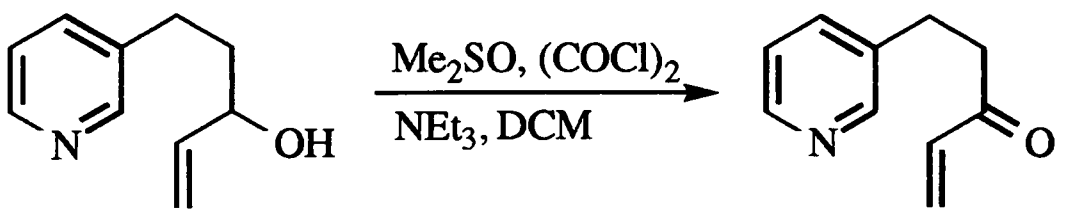
(211) **(212)**

Scheme 98

This reaction was attempted both at -78 °C and at 0 °C. Firstly, carrying out the reaction at -78 °C gave 3-(3-hydroxy-4-pentenyl)pyridine (**212**) in 56 % yield after very careful flash chromatography, but raising the reaction temperature to 0 °C gave the alcohol product (**212**) in improved 74 % yield.

Evidence for the nature of the product (**212**) came from the ^{1}H NMR spectrum. The vinylic resonances appeared as a two 1H double doublets at δ 5.26 ppm and δ 5.86 ppm for the *trans* and *cis* protons of the CH_2 respectively and a 1H multiplet at δ 5.95 - 5.88 ppm for the saturated CH. It also was possible to see the OH resonance at δ 1.95 ppm as a broad singlet. The ^{13}C NMR spectrum also supported product formation by the appearance of a vinylic CH_2 resonance at δ 114.98 ppm. It was not possible to assign unambiguously the vinylic CH as it appeared in the same region of the spectrum as the pyridine CH resonances. Again the MH^+ ion was detected in the mass spectrum at 164 Daltons and the IR spectrum showed the disappearance of the carbonyl stretching frequency at 1 723 cm^{-1} and the appearance of the hydrogen bonded OH with a broad absorption at 3 300 cm^{-1}.

The next step was to carry out the oxidation of the alcohol (**212**) to the carbonyl compound 3-(3-oxy-4-pentenyl)pyridine (**214**). Oxidation of the allylic alcohol (**212**) was attempted by the Swern oxidation and although it was successful, the product (**214**) was obtained in only 21 % yield (**Scheme 99**).[75]



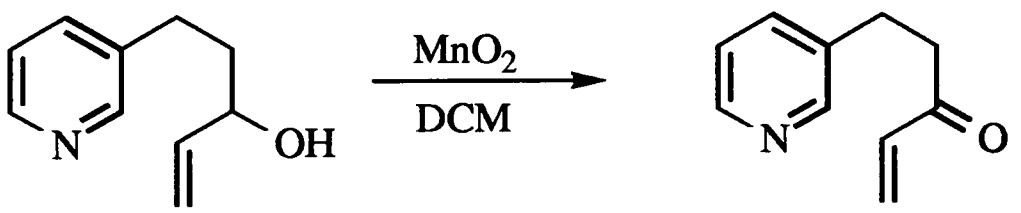
(**212**) (**214**)

Scheme 99

Separation of the desired product (**214**) from the crude reaction mixture, which also contained unreacted starting material (**212**), proved to be very difficult and required several flash chromatography columns in order to acquire an analytically pure sample.

Evidence for the product (**214**) came from the ^1H NMR spectrum, which showed loss of the 1H multiplet at δ 4.15 - 4.12 ppm relating to the proton on the carbon bearing the hydroxyl group and the loss of the OH resonance at δ 1.95 ppm. There was also a down field shift of the two saturated protons on the carbon adjacent to the hydroxyl group from a multiplet at δ 1.92 - 1.80 ppm to a singlet at δ 2.93 ppm since they were now next to the more electron withdrawing carbonyl group. Interestingly, both pairs of saturated CH_2 protons in the product (**214**) resonated at the same frequency in the ^1H NMR spectrum and appeared as a 4H singlet. There was also an α,β-unsaturated carbonyl stretching frequency at 1 682 cm^{-1} in the IR spectrum and the MH^+ peak was detected at 162 Daltons in the mass spectrum.

In an attempt to improve the yield of this oxidation step, active manganese dioxide was employed. The active manganese dioxide was made from potassium permanganate and activated carbon by the method described by Carpino.[76] This reagent was then used in the oxidation reaction (**Scheme 100**).



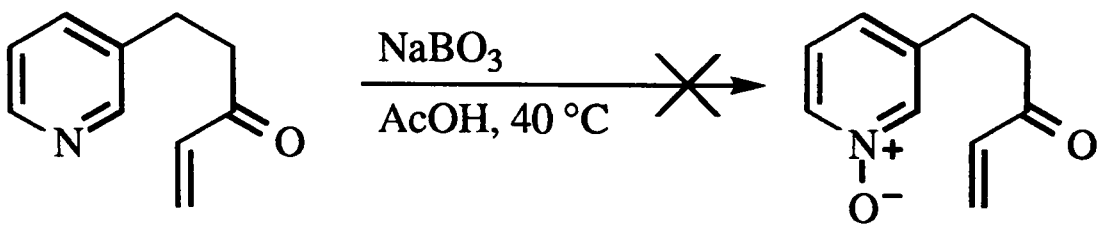
(212) **(214)**

Scheme 100

The yield did improve slightly to give 32 % of 3-(3-oxy-4-pentenyl)pyridine (**214**) but, as before, separation of the desired product from unreacted starting material was not easy.

Having achieved the oxidation of the alcohol, albeit in poor yield, a second oxidation reaction was now required to yield the [3+2] cycloaddition precursor 3-(3-oxy-4-pentenyl)pyridine *N*-oxide (**209**). As with the ester cycloaddition

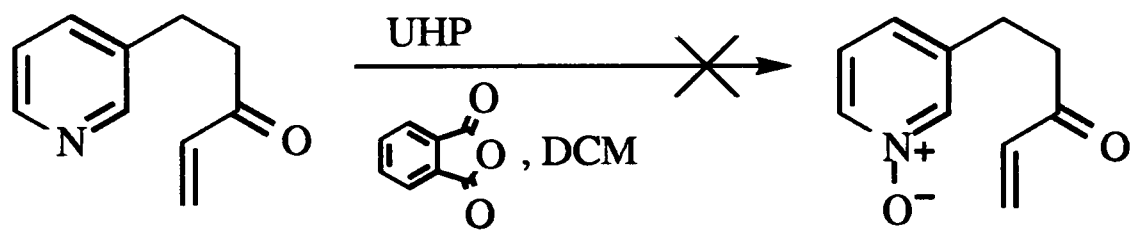
precursors, this oxidation was attempted by the method of McKillop using sodium perborate tetrahydrate (**Scheme 101**).[71]



(214) **(209)**

Scheme 101

Unlike the ester cycloaddition precursors, the reaction was found to be unsuccessful with recovery of 84 % of the starting material 3-(3-oxy-4-pentenyl)pyridine (**214**). As a result, the oxidation was then attempted by the method of Kaczmarek using UHP and phthalic anhydride in DCM (**Scheme 102**).[66]



(214) **(209)**

Scheme 102

Although initial attempts to form the cycloaddition precursor (**209**) were thought to have been successful, the crude product could not be adequately purified in order to confirm its structure. In the ^{1}H NMR spectrum of the crude material, the pyridine proton resonance were thought to have shifted to two 2H multiplets at δ 8.11 - 8.08 and 7.21 - 7.16 ppm, but the vinylic and saturated CH_2 proton resonances were obscured by the impurities present. Unfortunately, formation of the *N*-oxide (**209**) could not be inferred from the mass spectrum, as only a peak at 162 Daltons was detected, which could have corresponded to the starting material (**214**), rather than the MH^+ -16 fragment.

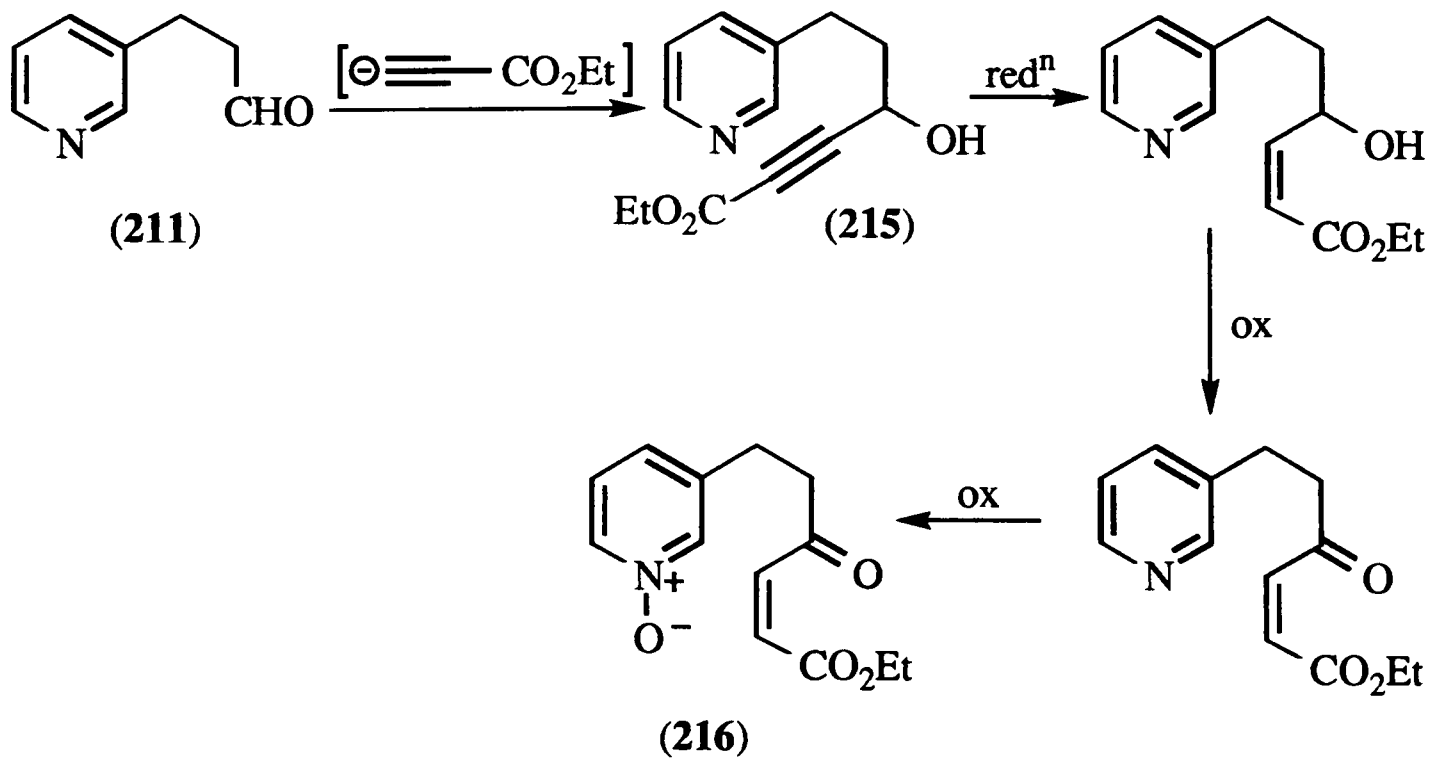
Since it was not possible to effect oxidation of the pyridine (**214**), in order to access the mono-activated cycloaddition precursor (**209**), it was decided to attempt construction of the di-activated [3+2] cycloaddition precursor; a derivative of (**210**).

5.3 Synthesis of the Di-Activated Cycloaddition Precursor

5.3.1 Methodology using Alkyl Propiolate Anions

The first di-activated cycloaddition precursor that was to be synthesised contained the ethyl ester group at the end of the dipolarophilic tether (R = ethyl in **Figure 17**). The reason for the choice of this *N*-oxide will become apparent.

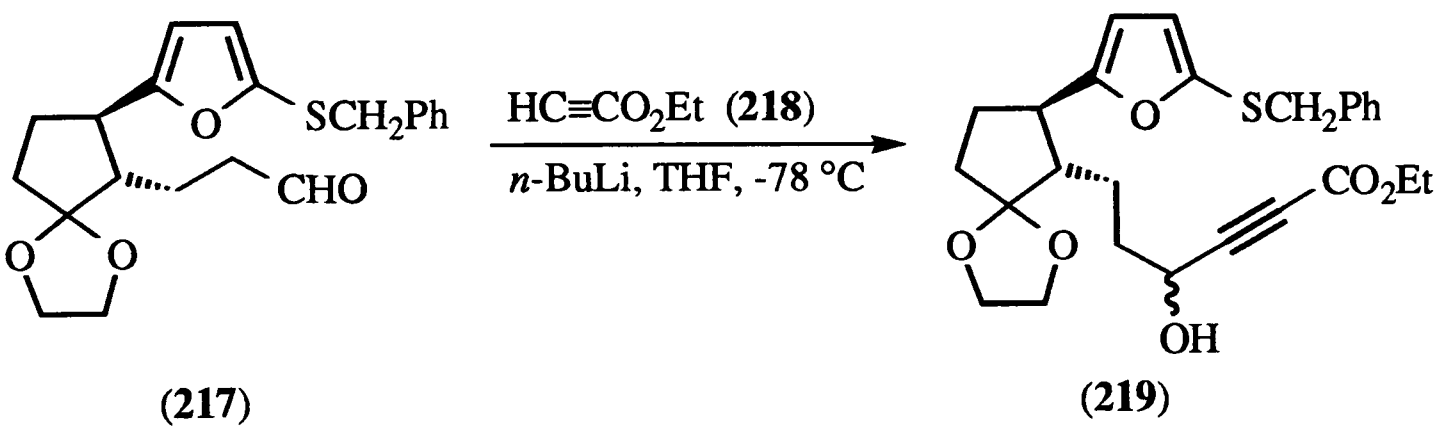
A similar route to that used for construction of the mono-activated cycloaddition precursor (**209**) was envisaged, commencing with the 3-(3-pyridine)propanal (**211**) that was formed *via* the Swern oxidation of 3-pyridinepropanol (**213**) and reacting this aldehyde with the anion of ethyl propiolate (**218**). Subsequent stereospecific reduction of the triple bond to a *cis* double bond, followed by two oxidation steps, would result in the *N*-oxide (**216**) (**Scheme 103**).



(**211**) (**215**) (**216**)

Scheme 103

Previous work within the group had shown the addition of the lithium anion of ethyl propiolate (**218**) to 1-ethylenedioxy-3β-[5-(2-phenylmethylthiofuryl)]-2α-(3-propanal)cyclopentane (**217**), formed the alcohol (**219**) in 82 % yield (**Scheme 104**),[77,78] following the procedure of Midland.[79]

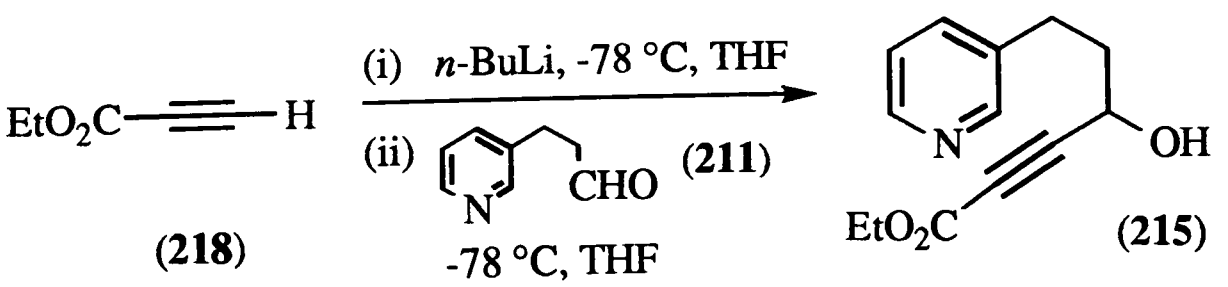


(**217**) (**219**)

Scheme 104

Midland had found the lithium anion of ethyl propiolate (**218**) much easier to work with than that of methyl propiolate (**220**), as polymerisation was minimal at -78 °C. Reactions involving the lithium anion of methyl propiolate (**220**) required reaction temperatures of -100 °C. For this reason, the reaction was initially attempted with ethyl propiolate (**218**).

In order to construct the desired alcohol (**215**), similar reaction conditions were applied to the reaction between ethyl propiolate (**218**) and 3-(3-pyridine)propanal (**211**). The lithium anion of ethyl propiolate (**218**) was generated by deprotonation with *n*-butyllithium in THF at -78 °C (**Scheme 105**).



(**218**) (**215**)

Scheme 105

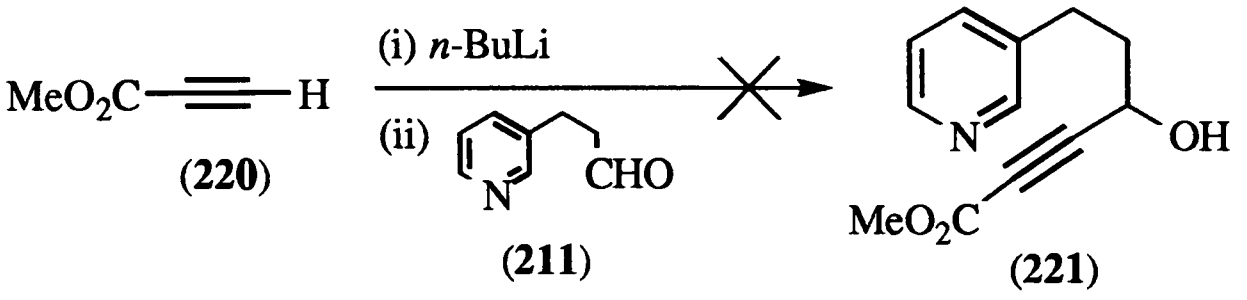
Initially the reaction was carried out at a concentration of 0.04 gml^{-1} of ethyl propiolate (**218**) in THF and was allowed to deprotonate for 1 hour before the addition of the aldehyde (**211**). During the very slow addition of the 1.5 equivalents of *n*-butyllithium, it was not possible to keep the temperature at -78 °C and it rose to -68 °C. After work up of the reaction, the crude product mixture contained only polymeric ethyl propiolate, as seen in the proton ^1H NMR spectrum by a large multiplet at δ 4.37 - 4.06 ppm and possible butyl residues, seen as multiplets from δ 1.72 ppm to δ 0.88 ppm.

In order to minimise the polymerisation of the ethyl propiolate anion once formed, the reaction was repeated at a much lower concentration 0.006 gml^{-1} of ethyl propiolate (**218**) in THF and using strictly 1 equivalent of *n*-butyllithium. During the addition of the *n*-butyllithium to the propiolate, the more dilute reaction conditions ensured that it was possible to keep the temperature below - 72 °C and as a result, work up of the reaction and purification of the crude product by flash chromatography resulted in a small amount of ethyl 4-hydroxy-6-(3-pyridine)hex-2-ynoate (**215**). Unfortunately the yield was a poor 10 %, upon which, it was found impossible to improve.

Carrying out the deprotonation of the ethyl propiolate (**218**) with *n*-butyllithium in the presence of the aldehyde (**211**) was hoped to be able to prevent polymerisation of the propiolate, as there was a more reactive centre available for nucleophilic attack, which would make the desired reaction path more favourable. Unfortunately, this was not found to be the case and none of the ethyl 4-hydroxy-6-(3-pyridine)hex-2-ynoate (**215**) was formed in this reaction.

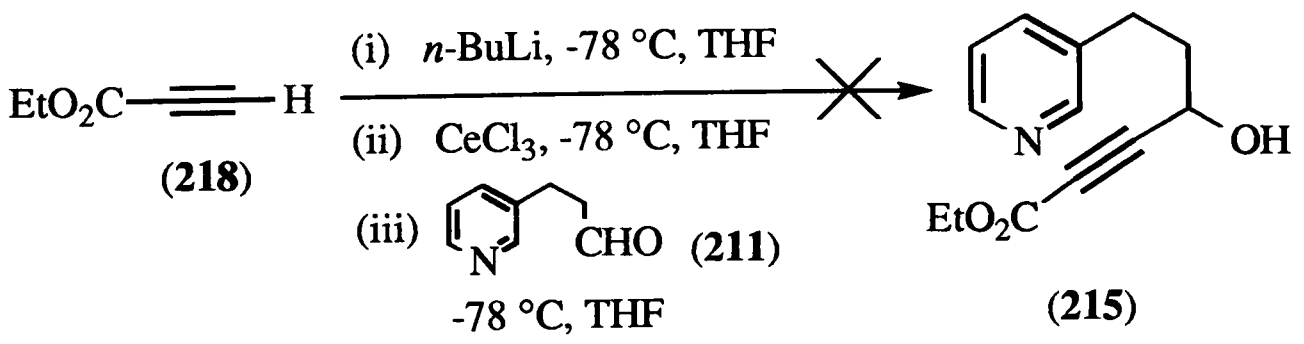
As feared, attempts to carry out the same reaction with methyl propiolate (**220**) resulted in polymerisation of the anion. Carrying out the reaction at -100 °C

with *n*-butyllithium and 3-(3-pyridine)propanal (**211**) was not successful in generating the required methyl 4-hydroxy-6-(3-pyridine)hex-2-ynoate (**221**) (**Scheme 106**).



Scheme 106

As a last resort for construction of the alkyl 4-hydroxy-6-(3-pyridine) hex-2-ynoate, the reaction of the cerium anion of ethyl propiolate (**218**) with 3-(3-pyridine)propanal (**211**) was attempted. It was hoped that this would be a less reactive anion and therefore less susceptible to polymerisation. Generation of the cerium anion followed the procedure of Imamoto, reacting the lithium anion with cerium (III) chloride.[80] It was hoped that the lithium anion of the ethyl propiolate (**218**) could be transmetalated by the cerium (III) chloride before it had a chance to polymerise (**Scheme 107**).



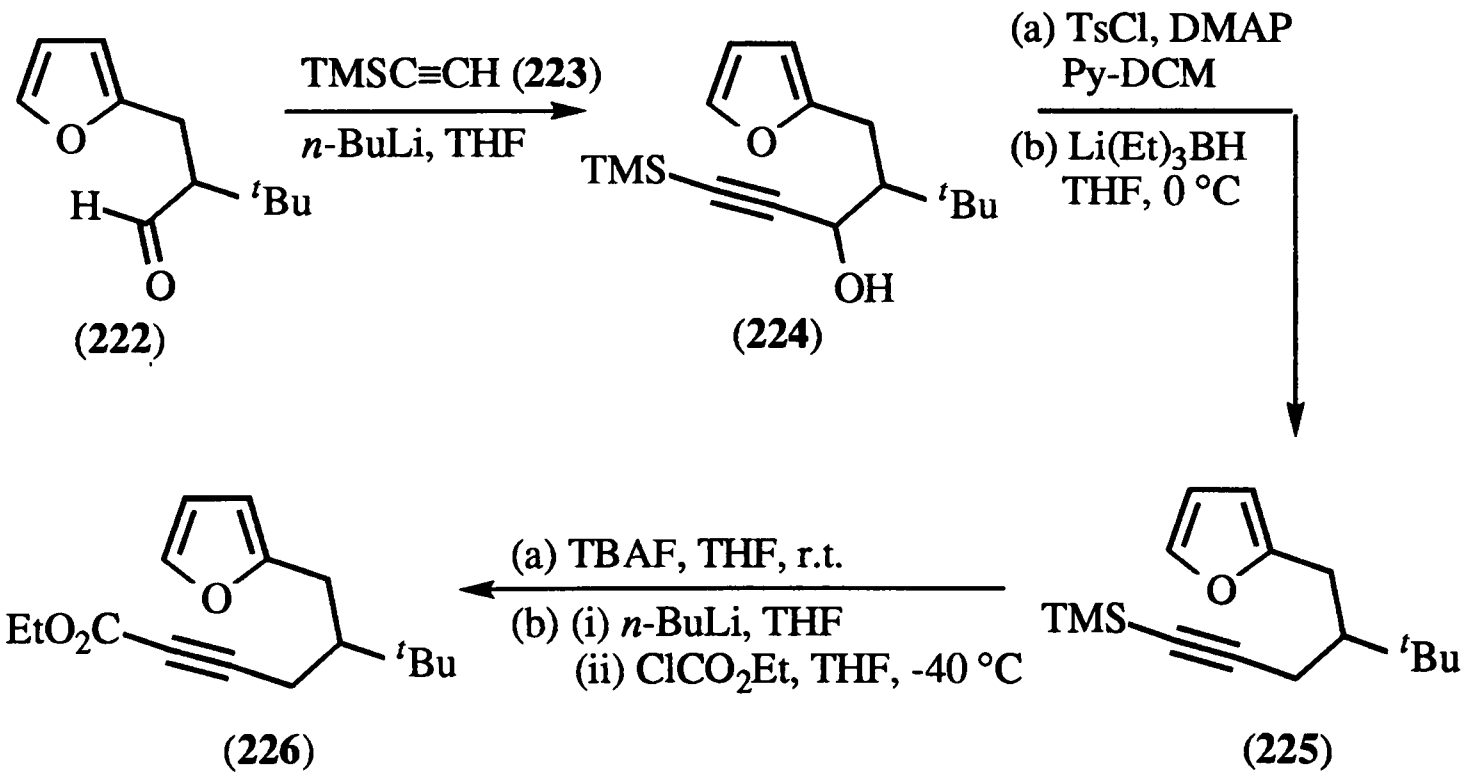
Scheme 107

Work up of the reaction mixture gave salts that were totally insoluble in organic solvent and these were presumed to be some sort of complex formed between the cerium metal and the pyridine.

It proved impossible to circumvent the problem of the polymerisation of the propiolates which was thought to be due to the ester group, so an alternative acetylide was sought which would add to the aldehyde (**211**) and could be converted to the ester later in the reaction sequence.

5.3.2 Analogous Route using Trimethylsilylacetylene

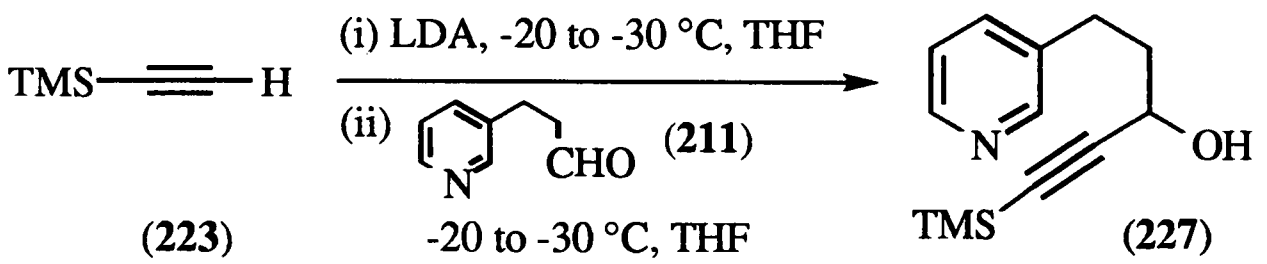
Recent work of De Clercq which involved construction of a Diels-Alder cyclisation precursor (**226**) bearing an ethyl propiolate sub-unit, used the anion of trimethylsilylacetylene (**223**).[81] Addition of this anion to the aldehyde (**222**), resulted in a TMS protected acetylene (**224**), that could later be deprotected and reacted with ethyl chloroformate to yield the cyclisation precursor (**226**) (**Scheme 108**).



Scheme 108

For the purposes of his research, De Clercq also wanted to remove the hydroxyl group, yielding the adduct (**225**) before TMS deprotection and subsequent reaction with ethyl chloroformate. This hydroxyl group, however, was required in the construction of the di-activated cycloaddition precursor (**216**) since it was to be oxidised to give the carbonyl.

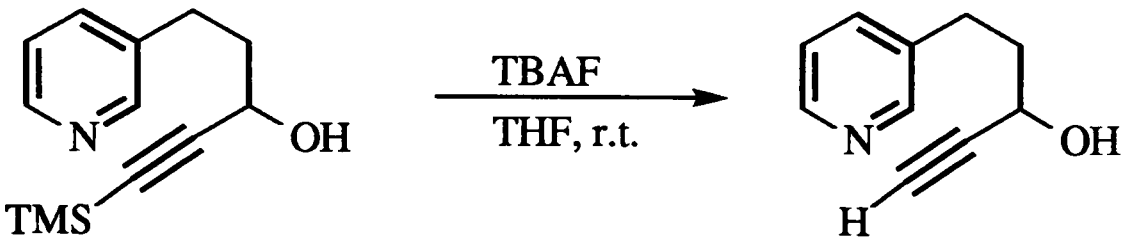
For the first step in construction of the adduct (**216**), it was necessary to add the anion of trimethylsilylacetylene (**223**) to the 3-(3-pyridine)propanal (**211**). Formation of the anion was achieved with LDA in THF and carrying out the reaction in THF between -20 and -30 °C, which gave the desired product (**227**) in 86 % yield (**Scheme 109**).



Scheme 109

3-(3-hydroxy-5-trimethylsilyl-4-pentynyl)pyridine (**227**) was obtained as a low melting point solid (solid < 4 °C) after flash chromatography on silica. Proof of product formation came from the mass spectrometric data which showed a peak at 234 Daltons that corresponded to the MH^+ ion. The IR spectrum also revealed loss of the carbonyl stretching frequency at 1 723 cm^{-1} but gain of a broad hydroxyl absorption at 3 190 cm^{-1}. There was also a weak absorption at 2 170 cm^{-1} which corresponded to the new triple bond. The ^1H NMR spectrum confirmed the assignation of the product showing a new resonance at δ 4.37 ppm as a 1H triplet with *J* 6.5 Hz corresponding to the proton on the carbon bearing the new hydroxyl group. The TMS group appeared as a 9H singlet at δ 0.17 ppm. In the ^{13}C NMR spectrum it was possible to see the carbon resonances corresponding to the acetylene at δ 106.41 and 89.84 ppm and the disappearance of the carbonyl resonance (δ 200.39 ppm) was noted and in its place was a resonance at δ 61.53 ppm. This corresponded to the carbon bearing the hydroxyl group and as a result was greatly shifted up field as it was much less deshielded in the product. The methyl resonances for the TMS group appeared at δ -0.15 ppm.

As the TMS protection group had served its purpose by enabling the addition reaction to take place without polymerisation, its removal, subsequently, was required. Attempted TBAF deprotection of the TMS protected adduct (**227**) gave only a 23 % yield of the desired product (**228**) after allowing the reaction to proceed for 1 hour at room temperature in THF (**Scheme 110**).

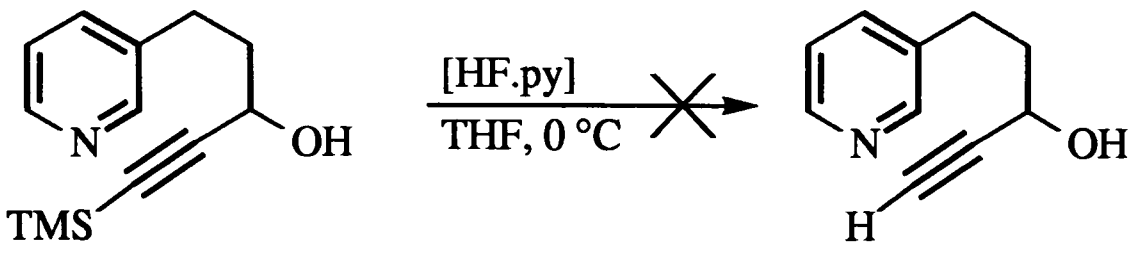


(227) **(228)**

Scheme 110

Indication of product formation came from the mass spectrum which showed the molecular ion MH^+ at 162 Daltons, a loss of 72 Daltons from the starting material MH^+ ion, corresponding to replacement of the TMS group by a proton. In the ^1H NMR spectrum, there was no longer a 9H singlet for the TMS group, but a 1H doublet at δ 2.45 ppm for the new acetylenic proton which showed a long range coupling (*J* 2.0 Hz) to the proton on the carbon bearing the hydroxyl group. The ^{13}C NMR spectrum also indicated a shift in the resonances corresponding to the acetylene, from δ 106.41 and 89.84 ppm in the TMS protected starting material (**227**), to δ 85.01 and 72.77 ppm in the deprotected product (**228**). The disappearance of the methyl TMS group resonances was also noted.

In an attempt to improve the yield of the reaction, an alternative deprotection was sought. Cox had found the hydrogen fluoride - pyridine complex to be an efficient source of anhydrous hydrogen fluoride.[82] As such, it would be expected to effect the deprotection, removing the TMS group. The reaction was carried out on the alcohol (**227**) in THF at 0°C, but after 10 hours, only unreacted starting material remained (**Scheme 111**).

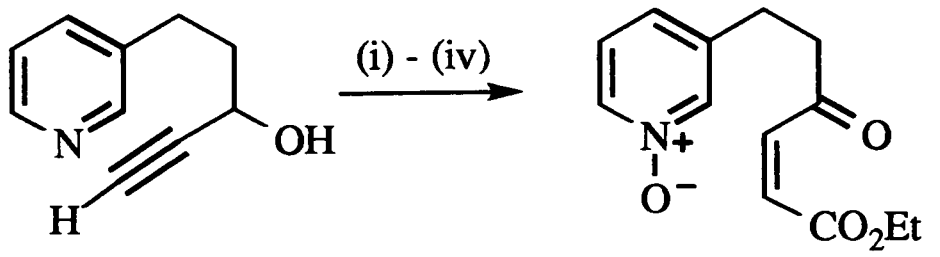


(227) **(228)**

Scheme 111

Therefore, it was decided to persevere with the TBAF deprotection. The reaction time and the temperature at which it allowed to proceed was carefully varied so that an optimum could be found. The time proved to be the crucial factor and if the TBAF residues remained in contact with the pyridine compound any longer than 30 minutes, gradual decomposition resulted. Consequently, as soon as the reaction was seen to reach completion, judged by the disappearance of the starting material by t.l.c analysis, removal of the TBAF residues was immediate, filtering the reaction mixture through a pad of silica gel. Following this procedure produced 3-(3-hydroxy-4-pentynyl)pyridine (**228**), in a much better 92 % yield, that could be used without further purification.

Now that the deprotection had taken place, there were four steps that needed to be carried out on the substrate (**228**) in order to reach the cycloaddition precursor (**216**) (**Scheme 112**).



(228) **(216)**

(i) oxidation of the hydroxyl group to the ketone,

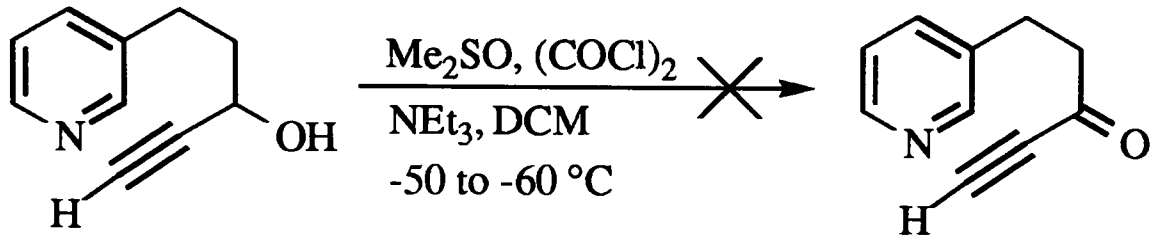
(ii) generation of acetylide anion and reaction with ethyl chloroformate,

(iii) stereospecific reduction of triple bond to *cis* double bond and

(iv) oxidation of pyridine ring to give the *N*-oxide (**216**).

Scheme 112

The order for carrying out these reactions was not trivial. The reaction with ethyl chloroformate had to be carried out with the acetylide anion, however the hydroxyl group also carried acidic proton. Therefore, it was decided that oxidation of the hydroxyl group to the ketone should be the first transformation. This oxidation was firstly attempted *via* the Swern oxidation with DMSO, oxalyl chloride and triethylamine in DCM at low temperature (**Scheme 113**).[75]

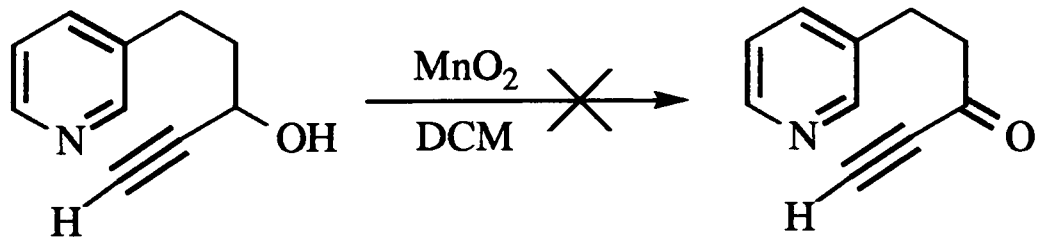


(228) **(229)**

Scheme 113

Unfortunately, the reaction was unsuccessful and resulted in degradation of the starting material (**228**) with no recognisable products being isolated from the reaction mixture.

Attempted oxidation with activated manganese dioxide also resulted in recovery of neither the desired product (**229**), nor the unreacted starting material (**228**) (**Scheme 114**).

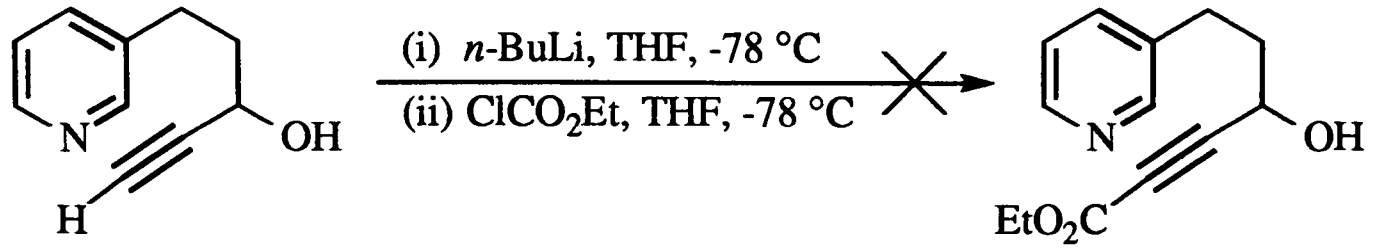


(228) **(229)**

Scheme 114

As all attempts to effect the oxidation proved unsuccessful, reaction of the alcohol (**228**) with ethyl chloroformate was tried. Since there were two acidic protons in the starting material (**228**), it was hoped that the use of 2 equivalents of base would

form the dianion and that the subsequent reaction with ethyl chloroformate may occur preferentially at the more accessible acetylide anion (**Scheme 115**).

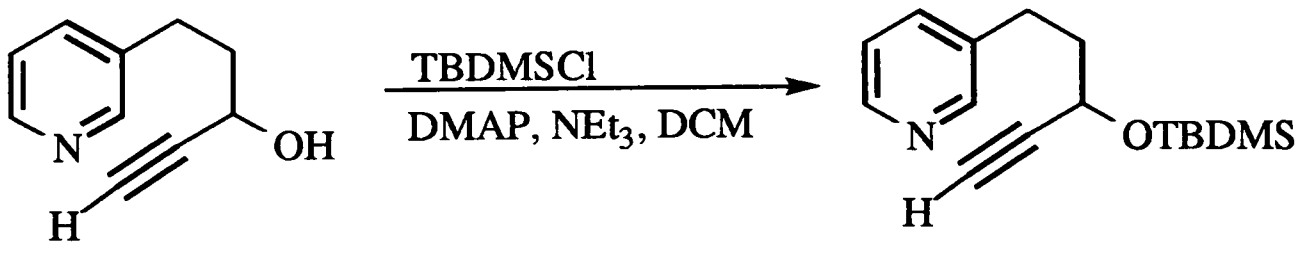


(228) **(215)**

Scheme 115

Unfortunately, work up of the reaction mixture revealed only polymeric material and none of the desired product (**215**).

Therefore, it firstly was necessary to protect the alcohol functionality of the starting material (**228**), before reaction with the ethyl chloroformate. This protection was accomplished by reaction with TBDMSCl in DCM with a catalytic amount of DMAP and one equivalent of triethylamine (**Scheme 116**).[69]



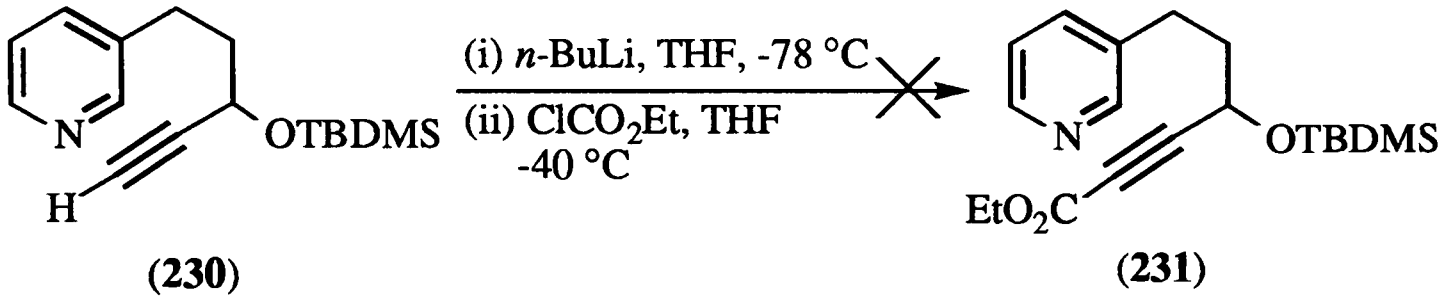
(228) **(230)**

Scheme 116

The reaction was successful and afforded the TBDMS protected alcohol (**230**) in 84 % yield. Evidence for product formation came from the mass spectrum in which the molecular ion MH^+ was detected at 276 Daltons. The IR spectrum also revealed disappearance of the broad absorption at 3 290 cm^{-1} for the hydroxyl group. The ^1H NMR spectrum showed inclusion of the TBDMS group with resonances at δ 0.92 ppm as a 9H singlet for the three methyls of the *t*-butyl group and two 3H singlets for the methyl groups attached to the silicon at δ 0.12 and 0.15 ppm. In the

^{13}C NMR spectrum, the TBDMS group appeared as resonances at δ 26.58, 25.75 and 18.17 ppm.

Since the alcohol functionality was now protected, reaction with ethyl chloroformate should yield the required product (**231**). The acetylene was deprotonated with *n*-butyllithium in THF at -78 °C and then after 1.5 hours, ethyl chloroformate was added and the reaction warmed to -40 °C and allowed to stir for 2 hours (**Scheme 117**).



(230) **(231)**

Scheme 117

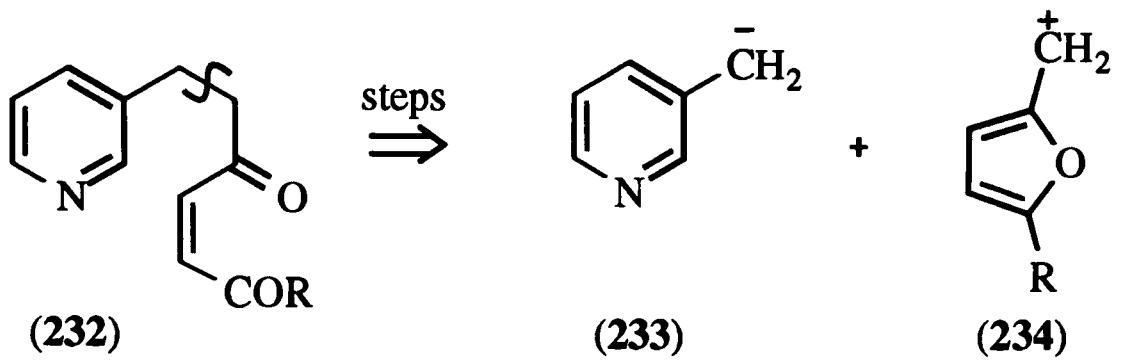
Work up of the reaction and attempted purification of the crude product mixture gave no recognisable products with much polymeric material isolated.

It was by now apparent that this reaction route would not allow access to the desired di-activated cycloaddition precursor (**216**), so an alternative route was investigated.

5.3.3 Syntheses using the Furan Template

Since addition of various anions to 3-substituted pyridines and subsequent manipulation had proven to be problematic, a new reaction sequence was sought. Retrosynthetic analysis of the cycloaddition precursor, prior to oxidation of the pyridine ring, i.e. (**232**), showed that disconnection between the two saturated CH_2 groups of the tethered chain, resulted in the 3-methylpyridine anion (**233**) and a

substituted furan (**234**). The furan could be oxidised to give the enone system required in the precursor (**232**) (**Scheme 118**).

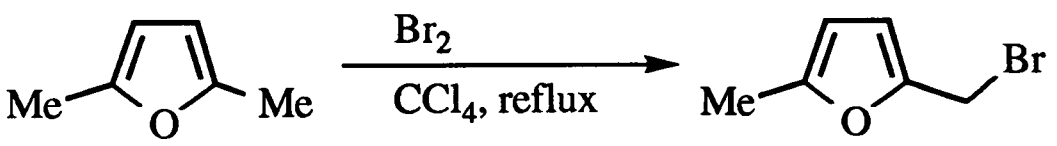


(**232**) (**233**) (**234**)

R = alkyl group

Scheme 118

As a consequence, construction of an appropriate substituted furan was sought. Since inclusion of an ester group on the dipolarophile tether had presented many problems, it was decided to make use of the methyl ketone group instead (R = Me in **Scheme 118**). The furan derivative that was selected was 2-methyl-5-bromomethylfuran (**236**). This compound had previously been synthesised by Meth-Cohn from the 2,5-dimethylfuran (**235**) using bromine in refluxing carbon tetrachloride (**Scheme 119**). [83]



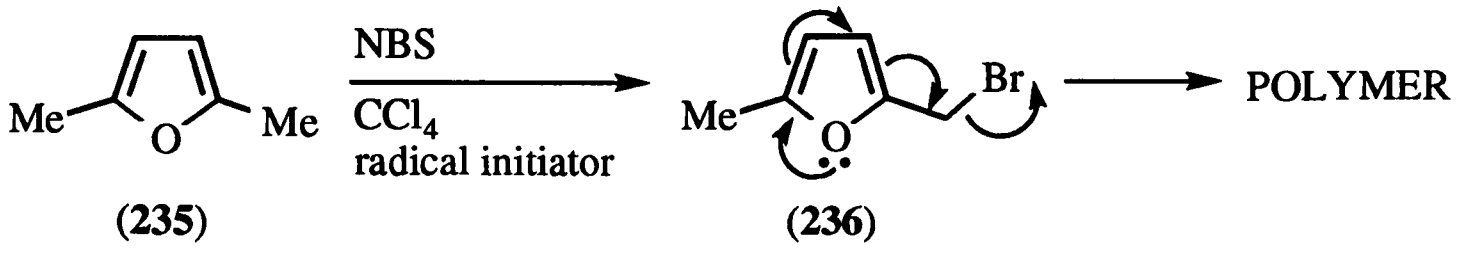
(**235**) (**236**)

Scheme 119

The maximum yield of 68 % of 2-methyl-5-bromomethylfuran (**236**) was achieved by Meth-Cohn with 1.2 equivalents of bromine, with the product resulting from mono-bromination on both methyl groups being obtained in 21 % yield. Unfortunately, precise reaction conditions and product data were not given and attempts to repeat the reaction and purify the products by flash chromatography were not successful, resulting instead in polymerisation. Carrying out the reaction in the

presence of the radical initiators AIBN and *t*-butyl hydroperoxide failed to produce the desired reaction product and an intractable black tar resulted in both cases.

N-Bromosuccinimide was utilised, also in refluxing carbon tetrachloride, with both AIBN and *t*-butyl hydroperoxide radical initiators and although the reaction was thought to be forming the desired 2-methyl-5-bromomethylfuran (**236**), attempts to purify the crude reaction mixture resulted in polymerisation (**Scheme 120**).

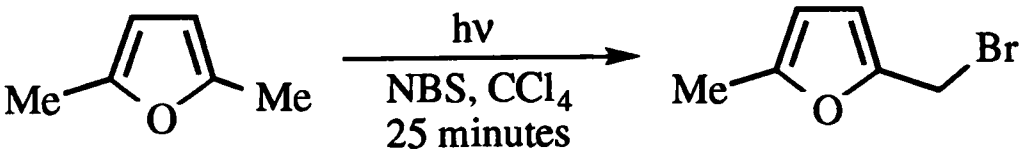


(235) **(236)**

Scheme 120

It was suspected that the failure of these reactions was due to the heating, which was necessary for formation of the bromine radicals, since all the reactions yielded a crude polymeric product which could not be purified.

As a result, the bromination reaction was repeating using UV irradiation for formation of the bromine radicals from *N*-bromosuccinimide rather than heating, in an attempt to minimise polymerisation (**Scheme 121**). The optimum irradiation time was found to be 25 minutes; longer times yielding tar-like material containing many products, as seen by t.l.c. analysis; shorter times yielding recovery of starting material.

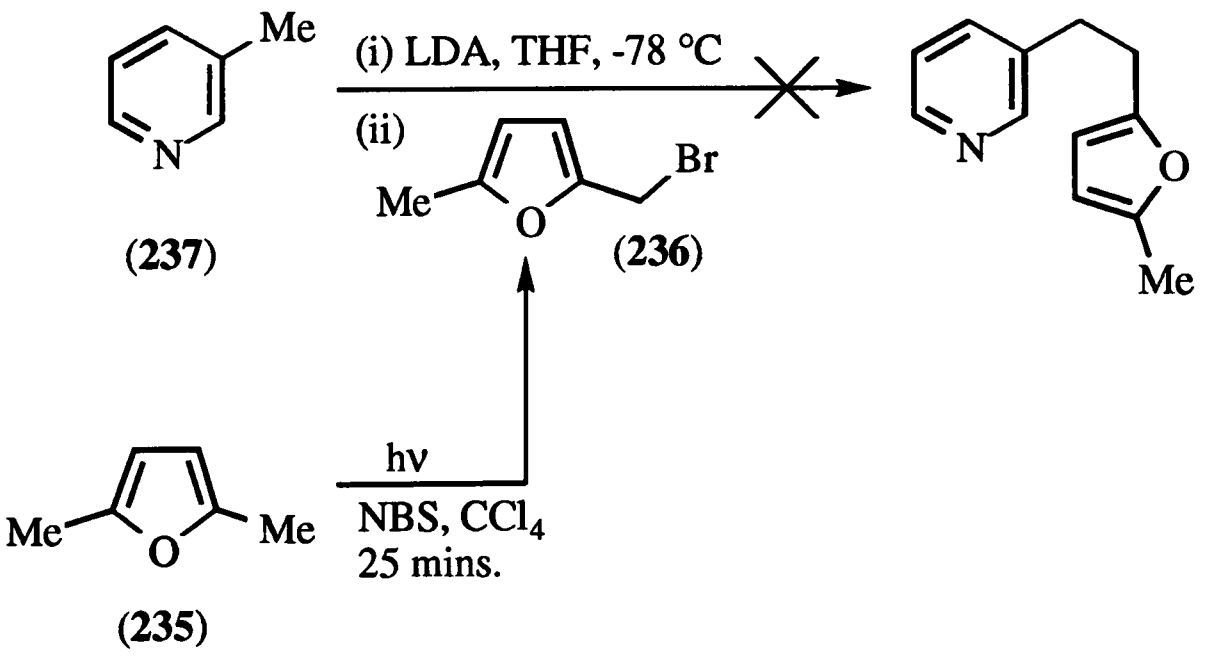


(235) **(236)**

Scheme 121

The desired 2-methyl-5-bromomethylfuran (**236**) appeared to be present in the crude reaction mixture and this was supported by ^1H NMR analysis. In the spectrum of the crude product, there was a CH_2 group resonance at δ 4.50 ppm. This was presumed to be the protons adjacent to the bromide which had been shifted from their position in 2,5-dimethylfuran (**235**) at δ 2.26 ppm where methyl group resonance appeared as a singlet. The furan protons also changed from a 2H singlet at δ 5.85 ppm in the symmetrical starting material to two 1H doublets at δ 6.28 and 5.93 ppm. Again, all purification attempts failed to isolate this adduct (**236**) from the crude product mixture.

Since the attempted purification by flash chromatography seemed to be causing the polymerisation, it was decided to use the crude 2-methyl-5-bromomethylfuran (**236**) in the reaction with the anion of 3-methylpyridine (**237**). This anion was formed by deprotonation of the 3-methylpyridine (**237**) with LDA, which was generated *in situ* by reaction of *n*-butyllithium with diisopropylamine at -78 °C in THF. After allowing the 3-methylpyridine (**237**) to deprotonate for 1 hour at -78 °C, the crude 2-methyl-5-bromomethylfuran (**236**) in solvent was added slowly to the reaction mixture (**Scheme 122**).

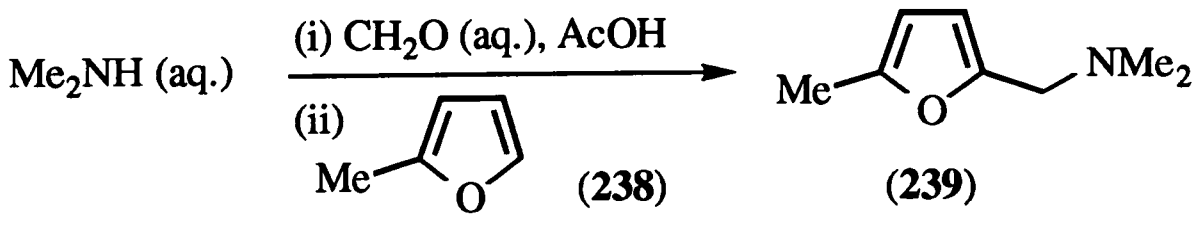


Scheme 122

Indication of some kind of addition product was seen in the crude reaction material, but attempts to purify it resulted in degradation. In the ^{1}H NMR spectrum of crude product mixture both pyridine and furan proton resonances were detected but the resonances corresponding to the two saturated CH_2 groups could not be distinguished from the other impurities in the spectrum. The four pyridine proton resonances appeared as a singlet at δ 9.35 ppm, a doublet (*J* 6.0 Hz) at δ 9.22 ppm, another doublet (*J* 7.8 Hz) at δ 8.23 ppm and a multiplet δ 7.98 - 7.91 ppm. The two furan proton resonances appeared as two doublet both with a coupling constant of *J* 2.7 Hz at δ 6.91 and 5.98 ppm.

Since the problems experienced with this reaction were attributed to the susceptibility of 2-methyl-5-bromomethylfuran (**236**) to polymerisation, a more stable furan derivative with a different leaving group was sought.

N,N,N-Trimethyl 2-(5-methylfuryl)methylammonium iodide (**240**) was the compound which was chosen and was synthesised *via* the Mannich reaction using 2-methylfuran (**238**), followed by addition of methyl iodide to form the quaternary ammonium salt (**240**). The first reaction involved addition of aqueous formaldehyde to aqueous methylamine in glacial acetic acid, followed by 2-methylfuran (**238**), which resulted in 68 % of *N,N*-dimethyl-2-(5-methylfuryl)methylamine (**239**) (**Scheme 123**). [84]



Scheme 123

Evidence for the product came from the mass spectrum where the molecular ion peak corresponding to MH^+ was detected at 142 Daltons. The ^{1}H NMR spectrum

provided further indication that the reaction had been successful, revealing new proton resonances at δ 3.38 ppm for the CH_2 group and at δ 2.28 ppm for the methyl groups attached to the nitrogen. The ^{13}C NMR spectrum confirmed this, showing these carbon resonances at δ 55.92 and 44.86 ppm, respectively.

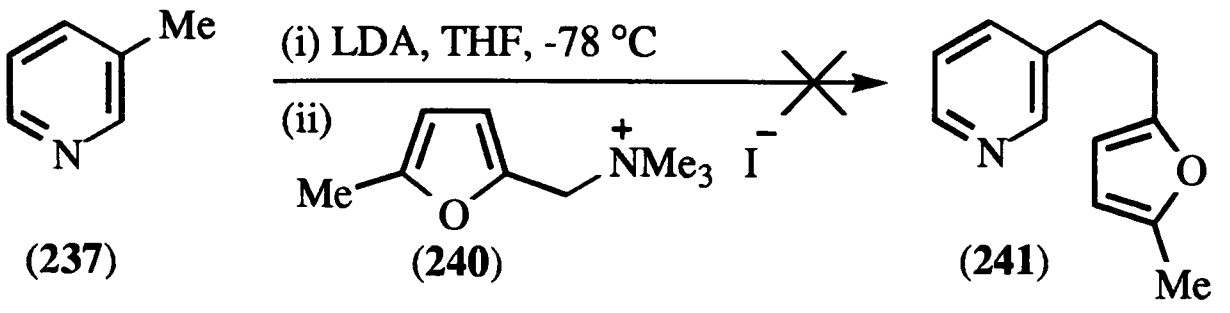
Formation of the quaternary ammonium salt (**240**) was easily achieved using the procedure of Sommer with methyl iodide in DMF (**Scheme 124**).[85]

(239) **(240)**

Scheme 124

N,N,N-trimethyl 2-(5-methylfuryl)methylammonium iodide (**240**) was obtained as a beige crystalline solid in 66 % yield. Proof of the cation of the product came from the mass spectrum which exhibited a M^+ peak at 154 Daltons. The ^1H NMR spectrum showed a shift in the resonance for the methyl groups attached to the nitrogen to δ 3.44 ppm which represented nine protons instead of six. A similar shift was noted in the ^{13}C NMR spectrum where the resonance for these methyl carbons appeared at δ 53.23 ppm. Confirmation of the iodide anion came from the micro analysis data.

The next step was to react this furan adduct (**240**) with the anion of 3-methylpyridine (**237**). The anion was formed, as before, with LDA which was generated *in situ* and after a deprotonation time of 1 hour, the *N,N,N*-trimethyl 2-(5-methylfuryl)methylammonium iodide (**240**) was added (**Scheme 125**).

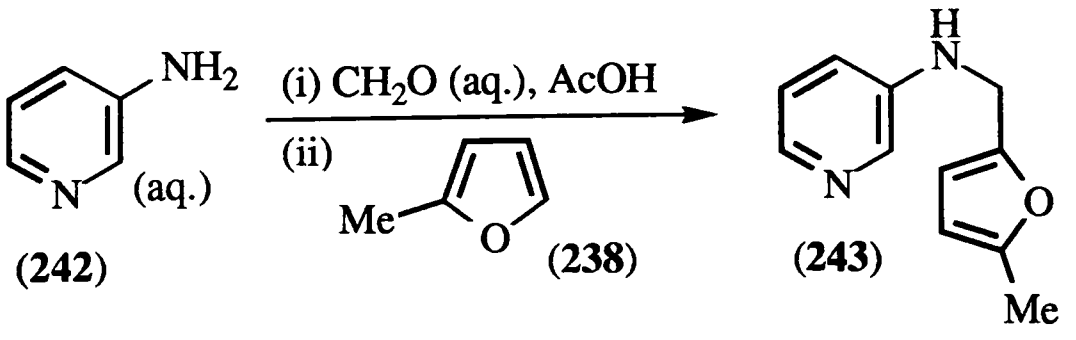


Scheme 125

Work up of the reaction mixture gave none of the adduct (**241**) and only the starting material *N,N,N*-trimethyl 2-(5-methylfuryl)methylammonium iodide (**240**) was recovered. None of the starting material 3-methylpyridine (**237**) was recovered and in the ^{1}H NMR spectrum of the crude product material, there were no pyridine proton resonances.

It was decided to abandon this approach, but use the Mannich reaction in the same manner as before, using instead, 3-aminopyridine (**242**) as the amine.

The Mannich reaction proved to be a very simple and easy way of introducing the furan sub-unit into the tether of the 3-substituted pyridine. Reacting an aqueous solution of 3-aminopyridine (**242**) with aqueous formaldehyde in glacial acetic acid, followed by 2-methylfuran (**238**), afforded *N*-(2-(5-methylfuryl)methane)-3-aminopyridine (**243**) in a 51 % yield (**Scheme 126**).

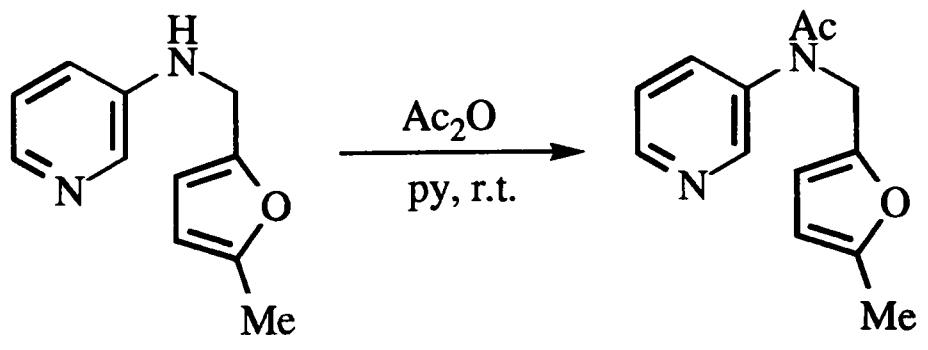


Scheme 126

Product formation was supported by the mass spectral data in which a peak corresponding to the MH^+ ion was detected at 189 Daltons. The ^{1}H NMR spectrum

also showed resonances consistent with product formation. The pyridine protons appearing at δ 8.10 ppm as a 1H doublet with *J* 2.8 Hz, δ 8.00 ppm as another 1H doublet with *J* 4.6 Hz, δ 7.09 ppm as a 1H double doublet with *J* 8.3 Hz and *J'* 4.6 Hz and as a 1H double double doublet at δ 6.95 ppm with *J* 8.3 Hz, *J'* 2.8 Hz and *J''* 1.3 Hz. The furan proton resonances both appeared as doublets (*J* 3.0 Hz) at δ 6.12 and 5.90 ppm. The saturated CH_2 protons were at δ 4.27 ppm and the methyl group at δ 2.28 ppm. It was possible also to see the broad NH resonance in the ^1H NMR spectrum at δ 4.06 ppm and in the IR spectrum there was a broad absorption at 3 260 cm^{-1} for this group. The ^{13}C NMR spectrum also showed pyridine resonances at δ 150.03, 147.48, 136.89, 135.79 and 123.26 ppm, furan resonances at δ 150.03, 140.32, 118.70 and 107.64 ppm with the methylene and methyl carbon resonances at δ 62.25 and 13.73 ppm.

The next step was the protection of the amine, prior to cleavage of the furan ring. This was accomplished by stirring the *N*-(2-(5-methylfuryl)methane)-3-aminopyridine (**243**) in pyridine with an excess of acetic anhydride (**Scheme 127**).



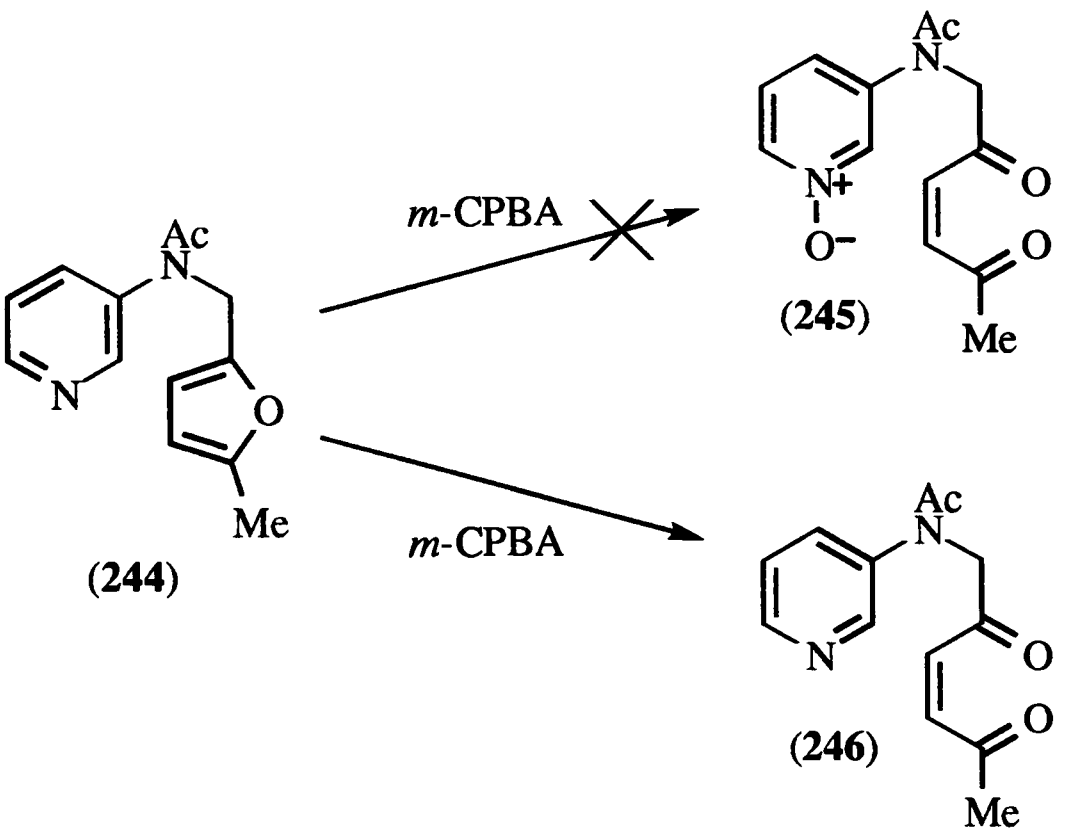
(243) **(244)**

Scheme 127

The acetylated product (**244**) was synthesised in 98 % yield. Again the mass spectrum confirmed product formation by a gain of 42 Daltons for the MH^+ peak due to addition of the acetyl group. There was also a carbonyl stretching frequency in the IR spectrum at 1 665 cm^{-1}. Both ^1H and ^{13}C NMR spectra could authenticate product

formation by the appearance of an additional methyl singlet at δ 1.87 ppm and a carbonyl resonance at δ 169.74 ppm respectively.

Stereospecific cleavage of the furan ring was subsequently required to give only the *cis* double bond in order to avoid steric hindrance in the ensuing cycloaddition reaction. *m*-CPBA was employed to bring about this transformation, and it was hoped that it also could achieve oxidation of the pyridine ring to give the *N*-oxide (**245**). For this reason, the reaction was carried out with 2 equivalents of *m*-CPBA in DCM (**Scheme 128**).



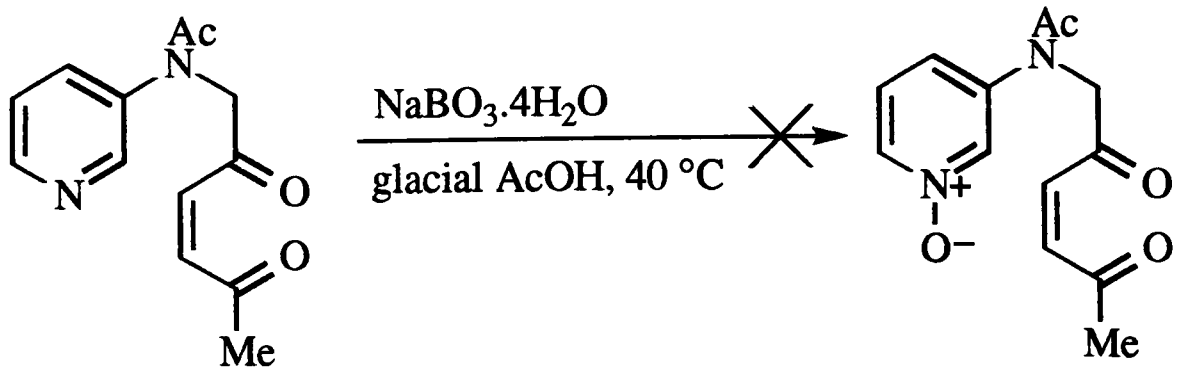
Scheme 128

Unfortunately, oxidation to give the *N*-oxide (**245**), did not occur but cleavage of the furan ring did take place to yield only the *cis* double bonded product (**246**), although in a rather disappointing 28 % yield. Carrying out the reaction with only one equivalent of *m*-CPBA resulted in an increased yield of (**246**) of only a few percent.

Evidence for the product came from the mass spectrum showing an increase in the MH^+ ion of 16 Daltons showing that oxidation of the furan had occurred. The IR

spectrum also showed three strong carbonyl stretching absorptions at 1 690, 1 680 and 1 667 cm^{-1}. In the ^1H NMR spectrum, there was a large shift down field of what were the furan proton resonances in the starting material, to δ 6.92 ppm, as they had become vinylic protons. The fact that they appeared as a 2H singlet could not confirm a *cis* double bond since the *trans* isomer also would be *quasi*-symmetrical. However, after standing in chloroform at room temperature for a few days, the ^1H NMR spectrum of the product (**246**) changed. The vinylic protons now appeared as two doublets at δ 6.94 and 6.90 ppm both with a *trans* coupling constant of *J* 16.3 Hz. *Cis* to *trans* isomerisation, seen previously for this type of system, had occurred.[86] In the ^{13}C NMR spectrum, there were now three carbonyl resonances, the two at δ 197.61 and 193.92 ppm were assumed to be from the new carbonyls formed by cleavage of the furan ring.

As *m*-CPBA had not brought about the pyridine oxidation, this was the last step required in order to form the cycloaddition precursor, *N*-acetyl-*N*-(2,5-dioxohex-3-ene)-3-aminopyridine *N*-Oxide (**245**). Oxidation was attempted using the sodium perborate oxidation reaction with the *N*-acetyl-*N*-(2,5-dioxohex-3-ene)-3-aminopyridine (**246**) in glacial acetic acid (**Scheme 129**).

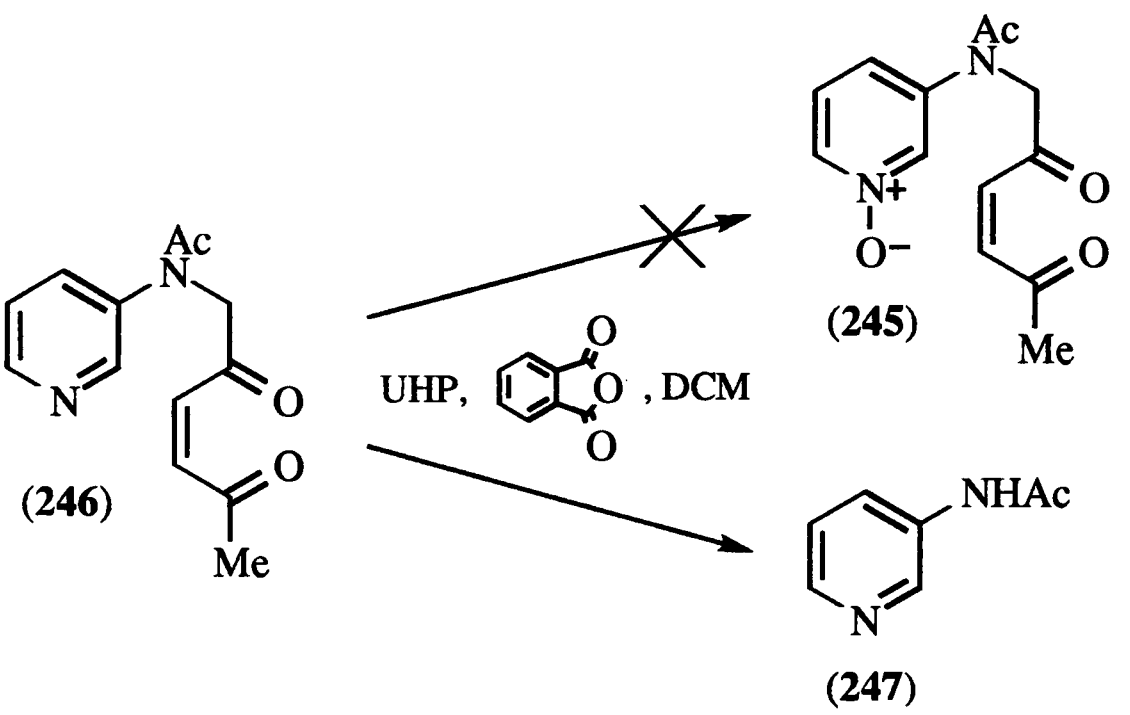


(246) **(245)**

Scheme 129

As in the attempted formation of the mono-activated cycloaddition precursor (**209**), the sodium perborate oxidation failed to produce the *N*-oxide (**245**) and starting material (**246**) was recovered.

Therefore, as before, oxidation using UHP with phthalic anhydride in DCM was attempted (**Scheme 130**).



Scheme 130

Purification of the crude product mixture, by reverse phase flash chromatography,[87] gave only *N*-acetyl 3-aminopyridine (**247**) in 43 % yield. Evidence for this product came from the mass spectrum which showed the MH^+ peak at 137 Daltons and the ^1H NMR spectrum which only revealed pyridine proton resonances and a methyl singlet for the acetyl group at δ 2.16 ppm. The IR spectrum also showed only one carbonyl stretching absorption at 1 689 cm^{-1}. Repeating this oxidation procedure did not yield any of the desired di-activated cycloaddition precursor (**245**).

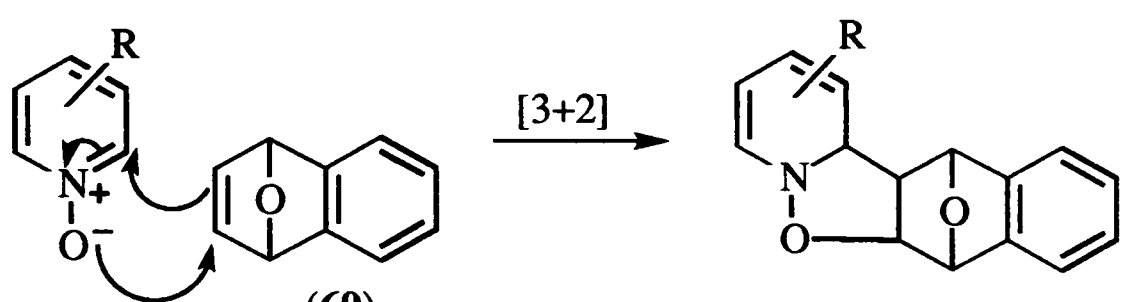
5.4 Summary

Since these approaches to the construction of the cycloaddition precursors (**209**), (**216**) and (**245**) were unsuccessful, the methodology of the intramolecular [3+2] cycloaddition reaction on these substrates could not be investigated. However, the methodology for the synthesis of a range of 3-substituted pyridines had been established.

5.5 Future Work

The procedure for effecting the [3+2] cycloaddition, both in an intermolecular and intramolecular sense, had proven to be a lot less general than was originally hoped.

In the intermolecular sense, cycloadditions had been attempted with a range of pyridine *N*-oxides with both methyl acrylate (**153**) and dimethyl maleate (**54**), under a range of conditions, but the appropriate combination of precursors and reaction condition was not found. Further studies on the intermolecular reaction could include attempted cycloaddition with electron rich dipolarophiles, such as 1,4-epoxy-1,4-dihydronaphthalene (**69**), for example, (**Scheme 131**).



(**69**)

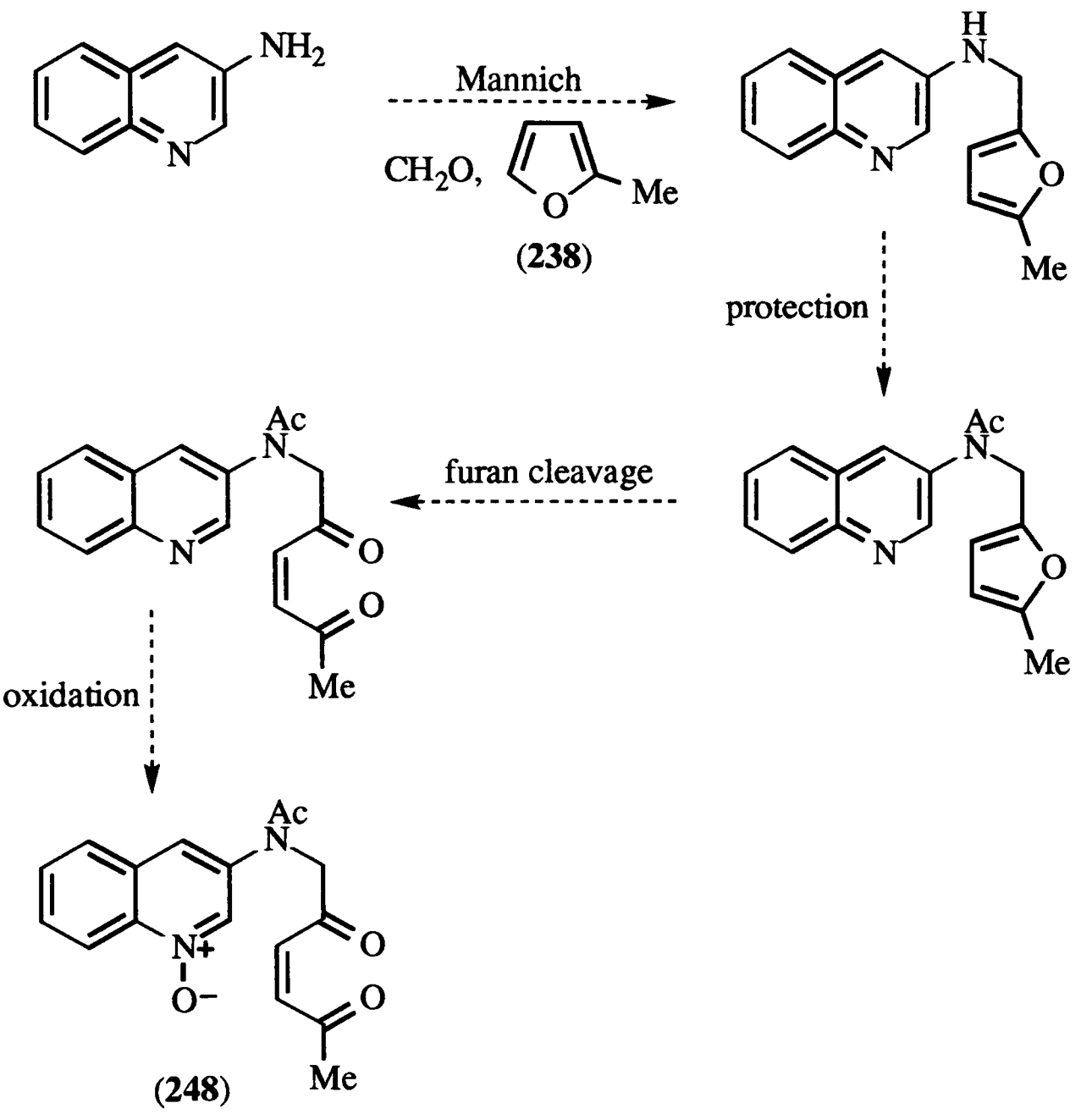
For *N*-oxide, R = H (**1**), Me (**71**), Cl (**151**), OMe (**79a**), CO_2Me (**152**)

Scheme 131

Use of electron rich dipolarophiles may cause cycloaddition to occur with inverse electron demand.

There is also a large loss in aromatic stabilisation energy of the pyridine *N*-oxide during cycloaddition, which may prevent the reaction from occurring. To circumvent this problem, inclusion of the 1,3-dipole in a quinoline *N*-oxide (**68**) or isoquinoline *N*-oxide (**161**) may facilitate the cycloaddition as the loss of aromatic stabilisation energy on cycloaddition is not as large for these compounds.[33]

In an intramolecular sense, for example, construction of adducts such as (**248**), were envisaged, with quinoline instead of pyridine. Synthesis of the quinoline *N*-oxide (**248**) could follow the established route and by successful oxidation, yield the cycloaddition precursor (**248**), on which subsequent [3+2] cycloaddition could be attempted (**Scheme 132**).



Scheme 132

Unfortunately, time did not permit further investigation of this approach to the [3+2] cycloaddition precursors.

CHAPTER 6
EXPERIMENTAL

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EXPERIMENTAL

6.1 Experimental Techniques

^1H NMR spectra were recorded in $CDCl_3$, D_2O, CD_3OD and CD_3CN as stated and referenced to the solvent peak. Instruments used were a Varian Gemini (200 MHz), a Bruker AC200 (200 MHz) and a Bruker AM500 (500 MHz) in the Dyson Perrins laboratory and a Bruker AC250P (250 MHz) at DowElanco, Letcombe Regis. Peak positions were recorded in δ ppm with the abbreviations s, d, t, q, dd, ddd, dt, td and m denoting singlet, doublet, triplet, quartet, double doublet, double double doublet, double triplet, triple doublet and multiplet respectively and br denoting a broad peak. 500 MHz ^1H NMR and 125.7 MHz ^{13}C NMR spectroscopy were performed in the Dyson Perrins laboratory by Mrs E. McGuinness and 250 MHz ^1H NMR and 62.9 MHz ^{13}C NMR spectroscopy were performed at DowElanco, Letcombe Regis by Dr. P. Graupner.

Infrared spectra were recorded on a Perkin Elmer 1750 FT-IR spectrometer as thin films or KBr discs as stated with the abbreviations w, m, s denoting weak, medium and strong absorptions respectively and br denoting a broad absorption.

Mass spectrometric data was recorded on a TRIO 1 GC, VG Autospec, VG 20-250, BioQ or ZAB1F mass spectrometer under conditions of chemical ionisation (C.I.), using ammonia as the ionising source, electron impact (E.I.) and electrospray (E.S.). Mass spectra were quoted in the form $^m/_z$ (relative intensity).

UV spectra were recorded in HPLC grade methanol on a Lambda 2 Perkin Elmer spectrometer.

Microanalyses were performed on a Carlo Erba 1106 elemental analyser in the Dyson Perrins laboratory by Mrs V. Lamburn.

Melting points (m.p.) were recorded using a Koffler hot stage microscope and are uncorrected.

T.l.c. analysis referred to analytical thin layer chromatography using Merck plastic backed plates coated with 0.2 mm silica 60 F_{254}. Product spots were visualised either by the quenching of UV fluorescence or by staining with 2% aqueous potassium permanganate solution. Flash column chromatography referred to column chromatography with Kieselgel 60 silica gel, using head pressure by means of compressed air by the method of Still.[88] Reverse phase chromatography was carried out on reverse phase Merck silica gel 60 prepared according to the method of O'Neil,[87] by suction in place of head pressure, by the dry flash methodology developed by Harwood.[89]

Short-path distillation (bulb-to-bulb) was performed using a horizontal Kugelrohr apparatus, recording the uncorrected oven temperature.

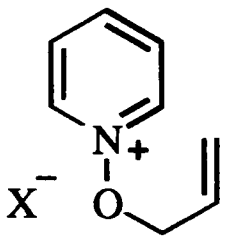
Solvents and reagents were purified according to the procedures of Perrin and Armarego.[90] In particular, acetonitrile, DMF, DMSO and DCM were dried by refluxing over and distilling from calcium hydride. Diethyl ether and THF were obtained dry and oxygen-free by distilling from sodium-benzophenone ketyl under nitrogen. Toluene and xylene were dried by standing over sodium wire. Light petroleum referred to the petroleum ether fraction boiling between 30 and 40°C and was fractionally distilled before use. Triethylamine and pyridine were dried by standing over potassium hydroxide.

The concentration of *n*-butyllithium was determined by titration of a THF solution of diphenyl acetic acid.[91]

Compounds, whose preparation is not described below, were obtained commercially from Aldrich, Avocado, BDH, Rathburn and Fisons chemical suppliers.

6.2 Experimental Procedures

Preparation of *1-(2-Allyloxy)pyridinium salt* (**142**)



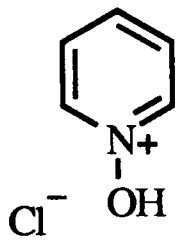
Allyl bromide (**138**) (3.65 mL, 5.10 g, 42.2 mmol, 4 equiv.) was added dropwise over 5 minutes to a stirred solution of pyridine *N*-oxide (**1**) (1.00 g, 10.6 mmol, 1 equiv.) and silver nitrate (1.87 g, 11.6 mmol, 1.1 equiv.) in dry acetonitrile (5 mL) at 0 °C under nitrogen. The reaction mixture was slowly allowed to warm to room temperature and then stirred for 22 hours. The precipitated silver bromide was filtered off and the solvent removed *in vacuo*. The pure *1-(2-allyloxy)pyridinium salt* (**142**) (m.p. 61 °C) was obtained as a pale pink hygroscopic solid by recrystallisation from a mixture of acetonitrile / water (95 : 5) (100 mL) and diethyl ether (100 mL) (275 mg).

ν_{max} (KBr disc) 3 099 and 3 050 (C-H, m), 1 610 (C=C, m), 1 272 (N-O, m) cm^{-1}; δ (500 MHz, D_2O) 8.97 (2H, dd, *J* 6.8 Hz, *J'* 1.1 Hz, py$\underline{H}_2$ and py$\underline{H}_6$), 8.49 (1H, t, *J* 7.8 Hz, py$\underline{H}_4$), 8.08 - 8.05 (2H, m, py$\underline{H}_3$ and py$\underline{H}_5$), 6.09 - 6.01 (1H, m, -C$\underline{H}$=CH_2), 5.41 (1H, dd, *J* 11.1 Hz, *J'* 1.0 Hz, -CH=CH($\underline{H}$)*cis*), 5.32 (1H, dd, *J* 16.1 Hz, *J'* 1.0 Hz, -CH=C$\underline{H}$(H)*trans*), 5.03 (2H, d, *J* 7.0 Hz, -O$C\underline{H}_2$-); $m/_z$ (E.S.$^+$) 136 (100 %, M^+).

Attempted Claisen rearrangement on the 1-(2-allyloxy)pyridinium salt (**142**)

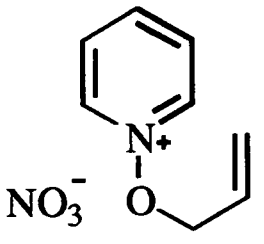
Following the procedure used previously within the group to effect Lewis acid catalysed Claisen rearrangement,[56] the 1-(2-allyloxy)pyridinium salt (**142**) (80.7 mg) was stirred in dry DCM (20 mL) under nitrogen and cooled to *ca.* -50 °C. Boron

trichloride (2.4 mL, 1.0 M solution in DCM, 2.4 mmol) was added dropwise and the reaction allowed to stir at this temperature for 1 hour before being warmed to -35 °C and stirring continued for a further 16 hours. The reaction mixture was then allowed to warm to room temperature, the reaction solution filtered to remove the borate salts and the solvent removed *in vacuo* to yield a white solid. This was not found to be the Claisen rearranged product (**136**), but was thought to be the pyridine *N*-oxide hydrochloride salt (**143**) (m.p. 178 °C; lit.[92] 179.5-181 °C) (16 mg).



ν_{max} (KBr disc) 3 400 (OH, br, s), 3 078 and 3 041 (C-H, m), 1 618 and 1 589 (C=C, m), 1 196 (N-O, s) cm^{-1}; δ (500 MHz, CD_3CN) 8.85 - 8.84 (2H, m, py<u>H</u>$_2$ and py<u>H</u>$_6$), 8.26 - 8.22 (1H, m, py<u>H</u>$_4$), 7.94 - 7.91 (2H, m, py<u>H</u>$_3$ and py<u>H</u>$_5$), 3.55 (1H, br s, -O<u>H</u>); $^m/_z$ (E.S.$^+$) 96 (100 %, M^+).

Preparation of *1-(2-Allyloxy)pyridinium) nitrate* (**145**)

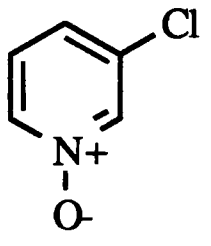


Pyridine *N*-oxide (**1**) (365 mg, 3.84 mmol, 1 equiv.) and silver nitrate (671 mg, 3.95 mmol, 1.1 equiv.) were stirred in dry acetonitrile (3 mL.) under nitrogen and cooled to 0 °C. Allyl iodide (**144**) (1.45 mL, 2.58 g, 15.4 mmol, 4 equiv.) was added dropwise over 5 minutes and the reaction mixture was slowly allowed to warm to room temperature and then stirred for 15 minutes. The precipitated

silver iodide was filtered off and the solvent removed *in vacuo*. Recrystallisation from a mixture of acetonitrile / diethyl ether afforded the pure *1-(2-allyloxy)pyridinium nitrate* (**145**) (m.p. <50 °C) as a yellow hygroscopic solid (491 mg, 65 %).

ν_{max} (KBr disc) 3 112 and 3 0350 (C-H, s), 1 612 (C=C, m), 1 348 (NO_3^-, s), 1 275 (N-O, s) cm^{-1}; δ (500 MHz, CD_3OD) 9.39 (2H, d, *J* 6.7 Hz, py$\underline{H}_2$ and py$\underline{H}_6$), 8.67 - 8.64 (1H, m, py$\underline{H}_4$), 8.29 - 8.22 (2H, m, py$\underline{H}_3$ and py$\underline{H}_5$), 6.25 - 6.14 (1H, m, -C$\underline{H}$=CH_2), 5.49 (1H, dd, *J* 10.2 Hz, *J'* 1.0 Hz, -CH=CH($\underline{H}$)*cis*), 5.46 (1H, dd, *J* 15.9 Hz, *J'* 1.0 Hz, -CH=C$\underline{H}$(H)*trans*), 5.18 (2H, d, *J* 7.1 Hz, -OC$\underline{H}_2$-); $m/_z$ (E.S.$^+$) 136 (100 %, M^+), 96 (30 %, M^+ -40).

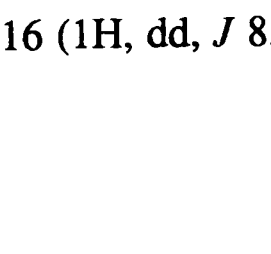
Preparation of 3-Chloropyridine *N*-oxide (**151**)



Hydrogen peroxide (19.1 mL, 100 volumes, 30 % in water, 168.24 mmol, 2 equiv.) was added dropwise to a stirred solution of 3-chloropyridine (9.55 g, 84.12 mmol, 1 equiv.) in acetic acid (65 mL) under nitrogen. The solution was warmed to 70 - 80 °C and allowed to stir for 15 hours until all the starting material was consumed as indicated by t.l.c. analysis in 4 : 1 ethyl acetate / glacial acetic acid. Anhydrous potassium carbonate was added slowly until the solution became strongly alkaline, followed by the addition of chloroform (65 mL). The reaction mixture was then left to stand for 10 minutes allowing the potassium acetate and potassium carbonate to settle. Filtration of the chloroform layer, drying ($NaSO_4$) and evaporation of the solvent yielded the crude *N*-oxide. Recrystallisation from DCM gave pure 3-chloropyridine *N*-oxide (**151**) (m.p. 54 °C; lit.[93] 57 °C) as a beige crystalline hygroscopic solid (9.93 g, 91 %).

Found C 46.35, H 2.81, N 10.79, C_5H_4ClNO requires C 46.36, H 3.11, N 10.81 %; ν_{max} (KBr) 3 103 (C-H, m), 1 595 and 1 545 (C=C, s), 1 247 (N-O, s) cm^{-1}; δ (500 MHz, $CDCl_3$) 8.21 (1H, t, *J* 1.5 Hz, py$\underline{H}_2$), 8.08 (1H, dt, *J* 6.3 Hz, *J'* 1.5 Hz, py$\underline{H}_6$), 7.24 (1H, dt, *J* 8.3 Hz, *J'* 1.5 Hz, py$\underline{H}_4$), 7.19 (1H, dd, *J* 8.3 Hz, *J'* 6.3 Hz, py$\underline{H}_5$); δ_C (125.7 MHz, $CDCl_3$) 138.77 (pyCH), 137.71 (pyCH), 133.37 (pyC), 125.69 (2 x pyCH); $^m/_z$ (C.I.) 132 (6 %, MH^+), 130 (18 %, MH^+), 116 (30 %, MH^+ -16), 114 (100 %, MH^+ -16); λ_{max} (ε) (MeOH) 268 (12 200), 222 (15 600).

Preparation of 3-Methoxypyridine *N*-oxide (**79a**)

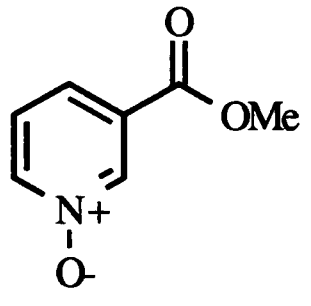


3-Chloropyridine *N*-oxide (**151**) (1.366 g, 10.55 mmol, 1 equiv.) was dissolved in dry methanol (15 mL) and stirred over activated 4 Å molecular sieves for 5 minutes. Sodium methoxide (684 mg, 12.65 mmol, 1.2 equiv.) was added portionwise and the mixture refluxed for 10 hours. After cooling to room temperature, the reaction mixture was filtered to remove the molecular sieves, quenched by the addition of water (5 mL) and extracted with chloroform (5 x 25 mL). The organic washings were combined, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the crude *N*-oxide. Recrystallisation from DCM afforded pure 3-methoxypyridine *N*-oxide (**79a**) (m.p. 80 °C; lit.[94] 83 °C) as a white crystalline hygroscopic solid (601 mg, 46 %).

Found C 57.39, H 5.93, N 10.99, $C_6H_7NO_2$ requires C 57.59, H 5.64, N 11.19 %; ν_{max} (KBr) 3 122 and 2 948 (C-H, s), 1 606 and 1 570 (C=C, s), 1 245 (N-O, m), 1 197 (C-O, s) cm^{-1}; δ (500 MHz, $CDCl_3$) 7.98 (1H, t, *J* 2.0 Hz, py$\underline{H}_2$), 7.90 (1H, dd, *J* 6.3 Hz, *J'* 0.4 Hz, py$\underline{H}_6$), 7.16 (1H, dd, *J* 8.6 Hz, *J'* 6.3 Hz, py$\underline{H}_5$), 6.88 (1H,

dd, *J* 8.6 Hz, *J'* 2.3 Hz, py$\underline{H}_4$), 3.85 (3H, s, -C$\underline{H}_3$); δ_C (125.7 MHz, $CDCl_3$) 158.05 (pyC), 132.47 (pyCH), 127.77 (pyCH), 125.34 (pyCH), 112.82 (pyCH), 56.10 (CH_3); $^m/_z$ (C.I.) 126 (57 %, MH^+), 110 (100 %, MH^+); λ_{max} (ε) (MeOH) 299 (2 430), 263 (8 900), 224 (14 100).

Preparation of Methyl pyridine-3-carboxylate *N*-oxide (**152**).

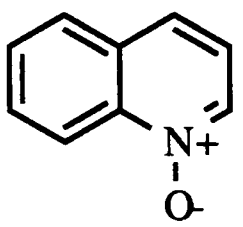


Hydrogen peroxide (14.5 mL, 100 volumes, 30 % in water, 128.41 mmol, 1.7 equiv.) was added dropwise to a stirred solution of methyl pyridine-3-carboxylate (10.30 g, 75.09 mmol, 1 equiv.) in acetic acid (50 mL) under nitrogen. The solution was warmed to 70 - 80 °C and allowed to stir for 15 hours until all the starting material was consumed as indicated by t.l.c analysis in 4 : 1 ethyl acetate / glacial acetic acid. Anhydrous potassium carbonate was added slowly until the solution was strongly alkaline followed by the addition of chloroform (50 mL). The reaction mixture was then left to stand for 10 minutes allowing the potassium acetate and potassium carbonate to settle. Filtration of the chloroform layer, drying ($NaSO_4$) and evaporation of the solvent yielded the crude *N*-oxide. Recrystallisation from DCM gave pure methyl pyridine 3-carboxylate *N*-oxide (**152**) (m.p. 100 °C; lit.[95] 97 °C) as a white crystalline hygroscopic solid (9.96 g, 87 %).

Found C 55.09, H 4.34, N 9.01, $C_7H_7NO_3$ requires C 54.90, H 4.61, N 9.15 %; ν_{max} (KBr) 3 088, 3 018 and 2 959 (C-H, m), 1 736 (C=O, s), 1 603 and 1 567 (C=C, m), 1 238 (N-O, s), 1 176 (C-O, s) cm^{-1}; δ (500 MHz, $CDCl_3$) 8.75 (1H, s, py$\underline{H}_2$), 8.32 (1H, d, *J* 6.4 Hz, py$\underline{H}_6$), 7.83 (1H, d, *J* 8.0 Hz, py$\underline{H}_4$), 7.35 (1H, t, *J* 7.2 Hz, py$\underline{H}_5$), 3.95 (3H, s, -OC$\underline{H}_3$); δ_C (125.7 MHz, $CDCl_3$) 163.12 (C=O),

142.35 (pyCH), 140.12 (pyCH), 129.81 (pyC), 125.98 (pyCH), 125.71 (pyCH), 52.92 (CH_3); $^{m}/_{z}$ (C.I.) 154 (77 %, MH^+), 138 (100 %, MH^+ -16); λ_{max} (ε) (MeOH) 226 (10 800), 267 (11 000).

Preparation of Quinoline *N*-oxide (**68**).

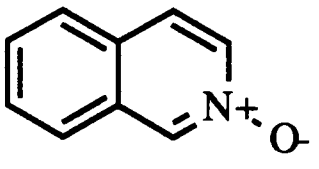


Hydrogen peroxide (11 mL, 100 volumes, 30 % in water, 97.35 mmol, 1.7 equiv.) was added dropwise to a stirred solution of quinoline (7.17 g, 55.48 mmol, 1 equiv.) in acetic acid (32 mL) under nitrogen. The solution was warmed to 70 - 80 °C and allowed to stir for 15 hours until all the starting material was consumed as indicated by t.l.c. analysis in 4 : 1 ethyl acetate / glacial acetic acid. Anhydrous potassium carbonate was added slowly until the solution was strongly alkaline, followed by the addition of chloroform (35 mL). The reaction mixture was then left to stand for 10 minutes allowing the potassium acetate and potassium carbonate to settle. Filtration of the chloroform layer, drying ($NaSO_4$) and evaporation yielded the crude *N*-oxide. Recrystallisation from DCM gave pure quinoline *N*-oxide (**68**) (m.p. 60 °C; lit.[92] 62 °C) as a beige crystalline hygroscopic solid (6.53 g, 81 %).

Found C 74.45, H 4.68, N 9.88, C_9H_7NO requires C 74.47, H 4.86, N 9.65 %; ν_{max} (KBr) 3 068 and 3 008 (C-H, m), 1 572 and 1 512 (C=C, s), 1 228 (N-O, s) cm^{-1}; δ (500 MHz, $CDCl_3$) 8.76 (1H, d, *J* 8.7 Hz, $\underline{H}_8$), 8.54 (1H, d, *J* 6.0 Hz, $\underline{H}_2$), 7.88 (1H, d, *J* 8.3 Hz, $\underline{H}_4$), 7.78 (1H, dd, *J* 7.3 Hz, *J'* 1.4 Hz, $\underline{H}_5$), 7.75 (1H, d, *J* 8.7 Hz, $\underline{H}_7$), 7.65 (1H, t, *J* 7.5 Hz, $\underline{H}_6$), 7.30 (1H, dd, *J* 8.3 Hz, *J'* 6.0 Hz, $\underline{H}_3$) ; δ_C (125.7 MHz, $CDCl_3$) 135.59, 130.54, 130.41, 128.76, 128.10, 120.95, 119.82;

$^{m}/_{z}$ (C.I.) 146 (62 %, MH^+), 130 (100 %, MH^+ -16); λ_{max} (ε) (MeOH) 324 (7 690), 230 (41 600).

Preparation of Isoquinoline *N*-oxide (**161**).



Hydrogen peroxide (6.3 mL, 100 volumes, 30 % in water, 55.30 mmol, 1.7 equiv.) was added dropwise to a stirred solution of isoquinoline (4.20 g, 32.53 mmol, 1 equiv.) in acetic acid (22 mL) under nitrogen. The solution was warmed to 70 - 80 °C and allowed to stir for 15 hours until all the starting material was consumed as indicated by t.l.c. analysis in 4 : 1 ethyl acetate / glacial acetic acid. Anhydrous potassium carbonate was added slowly until the solution was strongly alkaline, followed by the addition of chloroform (25 mL). The reaction mixture was then left to stand for 10 minutes allowing the potassium acetate and potassium carbonate to settle. Filtration of the chloroform layer, drying ($NaSO_4$) and evaporation yielded the crude *N*-oxide. Recrystallisation from DCM gave pure isoquinoline *N*-oxide (**161**) (m.p. 99 °C; lit.[96] 98 °C) as a white hygroscopic crystalline solid (3.73 g, 79 %).

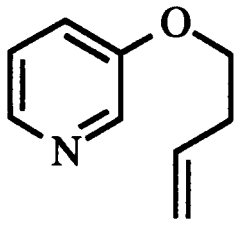
Found C 74.22, H 4.98, N 9.69, C_9H_7NO requires C 74.47, H 4.86, N 9.65 %; ν_{max} (KBr) 3 076 (C-H, m), 1 602 and 1 573 (C=C, s), 1 253 (N-O, s) cm^{-1}; δ (500 MHz, $CDCl_3$) 8.74 (1H, s, $\underline{H}_1$), 8.11 (1H, dd, *J* 7.1 Hz, *J'* 1.8 Hz, $\underline{H}_3$), 7.77 (1H, d, *J* 7.8 Hz, $\underline{H}_8$), 7.70 (1H, d, *J* 7.8 Hz, $\underline{H}_5$), 7.65 (1H, d, *J* 7.1 Hz, $\underline{H}_4$), 7.55 - 7.61 (2H, m, $\underline{H}_6$ and $\underline{H}_7$); δ_C (125.7 MHz, $CDCl_3$) 136.88, 136.12, 129.51, 129.00, 128.77, 126.68, 124.95, 124.23; $^{m}/_{z}$ (C.I.) 146 (90 %, MH^+), 130 (100 %, MH^+ -16); λ_{max} (ε) (MeOH) 297 (10 500), 256 (27 200).

Preparation of 4-Iodobut-1-ene (**174**)

The title compound was prepared by the Finkelstein reaction.[64] Sodium iodide (15.23 g, 102 mmol, 2 equiv.) was stirred in acetone (80 mL) under nitrogen for 10 minutes, allowing it to dissolve. 4-Bromobut-1-ene (**170**) (5.16 mL, 6.86 g, 50.8 mmol, 1 equiv.) was added dropwise and the reaction mixture refluxed for 4 hours. After cooling the reaction mixture to room temperature, the solvent was removed *in vacuo* to yield the crude product and sodium bromide. The residue was subsequently diluted with diethyl ether (60 mL) and extracted with water (50 mL). The aqueous layer was further extracted with diethyl ether (3 x 50 mL), the ethereal layers combined, dried ($MgSO_4$) and the solvent evaporated to yield the crude product. Purification by short path bulb-to-bulb distillation in a horizontal Kugelrohr apparatus under reduced pressure (bath temp 40 °C, 50 mmHg) gave pure 4-iodobut-1-ene (**174**) as a colourless liquid (5.80 g, 63 %).

Found C 26.11, H 3.84, C_4H_7I requires C 26.41, H 3.88 %; ν_{max} (thin film) 3 079, 3 002, 2 979, 2 960 and 2 917 (C-H, m), 1 640 (C=C, s) cm^{-1}; δ (500 MHz, $CDCl_3$) 5.80 - 5.72 (1H, m, -C<u>H</u>=CH_2), 5.14 - 5.10 (2H, m, -CH=C<u>H</u>$_2$), 3.19 (2H, t, *J* 7.2 Hz, -C<u>H</u>$_2$I), 2.65 - 2.60 (2H, m, -C<u>H</u>$_2$-CH_2I); δ_C (125.7 MHz, $CDCl_3$) 136.85 (vinylic CH), 116.99 (vinylic CH_2), 37.64 (CH_2), 4.64 (CH_2); $^m/_z$ (C.I.) 182 (14 %, MH^+), 55 (100 %, MH^+ -127).

Preparation of *3-(3-Butenyloxy)pyridine* (**171**)



(i) With potassium carbonate as base

3-Hydroxypyridine (**169**) (665 mg, 6.9 mmol, 1 equiv.) and potassium carbonate (976 mg, 6.9 mmol, 1 equiv.) were stirred in dry methanol (40 mL) under nitrogen for 10 minutes. 4-Bromobut-1-ene (**170**) (1.4 mL, 1.86 g, 13.8 mmol, 2 equiv.) was added dropwise and the reaction mixture refluxed for 17 hours. After cooling the reaction mixture to room temperature, the solvent was evaporated and the residue diluted with diethyl ether (40 mL). The ethereal solution was washed with water (40 mL) and then dried ($MgSO_4$) before removal of the solvent *in vacuo* to yield the crude product. Purification by flash chromatography on silica eluting with diethyl ether (R_f 0.31) gave pure *3-(3-butenyloxy)pyridine* (**171**) as a colourless oil (117 mg, 11 %).

(ii) With sodium hydride as base

Sodium hydride (430 mg, 60 % dispersion in mineral oil, 10.5 mmol, 1 equiv.) was stirred in light petroleum (20 mL) for 10 minutes under nitrogen to remove the mineral oil. The light petroleum was syringed off and the sodium hydride left very briefly under vacuum for removal of the remainder of the solvent. The washing process was repeated twice more to ensure complete removal of the mineral oil. The sodium hydride then was put under an atmosphere of nitrogen, before the addition of dry THF (10 mL). 3-Hydroxypyridine (**169**) (1.00 g, 10.5 mmol, 1 equiv.) was dissolved in dry THF (20 mL) and added dropwise to the sodium hydride and the reaction mixture allowed to stir for one hour at room temperature. 4-Bromobut-1-ene (**170**) (1.07 mL, 1.42 mg, 10.5 mmol, 1 equiv.) in THF (20 mL) was added dropwise over 45 minutes

and after stirring for 2 days at room temperature only starting materials remained in the reaction mixture as indicated by t.l.c. analysis. The reaction was put on to reflux and left for 2 days before being quenched with water (50 mL). The organic layer was separated and the aqueous layer extracted with diethyl ether (5 x 60 mL). The organic phases were combined and dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification of the crude reaction mixture by flash chromatography on silica eluting with diethyl ether (R_f 0.31) gave pure 3-(3-butenyloxy)pyridine (**171**) as a colourless oil (89 mg, 6 %).

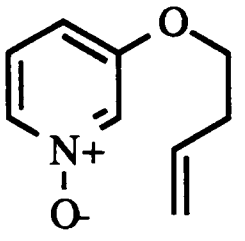
(iii) With 4-iodobut-1-ene

3-Hydroxypyridine (**169**) (118 mg, 1.2 mmol, 1 equiv.) and potassium carbonate (168 mg, 1.2 mmol, 1 equiv.) were stirred in dry methanol (4 mL) under argon for 15 minutes to dissolve the pyridine and partially dissolve the potassium carbonate. 4-Iodobut-1-ene (**174**) (260 mg, 1.4 mmol, 1.2 equiv.) was added and the reaction mixture refluxed for 17 hours. After cooling to room temperature, the solvent was evaporated and the residue diluted with diethyl ether (10 mL). The ethereal solution was washed with water (10 mL) and then dried ($MgSO_4$) before removal of the solvent *in vacuo* to yield the crude product. Purification by flash chromatography on silica eluting with diethyl ether (R_f 0.31) gave pure 3-(3-butenyloxy)pyridine (**171**) as a colourless oil (20 mg, 10 %).

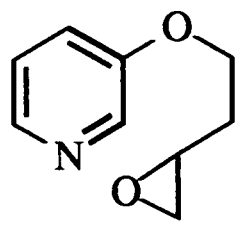
Found 150.0918, $C_9H_{11}NO(H^+)$ requires 150.0919; ν_{max} (thin film) 3 006, 2 981 and 2 932 (C-H, m), 1 586 and 1 576 (C=C, s), 1 232 (C-O, s) cm^{-1}; δ (500 MHz, $CDCl_3$) 8.32 (1H, d, *J* 2.3 Hz, py$\underline{H}_2$), 8.21 (1H, dd, *J* 4.1 Hz, *J'* 1.8 Hz, py$\underline{H}_6$), 7.23 - 7.18 (2H, m, py$\underline{H}_4$ and py$\underline{H}_5$), 5.94 - 5.86 (1H, m, -C$\underline{H}$=CH(H)), 5.18 (1H, ddd, *J* 17.2 Hz, *J'* 2.9 Hz, *J''* 1.5 Hz, -CH=C$\underline{H}$(H)*trans*), 5.13 (1H, ddd, *J* 10.3 Hz, *J'* 2.9 Hz, *J''* 1.5 Hz, -CH=CH($\underline{H}$)*cis*), 4.07 (2H, t, *J* 6.7 Hz, -O-C$\underline{H}_2$-), 2.59 - 2.55 (2H, m, -O-$CH_2C\underline{H}_2$-); δ_C (125.7 MHz, $CDCl_3$) 155.02 (pyC), 142.06 (CH), 138.00 (CH), 133.92 (CH), 123.78 (CH), 121.18 (CH), 117.37 (vinylic CH_2), 67.52 (CH_2),

33.48 (CH_2); $^{m}/_{z}$ (C.I.) 150 (100 %, MH^+), 95 (5 %, MH^+ -55); λ_{max} (ε) (MeOH) 278 (4 330), 219 (5 900).

Attempted preparation of *3-(3-butenyloxy)pyridine* N-*oxide* (**166**)



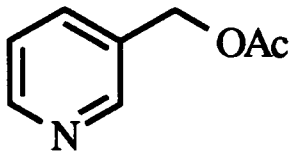
Following the procedure of Kaczmarek,[66] UHP (127 mg, 0.66 mmol of H_2O_2, 1 equiv.) and phthalic anhydride (98 mg, 0.66 mmol, 1 equiv.) were stirred in dry DCM (5 mL) under nitrogen for 15 minutes. 3-(3-Butenyloxy)pyridine (**171**) (89 mg, 0.60 mmol, 0.9 equiv.) in dry DCM (5 mL) was added dropwise and stirring continued for a further 14 hours until all starting material had disappeared, as shown by t.l.c analysis. The reaction mixture was subsequently neutralised with a few drops of aqueous saturated potassium carbonate, diluted with water (5 mL) and extracted with chloroform (6 x 10 mL). Drying ($MgSO_4$) of the organic phase followed by evaporation of the solvent, afforded the crude product which was not the *N*-oxide (**166**), but identified as the epoxide (**176**).



δ (200 MHz, $CDCl_3$) 8.02 (1H, t, *J* 1.8 Hz, py$\underline{H}_2$), 7.93 (1H, d, *J* 6.4 Hz, py$\underline{H}_6$), 7.18 (1H, dd, *J* 8.6 Hz, *J'* 6.4 Hz, py$\underline{H}_5$), 6.90 (1H, dd, *J* 8.6 Hz, *J'* 1.8 Hz, py$\underline{H}_4$), 4.18 - 4.11 (2H, m, -OC$\underline{H}_2$-), 3.17 - 3.09 (1H, m, epoxideC$\underline{H}$), 2.85 (1H, t, *J* 4.6 Hz, epoxideC$\underline{H}$(H)*trans*), 2.58 (1H, dd, *J* 4.6 Hz, *J'* 2.7 Hz,

epoxideCH(H)*cis*), 2.28 - 2.10 (1H, m, -OCH_2C<u>H</u>H-), 1.99 - 1.81 (1H, m, -OCH_2CH<u>H</u>-); $^m/_z$ (C.I.) 166 (100 %, MH^+), 95 (100 %, MH^+-71).

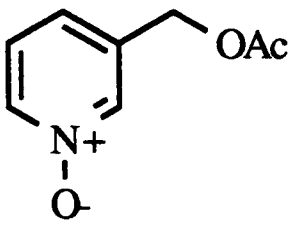
Preparation of *3-(Pyridyl)methyl acetate* (**185**)



3-Pyridinemethanol (**181**) (0.89 mL, 1.00 g, 9.16 mmol, 1 equiv.) in dry DCM (30 mL) was stirred under nitrogen for 5 minutes at room temperature, before the addition of DMAP (112 mg, 0.92 mmol, 0.1 equiv.). Triethylamine (1.28 mL, 929 mg, 9.16 mmol, 1 equiv.) was added dropwise and stirring continued for a further 10 minutes before the slow dropwise addition of acetyl chloride (0.65 mL, 718 mg, 9.16 mmol, 1 equiv.) in DCM (20 mL) over 1 hour. Stirring was continued overnight before the removal of the solvent *in vacuo* to yield the crude product. Purification by flash chromatography on silica eluting with ethyl acetate (R_f 0.34) afforded the pure *3-(pyridyl)methyl acetate* (**185**) as a yellow oil (1.01 g, 79 %).

Found 152.0708, $C_8H_9NO_2(H^+)$ requires 152.0711; ν_{max} (thin film) 3 035 and 2 958 (C-H, w), 1746 (C=O, s), 1 597 and 1 579 (C=C, m), 1 235 (C-O, s) cm^{-1}; δ (500 MHz, $CDCl_3$) 8.56 (1H, s, py<u>H</u>$_2$), 8.52 (1H, d, *J* 4.6 Hz, py<u>H</u>$_6$), 7.64 (1H, d, *J* 7.8 Hz, py<u>H</u>$_4$), 7.25 (1H, dd, *J* 7.8 Hz, *J'* 4.6 Hz, py<u>H</u>$_5$), 5.07 (2H, s -C<u>H</u>$_2$-), 2.05 (3H, s, -C<u>H</u>$_3$); δ_C (125.7 MHz, $CDCl_3$) 170.44 (C=O), 149.34 (pyCH), 149.27 (pyCH), 135.92 (pyCH), 131.50 (pyC), 123.29 (pyCH), 63.46 (CH_2), 20.63 (CH_3); $^m/_z$ (E.I.) 151 (67 %, M^+), 109 (100 %, M^+ -42); λ_{max} (ε) (MeOH) 260 (2 670), 202 (6 760).

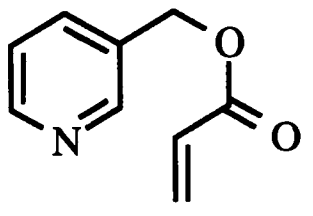
Preparation of *3-(Pyridyl)methyl acetate* N-*oxide* (**187**)



3-Pyridinemethanol *N*-oxide (**186**) (550 mg, 4.40 mmol, 1 equiv.) in dry DCM (15 mL) was stirred under nitrogen for 45 minutes at room temperature to effect complete dissolution, before the addition of DMAP (54 mg, 0.44 mmol, 0.1 equiv.). Triethylamine (0.62 mL, 450 mg, 4.40 mmol, 1 equiv.) was added dropwise and stirring continued for a further 10 minutes before the slow dropwise addition of acetyl chloride (0.31 mL, 342 mg, 4.40 mmol, 1 equiv.) in DCM (10 mL) over 1 hour. Stirring was continued for 24 hours before the removal of the solvent *in vacuo* to yield the crude solid product. The desired *3-(pyridyl)methyl acetate* N-*oxide* (**187**) proved impossible to separate from the triethylamine hydrochloride side product, but was seen in the ^{1}H NMR spectrum of the crude product.

δ (250 MHz, $CDCl_3$) 8.35 (1H, s, py$\underline{H}_2$), 8.27 (1H, m, py$\underline{H}_6$), 7.36 - 7.38 (1H, m, py$\underline{H}_4$ and py$\underline{H}_5$), 5.10 (2H, s, C$\underline{H}_2$), 2.06 (3H, s, C$\underline{H}_3$).

Preparation of *3-(Pyridyl)methyl propenoate* (**183**)



(i) <u>With potassium carbonate</u>

Potassium carbonate (1.43 g, 10.4 mmol, 1 equiv.) was stirred under nitrogen in dry DCM (50 mL) for 10 minutes. 3-Pyridinemethanol (**181**) (1 mL, 1.12 g, 10.4 mmol, 1 equiv.) was added dropwise and the reaction mixture allowed to stir for a

further 5 minutes. Acryloyl chloride (**182**) (0.84 mL, 936 mg, 10.4 mmol, 1 equiv.) was added dropwise. After stirring for 3 hours a thick, pale yellow precipitate had formed in a yellow solution. Neither precipitate, nor the supernatant liquid, contained any of the desired product.

(ii) Without potassium carbonate

3-Pyridinemethanol (**181**) (1 mL, 1.12 g, 10.3 mmol, 1 equiv.) was stirred under nitrogen in dry DCM (50 mL) for 5 minutes followed by the dropwise addition of acryloyl chloride (**182**) (0.84 mL, 936 mg, 10.4 mmol, 1 equiv.). After stirring for a further 3 hours a thick yellow precipitate had formed in a yellow solution. The precipitated gummy solid did not contain any of the desired 3-(Pyridyl)methyl propenoate (**183**) but the supernatant was found to contain the product. Purification of the supernatant by preparative t.l.c. on a neutral alumina plate eluting with ethyl acetate (R_f 0.39) afforded the pure *(3-pyridyl)methyl propenoate* (**183**) as a yellow oil, but in low yield (19 mg, 1 %).

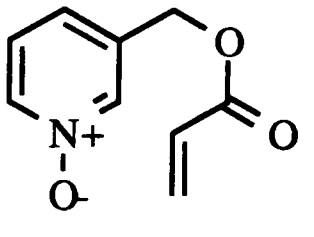
(iii) DMAP / triethylamine method

3-Pyridinemethanol (**181**) (5.33 mL, 5.99 g, 54.89 mmol, 1 equiv.) in dry DCM (180 mL) was stirred under nitrogen for 5 minutes at room temperature before the addition of DMAP (670 mg, 5.49 mmol, 0.1 equiv.). Triethylamine (7.65 mL, 5.55 g, 54.89 mmol, 1 equiv.) was added dropwise and stirring continued for a further 10 minutes before the slow, dropwise addition of acryloyl chloride (**182**) (4.46 mL, 4.97 g, 54.89 mmol, 1 equiv.) in DCM (120 mL) over 1 hour. Stirring was continued for 16 hours before the removal of the solvent *in vacuo* to yield the crude product. Purification by flash chromatography on silica eluting with ethyl acetate (R_f 0.39) afforded the pure (3-pyridyl)methyl propenoate as (**183**) a yellow oil (3.93 g, 44 %).

Found C 65.93, H 5.79, N 8.73, $C_9H_9NO_2$ requires C 66.25, H 5.56, N 8.58 %; ν_{max} (thin film) 3 036 and 2 958 (C-H, m), 1 724 (C=O, s), 1 597 and 1 579 (C=C,

m), 1 181 (C-O, s) cm^{-1}; δ (500 MHz, $CDCl_3$) 8.64 (1H, d, *J* 2.2 Hz, py$\underline{H}_2$), 8.57 (1H, dd, *J* 4.8 Hz, *J'* 1.6 Hz, py$\underline{H}_6$), 7.71 (1H, dt, *J* 7.9 Hz, *J'* 1.9 Hz, py$\underline{H}_4$), 7.29 (1H, dd, *J* 7.9 Hz, *J'* 4.8 Hz, py$\underline{H}_5$), 6.44 (1H, dd, *J* 17.3 Hz, *J'* 1.3 Hz, -CH=C$\underline{H}$(H)*trans*), 6.15 (1H, dd, *J* 17.3 Hz, *J'* 10.4 Hz, -C$\underline{H}$=CH(H)), 5.86 (1H, dd, *J* 10.4 Hz, *J'* 1.3 Hz, -CH=CH($\underline{H}$)*cis*), 5.21 (2H, s, py-C$\underline{H}_2$-); δ_C (125.7 MHz, $CDCl_3$) 165.73 (C=O), 149.57 (2 x CH), 135.99 (CH), 131.51 (vinylic CH_2 and pyC), 127.89 (CH), 123.42 (CH), 63.68 (CH_2); $^m/_z$ (C.I.) 164 (45 %, MH^+), 109 (100 %, MH^+ -55); λ_{max} (ε) (MeOH) 260 (2 800), 204 (13 900).

Preparation of *3-(Pyridyl)methyl propenoate* N-*oxide* (**178**)

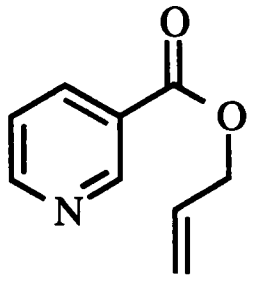


Following the procedure of Kaczmarek,[66] UHP (390 mg, 2.04 mmol of H_2O_2, 1 equiv.) and phthalic anhydride (300 mg, 2.04 mmol, 1 equiv.) were stirred under nitrogen in dry DCM (30 mL) for 15 minutes. (3-Pyridyl)methyl propenoate (**183**) (300 mg, 1.84 mmol, 0.9 equiv.) was added and stirring continued for 17 hours until all starting material had been consumed. The reaction mixture was subsequently neutralised with a few drops of aqueous saturated potassium carbonate, diluted with water (10 mL) and extracted with chloroform (6 x 20 mL). Drying ($MgSO_4$) of the organic phase, followed by evaporation of the solvent, afforded the crude solid product. Recrystallisation from DCM yielded the pure *(3-pyridyl)methyl propenoate* N-*oxide* (**178**) (m.p. <50 °C) as a white hygroscopic solid (270 mg, 82 %).

Found 180.0664, $C_9H_9NO_3(H^+)$ requires 180.0661; ν_{max} (KBr) 3 088, 2 984 and 2 948 (C-H, m), 1 728 (C=O, s), 1 592 and 1 580 (C=C, m), 1 280 (N-O, s), 1 240 (C-O, s) cm^{-1}; δ (500 MHz, $CDCl_3$) 8.28 (1H, s, py$\underline{H}_2$), 8.17 (1H, dt, *J* 5.6 Hz,

J' 1.8 Hz, py$\underline{H}_6$), 7.30 - 7.27 (2H, m, py$\underline{H}_4$ and py$\underline{H}_5$), 6.48 (1H, dd, *J* 17.3 Hz, *J'* 1.2 Hz, -CH=C$\underline{H}$(H)*trans*), 6.17 (1H, dd, *J* 17.3 Hz, *J'* 10.5 Hz, -C$\underline{H}$=CH_2), 5.93 (1H, dd, *J* 10.5 Hz, *J'* 1.2 Hz, -CH=CH($\underline{H}$)*cis*) 5.17 (2H, s, py-CH_2-); δ_C (62.9 MHz, $CDCl_3$) 165.31 (C=O), 138.65 (CH), 138.46 (CH), 135.61 (pyC), 132.26 (vinylic CH_2) 127.33 (CH), 125.83 (CH), 125.15 (CH), 62.20 (CH_2); $m/_z$ (C.I.) 180 (100 %, MH^+), 164 (25 %, MH^+ -16); λ_{max} (ε) (MeOH) 266 (11 100), 216 (18 700).

Preparation of *2-Propenyl (3-pyridine) carboxylate* (**180**)

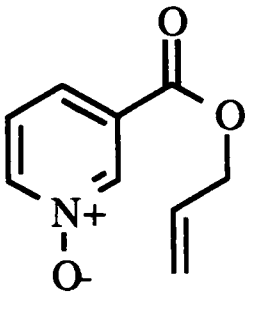


Propen-2-ol (**189**) (0.96 mL, 816 mg, 14.05 mmol, 1 equiv.) in dry DCM (150 mL) was stirred at room temperature under nitrogen for 5 minutes before the addition of DMAP (172 mg, 1.40 mmol, 0.1 equiv.) in DCM (25 mL). Triethylamine (3.92 mL, 2.84 g, 28.10 mmol, 2 equiv.) was added dropwise and stirring continued for a further 10 minutes before the portionwise addition of a suspension of the hyrochloride salt of 3-pyridinecarbonyl chloride (**188**) (2.50 g, 14.05 mmol, 1 equiv.) in DCM (75 mL). Stirring was continued for 16 hours before the removal of the solvent *in vacuo* to yield the crude product. Purification by flash chromatography on silica eluting with ethyl acetate (R_f 0.48) afforded the pure *2-propenyl (3-pyridine) carboxylate* (**180**) as a colourless oil (2.01 g, 88 %).

Found 164.0705, $C_9H_9NO_2(H^+)$ requires 164.0711; ν_{max} (KBr) 3 088 and 2 948 (C-H, w), 1 729 (C=O, s), 1592 (C=C, m), 1 279 (C-O, s) cm^{-1}; δ (500 MHz, $CDCl_3$) 9.25 (1H, d, *J* 1.6 Hz, py$\underline{H}_2$), 8.78 (1H, dd, *J* 4.8 Hz, *J'* 1.5 Hz, py$\underline{H}_6$),

8.32 (1H, dt, *J* 7.9 Hz, *J'* 2.0 Hz, py$\underline{H}_4$), 7.40 (1H, dd, *J* 7.9 Hz, *J'* 4.8 Hz, py$\underline{H}_5$), 6.07 - 6.02 (1H, m, -C$\underline{H}$=CH_2), 5.43 (1H, dd, *J* 17.2 Hz, *J'* 1.4 Hz, -CH=C$\underline{H}$(H)*trans*), 5.32 (1H, dd, *J* 10.4 Hz, *J'* 1.4 Hz, -CH=CH($\underline{H}$)*cis*), 4.86 (2H, dt, *J* 5.7 Hz, *J'* 1.4 Hz, -OC$\underline{H}_2$-); δ_C (125.7 MHz, $CDCl_3$) 164.91 (C=O), 153.44 (CH), 150.93 (CH), 137.06 (CH), 131.70 (CH), 126.05 (pyC), 123.26 (CH), 118.79 (vinylic CH_2), 65.92 (CH_2); $^m/_z$ (E.I.) 163 (18 %, M^+), 108 (25 %, M^+ -55); λ_{max} (ε) (MeOH) 263 (2 480), 219 (6 920).

Preparation of *2-Propenyl (3-pyridine) carboxylate* N-*oxide* (**177**)



(i) UHP oxidation

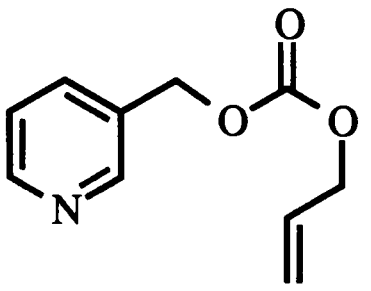
Following the procedure of Kaczmarek,[66] UHP (307 mg, 1.61 mmol of H_2O_2, 1 equiv.) and phthalic anhydride (238 mg, 1.61 mmol, 1 equiv.) were stirred in dry DCM (10 mL) under nitrogen for 15 minutes. 2-Propenyl (3-pyridine) carboxylate (**180**) (236 mg, 1.45 mmol, 0.9 equiv.) was added and stirring continued for 18 hours until all starting material had been converted into product. The reaction mixture was neutralised subsequently with an aqueous saturated potassium carbonate solution and diluted with water (5 mL), followed by extraction with chloroform (6 x 10 mL). Drying ($MgSO_4$) of the organic phase followed by evaporation of the solvent *in vacuo* afforded the crude solid product. Recrystallisation from DCM yielded the pure *2-propenyl 3-pyridine) carboxylate* N-*oxide* (**177**) (m.p. <50 °C) as a beige hygroscopic solid (206 mg, 79 %).

(ii) Sodium perborate oxidation

Following the procedure of McKillop,[71] 2-propenyl (3-pyridine) carboxylate (**180**) (264 mg, 1.62 mmol, 1 equiv.) was dissolved in glacial acetic acid (5 mL) and the solution stirred under nitrogen for 5 minutes at room temperature. The reaction mixture was then warmed to 40 °C and the sodium perborate tetrahydrate (272 mg, 1.77 mmol, 1.1 equiv.) added. After stirring for 4 hours, t.l.c. analysis of the reaction mixture (in 4 : 1 ethyl acetate / glacial acetic acid) revealed a large excess of starting material so a further amount of sodium perborate tetrahydrate (272 mg, 1.77 mmol, 1.1 equiv.) was added and stirring continued for a further 22 hours. The acetic acid was removed under high vacuum (*ca.* 0.01 mmHg), the residue diluted with DCM (10 mL) and the borate salts removed by filtration. Water (10 mL) was added and the DCM layer separated. The aqueous layer was then neutralised with aqueous saturated potassium carbonate and extracted with DCM (4 x 15 mL). Drying ($MgSO_4$) of the combined organic phases, followed by evaporation of the solvent afforded the crude solid product. Recrystallisation from DCM yielded the pure 2-propenyl (3-pyridine) carboxylate *N*-oxide (**177**) (m.p. <50 °C) as a beige crystalline hygroscopic solid (286 mg, 98 %).

Found 180.0659, $C_9H_9NO_3(H^+)$ requires 180.0661; ν_{max} (KBr) 3 085 and 2 952 (C-H, m), 1 729 (C=O, s), 1 593 and 1 562 (C=C, m), 1 340 (N-O, s), 1 226 (C-O, s) cm^{-1}; δ (500 MHz, $CDCl_3$) 8.83 (1H, s, py$\underline{H}_2$), 8.39 - 8.38 (1H, m, py$\underline{H}_6$), 7.91 (1H, dd, *J* 7.2 Hz, *J'* 1.2 Hz, py$\underline{H}_4$), 7.41 (1H, dd, *J* 7.2 Hz, *J'* 6.8 Hz, py$\underline{H}_5$), 6.08 - 6.00 (1H, m, -C$\underline{H}$=CH_2), 5.45 (1H, dd, *J* 17.1 Hz, *J'* 1.1 Hz, -CH=C$\underline{H}$(H)*trans*), 5.37 (1H, dd, *J* 10.1 Hz, *J'* 1.1 Hz, -CH=CH($\underline{H}$)*cis*), 4.89 - 4.88 (2H, m, -OC$\underline{H}_2$-); δ_C (125.7 MHz, $CDCl_3$) 162.84 (C=O), 142.95 (CH), 140.75 (CH), 131.46 (CH), 130.46 (pyC), 126.81 (CH), 126.27 (CH) 120.01 (vinylic CH_2), 67.16 (CH_2); $m/_z$ (C.I.) 180 (30 %, MH^+), 164 (100 %, MH^+ -16); λ_{max} (ε) (MeOH) 270 (8 590), 224 (19 300).

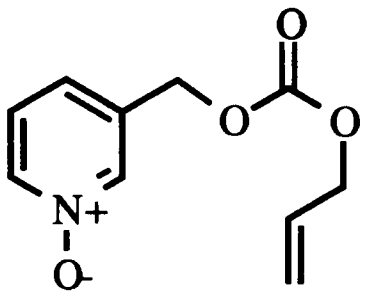
Preparation of *2-Propenyl (3-pyridyl)methyl carbonate* (**193**)



3-Pyridinemethanol (**181**) (0.81 mL, 905 mg, 8.30 mmol, 1 equiv.) in dry DCM (75 mL) was stirred under nitrogen for 5 minutes at room temperature before the addition of DMAP (102 mg, 0.83 mmol, 0.1 equiv.). Triethylamine (1.27 mL, 923 mg, 9.13 mmol, 1.1 equiv.) was added dropwise and stirring continued for a further 10 minutes before the slow dropwise addition of allyl chloroformate (**192**) (0.88 mL, 1 g, 8.30 mmol, 1 equiv.) in DCM (50 mL) over 1 hour. After stirring for 16 hours, t.l.c. analysis in ethyl acetate revealed the presence of a large amount of starting material still present in the reaction mixture. More allyl chloroformate (**192**) (0.44 mL, 500 mg, 4.15 mmol, 0.5 equiv.) in DCM (25 mL) was added dropwise and stirring continued for 3 hours before removal of the solvent *in vacuo* to yield the crude product. Purification by flash chromatography on silica eluting with ethyl acetate (R_f 0.44) afforded the pure *2-Propenyl (3-pyridyl)methyl carbonate* (**193**) as a yellow oil (1.4 g, 87 %).

ν_{max} (thin film) 3 035, 2 988 and 2 957 (C-H, w), 1 747 (C=O, s), 1 597 and 1 580 (C=C, m), 1 256 (C-O, s) cm^{-1}; δ (250 MHz, $CDCl_3$) 8.65 (1H, d, *J* 2.2 Hz, py$\underline{H}_2$), 8.60 (1H, dd, *J* 4.8 Hz, *J'* 1.7 Hz, py$\underline{H}_6$), 7.76 - 7.72 (1H, m, py$\underline{H}_4$), 7.31 (1H, ddd, *J* 7.8 Hz, *J'* 4.8 Hz, *J''* 0.8 Hz, py$\underline{H}_5$), 6.01 - 5.85 (1H, m, -C$\underline{H}$=CH_2), 5.36 (1H, ddd, *J* 17.3 Hz, *J'* 2.7 Hz, *J''* 1.3 Hz, -CH=C$\underline{H}$(H)*trans*), 5.28 (1H, ddd, *J* 10.4 Hz, *J'* 2.7 Hz, *J''* 1.3 Hz, -CH=CH($\underline{H}$)*cis*), 5.19 (2H, s, py-C$\underline{H}_2$-), 4.65 (2H, dt, *J* 5.8 Hz, *J'* 1.3 Hz, -C$\underline{H}_2$-CH=CH_2); $^{m}/_{z}$ (E.I.) 193 (2 %, M^+), 152 (20 %, M^+ -41), 108 (100 %, M^+ -85).

Preparation of *2-Propenyl (3-pyridyl)methyl carbonate* N-*oxide* (**191**)



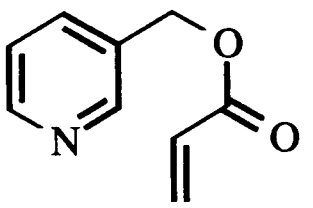
Following the procedure of McKillop,[71] 2-propenyl (3-pyridyl)methyl carbonate (**193**) (459 mg, 2.38 mmol, 1 equiv.) was dissolved in glacial acetic acid (7.5 mL) and the solution stirred under nitrogen for 5 minutes at room temperature. The reaction mixture was then warmed to 40 °C and the sodium perborate tetrahydrate (804 mg, 5.22 mmol, 2.2 equiv.) added and stirring continued for 21 hours. The acetic acid was removed under high vacuum (*ca.* 0.01 mmHg), the residue diluted with DCM (20 mL) and the borate salts removed by filtration. Water (20 mL) was added and the DCM layer extracted. The aqueous layer was then neutralised with aqueous saturated potassium carbonate and extracted with DCM (4 x 30 mL). Drying ($MgSO_4$) of the combined organic phases followed by evaporation of the solvent *in vacuo* afforded the crude solid product. Recrystallisation from DCM yielded the pure *2-propenyl (3-pyridyl)methyl carbonate* N-*oxide* (**191**) (m.p. 50 - 51 °C) as a beige crystalline hygroscopic solid (440 mg, 88 %).

Found C 57.41, H 5.40, N 6.96, $C_{10}H_{11}NO_4$ requires C 57.41, H 5.30, N 6.70 %; ν_{max} (KBr) 3 067, 2 983 and 2 963 (C-H, m), 1 748 (C=O, s), 1 609 and 1 568 (C=C, m), 1 270 (N-O, s), 1 250 (C-O, s) cm^{-1}; δ (500 MHz, $CDCl_3$) 8.33 (1H, s, py$\underline{H}_2$), 8.23 - 8.22 (1H, m, py$\underline{H}_6$), 7.35 - 7.32 (2H, m, py$\underline{H}_4$ and py$\underline{H}_5$), 6.02 - 5.94 (1H, m, -C$\underline{H}$=CH_2), 5.43 (1H, dt, *J* 18.2 Hz, *J'* 1.1 Hz, -CH=C$\underline{H}$(H)*trans*), 5.35 (1H, dt, *J* 10.3 Hz, *J'* 1.1 Hz, -CH=CH($\underline{H}$)*cis*), 5.17 (2H, s, py-C$\underline{H}_2$-), 4.71 (2H, dt, *J* 4.7 Hz, *J'* 1.1 Hz, -C$\underline{H}_2$CH=CH_2); δ_C (125.7 MHz, $CDCl_3$) 154.48 (C=O), 138.95 (CH), 138.61 (CH), 135.06 (pyC), 131.02 (CH), 125.89 (CH), 125.05 (CH) 119.49 (vinylic CH_2), 69.10 (py-$\underline{C}H_2$-), 65.38 (-$\underline{C}H_2$CH=CH_2); $^m/_z$ (E.I.) 209 (12 %, M^+),

193 (2 %, M^+ -16), 108 (84 %, M^+ -101); λ_{max} (ε) (MeOH) 266 (8 580), 218 (7 420).

Attempted Cycloaddition on 3-(Pyridyl)methyl propenoate *N*-oxide (**178**) at 18 KBar / 75 °C

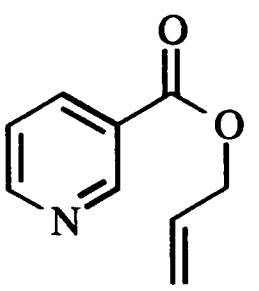
3-(Pyridyl)methyl propenoate *N*-oxide (**178**) (105 mg, 0.59 mmol) was dissolved in dry, freshly distilled DCM (*ca.* 3 mL) and put into the Teflon® reaction pot. It was then subjected to 18 KBar pressure before being warmed to 75 °C. The reaction was left at this temperature and pressure for 24 hours, then cooled to room temperature overnight before returning to atmospheric pressure. The crude product was removed from the Teflon® reaction pot and the solvent evaporated. NMR and mass spectrometric data revealed that no cycloaddition had occurred but cleavage of the N-O bond had resulted, yielding 3-(pyridyl)methyl propenoate (**183**) as a yellow oil (38 mg, 39 %).



The data was consistent with that already obtained for this product.

Attempted Cycloaddition on 2-Propenyl (3-pyridine) carboxylate *N*-oxide (**177**) at 18 KBar / 75 °C

2-Propenyl (3-pyridine) carboxylate *N*-oxide (**177**) (209 mg, 1.17 mmol) was dissolved in dry freshly distilled DCM (*ca.* 5 mL) and put into the Teflon® reaction pot. It was then subjected to 18 KBar pressure before being warmed to 75 °C. The reaction was left at this temperature and pressure for 24 hours, then allowed to cool to room temperature overnight, before returning to atmospheric pressure. The crude product was removed from the Teflon® reaction pot and the solvent evaporated. NMR and mass spectrometric data revealed that no cycloaddition had occurred, but cleavage of the N-O bond had resulted yielding 2-propenyl (3-pyridine) carboxylate (**180**) as a yellow oil (90 mg, 47 %).

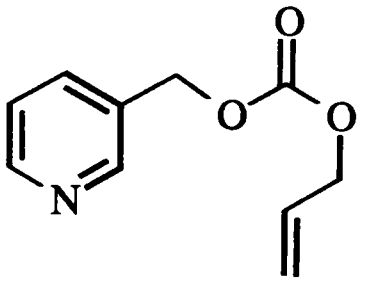


The data was consistent with that already obtained for this product.

Attempted Cycloaddition on 2-Propenyl (3-pyridyl)methyl carbonate *N*-oxide (**191**) at 18 KBar / 75 °C

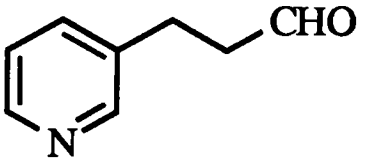
2-Propenyl (3-pyridyl)methyl carbonate *N*-oxide (**191**) (154 mg, 0.74 mmol) was dissolved in dry, freshly distilled DCM (*ca.* 4 mL) and put into the Teflon® reaction pot. It was then subjected to 18 KBar pressure before being warmed to 75 °C. The reaction was left at this temperature and pressure for 24 hours, then allowed to cool to room temperature overnight, before returning to atmospheric pressure. The crude product was removed from the Teflon® reaction pot and the solvent evaporated. NMR

and mass spectrometric data revealed that no cycloaddition had occurred, but cleavage of the N-O bond had resulted, yielding 2-propenyl (3-pyridyl)methyl carbonate (**193**) as a yellow oil (70 mg, 49 %).



The data was consistent with that already obtained for this product.

Preparation of *3-(3-Pyridine)propanal* (**211**)



(i) PCC oxidation

Pyridinium chlorochromate (2.36 g, 10.94 mmol, 1.5 equiv.) was added in one portion to a stirred suspension of anhydrous sodium acetate (1.20 g, 14.58 mmol, 3 equiv.) and Celite® (3.54 g, 1.5 times mass of PCC) in chloroform (150 mL) at room temperature and the mixture homogenised by vigorous stirring for 3-4 minutes under nitrogen. A solution of 3-pyridinepropanol (**213**) (0.94 mL, 1g, 7.29 mmol, 1.0 equiv.) in chloroform (50 mL) was added dropwise by syringe and the resultant solution stirred for 4 hours. The reaction mixture was subsequently filtered through a plug of Celite® and the residual cake washed successively with chloroform and diethyl ether. Evaporation of the solvent afforded the crude product. Purification by flash chromatography on silica, eluting with diethyl ether (R_f 0.15) afforded the pure product *3-(3-pyridine)propanal* (**211**) as a colourless oil (120 mg, 12 %).

(ii) PDC oxidation

3-(3-Pyridine)propanal (**211**) was prepared following the procedure used for the PCC oxidation. The reaction was carried out on 3-pyridinepropanol (**213**) (0.94 mL, 1 g, 7.29 mmol, 1.0 equiv.) in chloroform (150 mL), using pyridinium dichromate (4.11 g, 10.94 mmol, 1.5 equiv.) and Celite® (12.34 g, 3.0 times mass of PDC). After work up, the desired product 3-(3-pyridine)propanal (**211**) was obtained in very poor yield (69 mg, 7 %).

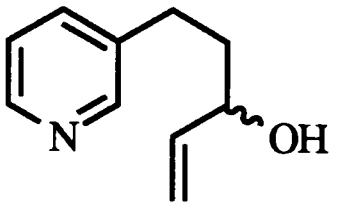
(iii) Swern oxidation

Following the procedure of Swern,[75] oxalyl chloride (4.0 mL, 44 mmol, 1.1 equiv.) in DCM (100 mL) was cooled to between -60 and -50 °C under an atmosphere of nitrogen. Distilled DMSO (6.8 mL, 88 mmol, 2.2 equiv.) in DCM (20 mL) was added dropwise and allowed to stir for 2 minutes. 3-Pyridinepropanol (**213**) (5.16 mL, 5.49 g, 40 mmol, 1 equiv.) in DCM (40 mL) was added dropwise within 5 minutes of the addition of DMSO and the reaction mixture stirred for 1.5 hours at this temperature. Distilled triethylamine (28 mL, 200 mmol, 5 equiv.) was added and after 5 minutes of agitation, the mixture was warmed to room temperature and stirring continued for a further 18 hours. The reaction was quenched by the addition of water (200 mL) and the DCM layer separated. The aqueous phase was extracted further with DCM (2 x 100 mL) and the organic layers combined, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the crude product. Pure 3-(3-pyridine)propanal (**211**) was obtained by flash chromatography on silica, eluting with ethyl acetate (R_f 0.32) as a colourless oil (5 17 g, 97 %).

Found 136.0762, $C_8H_9NO(H^+)$ requires 136.0762; ν_{max} (thin film) 3 030 and 2 928 (C-H, m), 1 723 (C=O, s), 1 593 and 1 576 (C=C, m) cm^{-1}; δ (500 MHz, $CDCl_3$) 9.84 (1H, s, -C<u>H</u>O), 8.49 (1H, s, py<u>H</u>$_2$), 8.47 (1H, d, *J* 4.8 Hz, py<u>H</u>$_6$), 7.53 (1H, d, *J* 7.8 Hz, py<u>H</u>$_4$), 7.23 (1H, dd, *J* 7.8 Hz, *J'* 4.8 Hz, py<u>H</u>$_5$), 2.96 (2H, t, *J* 7.3 Hz, py-$CH_2C\underline{H}_2$-), 2.82 (2H, t, *J* 7.3 Hz, py-C<u>H</u>$_2$-); δ_C (125.7 MHz) 200.39 (C=O),

149.47 (pyCH), 147.46 (pyCH), 135.92 (pyCH), 135.78 (pyC), 123.35 (pyCH), 44.59 (py-CH_2-), 24.99 (py-$CH_2\underline{C}H_2$-); $^{m}/_{z}$ (C.I.) 136 (100 %, MH^+), 107 (8 %, MH^+ -29); λ_{max} (ε) (MeOH) 263 (2 920), 204 (5 380).

Preparation of *3-(3-Hydroxy-4-pentenyl)pyridine* (**212**)



(i) <u>Reaction at -78 °C</u>

3-(3-Pyridine)propanal (**211**) (283 mg, 12.1 mmol, 1 equiv.) was dissolved in dry THF (30 mL) and stirred under nitrogen at -78 °C (CO_2 / acetone bath). Vinyl magnesium bromide (4.2 mL, 1.0 M solution in THF, 4.2 mmol, 2 equiv.) was added dropwise and the reaction mixture allowed to stir at this temperature for 2 hours. The reaction was quenched at -78 °C by the addition of saturated aqueous ammonium chloride (40 mL) and then allowed to warm slowly to room temperature. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (60 mL). The aqueous phase was extracted further with ethyl acetate (3 x 100 mL), the organic extracts combined, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the crude product. Purification by careful flash chromatography, eluting with ethyl acetate (R_f 0.21) yielded the pure *3-(3-hydroxy-4-pentenyl)pyridine* (**212**) as a colourless oil (192 mg, 56 %).

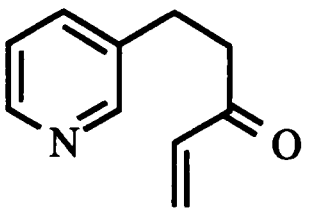
(ii) <u>Reaction at 0 °C</u>

3-(3-Pyridine)propanal (**211**) (56.8 mg, 0.42 mmol, 1 equiv.) was dissolved in dry THF (5 mL) and stirred under nitrogen at 0 °C. Vinyl magnesium bromide (0.84 mL, 1.0 M solution in THF, 0.84 mmol, 2 equiv.) was added dropwise and the

reaction mixture allowed to stir at the same temperature for 1.5 hours. After this period, t.l.c. analysis, eluting with ethyl acetate revealed large quantities of starting material aldehyde present in the reaction mixture so a further amount of vinyl magnesium bromide (0.21 mL, 1.0 M solution in THF, 0.21 mmol, 0.5 equiv.) was added. After stirring for a further 2 hours at 0 °C, the reaction was quenched by the addition of aqueous saturated ammonium chloride (10 mL) and then extracted with ethyl acetate (4 x 15 mL). The organic extracts were combined, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the crude product. Purification by careful flash chromatography eluting with ethyl acetate (R_f 0.21) yielded the pure 3-(3-hydroxy-4-pentenyl)pyridine (**212**) as a colourless oil (51 mg, 74 %).

Found 164.1076, $C_{10}H_{13}NO(H^+)$ requires 164.1075; ν_{max} (KBr) 3 300 (OH, br, s), 3 007, 2 980 and 2 927 (C-H, m), 1 574 (C=C, m), 1 193 (C-O, m) cm^{-1}; δ (500 MHz, $CDCl_3$) 8.47 (1H, d, *J* 2.0 Hz, py$\underline{H}_2$), 8.44 (1H, dd, *J* 4.8 Hz, *J'* 1.5 Hz, py$\underline{H}_6$), 7.53 (1H, dd, *J* 7.8 Hz, *J'* 1.9 Hz, py$\underline{H}_4$), 7.21 (1H, dd, *J* 7.8 Hz, *J'* 4.8 Hz, py$\underline{H}_5$), 5.95 - 5.88 (1H, m, -C$\underline{H}$=CH_2), 5.26 (1H, dt, *J* 17.2 Hz, *J'* 1.3 Hz, -CH=C$\underline{H}$(H)*trans*), 5.86 (1H, dd, *J* 10.4 Hz, *J'* 1.3 Hz, -CH=CH($\underline{H}$)*cis*), 4.15 - 4.12 (1H, m, -C$\underline{H}$(OH)), 2.84 - 2.68 (2H, m, py-C$\underline{H}_2$-), 1.95 (1H, br s, -OH), 1.92 - 1.80 (2H, m, py-CH_2C$\underline{H}_2$-); δ_C (125.7 MHz, $CDCl_3$) 149.78 (CH), 147.15 (CH), 140.94 (CH), 137.32 (pyC), 136.01 (CH), 123.35 (CH), 114.98 (vinylic CH_2), 71.91 (-CH(OH)-), 38.05 (CH_2), 28.70 (CH_2); $m/_z$ (C.I.) 164 (30 %, MH^+), 146 (100 %, MH^+ -18); λ_{max} (ε) (MeOH) 263 (2 900), 204 (6 180).

Preparation of *3-(3-Oxy-4-pentenyl)pyridine* (**214**)



(i) Swern oxidation

Following the procedure of Swern,[75] oxalyl chloride (0.33 mL, 3.6 mmol, 1.4 equiv.) in DCM (8.3 mL) was cooled to between -50 and -60 °C under an atmosphere of nitrogen. Distilled DMSO (0.57 mL, 7.3 mmol, 2.7 equiv.) in DCM (1.7 mL) was added dropwise and allowed to stir for 2 minutes. 3-(3-Hydroxy-4-pentenyl)pyridine (**212**) (442 mg, 2.7 mmol, 1 equiv.) in DCM (3.3 mL) was added dropwise within 5 minutes of the addition of DMSO and the reaction mixture stirred for 20 minutes at this temperature. Distilled triethylamine (2.33 mL, 16.6 mmol, 6.2 equiv.) was added and after 5 minutes of agitation, the mixture was warmed to room temperature and stirring continued for a further 2 hours. The reaction was quenched by the addition of water (17 mL) and the DCM layer separated. The aqueous phase was further extracted with DCM (3 x 8 mL) and the organic layers combined, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the crude product. *3-(3-Oxy-4-pentenyl)pyridine* (**214**) was obtained pure by flash chromatography on silica, eluting with ethyl acetate (R_f 0.32) as a colourless oil (93 mg, 21 %).

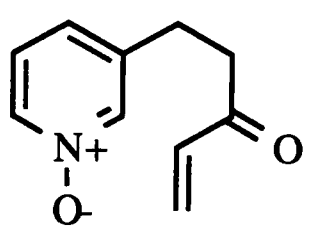
(ii) Manganese dioxide oxidation

3-(3-Hydroxy-4-pentenyl)pyridine (**212**) (100 mg, 0.61 mmol, 1 equiv.) was dissolved by stirring in dry chloroform (10 mL) under nitrogen. Freshly prepared activated manganese dioxide[97] (2.4 g, 24 times mass of alcohol) was added and stirring continued for a further 2 hours. The reaction mixture was then filtered through a pad of Celite® and the residual cake washed successively with chloroform. Evaporation of the solvent yielded the crude product. 3-(3-Oxy-4-pentenyl)pyridine (**214**) was obtained

analytically pure by flash chromatography on silica, eluting with ethyl acetate (R_f 0.32) as a colourless oil (32 mg, 32 %).

Found 162.0924, $C_{10}H_{11}NO(H^+)$ requires 162.0919; ν_{max} (thin film) 3 029, 2 960 and 2 920 (C-H, m), 1 682 (C=O, s), 1 593 and 1 576 (C=C, m) cm^{-1}; δ (200 MHz, $CDCl_3$) 8.45 - 8.43 (2H, m, py$\underline{H}_2$ and py$\underline{H}_6$), 7.51 (1H, dd, *J* 7.8 Hz, *J'* 1.8 Hz, py$\underline{H}_4$), 7.23 - 7.16 (1H, m, py$\underline{H}_5$), 6.35 (1H, dd, *J* 17.7 Hz, *J'* 9.9 Hz, -C$\underline{H}$=CH_2), 6.18 (1H, dd, *J* 17.7 Hz, *J'* 1.7 Hz, -CH=C$\underline{H}$(H)*trans*), 5.83 (1H, dd, *J* 9.9 Hz, *J'* 1.7 Hz, -CH=CH($\underline{H}$)*cis*), 2.93 (4H, s, py-C$\underline{H}_2$C$\underline{H}_2$-); $^m/_z$ (C.I.) 162 (100 %, MH^+), 106 (35 %, MH^+ -56); λ_{max} (ε) (MeOH) 262 (3 000), 211 (5 300).

Attempted preparation of *3-(3-Oxy-4-pentenyl)pyridine* N-*oxide* (**209**)



(i) Sodium perborate oxidation

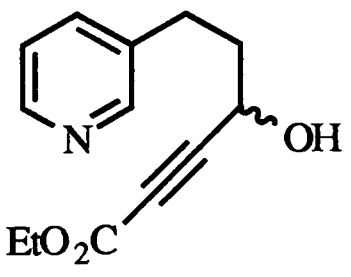
Following the procedure of McKillop,[71] 3-(3-oxy-4-pentenyl)pyridine (**214**) (32 mg, 0.20 mmol, 1 equiv.) was dissolved in glacial acetic acid (2 mL) and the solution stirred under nitrogen for 5 minutes at room temperature. The reaction mixture was warmed to 40 °C and the sodium perborate tetrahydrate (67 mg, 0.44 mmol, 2.2 equiv.) added and the reaction mixture stirred for 48 hours. The acetic acid was removed under high vacuum (*ca.* 0.01 mmHg), the residue diluted with DCM (10 mL) and the borate salts removed by filtration. Water (10 mL) was added and the DCM layer extracted. The aqueous layer was neutralised with aqueous saturated potassium carbonate and extracted with DCM (5 x 10 mL). Drying ($MgSO_4$) of the combined organic phases, followed by evaporation of the solvent *in vacuo*, afforded the crude

product which was found to be the starting material 3-(3-oxy-4-pentenyl)pyridine (**214**) (27 mg, 84 %).

(ii) <u>UHP oxidation</u>

Following the procedure of Kaczmarek,[66] UHP (123 mg, 0.64 mmol of H_2O_2, 1 equiv.) and phthalic anhydride (94 mg, 0.64 mmol, 1 equiv.) were stirred in dry DCM (10 mL) under nitrogen for 15 minutes. 3-(3-Oxy-4-pentenyl)pyridine (**214**) (93 mg, 0.58 mmol, 0.9 equiv.) was added and stirring continued for 24 hours. The reaction mixture was subsequently neutralised with a few drops of aqueous saturated potassium carbonate, diluted with water (5 mL) and extracted with chloroform (6 x 10 mL). Drying ($MgSO_4$) of the organic phase, followed by evaporation of the solvent, afforded the crude solid product which was initially thought to contain the desired product (**209**). Unfortunately, the crude product could not be adequately purified in order to confirm its structure.

Preparation of *Ethyl 4-hydroxy-6-(3-pyridyl)hex-2-ynoate* (**215**)



(i) <u>Initial reaction</u>[79]

Ethyl propiolate (**218**) (0.17 mL, 163 mg, 1.66 mmol, 1.5 equiv.) was dissolved in dry THF (4 mL) by stirring under an inert atmosphere of nitrogen in a 10 mL two neck flask fitted with a low temperature thermometer. The reaction mixture was cooled to -78 °C (CO_2 / acetone bath) before the controlled, dropwise addition of *n*-butyllithium (1.04 mL, 1.6 M solution in hexanes, 1.66 mmol, 1.5 equiv.) at a temperature maintained below -65 °C. The reaction mixture was then stirred at -78 °C

for an hour before the dropwise addition of 3-(3-pyridine)propanal (**211**) (150 mg, 1.11 mmol, 1 equiv.). Stirring was continued at -78 °C for 1.5 hours before the reaction was quenched at this temperature by the addition of aqueous saturated ammonium chloride (20 mL). The reaction mixture subsequently was warmed to room temperature over 30 minutes before the addition of water (20 mL) and separation of the organic layer. The aqueous phase was extracted with ethyl acetate (3 x 25 mL), the organic washings combined, dried ($MgSO_4$) and the solvent removed *in vacuo* yielding a crude reaction mixture that contained polymeric ethyl propiolate and none of the desired product (**215**).

(ii) <u>More dilute reaction conditions and only one equivalent of *n*-butyllithium</u>

The above reaction was repeated using ethyl propiolate (**218**) (0.24 mL, 233 mg, 2.38 mmol, 1 equiv.) in dry THF (40 mL). During dropwise addition of the *n*-butyllithium (1.49 mL, 1.6 M solution in hexanes, 2.38 mmol, 1 equiv.), the more dilute reaction conditions meant that it was possible to maintain the reaction temperature below -72 °C. The 3-(3-pyridyl)propanal (**211**) (321 mg, 2.38 mmol, 1 equiv.) in THF (25 mL) was cooled to -78 °C, before its addition to the reaction mixture, by use of a dropping funnel fitted with a cooling jacket, filled with CO_2 / acetone. Stirring was continued for 1.5 hours at -78 °C after the addition of all reagents, before work up of the reaction as before, using aqueous saturated ammonium chloride (35 mL), water (40 mL) and ethyl acetate (3 x 30 mL) as the extractant. Pure *ethyl 4-hydroxy-6-(3-pyridyl)hex-2-ynoate* (**215**) was obtained by flash chromatography on silica eluting with ethyl acetate (R_f 0.46) as a yellow oil (54 mg, 10 %).

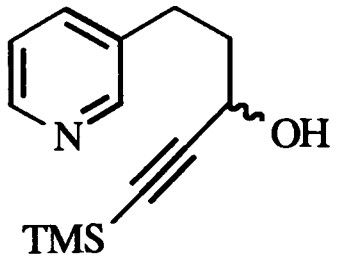
(iii) <u>Using *t*-butyllithium</u>

The reaction was repeated using the same method as described in (ii) with ethyl propiolate (**218**) (0.16 mL, 155 mg, 1.58 mmol, 1 equiv.) in THF (40 mL), *t*-butyllithium (0.93 mL, 1.7 M solution in pentane, 1.58 mmol, 1 equiv.) instead of *n*-butyllithium and 3-(3-pyridine)propanal (**211**) (214 mg, 1.58 mmol, 1 equiv.). The

reaction was stirred for 2 hours at -78 °C before a cautious quench with aqueous saturated ammonium chloride (30 mL). The reaction was worked up, as before, using water (40 mL) and ethyl acetate (3 x 50 mL). Pure ethyl 4-hydroxy-6-(3-pyridyl)hex-2-ynoate (**215**) was obtained by flash chromatography as before but in a very poor yield (4 mg, 1 %).

ν_{max} (thin film) 3 170 (OH, br, s), 2 982, 2 959 and 2 931 (C-H, m), 2 235 (C≡C, w), 1 712 (C=O, s), 1 615 and 1 581 (C=C, m), 1 250 (C-O, s) cm^{-1}; δ (500 MHz, $CDCl_3$) 8.48 - 8.45 (2H, m, py$\underline{H}_2$ and py$\underline{H}_6$), 7.57 (1H, d, *J* 8.0 Hz, py$\underline{H}_4$), 7.26 - 7.22 (1H, m, py$\underline{H}_5$), 4.49 (1H, t, *J* 6.6 Hz, -C$\underline{H}$(OH)-), 4.26 (2H, q, *J* 7.1 Hz, -$CO_2C\underline{H}_2CH_3$), 2.86 (2H, t, *J* 7.8 Hz, py-C$\underline{H}_2$-), 2.16 - 2.04 (2H, m, py-$CH_2C\underline{H}_2$-), 1.30 (3H, t, *J* 7.1 Hz, -$CO_2CH_2C\underline{H}_3$); δ_C (50.3 MHz, $CDCl_3$) 153.71 (C=O), 149.72 (pyCH), 147.38 (pyCH), 136.87 (pyC), 136.71 (pyCH), 136.53, (≡$\underline{C}$-CO_2Et), 123.82 (pyCH), 88.28 (≡$\underline{C}$-CH(OH)-), 62.11 (-$CO_2\underline{C}H_2CH_3$), 60.17 (-CH(OH)-), 37.82 (py-CH_2-), 28.19 (py-$CH_2\underline{C}H_2$-), 13.84 (-$CO_2CH_2\underline{C}H_3$); $^m/_z$ (C.I.) 234 (100 %, MH^+), 162 (28 %, MH^+ -74); λ_{max} (ε) (MeOH) 263 (3 140), 205 (4 710).

Preparation of *3-(3-Hydroxy-5-trimethylsilyl-4-pentynyl)pyridine* (**227**)

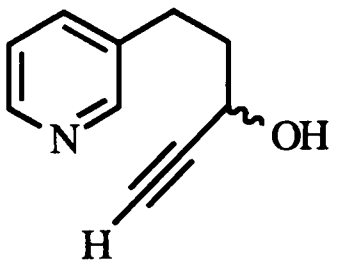


Trimethylsilylacetylene (**223**) (0.11 mL, 73 mg, 0.74 mmol, 1 equiv.) was dissolved by stirring in THF (15 mL) and cooled to between -20 °C and -30 °C under an atmosphere of nitrogen. *n*-butyllithium (0.55 mL, 1.6 M solution in hexanes, 0.89 mmol, 1.2 equiv.) was added dropwise at this temperature and the reaction mixture allowed to stir for 1 hour. 3-(3-Pyridine)propanal (**211**) (100 mg, 0.74 mmol,

1 equiv.) was added dropwise and the reaction allowed to stir between -20 °C and -30 °C for 26 hours. The reaction was quenched at this temperature by the addition of aqueous saturated ammonium chloride (10 mL) and diluted with water (10 mL). The organic layer was separated and the aqueous phase extracted with ethyl acetate (4 x 20 mL). The organic washings were combined, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the crude product. Pure *3-(3-hydroxy-5-trimethylsilyl-4-pentynyl)pyridine* (**227**) was obtained by flash chromatography on silica eluting with ethyl acetate (R_f 0.48) as a low melting point solid (solid < 4 °C) (148 mg, 86 %).

Found C 66.79, H 8.52, N 6.07, $C_{13}H_{19}NOSi$ requires C 66.90, H 8.21, N 6.00 %; ν_{max} (thin film) 3 190 (OH, br, s), 2 958 (C-H, m), 2 170 (C≡C, w), 1 596 and 1 580 (C=C, m), 1 250 (C-O, s) cm^{-1}; δ (500 MHz, $CDCl_3$) 8.47 (1H, d, *J* 1.9 Hz, py$\underline{H}_2$), 8.44 (1H, dd, *J* 4.8 Hz, *J'* 1.5 Hz, py$\underline{H}_6$), 7.54 (1H, dt, *J* 7.6 Hz, *J'* 1.9 Hz, py$\underline{H}_4$), 7.22 (1H, dd, *J* 7.6 Hz, *J'* 4.8 Hz, py$\underline{H}_5$), 4.37 (1H, t, *J* 6.5 Hz, -C$\underline{H}$(OH)-), 2.81 (2H, t, *J* 7.0 Hz, py-C$\underline{H}_2$-), 2.02 (2H, m, py-CH_2C$\underline{H}_2$-), 0.17 (9H, s, -Si(C$\underline{H}_3$)$_3$); δ_C (125.7 MHz, $CDCl_3$) 149.68 (pyCH), 147.19 (pyCH), 136.87 (pyC), 136.19 (pyCH), 123.41 (pyCH), 106.41 (≡C-), 89.84 (≡C-), 61.53 (-CH(OH)-), 38.73 (py-CH_2-), 28.53 (py-$CH_2\underline{C}H_2$-), -0.15 (-Si(CH_3)$_3$); $^m/_z$ (C.I.) 234 (100 %, MH^+); λ_{max} (ε) (MeOH) 262 (3 310), 208 (4 980).

Preparation of *3-(3-Hydroxy-4-pentynyl)pyridine* (**228**)



(i) <u>TBAF Deprotection / 1 Hour</u>

3-(3-Hydroxy-5-trimethylsilyl-4-pentynyl)pyridine (**227**) (143 mg, 0.61 mmol, 1 equiv.) was stirred in dry THF (75 mL) under nitrogen and TBAF

(0.61 mL, 1.0 M solution in THF, 0.61 mmol, 1 equiv.) added dropwise and the reaction was allowed to stir at room temperature for 1 hour. The reaction mixture was subsequently filtered through Celite® and the residual cake washed successively with ethyl acetate. The solvent was removed from the filtrate *in vacuo* to yield the crude product. *3-(3-Hydroxy-4-pentynyl)pyridine* (**228**) was obtained analytically pure by flash chromatography on silica eluting with ethyl acetate (R_f 0.42) as a low melting point solid (solid < 4 °C) (22 mg, 23 %).

(ii) [HF.Pyridine] Deprotection[82]

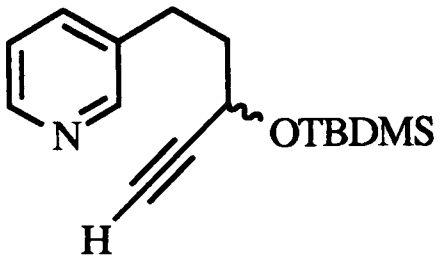
3-(3-Hydroxy-5-trimethylsilyl-4-pentynyl)pyridine (**227**) (345 mg, 1.48 mmol, 1 equiv.) was stirred in THF (7 mL) and the solution cooled to 0 °C under an atmosphere of nitrogen. [HF.pyridine] complex (1.69 mL, 1 equiv.), was added dropwise at 0 °C before the reaction was allowed to warm to room temperature and stirred for a further 10 hours. The reaction was quenched by the addition of aqueous saturated sodium bicarbonate (10 mL), diluted with ethyl acetate (10 mL) and the organic layer separated. The aqueous phase was washed with ethyl acetate (3 x 10 mL), the organic layers combined and washed successively with water (10 mL) and brine (10 mL). Drying of the combined organic phases ($MgSO_4$) and evaporation of the solvent gave a quantitative recovery of the starting material (**227**).

(iii) TBAF Deprotection / 30 Minutes

The reaction was carried out using the same procedure as in (i) with 3-(3-hydroxy-5-trimethylsilyl-4-pentynyl)pyridine (**227**) (396 mg, 1.70 mmol, 1 equiv.) in THF (150 mL) and TBAF (1.70 mL, 1.0 M solution in THF, 1.70 mmol, 1 equiv.). The reaction was allowed to stir for precisely 30 minutes before being immediately filtered though a pad of silica and washed continuously with ethyl acetate. Evaporation of the solvent yielded analytically pure 3-(3-hydroxy-4-pentynyl)pyridine (**228**) as a low melting point solid (solid < 4 °C) (252 mg, 92 %) that was used without further purification.

Found C 74.50, H 6.80, N 8.39, $C_{10}H_{11}NO$ requires C 74.51, H 6.88, N 8.69 %; ν_{max} (thin film) 3 290 (OH, br, s), 2 958 (C-H, m), 2 120 (C≡C, w), 1 597 and 1 580 (C=C, m), 1 246 (C-O, s) cm^{-1}; δ (500 MHz, $CDCl_3$) 8.42 (1H, d, *J* 1.8 Hz, py$\underline{H}_2$), 8.38 (1H, dd, *J* 4.8 Hz, *J'* 1.4 Hz, py$\underline{H}_6$), 7.53 (1H, dt, *J* 7.8 Hz, *J'* 1.8 Hz, py$\underline{H}_4$), 7.19 (1H, dd, *J* 7.8 Hz, *J* '4.8 Hz, py$\underline{H}_5$), 4.36 (1H, td, *J* 6.5 Hz, *J'* 2.0 Hz, -C$\underline{H}$(OH)-), 2.80 (2H, t, *J* 7.9 Hz, py-C$\underline{H}_2$-), 2.45 (1H, d, *J* 2.0 Hz, -C≡C$\underline{H}$), 2.00 (2H, m, py-$CH_2C\underline{H}_2$-); δ_C (125.7 MHz, $CDCl_3$) 149.29 (pyCH), 146.79 (pyCH), 136.98 (pyC), 136.37 (pyCH), 123.46 (pyCH), 85.01 (≡C-), 72.77 (≡CH), 60.43 (-CH(OH)-), 38.59 (py-CH_2-), 28.33 (py-$CH_2\underline{C}H_2$-); $^m/_z$ (C.I.) 162 (100 %, MH^+), 136 (18 %, MH^+ -26); λ_{max} (ε) (MeOH) 263 (3 050), 206 (5 150).

Preparation of *3-(3-*tert*-Butyldimethylsilyloxy-4-pentynyl)pyridine* (**230**)

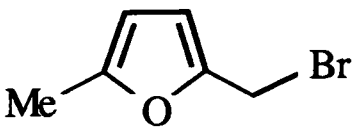


The reaction was carried out by the standard procedure[69] using 3-(3-hydroxy-4-pentynyl)pyridine (**228**) (327 mg, 2.03 mmol, 1 equiv.), TBDMSCl (336 mg, 2.23 mmol, 1.1 equiv.) and DMAP (25 mg, 0.20 mmol, 0.1 equiv.) in dry DCM (*ca.* 6 mL) under nitrogen at room temperature. Triethylamine (0.34 mL, 246 mg, 2.43 mmol, 1.2 equiv.) was added dropwise and the reaction mixture allowed to stir for 24 hours. T.l.c. analysis in 1 : 9 ethyl acetate / light petroleum revealed a large excess of starting material still present in the reaction mixture, so a further equivalent of TBDMSCl (336 mg, 2.23 mmol, 1.1 equiv.) and DMAP (25 mg, 0.20 mmol, 0.1 equiv.) was added. After stirring for a further 36 hours, the reaction was seen to have reached completion and was quenched by the addition of water (30 mL). The organic phase was separated and the aqueous layer extracted with ethyl acetate

(3 x 25 mL). The organic extracts were combined, washed with water (2 x 30 mL) and dried ($MgSO_4$). Evaporation of the solvent and purification of the residue by flash chromatography on silica eluting with 1 : 9 ethyl acetate / light petroleum (R_f 0.42) yielded pure *3-(3*-tert-*butyldimethylsilyloxy-4-pentynyl)pyridine* (**230**) as a low melting point beige solid (solid <4 °C) (472 mg, 84 %).

Found 276.1782 $C_{16}H_{251}NOSi(H^+)$ requires 276.1784; ν_{max} (thin film) 3 030, 2 955 and 2 930 (C-H, w), 2 111 (C≡C, w), 1 576 (C=C, m), 1 253 (C-O, s) cm^{-1}; δ (500 MHz, $CDCl_3$) 8.48 (1H, d, *J* 2.2 Hz, py$\underline{H}_2$), 8.45 (1H, dd, *J* 4.8 Hz, *J'* 1.5 Hz, py$\underline{H}_6$), 7.52 (1H, dt, *J* 7.8 Hz, *J'* 1.9 Hz, py$\underline{H}_4$), 7.21 (1H, dd, *J* 7.8 Hz, *J'* 4.8 Hz, py$\underline{H}_5$), 4.40 (1H, td, *J* 8.3 Hz, *J'* 2.1 Hz, -C$\underline{H}$(OTBDMS)-), 2.83 - 2.74 (2H, m, py-C$\underline{H}_2$-), 2.44 (1H, d, *J* 2.1 Hz, -C≡C$\underline{H}$), 2.03 - 1.98 (2H, m, py-$CH_2C\underline{H}_2$-), 0.92 (9H, s, -C(C$\underline{H}_3$)$_3$), 0.15 (3H, s, -SiC$\underline{H}_3$), 0.12 (3H, s, -SiC$\underline{H}_3$); δ_C (125.7 MHz, $CDCl_3$) 150.03 (pyCH), 147.48 (pyCH), 136.89 (pyC), 135.79 (pyCH), 123.26 (pyCH), 84.89 (≡C-), 72.77 (≡CH), 61.91 (-$\underline{C}$H(OTBDMS)-), 39.72 (py-CH_2-), 28.40 (py-$CH_2\underline{C}H_2$-), 26.58 (-Si$\underline{C}$(CH$_3$)$_3$), 25.75 (-SiC(C$\underline{H}_3$)$_3$), 18.17 (-Si(C$\underline{H}_3$)$_2$-); m/z (C.I.) 276 (100 %, MH^+), 144 (15 %, MH^+ -132); λ_{max} (ε) (MeOH) 263 (3 350), 209 (3 290).

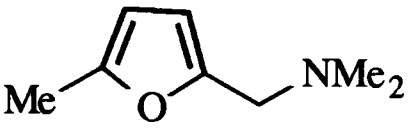
Preparation of 2-Bromo-5-bromomethylfuran (**236**)



2,5-Dimethylfuran (**235**) (65 μL, 58 mg, 0.61 mmol, 1 equiv.) was dissolved in distilled carbon tetrachloride (0.5 mL) and recrystallised *N*-bromosuccinimide (100 mg, 0.61 mmol, 1 equiv.) was added. The reaction was stirred under nitrogen at room temperature and irradiated with UV light for 25 minutes. The reaction mixture was subsequently filtered to remove the succinimide and the solvent removed *in vacuo*

to yield crude 2-bromo-5-bromomethylfuran (**236**) as a brown oil (85 mg, 80 %). Unfortunately all attempts to purify the crude product resulted in polymerisation.
δ (200 MHz, $CDCl_3$) 6.28 (1H, d, *J* 2.8 Hz, fuH), 5.93 (1H, d, *J* 2.8 Hz, fuH), 4.50 (2H, s, fu-CH_2-), 2.30 (3H, s, fu-CH_3).

Preparation of *N,N*-Dimethyl 2-(5-methylfuryl)methylamine (**239**)



The title compound was prepared according to the method of Rabjohn.[84] Aqueous dimethylamine (11.6 mL, 40 % w/v solution in water, 92.5 mmol, 1.2 equiv.) was added slowly, with cooling in an ice bath, to glacial acetic acid (15 mL), followed by aqueous formaldehyde (6.9 mL, 37 % w/v solution in water, 92.5 mmol, 1.2 equiv.). The ice bath was removed and the reaction flask fitted with a reflux condenser, through which 2-methylfuran (**238**) (6.32 g, 77.1 mmol, 1 equiv.) was added. Reflux did not spontaneously occur, so external heating was applied and the reaction mixture refluxed for 1 hour. After cooling, the reaction was quenched by pouring into a cold solution of sodium hydroxide (19.3 g of sodium hydroxide in 62 mL water). The reaction mixture was then steam distilled until the distillate was only faintly alkaline. Sodium hydroxide was added to the distillate (1 g per 10 mL of distillate) and the resultant solution cooled and extracted with diethyl ether (2 x 25 mL). The ethereal layers were combined, dried over potassium hydroxide pellets and the solvent removed *in vacuo* to yield the crude product. Purification by short path bulb-to-bulb distillation in a horizontal Kugelrohr apparatus, under reduced pressure, (bath temp 50 °C, 0.9 mmHg) gave pure *N,N*-dimethyl-2-(5-methylfuryl)methylamine (**239**) as a colourless liquid (7.30 g, 68 %).

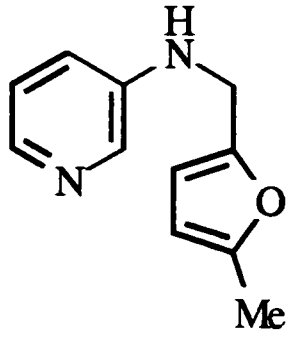
Found C 69.10, H 9.67, N 9.82, $C_8H_{13}NO$ requires C 69.03, H 9.41, N 10.06 %; ν_{max} (thin film) 3 105, 2 973 and 2 943 (C-H, m), 1 613 and 1 568 (C=C, m), 1 222 (C-O, m) cm^{-1}; δ (500 MHz, $CDCl_3$) 6.05 (1H, d, *J* 2.9 Hz, fuH), 5.88 (1H, d, *J* 2.9 Hz, fuH), 3.38 (2H, s, fu-CH_2-), 2.28 (3H, s, fu-CH_3), 2.25 (6H, s, -$N(CH_3)_2$); δ_C (125.7 MHz, $CDCl_3$) 151.63 (fuC), 150.42 (fuC), 108.99 (fuCH), 105.65 (fuCH), 55.92 (fu-CH_2-), 44.86 (-$N(CH_3)_2$), 13.47 (fu-CH_3); $^m/_z$ (C.I.) 140 (92 %, MH^+), 95 (100 %, MH^+ -45); λ_{max} (ε) (MeOH) 140 (9 070).

Preparation of N,N,N-*Trimethyl 2-(5-methylfuryl)methylammonium iodide* (**240**)

N,N-Dimethyl 2-(5-methylfuryl)methylamine (**239**) (247 mg, 1.77 mmol, 1 equiv.) was dissolved in dry distilled DMF (1.5 mL) and methyl iodide (0.22 mL, 502 mg, 3.53 mmol, 2 equiv.) added dropwise, following the procedure of Sommer.[85] The reaction mixture was stirred for 8 hours until the product was precipitated. The product was filtered from the mother liquor, washed with diethyl ether and then dried *in vacuo* to yield the pure N,N,N-t*rimethyl 2-(5-methylfuryl)methylammonium iodide* (**240**) (m.p. 161 °C) as a beige crystalline solid (326 mg, 66 %).

Found C 38.35, H 5.78, N 4.85, $C_9H_{16}INO$ requires C 38.45, H 5.74, N 4.98 %; ν_{max} (KBr) 3 091, 2 998 and 2 966 (C-H, m), 1 605 and 1 556 (C=C, m), 1 247 (C-O, s) cm^{-1}; δ (500 MHz, $CDCl_3$) 6.86 (1H, d, *J* 3.2 Hz, fuH), 6.06 (1H, d, *J* 3.2 Hz, fuH), 4.94 (2H, s, fu-CH_2-), 3.44 (9H, s, -$N^+(CH_3)_3$), 2.32 (3H, s, fu-CH_3); δ_C (125.7 MHz, $CDCl_3$) 155.85 (fuC), 140.32 (fuC), 118.70 (fuCH), 107.64 (fuCH), 62.25 (fu-CH_2-), 53.23 (-$N^+(CH_3)_3$), 13.73 (fu-CH_3); $^m/_z$ (E.S.$^+$) 154 (100 %, M^+); λ_{max} (ε) (MeOH) 223 (19 200).

Preparation of N-*(2-(5-Methylfuryl)methane)-3-aminopyridine* (**243**)

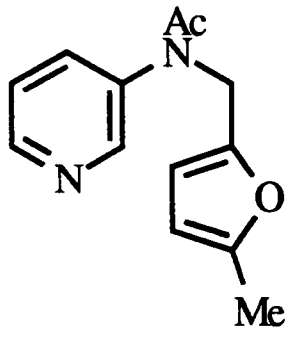


A solution of aqueous 3-aminopyridine (**242**) (2 g in 5 mL of water, 40 % solution w/v, 21.2 mmol, 1.2 equiv.) was added slowly, with cooling in an ice bath, to glacial acetic acid (4 mL), followed by the addition of aqueous formaldehyde (1.59 mL, 37 % solution w/v, 21.2 mmol, 1.2 equiv.). The reaction flask was removed from the ice bath and equipped with a reflux condenser, through which 2-methylfuran (**238**) (1.59 mL, 1.45 g, 17.7 mmol, 1 equiv.) was added. External heating was applied to bring the mixture to reflux and was continued for 3 hours. The reaction mixture was then allowed to cool and poured immediately into a cold solution of 1M sodium hydroxide (5 g of NaOH in 16 mL of water) and extracted with ethyl acetate (6 x 15 mL). The organic layers were combined, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the crude product as a black tar. Purification by flash chromatography on silica eluting with ethyl acetate / light petroleum (1 : 1) (R_f 0.29) afforded the pure N-*(2-(5-methylfuryl)methane)-3-aminopyridine* (**243**) as a low melting point yellow crystalline solid (solid <4 °C) (1.69 g, 51 %).

Found C 70.33, H 6.16, N 14.74; $C_{11}H_{12}N_2O$ requires C 70.19, H 6.43, N 14.88 %; ν_{max} (KBr) 3 260 (NH, br, s), 3 101 and 3 037 (C-H, m), 1 592 and 1 506 (C=C, s), 1 243 (C-O, s) cm^{-1}; δ (500 MHz, $CDCl_3$) 8.10 (1H, d, *J* 2.8 Hz, py$\underline{H}_2$), 8.00 (1H, d, *J* 4.6 Hz, py$\underline{H}_6$), 7.09 (1H, dd, *J* 8.3 Hz, *J'* 4.6 Hz, py$\underline{H}_5$), 6.95 (1H, ddd, *J* 8.3 Hz, *J'* 2.8 Hz, *J''* 1.3 Hz, py$\underline{H}_4$), 6.12 (1H, d, *J* 3.0 Hz, fu$\underline{H}$), 5.90 (1H, d, *J* 3.0 Hz, fu$\underline{H}$), 4.27 (2H, s, fu-C$\underline{H}_2$NH-), 4.06 (1H, br s, -N$\underline{H}$), 2.28 (3H, s, fu-C$\underline{H}_3$); δ_C (125.7 MHz, $CDCl_3$) 150.03 (pyCH), 147.48 (pyCH), 136.89 (pyC), 135.79 (pyCH), 123.26 (pyCH), 150.03 (fuC), 140.32 (fuC), 118.70 (fuCH),

107.64 (fuCH), 62.25 (fu-CH_2-), 13.73 (fu-CH_3); $^m/_z$ (C.I.) 189 (84 %, MH^+), 95 (100 %, MH^+ -94); λ_{max} (ε) (MeOH) 310 (3 680), 250 (16 800), 205 (15 500).

Preparation of N-*Acetyl*-N-*(2-(5-methylfuryl)methane)-3-aminopyridine* (**244**)

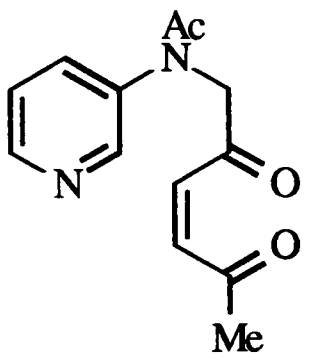


N-(2-(5-Methylfuryl)methane)-3-aminopyridine (**243**) (880 mg, 4.68 mmol) from the above reaction was dissolved in the minimum amount of pyridine (*ca.* 5 mL) and a large excess of acetic anhydride (*ca.* 4 mL) was added dropwise. The reaction mixture was allowed to stir at room temperature overnight. The excess acetic anhydride was quenched by the addition of ethanol and the resultant ethyl acetate removed *in vacuo*. This procedure was repeated three more times to ensure complete removal of the acetic anhydride. Pyridine was removed by evaporation at low pressure (*ca.* 0.01 mmHg) with toluene as the co-solvent. Pure N-*acetyl*-N-*(2-(5-methylfuryl)methane)-3-aminopyridine* (**244**) was obtained by flash chromatography on silica eluting with ethyl acetate / light petroleum (1 : 1) (R_f 0.17) as a low melting point yellow crystalline solid (solid <4 °C) (1.06g, 98 %).

Found C 67.94, H 6.04, N 12.18; $C_{13}H_{14}N_2O_2$ requires C 67.81, H 6.13, N 12.17 %; ν_{max} (KBr) 3 043, 3 013 and 2 976 (C-H, w), 1 665 (C=O, s), 1 585 and 1 571 (C=C, s), 1 251 (C-O, m) cm^{-1}; δ (500 MHz, $CDCl_3$) 8.58 (1H, m, py$\underline{H}_2$), 8.37 (1H, s, py$\underline{H}_6$), 7.40 (1H, d, *J* 7.9 Hz, py$\underline{H}_4$), 7.33 (1H, dd, *J* 7.9 Hz, *J'* 4.8 Hz, py$\underline{H}_5$), 6.01 (1H, d, *J* 3.0 Hz, fu$\underline{H}$), 5.83 (1H, s, fu$\underline{H}$), 4.82 (2H, s, fu-C$\underline{H}_2$-), 2.23 (3H, s, fu-C$\underline{H}_3$), 1.87 (3H, s, -C(=O)C$\underline{H}_3$); δ_C (125.7 MHz, $CDCl_3$) 169.74 (C=O), 152.11 (pyC), 149.69 (pyCH), 149.06 (pyCH), 148.02 (fuC), 139.01

(fuC), 135.65 (pyCH), 123.91 (pyCH), 110.28 (fuCH), 106.25 (fuCH), 45.29 (fu-CH_2-), 22.80 (CH_3), 13.50 (CH_3); $^m/_z$ (C.I.) 231 (100 %, MH^+), 137 (30 %, MH^+ -94), 95 (87 %, MH^+ -136); λ_{max} (ε) (MeOH) 258 (3 480), 215 (12 100), 202 (14 300).

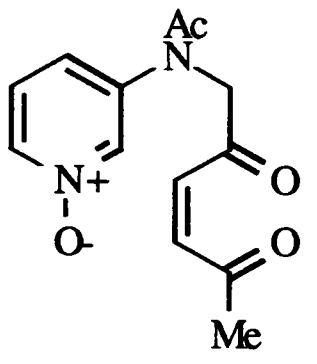
Preparation of N-*Acetyl*-N-*(2,5-dioxohex-3-ene)-3-aminopyridine* (**246**)



N-Acetyl-*N*-(2-(5-methylfuryl)methane)-3-aminopyridine (**244**) (896 mg, 3.89 mmol, 1 equiv.) was dissolved in DCM (10 mL) and cooled to 0 °C before the addition of *m*-CPBA (1.34 g, 50 % wet with water, 3.89 mmol, 1 equiv.) The reaction mixture was then stirred for 1 hour at room temperature, before the addition of 1M sodium thiosulphate (100 mL) to quench the excess *m*-CPBA. The organic layer was separated and the aqueous phase extracted with DCM (4 x 75 mL). Drying of the combined organic layers ($MgSO_4$) and evaporation of the solvent afforded the crude product. Pure N-*acetyl*-N-*(2,5-dioxohex-3-ene)-3-aminopyridine* (**246**) was obtained as only the *cis* isomer by flash chromatography on silica eluting with ethyl acetate (R_f 0.12) as a low melting point yellow crystalline solid (solid <4 °C) (307 mg, 32 %). Found C 63.61, H 5.46, N 11.16; $C_{13}H_{14}N_2O_3$ requires C 63.40, H 5.73, N 11.38 %; ν_{max} (KBr) 3 056, 3 009 and 2 960 (C-H, m), 1 690 (C=O, s), 1 680 (C=O, s), 1 667 (C=O, s), 1 586 and 1 575 (C=C, m) cm^{-1}; δ (500 MHz, $CDCl_3$) 8.64 (1H, d, *J* 2.4 Hz, py$\underline{H}_2$), 8.62 (1H, dd, *J* 4.8 Hz, *J'* 1.3 Hz, py$\underline{H}_6$), 7.40 (1H, m, py$\underline{H}_4$), 7.39 (1H, dd, *J* 8.1 Hz, *J'* 4.8 Hz, py$\underline{H}_5$), 6.92 (2H, s, -C$\underline{H}$=C$\underline{H}$- *cis*), 4.71 (2H, s, -N(Ac)-C$\underline{H}_2$-), 2.38 (3H, s, -C(=O)C$\underline{H}_3$) 1.96 (3H, s, -N(C(=O)C$\underline{H}_3$)-);

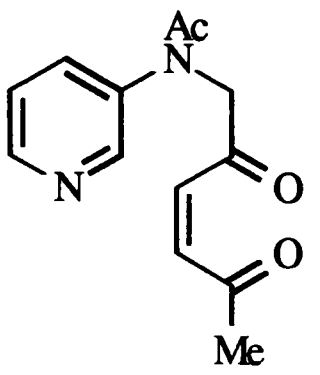
δ_C (125.7 MHz, $CDCl_3$) 197.61 (C=O), 193.92 (C=O), 170.43 (C=O), 149.44 (CH), 149.32 (CH), 139.68 (pyC), 137.89 (CH), 135.73 (CH), 133.96 (CH), 124.27 (CH), 57.85 (-N(Ac)-$\underline{C}H_2$-), 28.40 (CH_3), 22.05 (CH_3); $^m/_z$ (E.S.$^+$) 247 (100 %, MH^+); λ_{max} (ε) (MeOH) 373 (10 000), 229 (26 000).

Attempted preparation of N-*Acetyl*-N-*(2,5-dioxohex-3-ene)-3-aminopyridine* N-*oxide* (**245**)



(i) <u>*m*-CPBA oxidation of (**244**)</u>

N-Acetyl-*N*-(2-(5-methylfuryl)methane)-3-aminopyridine (**244**) (137 mg, 0.60 mmol, 1 equiv.) was dissolved in DCM (1.5 mL) and cooled to 0 °C before the addition of *m*-CPBA (460 mg, 50 % wet with water, 1.31 mmol, 2.2 equiv.) The reaction mixture was then stirred for 1 hour at room temperature before the addition of cold 1M sodium thiosulphate (15 mL) to quench the excess *m*-CPBA. The organic phase was separated and the organic layer extracted with DCM (4 x 10 mL). The organic layers were combined, dried ($MgSO_4$) and the solvent removed *in vacuo* to afford the crude product as a yellow solid. Spectroscopic inspection revealed that the pyridine moiety had not been oxidised to the *N*-oxide although the furan ring had been fully oxidised to the enone system. *N*-Acetyl-*N*-(2,5-dioxohex-3-ene)-3-aminopyridine (**246**) was isolated as the single *cis* isomer and was purified by flash chromatography on silica, eluting with ethyl acetate (R_f 0.12) and obtained as a low melting point yellow solid (solid <4 °C) (41 mg, 28 %).



The data was consistent with that already obtained for this product.

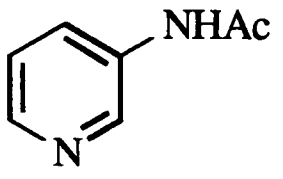
(ii) Sodium perborate oxidation of (**246**)

Following the procedure of McKillop,[71] *N*-acetyl-*N*-(2,5-dioxohex-3-ene)-3-aminopyridine (**246**) (95 mg, 0.39 mmol, 1 equiv.) was dissolved in glacial acetic acid (5 mL) and the solution stirred under nitrogen for 10 minutes at room temperature. The reaction mixture was then warmed to 40 °C and the sodium perborate tetrahydrate (272 mg, 0.85 mmol, 2.2 equiv.) added and stirring continued for 24 hours. The acetic acid was removed under high vacuum (*ca.* 0.01 mmHg), the residue diluted with DCM (5 mL) and the borate salts removed by filtration. Water (5 mL) was added and the DCM layer separated. The aqueous layer was then neutralised with aqueous saturated potassium carbonate and extracted with DCM (5 x 10 mL). Drying ($MgSO_4$) of the combined organic phases, followed by evaporation of the solvent, afforded the crude solid product which was seen to be recovered starting material (**246**).

(iii) UHP oxidation of (**246**)

Following the procedure of Kaczmarek,[66] UHP (86 mg, 0.45 mmol of H_2O_2, 1 equiv.) and phthalic anhydride (67 mg, 0.45 mmol, 1 equiv.) were stirred in dry DCM (7 mL), under nitrogen, for 20 minutes. *N*-Acetyl-*N*-(2,5-dioxohex-3-ene)-3-aminopyridine (**246**) (100 mg, 0.41 mmol, 0.9 equiv.) was added and stirring continued for 25 hours. The reaction mixture was subsequently neutralised with a few drops of aqueous saturated potassium carbonate, diluted with water (5 mL) and extracted with chloroform (6 x 10 mL). Drying ($MgSO_4$) of the organic phase followed by removal of the solvent *in vacuo*, afforded the crude solid product which, by

attempted purification by reverse phase flash chromatography,[87] gave *N*-acetyl 3-aminopyridine (**247**), which was isolated as a colourless oil (33 mg, 43 %).



Found 137.0708, $C_7H_8N_2O(H^+)$ requires 137.0714; ν_{max} (thin film) 3 400 (N-H, br, s), 3 021, 2 964 and 2 951 (C-H, w), 1 689 (C=O, s), 1 581 and 1 550 (C=C, m) cm^{-1}; δ (200 MHz, CD_3OD) 8.99 (1H, t, *J* 1.6 Hz, pyH_2), 8.07 (1H, d, *J* 6.3 Hz, pyH_6), 7.62 (1H, d, *J* 8.6 Hz, pyH_4), 7.47 (1H, dd, *J* 8.6 Hz, *J'* 6.3 Hz, pyH_5), 2.16 (3H, s, CH_3); $^m/_z$ (C.I.) 137 (100 %, MH^+), 95 (100 %, MH^+ -42); λ_{max} (ε) (MeOH) 244 (9 390), 202 (5 520).

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