

THE SYNTHESIS AND REACTIONS OF THIENOPYRIDINES

A THESIS SUBMITTED BY

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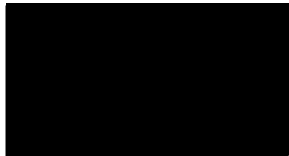
Dundee Institute of Technology

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DECLARATION

I hereby declare that the work presented in this thesis was carried out by me at Dundee Institute of Technology, Dundee except where due acknowledgement is made, and has not been submitted by me for any other Degree.

Signed



Date

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ABSTRACT

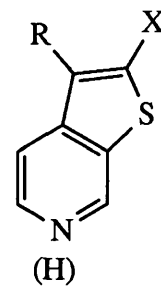
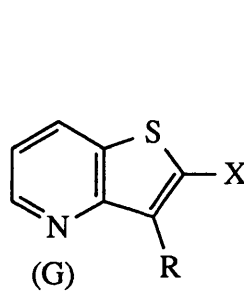
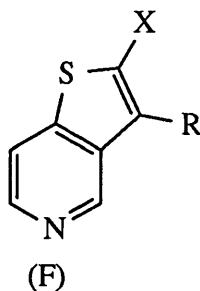
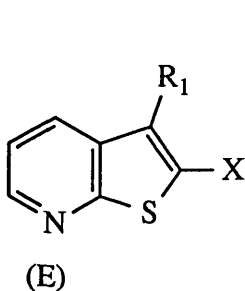
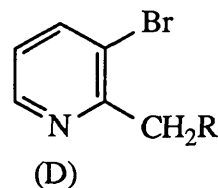
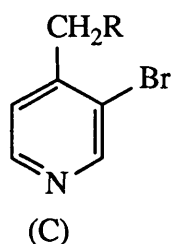
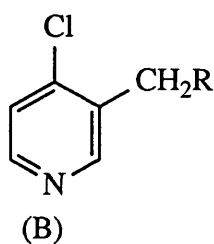
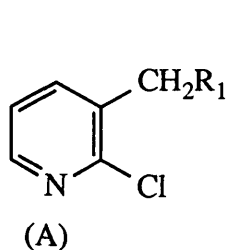
The synthesis of *ortho*-halogenated pyridine derivatives (A-D; R = CN, CO₂Et; R₁ = CN, CO₂Me, CO₂Et) containing methylene groups activated by the nitrile or ester functionality is described. Derivatives (A-D) are reacted with carbon disulfide in the presence of base, followed by alkylation with iodomethane, to afford novel thienopyridines (E-H; R = CN, CO₂Et; R₁ = CN, CO₂Me, CO₂Et; X = SMe).

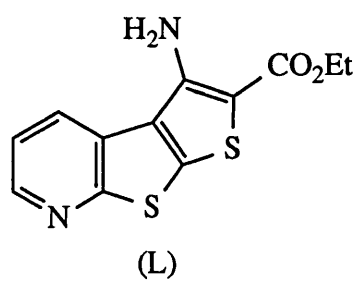
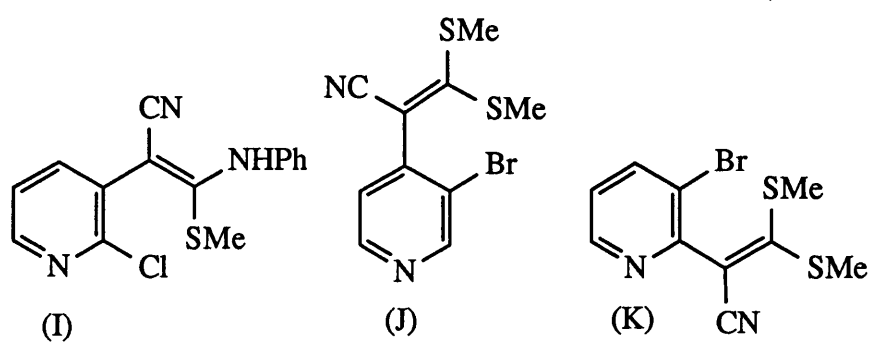
Pyridine derivative (B; R = CN) also reacts with phenyl isothiocyanate to form thienopyridine (F; R = CN; X = NHPh). Reaction of the nitriles (A, C and D; R, R₁ = CN) under identical conditions, however, does not give the bicyclic compounds but ketene dithioacetals (I, J and K). Increasing the reaction temperature allows formation of thienopyridines (E, G and H; R, R₁ = CN; X = NHPh). Thienopyridines (~~A-D~~; R = CO₂Et; R₁ = CO₂Me, CO₂Et; X = NHPh) are also synthesised from the reaction of the derivatives (A-D; R = CO₂Et; R₁ = CO₂Me, CO₂Et) with phenyl isothiocyanate.

Reaction of nitrile (A; R₁ = CN) with carbon disulfide in the presence of base, followed by quenching with ethyl chloroacetate affords thienopyridine (E; R₁ = CN; X = SCH₂CO₂Et) which in turn cyclises with base to give tricyclic compound (L).

Thienopyridines (E; R₁ = NH₂; X = CN, Ph, CO₂Et, COMe, CPh, COCH₂CO₂Et) are synthesised from reactions of 3-cyanopyridine-2(1H)-thione with compounds containing a halogen atom adjacent to an active methylene group.

Nucleophilic reactions of thienopyridines (E; R₁ = CN; X = SMe, SOMe, SO₂Me) are investigated, in an attempt to prepare tricyclic compounds.





FOREWORD

Bracketed Arabic numerals in the text refer to the diagrams of the formulae and the Arabic superscripts indicate references. The following abbreviations have been used in the text.

Ac	acetyl group CH_3CO
AIBN	2,2-azobis(2-methylpropionitrile)
bp	boiling point
<i>m</i> -CPBA	<i>meta</i> -chloroperoxybenzoic acid
δ	parts per million
DMAD	dimethylacetylene dicarboxylate
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
Et	ethyl group
HMPT	hexamethylphosphorous triamide
ir	infrared
LDA	lithium diisopropylamide
Me	methyl group
mp	melting point
NCS	N-chlorosuccinimide
NBS	N-bromosuccinimide
nmr	nuclear magnetic resonance
Ph	phenyl group
pmr	proton magnetic resonance
PPA	polyphosphoric acid

PTSA	<i>para</i> -toluenesulfonic acid
THF	tetrahydrofuran
tlc	thin layer chromatography
Ts	<i>para</i> -toluenesulfonyl chloride
uv	ultraviolet

INTRODUCTION

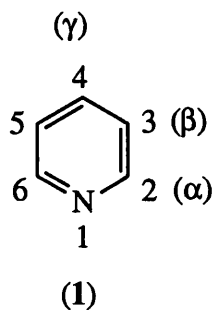
1 INTRODUCTION

1.0 Introduction

This thesis describes the synthesis and reactions of novel thienopyridines and therefore the majority of this introduction reviews in depth the chemistry of these bicycles. The thienopyridines were prepared from the reactions of *ortho*-halogenated pyridine derivatives, containing methylene groups activated by nitriles or esters, and heterocumulenes such as carbon disulfide and phenyl isothiocyanate. Since many of these *ortho*-halogenated pyridine derivatives were novel and the synthesis of these utilised basic pyridine chemistry it is also pertinent therefore to discuss, as an overview, some of the chemistry of pyridine and its derivatives.

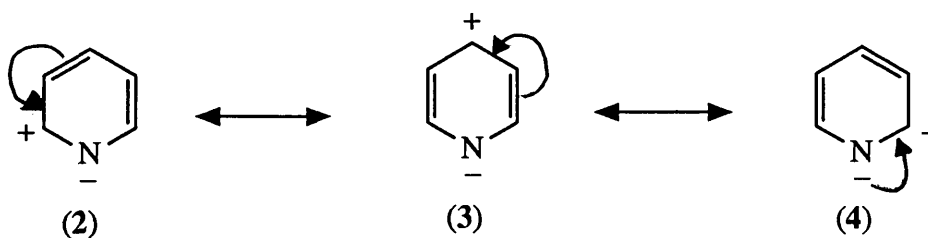
1.1 Pyridine and its Derivatives

Pyridine and its simple derivatives were first discovered in the nineteenth century by the Scottish chemist, Thomas Anderson. In a series of papers¹⁻³ he discussed the isolation of picoline from coal tar¹ and the basic oil obtained from the distillation of deer horn². In a third paper, the isolation of both pyridine and lutidine was reported³. The similarities in the structures of benzene and pyridine were first recognised⁴, independently, by Korner in 1869 and Dewar in 1871 and the formulation of pyridine as azabenzene (**1**) was finally established by Ladenburg⁵ in 1888.

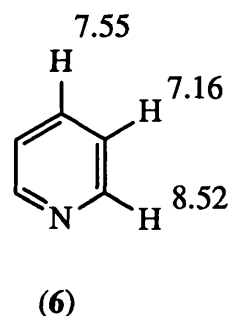
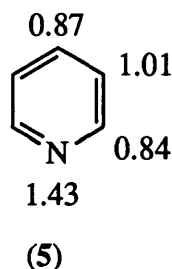


1.1.1 Pyridines

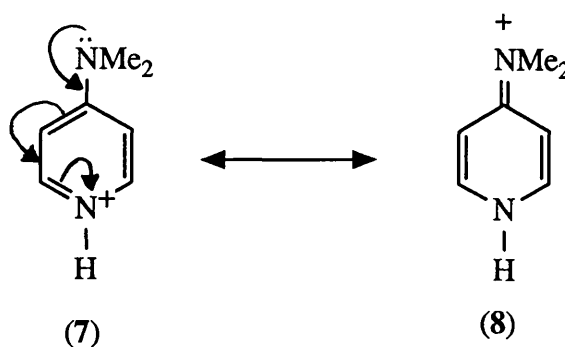
Pyridine, like benzene, contains a delocalised 6π -electron system. The bond lengths of pyridine (C-C 139.5pm and C-H 108.1pm) are very close to those of benzene (C-C 139.7pm and C-H 108.4pm). The resemblance to benzene is also apparent in the ultraviolet⁶ and infrared⁷ spectra. Pyridine however, differs from benzene, since it has a large dipole moment of 2.26D, and therefore the polarisation of the molecule can be represented by the canonical structures (2-4).



This polarisation is also reflected in the electron densities at the various ring positions, as seen from molecular orbital calculations⁸ and also from chemical shifts in the ^1H nmr spectra⁹. A typical set of calculated π -electron densities⁸ is shown in the structure (5) and these results show that the electron densities at the ring positions decrease in the order $1 > 3 > 4 \text{ \& } 2$. The chemical shift values for the proton magnetic resonance spectrum of pyridine⁹ relative to tetramethylsilane are shown in (6). The deshielding effect of the hetero atom is most pronounced at the 2- and 6-positions and is also noticeable at the 4-position.



Pyridine is a tertiary base and both pyridine and simple alkylpyridines are weakly basic with pKa values of 5.20 and 5.5-7.5 respectively¹⁰. The basicity is lowered by electron-withdrawing substituents, especially in the 2- and 6-positions while at the 4-position, groups capable of resonance stabilisation increase the basicity. An example of this¹¹ is 4-dimethylaminopyridine which may be protonated on the pyridine nitrogen to give (7) which is resonance stabilised as the cation (8) with a pKa value of 9.70.

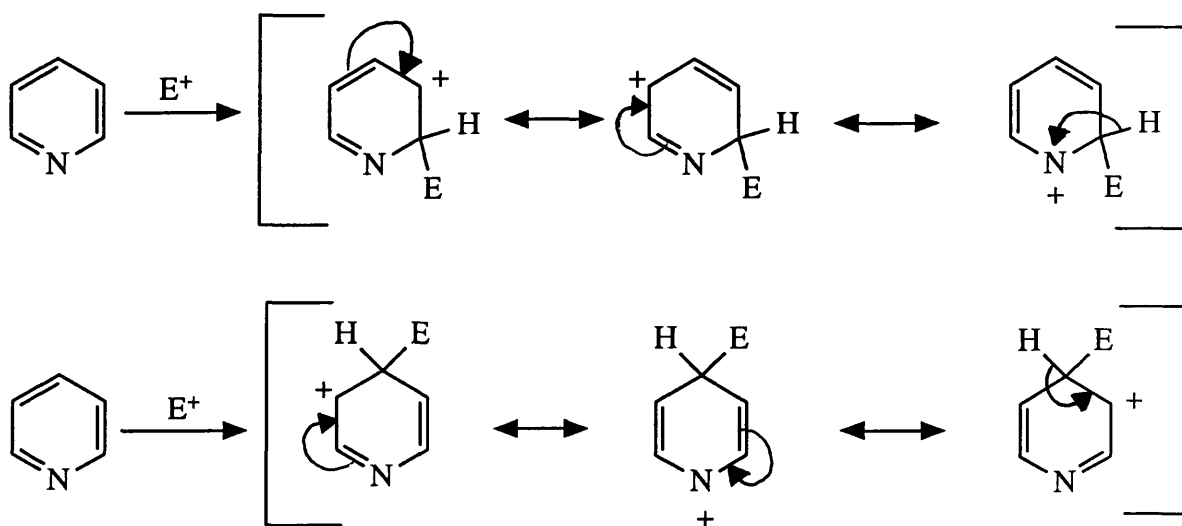


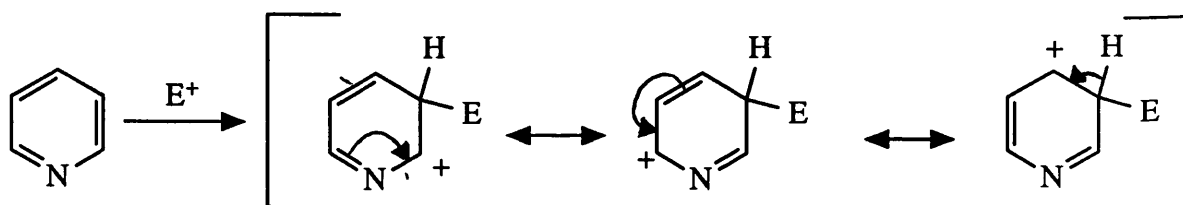
The lone pair of electrons from the nitrogen in the plane of the pyridine ring provides a site for protonation, alkylation, acylation, N-oxide formation and co-ordination to Lewis acids.

1.1.2 Reactions of Pyridines

1.1.2.1 Electrophilic Substitution Reactions

The electrophilic substitution of pyridine and its derivatives may be accomplished only with extreme difficulty. Firstly, since pyridines are basic they may undergo electrophilic attack at the nitrogen prior to reaction at a ring carbon atom. The result being that the species undergoing electrophilic substitution at carbon is frequently not the free base but one in which the nitrogen is protonated, quaternised or co-ordinated to another group or atom. Unfortunately, these pyridinium compounds are much less reactive towards electrophiles than the free bases^{12,13}. Secondly, the attack of the electrophile on carbon is selective; it occurs mainly at the 3- and 5-positions which is consistent with electron density calculations⁸. Attack here also leads to the formation of intermediates which are the least destabilised by the presence of the nitrogen atom. The resonance structures in Scheme 1 show this destabilising influence of the nitrogen atom on the intermediates produced by electrophilic attack at the 2- and 4-positions along with the more stable intermediate from the reaction at the 3-position.





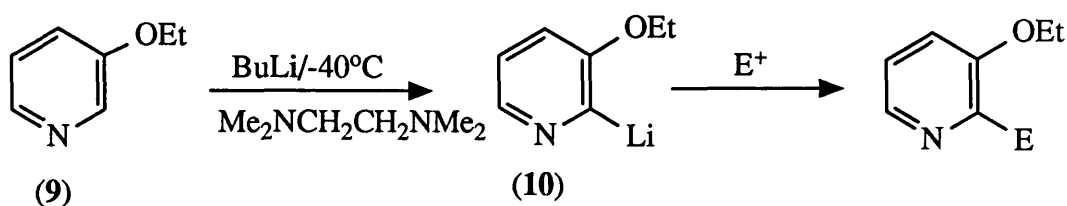
[Scheme 1]

Friedel-Crafts alkylation and acylation of pyridine is unsuccessful, but pyridine can be nitrated¹⁴⁻¹⁶ with sodium or potassium nitrate in fuming sulfuric acid at 300°C or by vapour phase nitration using N₂O₄ to afford very low yields of 3-nitropyridine. Higher yields have been achieved^{17,18} though using potassium nitrate in fuming sulfuric acid at 100°C.

The chlorination of pyridine requires severe conditions but can be accomplished by the reaction of chlorine and pyridine in the presence of a large excess of aluminium chloride¹⁹ to afford 3-chloropyridine in 30-35% yield. The bromination of pyridine, however, may be achieved relatively easily by the use of bromine and fuming sulfuric acid²⁰. The main product obtained is 3-bromopyridine (90% yield) along with small amounts of dibromopyridines. The sulfonation of pyridine^{21,22} takes place in fuming sulfuric acid and mercuric sulfate at 220-270°C to give pyridine-3-sulfonic acid in high yield. Pyridine N-oxides have been used as alternatives, since they undergo electrophilic substitution reactions easier than their parent pyridines and these reactions will be reviewed later (Section 1.1.4).

Electrophilic substitution in the pyridine ring is easier if electron-donating substituents are present. Methylpyridines are therefore better at undergoing such reactions than the unsubstituted pyridine^{17,18}. Alkoxypyridines and hydroxypyridines (or pyridones) undergo substitution very readily with the *ortho-para* effect of the activating substituent being dominant²³⁻²⁵. The 2- and

4-alkoxypyridines are therefore substituted preferentially at the 3- and 5-positions while 3-alkoxypyridines react mainly at the 2-position, with some substitution also taking place at the 6-position. An interesting method for the substitution of alkoxypyridines, uses lithiation followed by reaction of the lithio derivative. For example, 3-ethoxypyridine (**9**) is lithiated at the 2-position by butyllithium at -40°C and the lithiopyridine (**10**) can be reacted with a wide variety of electrophiles²⁶ [Scheme 2].



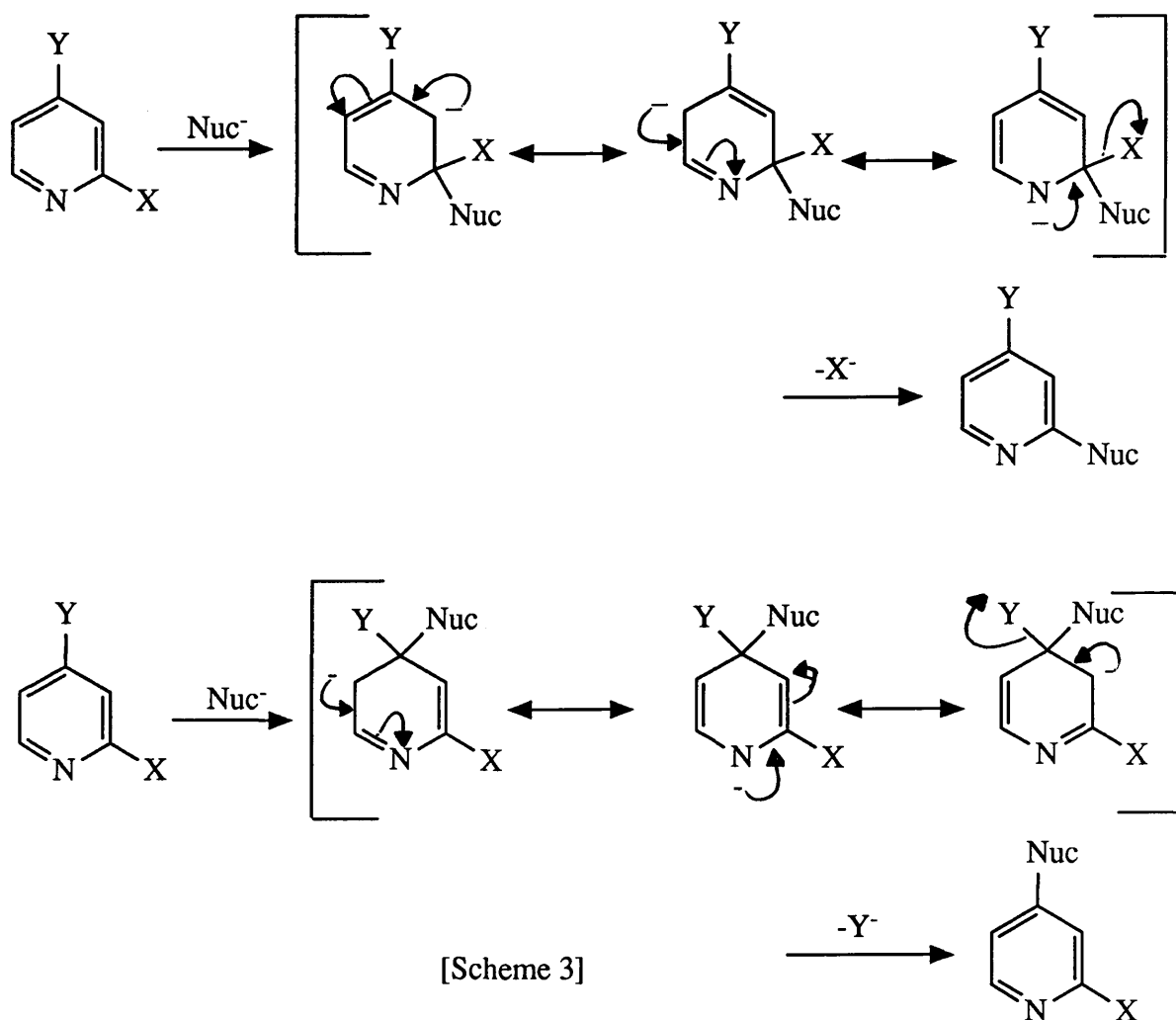
[Scheme 2]

Electrophilic substitution reactions have also been discussed in more detail²⁷.

1.1.2.2 Nucleophilic Substitution Reactions

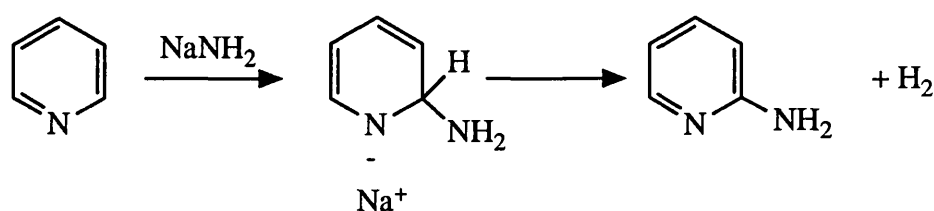
Although pyridine and its derivatives undergo electrophilic substitution reactions less readily than the corresponding benzene derivatives, they do undergo nucleophilic substitution with more ease. As with benzene, there are two principal mechanisms for nucleophilic substitution, the addition-elimination (AE) mechanism and the elimination-addition (EA) mechanism. In pyridine chemistry, there is also a third mechanism, an addition-elimination which leads to "cine-substitution" and this is often referred to as the "abnormal" addition-elimination (AE_a) mechanism²⁷.

Nucleophilic displacement of a good leaving group by an addition-elimination (AE) mechanism occurs most readily for leaving groups at the 2- and 4-positions. Stabilisation of the anion formed by addition of the nucleophile is best achieved when the partial negative charge can be delocalised onto the nitrogen and the canonical forms for the intermediates [Scheme 3] show stabilisation of this kind.



Molecular orbital calculations also indicate that anions arising from nucleophilic addition at the 2- and 4-positions are of lower energy than those arising from the addition at the 3-position²⁸. Nucleophilic displacement by this mechanism is easier still in N-alkylpyridinium salts and N-oxides which are readily attacked by nucleophiles at the 2- and 4-positions.

Possibly the best known and most studied nucleophilic substitution reaction is the Chichibabin reaction, in which pyridine is converted into 2-aminopyridine by reaction with sodamide. This reaction is widely applicable and has been extensively reviewed²⁹⁻³³. The mechanism is (AE) and the 2-position is preferred due to its higher electrophilicity and to the co-ordination of sodium at the nitrogen atom of the pyridine ring [Scheme 4].



[Scheme 4]

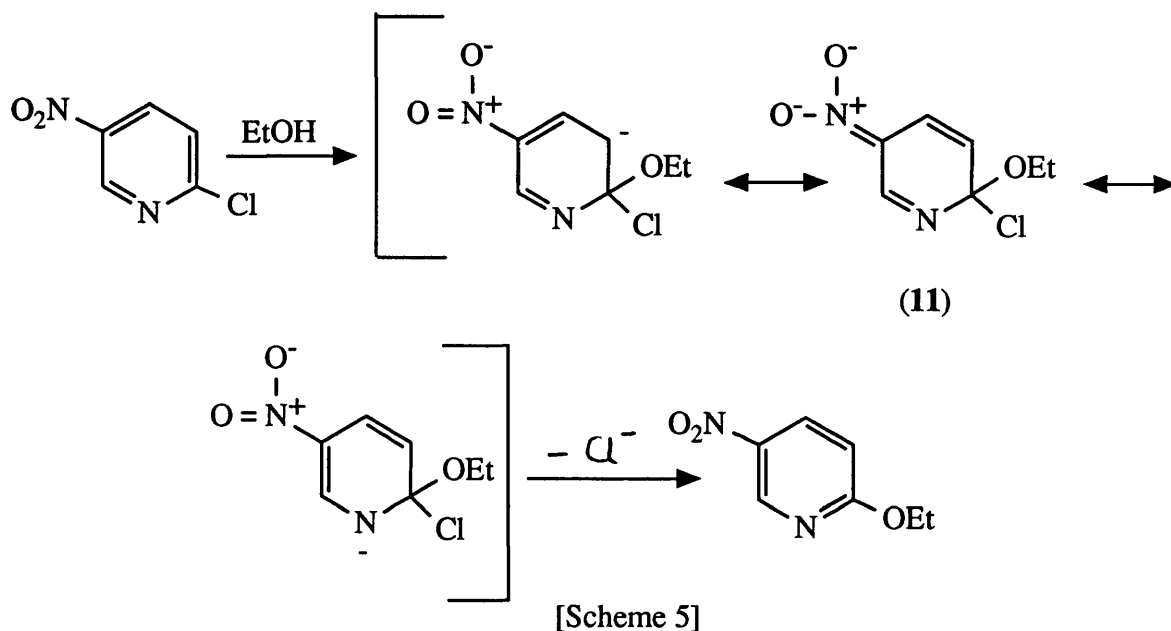
3-Methyl- and 4-methylpyridines are aminated in the 2-position while 2-methylpyridine reacts at the 6-position. When the 2- and 6-positions are occupied, then amination occurs in the 4-position.

Pyridine can be alkylated or arylated in the 2- and 6-positions by reaction with Grignard reagents or organolithium reagents. Grignard reagents generally give low yields²⁹ while organolithium reagents give moderate to good yields^{34,35}.

N-alkylpyridinium salts are more reactive towards nucleophiles than pyridines and are therefore able to react with less powerful nucleophiles. Pyridine N-oxides also react with nucleophiles and this will be discussed later (Section 1.1.4).

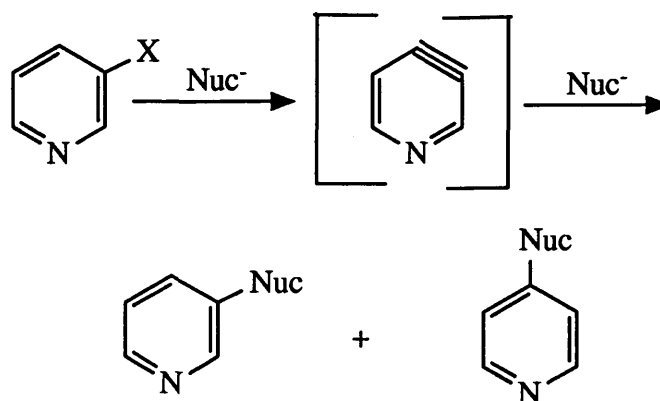
Halopyridines react with nucleophiles mostly by the (AE) mechanism. The 2- and 4-halo substituents are readily displaced while halogens in the 3-position undergo substitution less readily and usually by the (EA) mechanism. Replacement of halogens in the 2- and 4-positions can be achieved with good nucleophiles such as

hydrazines, thiolate anions and stabilised carbanions. These reactions are easier if additional activating substituents are present in the appropriate positions. For example, the reaction of 2-chloro-5-nitropyridine with ethanol is much faster than that of ethanol with 2-chloropyridine; the intermediate (11) gaining additional stabilisation from the nitro group^{36,37} [Scheme 5].



Halopyridinium salts are very much more activated than neutral halopyridines and therefore react with a wide variety of nucleophiles³⁸. Nucleophilic displacement of halopyridines can be catalysed by acids or Lewis acids. For example, 2- and 4-chloropyridines are converted into their amino compounds by reaction with a zinc chloride-ammonia complex. The chloropyridine N-oxides are also more reactive than the corresponding chloropyridines towards nucleophiles (Section 1.1.4).

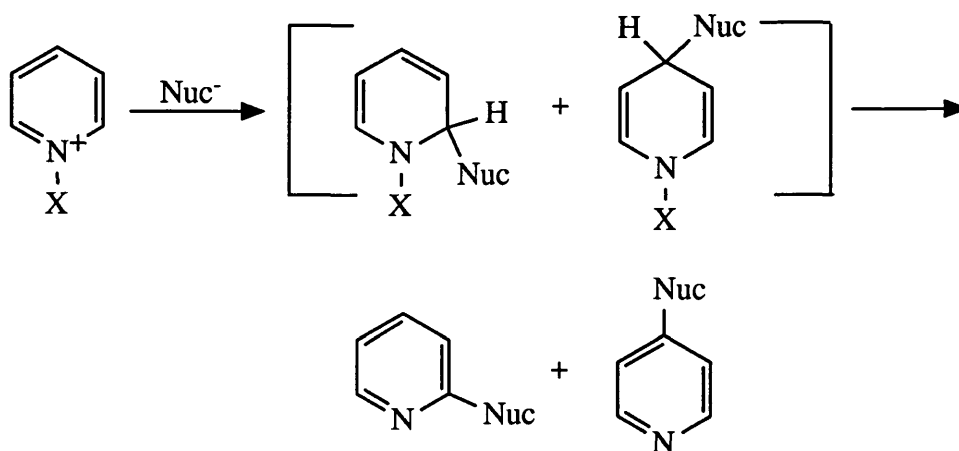
The elimination-addition (EA) mechanism²⁷ is generally observed only when the leaving group is situated in an unactivated (i.e. 3-) position, and the nucleophile is strongly basic. The reactive intermediate involved in this mechanism is known as a pyridyne [Scheme 6].



[Scheme 6]

Most examples of nucleophilic attack proceed *via* the (AE) mechanism but one example that does undergo nucleophilic substitution by the (EA) mechanism is the reaction of 3-halogenopyridines with potassium amide in liquid ammonia or with potassium *t*-butoxide to afford the 2-amino and 4-aminopyridines³⁹.

The abnormal addition-elimination (AE_a) mechanism can occur when the pyridinium salt in which the N-substituent is a leaving group (usually alkoxy or acyloxy) reacts with nucleophiles by addition at the 2- or 4-position followed by elimination of the N-substituent²⁷ [Scheme 7].



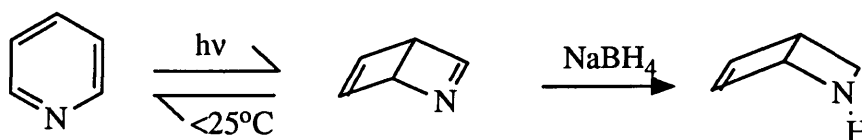
[Scheme 7]

Along with alkoxy- and acyloxypyridines, pyridine N-oxides also undergo nucleophilic attack by the (AE_a) mechanism and these will be discussed later. The chemistry of general nucleophilic substitution of pyridines has been extensively reviewed^{27,36,37}.

1.1.2.3 Miscellaneous Reactions

Pyridines undergo homolytic substitution (replacement of $H\cdot$ by $R\cdot$) with a variety of radical species and the chemistry of radical substitution has been reviewed^{27,40}.

When pyridines are irradiated, then valence isomers, azabicyclohexadienes ("Dewar pyridines") are obtained. These isomers are in general, very unstable but can be intercepted, for example, by reduction with sodium borohydride [Scheme 8].



[Scheme 8]

The photochemistry of pyridines has also been extensively reviewed^{27,41}.

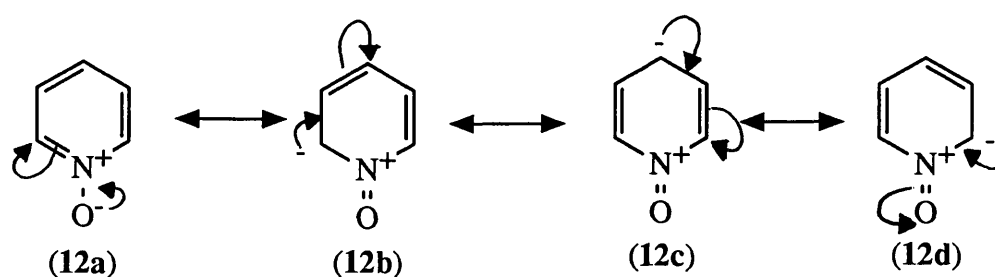
The reaction of pyridines and pyridinium salts with reducing agents of the complex hydride type is essentially a nucleophilic reaction and therefore it is easier to reduce pyridines than the corresponding benzenes. In simple pyridines, however, it is difficult to achieve selective reduction. Pyridine does react with lithium aluminium hydride to form a complex containing both 1,2- and

1,4-dihydropyridines⁴² but isolation of the dihydropyridines proved unsuccessful. However, reduction of pyridine and its simple analogues by lithium aluminium hydride in the presence of aluminium chloride⁴³ gives mixtures of 1,2,3,6-tetrahydropyridines and piperidines. Again this area of pyridine chemistry has been extensively reviewed^{27,44,45}.

1.1.3 Pyridine N-oxides

The N-oxidation of pyridines is normally carried out by the reaction with peracids such as peracetic acid⁴⁶⁻⁴⁸. The aromatic peracids, perbenzoic acid and *m*-chloroperbenzoic acid, have also been used^{49,50} and have an advantage in that the reaction may be carried out under mild conditions in non-polar solvents such as chloroform.

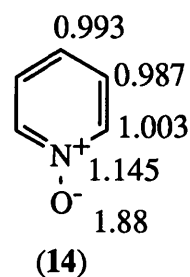
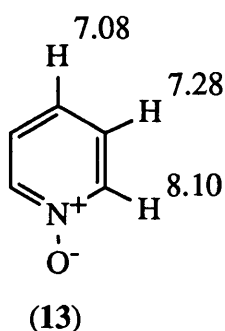
The simple structure (12a) which represents pyridine N-oxide, takes no account of any back donation of electrons from the oxygen into the ring. This effect can be seen from the canonical forms (12b-12d) [Scheme 9].



[Scheme 9]

This back donation of electrons is very important and there is ample evidence to support this. The dipole moment of pyridine N-oxide, for example⁵¹⁻⁵³, is found to

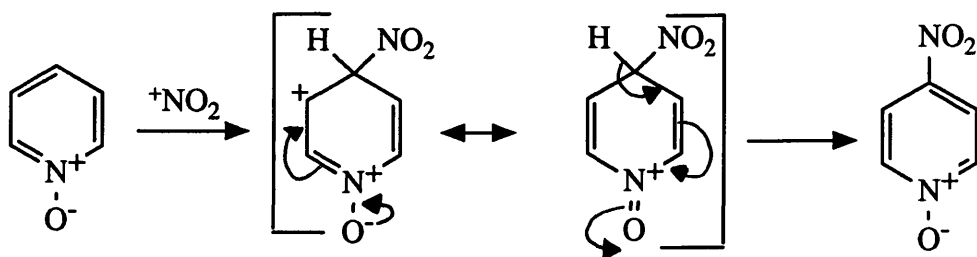
be 4.24D which is much less than the sum of the dipole moment of pyridine and the N⁺-O⁻ bond moment (*ca.* 6.6D). The chemical shift values for the proton magnetic resonance spectrum^{54,55} of pyridine N-oxide show that the deshielding effect in the 2- and 4-positions is less than in pyridine (structure (13)) while the calculated π -electron densities⁵⁶ for various atoms in pyridine N-oxide reveal higher densities at the 2- and 4-positions than in pyridine (structure (14)).



1.1.4. Reactions of Pyridine N-oxides

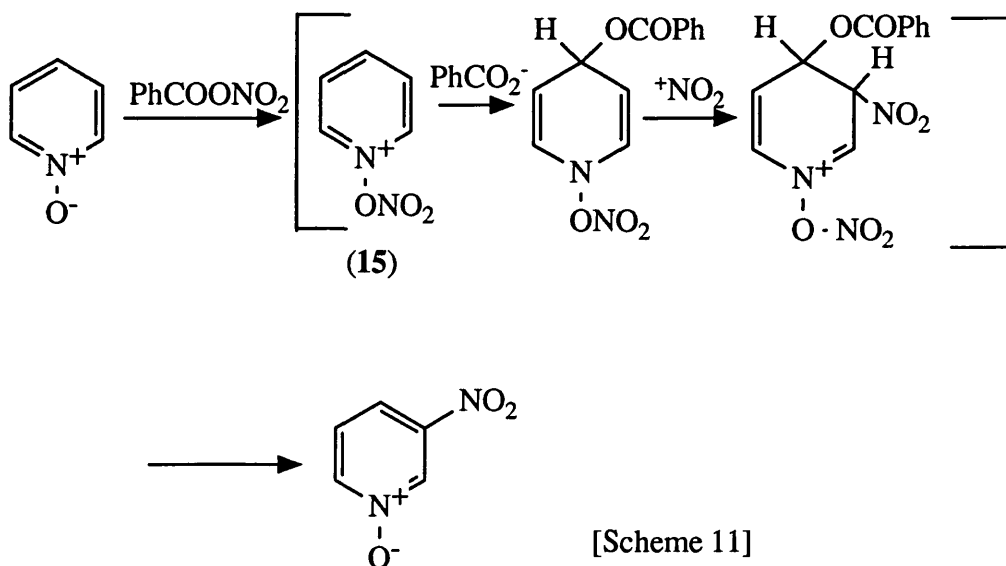
1.1.4.1 Electrophilic Substitution Reactions

Pyridine N-oxides undergo electrophilic substitution more easily than their parent pyridines. For example, the nitration of pyridine N-oxide with nitric acid or potassium nitrate in sulfuric acid^{57,58} gives high yields of 4-nitropyridine N-oxide [Scheme 10]. Nitration occurs on the unprotonated N-oxide and the higher reactivity and the position of the substituent may be rationalised in terms of back donation of electrons (as shown in (12a-d)).



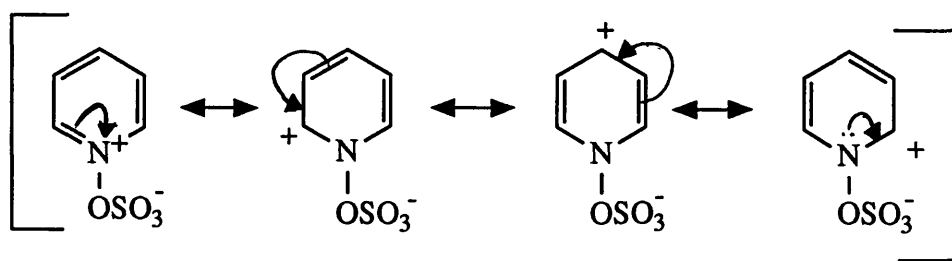
[Scheme 10]

Although Scheme 10 represents one mechanism, others have been proposed⁵⁹ in which the formation of the O-nitro cation (**15**) is involved. The authors⁶⁰ have suggested that the intermediate (**15**) is involved in the nitration of pyridine N-oxide with benzoyl nitrate which gives 3-nitro- and 3,5-dinitropyridine N-oxide [Scheme 11].



[Scheme 11]

Unlike nitration, the halogenation of pyridine N-oxides is much more difficult but direct bromination⁶¹ in fuming sulfuric acid affords the 3-bromo derivative in good yields. The reason suggested why substitution occurs at the 3-position is that in fuming sulfuric acid a complex is formed between the N-oxide and sulfur trioxide, thus deactivating the 2-, 4- and 6-positions towards electrophilic attack⁶² [Scheme 12].



[Scheme 12]

Sulfonation of N-oxides requires vigorous conditions. For example, pyridine-3-sulfonic acid N-oxide is the major product⁶³ from the reaction of pyridine N-oxide with catalytic amounts of mercuric sulfate in 20% sulfuric acid at 220-240°C.

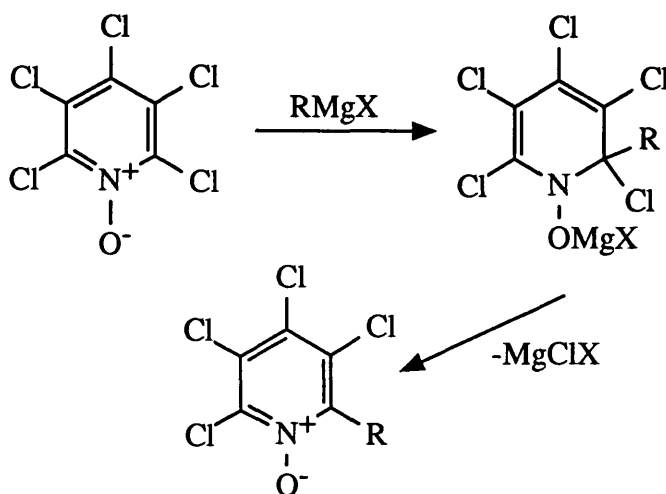
1.1.4.2 Nucleophilic Substitution Reactions

Like pyridine, there are three principal mechanisms for the nucleophilic substitution of pyridine N-oxides, the addition-elimination mechanism (AE), the abnormal addition-elimination mechanism (AE_a) and the elimination-addition mechanism (EA). This section will be subdivided into a discussion of these three types of reactions.

a) The Addition-Elimination Mechanism

This mechanism has been discussed previously (Section 1.1.2.2) but the positively charged nitrogen in the pyridine ring is more strongly electron-attracting than the uncharged nitrogen and so N-oxides are even more reactive than the parent pyridine. Quantitative comparisons for the nucleophilic displacements of halogens

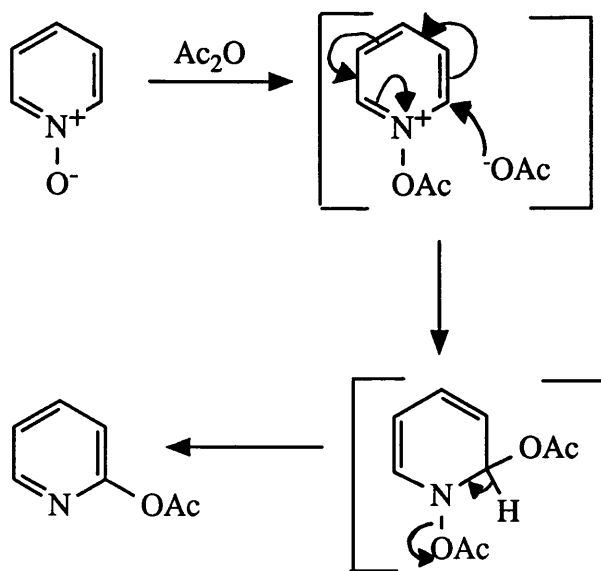
by the methoxide anion have been made⁶⁴ and show that halogens in all three positions of the pyridine N-oxide are considerably more reactive than those of the parent pyridines. However, replacement of halogens by alkyl or aryl groups is not easily achieved but in the more reactive pentachloropyridine N-oxide, chlorine displacement occurs at the 2- and 6-positions⁶⁵ [Scheme 13].



[Scheme 13]

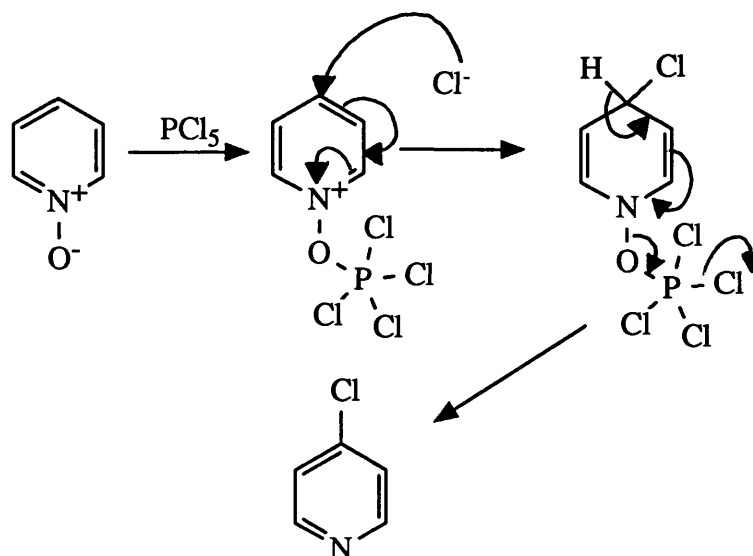
b) The Abnormal Addition-Elimination Mechanism

As discussed previously (Section 1.1.2.2), the abnormal addition mechanism occurs when pyridinium salts in which the N-substituent is a leaving group, react with nucleophiles by addition to the 2- or 4-position followed by elimination of the N-substituent. When pyridine N-oxides undergo abnormal addition-elimination reactions, electrophilic attack on the oxygen atom precedes the nucleophilic addition, followed by elimination of the N-substituent. For example, pyridine N-oxide reacts with acetic anhydride⁶⁶ to afford 2-acetoxypyridine *via* the N-acetate salt [Scheme 14].

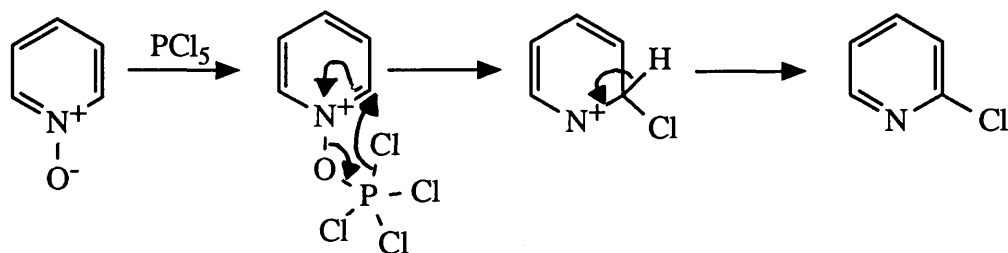


[Scheme 14]

Chlorination in the 2- and 4-positions of pyridine N-oxides may be achieved by reacting the N-oxide with inorganic acid halides such as phosphorus pentachloride, phosphoryl chloride or sulfuryl chloride^{67,68}. These inorganic acid halides interact with the N-oxide function to give a complex which undergoes nucleophilic attack by the halide ion (both intermolecularly and intramolecularly) to give 2- and 4-halopyridines. Halogenation by the intermolecular mechanism is shown at C-4 in Scheme 15. A virtually identical scheme can be drawn for attack at C-2. The intramolecular mechanism is shown in Scheme 16. In this scheme the nitrogen atom is shown having a positive charge prior to loss of a proton. An alternative mechanism could involve intramolecular transfer of the chloride anion leaving a positive charge on the phosphorus, followed by aromatisation as before.



[Scheme 15]



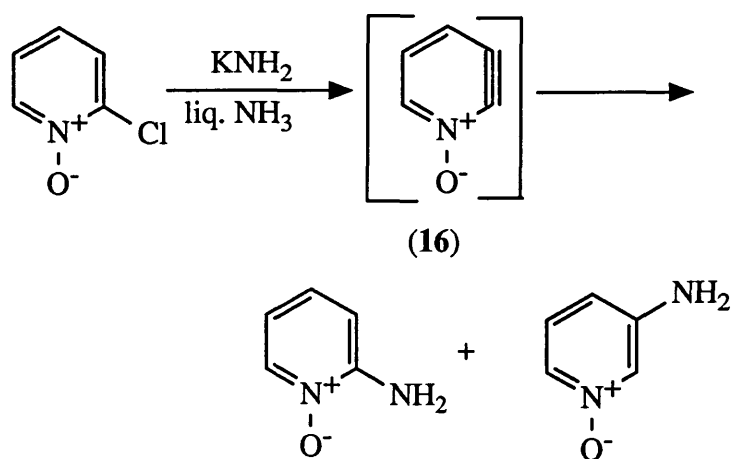
[Scheme 16]

Chlorination of pyridine N-oxide affords more 4-chloropyridine than 2-chloropyridine, indicating that the intermolecular process is more prominent than the intramolecular process⁶⁹. The reaction of phosphoryl chloride with pyridine N-oxide however, gives slightly more of the 2-chloro substituent, suggesting that with this reagent, intramolecular attack is important⁶⁹.

c) The Elimination-Addition mechanism

Pyridine N-oxides may also undergo nucleophilic substitution reactions by the EA mechanism. For example, 2-chloropyridine N-oxide reacts with potassium amide

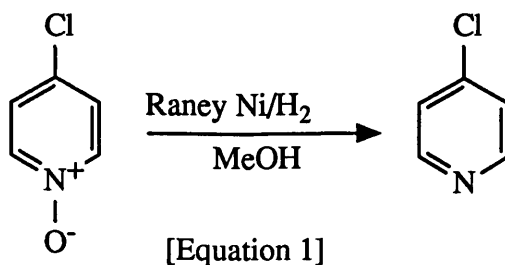
in liquid ammonia to give very low yields of 2- and 3-aminopyridine N-oxides^{70,71} [Scheme 17]. This reaction proceeds *via* the 2,3-pyridyne N-oxide intermediate (16) although the 2-amino compound probably arises mainly by the AE mechanism. The triple bond in the pyridyne N-oxide is highly polarised and this accounts for the fact that the products are rarely obtained in equal proportions. Amination of 3-chloro- and 3-bromopyridine N-oxides also give the 2- and 3-amino products⁷⁰ while other examples of nucleophilic reactions which involve pyridyne intermediates exist²⁷.



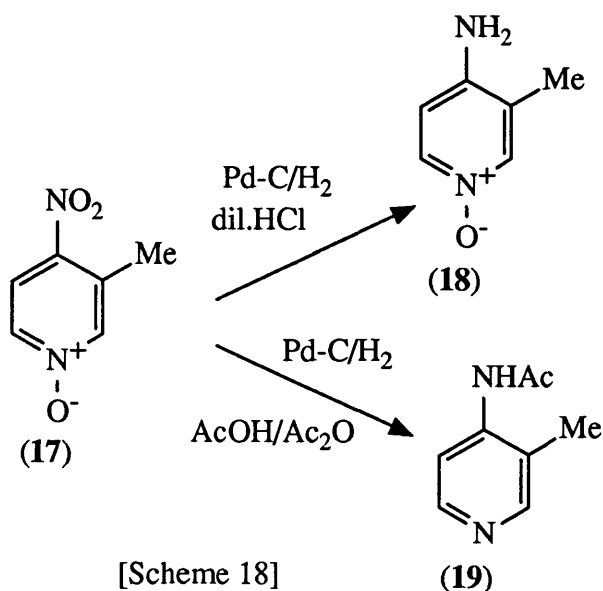
[Scheme 17]

1.1.4.3 Deoxygenation of Pyridine N-oxides

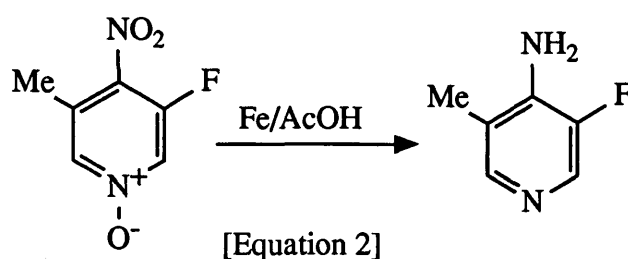
Pyridine N-oxides may be deoxygenated by a variety of methods. Catalytic reduction of the N-oxide function to afford the parent pyridine is one example and when carried out over Raney nickel, the method is selective for the reduction of the N-oxide group. For example, the catalytic reduction of 4-chloropyridine N-oxide results in the deoxygenation but not the dehalogenation⁷² [Equation 1].



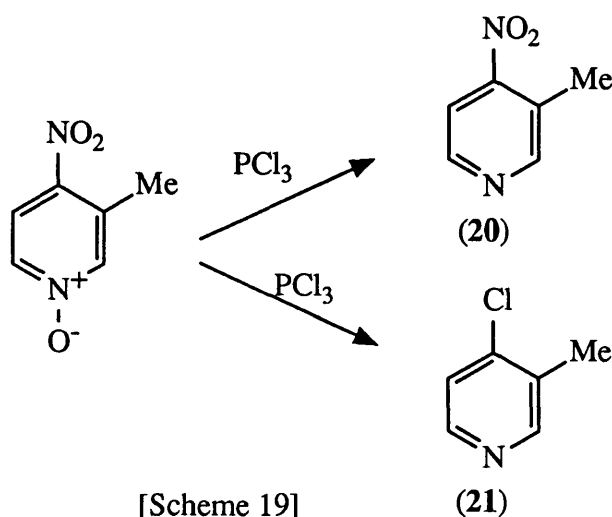
Unlike the easy deoxygenation of N-oxides in the presence of a nickel catalyst, reduction with palladium catalysts in acid are slow and not as selective. For example, reduction of 4-nitro-3-methylpyridine N-oxide (**17**) over a palladium catalyst gives 4-amino-3-methylpyridine N-oxide (**18**) but when carried out in the presence of acetic anhydride and glacial acetic acid, deoxygenation occurs as well as the reduction of the nitro group⁷³ to give 4-acetamido-3-methylpyridine (**19**) [Scheme 18].



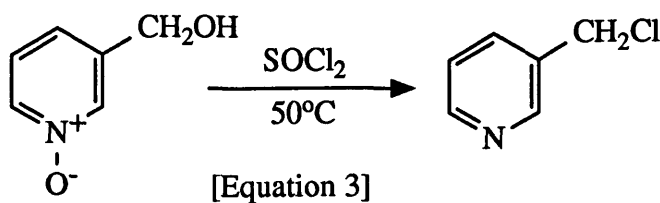
The reaction of the pyridine N-oxide with metals or metal salts in acid has also been carried out. Thus, 5-fluoro-4-nitro-3-methylpyridine N-oxide has been reduced with iron and glacial acetic acid⁷⁴ to give 4-amino-5-fluoro-3-methylpyridine [Equation 2]. Ferrous sulfate⁷⁵ may also be used to deoxygenate N-oxide groups.



Pyridine N-oxides are readily deoxygenated with phosphorus trihalides such as phosphorus trichloride. When the reaction conditions are controlled, 4-nitro-3-methylpyridine N-oxide is converted to 4-nitro-3-methylpyridine (**20**) but if the reaction is prolonged, then 4-chloro-3-methylpyridine (**21**) is obtained^{76,77} [Scheme 19].



Mercapto compounds, sulfides, thiourea and sulfur may be used to effect deoxygenation with the oxygen atom either being bonded to the sulfur atom or released as water⁷⁸. Deoxygenation of 3-hydroxymethylpyridine N-oxide with thionyl chloride⁷⁹ is accompanied by side chain chlorination to give 3-chloromethylpyridine [Equation 3].

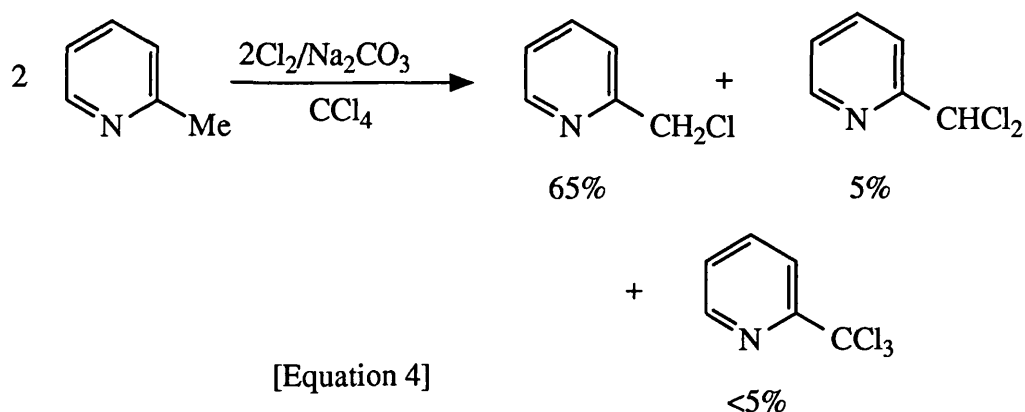


1.1.5 Side Chain Derivatives of Pyridine

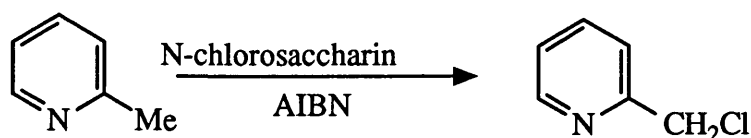
The reactions described later in this thesis utilise substituted methyl pyridines as precursors to the *ortho*-halogenated pyridine derivatives containing activated methylene groups and therefore, at this stage, it is relevant to discuss the methods of preparation of some of these derivatives.

1.1.5.1 The Synthesis of Chloromethylpyridines

The earliest attempts to chlorinate the methyl group of picolines⁸⁰⁻⁸⁴, afforded only the trichloromethyl products. 2-Chloromethylpyridine was later prepared by a one-step process⁸⁵⁻⁸⁷ in which 2-picoline was chlorinated with chlorine in the presence of anhydrous sodium carbonate [Equation 4].

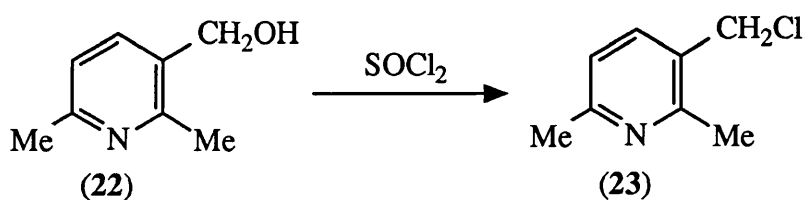


Other direct chlorination routes to chloromethylpyridines from picolines include free radical reactions of N-chlorosaccharin in the presence of free radical initiators such as azobis(isobutyronitrile). For example, 2-methylpyridine affords 2-chloromethylpyridine⁸⁸ in 78% yield [Equation 5].



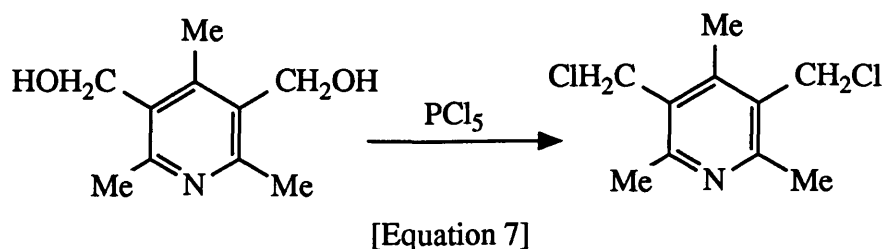
[Equation 5]

Chloromethylpyridines may also be prepared from the corresponding hydroxymethylpyridines, using a variety of reagents, such as thionyl chloride⁸⁹⁻⁹⁷, phosphoryl chloride⁹³, phosphorus pentachloride⁹⁶ and trichloroacetyl chloride⁹⁸. For example, when 2,6-dimethyl-3-hydroxymethylpyridine (22) is treated with thionyl chloride⁹², 3-chloromethyl-2,6-dimethylpyridine (23) is obtained in 84% yield [Equation 6]. 3-Chloromethyl-2,5-dimethyl- and 5-chloromethyl-2,4-dimethylpyridines are obtained from the corresponding alcohols⁹² in 90% and 78% yields respectively, under identical conditions.



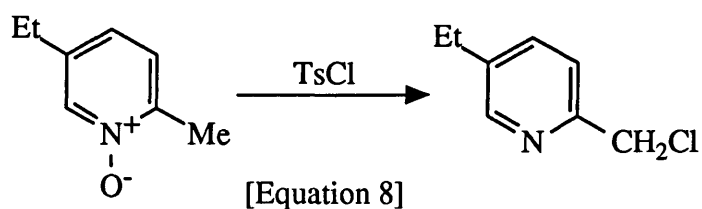
[Equation 6]

Highly substituted hydroxymethylpyridines have also been converted into their corresponding chloromethyl derivatives by, for example, phosphorus pentachloride⁹⁶ [Equation 7].

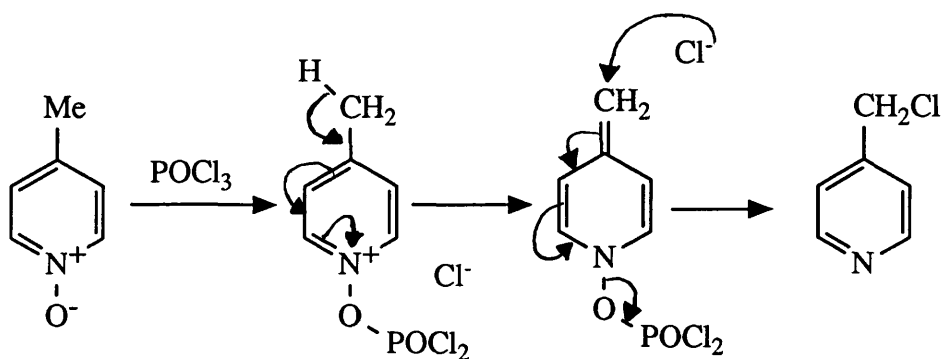


Chloromethylpyridines have also been prepared from methylpyridine N-oxides.

The reaction of methylpyridine N-oxides and tosyl chloride⁹⁹⁻¹⁰¹ affords the tosylate complex with the N-oxide which in turn leads to nucleophilic attack by the chloride anion. For example, 5-ethyl-2-methylpyridine N-oxide reacts with tosyl chloride to give 2-chloromethyl-5-ethylpyridine in 70% yield [Equation 8].



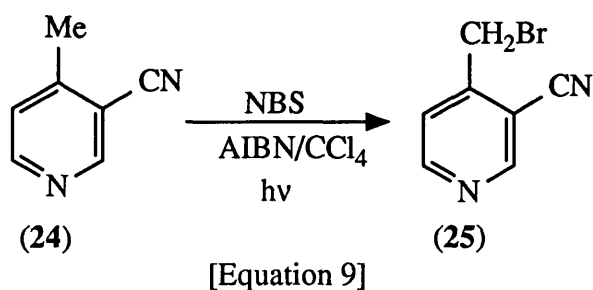
The reaction of methylpyridine N-oxides and reactive halides such as phosphoryl chloride also give chloromethyl derivatives. The proposed mechanism for this reaction¹⁰² is shown in Scheme 20.



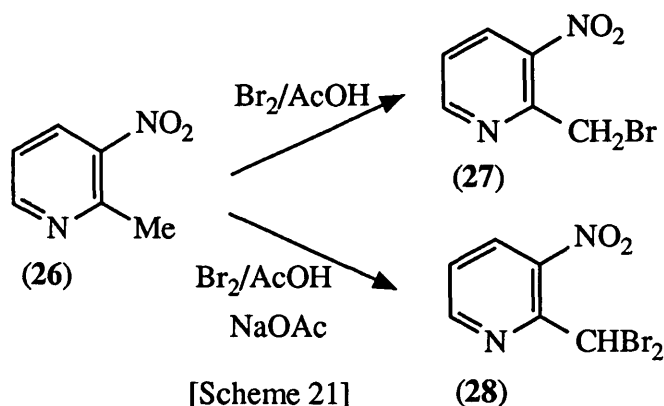
[Scheme 20]

1.1.5.2 The Synthesis of Bromomethylpyridines

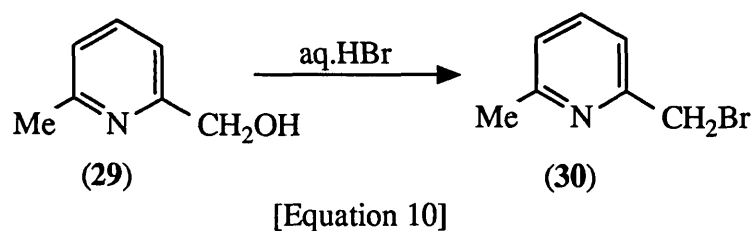
Picolines may be brominated to afford the bromomethyl derivatives by the use of N-bromosuccinimide^{103,104} and/or bromine in acetic acid¹⁰⁵. Kutney and co-workers¹⁰⁶, observed the following order of reactivity rates for the isomeric picolines towards N-bromosuccinimide/benzoyl peroxide: 4 > 2 >> 3. The 4-isomer gives only the 4-tribromomethylpyridine, the 2-isomer gives a mixture of the mono- and dibromomethylpyridines while the 3-isomer is not brominated. Substituted picolines have also been brominated in this manner as in the preparation of 4-bromomethyl-3-cyanopyridine (**25**) from the reaction of 3-cyano-4-methylpyridine (**24**) and N-bromosuccinimide¹⁰⁴ in the presence of AIBN, under irradiation [Equation 9].



Methylpyridines are also brominated with bromine in acetic acid. Thus, the treatment of 2-methyl-3-nitropyridine (**26**) with bromine in acetic acid¹⁰⁵ produces the bromomethyl derivative (**27**) in 31% yield but when the same reaction is carried out with sodium acetate present, the dibromomethyl derivative (**28**) is isolated in 39% yield [Scheme 21].

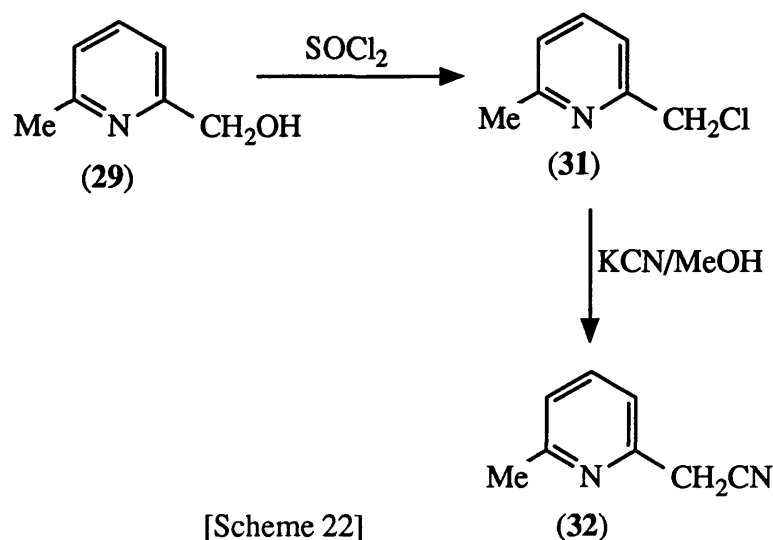


Hydrogen bromide has been used to brominate alcohols^{92,107,108} and also to cleave esters^{109,110} and ethers¹⁰⁷ to give bromomethylpyridines. When 2-methyl-6-hydroxymethylpyridine (29) was treated with aqueous hydrogen bromide¹⁰⁸, 2-bromomethyl-6-methylpyridine (30) was produced in 60% yield [Equation 10].

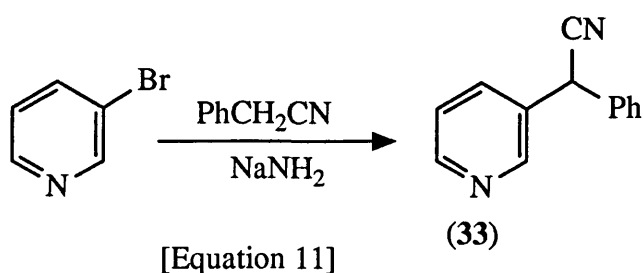


1.1.5.3 The Synthesis of Cyanomethylpyridines

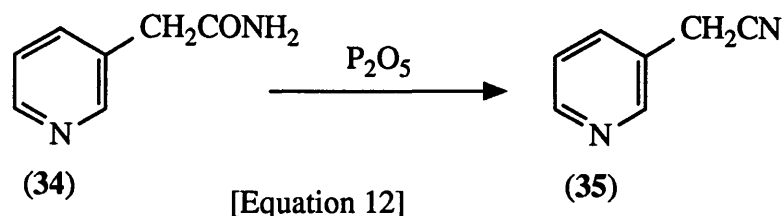
Cyanomethylpyridines are invariably made by the reaction of halogenomethylpyridines with either sodium cyanide or potassium cyanide. There is a large amount of literature^{89,93,95,108,111} which discusses the cyanation of halogenomethyl groups by this method and one example of this type of reaction is the reaction of 2-chloromethyl-6-methylpyridine (31), prepared from the reaction of thionyl chloride and the alcohol (29), with potassium cyanide in methanol to afford 2-cyanomethyl-6-methylpyridine (32) [Scheme 22].



It is possible to prepare cyanomethylpyridines using other methods such as the introduction of a complete side chain in the presence of a base catalyst. For example, the reaction of 3-bromopyridine and benzyl cyanide in the presence of sodium amide⁹⁵ afforded 3-pyridyl-1-phenylacetonitrile (33) [Equation 11]. The chlorine atom in methyl 2-chloropyridine-3-carboxylate has also been displaced by benzyl cyanide in the presence of sodium amide to afford the corresponding nitrile¹¹².



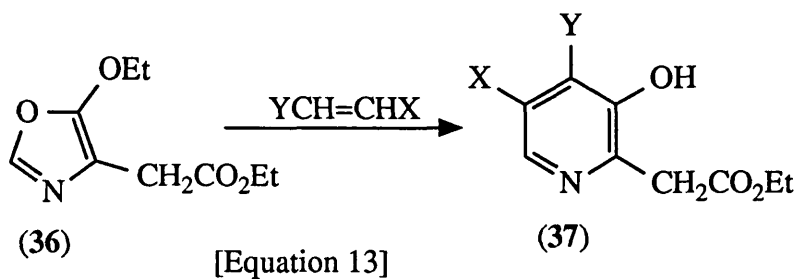
Side chain nitriles are also obtained by the dehydration of the corresponding amides¹¹³. Thus, the amide (34) affords 3-cyanomethylpyridine (35) in 42% yield when treated with phosphorus pentoxide [Equation 12].



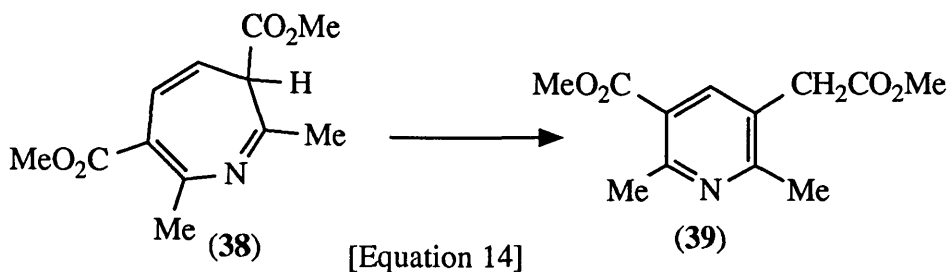
1.1.5.4 The Synthesis of Pyridine Acetic Esters

a) From Non-Pyridines

Pyridine acetic esters have been prepared from non-pyridines as well as pyridines. Several esters, such as (37), have been synthesised¹¹⁴ from the Diels-Alder cycloaddition type reaction between the oxazole (36) and activated olefins [Equation 13].

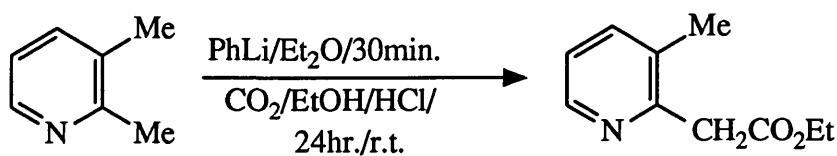


When appropriate conditions are employed, the 3H-azepine (38) is converted to the pyridine ester (39) in good yield¹¹⁵ [Equation 14].



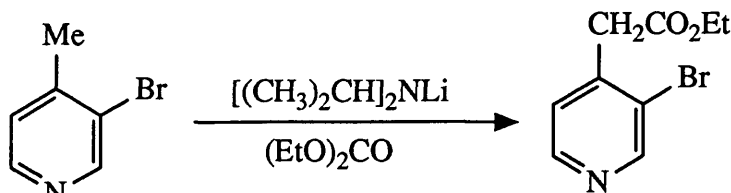
b) Carboxylation of Organometallic Compounds

The carboxylation of side-chain metallated picolines and lutidines has been investigated^{116,117}. It has been reported that 2-methylpyridine is carboxylated at the 2-position^{116,118} while 2,3-, 2,4-, 2,5- and 2,6-lutidines are also carboxylated at the 2-position¹¹⁷. For example, when 2,3-dimethylpyridine is reacted with phenyllithium, followed by carboxylation¹¹⁷, ethyl 3-methyl-2-pyridylacetate is obtained in 34% yield [Equation 15].



[Equation 15]

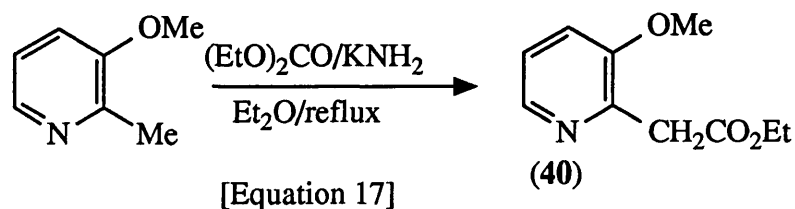
The conversion of methyl groups in the 4-position of the pyridine ring into acetic esters has also been achieved¹¹⁹. For example, treatment of 3-bromo-4-methylpyridine with lithium diisopropylamide in THF, followed by the addition of diethyl carbonate produced ethyl 3-bromo-4-pyridylacetate in 82% yield [Equation 16].



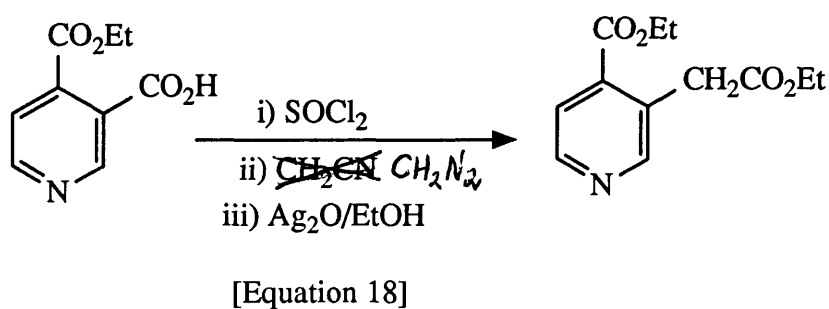
[Equation 16]

Other pyridine derivatives such as 4-methoxy-2-methylpyridine have also been used as precursors to pyridine acetic esters¹²⁰.

The condensation of picolines to give both side chain acids and esters has been reviewed⁶². The synthesis of pyridine acetic esters has been achieved, for example, from the condensation of 3-methoxy-2-methylpyridine with diethyl carbonate¹²¹ to afford ethyl 3-methoxy-2-pyridylacetate (**40**) [Equation 17].



Finally, pyridine acetic esters may be prepared from carboxylic acids¹²² by the treatment of the acid with thionyl chloride followed by diazomethane [Equation 18].

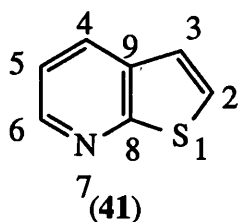


1.2 Thienopyridines

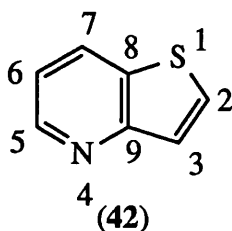
1.2.1 Introduction

Quinolines and isoquinolines are found widely in nature^{123,124}, however their isosteres, thienopyridines have only been isolated¹²⁵ from the base fraction of shale oil with a high sulfur content. Thienopyridines are bicyclic compounds which consist of a pyridine ring fused to a thiophene ring. There are six possible

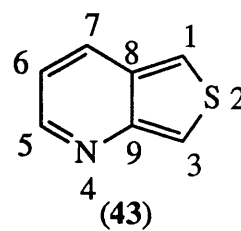
thienopyridine ring systems and these fall into two groups, the [b] fused systems (41-43) which are analogues of quinoline and the [c] fused systems (44-46) which are analogues of isoquinolines.



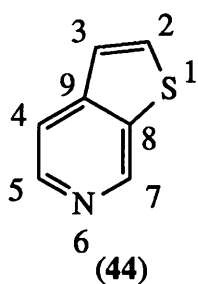
[2,3-b]



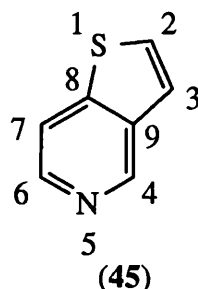
[3,2-b]



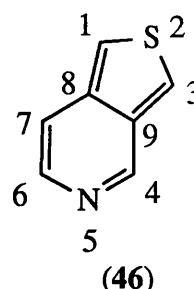
[3,4-b]



[2,3-c]

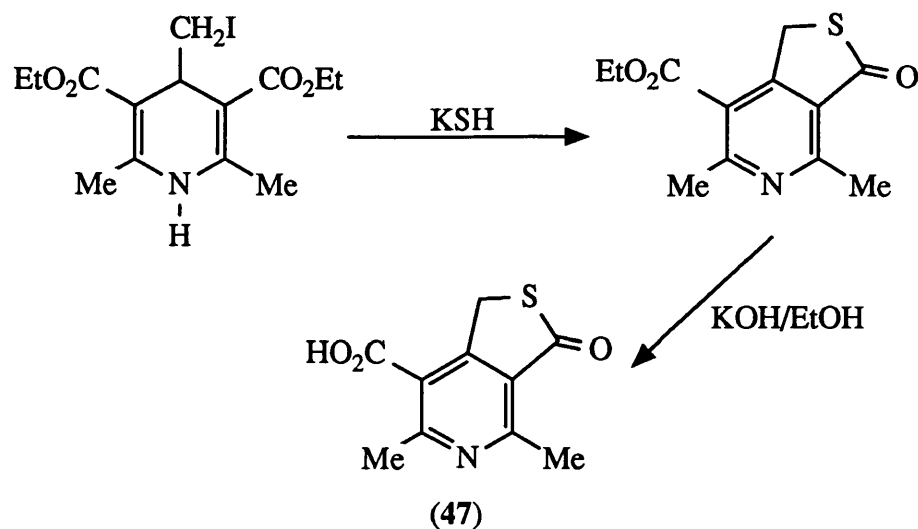


[3,2-c]



[3,4-c]

The earliest synthesis of a thienopyridine was reported in 1912 by Steinkopf^{126,127}, who applied a Skraup type synthesis to 2-aminothiophene to obtain a low yield of the thienopyridine (41). In 1918, Benary¹²⁸ prepared the thieno[3,4-c]pyridine (47) [Scheme 23] and this synthesis is of particular interest since it was the first thienopyridine preparation which used a substituted pyridine precursor.



[Scheme 23]

During the years that followed there were very few publications in this field and those that did appear were mostly concerned with approaches to thiophene analogues of indigo dyes¹²⁹⁻¹³².

From 1950 onwards there was increased interest in the area of thienopyridines which was probably due to two main reasons. Firstly, the theoretical interest in the behaviour of systems containing both a π -excessive (thiophene) and a π -deficient (pyridine) ring. Efforts have been made to calculate π -electron densities and to correlate them with experimental observations¹³³⁻¹³⁶. Calculations indicate that electrophilic substitution should occur in the thiophene ring β to the sulfur atom when that position is free while nucleophilic attack is expected in the pyridine ring with a slight preference for the γ carbon over that α to the nitrogen atom where such a choice exists. Secondly, the search for new pharmacologically active substances has led to the synthesis of analogues of various important quinolines and isoquinolines. Thus the benzene ring has been replaced with a thiophene nucleus, resulting in a thienopyridine.

Thienopyridine chemistry has previously been reviewed, both as an overview¹³⁹ and in a more detailed manner^{140,141}. The latter article¹⁴¹ presents a correlation of the chemistry of thieno[2,3-b]- and [3,2-b]pyridines with those of benzo[b]thiophene and quinoline. The early reviews^{139,140} cover the literature up to the end of June 1975 while the other¹⁴¹ discusses work carried out up to 1981. Since these reviews considerable advances in thienopyridine synthesis and reactions have been reported and it is relevant to review these along with salient points from earlier publications in this introduction.

Synthetic approaches to thienopyridines will be considered under two headings:

- a) Synthesis from a preformed thiophene in which the pyridine ring is constructed (Section 1.2.2).
- b) Construction of a thiophene ring from a preformed pyridine derivative (Section 1.2.3).

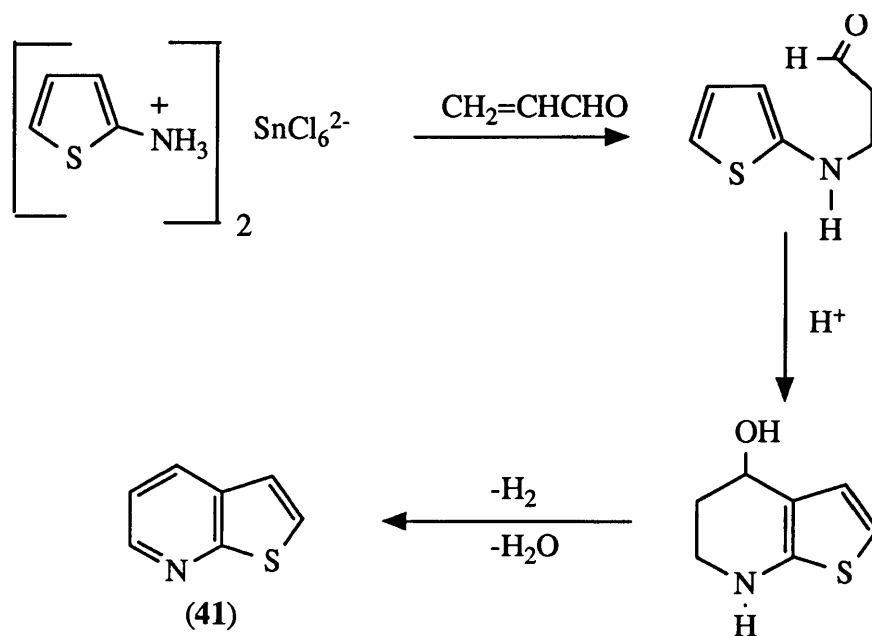
1.2.2. Synthesis of Thienopyridines from Thiophene Precursors

Many of the syntheses reported in the past, involving the formation of the pyridine ring have been adaptations of classical quinoline and isoquinoline syntheses^{123,124}. Such reactions include the Skraup reaction, the Bischler-Napieralski synthesis, the Pictet-Spengler synthesis and a number of other reaction types.

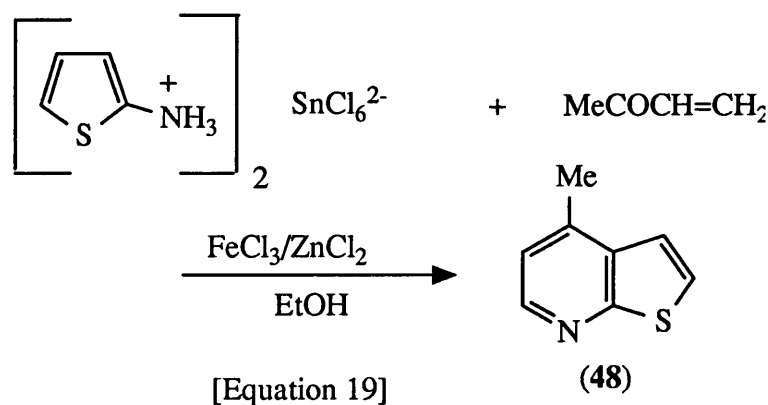
1.2.2.1 The Skraup Type Synthesis of Thienopyridines

The Skraup synthesis of quinolines involves heating an aniline with glycerol and sulfuric acid; the latter acts as a dehydrating agent and an acid catalyst. The details of the reaction sequence have not all been established but it seems most likely that glycerol is dehydrated to acrolein which then reacts with the aniline by conjugate addition. This intermediate is then cyclised, oxidised and dehydrated to give the quinoline^{123,124}.

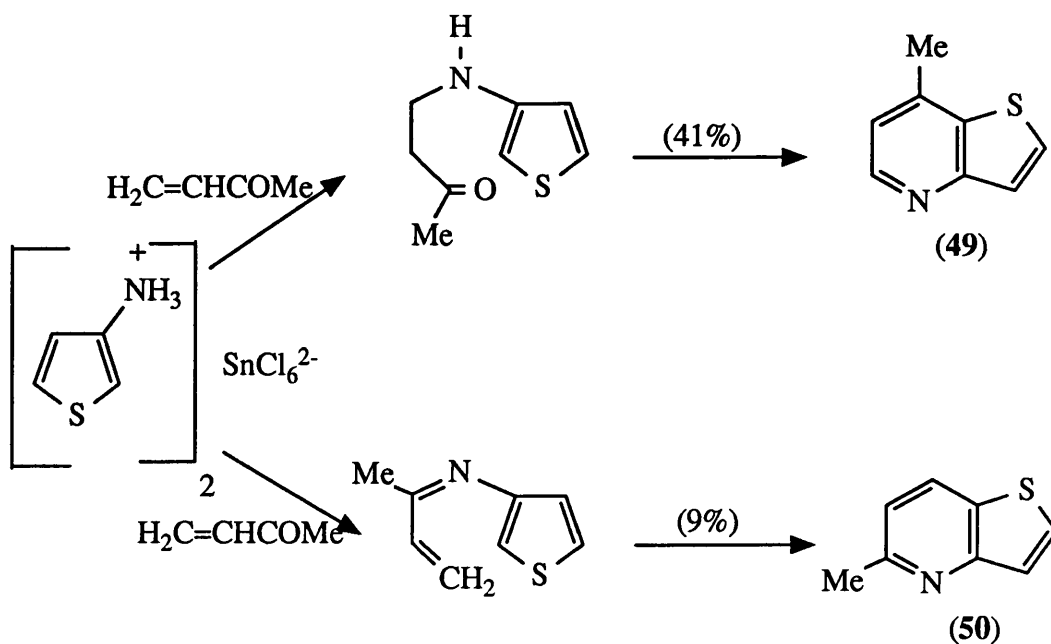
In the synthesis of thieno[2,3-b]pyridine (**41**), Steinkopf^{126,127} did not use free 2-aminothiophene due to its instability. Instead, the tin double salt $(C_4H_3S-N^+H_3)_2SnCl_6^{2-}$ obtained directly by reduction of 2-nitrothiophene was utilised [Scheme 24].



In the Doebner-Von Miller variation of the Skraup synthesis, α,β -unsaturated aldehydes or ketones are used in place of glycerol. This variation has also been utilised in thienopyridine chemistry¹⁴² wherein 2-aminothiophene double salt reacts under Friedel-Crafts catalysis with methyl vinyl ketone to give 4-methylthieno[2,3-b]pyridine (**48**) [Equation 19]. Klemm¹³³, later showed that a smaller quantity of the 6-methyl isomer was also produced in this reaction.

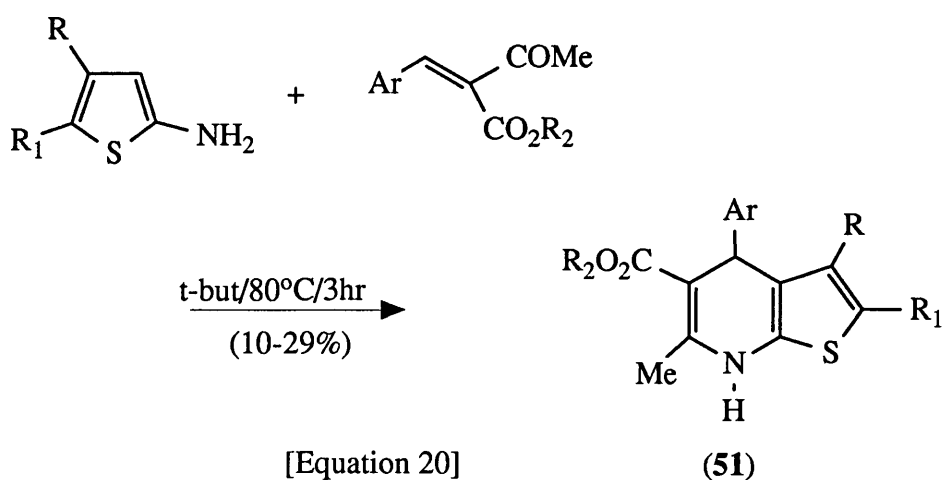


When 3-aminothiophene double salt was reacted with methyl vinyl ketone¹⁴² a mixture of products was also obtained. The major product, 7-methylthieno[3,2-b]pyridine (**49**) was obtained by a Michael addition while a Schiff base intermediate gave the minor product, 5-methylthieno[3,2-b]pyridine (**50**) [Scheme 25]. There appears to be some discrepancy in the literature about the structure of (**50**). The initial publication¹⁴² indicated a [3,4-b] system while the review by Barker¹⁴⁰ suggests the [3,2-b] system.



[Scheme 25]

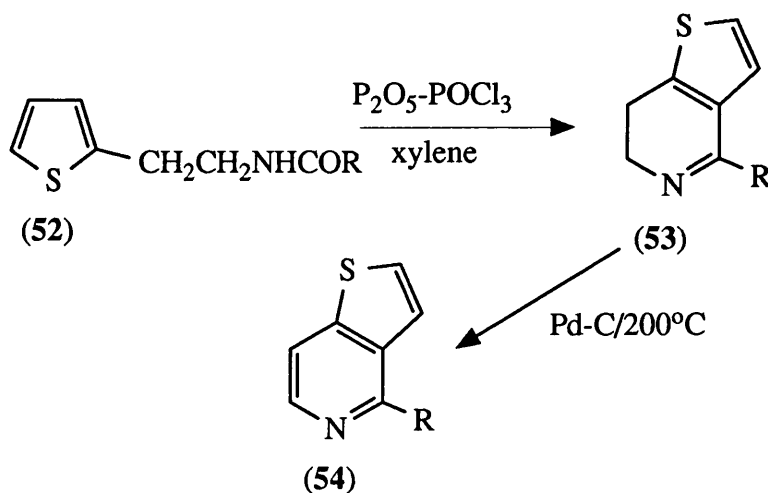
A series of alkyl 4-aryl-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylates (**51**) have been synthesised¹⁴³ from the Michael addition of 2-aminothiophenes to α,β -unsaturated ketones followed by cyclocondensation [Equation 20]. A range of side products (thiophene derivatives) were also obtained from these reactions in small yields.



1.2.2.2 Bischler-Napieralski Synthesis of Thienopyridines

In the Bischler-Napieralski reaction β -phenylethylamines or similar compounds are acylated and then cyclodehydrated by reaction with phosphoryl chloride, phosphorus pentoxide or other Lewis acids. This gives a 1-substituted-3,4-dihydroisoquinoline which is dehydrogenated by heating with palladium.

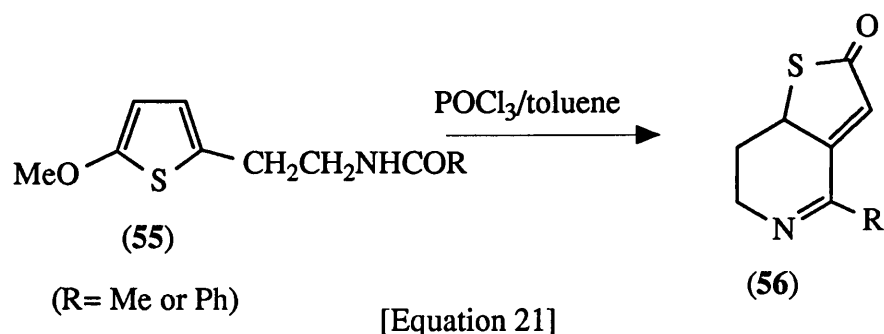
In 1938 Barger and Easson¹⁴⁴ made the first reported attempt to prepare a thieno[3,2-c]pyridine by ring closure of N-formyl-2-(2'-thienyl)ethylamine (**52**, R=H) but found that both phosphorus pentachloride and pentoxide failed to produce the desired compound. Later, Herz¹⁴⁵ showed that the corresponding acetyl- and benzoylamines (**52**) were cyclised in reasonable yields by treatment with a mixture of phosphorus pentoxide and phosphoryl chloride in xylene. The resulting 4-substituted-6,7-dihydrothieno[3,2-c]pyridines (**53**) were dehydrogenated to the fully aromatic systems (**54**) [Scheme 26].



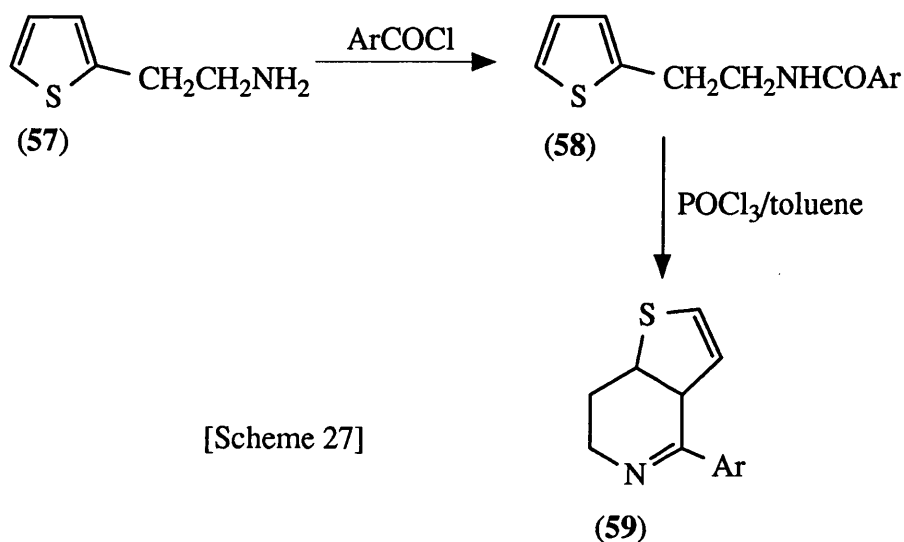
[Scheme 26]

Similar treatment of N-acyl-2-(3-thienyl)ethylamines gave the corresponding dihydrothieno[2,3-c]pyridines¹⁴⁴ which were not dehydrogenated to the fully

aromatic compounds. Herz¹⁴⁶ also applied the reaction to the 2-(5'-methoxy-2'-thienyl)ethylamides (**55**) but found that the conditions required to bring about ring closure also caused demethylation of the rather labile methoxy group to give the product (**56**) [Equation 21].

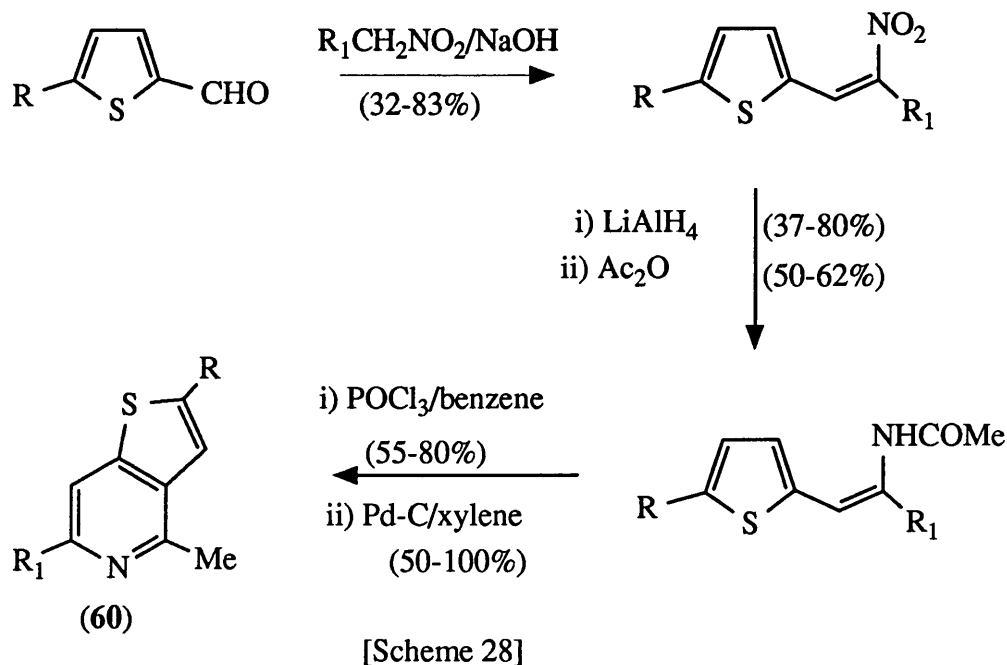


Kametani¹⁴⁷ has reported the synthesis of several kinds of 1-aryl-3,4-dihydrothieno[3,2-c]pyridines by the condensation of a β-2-thienylethylamine (**57**) with acid chlorides followed by cyclisation of the resulting amides (**58**) to 4-aryl-6,7-dihydrothieno[3,2-c]pyridines (**59**) [Scheme 27].

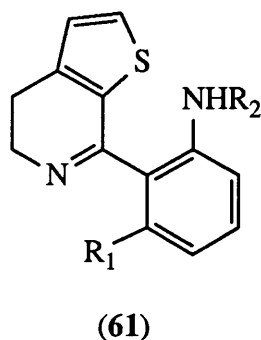


The same reagent was also used¹⁴⁸ to cyclise amides of the type (**58**) where Ar = Ph, 4-MeOC₆H₄, 3,4,5-trimethoxyphenyl. The yields were high (72-86%) and the

resulting dihydro compounds were successfully dehydrogenated to the corresponding fully aromatic thienopyridines (65-70%). More highly substituted thieno[2,3-c]pyridines (**60**) have also been synthesised¹³⁶ using the Bischler-Napieralski synthesis as shown in Scheme 28.

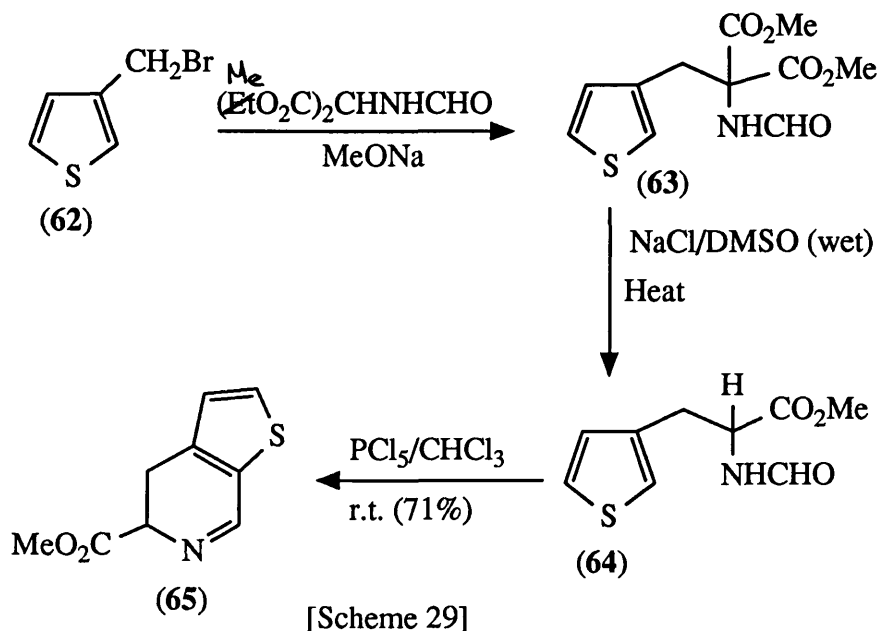


A series of patents¹⁴⁹⁻¹⁵³ has described the synthesis of both the [2,3-c] and [3,2-c] isomers of (**61**) using the Bischler-Napieralski synthesis.

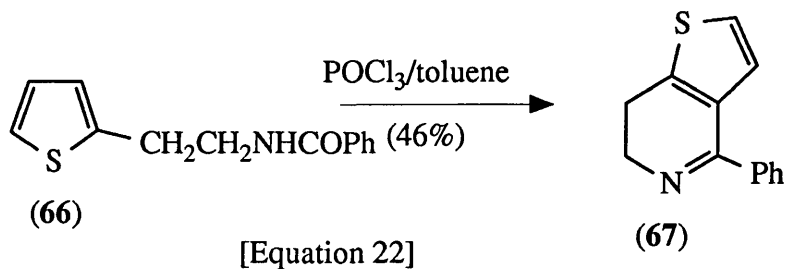


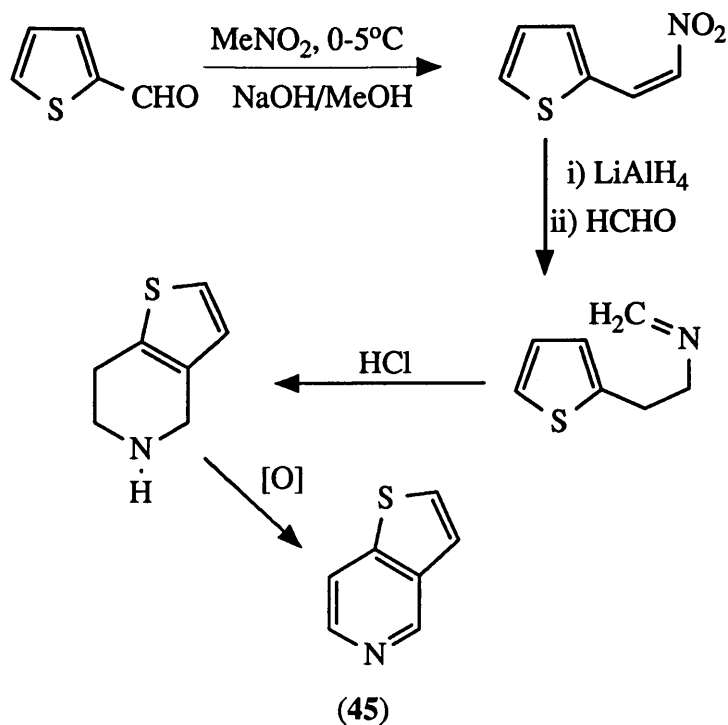
Kametani¹⁵⁴ prepared 4,5-dihydro-5-methoxythieno[2,3-c]pyridine (**65**), an intermediate to novel tricyclic β -lactams, by condensation of

3-bromomethylthiophene (**62**) with diethyl formamidomalonate, followed by demethoxycarbonylation of the resulting dimethyl ester (**63**) to afford the ester (**64**). Bischler-Napieralski reaction of (**64**) gave 5-carbomethoxy-4,5-dihydrothieno[2,3-*c*]pyridine (**65**) in 71% yield [Scheme 29]. The imine group in the dihydropyridine ring was reacted with a ketene to yield β -lactam compounds.



Bremner¹⁵⁵ has also reported the synthesis of dihydrothienopyridines. In this case, 4-phenyl-6,7-dihydrothieno[3,2-*c*]pyridine (**67**) was prepared from the benzoyl derivative of 2-(2'-thienyl)ethylamine (**66**) by Bischler-Napieralski cyclisation [Equation 22].

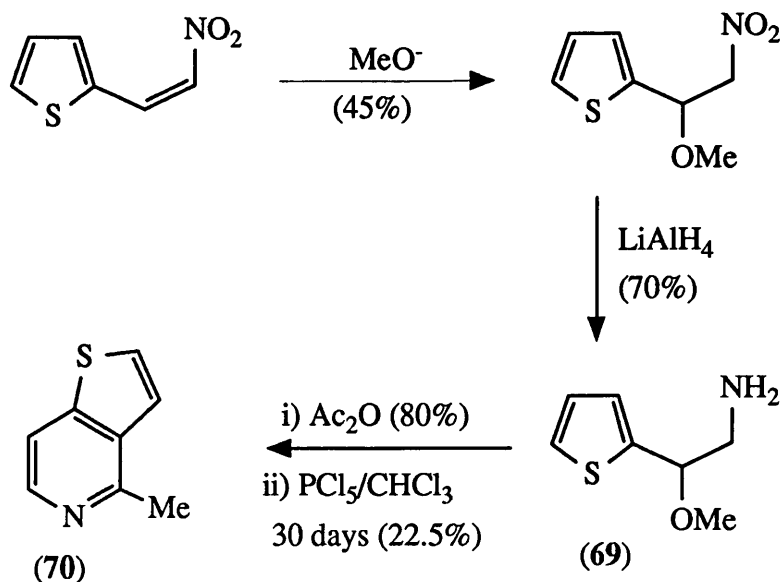




[Scheme 31]

The application of this reaction sequence to 4-bromo- and 5-chlorothiophene-2-aldehyde and to 4-bromothiophene-3-aldehydes yielded the appropriate halothienopyridines. In the case of 5-bromothiophene-2-aldehyde however, reductive debromination occurred during the reduction of the thienylnitroethylene.

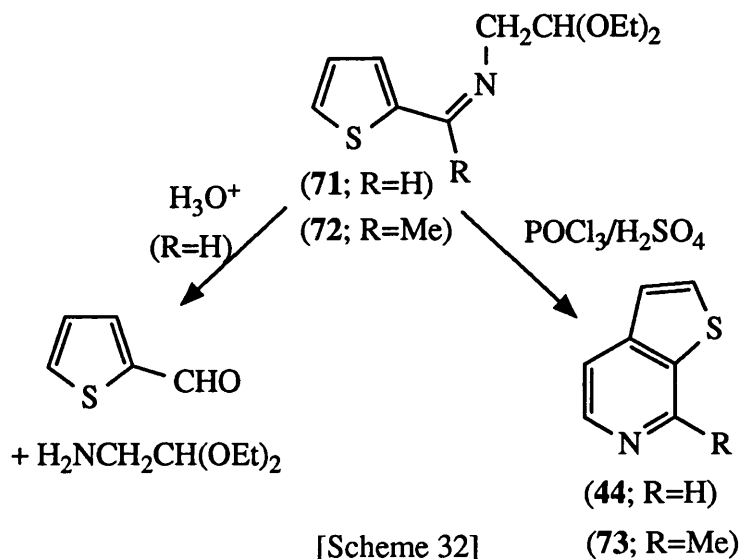
The Pictet-Gams synthesis is another modification of the Bischler-Napieralski reaction which avoids the dehydrogenation step by the construction of a β -phenylethylamine type compound with a hydroxyl group in the side chain. The Pictet-Gams synthesis was used¹⁴⁶ in the preparation of 4-methylthieno[3,2-c]-pyridine (**70**) [Scheme 32]. The β -thienylamine (**69**) with a methoxy group in the side chain was constructed and then cyclised after forming the amide.



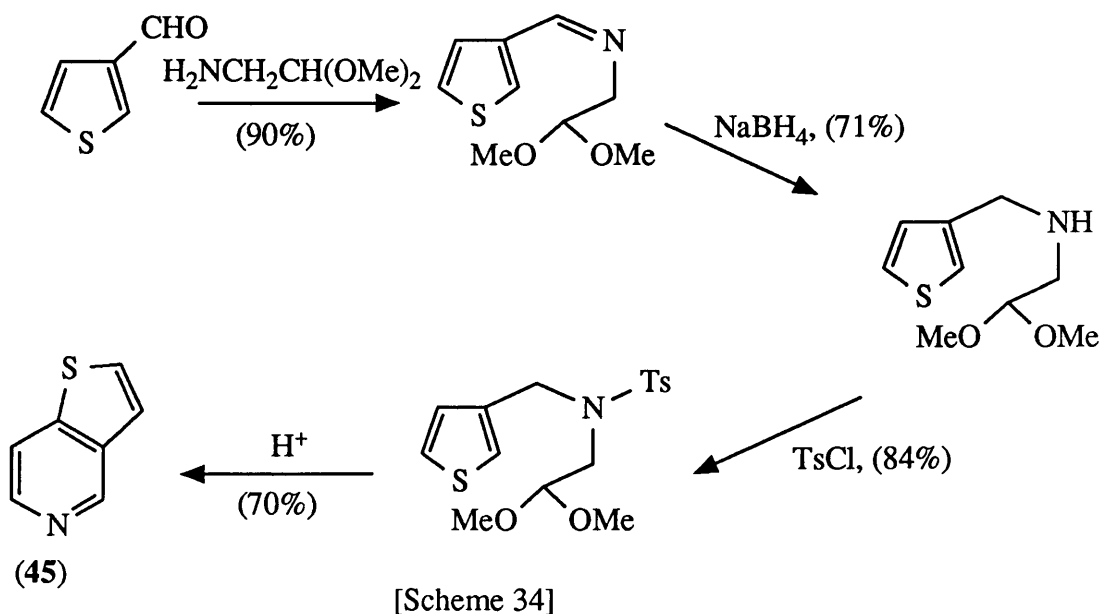
[Scheme 32]

1.2.2.4 The Pomeranz-Fritsch Synthesis

This synthesis involves the acid-induced cyclisation of a Schiff base derived from an aryl aldehyde or ketone and aminoacetaldehyde diethyl acetate. This method has not been extensively used in the thienopyridine field but Herz and Tsai¹⁵⁹ applied the reaction to the Schiff base (71) to give very low yields of thienopyridine (44) [Scheme 33]. Hydrolysis of the imino function (71) and subsequent polymerisation of the hydrolysis products competes with the desired reaction and therefore accounts for the low yields of (44). Schiff bases from thienyl ketones appear to be less susceptible to hydrolysis since the ketimine (72) gave 7-methylthieno[2,3-c]pyridine (73) in 60% yield¹³⁶.

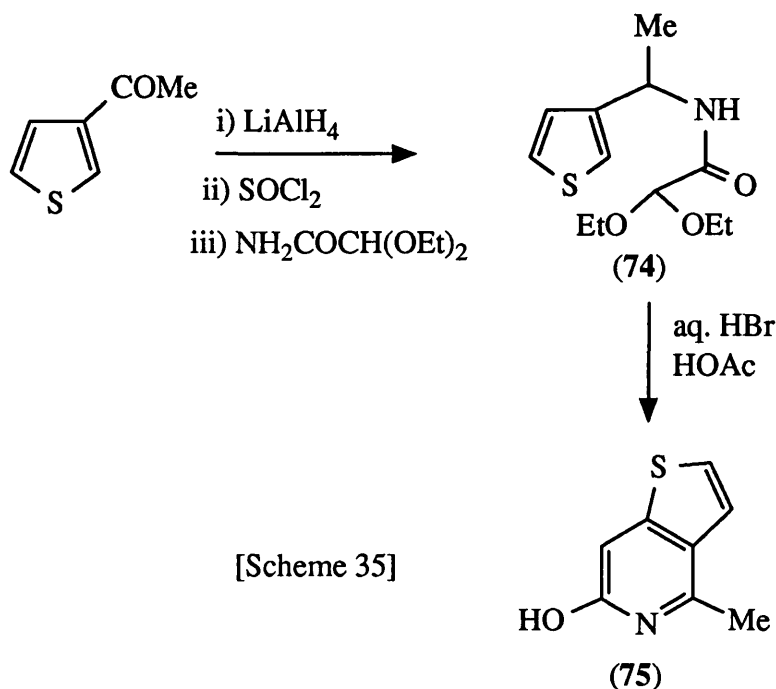


Thieno[2,3-c]pyridine (44) and thieno[3,2-c]pyridine (45) and their tetrahydro derivatives were prepared¹⁶⁰ by a process based on some modifications of the Pomeranz-Fritsch reaction [Scheme 34].



A Pomeranz-Fritsch type synthesis was used to prepare¹⁶¹ 4-methylthieno[3,2-c]-pyridin-6-ol (75) from the cyclisation of N-[1-(3'-thienyl)-1-ethyl]diethoxyacetamide (74) [Scheme 35]. The authors found difficulties in the cyclisation of

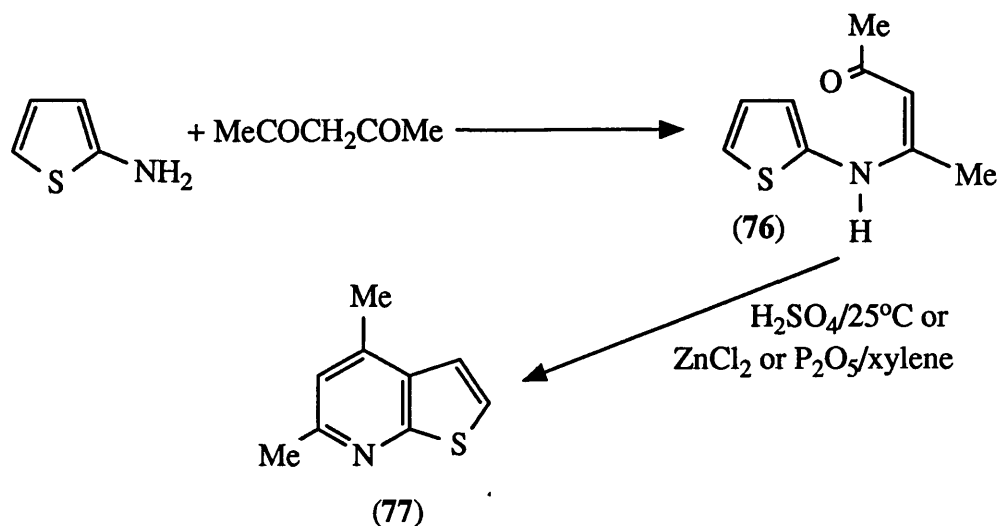
(74) to the thienopyridinol (75) but when (74) was treated with 48% aqueous hydrobromic acid in acetic acid in an attempt to prepare the aldehyde, the hydrobromic acid salt of (75) precipitated directly in 70% yield. Presumably the aldehyde was formed and cyclised immediately.



1.2.2.5 Combes Synthesis

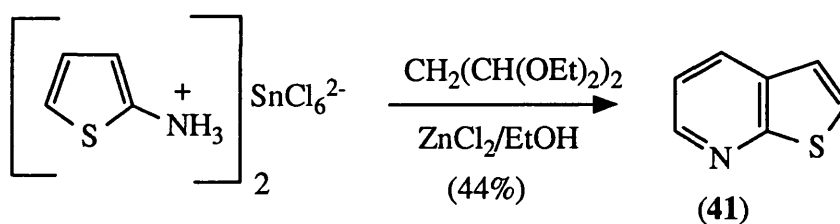
In the Combes synthesis of quinolines, aniline is reacted with a 1,3-diketone in the presence of an acid. After formation of the Schiff base, cyclisation probably takes place by way of the diprotonated form and the intermediate is then dehydrated.

The first application of this approach to the thienopyridine system was reported by Klemm¹⁶² who cyclised the Schiff base (76) to obtain 4,6-dimethylthieno[2,3-b]-pyridine (77) in 80% yield [Scheme 36].



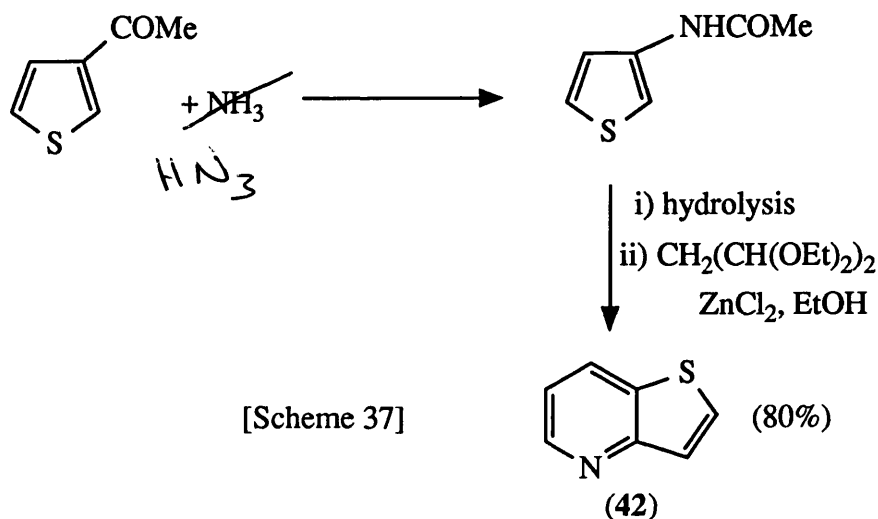
[Scheme 36]

Abramenko¹⁶³ also reported the above reaction and in addition, prepared the corresponding dimethylthieno[3,2-b]pyridine from the same dione and 3-aminothiophene double salt using zinc chloride in ethanol¹⁶⁴. The acetals and ketals of 1,3-dicarbonyl compounds are also effective in this synthesis. Thus, thienopyridines have been prepared¹³³ from the condensation/cyclisation of 2- and 3-aminothiophene double salts with malonaldehyde bis(diethyl acetal) [Equation 23].



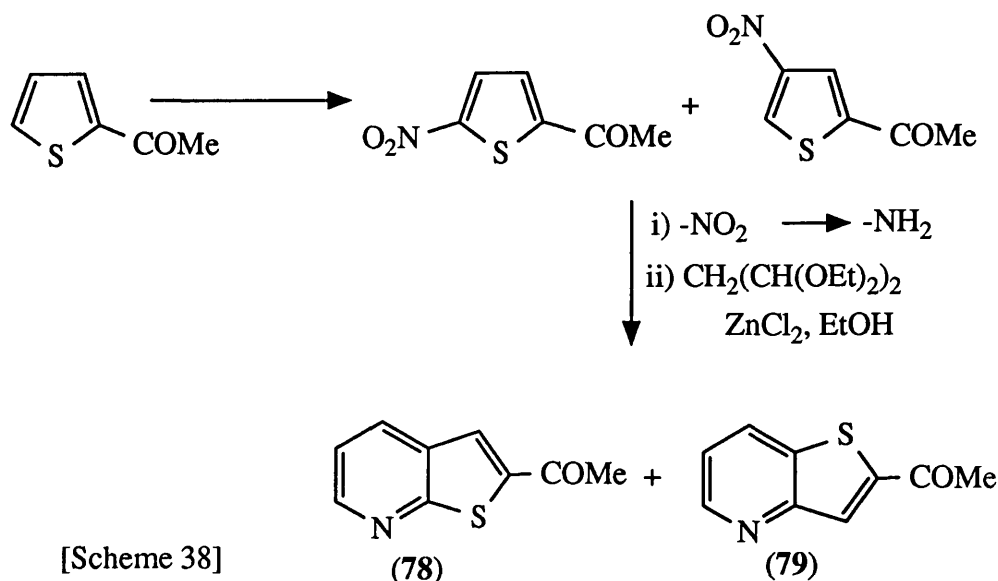
[Equation 23]

The inaccessibility of 3-aminothiophene has been a considerable practical problem but an alternative synthesis^{165,166} of thieno[3,2-b]pyridine (42) from 3-acetylthiophene *via* a Schmidt reaction [Scheme 37] has been reported.



A deactivating group on the thiophene ring does not prevent cyclisation¹³³.

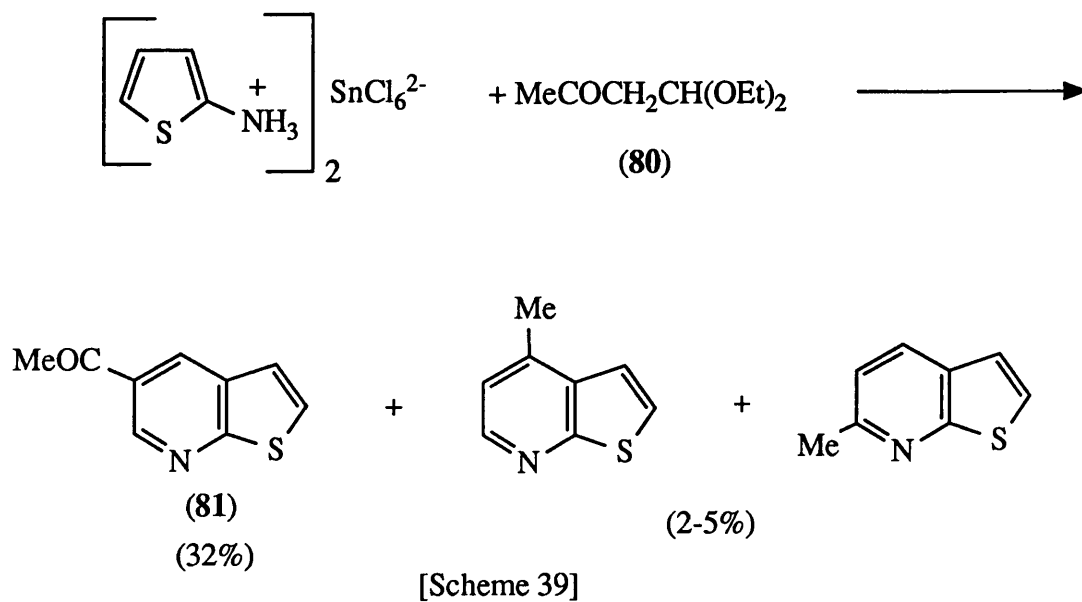
Nitration and then reduction of 2-acetylthiophene gives a mixture of amines which can be cyclised to give low yields of 2-acetylthieno[2,3-b]pyridine (78) and 2-acetylthieno[3,2-b]pyridine (79) [Scheme 38].



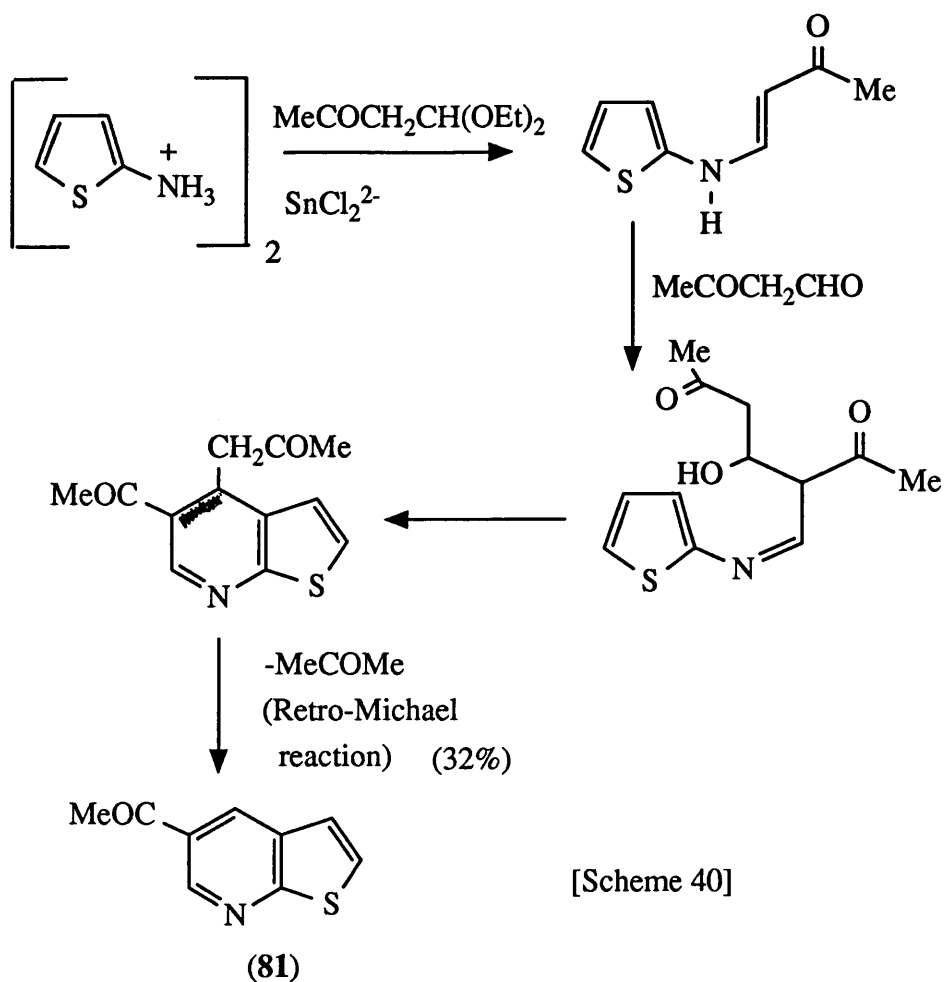
Zhiryakov and Abramenko¹⁶⁷ have claimed that the reaction of 2-aminothiophene double salt with the diethylacetal (80) leads to 6-methylthieno[2,3-b]pyridine.

However Klemm¹³³ reported that the diethylacetal (80) gave mainly

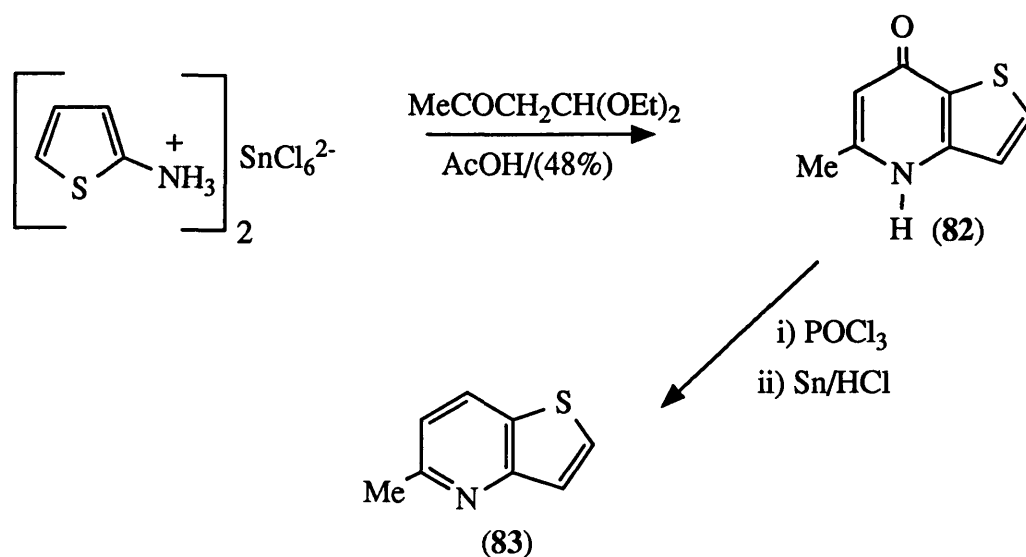
5-acetylthieno- [2,3-b]pyridine (**81**) with only minor amounts of the methylthienopyridines [Scheme 39].



The mechanism suggested by Klemm for the formation of (**81**) by this method is given in Scheme 40.



Ethyl acetoacetate also condenses with 3-aminothiophene double salts, in the presence of acetic acid to afford 5-methylthieno[3,2-b]pyridin-7(4H)-one (**82**) which was converted into 5-methylthieno[3,2-b]pyridine (**83**) by the usual method [Scheme 41]. The same compound was also obtained from the double salt and paraformaldehyde^{163,167}.

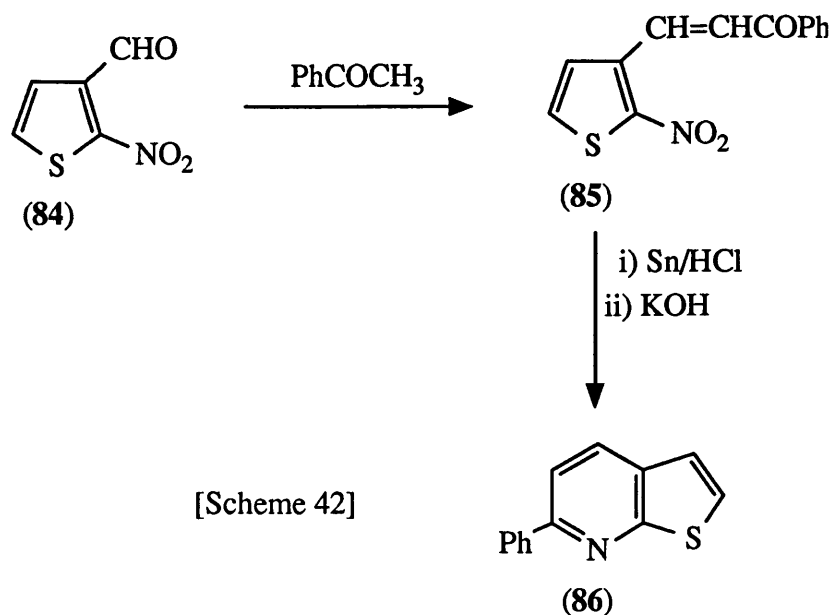


[Scheme 41]

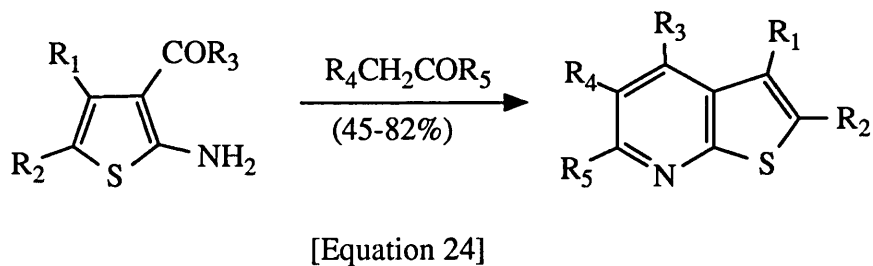
1.2.2.6 Friedländer Synthesis

The reaction of an *o*-aminobenzaldehyde or an *o*-aminoketone which is cyclised by reaction with an α -methylene ketone in the presence of a base is known as the Friedlander synthesis of quinolines. The principal difficulty lies in the preparation of the *o*-aminocarbonyl compounds but a modification of this synthesis uses an *o*-nitrocarbonyl compound which is reacted with the activated methylene species. Subsequent reduction of the nitro group then leads to the amino compound which can be cyclised.

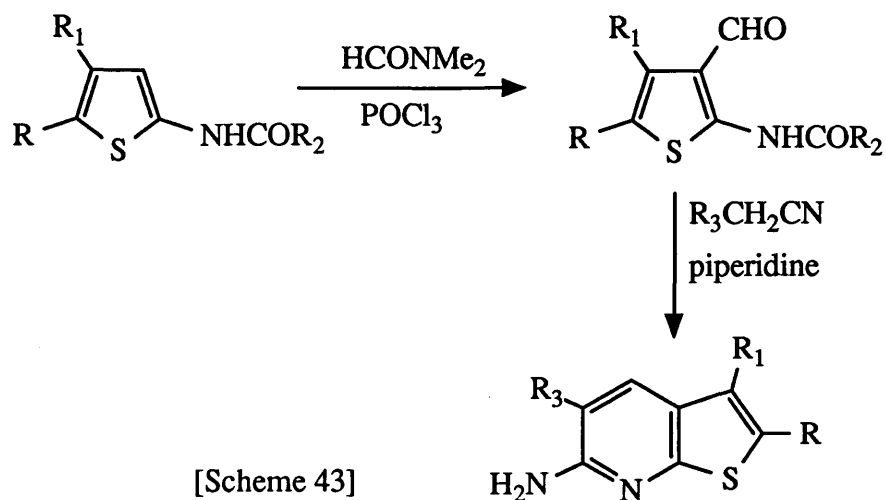
The first reported application of this synthesis in the thienopyridine area¹⁶⁸, gave 6-phenylthieno[2,3-*b*]pyridine (86) [Scheme 42]. The *o*-nitrocarbonylthiophene (84) was condensed with acetophenone and the resulting product (85) was reduced to the amine and then cyclised by base to the thienopyridine.



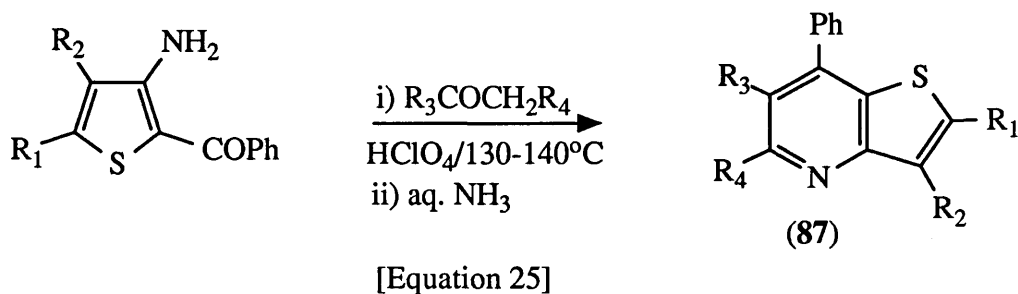
Corral and co-workers¹⁶⁹ have also used the Friedlander reaction to prepare a series of thieno[2,3-b]pyridines [Equation 24].



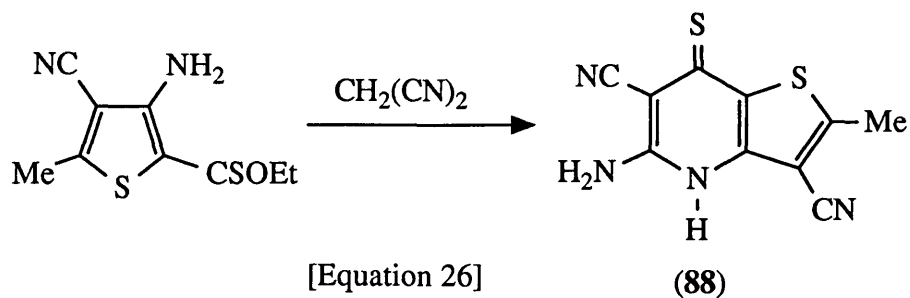
Similar reactions have been carried out by others^{170,171} who utilised Vilsmeier reactions on various 4,5-disubstituted 2-acylthienylamines and then condensed and cyclised the resulting 3-formyl derivatives with a variety of compounds containing active methylene groups [Scheme 43].



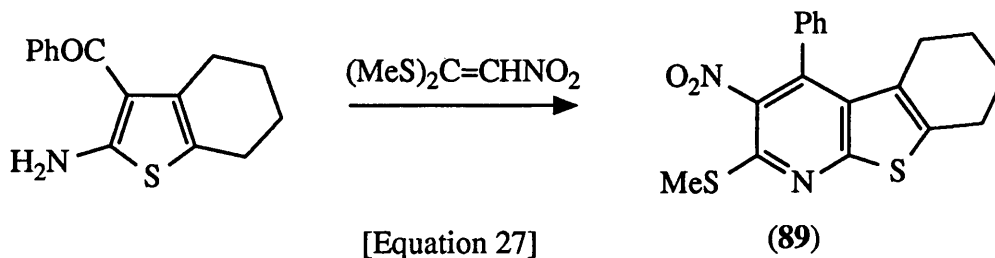
Schaefer¹⁷² has used perchloric acid to effect condensation of 3-amino-2-benzoylthiophenes with ketones to afford thieno[3,2-b]pyridines (**87**) [Equation 25].



A variation¹⁷³ in which the acyl function on the thiophene ring is replaced with a thioester group gives a thienopyridinethione (**88**) [Equation 26].

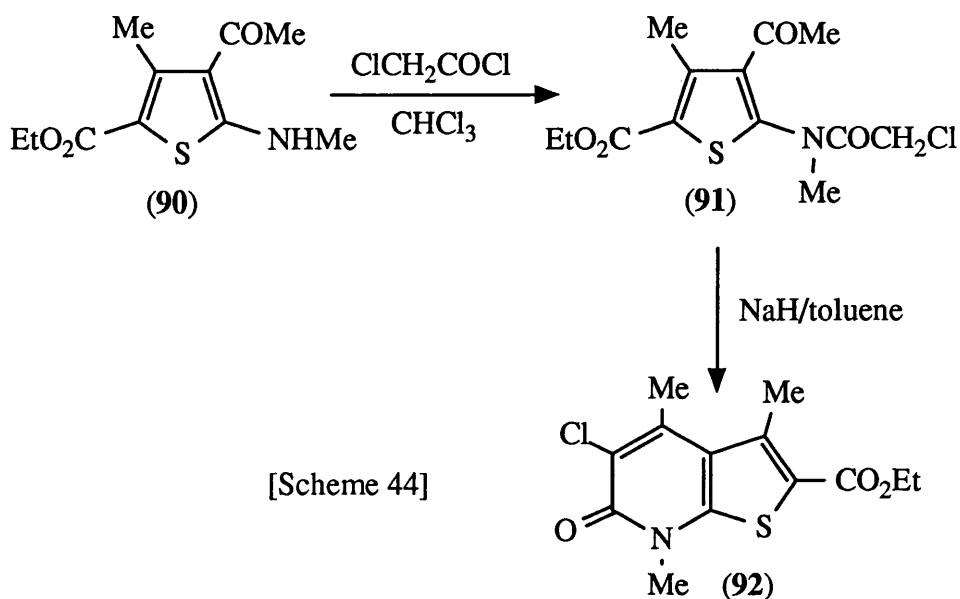


The tricycle (**89**) was prepared¹⁷⁴ from the reaction of 3-benzoyl-2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene and 1,1-dimethylthio-2-nitroethylene [Equation 27].



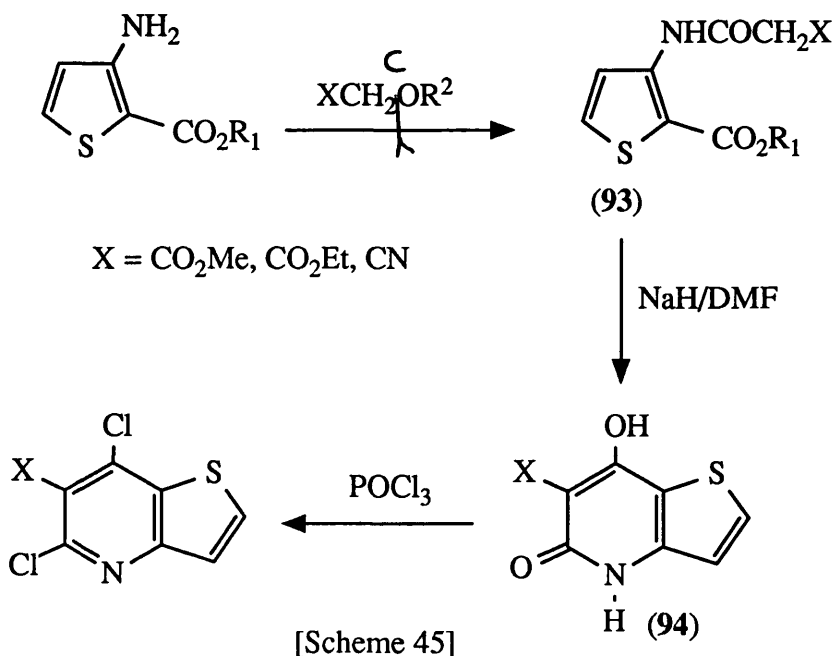
1.2.2.7 Base Catalysed Cyclisation of Amides

The thienopyridone (**92**) was prepared¹⁷⁵ from the aminothiophene-2-carboxylate derivative (**90**) *via* the chloroacetyl derivative (**91**) which was then cyclised to the thienopyridone (**92**) with base [Scheme 44].

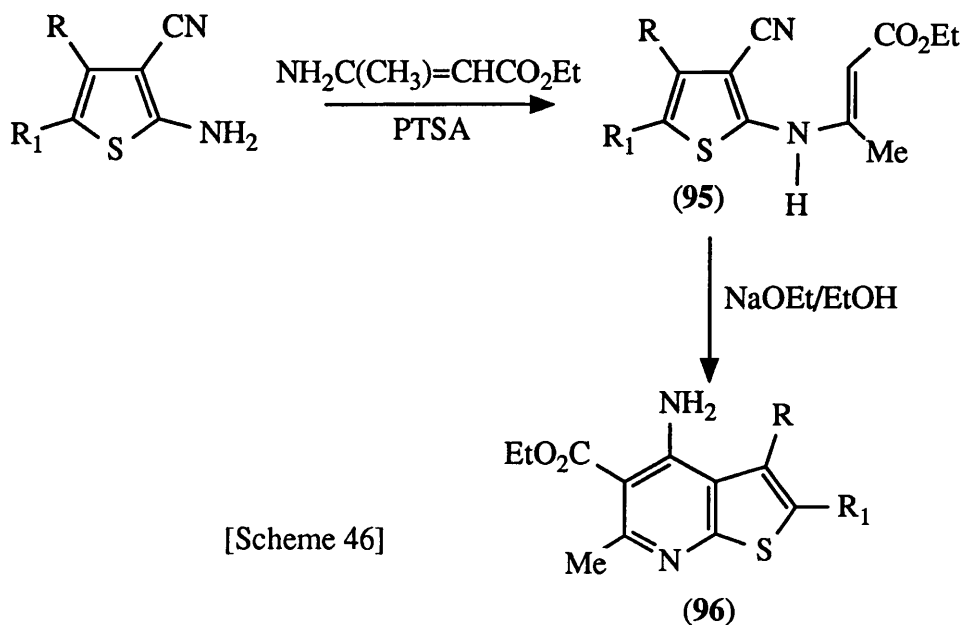


Base catalysed cyclisation of amides derived from anthranilic esters and β -oxo esters or diethyl malonate are established routes to quinolines^{176,177}. Barker^{178,179}

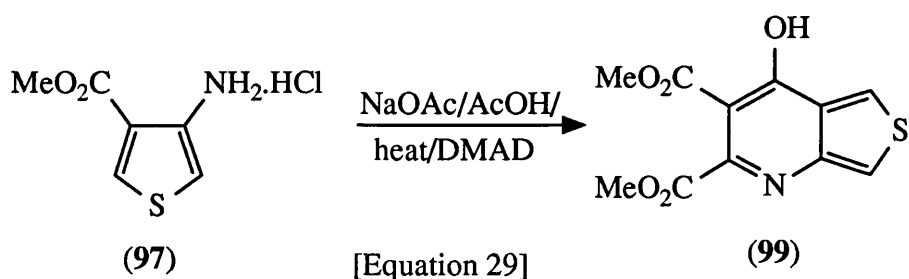
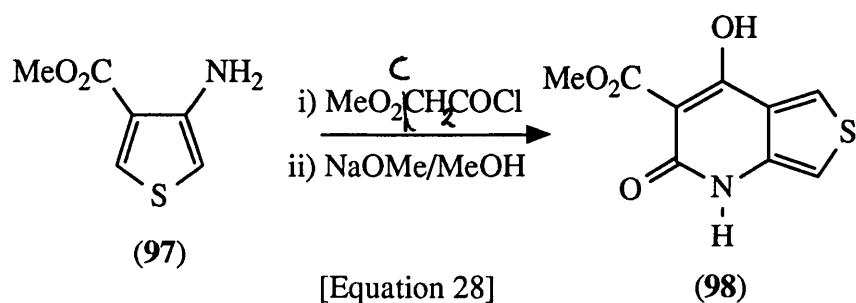
was first to adapt this synthesis to thienopyridine chemistry by preparing 6-substituted 7-hydroxythieno[3,2-b]pyridin-5(4H)-ones (**94**) in moderate yields (30-50%) from the amides (**93**) [Scheme 45]. These thienopyridones were then converted into their corresponding chlorothienopyridines with phosphoryl chloride.



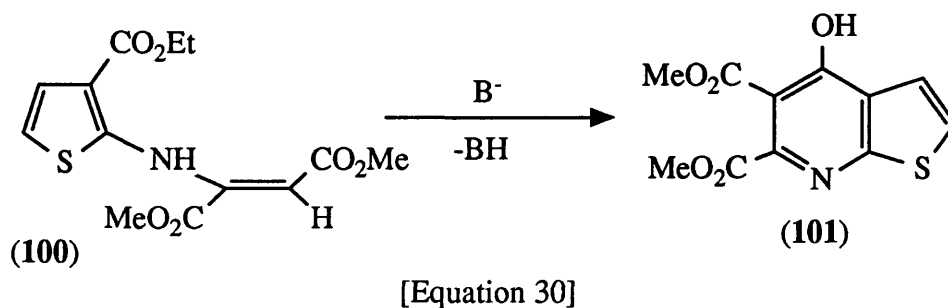
Lalezari¹⁸⁰ has reported the base catalysed cyclisation of the intermediates (**95**), obtained from the reactions of 3-cyano-2-aminothiophenes with ethyl aminocrotonate in the presence of catalytic amounts of *p*-toluene sulfonic acid in refluxing benzene. The cyclisation of (**95**) was completed with sodium ethoxide in refluxing ethanol to afford 2,3-substituted ethyl 4-aminothieno[2,3-b]pyridine-5-carboxylates (**96**) [Scheme 46].



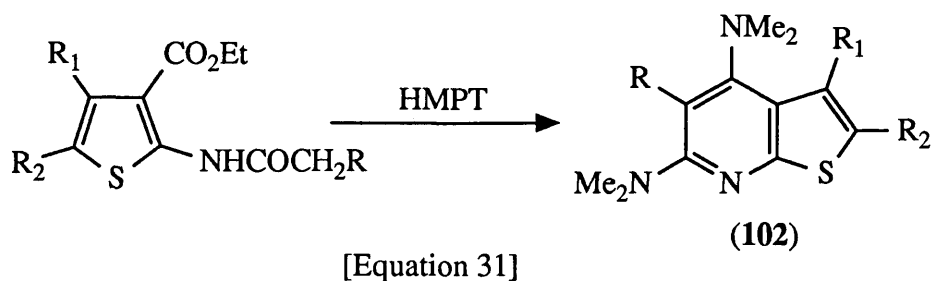
Base catalysed cyclisation has also been used¹⁸¹ to prepare thieno[3,4-b]pyridones (98) [Equation 28] which have then been converted to chlorothienopyridines with phosphoryl chloride. In the same paper, the synthesis of thieno[3,4-b]pyridine (99) was described from the reaction of the hydrochloride of the amine (97), sodium acetate and dimethyl acetylenedicarboxylate (DMAD) in boiling acetic acid [Equation 29].



Michael adduct (**100**), prepared from the corresponding aromatic *o*-amino esters and dialkyl acetylene dicarboxylates, undergoes base catalysed intramolecular cyclisation¹⁸² to afford thienopyridine (**101**) [Equation 30].

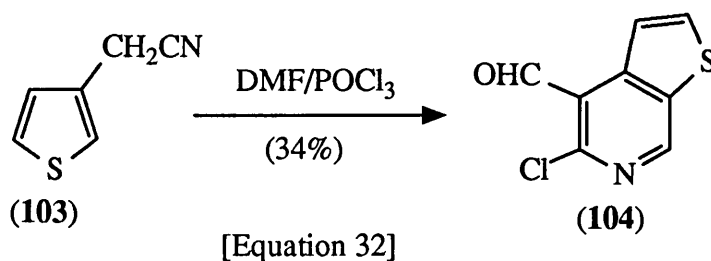


The synthesis of thienopyridines has also been carried out by a hexamethylphosphorous triamide (HMPT) induced ring closure reaction¹⁸³ under the same conditions used for the preparation of quinolines¹⁸⁴. Ethyl 2-acetamido-3-thiophenecarboxylates and HMPT were refluxed and the thieno[2,3-b]pyridine derivatives (**102**) were produced in 35-48% yields [Equation 31] when alkyl or phenyl groups were in the 2-position. It was observed that yields fell to less than 10% when substituted in the 3-position by methylene or methyl groups and that no thienopyridine was isolated when the 3-position was substituted by a phenyl group. This observation was explained by the authors as being due to steric hindrance.

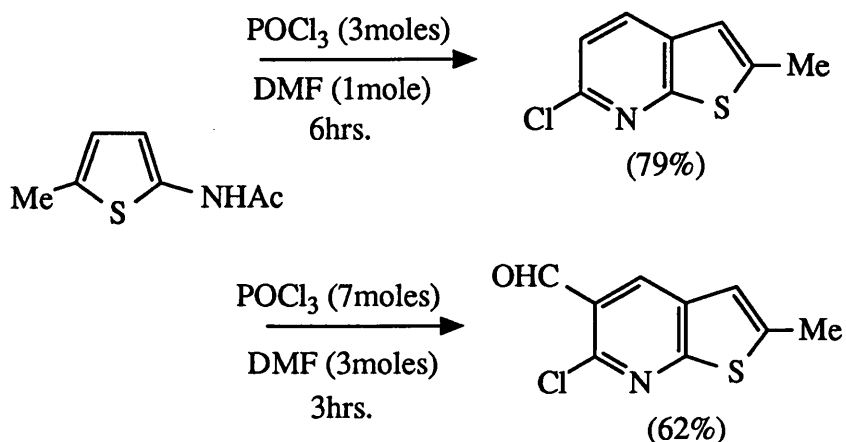


1.2.2.8 Miscellaneous Syntheses

The Vilsmeier-Haack reaction is a mild but effective method for the formylation of reactive aromatic substances. Occasionally unexpected cyclisations are noted accompanying or following such formylations. One example of this is the formation of isoquinolines in low yield, during attempts to formylate phenylacetonitriles¹⁸⁵. This method has been applied to thiophenes in an attempt to prepare thienopyridines¹⁸⁶⁻¹⁸⁹. Paulmier and Outurquin¹⁸⁶ prepared 5-chloro-4-formylthieno[2,3-c]pyridine (**104**) from the β -thienylacetonitrile (**103**) [Equation 32].

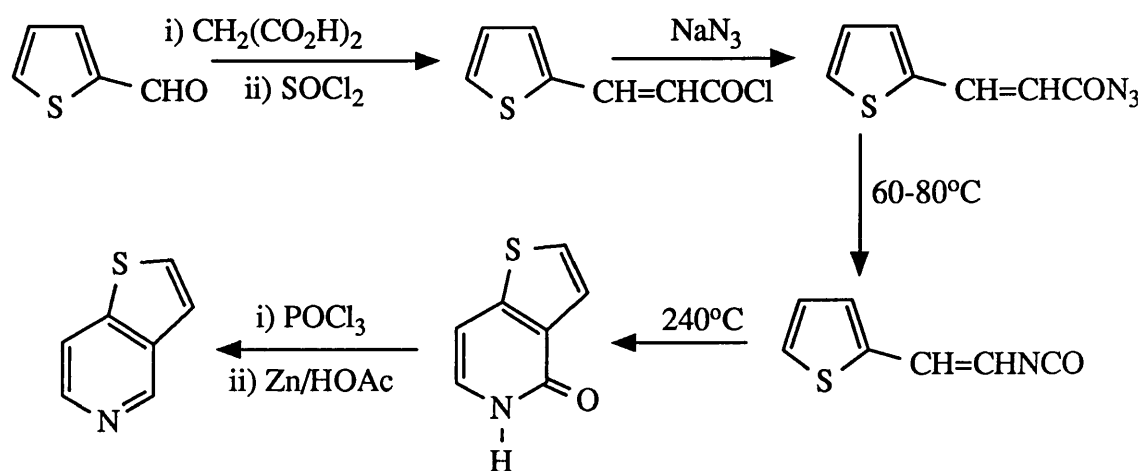


Further attempts to extend this reaction to 3-acetamidothiophenes led to mixtures^{186,187} but under controlled conditions either of the products can be formed selectively^{188,189}. Using this method, Meth-Cohn^{188,189} was able to synthesise thieno[2,3-b]-, thieno[3,2-b]- and thieno[3,4-c]pyridines in moderate to good yields (39-92%) starting with the appropriate acetamidothiophenes [Scheme 47].



[Scheme 47]

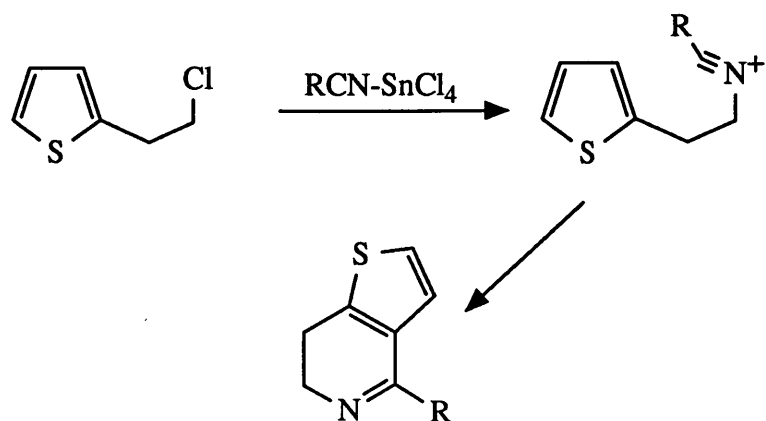
The synthesis of thieno[2,3-*c*]- and -[3,2-*c*]pyridines from β -thienylvinyl isocyanates [Scheme 48] has been reported^{190,191}.



[Scheme 48]

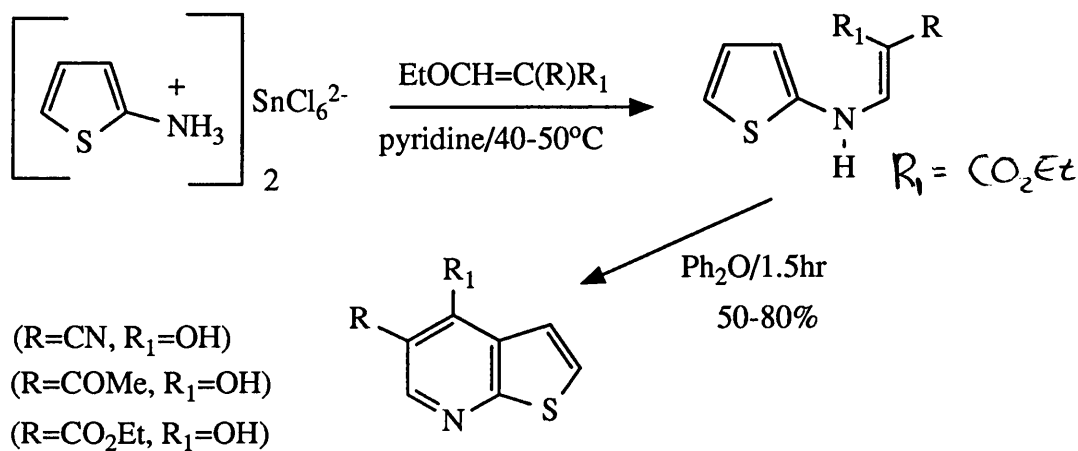
Isothiocyanates have also been used in the formation of thienopyridines^{192,193}. For example, 4-methylthio-6,7-dihydrothieno[3,2-*c*]pyridine (**106**) was produced from the cyclisation of 2-(2'-thienyl)ethyl isothiocyanate (**105**) with methyl fluorosulfate [Equation 33].

the yields with a variety of nitriles were low (8-17%) [Equation 34].



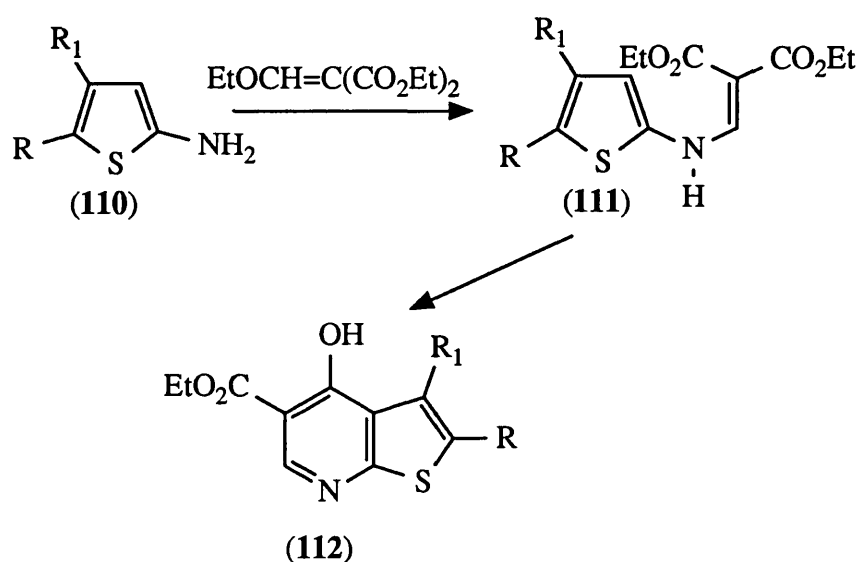
[Equation 34]

The attempted synthesis of thieno[2,3-b]pyridine and thieno[3,2-b]pyridine by the method of Gould-Jacobs was first reported by Khan¹⁹⁷. Both 2- and 3-aminothiophene double salts were condensed with various ethoxymethylene derivatives of active methylene compounds and the resulting condensation products were refluxed in diphenyl ether to afford various 5-substituted 4-hydroxythieno[2,3-b]pyridines and 6-substituted 7-hydroxythieno[3,2-b]-pyridines [Scheme 50].



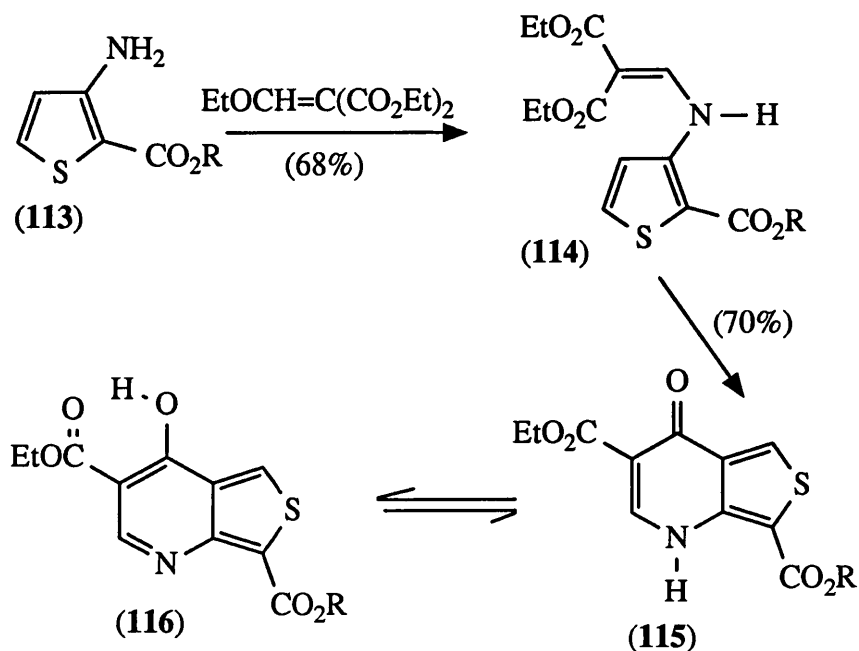
[Scheme 50]

Two patents have also described the synthesis of some derivatives of thieno[2,3-b]pyridines by this method^{198,199}. Gilis²⁰⁰ reported that condensation of a substituted 2-aminothiophene (**110**) with diethyl ethoxymethylenemalonate afforded a diethyl (2'-thienyl)aminomethylene malonate (**111**) which was converted to substituted ethyl 4-hydroxythieno[2,3-b]pyridine-5-carboxylate (**112**) by thermal cyclisation [Scheme 51].



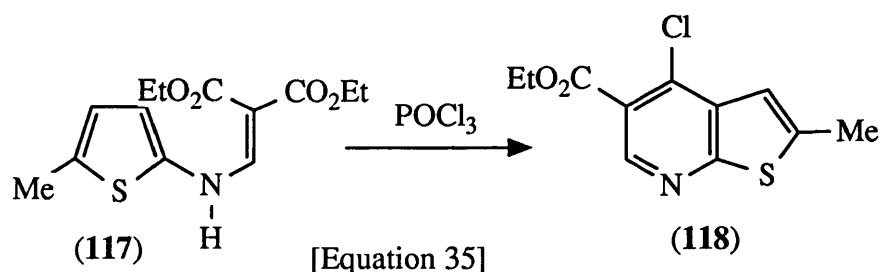
[Scheme 51]

Barker^{201,202} has also reported the use of the Gould-Jacobs reaction involving the thermal cyclisation of the enamines (**114**), obtained in good yield from 3-amino-2-alkoxycarbonylthiophene (**113**) and diethyl ethoxymethylenemalonate. The cyclisation of the enamines could not be achieved thermally but did take place in ethyl polyphosphate at 130°C to give the thienopyridones (**115**). Intramolecular H-bonding might favour the hydroxy form thus giving the fully aromatic thienopyridine (**116**) [Scheme 52].

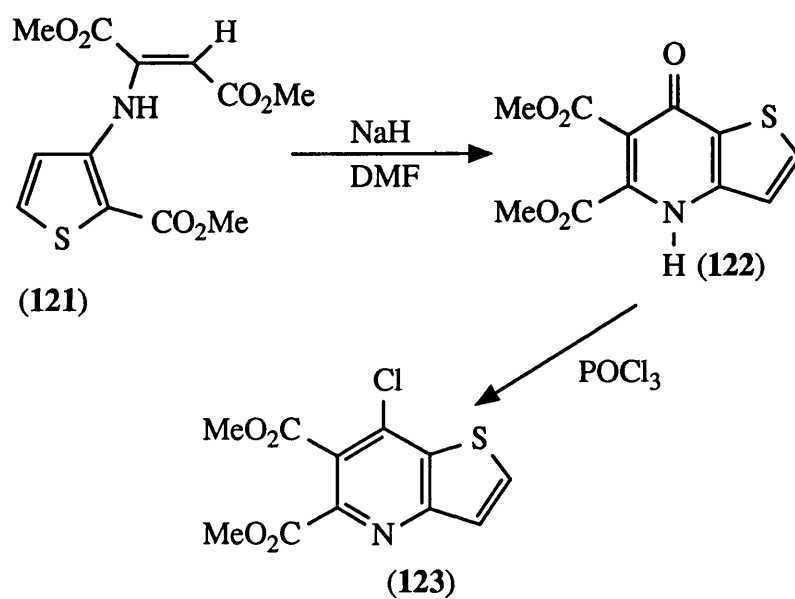
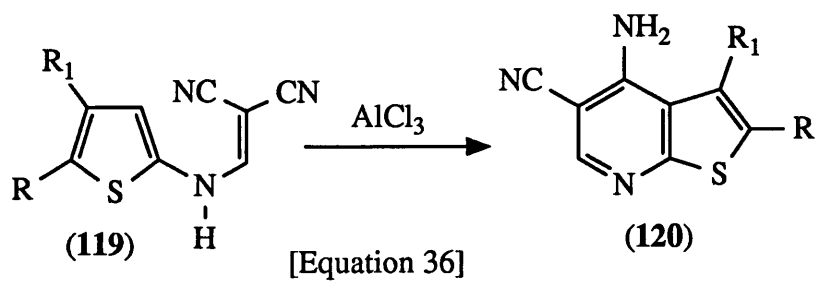


[Scheme 52]

Direct cyclisation of the enamine (117) with phosphoryl chloride at reflux temperature²⁰³ afforded ethyl 4-chloro-2-methylthieno[2,3-b]pyridine-5-carboxylate (118) [Equation 35].

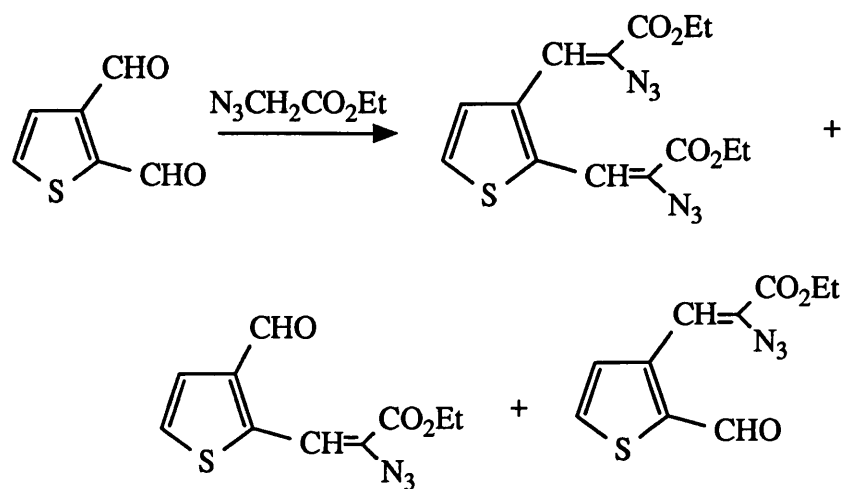


Other methods for cyclising enamines include the reaction of (119) with aluminium chloride²⁰⁴ to afford the thieno[2,3-b]pyridines (120) [Equation 36] and the use of sodium hydride²⁰² on the enamine (121) to give the thieno[3,2-b]-pyridin-7(4H)-one (122) which was converted to the 4-chlorothienopyridine derivative (123) using phosphoryl chloride [Scheme 53].

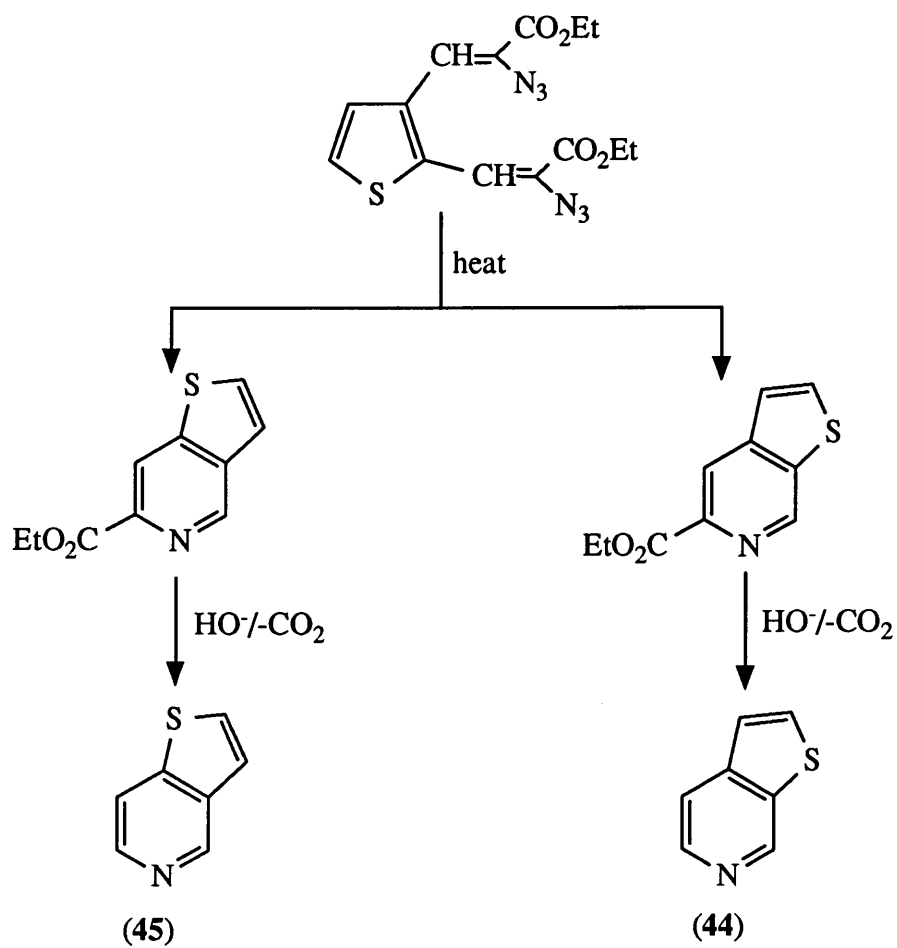


[Scheme 53]

When ethyl azidoacetate is reacted with a range of thiophene aldehydes [Equation 37] the resulting azides can be thermally cyclised to form thienopyridines²⁰⁵⁻²⁰⁷ [Scheme 54].

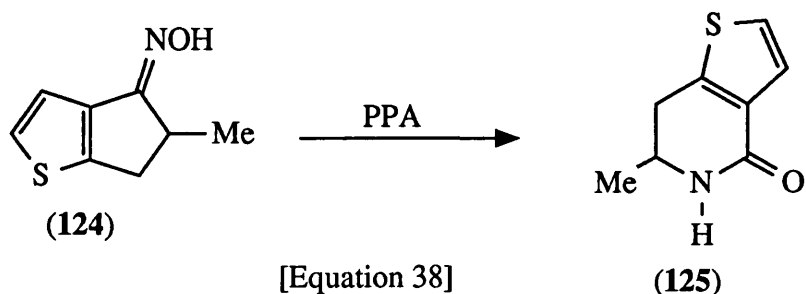


[Equation 37]

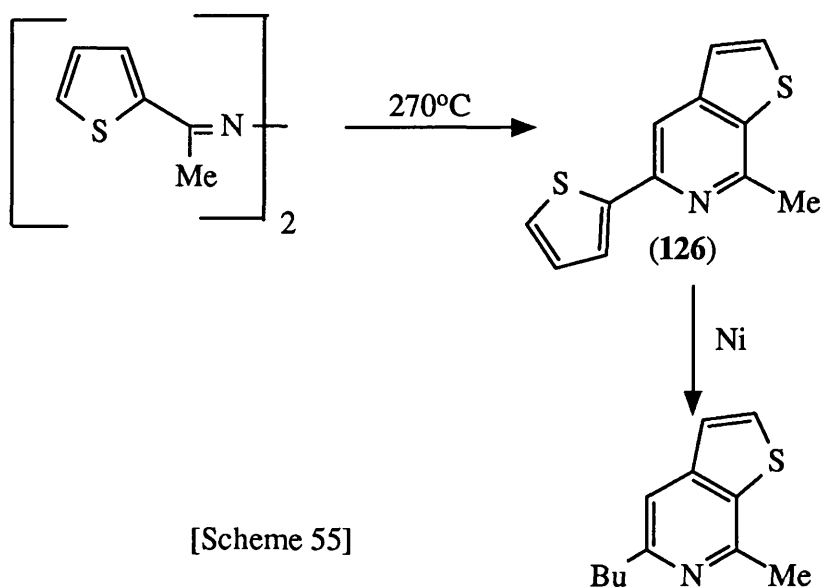


[Scheme 54]

Beckmann rearrangement of oximes derived from thiophene analogues of indanones give rise to dihydrothienopyridones^{208,209}. For example, 5-methylthieno[b]indan-4-one oximes (**124**) gave 6,7-dihydro-6-methylthieno-[3,2-c]pyridin-4(5H)-one (**125**) in 60% yield with polyphosphoric acid [Equation 38].

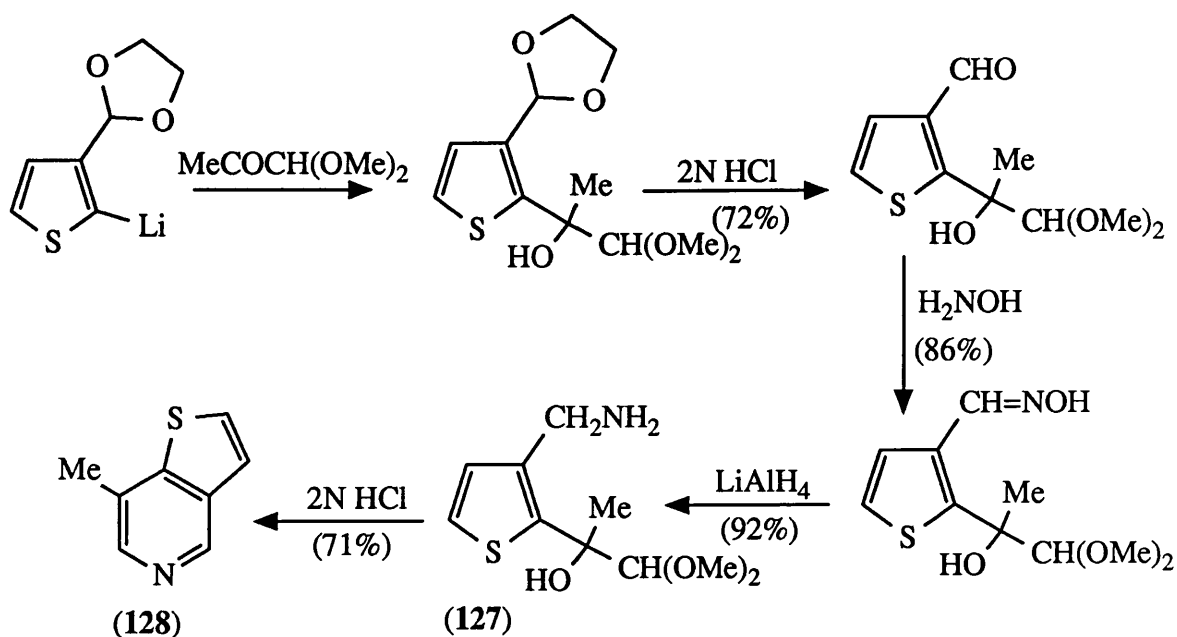


Tsuge²¹⁰ isolated 7-methyl-5-(2'-thienyl)thieno[2,3-c]pyridine (**126**) from the pyrolysis products of 2-acetylthiophene ketazine. The thiophene side chain of the thienopyridine was selectively desulfurised by Raney nickel [Scheme 55].



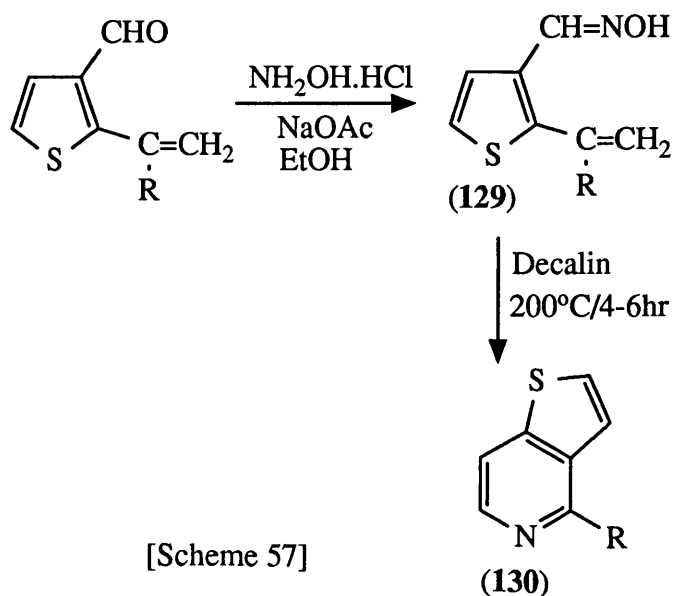
A novel cyclisation process for the preparation of thieno[2,3-c]- and [3,2-c]pyridines has been reported^{211,212}. For example, 7-methylthieno[3,2-c]-

pyridine (**128**) was prepared from 2-hydroxy-2-[(3-methylamino)thienyl]propanal-dimethylacetal (**127**) by hydrolysis with hydrochloric acid which led to cyclisation and dehydration in one step [Scheme 56].



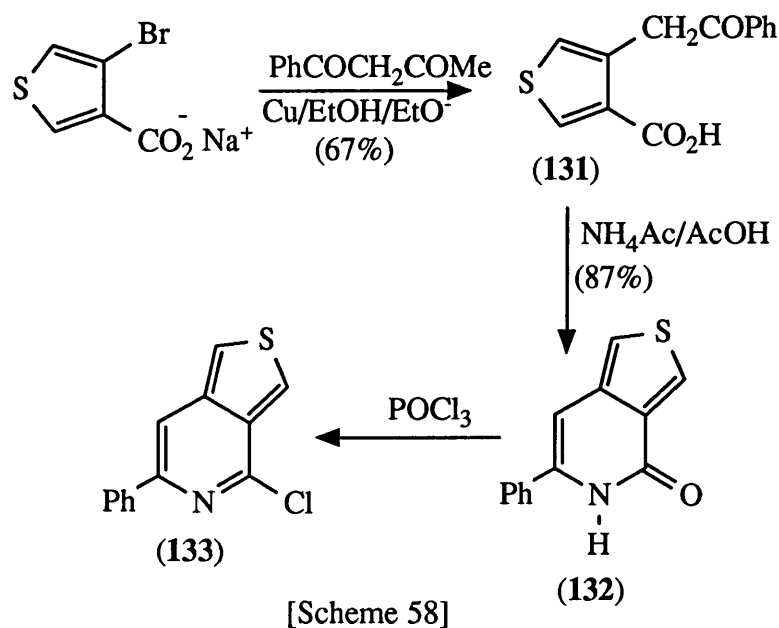
[Scheme 56]

Similar products (**130**) were obtained when oximes of type (**129**) were cyclised²¹³ by heating in decalin at 200-210°C [Scheme 57].

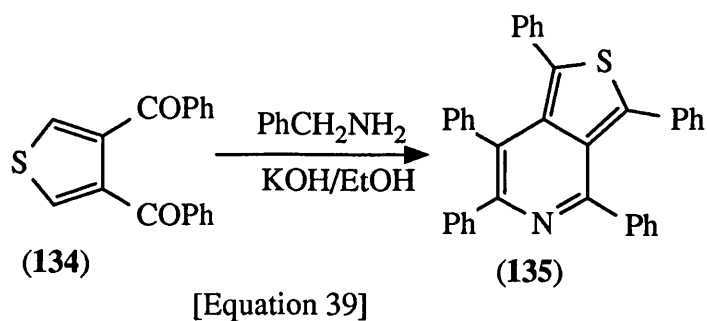


[Scheme 57]

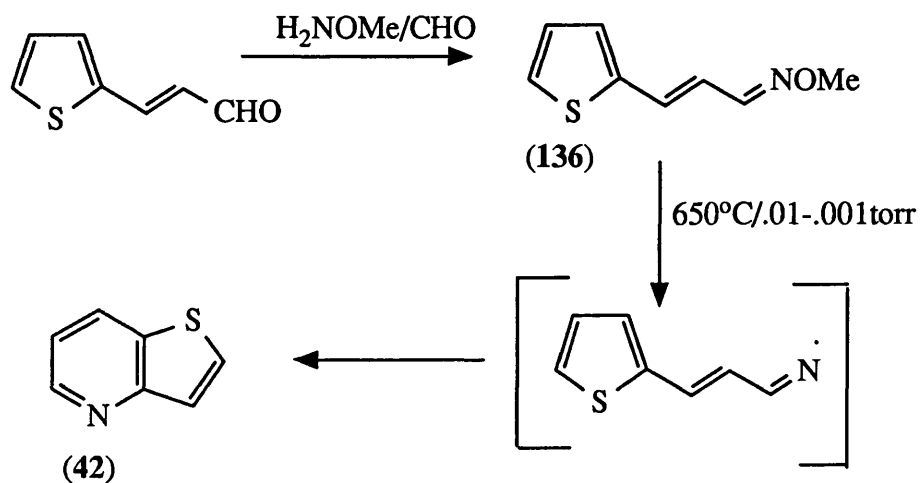
Ames and Riberio²¹⁴ described a general method for the synthesis of [c]-fused thienopyridones (and hence thienopyridines) from *o*-bromothiophene carboxylic acids. The sodium salt of 4-bromothiophene-3-carboxylic acid for example, reacts with carbanions to give, after deacylation, the acid (131). Cyclisation with ammonium acetate gave the thieno[3,4-c]pyridone (132) which was converted to 4-chloro-6-phenylthieno[3,4-c]pyridine (133) [Scheme 58].



Dibenzoylthiophenes (134) have been reported²¹⁵ to react with amines in refluxing ethanolic potassium hydroxide to afford the corresponding thieno[3,4-c]pyridines (135) [Equation 39].



A simple route to thienopyridines, based on one-step generation of the pyridine ring by gas-phase cyclisation of conjugated iminyl radicals has been reported²¹⁶. Suitable iminyl precursors include *o*-alkyloximes (**136**) which are prepared by the condensation of the corresponding aldehyde with *o*-methylhydroxylamine. Flash vacuum thermolysis of (**136**) at 650°C gives the product (**42**) [Scheme 59].



[Scheme 59]

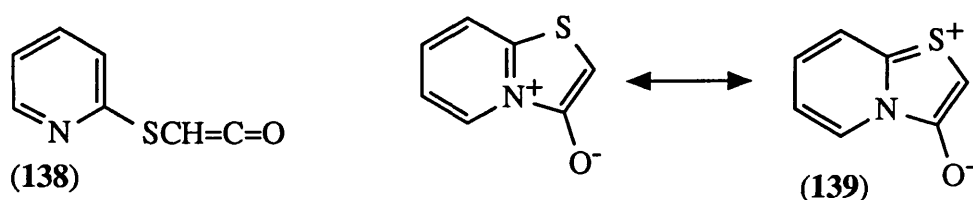
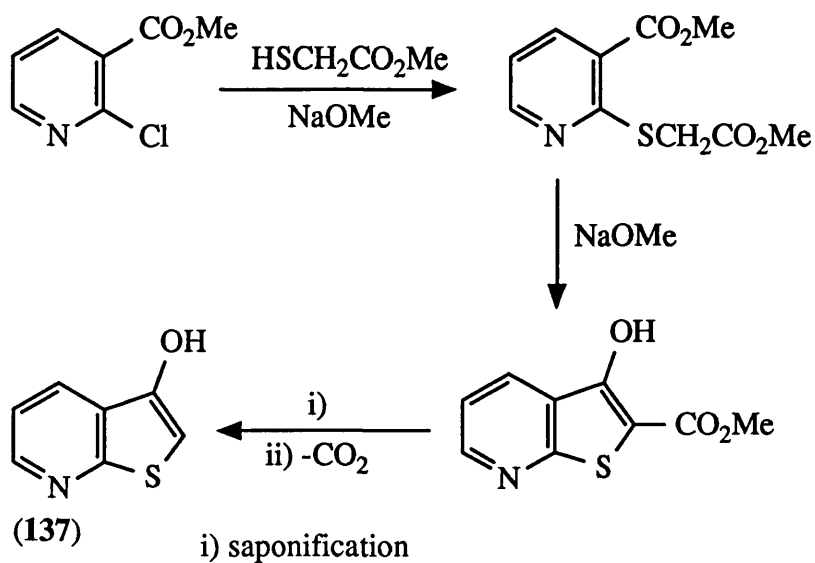
1.2.3 Synthesis of Thienopyridines from Pyridine Precursors

The synthesis of thienopyridines from thiophene precursors have already been reviewed (Section 1.2.2). There is, however, a large amount of literature on the synthesis of thienopyridines from pyridine precursors and these reactions will be discussed in this section.

1.2.3.1 Intramolecular Cyclisation of Pyridylthioacetic Acid Derivatives with Adjacent Electron Withdrawing Groups.

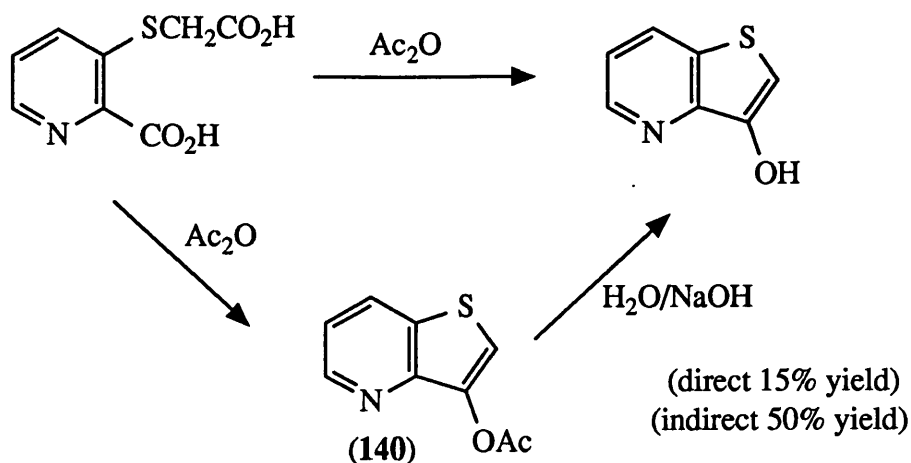
The majority of the literature on the synthesis of thienopyridines from pyridine precursors can be considered under this heading. The preparation of the thienopyridines involves the intramolecular cyclisation of pyridylthioacetic acid derivatives which possess electron withdrawing groups *ortho* to the sulfur atom. The preparation of the pyridylthioacetic acid derivatives themselves can be classified into two types of reactions: i) those which involve the reaction of *ortho*-halogenated pyridine derivatives with electron withdrawing groups and mercaptoacetic esters, and ii) the reaction of pyridine-2(1H)-thione-3-carboxylic acids with compounds containing a halogen atom adjacent to an active methylene group.

Early reports were concerned with the preparation of thienopyridines from the cyclisation of carboxypyridylthioacetic acids. Koenigs¹³⁰ claimed that 3-hydroxy-thieno[2,3-b]pyridine (**137**) was formed from the reaction of 2-pyridylthioacetic acid with acetic anhydride. Chichibabin and Vorozhtov²¹⁷ however, prepared (**137**) [Scheme 60] and showed this product to differ from the product obtained by Koenigs. It was suggested that the structure for Koenigs' product was (**138**) but this was also found to be incorrect and Duffin and Kendall²¹⁸ finally established its true structure as (**139**).



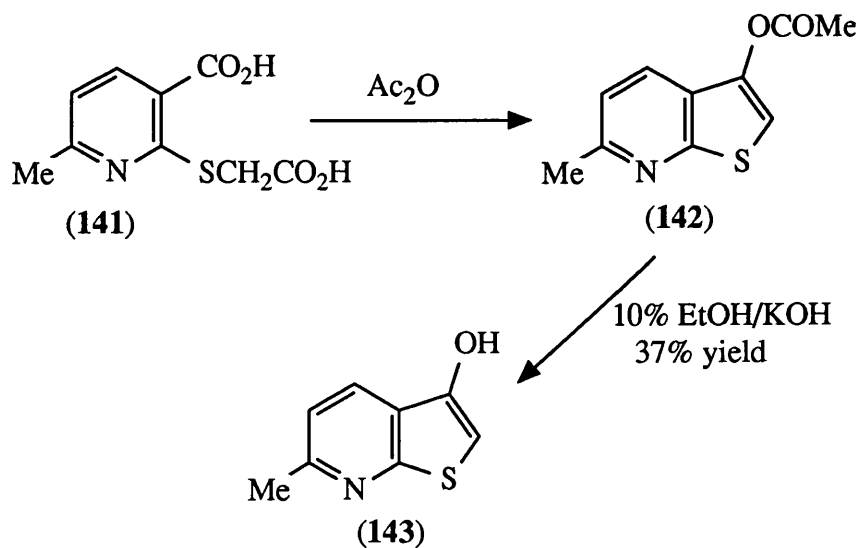
3-Hydroxythieno[2,3-b]pyridines have also been implicated, as intermediates, in the synthesis of thioindigo dyes^{129,219} but were never isolated.

Generally the yields in the synthesis of hydroxythienopyridines from the cyclisation of thioacetic acids with acetic anhydride are poor. However, when the intermediate acetoxy compound (**140**) is isolated, an improvement in the yields is observed²²⁰ [Scheme 61].



[Scheme 61]

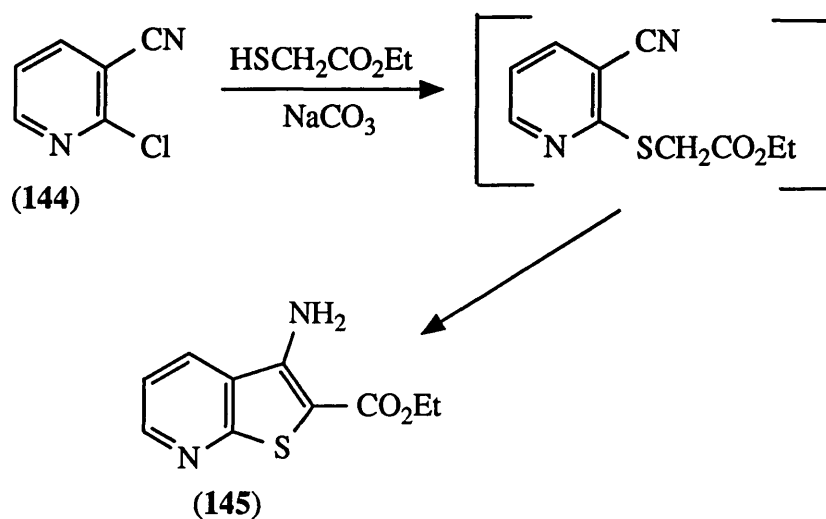
This method of isolating the acetoxy intermediate has also been employed by Russian workers¹⁶⁷ who synthesised 3-hydroxy-6-methylthieno[2,3-b]pyridine (143) from 3-carboxy-6-methyl-2-pyridylthioacetic acid (141) *via* the acetoxy intermediate (142) [Scheme 62].



[Scheme 62]

Similar reactions using cyanopyridylthioacetic acids have been used to prepare 3-aminothienopyridines^{221,222}. For example, 3-amino-2-ethoxycarbonylthieno[2,3-b]pyridine (145) is formed from 2-chloro-3-cyanopyridine (144) [Scheme 63].

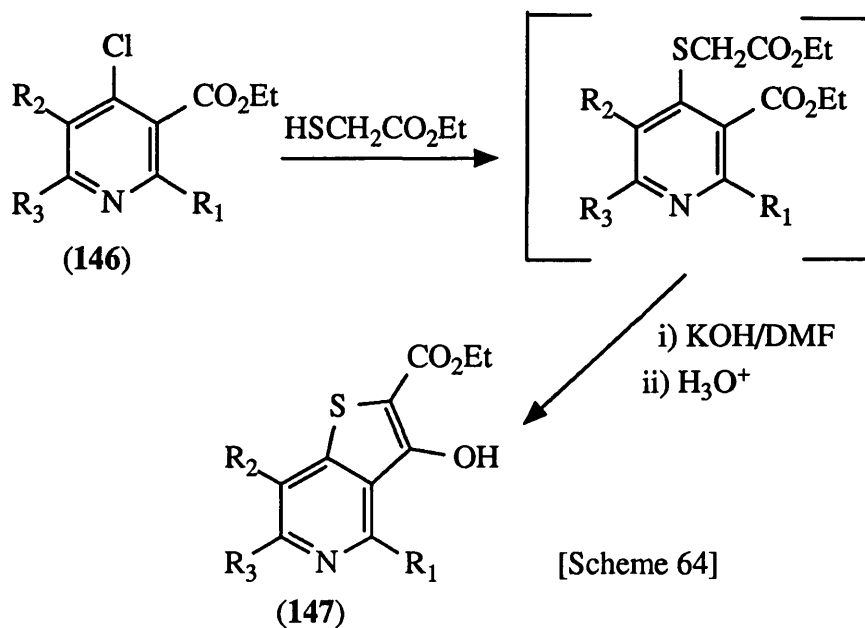
The reaction proceeds *via* a nucleophilic substitution reaction by ethyl mercaptoacetate at the 2-position of (144), followed by base promoted intramolecular ring formation involving the nitrile group to afford (145).



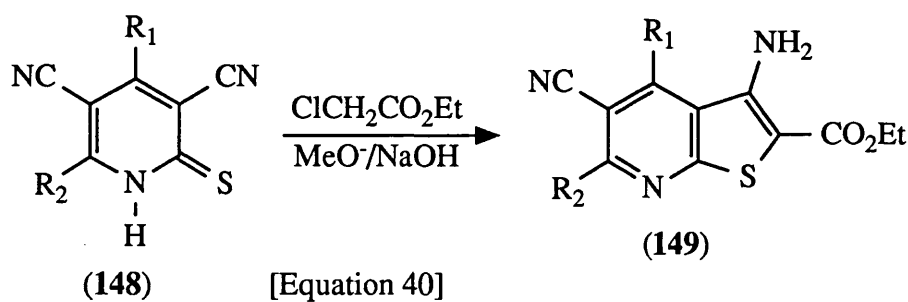
[Scheme 63]

The formation of more complex derivatives by similar reactions of more highly substituted pyridines have also been reported by a number of authors²²³⁻²³⁰.

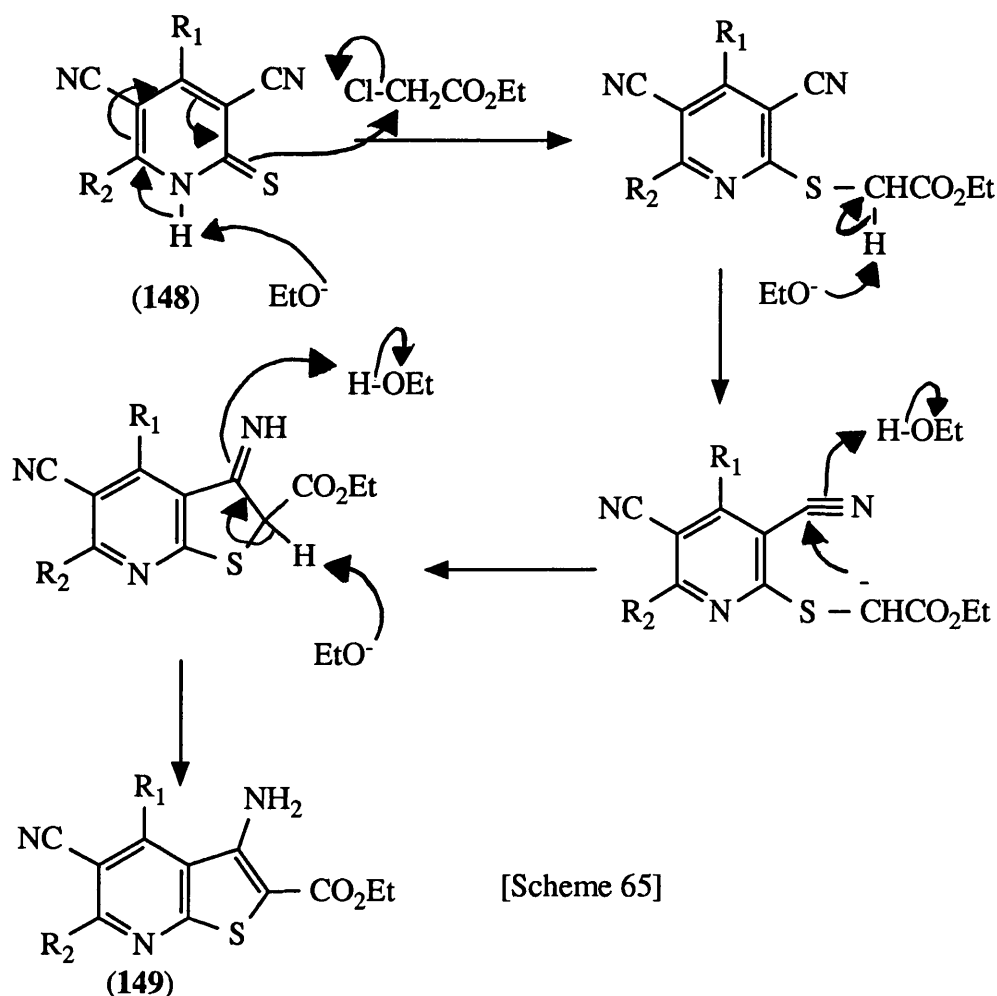
Scheme 64, for example, shows the nucleophilic displacement of the chlorine atom in the 4-position of (146), by ethyl mercaptoacetate, followed by a Dieckmann type condensation of the intermediate²²⁵ to afford the thienopyridine (147).



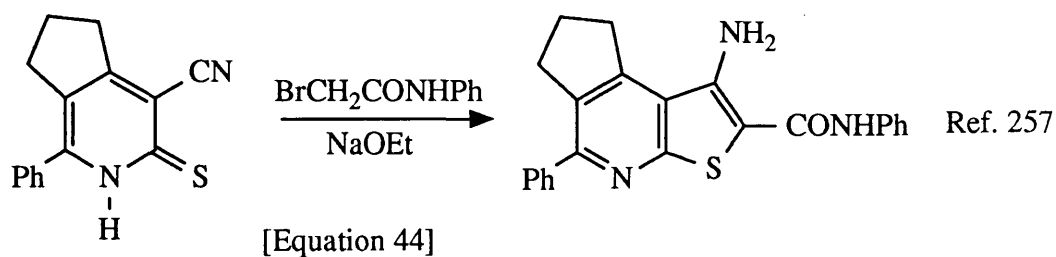
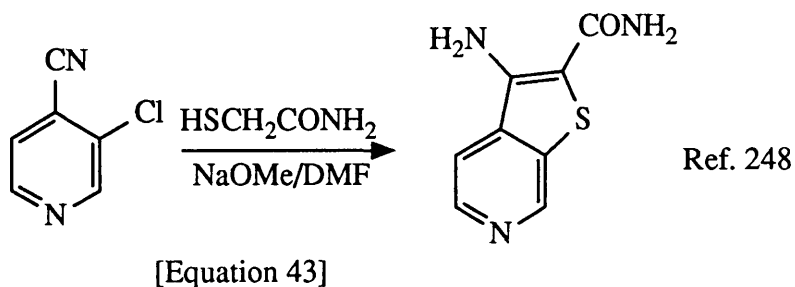
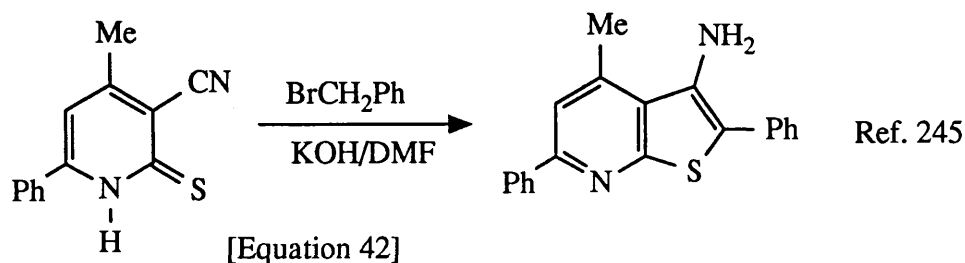
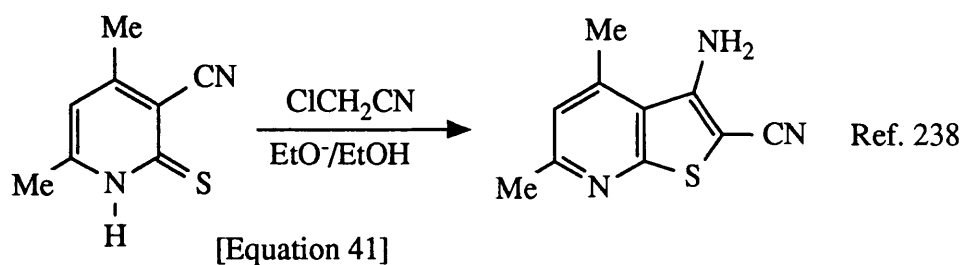
A similar type of reaction using a pyridinethione²²⁶ as the starting material is shown in Equation 40.



The pyridinethione (148) is alkylated by compounds, such as ethyl chloroacetate, which contain a halogen atom adjacent to an active methylene group, followed by subsequent base promoted cyclisation to afford the thienopyridine (149) [Scheme 65].



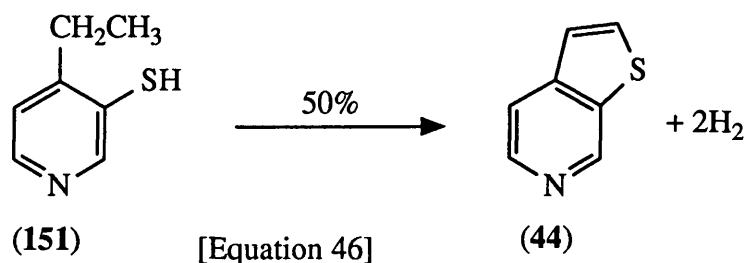
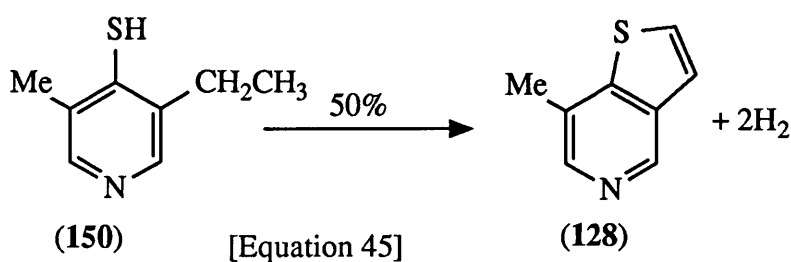
There have been a large number of reports²³¹⁻²⁶⁰ that have discussed the synthesis of thienopyridines from mercaptoacetic esters and haloalkanes in which the ethoxycarbonyl function has been replaced by other electron withdrawing substituents, such as CN, COMe, CPh, CONH₂, CO₂Me, NO₂, CONHPh, C₆H₅, *p*-C₆H₄NO₂, *p*-C₆H₄Br, CONHC₅H₄N, etc. Examples of these reactions are shown in Equations 41-44.



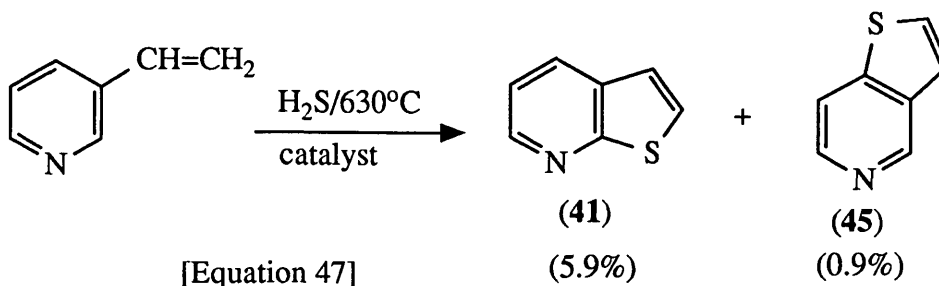
1.2.3.2 High-Temperature Catalytic Methods

The first reported attempt to synthesise thienopyridines utilising high-temperature catalysis, was made by Hansch and Carpenter²⁶¹, who were unsuccessful in preparing thieno[2,3-c]pyridine by the reaction of 4-vinylpyridine and hydrogen sulfide over an alumina catalyst at 600°C. The same authors, however, did succeed

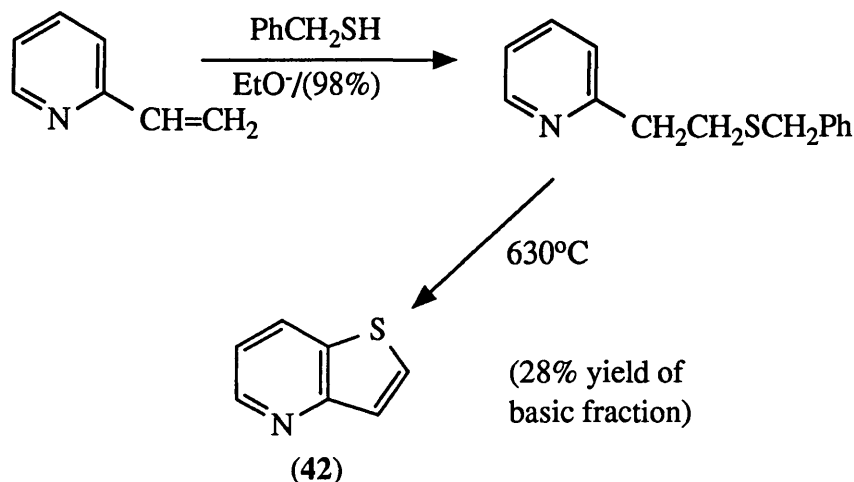
in the synthesis of 7-methylthieno[3,2-c]pyridine²⁶¹ (**128**) and thieno[2,3-c]pyridine²⁶² (**44**) by cyclisation-dehydrogenation, at 425°C over a copper-chromium catalyst, of 3-ethyl-5-methylpyridine-4-thiol (**150**) and 4-ethylpyridine-3-thiol (**151**) respectively [Equations 45 and 46]. Although the yields of the cyclisation step (20-25% and 50% respectively) were acceptable the overall yields of the multistep synthesis were less than 5%.



After the failed attempt²⁶¹ to cyclise 4-vinylpyridine, 2-vinylpyridine was cyclised²⁶³ with hydrogen sulfide over an iron (II) sulfide-alumina catalyst at 630°C to afford thieno[2,3-b]pyridine (**41**) in only 1.6% yield. It has also been reported²⁶⁴ that 3-vinylpyridine gives a mixture of thieno[2,3-b]pyridine (**41**) and thieno[3,2-c]pyridine (**45**) under similar conditions [Equation 47].



Thienopyridines could be obtained in much higher yields if the vinylpyridines were first converted into the corresponding benzyl pyridylethyl sulfides²⁶⁵ followed by pyrolysis over glass helices at high temperature with either nitrogen or hydrogen sulfide as the carrier gas [Scheme 66].

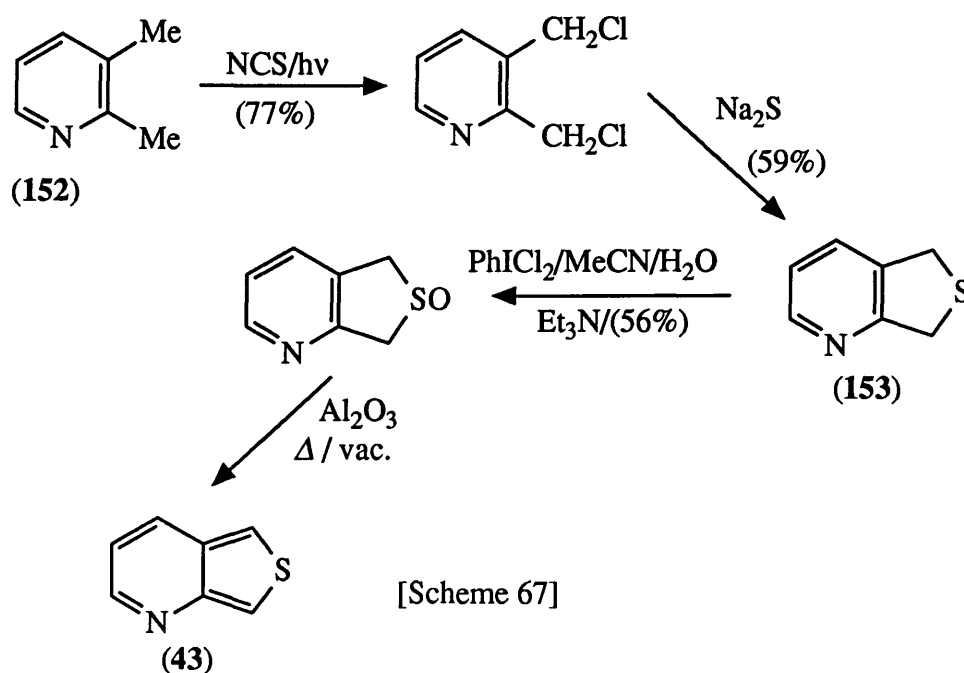


[Scheme 66]

This method has also been used²⁶⁶ for the synthesis of thieno[2,3-*c*]pyridines in 58% yield.

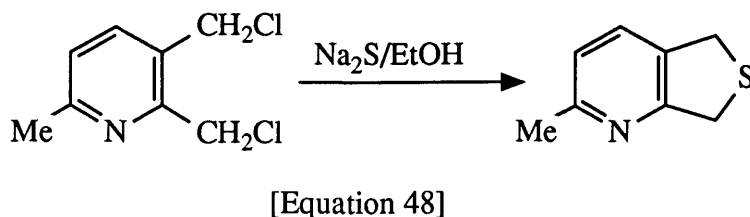
1.2.3.3 Synthesis using Thiolates

The preparation of thieno[3,4-*b*]pyridines and thieno[3,4-*c*]pyridines has been achieved by the condensation of halomethylpyridine derivatives with sulfides. Benary¹²⁸ first reported the synthesis of thieno[3,4-*c*]pyridines (Section 1.2.2) but a later series of papers^{135266,267} reported the preparation of thieno[3,4-*b*]pyridines (43) and thieno[3,4-*c*]pyridines (46) from 2,3-dimethylpyridine (152) and 3,4-dimethylpyridine respectively.

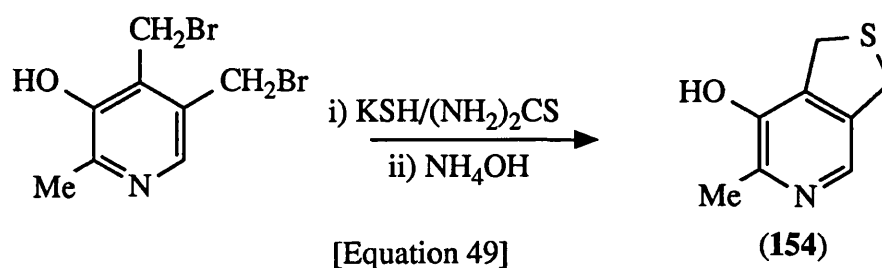


The reaction sequence, shown in Scheme 67, involves the ultraviolet irradiation of a refluxing solution of (152) and N-chlorosuccinimide to give 2,3-dichloromethylpyridine which on treatment with aqueous ethanolic sodium sulfide gave the cyclised product (153). Oxidation followed by heating with neutral alumina *in vacuo* afforded the thienopyridine (43).

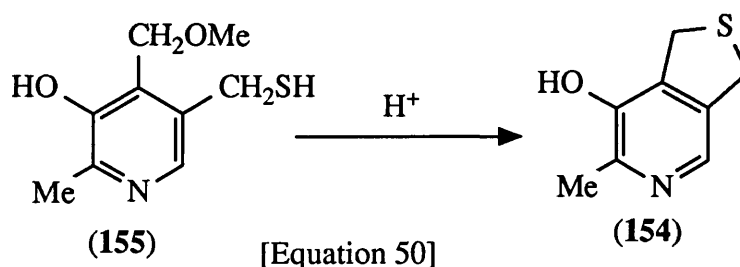
1,3-Dihydrothieno[3,4-b]pyridines have also been prepared by Spinner and Yeoh²⁶⁸ from dichloromethylpyridines [Equation 48].



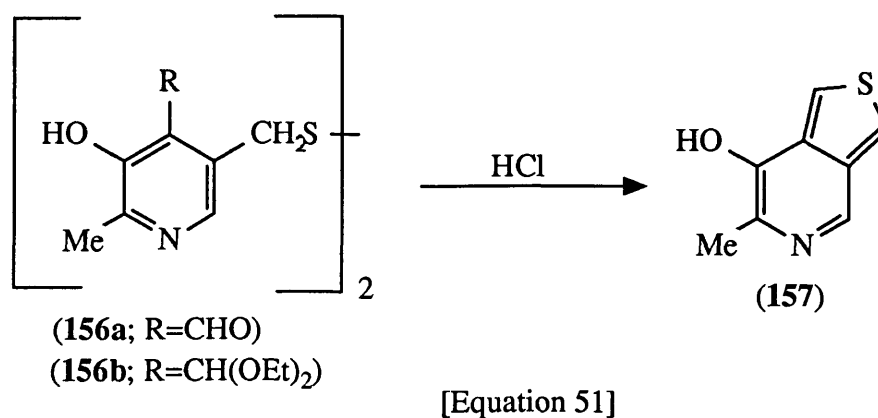
4-Hydroxy-5-methyl-1,3-dihydrothieno[3,4-c]pyridine (154) was reported²⁶⁹ to have been the product from the reaction of substituted 3,4-dibromomethylpyridines with KSH or thiourea followed by ammonia [Equation 49].



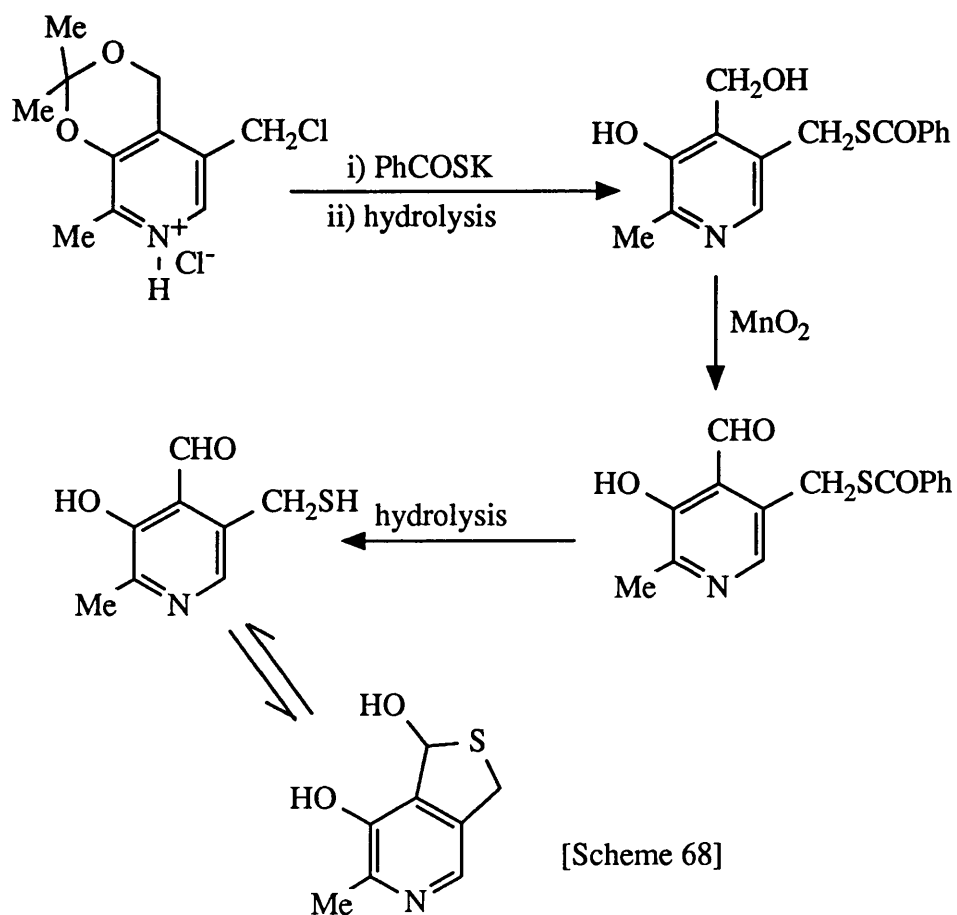
The structure of the product (154) prepared in Equation 49 was disputed by Schmidt and Giesslmann²⁷⁰ who claimed to have prepared (154) from the acid-catalysed cyclisation of (155) [Equation 50] and found it to have a completely different melting point. Unfortunately the literature gives no indication, which starting material actually produces the thienopyridine (154).



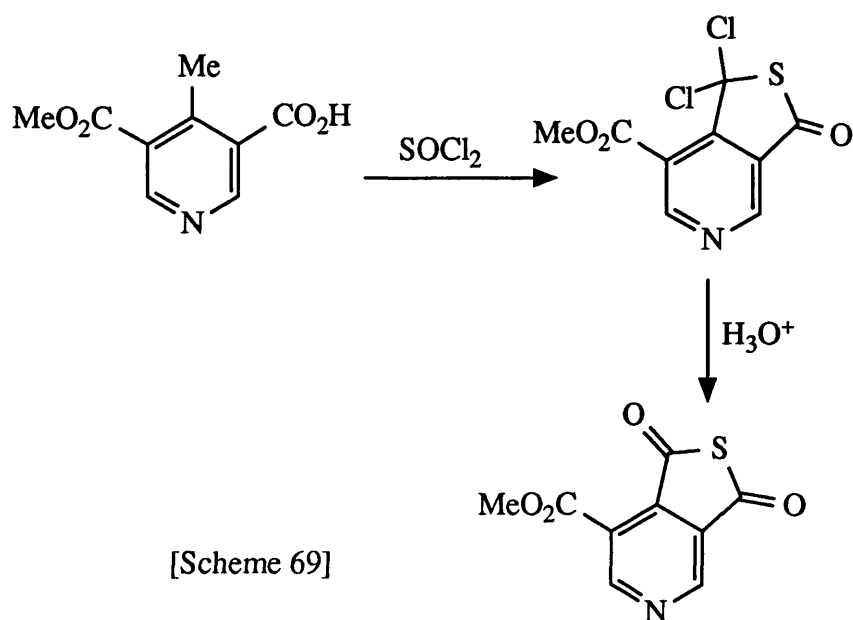
In a series of patents, the synthesis of 4-hydroxy-5-methylthieno[3,4-c]pyridine (157), the fully aromatic analogue of (154), from both (156a) and (156b) has been reported^{271,272} [Equation 51].



Thieno[3,4-b]- and [3,4-c]pyridines have also been prepared from other salts of thioacids²⁷³ such as that shown in Scheme 68.

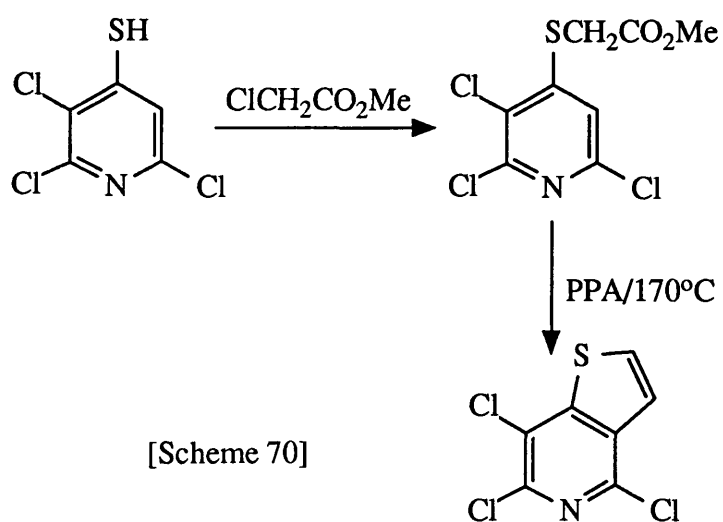


Another interesting synthesis of thieno[3,4-c]pyridines involves the reaction of various 4-methylnicotinic acids in which the activated 4-methyl group is involved in the reaction of the carbonyl group with thionyl chloride to afford a 1,3-dioxo-1,3-dihydrothieno[3,4-c]pyridine [Scheme 69].

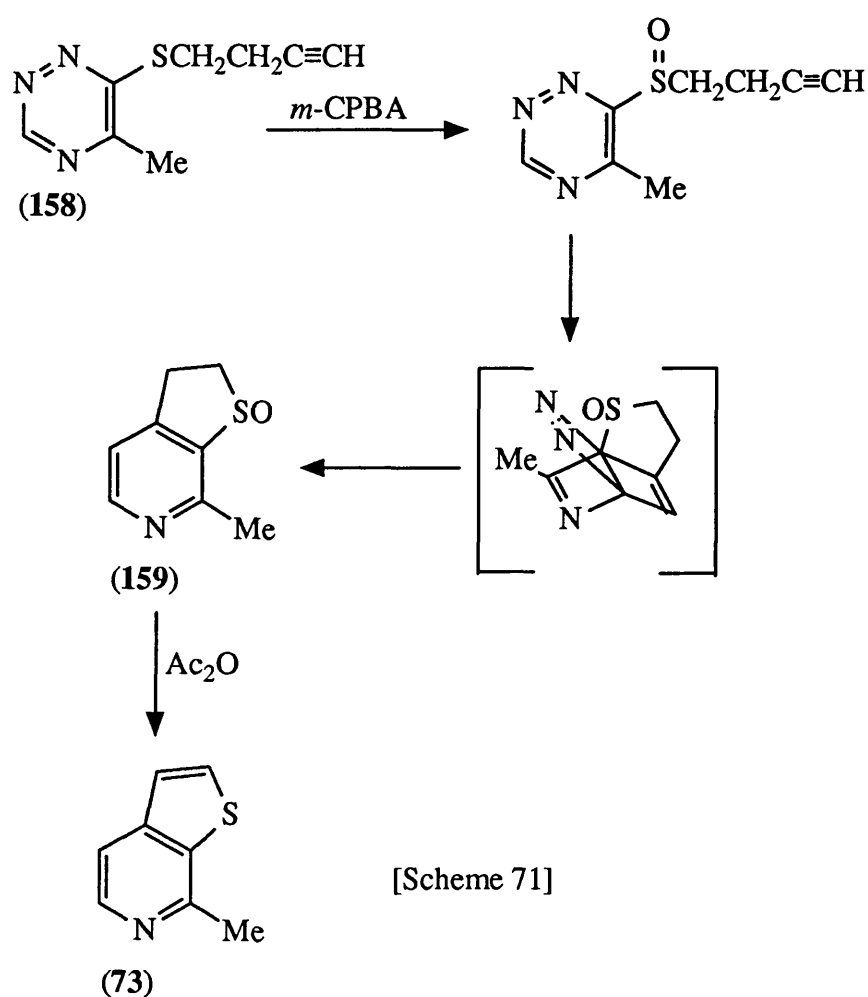


1.2.3.4 Miscellaneous Syntheses

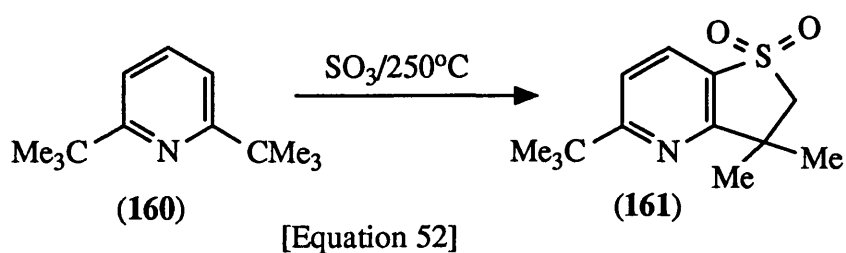
In a series of reports²⁷⁴⁻²⁷⁶, thieno[3,2-c]pyridines were prepared from the reaction between 2,3,6-trichloropyridine-4-thiol and methyl chloroacetate followed by cyclisation with polyphosphoric acid [Scheme 70].



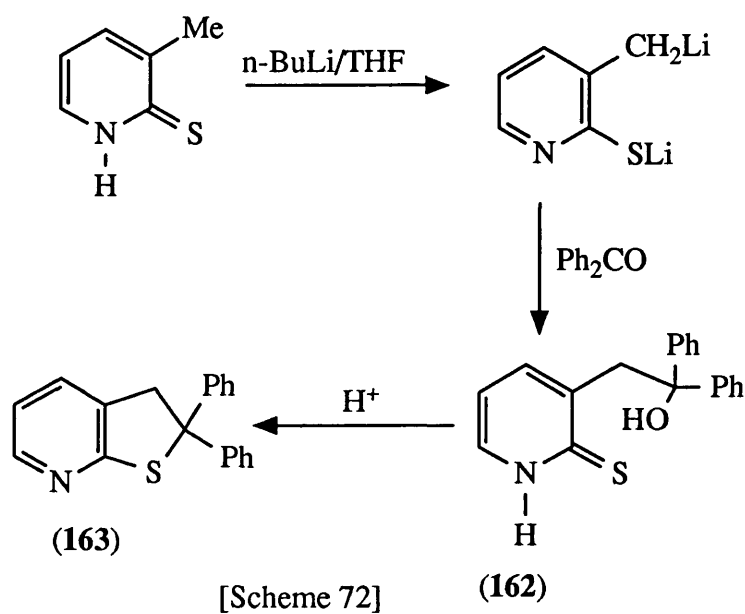
Thienopyridines have also been obtained from the intramolecular Diels-Alder reaction of substituted thio-1,2,4-triazines^{277,278}. When 6-(3-butynylthio)-5-methyl-1,2,4-triazine (**158**) was oxidised with *m*-chloroperbenzoic acid, the resulting sulfoxide underwent an intramolecular Diels-Alder reaction to afford 7-methyl-2,3-dihydrothieno[2,3-*c*]pyridine 1-oxide (**159**), which when refluxed in acetic anhydride gave 7-methylthieno[2,3-*c*]pyridine (**73**) in 88% yield [Scheme 71].



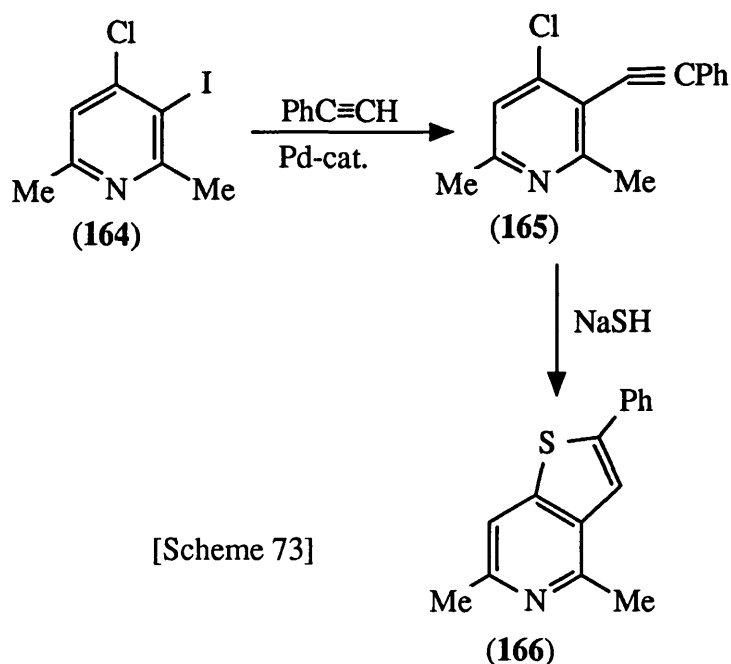
When 2,6-di-*t*-butylpyridine (**160**) was heated²⁷⁹ with sulfur trioxide at 240-250°C for 15 hours in a sealed tube, 2,3-dihydro-3,3-dimethyl-5-*t*-butylthieno[3,2-*b*]pyridine 1,1-dioxide (**161**) was formed [Equation 52].



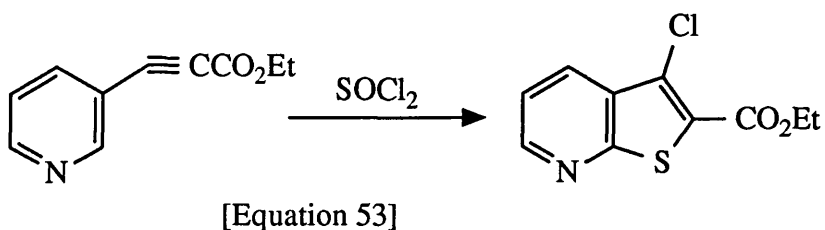
2,3-Dihydro-2,2-diphenylthieno[2,3-b]pyridine (**163**)²⁸⁰ was synthesised from the acid catalysed cyclisation of (**162**) from the condensation reaction of 3-methylpyridine-2(1H)-thione (through its dilithio salt) with benzophenone [Scheme 72].



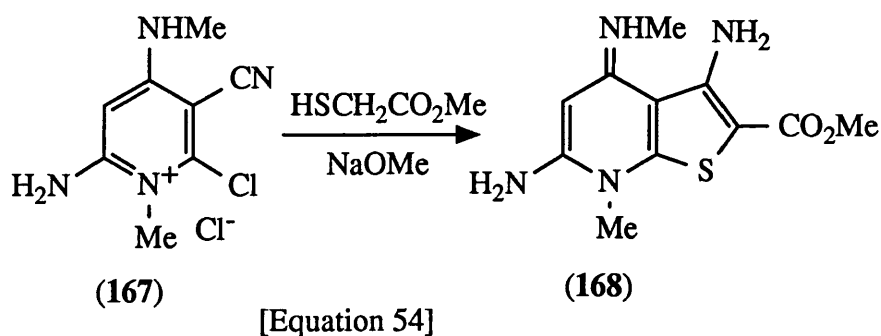
Reaction of 4-chloro-3-iodo-2,6-dimethylpyridine (**164**) with phenylacetylene in the presence of a palladium catalyst²⁸¹ affords 4-chloro-2,6-dimethyl-3-phenylethynylpyridine (**165**), which on treatment with sodium hydrosulfide is converted into 4,6-dimethyl-2-phenylthieno[3,2-c]pyridine (**166**) [Scheme 73].



When pyridin-3-ylpropionic acid was refluxed with thionyl chloride over six days²⁸², a small amount (4%) of 2-carboethoxy-3-chlorothieno[2,3-b]pyridine was obtained [Equation 53]. The authors suggested that the formation of the thienopyridine was due to the nucleophilic attack of a sulfur containing intermediate, formed from the addition reaction to the triple bond, on the pyridinium salt formed from the starting material and thionyl chloride.



The reactions of pyridinium salts with methyl thioglycolate have also produced thienopyridines²⁸³. An example is shown in equation 54, where 3,6-diamino-7-methyl-4-methyliminothieno[2,3-b]pyridine (168) was prepared from the reaction of the pyridinium salt (167) and methyl thioglycolate.

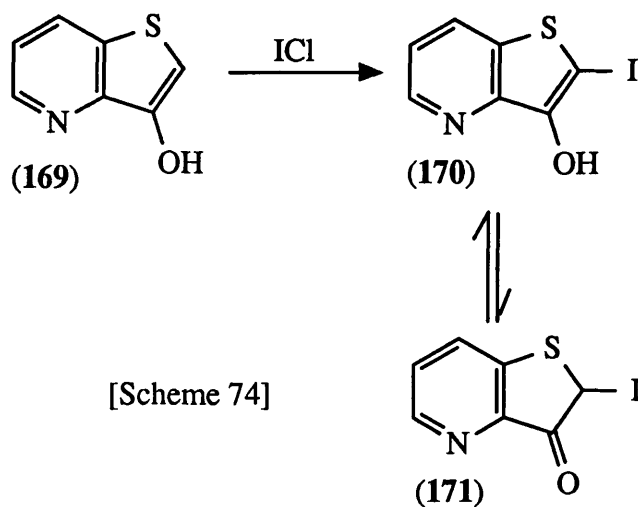


1.2.4 Reactions of Thienopyridines

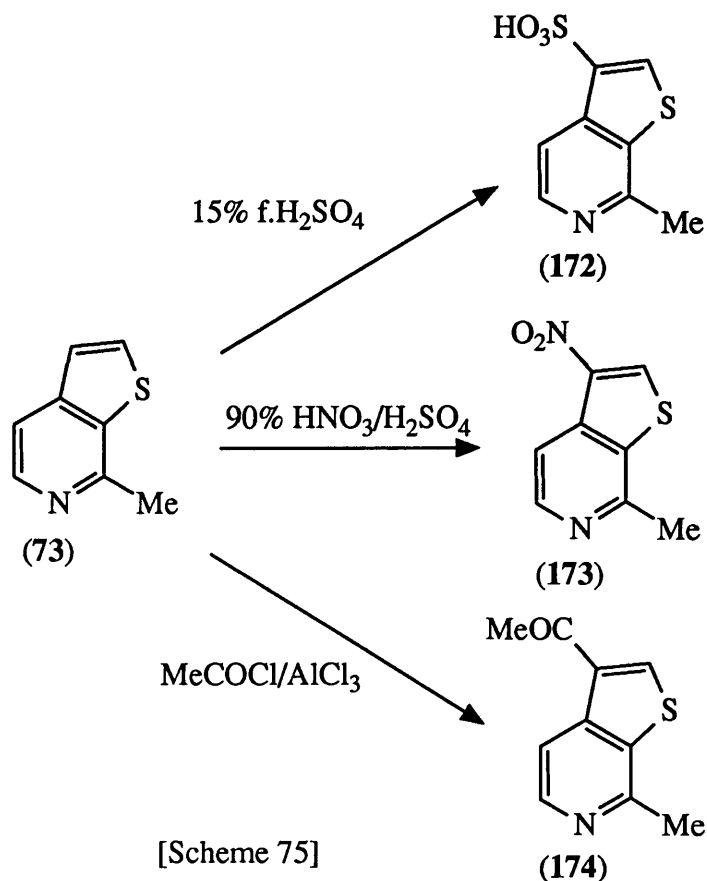
Thienopyridines are bicyclic molecules with a π -electron excessive (thiophene) ring and a π -electron deficient (pyridine) ring. This ring system allows thienopyridines to undergo electrophilic substitution in the thiophene ring and nucleophilic substitution in the pyridine ring. These reactions and others, will be discussed in this section.

1.2.4.1 Electrophilic Substitution Reactions

The majority of electrophilic substitution reactions that have been reported fall into four categories; nitration, halogenation, sulfonation and deuterium exchange catalysed by acid. Sheehan and Leitner first reported²²⁰ the electrophilic substitution reaction of a thienopyridine. Treatment of 3-hydroxythieno[3,2-b]-pyridine (**169**) with iodine monochloride [Scheme 74] gives a product in which the iodine atom is very labile. Although the structure of the compound was never established, it seems probable that it was 3-hydroxy-2-iodothieno[3,2-b]pyridine (**170**). The lability of the halogen atom could be due to its position α to the carbonyl function in the keto tautomer (**171**).

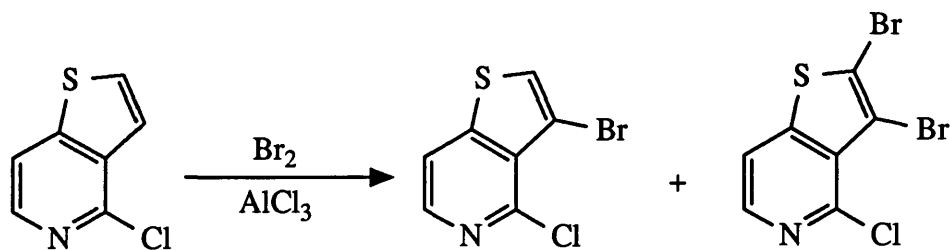


The majority of publications have indicated that the C-3 position is the most favourable for electrophilic attack. When sulfonation, nitration and Friedel-Crafts acetylation are carried out¹³⁶ on 7-methylthieno[2,3-c]pyridine (**73**) the corresponding products (**172**), (**173**) and (**174**) are obtained as a result of attack at the C-3 position [Scheme 75].



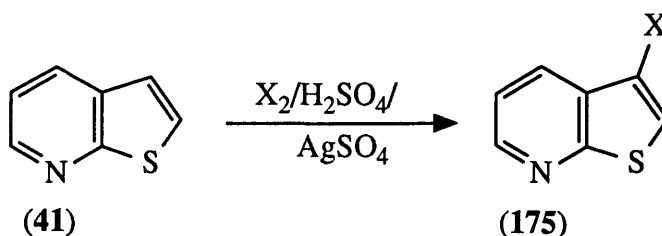
A study of the electrophilic substitution of thieno[2,3-c]- and [3,2-c]pyridines has been carried out by Gronowitz and Sandberg²⁸⁴. Deuterium exchange (using D_2O), rapidly followed by NMR spectroscopy, was found to be temperature dependent. At 55°C deuterio deprotonation occurs in the 3-position but at 100°C it occurs in both the 3- and 2-positions. Nitration with fuming nitric acid in concentrated sulfuric acid gives good yields of the 3-nitro derivative while bromination occurs most successfully with bromine in 48% hydrobromic acid or thionyl bromide to afford the 3-bromo derivative, in 60-80% yields. Dibromoisocyanuric acid in sulfuric acid also gives good yields of the 3-bromo derivative but with excess amounts of the reagent in fuming sulfuric acid, the 2,3-dibromo derivative is also obtained. Bromination of 4-chlorothieno[3,2-c]-pyridine using bromine and a large excess of aluminium chloride catalyst²⁸⁵ produces 3-bromo-4-chlorothieno[3,2-c]pyridine and 4-chloro-2,3-dibromothieno-

[3,2-c]pyridine [Equation 55].



[Equation 55]

Much work on the electrophilic substitution of thienopyridines has been carried out by Klemm and his group^{133,134,286-288}. The reaction of thieno[2,3-b]pyridine (**41**) with deuteriosulfuric acid¹³³ at 98.5°C has been studied by NMR which has shown that the proton at the C-3 position is replaced much more rapidly than at the C-2. Bromination with an excess of bromine¹³³ leads to a low yield (17%) of the 2,3-dibromo derivative, while chlorination under similar conditions²⁸⁶ gives both the mono- and the dichlorothieno[2,3-b]pyridines. Halogenation²⁸⁶ with elemental halogen in sulfuric acid/silver sulfate, however, gives 3-halothieno[2,3-b]pyridine (**175**) in moderate yields [Equation 56].



[Equation 56]

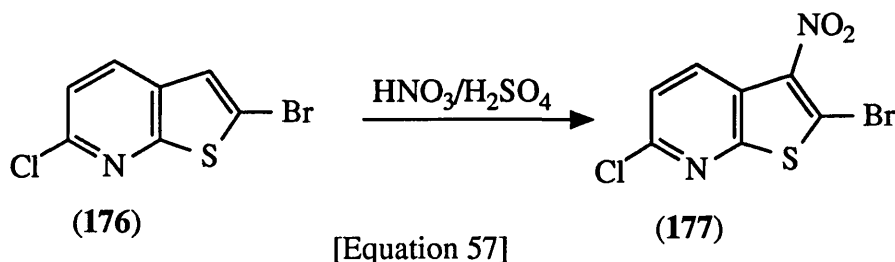
a; X=Cl (26%)

b; X=Br (47%)

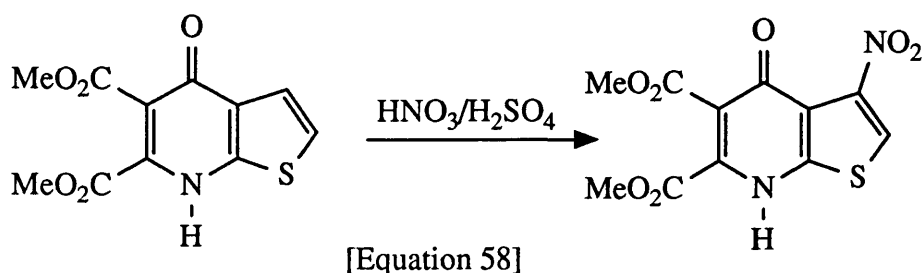
c; X=I (22%)

Improved yields of (**175a-c**, 44-57%) are obtained^{286,289} by the reaction of thieno[2,3-b]pyridine (**41**) with bromine (for example) in chloroform in the presence of a buffer. Nitration of (**175a-c**) affords 3-halo-2-nitrothieno[2,3-b]-

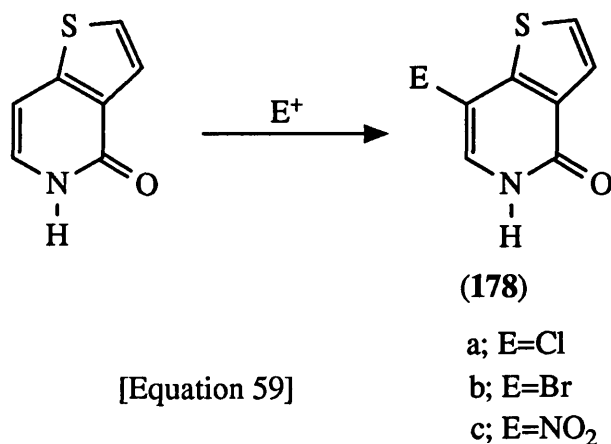
pyridines in 22-47% yields. Both thieno[2,3-b]- and [3,2-b]pyridines¹³⁴ and also 5-ethylthieno[2,3-b]pyridine²⁸⁷ have been nitrated (mixed acid) at the C-3 position in approximately 50% yield. It has also been reported¹⁸⁸ that the nitration of 2-bromo-6-chlorothieno[2,3-b]pyridine (**176**) provides 2-bromo-6-chloro-3-nitrothieno[2,3-b]pyridine (**177**) in 96% yield [Equation 57].



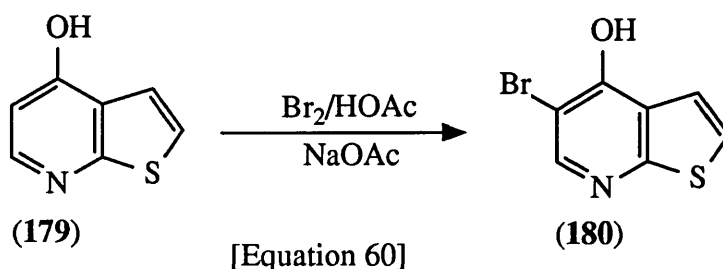
Electrophilic reactions have also been carried out on both thienopyridones and thienopyridinols. When the pyridine ring is highly substituted²⁰² then electrophilic substitution occurs, as usual, at the C-3 position [Equation 58].



When the pyridine ring is unsubstituted, however, electrophilic substitution will take place in the pyridine ring. This was first observed²⁸⁵ when thieno[2,3-c]- and [3,2-c]pyridones were reacted with hydrogen halides and hydrogen peroxide or with nitric acid to give products (**178a-c**) [Equation 59].

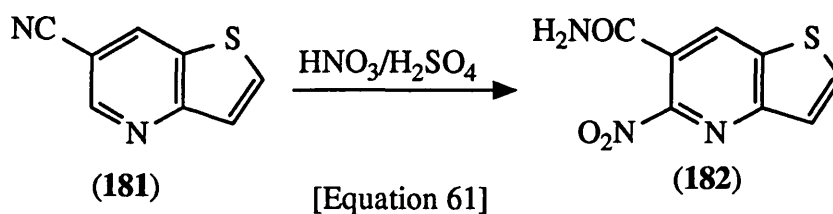


Barker^{178,201,289} has also reported examples of electrophilic substitution reactions in the pyridine ring rather than the thiophene ring. For example, 4-hydroxythieno-[2,3-b]pyridine (179) reacts readily²⁸⁹ at room temperature with one mole equivalent of bromine in acetic acid in the presence of sodium acetate to give 5-bromo-4-hydroxythieno[2,3-b]pyridine (180) [Equation 60].



Similar reactions in which electrophilic substitution occurs α to the hydroxy group have also been reported¹⁶¹.

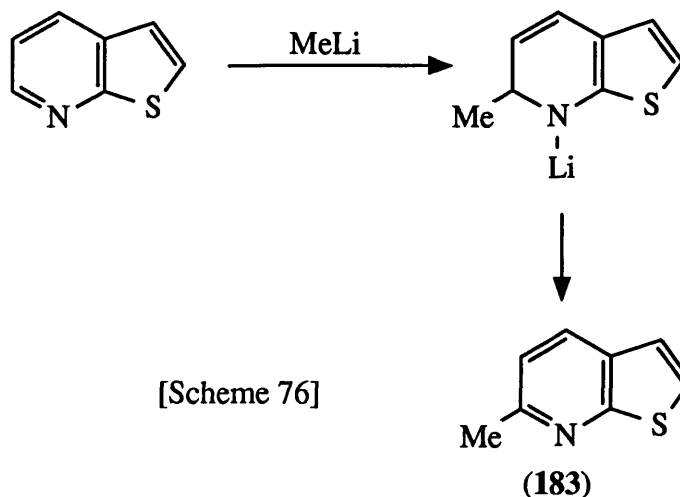
An interesting reaction reported by Klemm²⁹⁰ is the nitration of 6-cyanothieno-[3,2-b]pyridine (181) which occurs at the C-5 position to give 11% yield of 6-carbamoyl-5-nitrothieno[3,2-b]pyridine (182) [Equation 61]. This was of particular interest because Klemm and his co-workers had expected the nitration to occur at C-3. To account for this, the authors suggested that the reaction occurs intramolecularly *via* a complex or intermediate involving the amide group and nitric acid.



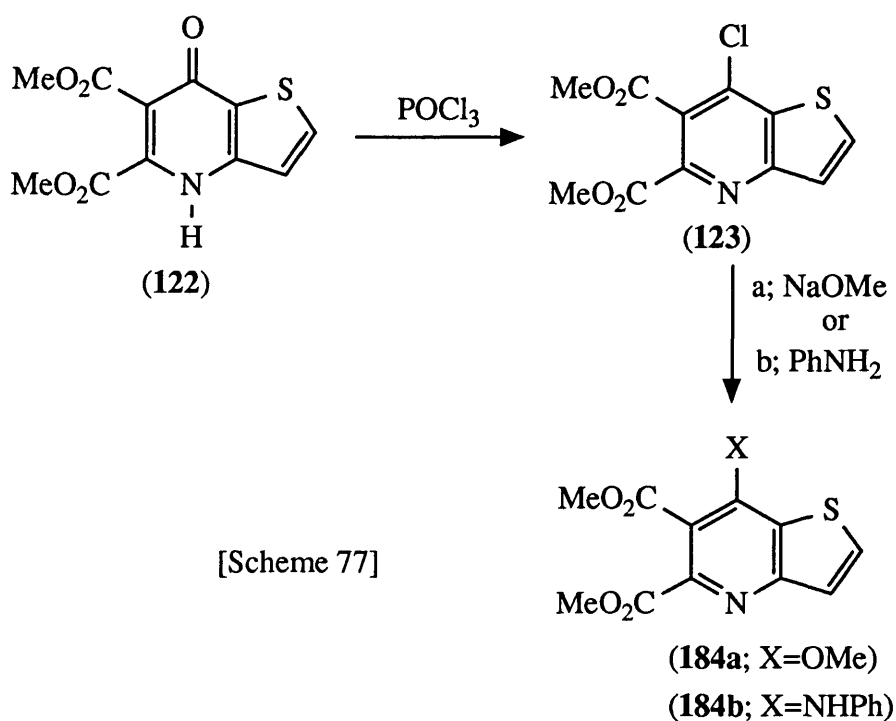
The reaction of thienopyridine N-oxides with electrophiles also results in substitution of the pyridine ring but this will be discussed in Section 1.2.4.4.a.

1.2.4.2 Nucleophilic Substitution Reactions

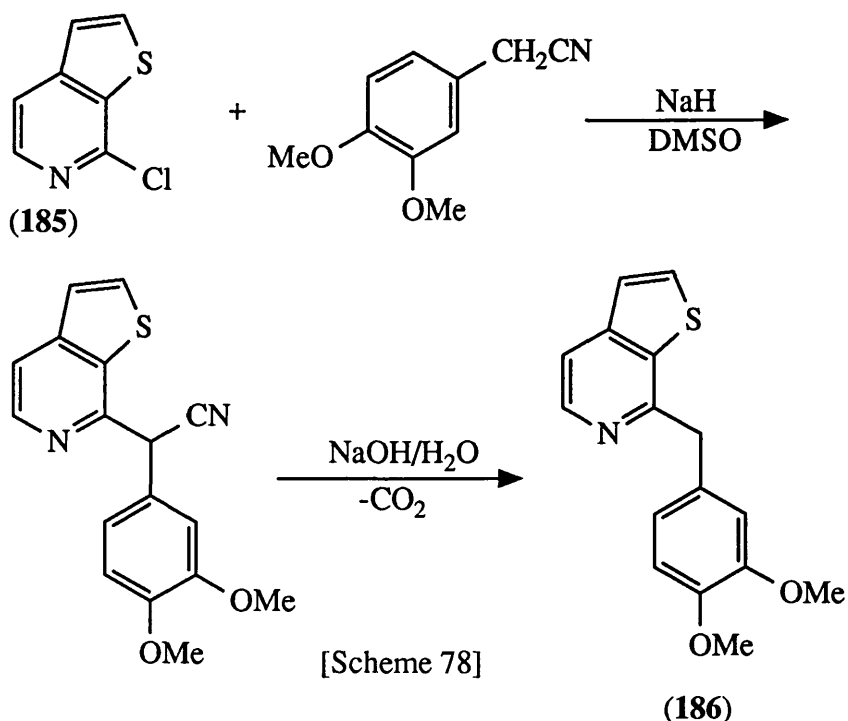
The only nucleophilic substitution reaction to occur on non-substituted thienopyridines involves the intermediacy of organolithium derivatives. When the thienopyridine is treated with organolithium compounds, nucleophilic attack at the 6-position occurs but metallation of the 2-position to afford the 2-lithiated product is also possible (see also Section 1.2.4.3). Thus, treatment of thieno[2,3-b]pyridine with N-butyl lithium¹³³ at 25-30°C followed by loss of lithium hydride gives the 6-butyl derivative (47%) and also recovered starting material (53%). At lower temperatures, with methyl lithium, the same thienopyridine is converted into 6-methylthieno[2,3-b]pyridine (**183**) in only 25% yield but recovered starting material is also obtained in 75% yield [Scheme 76]. The authors believed that the starting material was a result of hydrolysis during work-up of the 2-lithio derivative (see Section 1.2.4.3) and therefore lower temperatures appeared to favour formation of the 2-substituted derivative over that of the 6-substituted derivative.



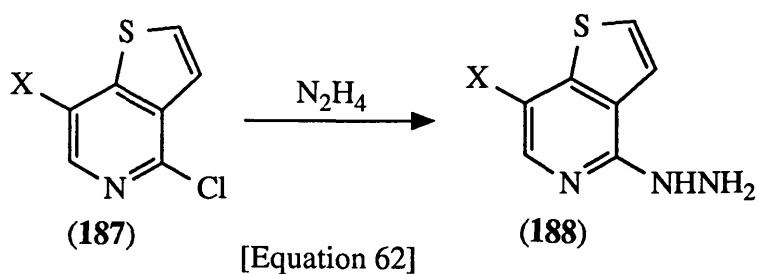
Nucleophilic substitution reactions occur more readily in substituted thienopyridines. For example, chlorothienopyridines, prepared from the reaction of thienopyridones and phosphoryl chloride¹⁹⁰, may be attacked by a variety of nucleophiles^{178,179,190,202,285,291,292}, including alkoxides, thiols and primary and secondary amines. Examples include the reaction of the thienopyridone (122) with phosphoryl chloride followed by treatment with sodium methoxide or aniline to afford the corresponding substituted products (184a and b) [Scheme 77].



7-Chlorothieno[2,3-c]pyridine (**185**) and 4-chlorothieno[3,2-c]pyridine have been used as intermediates in the preparation of substances of potential pharmacological activity²⁹³. For example, the chlorine atom in (**185**) was displaced by the anion derived from 3,4-(dimethoxy)phenylacetonitrile to give product (**186**) [Scheme 78].



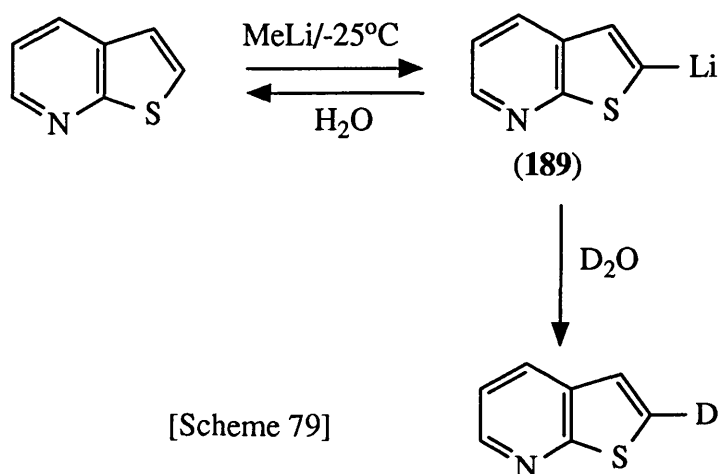
Halogen atoms α to the nitrogen in the pyridine ring are more reactive towards nucleophiles than halogens in other sites. For example, the 4-substituent in 4-chloro-7-halothieno[3,2-c]pyridines (**187**) is selectively substituted by hydrazine²⁸⁵ to afford (**188**) [Equation 62].



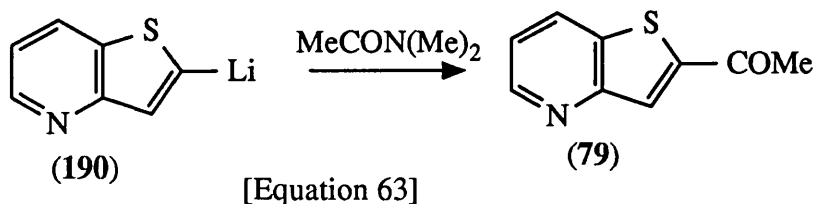
Under more forcing conditions, however, the halogen atoms at less reactive sites can be substituted. For example, both 3-bromothieno[2,3-b]pyridine²⁸⁶ and 5-bromothieno[2,3-b]pyridine²⁹³ give the corresponding nitrile derivatives with copper (I) cyanide in refluxing DMF. Thienopyridine N-oxides also undergo reactions of this type and these will be discussed in Section 1.2.4.4.

1.2.4.3 Lithium Derivatives of Thienopyridines

As discussed in the previous section, treatment of thieno[2,3-b]pyridine with methyl lithium¹³³ gives the 6-methyl derivative (**183**) in 25% yield and starting material in 75% yield. It was believed that the starting material was obtained as a result of hydrolysis of 2-lithiothieno[2,3-b]pyridine (**189**) during work-up. Evidence to support this theory was obtained when the reaction mixture was treated with deuterium oxide, then water and in this case, the recovered thieno[2,3-b]pyridine consisted of approximately equal amounts of 2-D and 2-H isomers [Scheme 79].

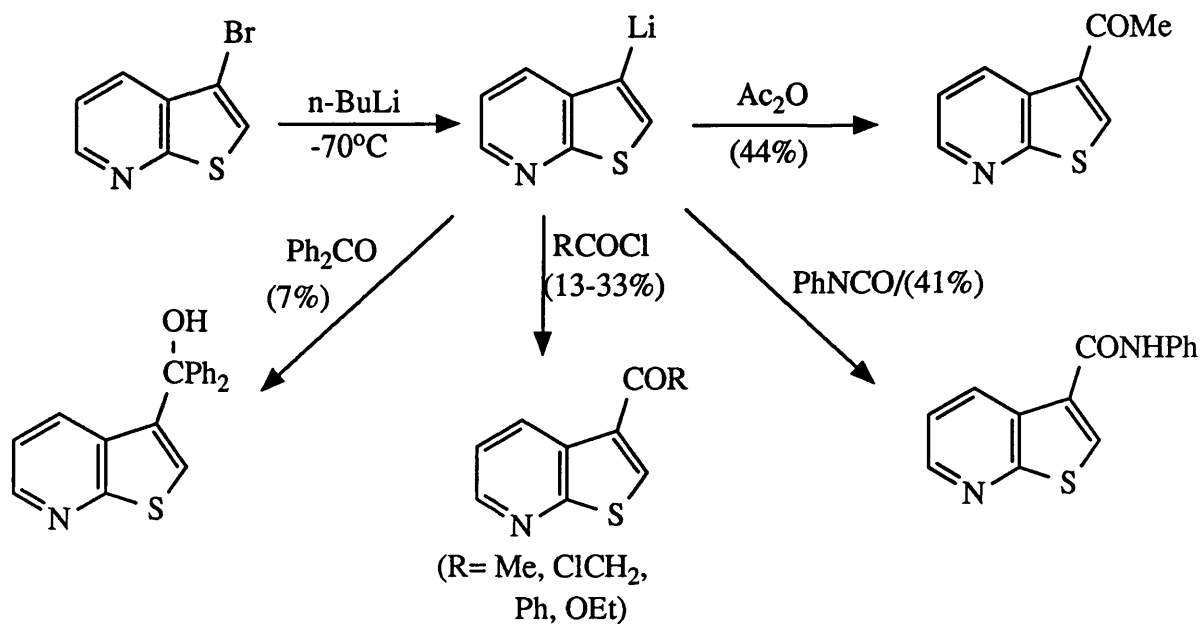


Although Klemm did not report further reactions of (189) with other electrophiles in that paper¹³³, thienopyridines which are lithiated at C-2 have been reacted with electrophiles to afford 2-substituted products²⁸⁸. For example, 2-lithiothieno[3,2-b]pyridine (190) may be reacted with N,N-dimethylacetamide to afford 2-acetylthieno[3,2-b]pyridine (79) [Equation 63].



As discussed previously (Section 1.2.4.2) ~~that~~ formation of the 6- and 2-isomers result from competing processes but lithiation at the C-2 position appears to be favoured by low reaction temperatures¹³³. Thus, thieno[2,3-b]pyridine-2-aldehyde is obtained in 66% yield by the formylation of the lithio derivative²⁹⁵, prepared at -70°C. However, it has been reported²⁸⁴ that thieno[2,3-c]- and [3,2-c]pyridines are not metallated in the thiophene ring by n-butyl lithium at -70°C, but undergo an addition reaction at the carbon-nitrogen double bond.

Lithiation may be carried out more effectively on thienopyridines, by halogen-metal interchange at low temperatures. The lithiation of 3-bromothieno[3,2-c]pyridine with ethyl lithium at -70°C followed by reaction with carbon dioxide affords thieno[3,2-c]pyridine-3-carboxylic acid²⁸⁴. Klemm and Merrill²⁹⁵ prepared 3-lithiothieno[2,3-b]pyridine similarly and have used it as an intermediate to a number of thienopyridines [Scheme 80]. Other examples have also been reported^{188,296}.

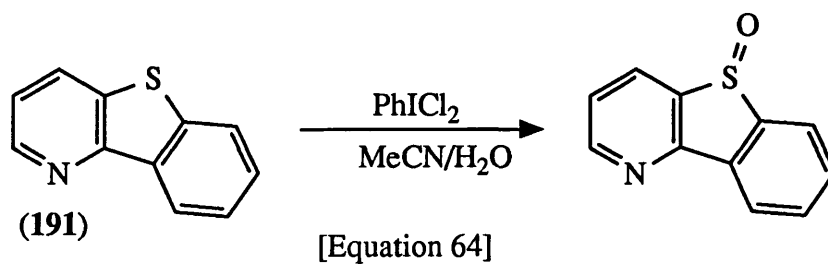


[Scheme 80]

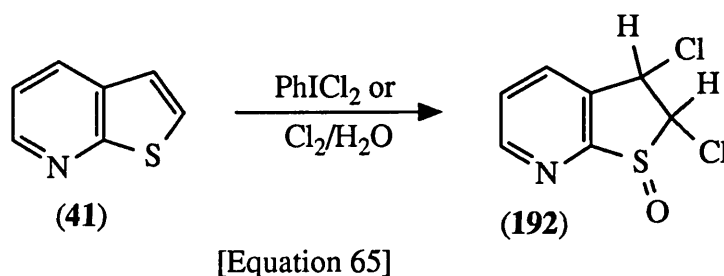
1.2.4.4 Oxidation of Thienopyridines

In thienopyridine chemistry, there is the possibility of oxidation on the nitrogen atom of the pyridine ring to form N-oxides or oxidation on the sulfur atom of the thiophene ring to form either sulfoxides or sulfones. Peracids, such as peracetic acid or *m*-chloroperbenzoic acid selectively oxidise the nitrogen atom in thienopyridines^{136,297,298}. Recently a new reagent, magnesium monoperoxyphthalate hexahydrate has also been utilised to afford thienopyridine N-oxides²⁹⁹ in 67% yield.

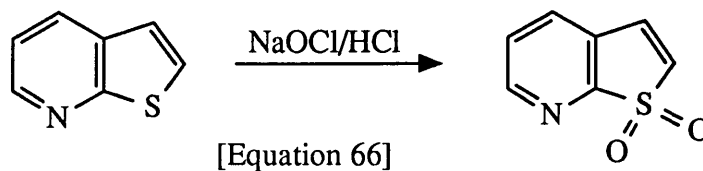
Oxidation of the sulfur atom to afford sulfoxides or sulfones is less easily achieved but iodobenzene dichloride converts nonaromatic cyclic sulfides such as 1,3-dihydrothieno[3,4-b]- and [3,4-c]pyridines into sulfoxides²⁶⁶. Certain aromatic tricyclic structures such as benzothieno[3,2-b]pyridine (**191**) also give sulfoxides with this reagent²⁹⁸ [Equation 64].



When iodobenzene dichloride or chlorine water²⁶⁶ are used to oxidise thieno[2,3-b]pyridine (**41**), the expected sulfoxide is not obtained but instead, a low yield of the oxidation/addition product, 2,3-dichloro-2,3-dihydrothieno[2,3-b]-pyridine 1-oxide (**192**) is obtained [Equation 65].

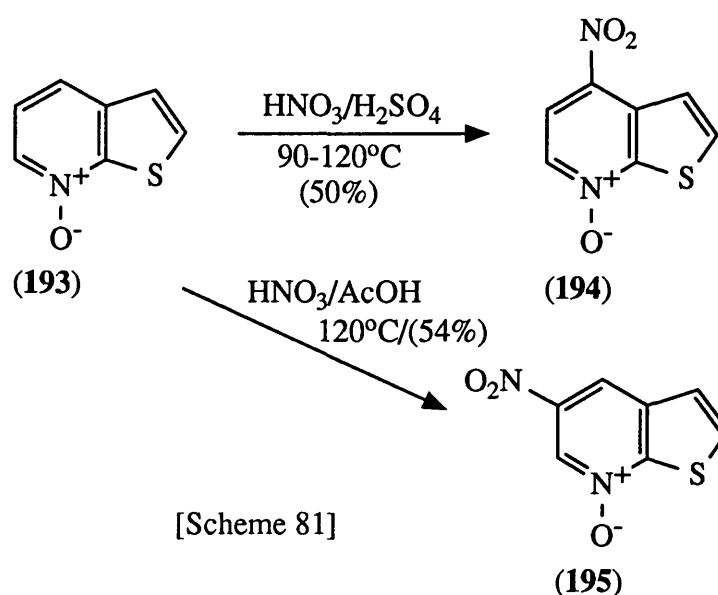


Sulfones of thieno[2,3-b]-, [3,2-b]- and [2,3-c]pyridines have been prepared³⁰⁰ by the reaction of the thienopyridine with sodium hypochlorite and dilute hydrochloric acid [Equation 66].



a) Reactions of Thienopyridine N-oxides

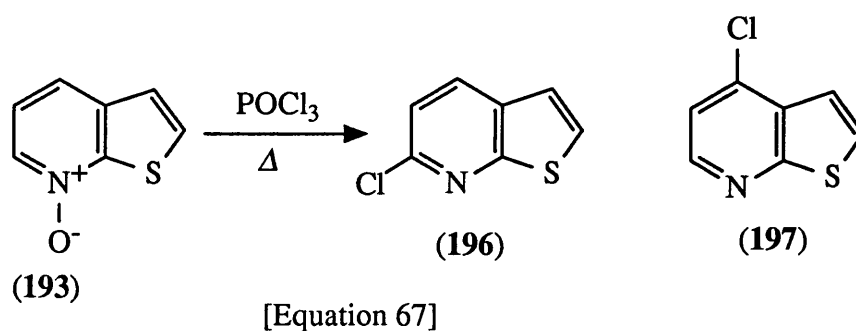
Thienopyridine N-oxides undergo electrophilic substitution reactions in the pyridine ring whereas thienopyridines are substituted in the thiophene ring. Nitration²⁹⁷ of thieno[2,3-b]pyridine N-oxide (**193**) in sulfuric acid gives 4-nitrothieno[2,3-b]pyridine N-oxide (**194**) in 50% yield, while nitration in acetic acid forms the isomeric 5-nitrothieno[2,3-b]pyridine (**195**) in 54% yield [Scheme 81].



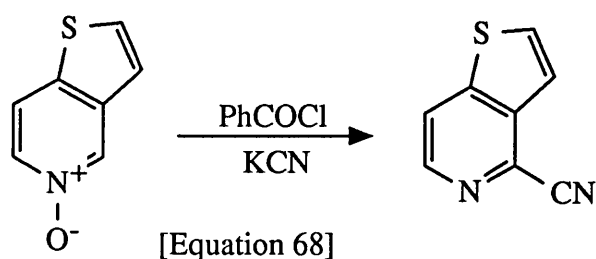
Formation of the 4-nitro derivative (**194**), is in close analogy with electrophilic substitution reactions of pyridine N-oxides, with nitration occurring by attack of the nitronium ion on the unprotonated N-oxide (Section 1.1.4.1). The authors suggested a complex reaction mechanism, for the formation of the 5-nitro derivative, involving a mixture of nitrate and acetate anions (NO₃⁻ and AcO⁻) and the cations resulting from the protonation of water, nitric acid and acetic acid (H₃O⁺, H₂NO₃⁺ and AcOH₂⁺).

Other electrophilic substitution reactions of thienopyridine N-oxide derivatives have also been reported^{290,301}.

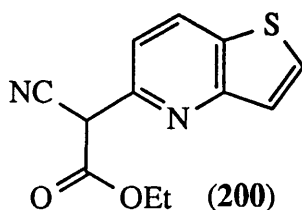
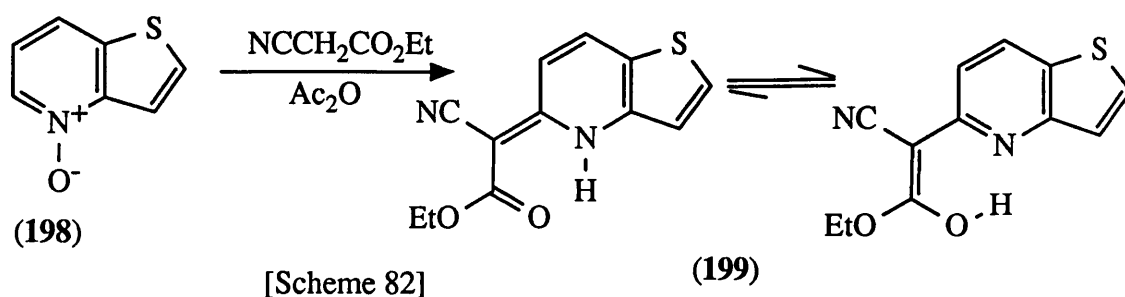
Thienopyridine N-oxides also undergo nucleophilic substitution reactions with phosphoryl chloride^{301,302} to afford chlorothienopyridines. For example, thieno[2,3-b]pyridine N-oxide (**193**) was refluxed with phosphoryl chloride to afford 6-chloro- (**196**) and 4-chlorothieno[2,3-b]pyridine (**197**) in 31% and 54% yields respectively [Equation 67].



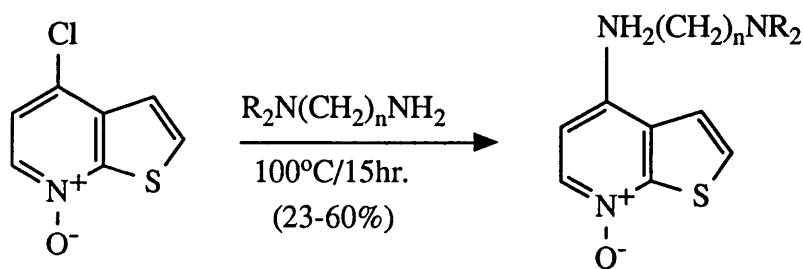
Thienopyridine N-oxides may also react with benzoyl chloride and the cyanide ion (Riessert-Henze reaction) to produce cyanothienopyridines^{303,304} [Equation 68].



Treatment of thieno[3,2-b]pyridine N-oxide (**198**) with ethyl cyanoacetate and acetic anhydride at room temperature³⁰⁵ gives the thienopyridine derivative (**199**) in 27% yield [Scheme 82]. This tautomeric mixture (**199**), is a more accurate representation of the product (on the basis of IR spectroscopy) rather than the simpler structure (**200**).



Finally, halogen atoms in the 4-position of thieno[2,3-b]pyridine N-oxides undergo nucleophilic substitution but not particularly readily²⁹⁷. This may be due to the electron release from the thiophene ring, reducing the activating influence of the N-oxide group [Scheme 83].

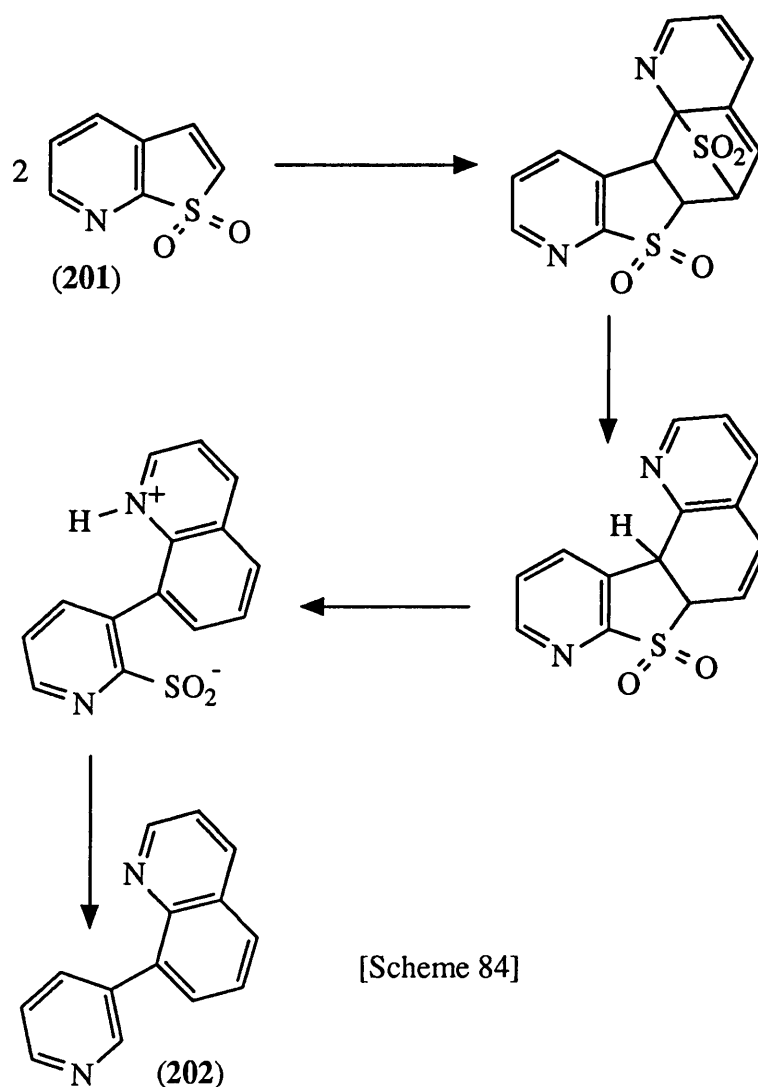


[Scheme 83]

b) Reactions of Thienopyridine Sulfones

Thienopyridine sulfones can undergo Diels-Alder reactions with the dienophiles

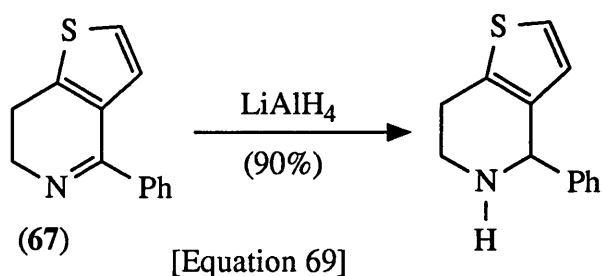
cyclopentadiene, anthracene and naphthacene^{300,306}. Thieno[2,3-b]pyridine sulfones (**201**) can also undergo self condensation³⁰⁰ with elimination of sulfur dioxide to give 8-(3'-pyridyl)quinoline (**202**). The mechanism proposed for this reaction is shown in Scheme 84.



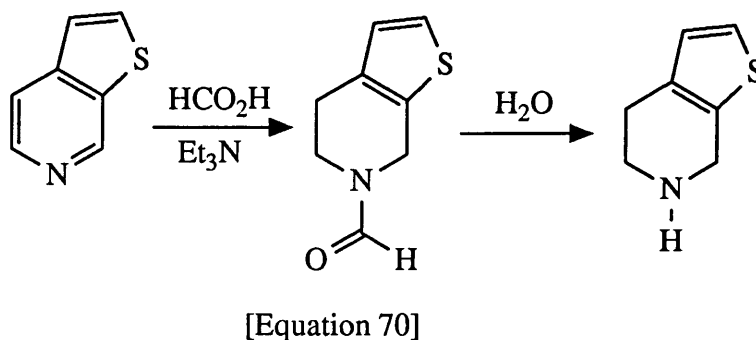
Sulfones also undergo 1,3-dipolar cycloadditions³⁰⁷ with diazomethane, diazoethane, ethyl diazoacetate, phenyldiazomethane and phenyl azide to give tricyclic compounds (Section 1.2.4.9).

1.2.4.5 Reduction of Thienopyridines

Thienopyridine quaternary salts may be reduced by sodium borohydride^{136,146,308,309} to afford the N-alkyl-4,5,6,7-tetrahydrothienopyridine while the azomethine bond in the dihydro derivative such as (67) may be reduced by lithium aluminium hydride¹⁴⁸ [Equation 69].



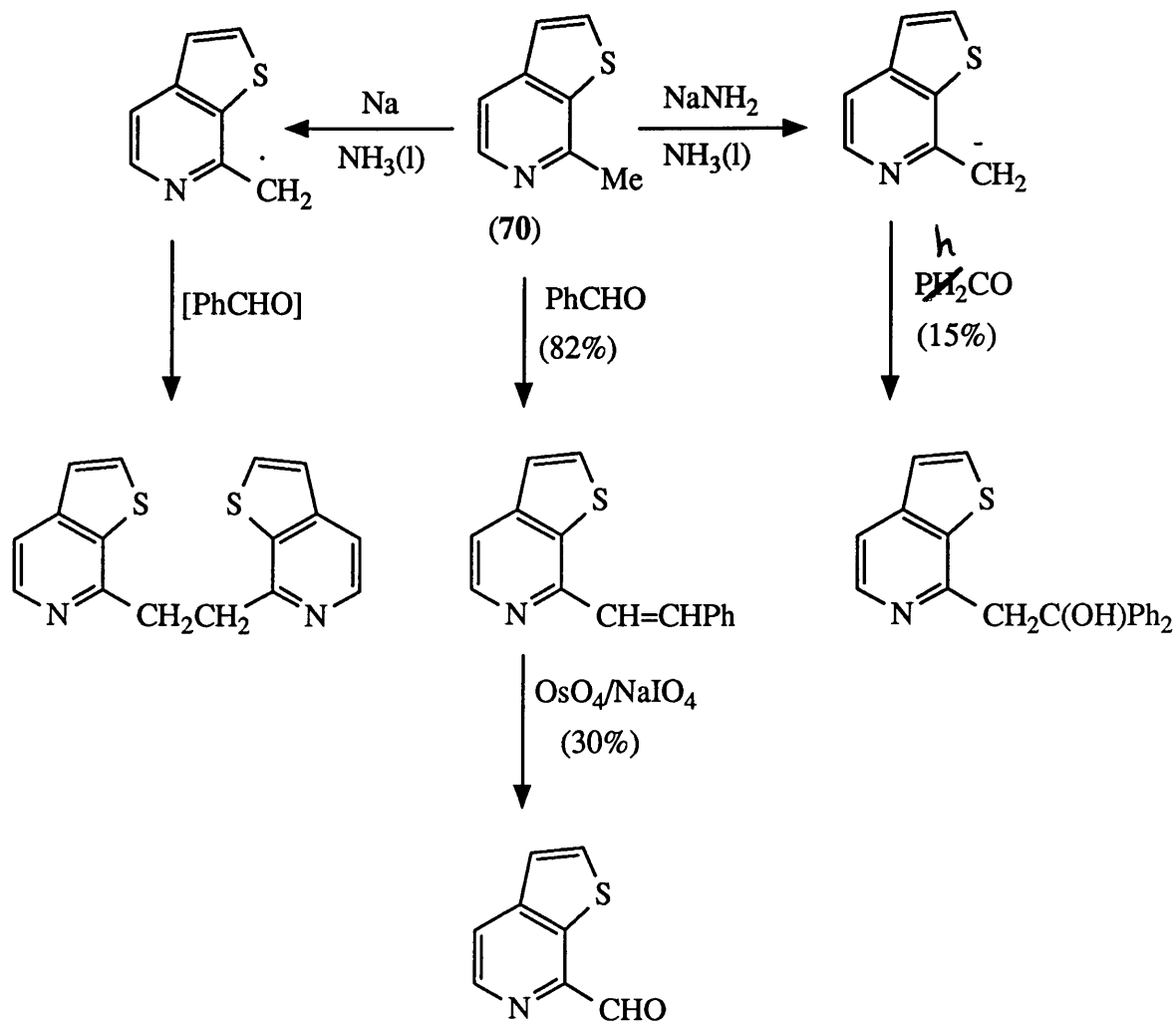
Reductive N-formylation followed by hydrolysis has been employed³⁰⁸ as a route to 4,5,6,7-tetrahydrothieno[2,3-c]- and [3,2-c]pyridines [Equation 70].



1.2.4.6 Reactions of Active Methyl Groups

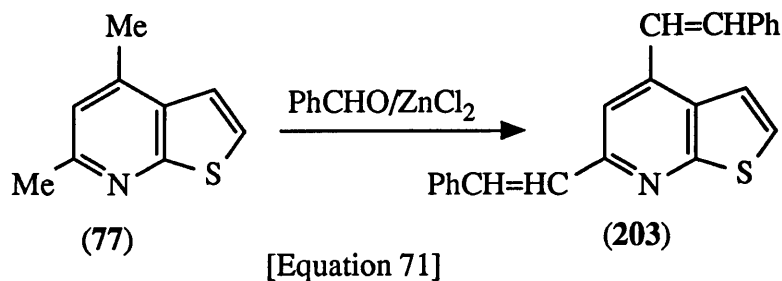
Methyl groups in the active positions of thienopyridines, like 7-methylthieno-[2,3-c]pyridine (70), undergo a variety of reactions¹³⁶, some of which are shown in

Scheme 85.



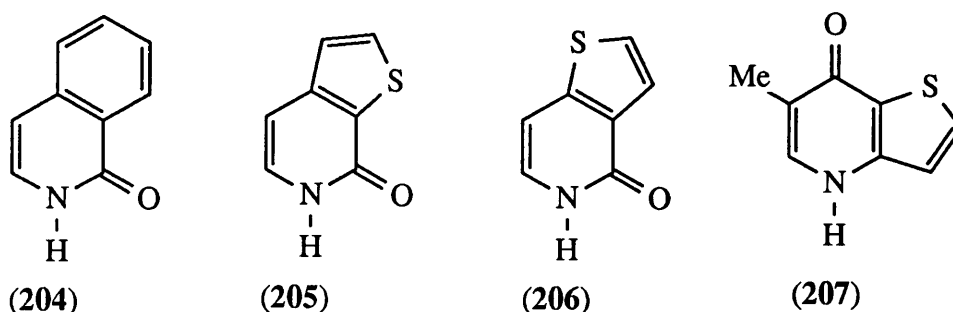
[Scheme 85]

Various thienopyridines have also undergone similar reactions¹³⁶. The reaction of 4,6-dimethylthieno[2,3-b]pyridine (77) with benzaldehyde¹⁶² in the presence of zinc chloride affords the dibenzylidene (203) [Equation 71].



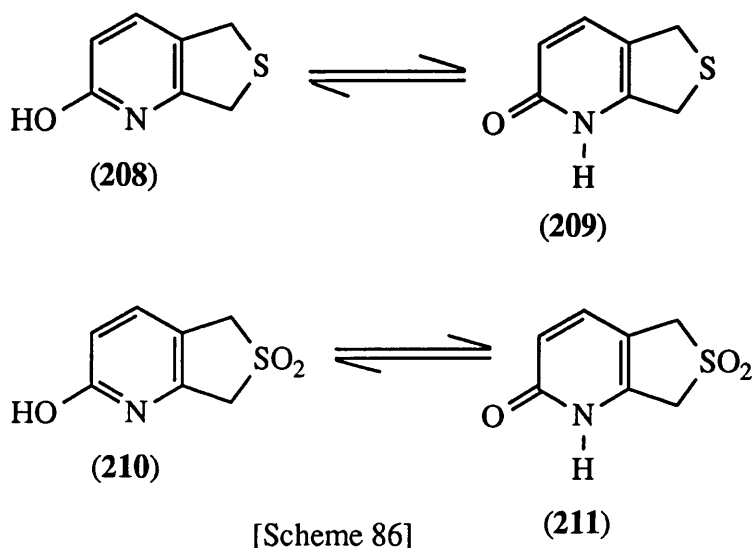
1.2.4.7 Hydroxythienopyridines

There have been only a few hydroxythienopyridines described in the literature, but the major point of interest is the extent to which these compounds exist as the hydroxy or keto tautomer. Both UV and NMR spectroscopy have been used to determine the preferred structure. For example, the UV²⁹⁵ and NMR²⁸⁵ spectra of isocarbostyryl (**204**) and its analogues thieno[2,3-*c*]pyridine (**205**) and thieno[3,2-*c*]pyridine (**206**) are very similar and exist in the keto form as does (**207**).

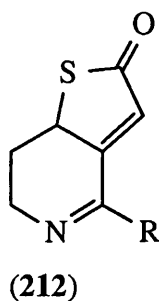


However, 5-hydroxythieno[2,3-*b*]pyridine²⁹⁴ exists totally in the hydroxy form while studies on pyridoxine-type analogues^{269,271,272,310-313}, which contain a 7-hydroxythieno[3,4-*c*]pyridine system, show that the oxygen function β to the nitrogen exists in the hydroxy form. It has also been reported²⁶⁸ that 1,3-dihydro-5-hydroxythieno[3,4-*b*]pyridine derivatives (**208-211**) exist in the keto

form exclusively in the solid state, but in dioxan (208)-(209) and (210)-(211) existed in the ratios 0.43:1 and 0.49:1 respectively [Scheme 86].

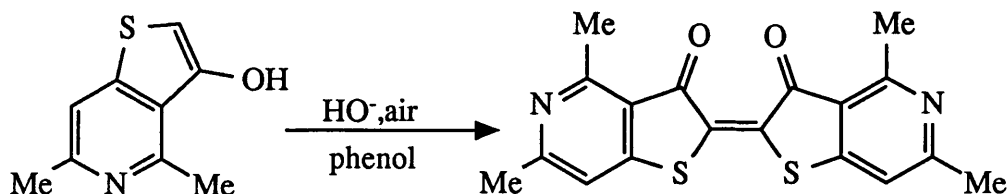


No 2-hydroxy derivatives of fully aromatic thienopyridines are known, and the UV and IR spectra of (212), the only 2-oxygenated compound recorded to date¹⁴⁶, indicates no evidence of the hydroxy tautomer. 3-Hydroxythienopyridines appear to exist in the enolic form. For example, Sheehan and Leitner²²⁰ found no chemical or spectroscopic evidence for the keto form in 3-hydroxythieno[3,2-b]-pyridine



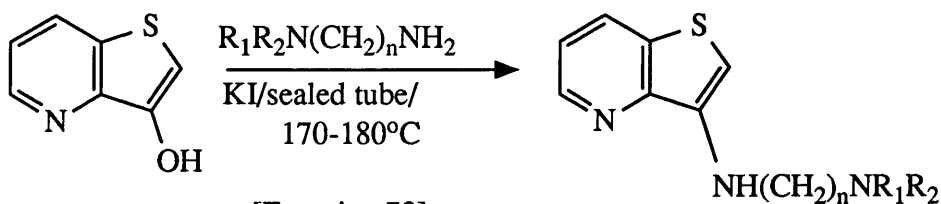
Early interest in hydroxythienopyridines centred on their potential use for the preparation of thioindigo dyes^{129,131,132,219}. Oxidative coupling occurs after brief treatment with concentrated sulfuric acid at 200-230°C, or exposure of an alkaline

solution of phenol to air [Equation 72].



[Equation 72]

Nucleophilic displacement of the hydroxy group in 3-hydroxythieno[3,2-b]pyridine by a variety of amines has been reported^{314,315} [Equation 73]. The reaction proceeds in the presence of a catalytic quantity of potassium iodide and it seems likely that the 3-iodo compound is an intermediate.

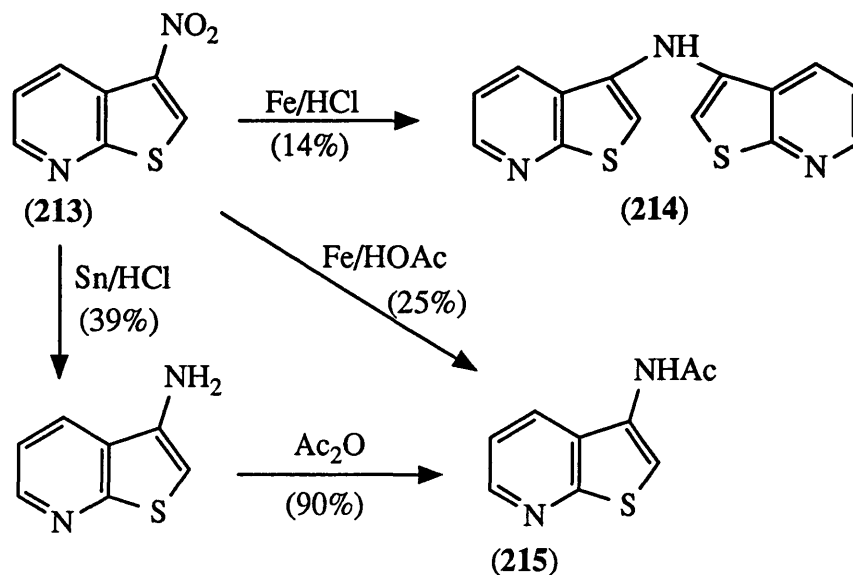


[Equation 73]

1.2.4.8 Aminothiopyridines

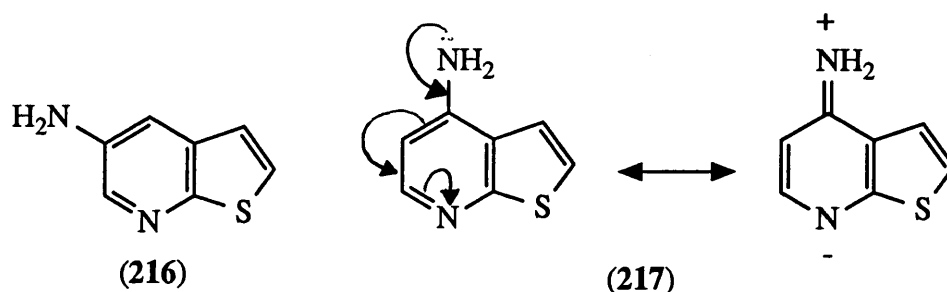
When a primary amine group is attached directly to the thiophene ring of thienopyridines, the compound is unstable as the free base but stable as the N-acetyl derivative, like simple aminothiophenes. Klemm *et al*¹³⁴ reported the reduction of 3-nitrothieno[2,3-b]pyridine (**213**) with tin/hydrochloric acid to give the 3-amino derivative which was acylated with acetic anhydride to give the amide (**215**) [Scheme 87]. However, the attempted reduction with iron/hydrochloric acid gave only the diamine (**214**). Amide (**215**) may also be obtained directly from (**213**) in 25% yield by the reaction with iron/acetic acid, at 100°C. A more efficient method using iron/acetic acid/acetic anhydride, has also been

described²⁸⁷.

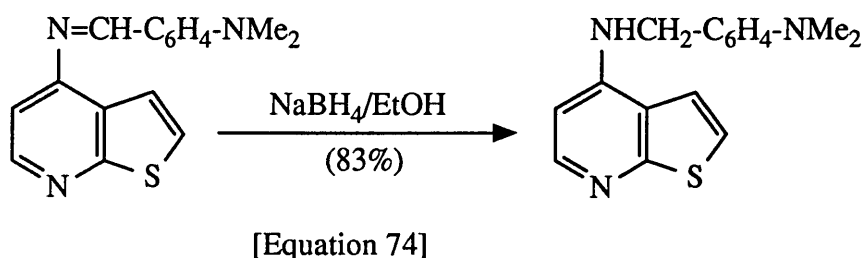


[Scheme 87]

Nitro groups attached to the pyridine nucleus of thienopyridines are reduced without complications, thus, both 4- and 5-nitrothieno[2,3-b]pyridine N-oxides give amines on treatment with iron/acetic acid (67%) and tin/hydrochloric acid (41%) with the N-oxide group also being removed during reduction²⁹⁷. Stable 3-aminothienopyridine derivatives can also be prepared from the intramolecular cyclisation of cyanopyridine derivatives (Section 1.2.3.1). One report²⁹⁴ has shown that 5-aminothieno[2,3-b]pyridine (**216**) readily gives Schiff bases when reacted with a variety of aldehydes. Under the same conditions however, 4-aminothieno[2,3-b]pyridine (**217**) failed to react with these aldehydes²⁹⁷. This difference in reactivity was ascribed to the decreased nucleophilicity of the 4-amino derivative due to the resonance stability of (**217**) which was not possible in (**216**).



Schiff bases were eventually prepared²⁹⁷ from (217) by using molecular sieves in refluxing xylene containing a few drops of glacial acetic acid. These Schiff bases are readily reduced to secondary amines by sodium borohydride [Equation 74].

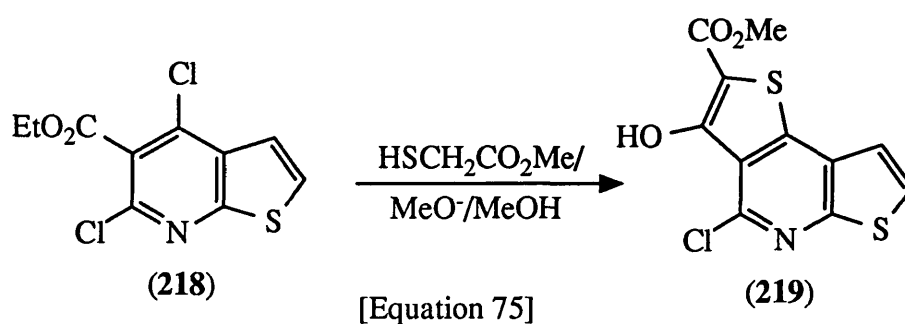


5-Aminothieno[2,3-b]pyridine behaves as a typical primary amine; it can be diazotised³¹⁶, the diazonium salt yielding 5-bromo- (48%), 5-chloro- (40%), 5-hydroxy- (65%) and 5-cyanothieno[2,3-b]pyridine (13%) under the usual conditions.

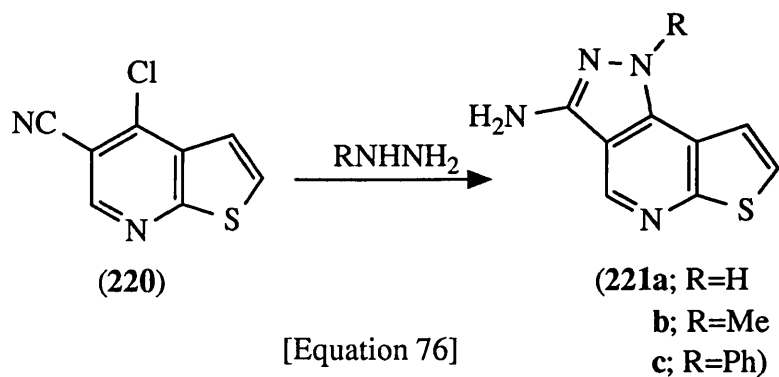
1.2.4.9 Tricyclic Compounds from Thienopyridines

Thienopyridines have been used to prepare a wide range of tricyclic compounds. Both Meth-Cohn¹⁸⁸ and Barker^{179,201,292} have reacted halogenated thienopyridines with thioglycolate anions in the presence of a base to displace the halogen atom and give dithienopyridines after a Dieckmann type cyclisation. For example, 5-carboethoxy-4,6-dichlorothieno[2,3-b]pyridine (218) was treated with methyl

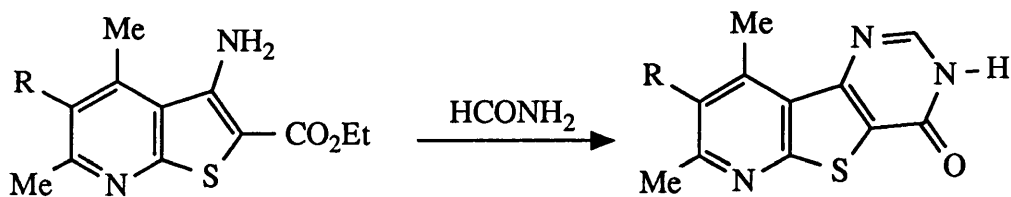
thioglycolate in the presence of sodium methoxide in methanol¹⁷⁹ to afford dithienopyridine (**219**) [Equation 75]. The tricyclic compound (**219**) has a [2,3-b:2',3'-d] type structure indicating that the halogen atom at C-4 is more reactive than the one at C-6.



Other reports have discussed the synthesis of tricyclic compounds from the reaction of thienopyridines and nitrogen nucleophiles. When 4-chloro-5-cyano-thieno[2,3-b]pyridine (**220**) is treated with hydrazine, methylhydrazine or phenylhydrazine³¹⁷, the products (**221a-c**) are obtained in 68-80% yields [Equation 76]. The tricyclic compounds are formed by the nucleophilic attack of the more basic nitrogen of the hydrazine, on the 4-position of the thienopyridine followed by cyclisation involving the cyano group at the 5-position.

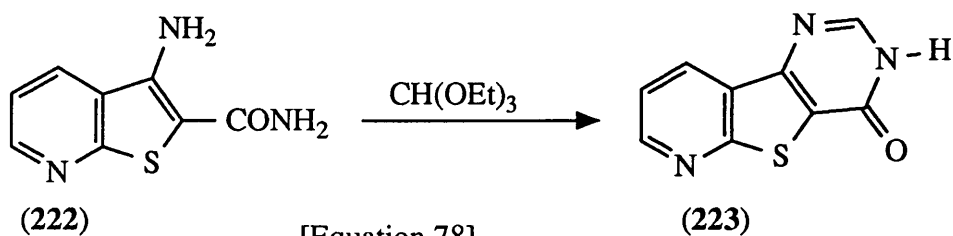


Russian workers^{318,319} have prepared tricyclic compounds from the reaction of thienopyridines with amides [Equation 77].



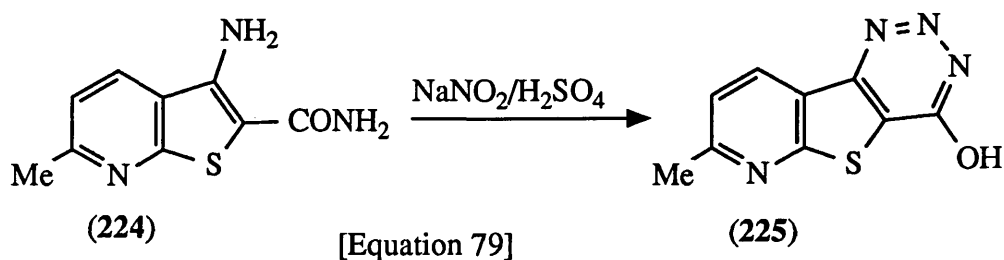
[Equation 77]

Thienopyridines have been reacted with both phenyl isothiocyanate³²⁰ and methyl isothiocyanate³²¹ to afford tricyclic compounds. Other authors have reported^{202, 230,322} the use of acetic anhydride to cyclise thienopyridines whilst the treatment of (222) with triethyl orthoformate²⁴⁸, gives the tricyclic compound (223) in 49% yield [Equation 78].

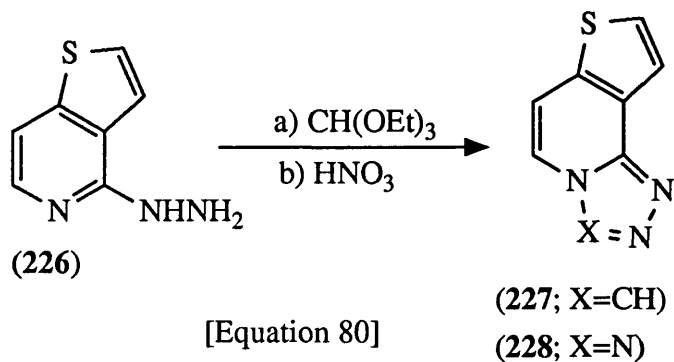


[Equation 78]

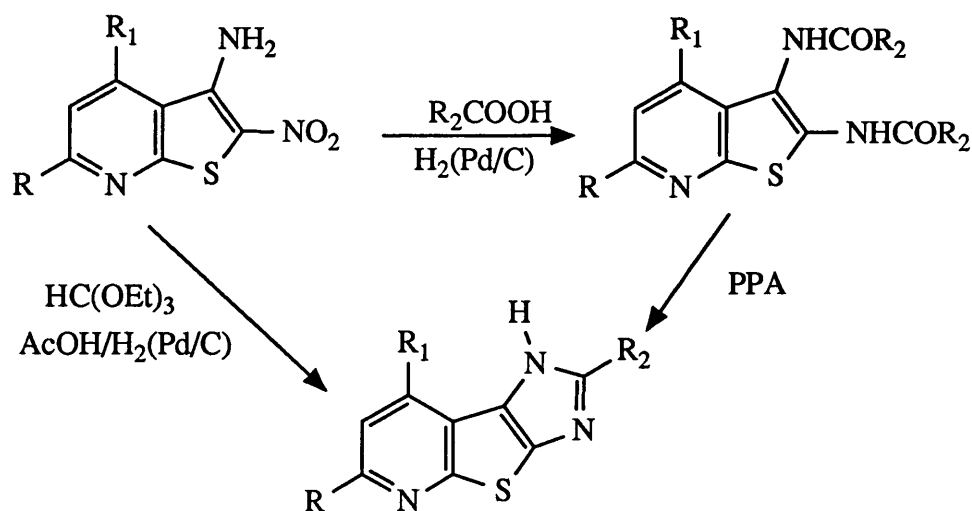
The diazotisation of thienopyridines such as (224) with sodium nitrite in concentrated sulfuric acid / acetic acid²⁴¹ gives tricyclic compounds such as the triazin-4(3H)-one (225) [Equation 79]. Other reports³²⁰ have also discussed the use of sodium nitrite to prepare tricyclic compounds.



Thienopyridines have also been cyclised on the nitrogen atom of the pyridine ring³²³⁻³²⁵. Reaction of 4-hydrazinothieno[3,2-c]pyridine (**226**) with triethyl orthoformate gives the 1,2,4-triazole (**227**), while then reaction of (**226**) with nitric acid gives the tetrazole (**228**)³²³ [Equation 80].

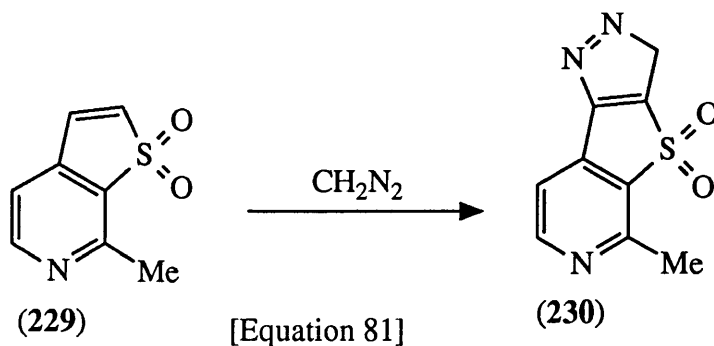


Guerrera *et al*³²⁶ reported an interesting synthesis of tricyclic compounds from thienopyridines. They described the preparation of 1H-imidazo[3',4':4,5]thieno[2,3-b]pyridines from thienopyridine derivatives by the two methods as shown in Scheme 88.



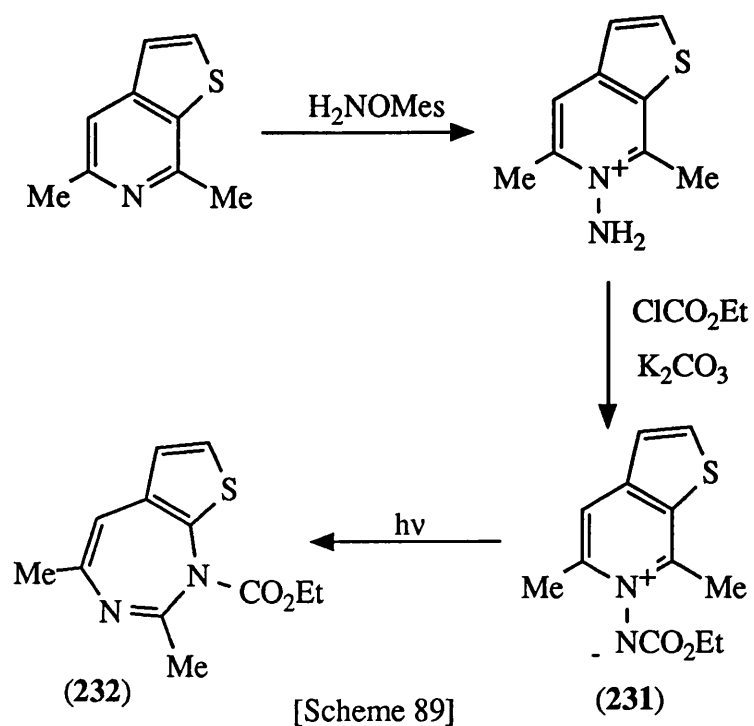
[Scheme 88]

Finally, 1,3-dipolar additions of diazomethane, diazoethane, ethyl diazoacetate, phenyldiazomethane and phenyl azide to 7-methylthieno[2,3-c]pyridine sulfone (229) produced tricyclic compounds³⁰⁷ such as (230) [Equation 81].

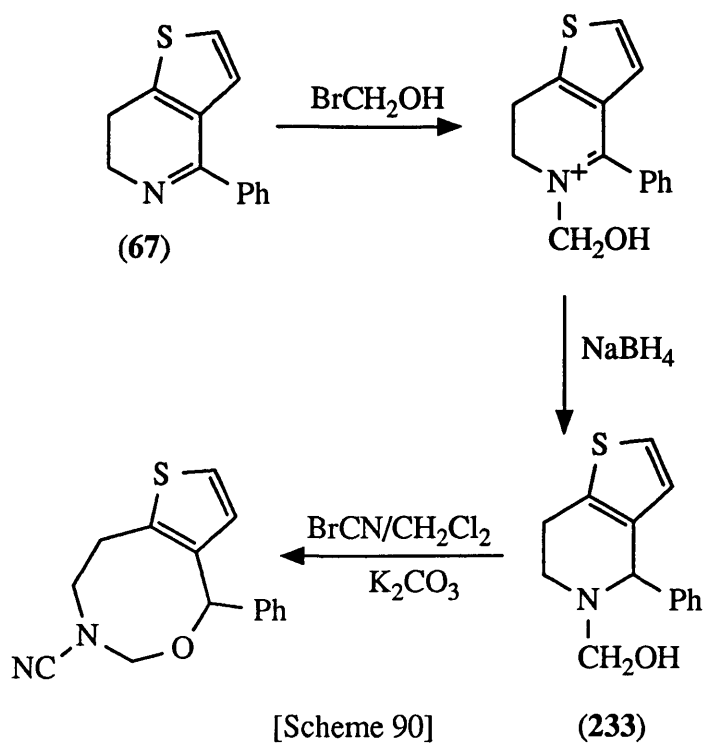


1.2.4.10 Miscellaneous Reactions

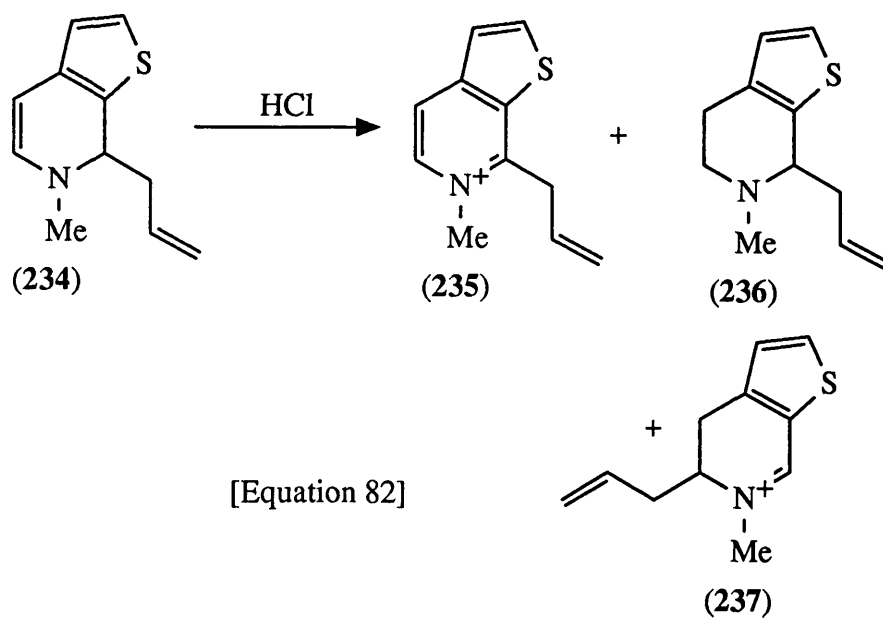
In a series of papers³²⁷⁻³²⁹ the synthesis of diazepines from thienopyridines has been discussed. Irradiation of 5,7-dimethylthieno[2,3-c]pyridine N-imide (231) for example results in the formation of the corresponding 1,3-diazepine (232) [Scheme 89].



Cyanogen bromide induced ring expansion of cyclic amino alcohols³³⁰ (233) affords medium-sized (8-11 membered) thieno-oxaza ring compounds [Scheme 90].



Thienopyridines may also undergo rearrangement reactions³³¹⁻³³³. For example, when the thienopyridine (234) is treated with hydrochloric acid, the disproportionation products (235) and (236) are obtained as the minor products while the main product is the rearranged compound (237) [Equation 82].



DISCUSSION

2. DISCUSSION

2.1 Introduction

The aim of this research project was to synthesise *ortho*-halogenated pyridine derivatives containing methylene groups activated by nitriles or esters, and then to react these derivatives with heterocumulenes such as carbon disulfide and phenyl isothiocyanate to prepare novel thienopyridines. In addition, thienopyridines were synthesised from the reaction of 3-cyano-2(1H)-pyridinethione with compounds containing a halogen atom adjacent to an active methylene group. The chemistry of these novel compounds was investigated with a view to preparing substituted thienopyridines and also new tricyclic compounds.

The discussion of this work will be sub-divided into six main sections:

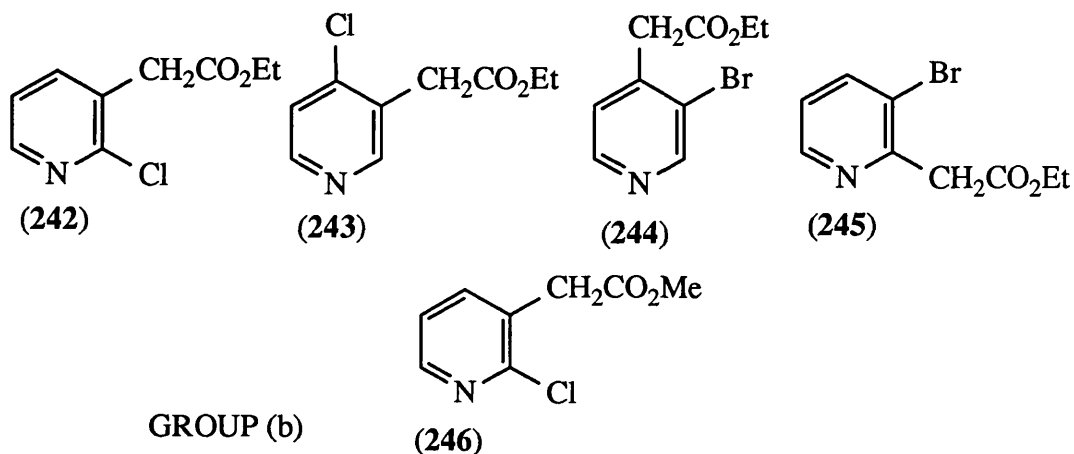
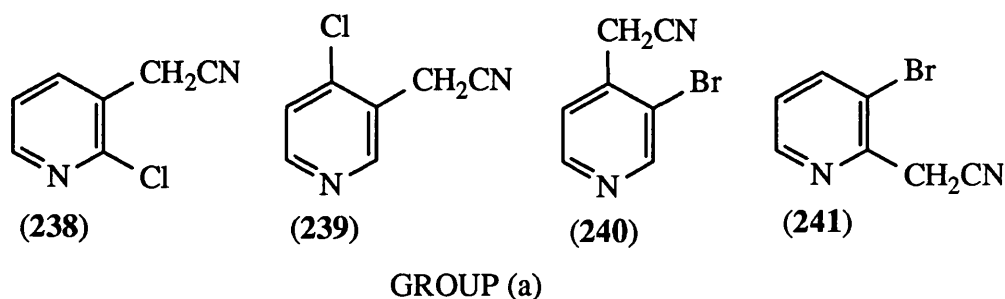
1. The synthesis of *ortho*-halogenated pyridine derivatives containing active methylene groups.
2. The synthesis of thienopyridines from the reaction of pyridine derivatives with heterocumulenes.
3. The synthesis of thienopyridines from pyridinethiones.
4. The reactions of thienopyridines.
5. Miscellaneous reactions.
6. Biological evaluation

2.2 Synthesis of *Ortho*-Halogenated Pyridine Derivatives Containing Active Methylene Groups.

The aim of the first area of study was to synthesise all eight *ortho*-halogenated pyridine derivatives (238-245). Of the possible isomers, only two, (238)³³⁴ and (244)¹¹⁹ had been previously reported. In addition derivative (246) was prepared. For the purpose of this discussion, compounds (238-246) will be classified into two sub-sections:

2.2.1 The synthesis of *ortho*-halogenated pyridine derivatives with methylene groups activated by nitriles (238-241).

2.2.2 The synthesis of *ortho*-halogenated pyridine derivatives with methylene groups activated by esters (242-246).



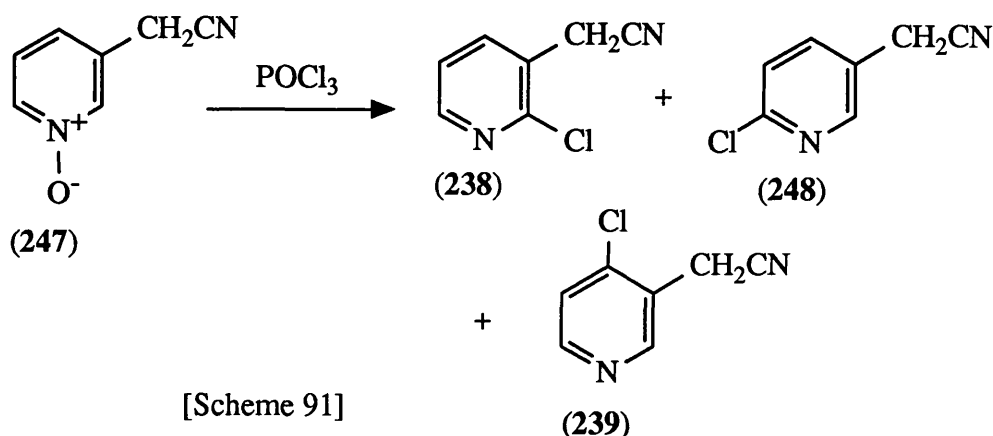
2.2.1 Synthesis of *Ortho*-Halogenated Pyridine Derivatives Containing Methylene Groups Activated by Nitriles

2-Chloro-3-cyanomethylpyridine (**238**) has been synthesised³³⁴ by the reaction of 3-cyanomethylpyridine N-oxide (**247**) (which had been prepared³³⁴ using a modification of the method of Mosher and Tessieri⁹⁶) in refluxing phosphoryl chloride. According to Okuda and Robison³³⁴, three products were obtained from this reaction: 2-chloro-3-cyanomethylpyridine (**238**) in 37% yield, 2-chloro-5-cyanomethylpyridine (**248**) in 14% yield and 3-cyanomethyl-5-hydroxypyridine in 7.8% yield. When this reaction was repeated as part of this study, however, the product mixture differed from that reported previously. The compounds (**238**) and (**248**) were obtained in 37% and 21% yields respectively while a third product was isolated in 5% yield [Scheme 91]. The mixture of three products obtained from the organic extractions was separated by column chromatography. The isolation of 3-cyanomethyl-5-hydroxypyridine (obtained from the aqueous phase³³⁴) was not attempted since it was not required as part of this study.

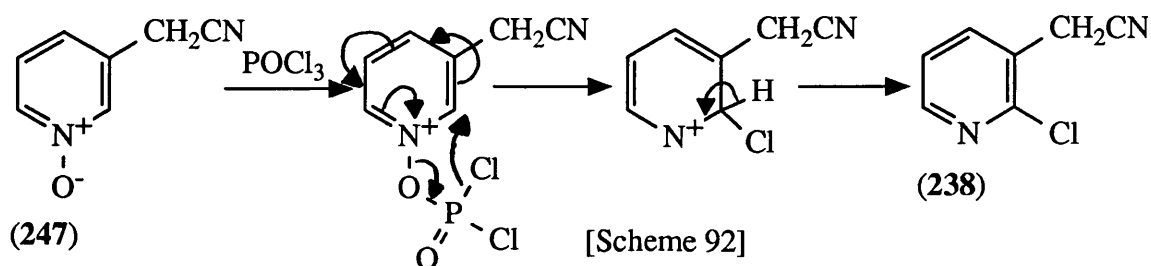
The melting points, IR and NMR spectra for (**238**) and (**248**) corresponded to those reported in the literature³³⁴. The IR spectrum of the third product confirmed the presence of a nitrile (CN_{str} at 2247cm^{-1}) while the molecular ions (m/z 154 and 152) and microanalysis indicated that the product could be an isomer of (**238**) and (**248**). The NMR spectrum appeared to be very similar to those obtained for the other products except the peaks for the protons of the pyridine ring were of the pattern expected for 3,4-disubstituted pyridines ie: a singlet at 8.56 δ for the proton at C-2 plus two doublets at 7.28 δ and 8.40 δ for the protons at C-5 and C-6 respectively. A singlet was also present at 3.82 δ for the alkyl CH_2 protons. All the analytical data indicated that the third product was 4-chloro-3-cyanomethylpyridine (**239**). This fortuitous synthesis of (**239**) allowed direct access to one of

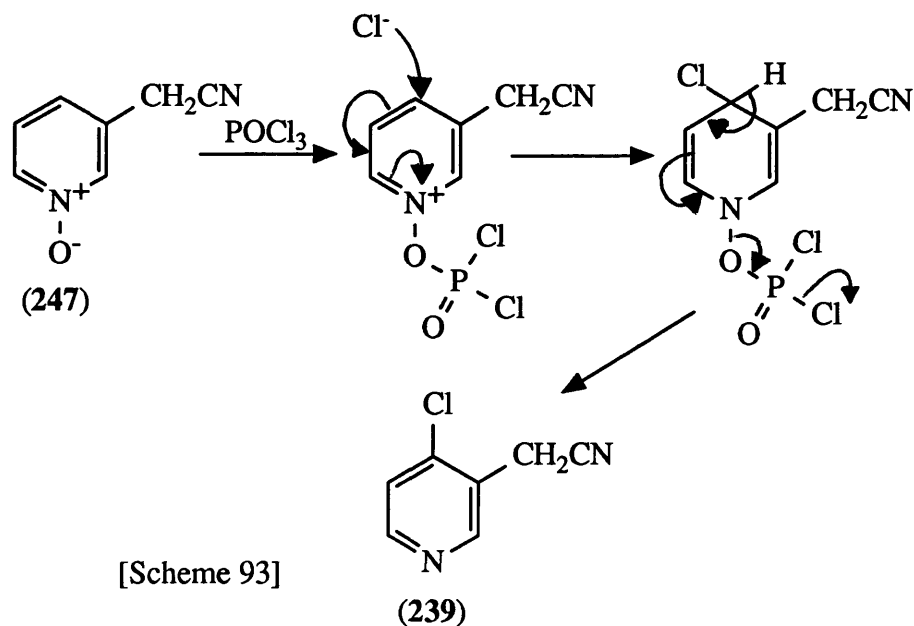
the desired cyanomethylpyridines in a single step from (247), albeit in very low yield.

It is impossible to say why (239) was never reported by Okuda and Robison³³⁴ but it may have involved the different techniques used in the working up of the reaction during this study compared to the original report.

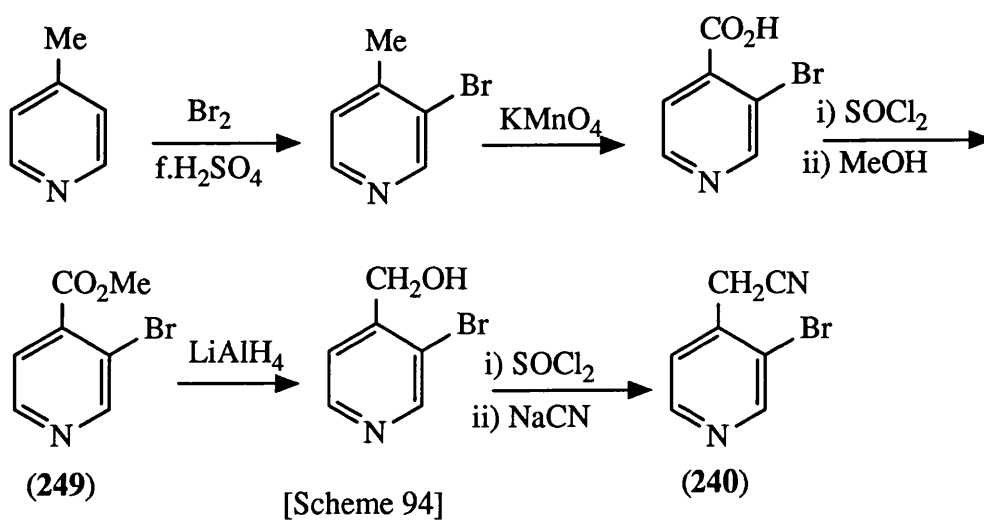


As discussed in Section 1.1.4.2.b, the mechanism for the reaction of a pyridine N-oxide and phosphoryl chloride involves both an intramolecular and an intermolecular process. Chlorination of (247) affords more of (238) and (248), than the 4-chloropyridine derivative (239), indicating that the intramolecular process is more prominent. A possible mechanism for the formation of (238) by an intramolecular route is shown in Scheme 92 while the formation of (239) *via* an the intermolecular mechanism is shown in Scheme 93.



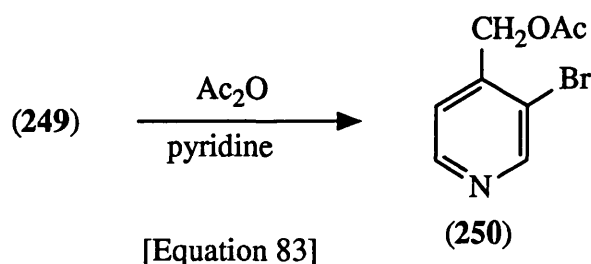


Originally it was believed that 3-bromo-4-cyanomethylpyridine (240) could be synthesised using the reaction sequence shown in Scheme 94.



This scheme, however, proved troublesome since the reaction of methyl 3-bromopyridine-4-carboxylate³³⁵ (249) and lithium aluminium hydride formed a complex from which the alcohol could not be isolated. In an attempt to prove that the hydroxy compound was formed during this reaction, the complex was stirred with a mixture of pyridine and acetic anhydride to give 4-acetoxymethyl-3-bromo-

pyridine (**250**) in only 6% yield [Equation 83]. The IR and NMR spectra were consistent with the proposed structure for (**250**), as was the molecular ion and microanalysis data.

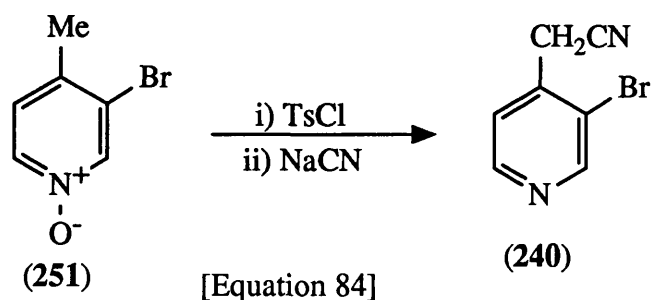


The synthesis of (**240**) by this route was not developed further since the yields were so low and difficulties were experienced in attempting to isolate the alcohol.

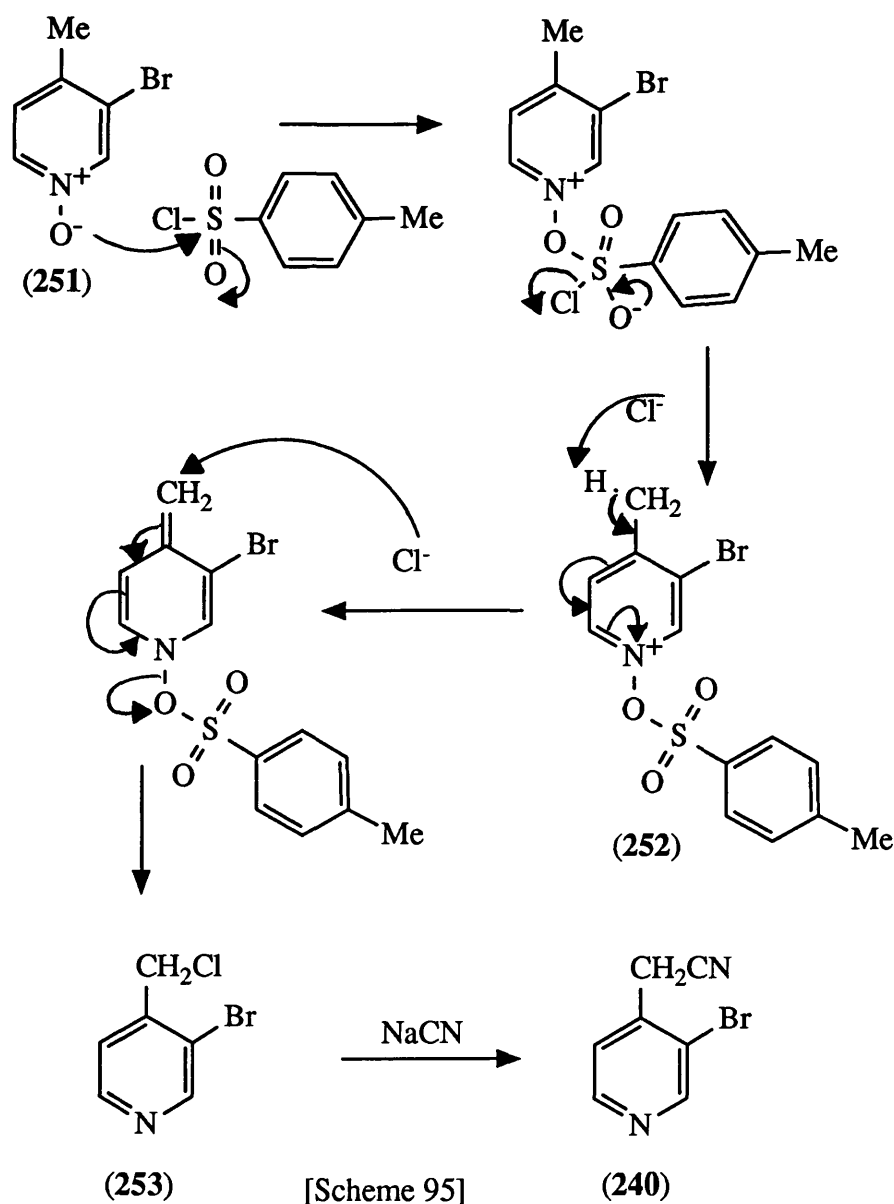
In an attempt to prepare (**240**) by alternative means, 3-bromo-4-methylpyridine³³⁶ was treated with N-bromosuccinimide (NBS) followed by reaction with sodium cyanide but no product was isolated. Further investigation indicated that 3-bromo-4-methylpyridine did not react with NBS to afford the desired bromomethyl intermediate.

An alternative synthesis was proposed for the preparation of (**240**) utilising the reaction of methylpyridine N-oxides and *p*-toluenesulfonyl chloride⁹⁹⁻¹⁰¹. Thus, the reaction of 3-bromo-4-methylpyridine N-oxide³³⁷ (**251**) and *p*-toluene sulfonyl chloride, followed immediately by addition of sodium cyanide [Equation 84] gave (**240**) in 19% yield after chromatography. The IR spectrum confirmed the presence of a nitrile group (2250cm^{-1}) while the NMR spectrum showed characteristic peak patterns for 3,4-disubstituted pyridines, a singlet at 8.66 δ for the proton at C-2 and two doublets at 7.42 δ and 8.48 δ for the protons at C-5 and C-6 respectively. A singlet at 3.82 δ for the two protons of the alkyl CH₂ group were also present. These spectra allied to the molecular ions (198 & 196) and the

were also present. These spectra allied to the molecular ions (198 & 196) and the microanalysis confirmed the structure of the product as being 3-bromo-4-cyano-methylpyridine (**240**).

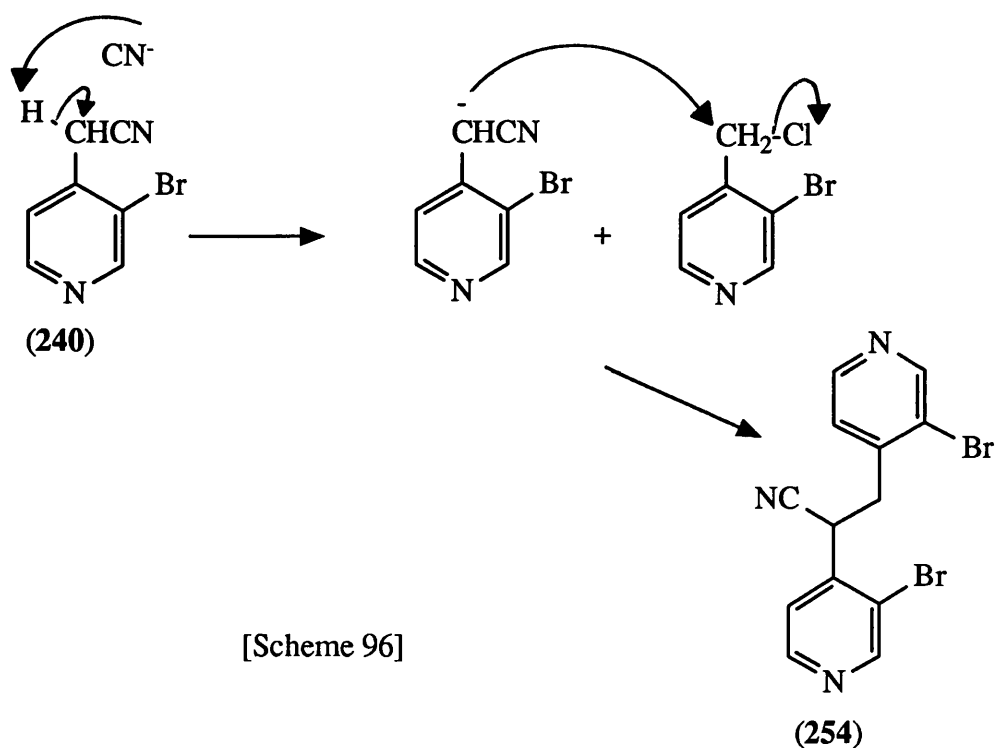


The reaction of the N-oxide (**251**) and tosyl chloride to afford the chloromethylpyridine derivative probably proceeds as shown in Scheme 95. Tosyl chloride is attacked by the oxygen anion of the N-oxide (**251**) to form the tosylate salt (**252**). A hydrogen atom on the methyl group, at the 4-position, is removed, resulting in the negative charge being delocalised into the pyridine ring. The $\text{CH}_2=$ group is now more susceptible to nucleophilic attack and therefore the chloride anion can attack this $\text{CH}_2=$ group, resulting in cleavage of the N-oxide bond to afford 3-bromo-4-chloromethylpyridine (**253**) which, being relatively unstable, is reacted immediately with sodium cyanide to afford (**240**).

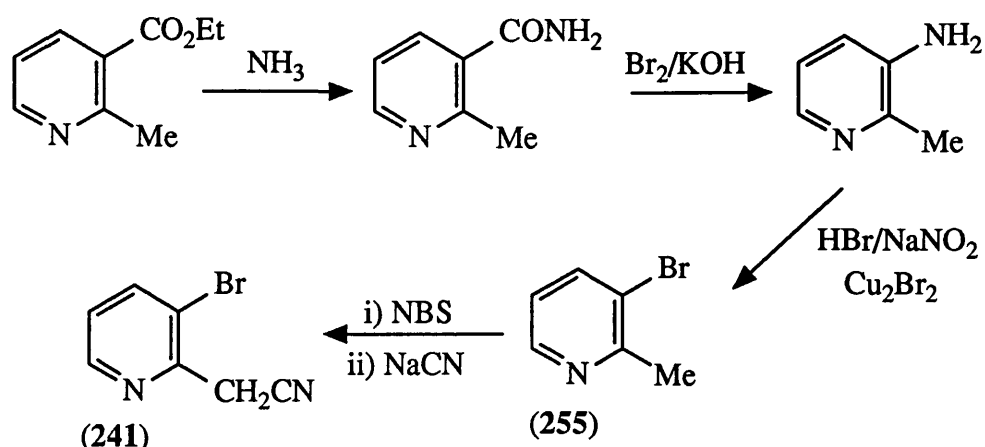


The low yield obtained in this reaction may be a result of the poor conversion of starting material into the chloromethyl intermediate. Other reactions of this type⁹⁹⁻¹⁰¹, have shown higher conversions to the chloromethyl derivatives. For example, under similar reaction conditions 2,6-dimethylpyridine N-oxide gives the 2-chloromethyl derivative in 72% yield whilst 5-ethyl-2-methylpyridine N-oxide provides the corresponding 2-chloromethyl derivative in 71% yield. In the case of (251), the bromine atom in the 3-position of the pyridine ring may have had an adverse influence on the yield due to electronic effects.

Also isolated from the reaction as a by-product, obtained in 5% yield, is a compound with an IR spectrum which confirms the existence of a nitrile function within the molecule (2246cm^{-1}) while the NMR spectrum has two sets of peaks for the protons belonging to the pyridine ring, indicating two pyridine rings. Both sets of peaks showed the configuration for 3,4-substitution and the two singlets for the protons at C-2 appeared at 8.81 δ and 8.74 δ . The doublets for the protons at C-5 in the two ring systems were found at 7.50 δ and 7.62 δ , while the doublets for the protons at the C-6 position of the rings were found at 8.55 δ and 8.64 δ . The peaks for the alkyl protons, however, were more complex and a multiplet was obtained corresponding to three alkyl protons instead of the expected peak pattern. The molecular ions (369, 367 and 365) and the microanalysis along with the IR and NMR data suggests the structure for the by-product to be 3-bromo-4[1-cyano-2-(3'-bromopyrid-4'-yl)-ethyl]pyridine (**254**). The compound (**254**) is probably produced by abstraction of a proton from the relatively acidic benzylic position of nitrile (**240**) followed by reaction of the resulting anion with 3-bromo-4-chloromethylpyridine generated in the previous step of the reaction [Scheme 96].



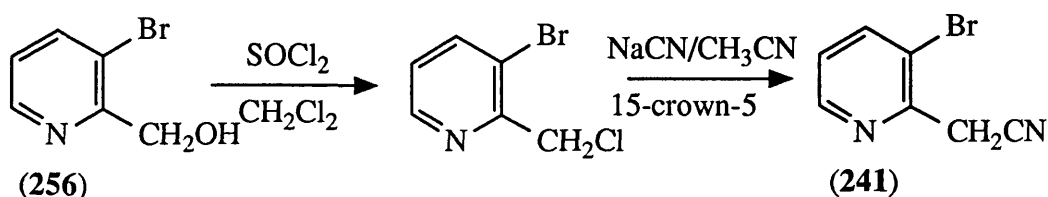
The synthesis of the final pyridine derivative containing a methylene group activated by a nitrile function was attempted using the reaction sequence shown in Scheme 97. This sequence uses classical chemical reactions, including the Hofmann degradation, diazotisation and the Sandmeyer reaction, in order to obtain the precursor 3-bromo-2-methylpyridine³³⁸ (255). Compound (255) was then reacted with N-bromosuccinimide followed by sodium cyanide [Scheme 97] to afford a crude product which was isolated by column chromatography and recrystallised from petrol / diethyl ether to afford a white crystalline product in 32% yield. The IR spectrum indicated the presence of a nitrile function (2248cm^{-1}) while the NMR spectrum showed a typical pattern of peaks for a 2,3-disubstituted pyridine, three sets of double of doublets at 7.40 δ , 7.91 δ and 8.57 δ for the protons at C-5, C-4 and C-6 respectively. The single peak for the CH_2 alkyl protons appeared at 4.09 δ . These results along with the molecular ions (198 and 196) and microanalysis data were consistent with the structure of the proposed product, 3-bromo-2-cyanomethylpyridine (241).



[Scheme 97]

The low yield of (241) may be attributed to the poor conversion of (255) into the bromomethyl intermediate. NMR of the crude reaction mixture indicated that this intermediate was only formed in approximately 40% yield from the reaction of (255) with 1.1 molar equivalents of NBS and therefore the yields of the final product (241) suffered. This reaction requires further study in an attempt to optimise yields but the yield actually obtained was sufficient to proceed.

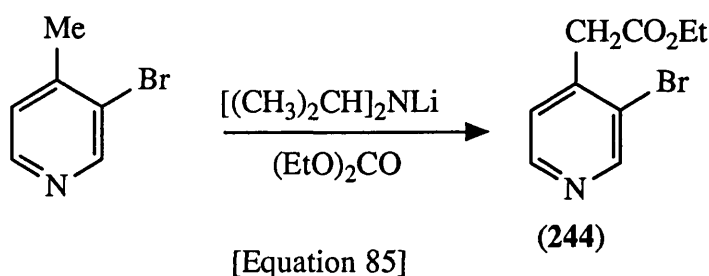
An alternative synthesis of the pyridine derivative (241) has also recently been reported³³⁹. Reaction of 3-bromo-2-hydroxymethylpyridine (256) with thionyl chloride followed by treatment with sodium cyanide gave the desired nitrile in 74% yield [Scheme 98].



[Scheme 98]

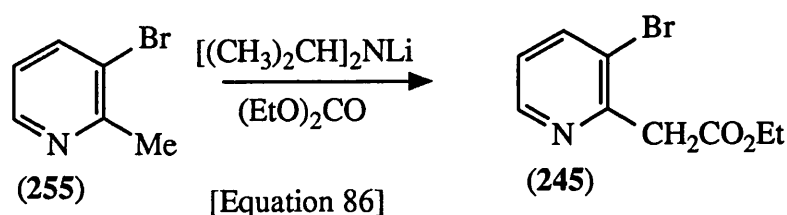
2.2.2 Synthesis of *Ortho*-Halogenated Pyridine Derivatives Containing Methylene Groups Activated by Esters

As mentioned earlier, ethyl 3-bromo-2-pyridylacetate (**244**) has been synthesised¹¹⁹, in 82% yield, from the treatment of 3-bromo-4-methylpyridine³³⁶ with lithium diisopropylamide in THF followed by the addition of diethyl carbonate [Equation 85].



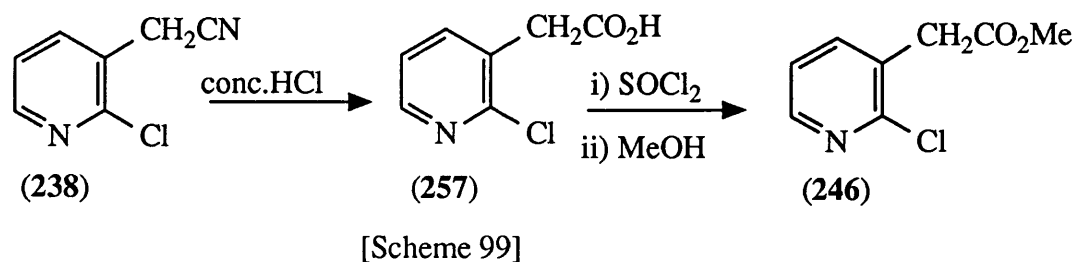
When this reaction was carried out as part of this study, however, the highest yield obtained for (**244**) was only 68% with recovered starting material obtained in 13% yield. The boiling point, IR spectrum and NMR spectrum gave identical results to those already reported in the literature¹¹⁹.

The chemistry used in the preparation of (**244**) was adapted for the synthesis of the novel pyridine derivative (**245**). Thus, the reaction of 3-bromo-2-methylpyridine³³⁸ (**255**) with lithium diisopropylamide followed by the addition of diethyl carbonate [Equation 86] gave a liquid which the IR spectrum indicated the presence of an ester carbonyl group (1737cm^{-1}). The NMR spectrum showed a peak pattern typical for a 2,3-disubstituted pyridine and also present were peaks typical for ethyl esters, ie: a triplet at 1.24δ ($J=12\text{Hz}$) and a quartet at 4.15δ ($J=12\text{Hz}$). Finally a singlet for the alkyl protons of the CH_2 group was observed. The microanalysis agreed with the proposed structure for (**245**).



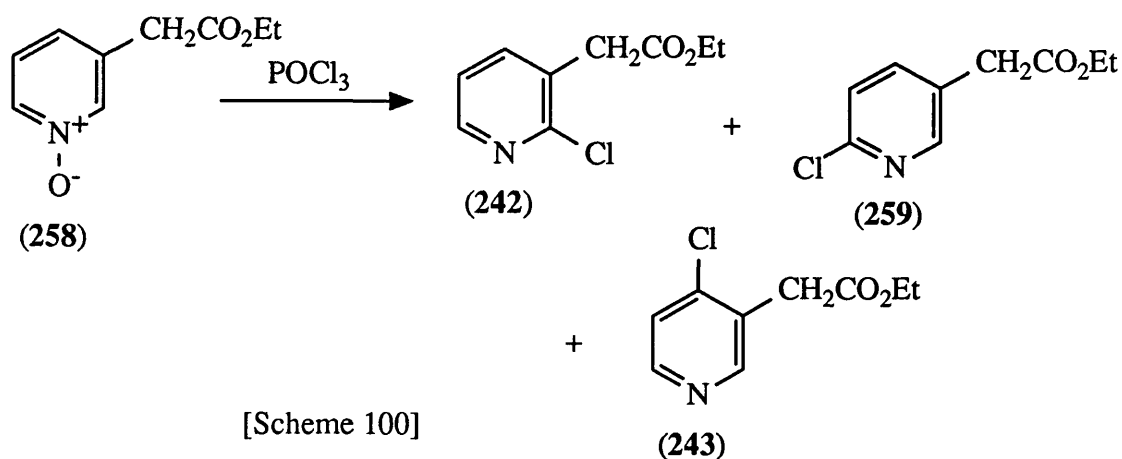
Unfortunately, the yields of (245) were rather lower than expected but the fact that starting material was recovered in 55% yield explains this fact. The starting material and product were readily separated by column chromatography.

Hydrolysis of (238) by refluxing in concentrated hydrochloric acid gave 2-chloropyridine-3-acetic acid³³⁴ (257) which, on treatment with thionyl chloride followed by addition of methanol, afforded methyl 2-chloro-3-pyridylacetate (246) in 35% yield [Scheme 99]. The analytical data for (246) were consistent with the proposed structure.



Finally, since 3-cyanomethylpyridine N-oxide (247) had been found to react with phosphoryl chloride to afford the products (238), (239) and (248), it was decided to attempt the reaction with ethyl 3-pyridylacetate N-oxide in order to see if the corresponding ester products could be prepared. Thus, ethyl 3-pyridylacetate N-oxide (258), prepared from the reaction of ethyl 3-pyridylacetate and 30% hydrogen peroxide in glacial acetic acid³⁴⁰, was reacted with phosphoryl chloride [Scheme 100] to give a mixture of three products which were separated by column chromatography. IR spectroscopy of all three compounds indicated the presence

of ester carbonyls at 1735, 1737 and 1732 cm^{-1} respectively. The NMR spectra for the three products had peaks present which were typical for 2,5-, 2,3- and 3,4-disubstituted pyridines respectively. Also present in all three spectra were peaks typical of ethyl ester groups and singlet peaks of the alkyl protons at the CH_2 group. The microanalysis figures indicated that the three compounds were isomers and the data indicated that the least polar product was ethyl 2-chloro-5-pyridylacetate (**259**) obtained in 22% yield, while the second product was ethyl 2-chloro-3-pyridylacetate (**242**), obtained in 33% yield, and finally the last product was ethyl 4-chloro-3-pyridylacetate (**243**), obtained in 13% yield.



By comparing the chlorination of both the nitrile derivative (**247**) and the ester derivative (**258**) with phosphoryl chloride, there are some interesting observations. Both the yields [Table 1] and the relative polarities of the isomers vary. For example, the least polar nitrile product was the 2,3-isomer (**238**), while the least polar ester product was the 2,5-isomer (**259**).

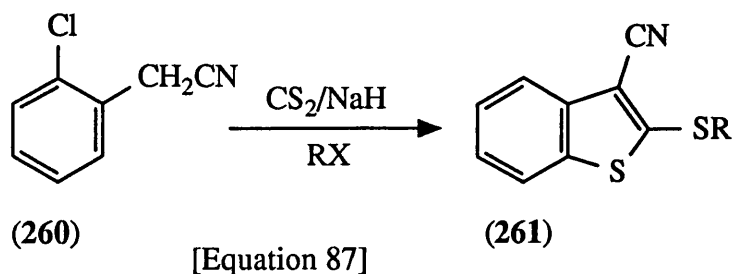
[Table 1]

	Nitrile	Ester
2,3-isomer	37%	33%
3,4-isomer	5%	13%
2,5-isomer	21%	22%

The 2-position may be more sterically hindered in the ester (**258**), thus reducing the possibility of intramolecular delivery of the halogen as evidenced by the lower yield obtained of the 2-chloro derivative in the ester reaction. There is also a corresponding increase in the intermolecular product at the 4-position. Also, the difference in yields may be due to subtle electronic effects caused by the different substituents.

2.3 Synthesis of Thienopyridines from the *Ortho*-Halogenated Pyridine Derivatives Containing Active Methylene Groups.

It has been reported³⁴¹ that benzyl cyanides possessing an *ortho*-halogen atom react with heterocumulenes such as carbon disulfide in the presence of a base to afford benzo[b]thiophenes. Thus, 1-chloro-2-cyanomethylbenzene (**260**), is converted into the benzo[b]thiophene (**261**) by the reaction of carbon disulfide in the presence of sodium hydride, followed by quenching with a haloalkane [Equation 87].



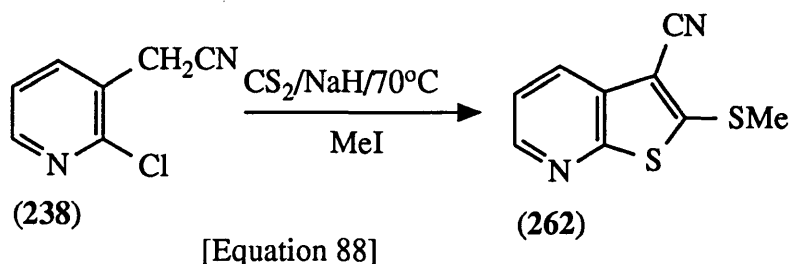
It was the aim of this study to investigate corresponding reactions in the pyridine series, with both carbon disulfide and phenyl isothiocyanate, in an attempt to prepare thienopyridines. This section can therefore be subdivided into reactions of *ortho*-halogenated pyridine derivatives with methylene groups activated by nitriles and those activated by esters.

2.3.1 Reactions of *Ortho*-Halogenated Pyridine Derivatives Containing Methylene Groups Activated by Nitriles.

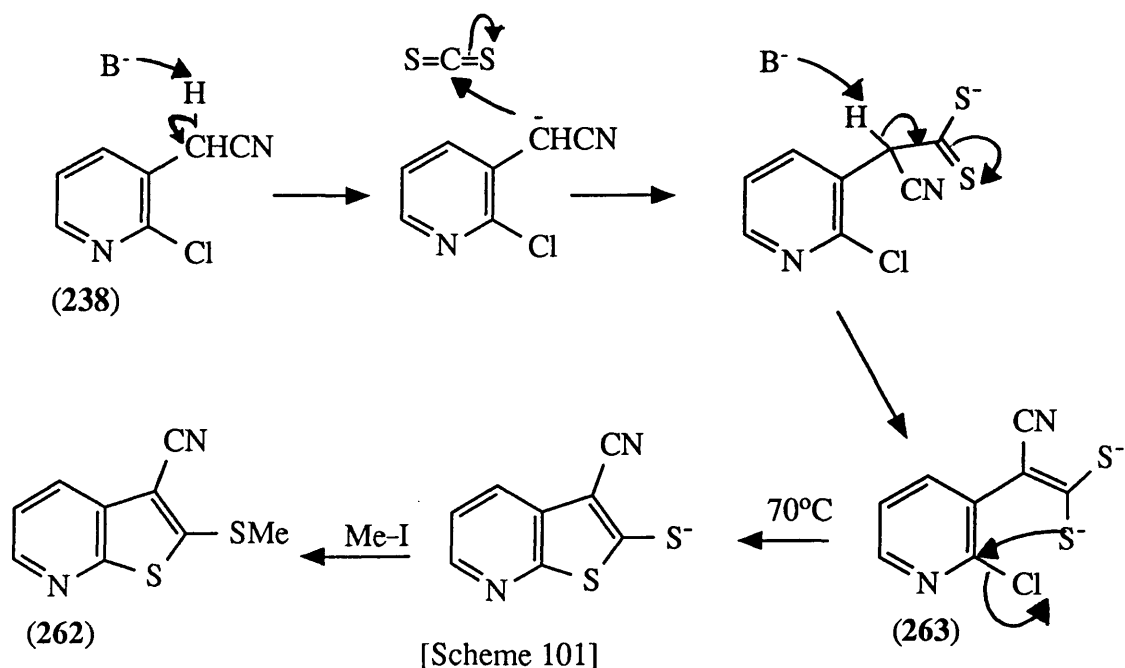
2.3.1.1 Reactions with Carbon Disulfide

2-Chloro-3-cyanomethylpyridine (**238**) was reacted with carbon disulfide in the presence of sodium hydride in dimethyl sulfoxide at 70°C, followed by quenching with iodomethane after cooling to room temperature. The reaction mixture was poured onto ice/water and the resulting solid recrystallised from ethyl acetate to afford 3-cyano-2-methylthiothieno[2,3-*b*]pyridine (**262**) in 80% yield [Equation 88]. The IR spectrum of (**262**) confirmed the presence of a nitrile group (2213cm⁻¹) while the NMR spectrum showed the expected peaks for a 2,3-disubstituted pyridine, along with a singlet at 2.79 δ for the protons in the SMe group. Also, importantly, the peak for the CH₂ group, present in the starting material (**238**), was not observed. The molecular ion (206) and microanalysis

figures were consistent with the proposed structure for the thienopyridine, 3-cyano-2-methylthiothieno[2,3-b]pyridine (**262**).

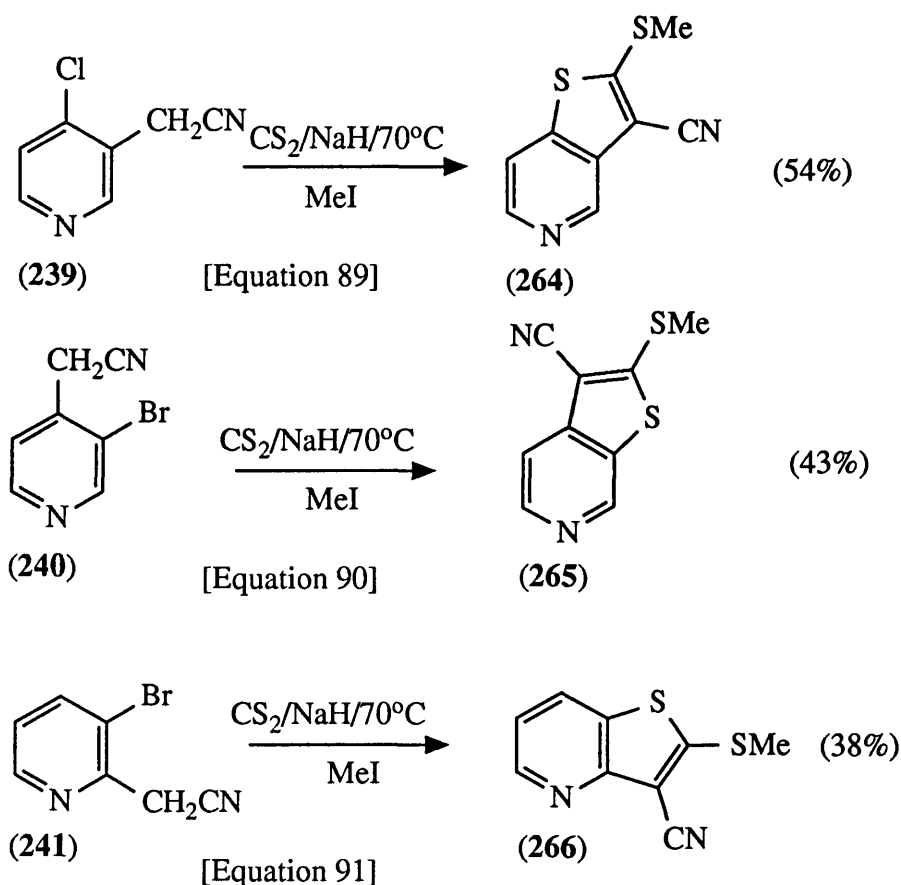


Reactions of this type are believed to proceed *via* the intermediacy of a ketene dithioacetal dianion³⁴¹ (**263**) generated by reaction of the resonance stabilised anion with carbon disulfide. One of the thiolate anions then displaces the halogen atom from the pyridine ring in an intramolecular reaction to produce the bicycle. The other anion is alkylated with iodomethane [Scheme 101].



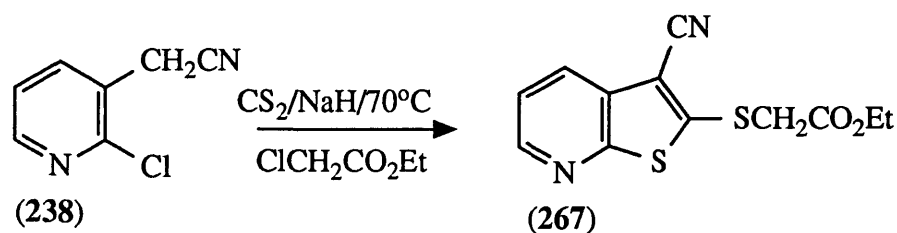
The reaction of carbon disulfide with the pyridine derivative (**239**) under the same reaction conditions as (**238**), afforded 3-cyano-2-methylthiothieno[3,2-c]pyridine (**264**) in 54% yield [Equation 89]. Likewise, the pyridine derivative (**240**) gave

(265) in 43% yield [Equation 90], whilst the thienopyridine (266) was synthesised from (241) in 38% yield [Equation 91]. The IR spectra of the thienopyridines (264), (265) and (266) all indicated the presence of nitrile groups. The NMR spectra, molecular ions (all 206) and microanalyses were all consistent with the proposed structures and indicated that the thienopyridines (262) and (264-266) were isomers of each other.

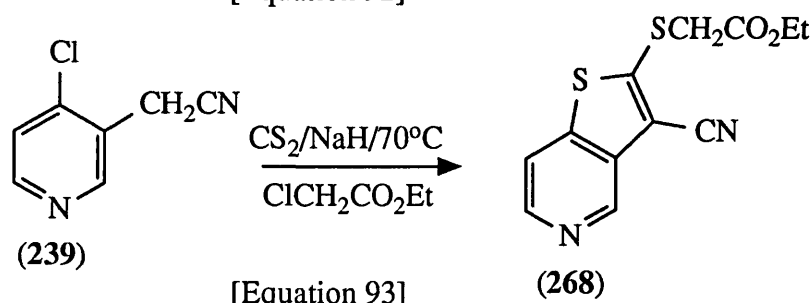


It was envisaged that reactions of the above type could be utilised to synthesise tricyclic thienopyridines if alkylation of the second thiolate anion was accomplished using haloesters such as ethyl chloroacetate. Subsequent cyclisation with base should form the desired tricyclic compounds (as discussed in Section 2.4). Thus, pyridine derivative (238) was reacted with carbon disulfide in the presence of sodium hydride in dimethyl sulfoxide, followed by quenching with

ethyl chloroacetate. Addition of the reaction mixture to ice/water gave crude product which was recrystallised from ethyl acetate to give the pure compound in 52% yield. The IR spectrum of the product obtained indicated the presence of both a nitrile group (2218cm^{-1}) and an ester carbonyl group (1725cm^{-1}). The NMR spectrum and microanalysis were also consistent with the proposed structure for 2-carboethoxymethylthio-3-cyanothieno[2,3-b]pyridine (**267**) [Equation 92]. In an identical manner, 2-carboethoxymethylthio-3-cyanothieno[3,2-c]pyridine (**268**) was synthesised in 43% yield from (**239**) [Equation 93]. Spectroscopic and analytical data were again consistent with the proposed structure.



[Equation 92]

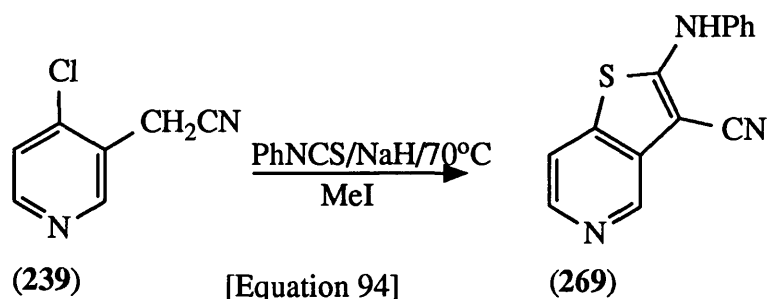


[Equation 93]

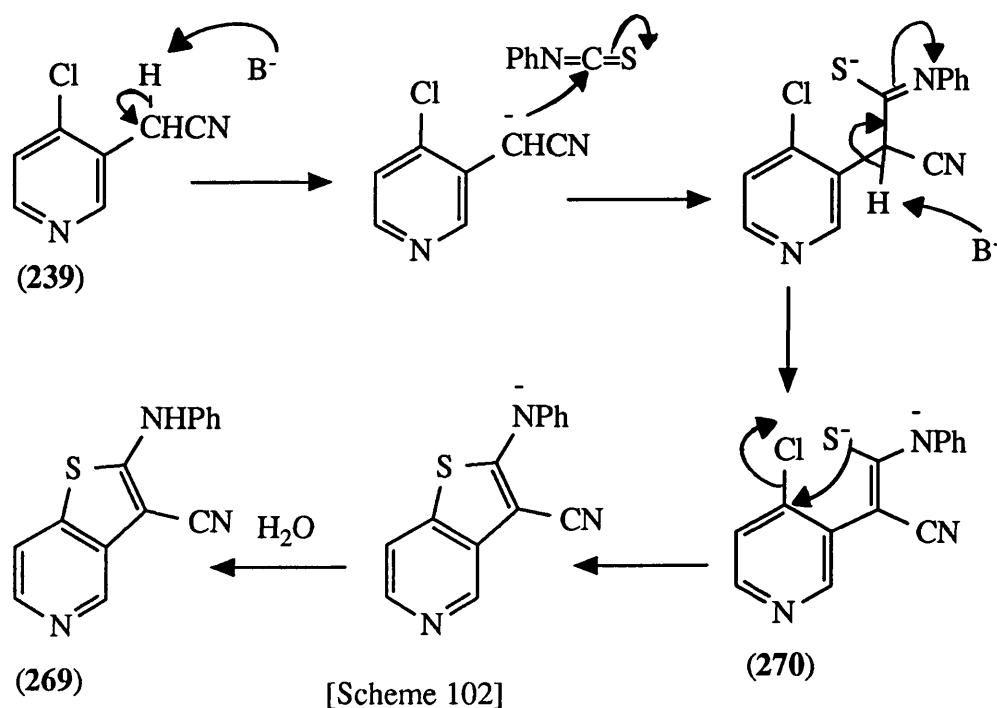
2.3.1.2 Reactions with Phenyl Isothiocyanate

In order to extend the scope of the reaction sequence, the pyridine derivatives (**238-241**) were reacted with phenyl isothiocyanate in an attempt to prepare thienopyridines. Thus, the *ortho*-halogenated pyridine derivative (**239**) was reacted with phenyl isothiocyanate in the presence of sodium hydride in dimethyl sulfoxide, under identical conditions to those reactions with carbon disulfide. The

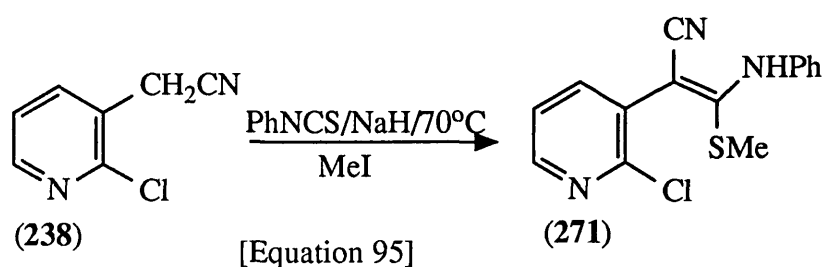
reaction mixture was poured onto ice/water and the crude product was recrystallised from ethyl acetate to afford the product in 36% yield. The IR spectrum of the product confirmed the presence of a secondary amine (3175cm^{-1}) and also a nitrile (2210cm^{-1}). The NMR spectrum indicated that the product was a 3,4-disubstituted pyridine and had peaks which corresponded to the protons of the phenyl group and the NH group. The molecular ion (251) and the microanalysis along with NMR and IR spectra confirmed the structure of the product as being 2-anilino-3-cyanothieno[3,2-c]pyridine (**269**) [Equation 94].



It is believed that the mechanism for the reaction of the pyridine derivative (**239**) and phenyl isothiocyanate is similar to the mechanism proposed for those reactions of the pyridine derivatives with carbon disulfide. Thus, the reaction appears to proceed *via* the dianion intermediate (**270**) formed by the reaction of the resonance stabilised anion and phenyl isothiocyanate. The thiolate anion then displaces the halogen atom from the pyridine ring to produce the bicycle. The nitrogen anion is not alkylated with iodomethane but is protonated when the reaction mixture is added to water [Scheme 102].



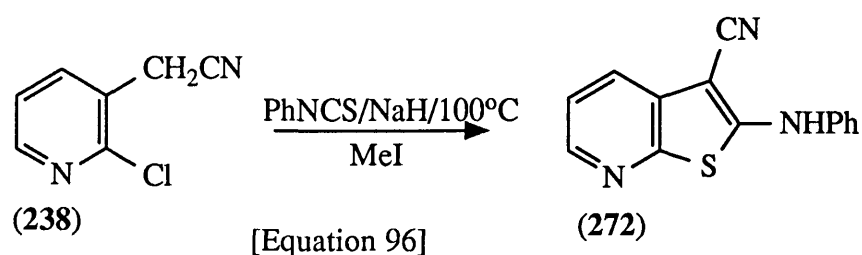
The pyridine derivative (238) has also been reacted with phenyl isothiocyanate in the presence of sodium hydride in dimethyl sulfoxide at 70°C , followed by quenching with iodomethane at room temperature. The product obtained from this reaction gave the expected IR spectrum (peaks at 3172 and 2192cm^{-1}), but the NMR spectrum, although having the expected peaks, also had a singlet which corresponded to three alkyl protons. The only explanation for this observation is that the product obtained is not the thienopyridine but the uncyclised product in which the thiolate anion had been alkylated by the iodomethane (singlet in NMR). The molecular ions (303 and 301) and the microanalysis, which confirmed the presence of a chlorine atom, were consistent with 3-(2'-anilino-1'-cyano-2'-methylthio)ethenyl-2-chloropyridine (271), obtained in 37% yield [Equation 95].



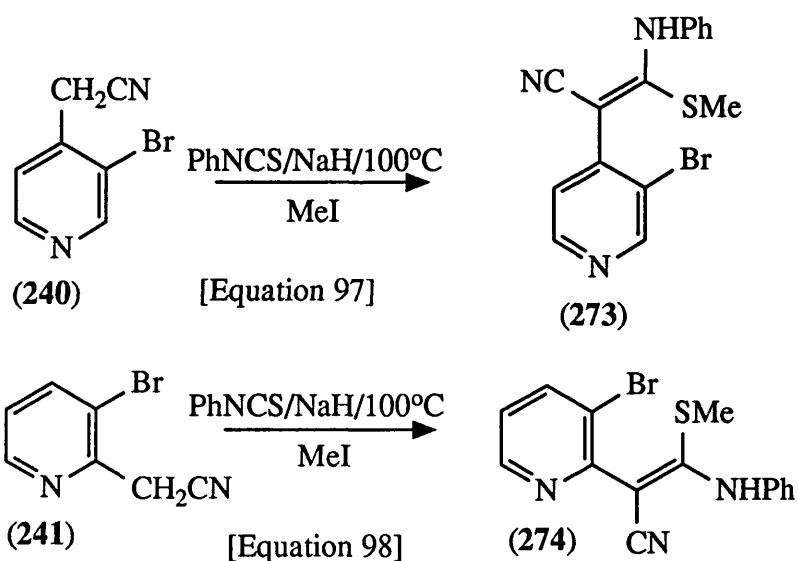
It was assumed that the stereochemistry of the uncyclised product was as indicated in (271), however, it is possible for the other geometric isomer to exist (see later in this section).

The formation of the uncyclised product (271) from pyridine (238) was unexpected since its isomer (239) gave thienopyridine (270) under the same conditions. One explanation for this is that the halogen atom at the 4-position of the pyridine ring is more labile than that at the 2-position, and therefore easier to displace with the thiolate anion.

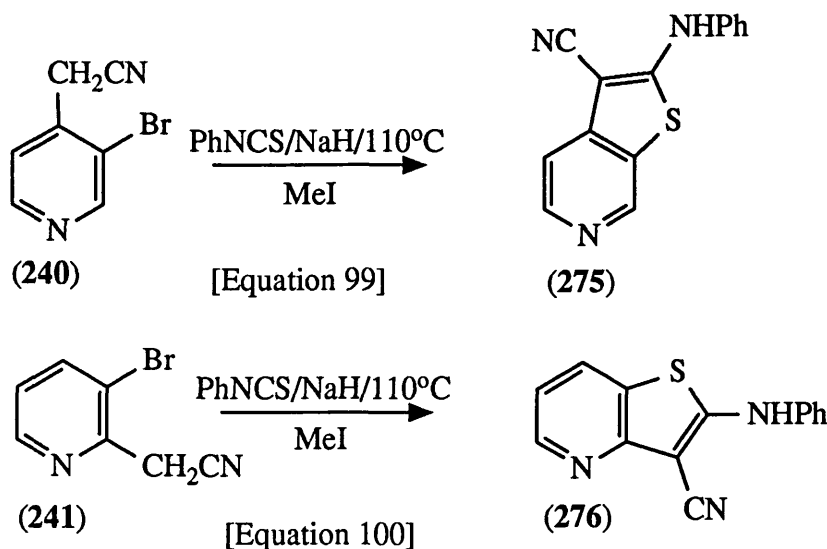
In an attempt to form the cyclised product, the pyridine derivative (238) was reacted with phenyl isothiocyanate under more forcing conditions (100°C), quenched with iodomethane at room temperature and then poured onto ice/water. Recrystallisation of the crude product gave a white crystalline solid in 20% yield. The analytical data obtained was consistent for the proposed structure of the thienopyridine, 2-anilino-3-cyanothieno[2,3-b]pyridine (272) [Equation 96].



When the pyridine derivative (240) was treated with phenyl isothiocyanate at 100°C, the uncyclised product (273) was isolated in 32% yield [Equation 97] whilst (274) was obtained in 69% yield from the reaction of (241) and phenyl isothiocyanate under the same conditions [Equation 98]. Spectroscopic and analytical data were consistent with the proposed structures for the products.

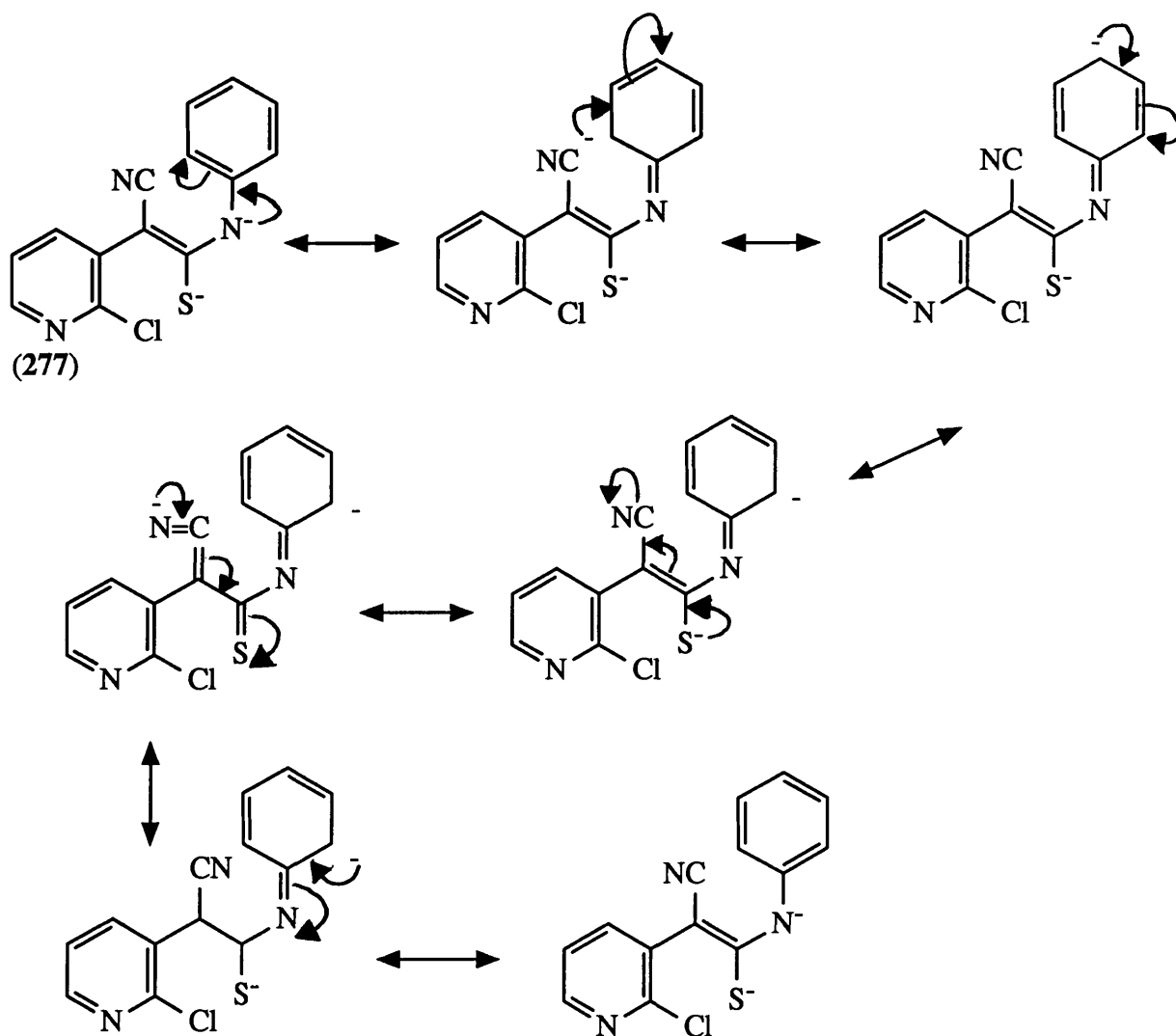


Halogen atoms in the 3- and 5-positions of the pyridine ring are less labile than those in the 2-, 6-, and 4-positions²⁷ and therefore are more difficult to displace with nucleophiles. If more forcing conditions are used, however, intramolecular nucleophilic displacement of the bromine atom, in the 3-position of the pyridine ring of (240) and (241), should occur to give the corresponding thienopyridines. This proved to be the case since (240) and (241) were reacted with phenyl isothiocyanate at 110°C and the products were identified as the thienopyridines, 2-anilino-3-cyanothieno[2,3-c]pyridine (275) and 2-anilino-3-cyanothieno[3,2-b]-pyridine (276) obtained in 19% and 28% yields respectively [Equations 99 and 100].



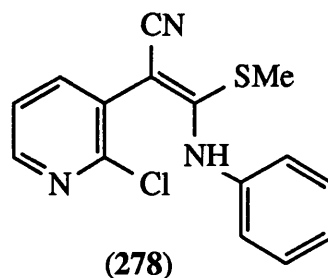
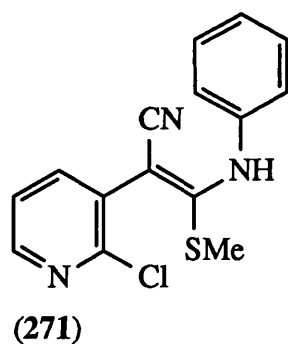
As discussed previously, the formation of the uncyclised compounds (271), (273) and (274) may be explained by the fact that the halogen atoms in (239), (240) and (241), the precursors to the uncyclised compounds, are less labile than the halogen atom in (239) which formed the cyclised product (269). This explanation however, does not explain the fact that the pyridine derivatives (238), (240) and (241) afford thienopyridines at 70°C when reacted with carbon disulfide, but uncyclised products when reacted with phenyl isothiocyanate under the same conditions. In an attempt to account for these observations, the mechanisms for the two reactions need to be considered. The mechanisms for both the carbon disulfide reaction and the phenyl isothiocyanate reaction have been discussed (Sections 2.3.1.1 and 2.3.1.2) and it is presumed that the dianions (263) and (270) are formed during these reactions. If these dianions are compared, then it is seen that the negative charge on the nitrogen atom in (277) may be delocalised around the phenyl ring thus reducing electron density on the anilino nitrogen. As a consequence, this allows delocalisation of the negative charge on the sulfur into the nitrile group and also the pyridine ring [Scheme 103]. This will have the effect of reducing the nucleophilicity of the thiolate ion in (277) compared to that in (263) where no such possibility of enhanced resonance stabilisation exists and so the reactions with

carbon disulfide afford the thienopyridines while those with phenyl isothiocyanate do not give cyclised products under comparable conditions.



[Scheme 103]

As discussed earlier, the stereochemistry of the uncyclised products was assumed. Thus, the product from the reaction of (238) and phenyl isothiocyanate was assumed to be (271) but it is possible for the other geometric isomer (278) to exist. However, if the other isomer was formed then the uncyclised product should have been isolated as a mixture of the two isomers (271) and (278). This was never observed and it is believed that only (271) is obtained due to steric hindrance of the other isomer.



More sterically hindered

In conclusion, reactions of pyridine derivatives (238-241) with the heterocumulenes carbon disulfide and phenyl isothiocyanate have resulted in successful preparation of the corresponding thienopyridines. The reactions of the derivatives (238-241) with carbon disulfide produced the corresponding thienopyridines without any difficulties but when reacted with phenyl isothiocyanate, problems in cyclisation were encountered. Although (239) produced the thienopyridine (269) at 70°C, the other derivatives (238), (240) and (241) afforded uncyclised products at this temperature. These derivatives formed the cyclised products when reacted with phenyl isothiocyanate under more forcing conditions. It was suggested that the dianions formed during the reactions with carbon disulfide were more nucleophilic than those formed during the reactions with phenyl isothiocyanate and therefore the phenyl isothiocyanate reactions required more forcing conditions to achieve cyclisation.

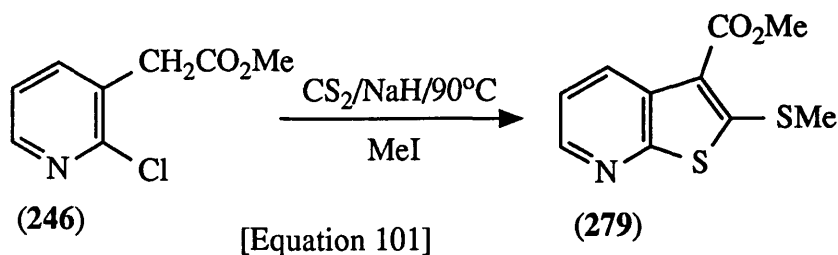
Only one geometric isomer of the uncyclised compounds (271), (273) and (274) were formed since steric hindrance of the other possible isomer prevented its formation.

2.3.2 Reactions of *Ortho*-Halogenated Pyridine Derivatives Containing Methylene Groups Activated by Esters.

Since the pyridine derivatives containing methylene groups activated by nitriles reacted readily with both the heterocumulenes, carbon disulfide and phenyl isothiocyanate to afford the corresponding thienopyridines, similar reactions were attempted on similar derivatives activated by esters. The aim was to compare and contrast the reactivity of the ester and nitrile activating groups and furthermore, to afford different functionality attached to thienopyridines for further manipulation to form tricycles.

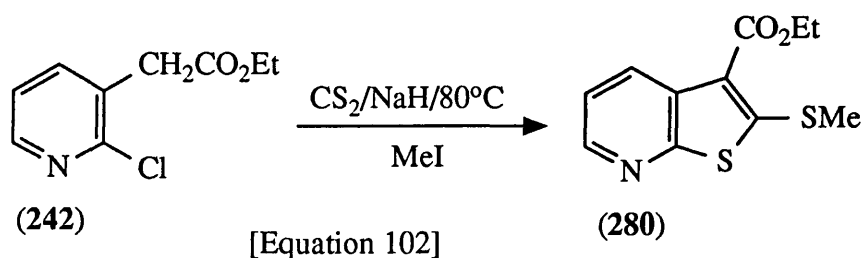
2.3.2.1 Reactions with Carbon Disulfide

Methyl 2-chloro-3-pyridylacetate (**246**) was treated with carbon disulfide in the presence of sodium hydride in dimethyl sulfoxide, at 90°C, followed by quenching with iodomethane. The reaction mixture was added to ice/water, the crude product was obtained by filtration and recrystallised from ethyl acetate to afford a white crystalline product in 41% yield. The IR spectrum of the product indicated the presence of an ester carbonyl (1688cm^{-1}) and although this figure is low it is typical for these derivatives. The NMR spectrum showed two singlets, one at 2.66 δ for the SMe protons and one at 3.98 δ for the CO₂Me protons. The microanalysis data were consistent with the IR and NMR data and confirmed that the product was the proposed thienopyridine, 3-carbomethoxy-2-methylthiothieno-[2,3-b]pyridine (**279**) [Equation 101].



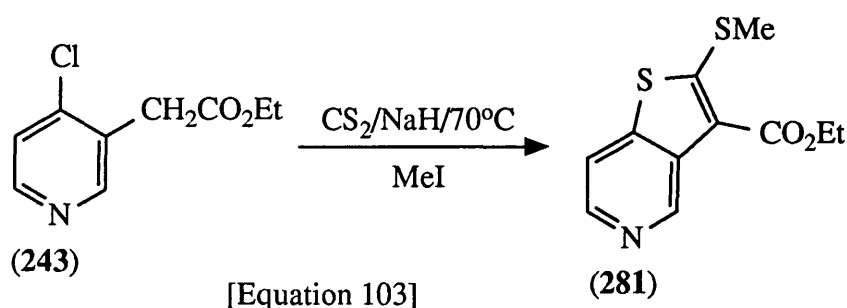
The pyridine derivative (242) was treated with carbon disulfide in the presence of sodium hydride at 90°C in the usual manner but on addition to ice/water an oil was formed. Isolation of the crude product was achieved by column chromatography and recrystallisation from ethyl acetate gave the product in 36% yield.

Spectroscopic and analytical data were again consistent with the proposed structure 3-carboethoxy-2-methylthiothieno[2,3-b]pyridine (280) [Equation 102].

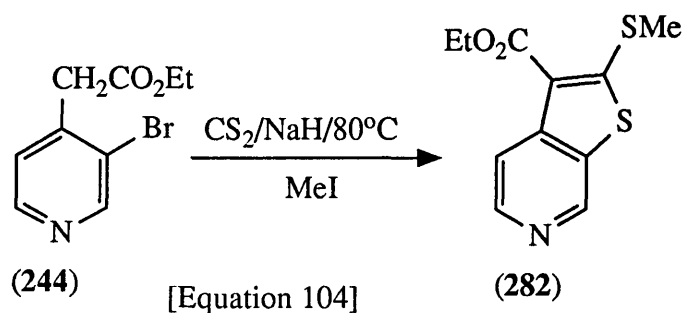


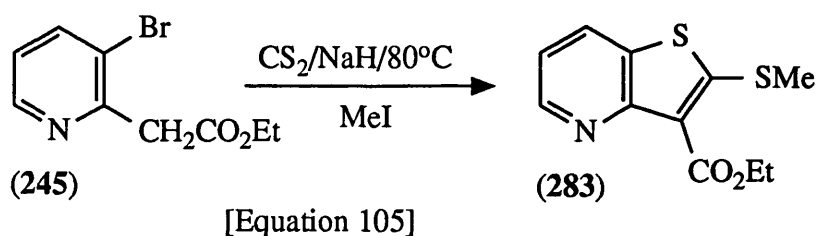
When (243) was reacted with carbon disulfide at 100°C, an extremely polar product was obtained which was insoluble in virtually all organic solvents and water. It was possible, however, to recrystallise the compound from copious amounts of methanol. The IR spectrum indicated the presence of an ester carbonyl (1682cm⁻¹) but no NMR spectrum was obtained due to solubility problems. The product decomposed at approximately 250°C and microanalysis showed the presence of carbon, hydrogen, nitrogen and sulfur but no halogen atom appeared to be present.

The reaction of the ester (243) with carbon disulfide was repeated but the temperature was maintained at 70°C [Equation 103]. On this occasion the product, obtained in 17% yield was soluble in ethyl acetate. The IR spectrum of the product indicated the presence of an ester carbonyl group (1681cm⁻¹) while the NMR spectrum indicated that the product was a 3,4-disubstituted pyridine. Also present in the spectrum were peaks typical for an ethyl ester and a thiomethyl group. These analysis figures plus the microanalysis data were consistent with the proposed structure, 3-carboethoxy-2-methylthiothieno[3,2-c]pyridine (281).

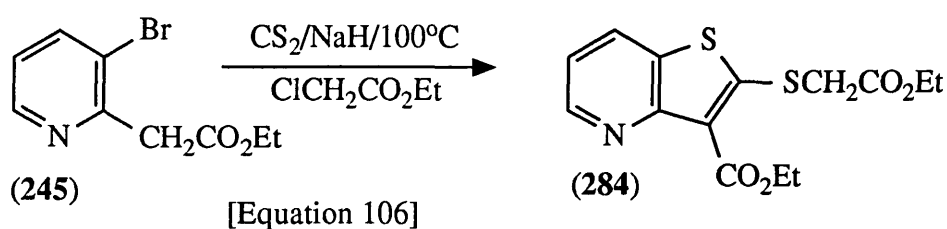


When the pyridine derivative (244) was treated with carbon disulfide at 80°C, the thienopyridine (282) was isolated in 42% yield [Equation 104] whilst (283) was obtained in 50% yield from the reaction of (245) and carbon disulfide under the same conditions [Equation 105]. Spectroscopic and analytical data were consistent with the proposed structures for the products.



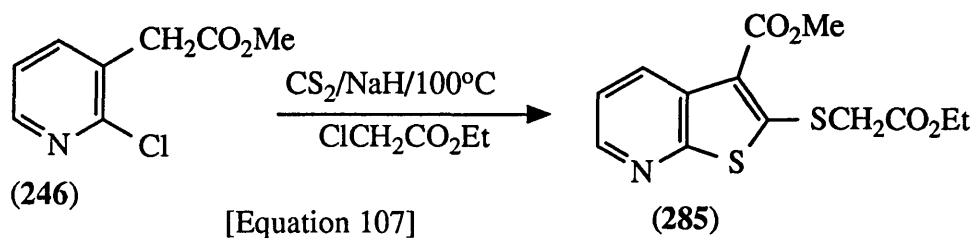


Again in an attempt to prepare thienopyridines that would react with a base to afford tricyclic compounds (which will be discussed in Section 2.5.4), the pyridine derivative (245) was treated with carbon disulfide in the presence of sodium hydride in dimethyl sulfoxide, followed by quenching with ethyl chloroacetate. The reaction was poured into ice/water, the crude product was filtered and then recrystallised from ethyl acetate to afford 2-carboethoxymethylthio-3-carboethoxythieno[3,2-c]pyridine (284) in 67% yield [Equation 106]. The IR spectrum of the product obtained indicated the presence of two ester carbonyl groups (1725 & 1678cm⁻¹) while the NMR spectrum was typical for a 2,3-disubstituted pyridine. The NMR also showed peaks corresponding to two ethyl ester groups along with a singlet for the CH₂ protons. The microanalysis data was also consistent with the proposed structure.



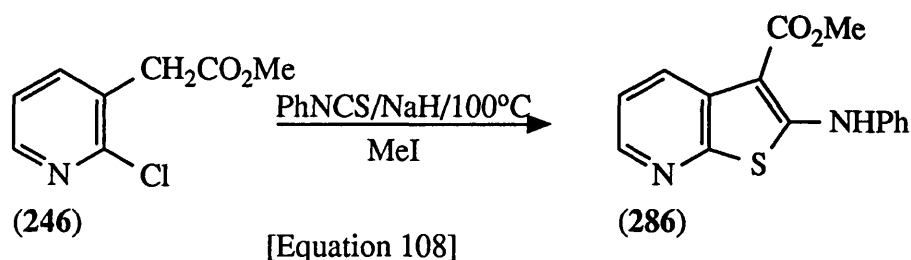
The thienopyridine (285) was prepared in 56% yield from the reaction of (246) and carbon disulfide under identical conditions to that for the preparation of (284) [Equation 107]. The IR spectrum of the product obtained indicated the presence of two ester carbonyl groups (1725 & 1678cm⁻¹) while the NMR spectrum was typical for a 2,3-disubstituted pyridine. The NMR also had peaks corresponding to

an ethyl ester group and a methyl ester group, along with a singlet for the CH₂ group. The microanalysis data was also consistent with the proposed structure for (285).

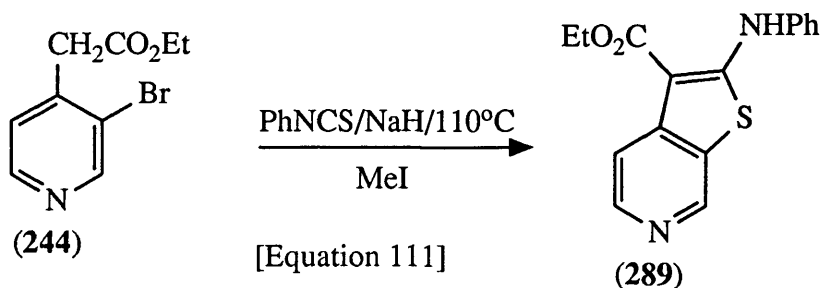
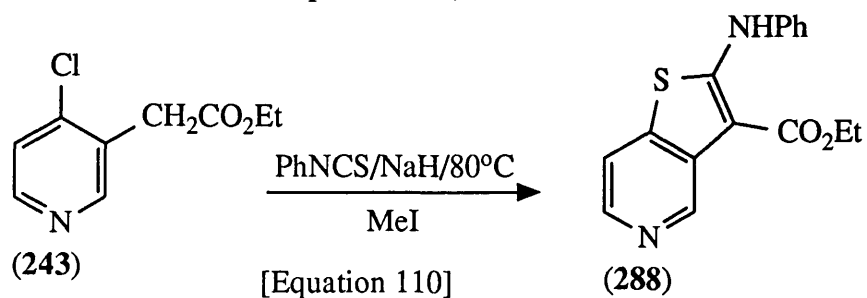
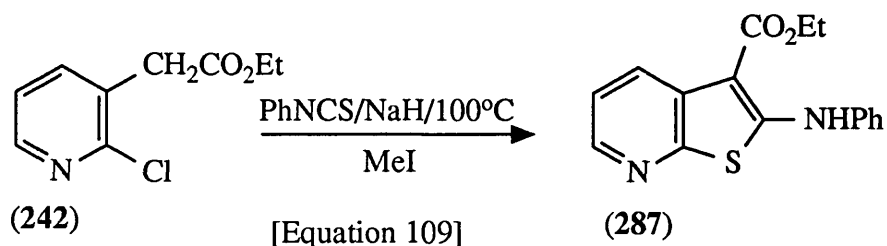


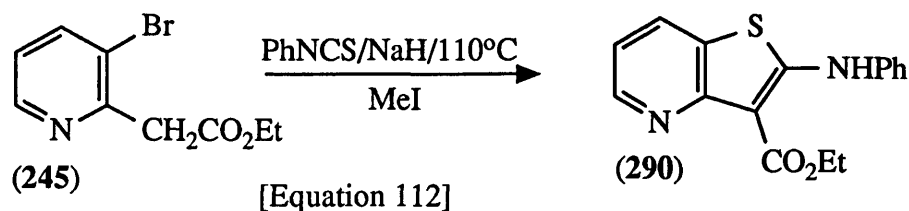
2.3.2.2 Reactions with Phenyl Isothiocyanate.

Phenyl isothiocyanate has been reacted with pyridine derivatives (238-241) to afford thienopyridines (Section 2.3.1.1). However, due to the difficulties incurred in attempting to cyclise derivatives (238), (240) and (241), it was decided that the reactions between the esters (242-246) and phenyl isothiocyanate should be carried out at higher temperatures in an attempt to promote cyclisation and avoid formation of uncyclised products. Thus, the ester (246) reacted with phenyl isothiocyanate at 100°C and a product was isolated in 22% yield. The IR spectrum indicated the presence of a secondary amine (3192cm⁻¹) and an ester carbonyl group (1666cm⁻¹). The NMR spectrum showed typical peaks for a 2,3-disubstituted pyridine, an ethyl ester group and a CH₂ group adjacent to a carbonyl. The microanalysis data was also consistent with 2-anilino-3-carbo-methoxythieno[2,3-b]pyridine (286), [Equation 108].



Phenyl isothiocyanate was also reacted with (242) at 100°C to afford the product (287) in 36% yield [Equation 109]. In a similar reaction the derivative (243) was reacted with the heterocumulene at 80°C to give (288) in 67% yield [Equation 110]. Likewise phenyl isothiocyanate reacted with both (244) and (245) at 110°C to give the thienopyridines (289) and (290) in 8% and 14% yields [Equations 111 and 112]. As expected, the spectroscopic and analytical data for the compounds (287-290) were consistent with the proposed structures.



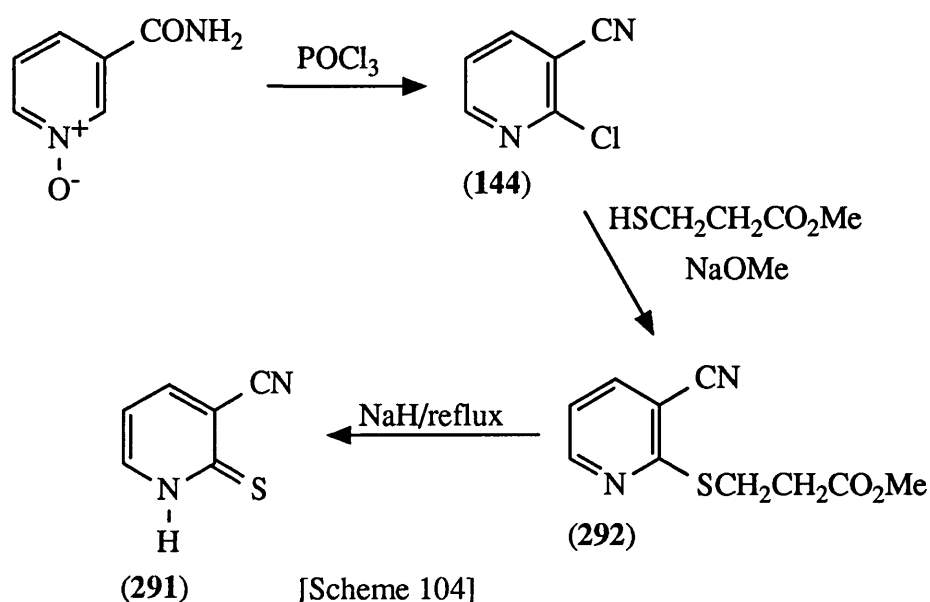


The very poor yields obtained for the formation of the thienopyridines (289) and (290) is a result of the formation of polar by-products in each case. As with the polar product obtained in the reaction of (243) with carbon disulfide at 100°C (Section 2.3.2.1), the by-products obtained in these reactions were insoluble in organic solvents or water but could be recrystallised from copious amounts of methanol. The IR spectra of these polar materials indicated the presence of ester carbonyl groups (1685 and 1674cm^{-1}) but no NMR spectra were obtained due to the solubility problems of the compounds. The microanalyses were identical to the data obtained for the very polar material afforded by the reaction of (243), but still no structure could be assigned to these compounds.

2.4 Synthesis of Thienopyridines from 3-Cyano-2(1H)-pyridinethione

An alternative route to thienopyridines utilising cyanopyridinethione derivatives was also investigated as part of this research programme. Much work has been carried out in this area (section 1.2.3.1) but the majority of researchers have concentrated on the synthesis of thienopyridines from highly substituted 3-cyanopyridinethiones^{226,228,229,236,238,239,242-250,253,257,260}. Thus, it was decided to investigate the synthesis of thienopyridines from 3-cyanopyridine-2(1H)-thione (291).

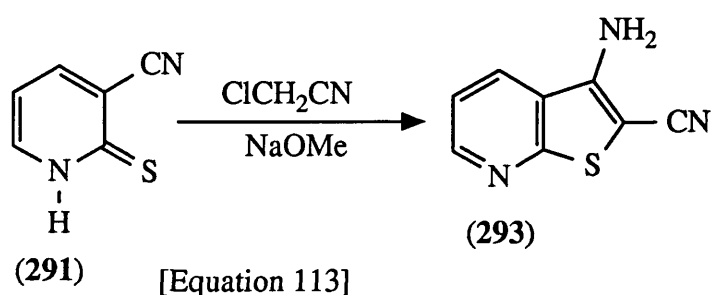
Dunn and Norrie reported²⁴⁸ that treatment of 2-chloro-3-cyanopyridine (**144**) with methyl 3-mercaptopropionate in the presence of a base caused rapid substitution of the halogen atom to yield 2-(2'carbomethoxyethylthio)-3-cyanopyridine (**292**) which underwent a retro-Michael addition when treated with sodium hydride in refluxing THF to afford 3-cyanopyridine-2(1H)-thione (**291**) in 68% yield [Scheme 104].



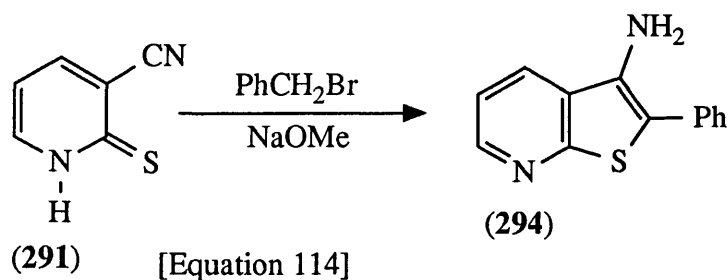
It has been widely reported^{226,228,229,236,238,239,242-250,253,257,260} that the reaction of substituted 3-cyanopyridinethione derivatives with haloalkanes (which are activated with a variety of substituents), in the presence of a base affords thienopyridines. Thus, the intention was to investigate the reactions of the unsubstituted thione (**291**) with a range of activated haloalkanes in an attempt to prepare thienopyridines.

Thione (**291**) was treated with chloroacetonitrile in the presence of sodium methoxide in DMF at room temperature for two hours, poured onto ice and the product isolated by filtration and recrystallised from ethyl acetate (72% yield).

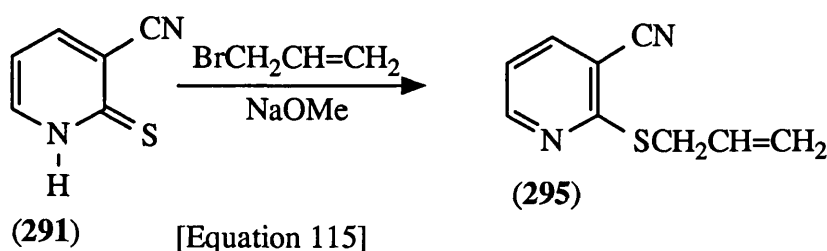
The IR spectrum indicated the presence of both a primary amine (3399 & 3344 cm^{-1}) and a nitrile group (2199 cm^{-1}). The NMR spectrum showed no peaks for alkyl protons but a singlet for the two primary amine protons was observed. The melting point (218-219 $^{\circ}\text{C}$) obtained for the proposed product was analogous to that obtained for the product reported previously²³¹. Thus, the product obtained from the reaction of (291) and chloroacetonitrile [Equation 113] was 3-amino-2-cyanothieno[2,3-b]pyridine (293).



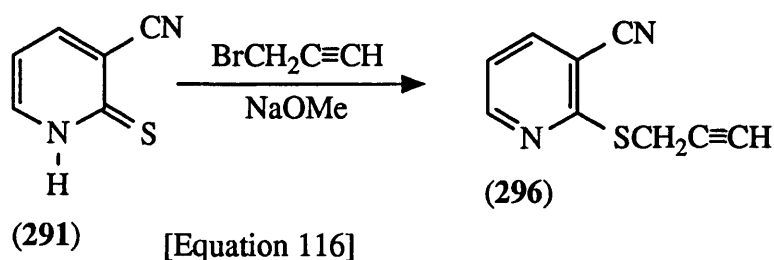
The thione (291) has also been treated with benzyl bromide under the same conditions [Equation 114] but an oil formed when the reaction mixture was added to ice, however, the product was isolated in 24% yield after chromatography. The IR spectrum of the product again indicated the presence of a primary amine group (3340 & 3221 cm^{-1}), although no nitrile group was present. The fact that an amine group had replaced the nitrile indicated that the reaction had formed the cyclised product. Both the NMR spectrum and microanalysis were consistent with the proposed structure for the cyclised product, 3-amino-2-phenylthieno[2,3-b]pyridine (294).



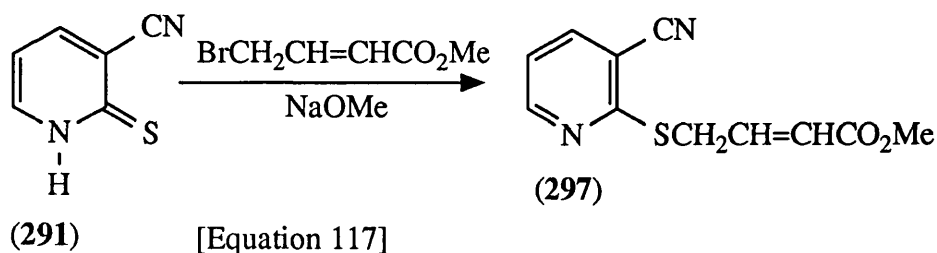
When the thione (**291**) was reacted with allyl bromide, however, the IR spectrum of the product did not show the expected peaks corresponding to a primary amine but did confirm that the nitrile group (2224cm^{-1}) was still present, indicating that the reaction had not formed the cyclised product. The NMR spectrum confirmed this since the peaks in the spectrum were typical for an allyl system ie: a large three proton multiplet at 5.00-6.28 δ for alkene protons and a peak at 3.92 δ for the $-\text{CH}_2-$ protons. The microanalysis also indicated the proposed uncyclised structure, 3-cyano-2-(propen-1'-yl-3'-thio)pyridine (**295**) obtained in 70% yield [Equation 115].



An uncyclised product was also obtained in 93% yield when (**291**) was treated with propargyl bromide [Equation 116]. The IR spectrum showed the presence of a nitrile group (2226cm^{-1}) and an alkyne group (3245cm^{-1}) while NMR spectroscopy showed peaks at 2.18 δ and 4.01 δ for the protons at the CH and CH_2 groups respectively. Long range coupling across the triple bond was responsible for the peaks appearing as a triplet and a doublet respectively. The microanalysis was also consistent with the proposed structure of the uncyclised product, 3-cyano-2-(propyn-1'-yl-3'-thio)pyridine (**296**).

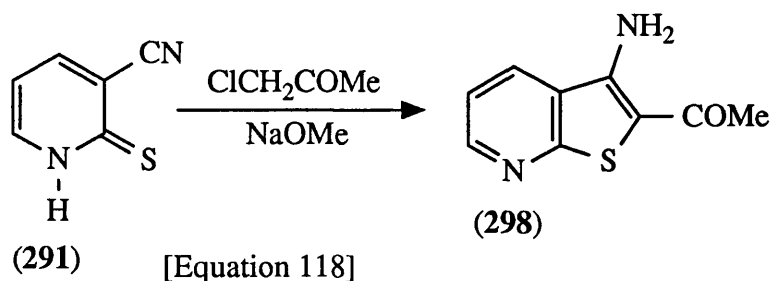


Both of the uncyclised compounds (295) and (296) were treated with sodium methoxide in DMF but still failed to form the thienopyridines. A more activated unsaturated haloalkane, methyl 4-bromocrotonate, was also employed as an alkylating agent in an attempt to achieve cyclisation. However, the product obtained, in 65% yield, from this reaction appeared to be the uncyclised product (297) [Equation 117], since the IR spectrum showed an absorption peak at 2220cm^{-1} , indicating the presence of a nitrile group. Also present in the IR spectrum were peaks for an alkene (3063cm^{-1}) and for an ester carbonyl (1727cm^{-1}) while the NMR spectrum and the microanalysis confirmed that the uncyclised product had been formed.

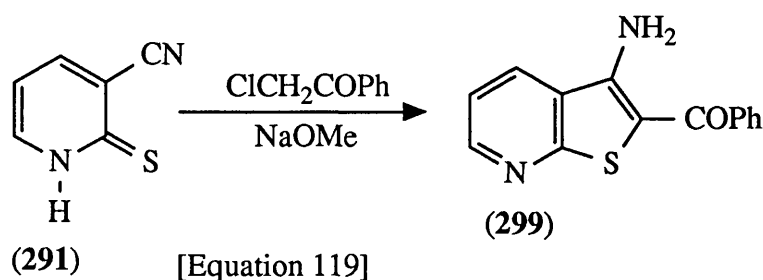


It is probable that the uncyclised products (295-297) are formed instead of the expected thienopyridines because the unsaturated haloalkanes used as alkylating agents are not sufficiently activated i.e. protons on the CH_2 are not acidic enough for removal by sodium methoxide. It is possible that stronger bases might effect cyclisation but instead, more activated alkylating agents such as α haloketones were investigated. Thus, thione (291) was treated with chloroacetone in the

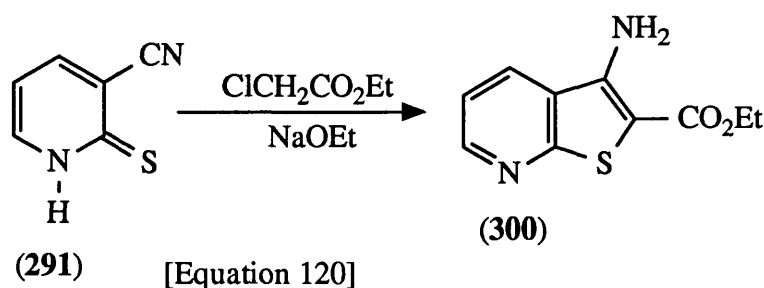
presence of sodium methoxide in DMF at room temperature [Equation 118]. The reaction mixture was poured onto ice/water and the crude product was recrystallised from ethyl acetate to afford the cyclised product (**298**) in 25% yield. The IR spectrum of the product indicated the presence of a primary amine (3440 & 3328 cm^{-1}) and a ketone carbonyl group (1607 cm^{-1}) which suggested that the cyclised product had been formed. The ketonic carbonyl stretch at 1607 cm^{-1} is very low and may be due to intramolecular hydrogen bonding which may exist between the primary amine in the 3-position and the carbonyl of the ketone in the 2-position. Both the NMR spectrum and the microanalysis were consistent with the proposed structure for the thienopyridine, 2-acetyl-3-aminothieno[2,3-b]-pyridine (**298**).



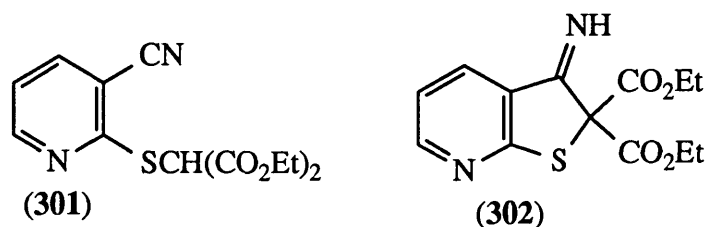
Chloroacetophenone has also been reacted with (**291**) under identical conditions to the previous reaction to afford 3-amino-2-benzoylthieno[2,3-b]pyridine (**299**) in 35% yield [Equation 119]. The melting point (181-182 $^{\circ}\text{C}$) was identical to the literature value²³¹.



Thienopyridines were also prepared from α haloesters. When thione (**291**) was treated with ethyl chloroacetate in the presence of sodium ethoxide [Equation 120] a crystalline solid was isolated in 56% yield after recrystallisation from ethyl acetate. The IR spectrum showed absorption peaks at 3414cm^{-1} and 3312cm^{-1} for a primary amine and at 1673cm^{-1} for an ester carbonyl group. The NMR spectrum showed a singlet peak at 7.20 δ for the two amine protons, plus peaks typical of an ethyl ester and a 2,3-disubstituted pyridine. The spectral data and the melting point (184-185°C) were analogous to those quoted in the literature²³¹ for 3-amino-2-carboethoxythieno[2,3-b]pyridine (**300**).

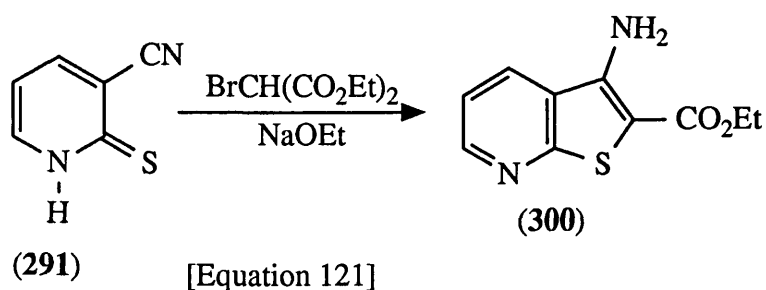


The reaction of thione (**291**) with the α -haloester, diethyl bromomalonate, was investigated to determine whether the uncyclised product (**301**) or the cyclised thienopyridine (not fully aromatic) with an imine group at the 3-position (**302**) was formed.

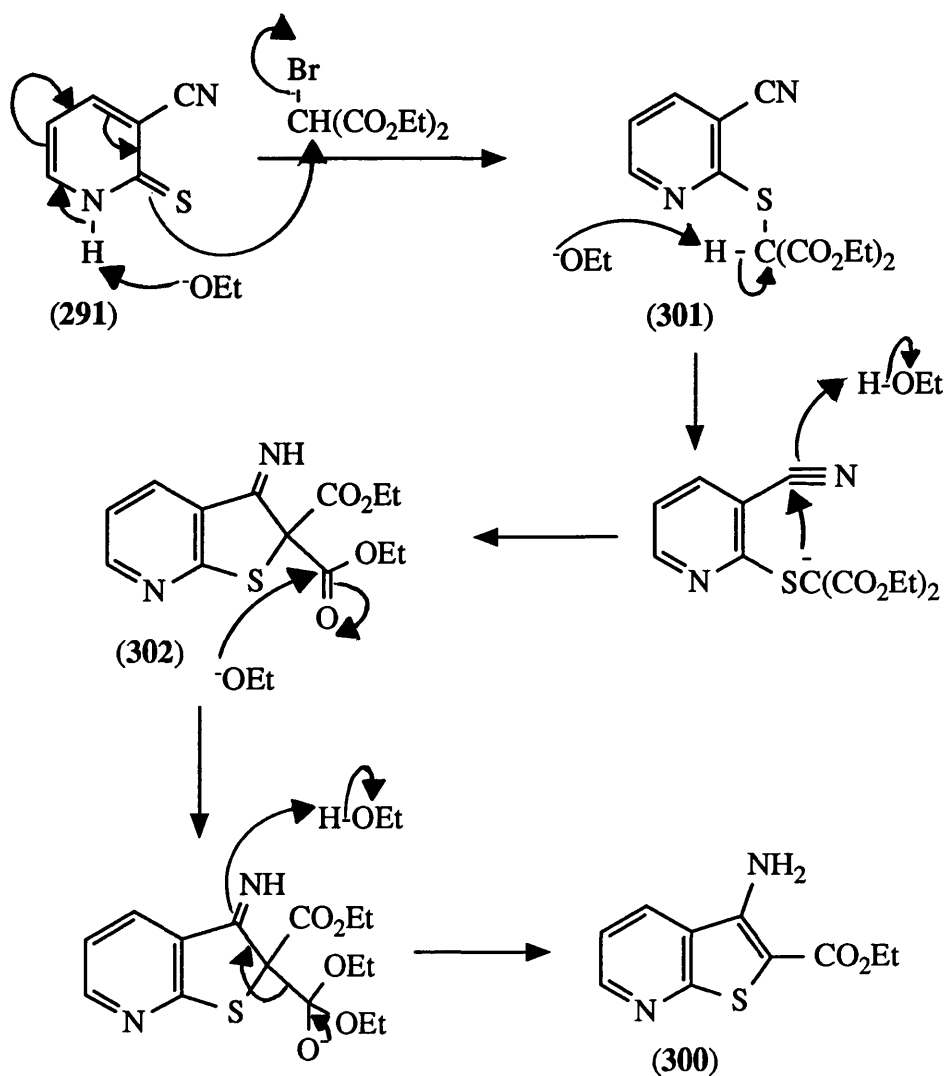


Thus, (**291**) was treated with diethyl bromomalonate in the presence of sodium ethoxide in DMF at room temperature and the product obtained by filtration was recrystallised from ethyl acetate. The IR spectrum of the product did not indicate

the presence of a nitrile and therefore it appeared that a cyclised product had formed. However, absorption peaks at 3413cm^{-1} and 3311cm^{-1} suggested the presence of a primary amine rather than the expected imine. Also present in the IR was an absorption peak at 1673cm^{-1} for an ester carbonyl group. The NMR spectrum indicated the presence of only one ethyl ester instead of the expected two which meant that one of the ester groups had been lost. Also present at 7.20δ was a singlet peak for two protons which could correspond to a primary amine. After comparing all of the analytical data with that of the thienopyridine (**300**), it was discovered that the two were identical. Thus, thienopyridine (**300**) had been isolated from the reaction of (**291**) and diethyl bromomalonate [Equation 121].

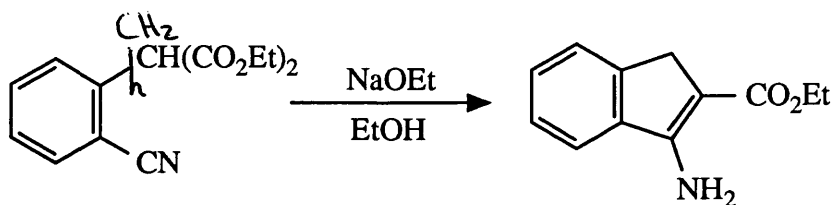


It is proposed that the thienopyridine (**300**) is formed by the mechanism shown in Scheme 105. The reaction proceeds as usual with initial base attack on the thione resulting in alkylation of the sulfur atom at the 2-position. The proton on the CH is very acidic and therefore is removed by base which promotes cyclisation to the thienopyridine (**302**). Regeneration of the base results in attack on one of the ester carbonyl groups leading to de-esterification and formation of the thienopyridine (**300**), with loss of diethyl carbonate.



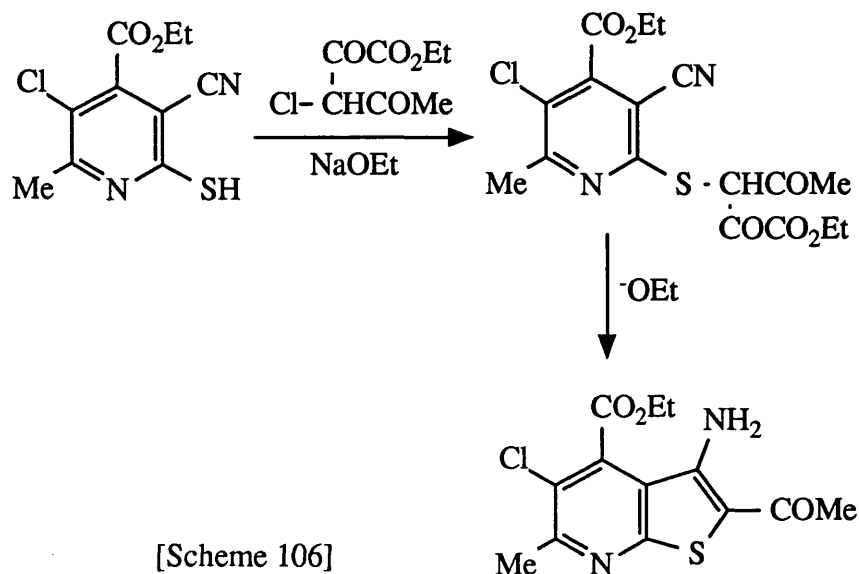
[Scheme 105]

This type of reaction has been extensively reported³⁴²⁻³⁴⁷ and these Claisen-type condensations readily occur with compounds in which intramolecular condensation is possible. The example shown in Equation 122 illustrates both the Claisen condensation and subsequent elimination of the carboxy group.

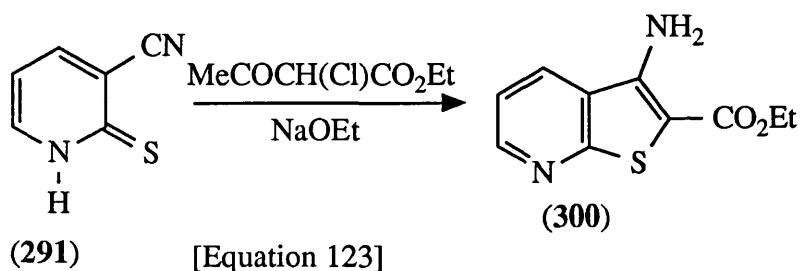


[Equation 122]

Reactions of this type have also been utilised²³³ in the preparation of thienopyridines [Scheme 106].

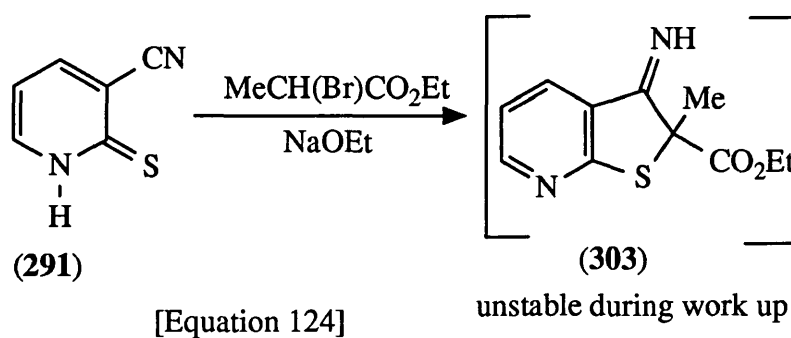


Since the thienopyridine (300) was formed from the reaction of the thione (291) and an α haloester, it was possible that thienopyridine (298) could be prepared from the reaction of (291) and ethyl 2-chloroacetoacetate. Thus, (291) was treated with ethyl 2-chloroacetoacetate in the presence of sodium ethoxide under the same conditions as before. The analytical data for the product, however, differed from that expected for the thienopyridine (298) but was identical to the analytical data obtained for (300). Thus, the reaction of (291) and ethyl 2-chloroacetoacetate afforded the thienopyridine (300) [Equation 123].



Surprisingly, the ketone was removed by base with loss of ethyl acetate, rather than the ester group. This was unexpected since it is believed that the carbon of the ester group might be more susceptible to nucleophilic attack than the carbon of the ketone, since the ester has an alkoxy group as well as a carbonyl group. However, the fact that the ketone group was displaced might be because ethyl acetate is a better leaving group than diethyl carbonate and therefore the thienopyridine (300) was obtained instead of (298).

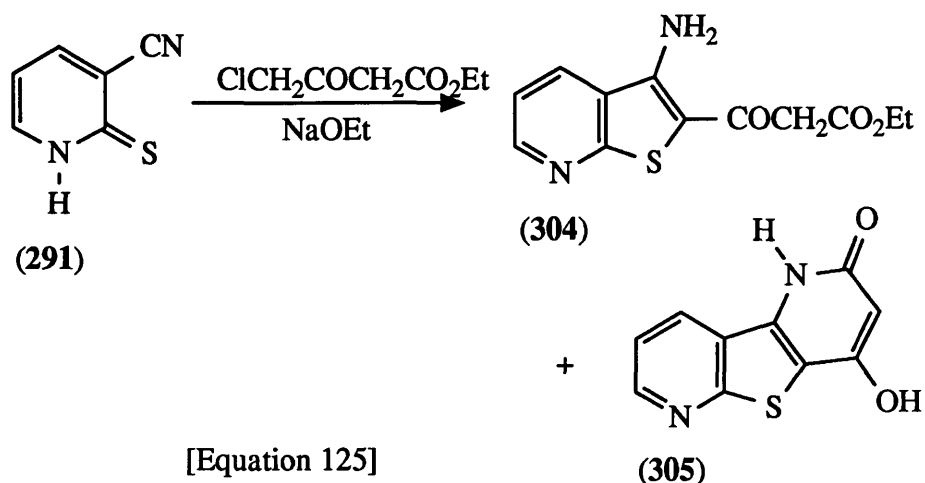
When the same type of reaction was attempted with ethyl 2-bromopropionate, under identical conditions, no product was isolated. It is possible that cyclisation to the imine (303) was achieved [Equation 124] but the decarboxylation stage, to afford the fully aromatic thienopyridine, was not successful. The imine (303) was unstable during work up and therefore no product was isolated. It may have been possible to isolate an imine derivative such as the acetyl derivative, which may have been stable during work up, to prove that the intermediate (303) had been prepared but this was never attempted.



When thione (291) was treated with ethyl 4-chloroacetoacetate, a more complex reaction occurred which afforded two products. These products were separated by solubility differences, since the first compound was soluble in ethyl acetate while the second, more polar compound was not, but was soluble in ethanol. The IR spectrum of the first product indicated the presence of a primary amine (3410 &

3308cm⁻¹) plus peaks for both the ketone carbonyl and the ester carbonyl groups (1740 and 1720cm⁻¹). These absorption values for the carbonyl groups are higher than those observed previously and it is believed that this is due to the electron withdrawing effect of the carboethoxy group. This significantly reduces the tendency for intramolecular hydrogen bonding, which is the cause of the low frequency of the carbonyl stretch in previous thienopyridines. The NMR spectrum contained a singlet at 6.90δ which corresponds to the protons on the primary amine plus a singlet at 3.80δ for the alkyl CH₂ protons which are deshielded by both the ketone and the ester groups. Also present are the typical peaks for an ethyl ester group. The spectral data and the microanalysis of this product are consistent with the proposed structure for the thienopyridine (304).

The IR spectrum of the more polar product showed the presence of secondary amide, enol and amide carbonyl functionalities. The NMR spectrum had a very broad peak (integral 2) at 13.5δ which is attributed to the proton on the alcohol and the secondary amide. The spectral data and the microanalysis for this product were consistent with the proposed structure for the tricyclic compound (305). Thus, the reaction of (291) and ethyl 4-chloroacetoacetate afforded the thienopyridine (304) and the tricyclic compound (305) in 10% and 38% yield respectively [Equation 125].



The reaction mechanism for the formation of the thienopyridine (304) proceeds as usual with base attack on the thione resulting in alkylation of the sulfur atom at the 2-position of the pyridine ring, to afford the keto ester. The CH_2 group α to the sulfur is extremely acidic and removal of a proton is easily carried out using ethoxide. Cyclisation on to the nitrile forms an imino intermediate which is tautomerised to the amine. Intramolecular displacement of the ethoxide ion forms tricycle (305) after enolisation of the acidic CH_2 proton.

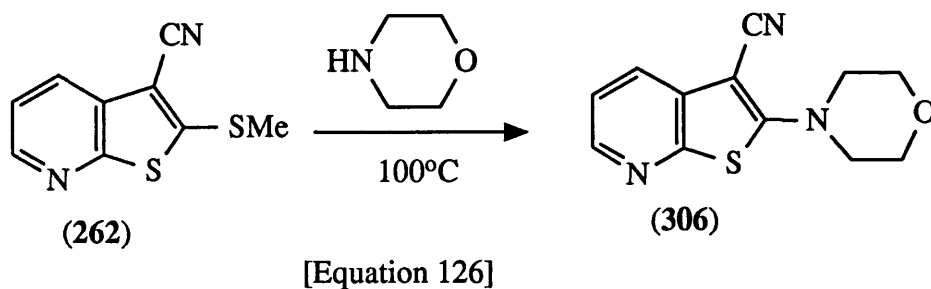
thienopyridine (**262**), which was the most readily accessible. This section will be subdivided into four different types of reactions:

- a) Reaction of thienopyridine (**262**) with nucleophiles.
- b) Synthesis of sulfoxides and sulfones of thienopyridine (**262**).
- c) Reactions of these thienopyridine sulfoxides and sulfones.
- d) Formation of tricyclic thienopyridines.

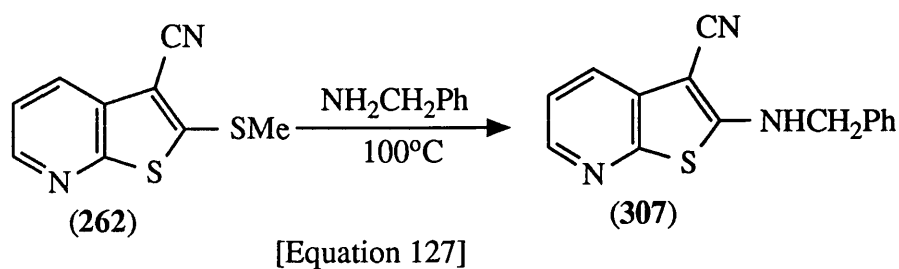
2.5.1 Reactions of Thienopyridine (262) with Nucleophiles

It was envisaged that the nucleophilic displacement of the thiomethyl group at the 2-position of (**262**) with a range of nucleophiles could be utilised to synthesise novel thienopyridine derivatives. These derivatives could then be used as precursors to novel tricyclic thienopyridines.

Thienopyridine (**262**) was reacted with neat morpholine at 100°C and the product isolated in 45% yield after chromatography. Recrystallisation from ethyl acetate afforded a product whose IR spectrum showed absorption peaks at 2980cm⁻¹ for alkyl CH stretch and 2199cm⁻¹ for the nitrile group. The NMR spectrum had a multiplet at 3.66-4.00δ for the eight alkyl protons of the morpholino group indicating that the thiomethyl group of (**262**) had been displaced by the nitrogen nucleophile of morpholine. The spectral data along with the microanalysis and the molecular ion (245) were consistent with the proposed structure for the thienopyridine, 3-cyano-2-morpholinothieno[2,3-b]pyridine (**306**) [Equation 126].



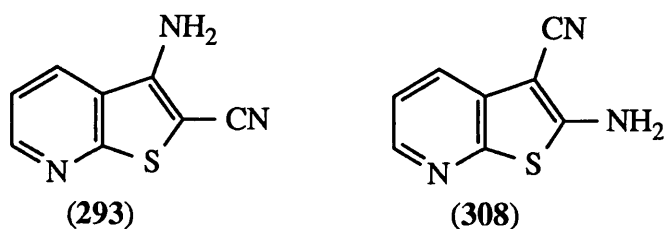
When (262) was treated with benzylamine in refluxing xylene, no reaction was observed and starting material was recovered quantitatively. However, when (262) was reacted with neat benzylamine at 100°C, a product was isolated in 45% yield after chromatography. The product obtained had absorption peaks at 3290 cm^{-1} and 2201 cm^{-1} in the IR spectrum corresponding to a secondary amine group and a nitrile group respectively. The NMR spectrum had a multiplet at 7.37 δ for five protons in the phenyl ring, a singlet at 6.25 δ for the amine proton and a doublet at 4.56 δ for the alkyl protons of the benzylamino group. The molecular ion (265) and the microanalysis were also consistent with the proposed structure of the thienopyridine derivative, 2-benzylamino-3-cyanothieno[2,3-b]pyridine (307) [Equation 127].



Both these reactions show that the thiomethyl group in the 2-position of the thienopyridine (262) can be displaced by a nitrogen nucleophile but reactions of (262) with oxygen nucleophiles have also been investigated. Thus, (262) has been treated with methanol, butanol and pentanol at reflux temperature but only

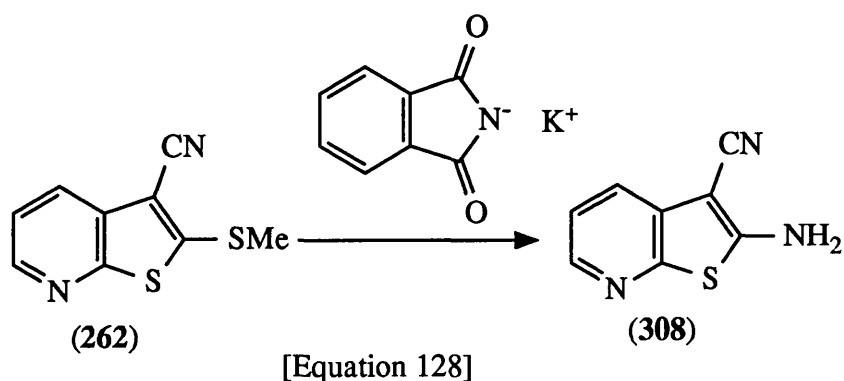
recovered starting material was obtained in each case and it appeared therefore that the oxygen atom was not a good enough nucleophile to displace the thiomethyl group. In an attempt to achieve displacement, (262) was treated with sodium methoxide in methanol at room temperature, and also at reflux temperature but again no reaction was observed. The boiling point of methanol is only 64.6°C and this may be a factor in the lack of reaction. The possible higher temperatures offered by the use of pentanol as a solvent, led to (262) being reacted with sodium pentoxide in pentanol at 100°C and at reflux temperature (136-138°C). Only recovered starting material was obtained from the reaction at 100°C but the reaction at reflux temperature (136-138°C) yielded a product which was soluble in water. The product was insoluble in organic solvents and appeared to be a salt, however, no NMR spectrum, mass spectrum or microanalysis were obtained for the salt and therefore no structure could be assigned to the product. At this point it was decided to abandon the investigations into the nucleophilic displacement of the thiomethyl group by oxygen nucleophiles.

Since the thienopyridine (293) could be readily prepared from thione (291) on reaction with chloroacetonitrile [Equation 113], the preparation of the isomer (308) was attempted. The aim was to compare the reactivity of the two isomers.

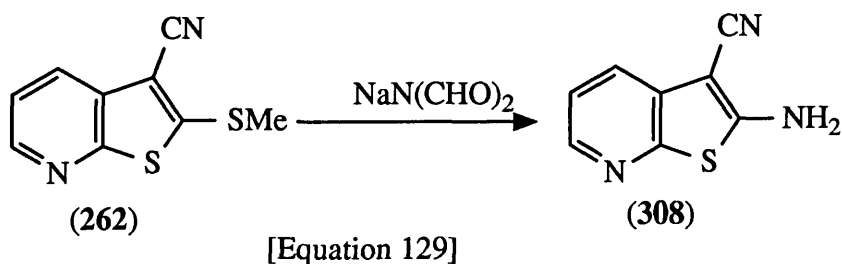


Thienopyridine (262) was reacted with a saturated solution of ammonia in methanol, in a Berghorf pressure vessel (Teflon lined) at 160°C / 10bar for 18 hours. Thin layer chromatography indicated that no reaction had occurred so the

experiment was repeated at 200°C / 20bar for 15 hours. This time tlc indicated that a large number of components were present in the reaction mixture and no homogenous product could be isolated after chromatography. An alternative route to (308) utilising the Gabriel synthesis was investigated [Equation 128]. Thus, (262) was treated with potassium phthalimide in DMF at different temperatures (room temperature to reflux temperature) but no reaction occurred. Different solvents such as ethanol and propanol were also used but still no reaction was observed.



A modified Gabriel synthesis using sodium diformylamide as a substitute for phthalimide has been reported³⁴⁸ and this modification of the Gabriel synthesis was utilised to try and synthesise (308) from (262) [Equation 129]. The thienopyridine (262) was treated with sodium diformylamide in ethanol at varying temperatures but again, only recovered starting material was isolated.



Neither the Gabriel synthesis nor the modified Gabriel synthesis were successful in obtaining the required thienopyridine (308) from (262), so another method was attempted for its synthesis. Thienopyridine (262) was treated with sodium amide in DMF at room temperature and also at 100°C but again only recovered starting material was obtained. Thus it was concluded that the desired compound (308) could not be synthesised using nitrogen nucleophiles with the thiomethyl group as the leaving group so an alternative route was investigated.

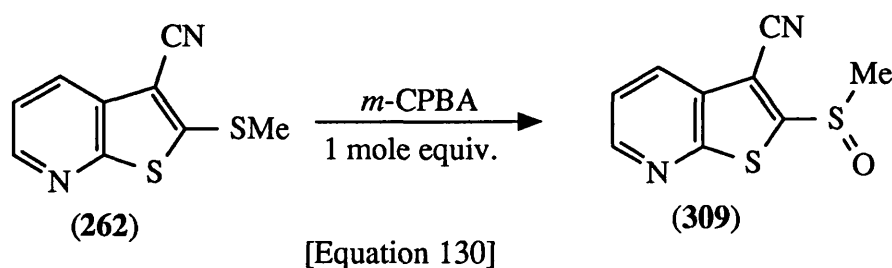
2.5.2 Synthesis of the Sulfoxide and Sulfone of Thienopyridine (262).

Of all the nucleophilic reactions carried out on thienopyridine (262), only the reactions of the nitrogen nucleophiles morpholine and benzylamine have proved successful. Both morpholine and benzylamine are liquids and therefore it is possible to carry out these reactions in the neat reagent. This is not possible however, with reagents such as sodium amide and potassium phthalimide which have to be reacted in a solvent and are therefore diluted. This is not the only factor to be considered but it may account for the reason why some nitrogen nucleophiles displace the thiomethyl group while others do not. The fact that many nucleophiles failed to displace the thiomethyl group in the 2-position of (262) indicated that the group was not particularly labile. However, if the thiomethyl group was substituted by, or converted into, a more labile substituent, then it may be possible to displace this substituent by nucleophiles. The thiomethyl substituent was converted into a potentially more labile derivative by oxidising the sulfur atom to the sulfoxide or sulfone.

On oxidation it is possible to oxidise the thienopyridine (262) in one or more of three positions: the nitrogen atom of the pyridine ring, which would give the

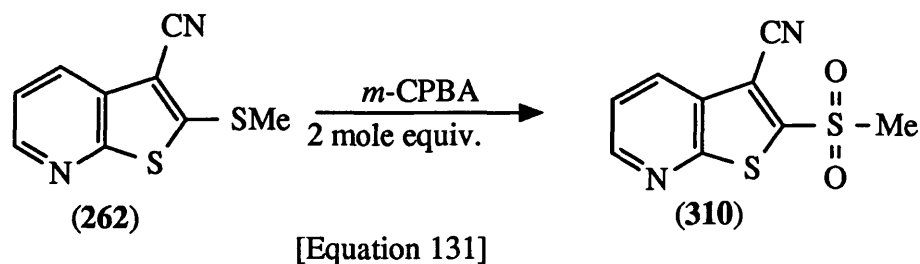
N-oxide; the sulfur atom of the thiophene ring to give the sulfoxide or the sulfone; and the sulfur atom of the thiomethyl group in the 2-position to give the sulfoxide or the sulfone. Only the last reaction product is suitable for the required manipulation.

Thienopyridine (**262**) was treated with one mole equivalent of *m*-chloroperbenzoic acid in dichloromethane. The NMR spectrum of the product was identical to that of the starting material except the singlet for protons of the thiomethyl group was at 3.20 δ instead of at 2.79 δ . This indicated that the protons of the methyl group of the product had been deshielded and therefore that oxidation had probably occurred at the sulfur atom of the thiomethyl group. The IR and NMR spectra of the product along with microanalysis indicated that the product from the oxidation reaction was 3-cyano-2-methylsulfinylthieno[2,3-*b*]pyridine (**309**), obtained in 71% yield [Equation 130].



Thienopyridine (**262**) was also oxidised with two mole equivalents of *m*-chloroperbenzoic acid in an attempt to oxidise the sulfur atom of the thiomethyl group to the sulfone. The NMR spectrum was again similar to (**262**) and (**309**) except the peak for the alkyl protons of the thiomethyl group now appeared at 3.62 δ . Thus, the protons had been deshielded more than in sulfoxide (**309**) and therefore the oxidation had occurred on the sulfur atom to afford the sulfone. The IR and NMR spectra along with the microanalysis were all consistent with the proposed structure for the thienopyridine, 3-cyano-2-methylsulfonylthieno[2,3-*b*]-

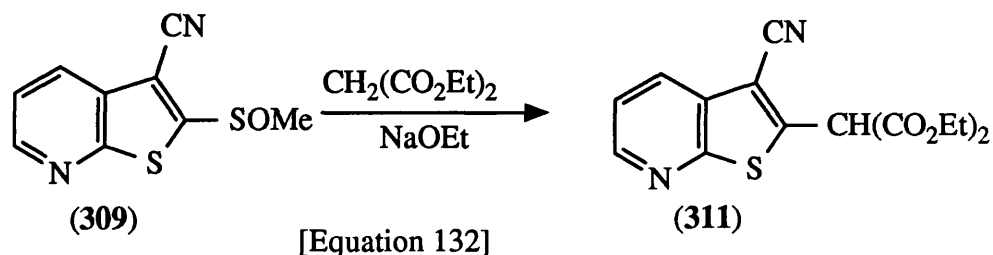
pyridine (310), obtained in 70% yield [Equation 131].



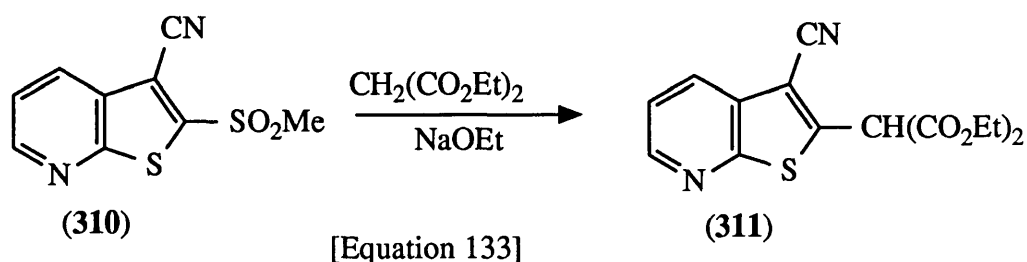
2.5.3 Reaction of the Thienopyridine Sulfoxide and Sulfone with Nucleophiles.

The reactions of the sulfide (262), the sulfoxide (309) and the sulfone (310) with the same nucleophile, under identical reaction conditions, were investigated to determine which thienopyridine has the more labile group at the 2-position. Thus, sulfide (262) was treated with neat diethyl malonate in the presence of sodium ethoxide at 100°C and at reflux temperature but no product was isolated in either case. Starting material was recovered when the reaction was carried out at 100°C but at reflux temperature (199°C) no recovered starting material or product was isolable. When the sulfoxide (309) was treated with neat diethyl malonate in the presence of sodium ethoxide at 100°C, an oil was isolated in 56% yield by chromatography. The IR spectrum of the product showed absorption peaks at 2226cm⁻¹ for the nitrile group and a very strong peak at 1740cm⁻¹ for an ester carbonyl group. The NMR spectrum showed peaks typical of an ethyl ester group but the triplet at 1.16δ corresponded to six protons while the quartet at 4.00δ corresponded to four protons, indicating the presence of two identical ethyl ester groups. Also present in the spectrum was a singlet at 3.40δ for the alkyl proton of the CH group which had been deshielded by two carbonyl groups. No peak was observed in the spectrum for the SOMe protons indicating that the SOMe group

had been displaced. The spectral data along with the microanalysis indicated that the methylsulfoxide group in the 2-position of (309) had been displaced by the diethyl malonate anion to afford the thienopyridine, 3-cyano-2-dicarboethoxy-methylthieno[2,3-b]pyridine (311) [Equation 132].

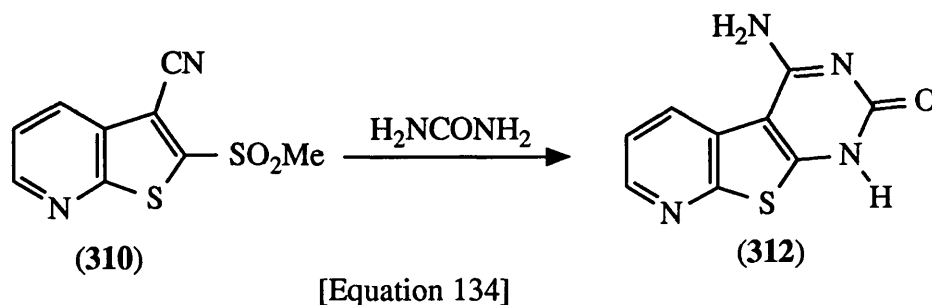


The sulfone (310) was also reacted with the anion of diethyl malonate, under identical conditions to (309). The isolation of an oil, in 83% yield, was again achieved after chromatography. The IR and NMR spectra were identical to the product (311) obtained from the reaction of (309) and therefore the reaction of (310) with the anion of diethyl malonate results in the displacement of the methylsulfonyl group to afford (311) [Equation 133].



The results obtained by comparing these reactions indicate that the thienopyridine (310), which had been oxidised to the sulfone, had the most labile substituent at the 2-position, since the substitution product was isolated in 83% yield compared to only 56% for the sulfoxide (309) and no reaction for the sulfide (262). Due to the fact that (310) had the most labile substituent, it was decided to attempt further nucleophilic displacement reactions on this thienopyridine. Thus, (310) was

treated with sodium methoxide in methanol at room temperature but no product was isolated. The compound (310) was also reacted with sodium amide in DMF but again no product was isolated. The thienopyridine (310) was also reacted with urea in an attempt to synthesise the tricyclic compound (312) [Equation 134]. However, only recovered starting material was isolated from the reaction mixture.

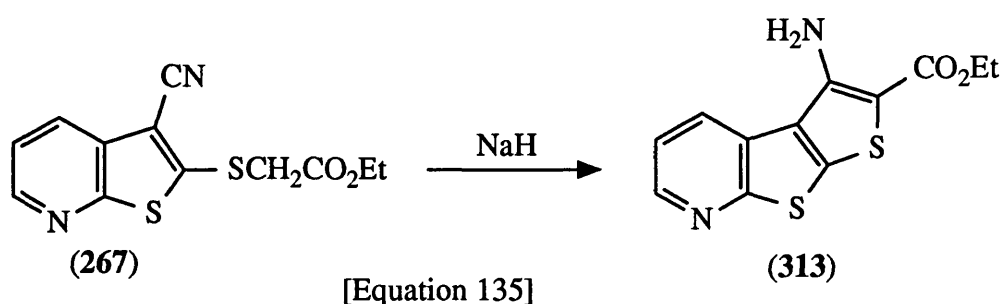


Unfortunately, due to the time limitations of the project the investigation of these reactions was not continued but it is believed that there is considerable work to be carried out in this area now that a more labile substituent at the 2-position has been prepared. Many more nucleophilic reactions could be attempted under varying conditions with different nucleophiles such as hydrazines (e.g. phenylhydrazine), ureas (e.g. urea and thiourea) and carbon nucleophiles (e.g. the anion of ethyl acetoacetate or acetyl acetone) amongst others.

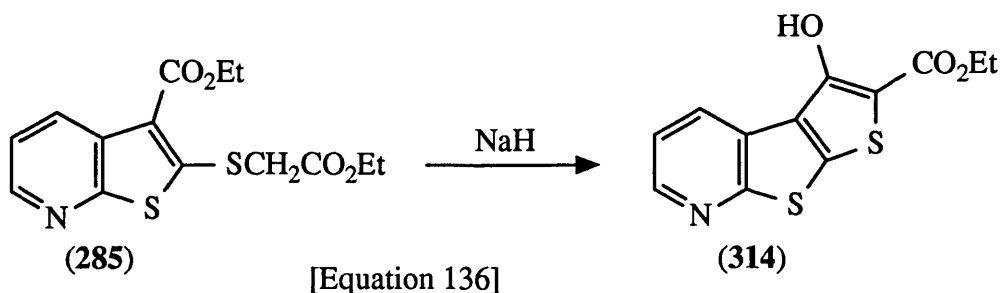
2.5.4 The Synthesis of Tricyclic Thienopyridines

Reactions have been attempted with thienopyridine derivatives in order to prepare novel tricyclic thienopyridines. Thus, 2-carboethoxymethylthio-3-cyanothieno-[2,3-b]pyridine (267) (prepared as described in [Equation 92], Section 2.3.1.1) has been treated with sodium hydride in DMF at room temperature. The reaction mixture was added to ice/water and the crude product isolated by filtration.

Recrystallisation from ethyl acetate gave the tricyclic product (313) in 26% yield. The IR spectrum of the product had absorption peaks at 3377cm^{-1} and 3294cm^{-1} for a primary amine and a peak at 1673cm^{-1} for an ester carbonyl group. The fact that no absorption for a nitrile group was observed and that a primary amine appeared to be present, indicated that ester (267) had cyclised to the tricyclic product. The NMR and the microanalysis were both consistent with the proposed structure of the tricyclic compound (313) [Equation 135].

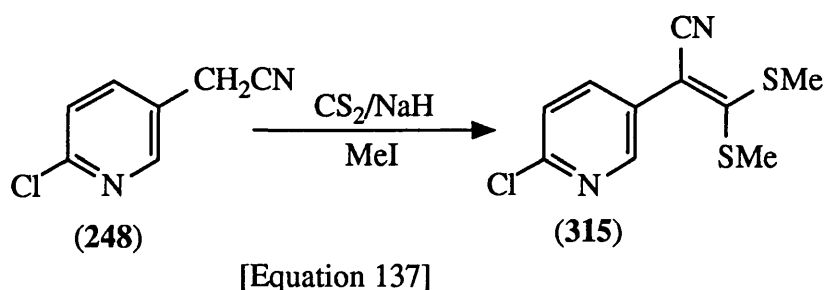


2-Carboethoxymethylthio-3-carbomethoxythieno[2,3-b]pyridine (285) (description of preparation in [Equation 93] Section 2.2.2.a) has also been treated with sodium hydride in DMF, in an attempt to prepare the tricyclic compound (314) [Equation 136]. However, (314) was not isolated and starting material (285) was recovered quantitatively.

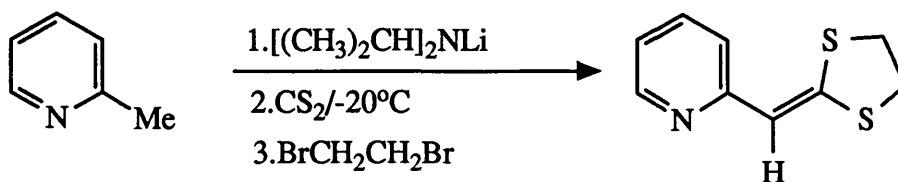


2.5.0 Miscellaneous Reactions

During the synthesis of the pyridine derivatives (238-246) some by-products were also isolated. Of particular interest was the by-product from the synthesis of (238) and (239) which was found to be 2-chloro-5-cyanomethylpyridine (248). Due to the fact that (238) was prepared in large amounts, by-product (248) was also obtained in large quantities and therefore several reactions of (248) were investigated. Thus, (248) was treated with carbon disulfide in the presence of sodium hydride in dimethyl sulfoxide, followed by quenching with iodomethane. The reaction mixture was poured onto water and crude product was isolated by filtration. Recrystallisation afforded (315) in 51% yield. The IR spectrum of the product indicated the presence of a nitrile group at 2206cm^{-1} , while the NMR spectrum showed two singlet peaks at 2.36δ and 2.60δ for the protons of the methyl groups. The IR and NMR spectra along with microanalysis were consistent with the proposed structure of the ketene dithioacetal (315) [Equation 137].

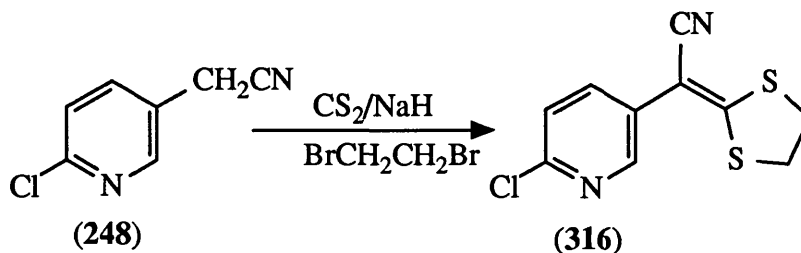


Similar pyridyl ketene dithioacetals have been prepared^{339,349,350}. The reaction of 2-methylpyridine with, successively, lithium diisopropylamide, carbon disulfide and 1,2-dibromoethane gives the ketene dithioacetal product in 57% yield [Equation 138].



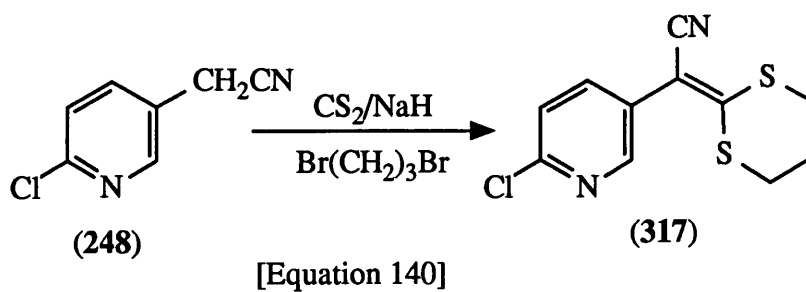
[Equation 138]

The by-product (**248**) was also treated with carbon disulfide under identical conditions as before, followed by quenching with 1,2-dibromoethane to afford a product, after filtration, in 54% yield. The IR spectrum of the product had a peak at 2205cm^{-1} indicating the presence of a nitrile group. The NMR spectrum had a peak at 3.20δ for four alkyl protons indicating that the expected product had been formed and the microanalysis also confirmed that the ketene dithioacetal (**316**) had been produced [Equation 139].



[Equation 139]

Finally, product (**317**) was obtained in 58% yield from the reaction of (**248**) with carbon disulfide, followed by quenching with 1,3-dibromopropane [Equation 140]. Spectroscopic and analytical data were again consistent with the proposed structure.



2.6 Biological Evaluation

A number of these compounds have been submitted to Shell Research in Sittingbourne, Kent for evaluation as agrochemicals. However, none of the results thus far have indicated any significant biological activity although some compounds are still being tested and these results are awaited.

EXPERIMENTAL

3. EXPERIMENTAL

Infrared spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrophotometer and NMR spectra were recorded in deuteriochloroform (except where otherwise stated) on a ^{Jeol}~~Jeol~~ PMX 60si spectrometer using tetramethylsilane as internal reference. Mass spectra were measured using an AEI MS920s spectrometer while melting points were determined with an Electrothermal melting point apparatus and are uncorrected. Column chromatography was performed using pressurised short path columns with Kieselgel 60, particle size < 0.063mm (Merck # 7729). Reactions were monitored by thin layer chromatography on Merck DC-Alufolien Kieselgel 60 F₂₅₄ (Merck # 5554) plates which were visualised under ultraviolet irradiation.

3-Cyanomethylpyridine N-oxide (247).

3-Cyanomethylpyridine⁹⁶ (10.0g, 0.0846mol), glacial acetic acid (50mL) and 30% hydrogen peroxide (15mL) were heated on a steam bath for 11 hours and then cooled to room temperature. More hydrogen peroxide (8mL) was added and the reaction mixture heated for a further 8 hours. Approximately 50mL of solvent was removed *in vacuo* and water (100mL) was added to the reaction mixture. The volatile components were removed *in vacuo* and the water addition / evaporation repeated. The brown solid obtained was extracted into a toluene / dichloromethane mixture, dried over magnesium sulfate and solvent removed *in vacuo* to afford a white solid. Recrystallisation from toluene gave 3-cyanomethylpyridine N-oxide³³⁴ (**247**) (10.6g, 93.4%) as a white crystalline solid. mp 134.5-135.5°C, (literature³³⁴ mp 134.5-136°C). $\nu_{\max}(\text{KBr})$ 3027, 2905, 2257, 1274cm⁻¹.

Reaction of 3-Cyanomethylpyridine N-oxide (247) with Phosphoryl Chloride.

3-Cyanomethylpyridine N-oxide³³⁴ (247) (10.0g, 0.0745mol) was added to phosphoryl chloride (100mL) and the mixture warmed slowly with vigorous shaking until all the solid had dissolved, then refluxed for 3 hours. Excess phosphoryl chloride was removed *in vacuo* and the residue poured onto ice (150g), neutralised with a dilute solution of ammonia and extracted with ethyl acetate (3 x 100mL). The organic extracts were dried over magnesium sulfate and solvent removed *in vacuo* to afford a dark residue. This residue was dissolved in toluene and chromatographed on silica gel (200g). Gradient elution with light petroleum / diethyl ether (10-30%) afforded as the least polar compound, 2-chloro-3-cyanomethylpyridine³³⁴ (238) (4.21g, 37%) as a white crystalline solid. mp 84-84.5°C (literature³³⁴ mp 83-85°C). $\nu_{\max}(\text{KBr})$ 2952, 2923, 2242 cm^{-1} . $\delta_{\text{H}}(\text{CDCl}_3)$ 3.80 (s, 2H, CH_2), 7.13 (dd, 1H, $J=8.0$ & 12.0Hz, H-5), 7.74 (dd, 1H, $J=12.0$ & 4.0Hz, H-4), 8.24 (dd, 1H, $J=4.0$ & 8.0Hz, H-6).

Also isolated was 2-chloro-5-cyanomethylpyridine³³⁴ (248) (2.4g, 21%) as a white crystalline solid. mp 51-52°C (literature³³⁴ mp 51-52°C). $\nu_{\max}(\text{KBr})$ 3089, 3047, 2968, 2256 cm^{-1} . $\delta_{\text{H}}(\text{CDCl}_3)$ 3.76 (s, 2H, CH_2), 7.29 (d, 1H, $J=14.0$ Hz, H-5), 7.62 (dd, 1H, $J=14.0$ & 4.0Hz, H-4), 8.27 (d, 1H, $J=4.0$ Hz, H-2).

The most polar product isolated was 4-chloro-3-cyanomethylpyridine (239) (50mg, 5%). mp 53-55°C. $\nu_{\max}(\text{KBr})$ 2887, 2247 cm^{-1} . $\delta_{\text{H}}(\text{CDCl}_3)$ 3.82 (s, 2H, CH_2), 7.28 (d, 1H, $J=8.0$ Hz, H-5), 8.40 (d, 1H, $J=8.0$ Hz, H-6), 8.56 (s, 1H, H-2). (Found: C,55.5; H,3.3; N,18.4; Cl,23.4. $\text{C}_7\text{H}_5\text{ClN}_2$ requires C,55.3; H,3.5; N,18.0; Cl,23.4%). $m/e(\%)$ 154(M^+ ,32), 152(100), 125(47), 117(53), 90(36).

Reaction of (249) with Lithium Aluminium Hydride.

A solution of methyl 3-bromopyridine-4-carboxylate³³⁵ (249) (13.0g, 0.06mol) in dry ether (50mL) was added dropwise, over one hour, to a mixture of lithium aluminium hydride (2.3g, 0.06mol) in dry ether (250mL). Once the addition was complete, the reaction mixture was stirred for 4 hours. Ethanol (25mL) was added (to destroy any excess lithium aluminium hydride) and then dilute hydrochloric acid (100mL) was added dropwise. The ether layer was dried over magnesium sulfate and solvent removed *in vacuo* but no product was isolated. Further extraction of the aqueous layer with ether and then ethyl acetate gave no product so the aqueous layer was neutralised with sodium hydrogen carbonate and solvent removed *in vacuo* to afford a solid. The solid was boiled in ethyl acetate but tlc indicated that no components had been extracted from the solid. The solid appeared to be an inorganic / organic complex in which the product was trapped.

If the hydroxymethyl compound was formed it may have been too polar to be extracted from the complex so to prove that this product had been formed, the solid was shaken with a mixture of pyridine (50mL) and acetic anhydride (15mL) in an attempt to prepare a less polar derivative. The mixture was extracted with ethyl acetate and solvent removed *in vacuo* to afford a solid which was dissolved in toluene and chromatographed on silica gel (20g). Elution with light petroleum ether / diethyl ether (10-50%) afforded 4-acetoxymethyl-3-bromopyridine (250) (900mg, 6.5%) as a white crystalline solid. mp 83-83.5°C. $\nu_{\max}(\text{KBr})$ 2930, 1732 cm^{-1} . δ_{H} (CDCl_3) 2.20 (s, 3H, CH_3), 5.18 (s, 2H, CH_2), 7.33 (d, 1H, $J=5.4\text{Hz}$, H-5), 8.53 (d, 1H, $J=5.4\text{Hz}$, H-6), 8.70 (s, 1H, H-2). (Found: C,41.9; H,3.5; N,6.0. $\text{C}_8\text{H}_8\text{NBrO}_2$ requires C,41.8; H,3.5; N,6.1; Br,34.7%). $m/e(\%)$ 150(100), 108(50), 43(54).

Attempted Reaction of 3-Bromo-4-methylpyridine with N-Bromosuccinimide.

3-Bromo-4-methylpyridine³³⁷ (5.1g, 0.03mol), N-bromosuccinimide (10.6g, 0.06mol), carbon tetrachloride (50mL) and 2,2-azobis(2-methylpropionitrile) (AIBN) (25mg) were refluxed under irradiation for 3 hours. The cooled reaction mixture was filtered and the solid washed with ether. The solvent from the filtrate and washings were concentrated *in vacuo*. The liquid obtained was identical (tlc, ir and nmr) to unreacted starting material.

3-Bromo-4-cyanomethylpyridine (240).

3-Bromo-4-methylpyridine N-oxide³³⁷ (**251**) (10.0g, 0.05mol), *p*-toluenesulfonyl chloride (20.3g, 0.11mol) and dioxan (50mL) were refluxed for 4 hours. The cooled reaction mixture was treated with hydrochloric acid (10% v/v, 100mL), stirred for 15 minutes and then extracted with ether (4 x 50mL) to remove excess tosyl chloride. The aqueous phase was neutralised with sodium hydrogen carbonate and extracted with ether (2 x 100mL). The organic extracts were dried over magnesium sulfate and solvent removed *in vacuo*.

A mixture of water (10mL) and ethanol (25mL) was added to the residue and this mixture was added dropwise to a refluxing solution of sodium cyanide (13.0g, 0.27mol) in water (25mL) and ethanol (125mL). The reaction mixture was refluxed for 1 hour, cooled and solvent removed *in vacuo* to afford a dark residue. Water (50mL) was added to the residue and extracted with ethyl acetate. The organic extracts were dried over magnesium sulfate, solvent was removed *in vacuo* and the residue was chromatographed on silica gel (200g). Gradient elution with light petroleum ether / diethyl ether (10-50%) afforded 3-bromo-4-cyanomethylpyridine (240) (2.0g, 19%) as a white crystalline solid. mp 93-94°C. ν_{\max} (KBr) 2859, 2250cm⁻¹. δ_{H} (CDCl₃) 3.82 (s, 2H, CH₂), 7.42 (d, 1H, J=4.8Hz, H-5), 8.48 (d, 1H, J=4.8Hz, H-6), 8.66 (s, 1H, H-2). (Found C,43.0; H,2.85; N,13.9; Br,40.8.

$C_7H_5N_2Br$ requires C,42.7; H,2.55; N,14.2; Br,40.6%). $m/e(\%)$ 198(M^+ , 97), 196(100), 117(46), 116(74), 90(30).

Further elution afforded 3-bromo-4-[1-cyano-2-(3-bromopyrid-4-yl)ethyl]pyridine (254) (1.05g, 5%) as a white solid. mp 120-122°C. $\nu_{max}(KBr)$ 3039, 2921, 2246 cm^{-1} . δ_H (d_6 -DMSO) 3.39-3.48 (m, 2H, alkyl CH_2), 4.86-5.02 (m, 1H, alkyl CH), 7.50 (d, 1H, $J=5.5Hz$, H-5), 7.62 (d, 1H, $J=4.8Hz$, H-5), 8.55 (d, 1H, $J=4.8Hz$, H-6), 8.64 (d, 1H, $J=5.5Hz$, H-6), 8.74 (s, 1H, H-2), 8.81 (s, 1H, H-2). (Found: C,42.4; H,2.4; N,11.4; Br,43.6. $C_{13}H_9N_3Br_2$ requires C,42.5; H,2.45; N,11.4; Br,43.6%). $m/e(\%)$ 369(M^+ , 40), 367(80), 365(40), 171(100), 169(99).

3-Bromo-2-cyanomethylpyridine (241).

3-Bromo-2-methylpyridine³³⁸ (**255**) (5.1g, 0.03mol), N-bromosuccinimide (10.6g, 0.06mol), carbon tetrachloride (50mL) and 2,2-azobis(2-methylpropionitrile) (AIBN) (25mg) were refluxed under irradiation for 3 hours. The cooled reaction mixture was filtered and the solid washed with ether. The solvent from the filtrate and washings were concentrated *in vacuo* and dissolved in water (10mL) and ethanol (25mL). This was then added to a refluxing solution of sodium cyanide (4.5g, 0.09mol) in water (25mL) and ethanol (75mL) and refluxed for 1 hour. Solvent was removed *in vacuo* to afford a dark residue, water (50mL) was added and the aqueous mixture extracted with ethyl acetate (3 x 100mL). The organic extracts were dried over magnesium sulfate and solvent removed *in vacuo* to afford a dark residue which was dissolved in toluene and chromatographed on silica gel (100g). Gradient elution with light petroleum ether / diethyl ether (10-50%) afforded 3-bromo-2-cyanomethylpyridine (241) (1.7g, 32%) as a white crystalline solid. mp 64-65°C. $\nu_{max}(KBr)$ 2925, 2248 cm^{-1} . δ_H ($CDCl_3$) 4.09 (s, 2H, CH_2), 7.40 (dd, 1H, $J=4.4$ & 7.8Hz, H-5), 7.91 (dd, 1H, $J=1.3$ & 4.4Hz, H-4), 8.57 (dd, 1H, $J=1.3$ & 4.4Hz, H-6). (Found: C,42.7; H,2.75; N,14.1; Br,40.5. $C_7H_5N_2Br$

requires C,42.7; H,2.55; N,14.2; Br,40.6%). $m/e(\%)$ 198(M^+ ,95), 196(100), 117(58), 90(35).

Ethyl 3-bromo-4-pyridylacetate¹¹⁹ (244).

A solution of diisopropylamine (25mL, 0.180mol) and dry THF (250mL) were stirred under nitrogen at room temperature and phenyllithium (1.8M solution in cyclohexane / diethyl ether (70/30) 100mL, 0.180mol) was added over 30 minutes. The reaction mixture was stirred for a further 30 minutes and 3-bromo-4-methylpyridine³³⁶ (10g, 0.058mol) was added over 10 minutes. The reaction mixture was stirred for 5 minutes, diethyl carbonate (20mL, 0.180mol) was added, followed by stirring for 1 hour then poured onto ether (500mL). The organic phase was washed with water (4 x 100mL), dried over magnesium sulfate and solvent removed *in vacuo* to afford a liquid. The liquid was chromatographed on silica gel (200g) and gradient elution with light petroleum ether / diethyl ether (10-50%) to afford starting material (1.3g, 13%).

Further elution afforded ethyl 3-bromo-4-pyridylacetate¹¹⁹ (244) (9.6g, 68%) as a colourless liquid. bp 110°C at 1.0 mbar (literature¹¹⁹ bp 91-95°C at 0.06mm). ν_{\max} 2981, 1735cm⁻¹. δ_H (CDCl₃) 1.26 (t, 3H, J=12.0Hz, CH₃), 3.74 (s, 2H, CH₂), 4.17 (q, 2H, J=12.0Hz, CH₂), 7.20 (d, 1H, J=8.0Hz, H-5), 8.36 (d, 1H, J=8.0Hz, H-6), 8.60 (s, 1H, H-2).

Ethyl 3-bromo-2-pyridylacetate (245).

A solution of diisopropylamine (2.5mL, 0.018mol) and dry THF (25mL) were stirred under nitrogen at room temperature and phenyllithium (1.8M solution in cyclohexane / diethyl ether (70/30) 10mL, 0.018mol) was added over 30 minutes. The reaction mixture was stirred for 30 minutes and 3-bromo-2-methylpyridine³³⁸ (255) (1.4g, 0.008mol) was added over 10 minutes. The reaction mixture was

stirred for 5 minutes, diethyl carbonate (2mL, 0.018mol) was added, stirred for a further 1 hour and then diluted with ether (50mL). The organic layer was washed with water (3 x 25mL), dried over magnesium sulfate and solvent removed *in vacuo* to afford a liquid (2.3g). The liquid was chromatographed on silica gel (100g) and elution with light petroleum ether / diethyl ether (10-50%) afforded starting material (770mg, 55%).

Further elution afforded ethyl 3-bromo-2-pyridylacetate (245) (650mg, 33%) as a colourless liquid. bp 100°C at 0.7 mbar. ν_{\max} 2981, 1737cm⁻¹. δ_{H} (CDCl₃) 1.24 (t, 3H, J=12.0Hz, CH₃), 3.98 (s, 2H, CH₂), 4.15 (q, 2H, J=12.0Hz, CH₂), 6.98 (dd, 1H, J=6.0 & 12.0Hz, H-5), 7.75 (dd, 1H, J=2.0 & 12.0Hz, H-4), 8.38 (dd, 1H, J=2.0 & 6.0Hz, H-6). (Found: C,44.3; H,4.1; N,5.6; Br,32.7. C₉H₁₀NBrO₂ requires C,44.3; H,4.1; N,5.7; Br,32.7%).

2-Chloropyridine-3-acetic acid³³⁴ (257).

2-Chloro-3-cyanomethylpyridine (238) (4.0g, 0.03mol) in concentrated hydrochloric acid (160mL) was refluxed for 5 hours. Solvent was removed *in vacuo* to afford a white solid which was dissolved in 10% sodium hydrogen carbonate a little insoluble material was separated by filtration and the acid was precipitated from the filtrate by the addition of concentrated hydrochloric acid. The solid was recrystallised from toluene to afford 2-chloropyridine-3-acetic acid³³⁴ (257) (4.4g, 98%) as a white crystalline solid. mp 204-206°C (literature³³⁴ mp 203-204°C). ν_{\max} (KBr) 3000-2480, 1908, 1700cm⁻¹.

Methyl 2-chloro-3-pyridylacetate (246).

2-Chloropyridine-3-acetic acid (257) (2.3g, 0.013mol) and thionyl chloride (20mL) were refluxed for 1.5 hours. Solvent was removed *in vacuo* and the residue poured onto a stirred mixture of methanol (50mL) and triethylamine (15mL). The mixture

was stirred for 30 minutes, solvent removed *in vacuo*, water (25mL) added to the residue and the aqueous mixture extracted with ether (2 x 100mL). The organic extracts were dried over magnesium sulfate and solvent removed *in vacuo* to afford an oil which was chromatographed on silica gel (40g). Gradient elution with light petroleum ether / diethyl ether (10-50%) afforded methyl 2-chloro-3-pyridylacetate (246) (880mg, 35%) as a colourless liquid. bp 95°C at 0.6 mbar. ν_{\max} 2953, 1740cm⁻¹. δ_{H} (CDCl₃) 3.74 (s, 3H, CH₃), 3.79 (s, 2H, CH₂), 7.25 (dd, 1H, J=5.4 & 8.3Hz, H-5), 7.66 (, 1H, J=2.4 & 8.3Hz, H-4), 8.34 (dd, 1H, J=2.4 & 5.4Hz, H-6); (Found: C,51.7; H,4.4; N,7.3; Cl,19.2. C₈H₈NO₂Cl requires C,51.7; H,4.3; N,7.5; Cl,19.1%). m/e(%) 150(M⁺,100), 128(17), 126(67), 91(22), 90(16).

Ethyl 3-pyridylacetate N-oxide³⁴⁰ (258).

Ethyl 3-pyridylacetate³⁴² (10.0g, 0.06mol), glacial acetic acid (50mL) and hydrogen peroxide (10mL) were heated at 70°C for 24 hours. Excess hydrogen peroxide was destroyed by the addition of ferrous sulfate and solvent removed *in vacuo* to afford a solid. The solid was extracted with boiling ethyl acetate (5 x 100mL), the organic extracts were dried over magnesium sulfate and solvent removed *in vacuo* to afford a liquid. The liquid was chromatographed on silica gel (200g) and elution with light petroleum ether / ethyl acetate (50%) afforded starting material (2.4g, 24%). Further elution with neat ethyl acetate gave ethyl 3-pyridylacetate N-oxide³⁴⁰ (258) (6.0g, 55%) as a white solid. mp 95-97°C (literature³⁴⁰ mp 97-98°C). ν_{\max} (KBr) 3081, 3051, 2990, 1731, 1271cm⁻¹.

The reaction of ethyl 3-pyridylacetate N-oxide (258) with phosphoryl chloride.

Ethyl 3-pyridylacetate N-oxide (258) (2.8g, 0.015mol) was added to phosphoryl chloride (35mL) and the mixture warmed slowly with vigorous shaking until all solid had dissolved, then refluxed for 3 hours. Excess phosphoryl chloride was removed *in vacuo*, the residue poured onto ice (100g), neutralised with a dilute

solution of ammonia and extracted with ethyl acetate (3 x 100mL). The organic extracts were dried over magnesium sulfate and solvent removed *in vacuo* to afford a dark oil. The oil was chromatographed on silica gel (100g) and gradient elution with light petroleum ether / diethyl ether (10-50%) afforded as the least polar compound ethyl 2-chloro-5-pyridylacetate (259) (1.3g, 22%) as a colourless liquid. bp 75°C at 0.2mbar. ν_{\max} 2982, 1732cm⁻¹. δ_{H} (CDCl₃) 1.24 (t, 3H, J=12.0Hz, CH₃), 3.58 (s, 2H, CH₂), 4.18 (q, 2H, J=12.0Hz, CH₂), 7.23 (d, 1H, J=14.0Hz, H-3), 7.57 (dd, 1H, J=4.0 & 14.0Hz, H-4), 8.24 (d, 1H, J=4.0Hz, H-6); (Found: C,54.0; H,5.1; N,7.0; Cl,17.8. C₉H₁₀NClO₂ requires C,54.1; H,5.0; N,7.0; Cl,17.8%).

Also isolated was ethyl 2-chloro-3-pyridylacetate (242) (1.8g, 33%) as a colourless liquid. bp 85°C at 0.5mbar. ν_{\max} 2983, 1735cm⁻¹. δ_{H} (CDCl₃) 1.26 (t, 3H, J=12.0Hz, CH₃), 3.74 (s, 2H, CH₂), 4.16 (q, 2H, J=12.0Hz, CH₂), 7.16 (dd, 1H, J=8.0 & 12.0Hz, H-5), 7.50 (dd, 1H, J=4.0 & 12.0Hz, H-4), 8.26 (dd, 1H, J=4.0 & 8.0Hz, H-6). (Found: C,54.0; H,5.1; N,7.3; Cl,17.8. C₉H₁₀NClO₂ requires C,54.1; H,5.0; N,7.0; Cl,17.8%).

The most polar product isolated was ethyl 4-chloro-3-pyridylacetate (243) (700mg, 13%) obtained as a clear liquid. ν_{\max} 2982, 1737cm⁻¹. δ_{H} (CDCl₃) 1.24 (t, 3H, J=12.0Hz, CH₃), 3.76 (s, 2H, CH₂), 4.16(q, 2H, J=12.0Hz, CH₃), 7.28(d, 1H, J=8.0Hz, H-5), 8.36(d, 1H, J=8.0Hz, H-6), 8.56(s, 1H, H-2). (Found: C,54.0; H,5.1; N,5.3; Cl,17.8. C₉H₁₀NClO₂ requires C,54.1; H,5.0; N,7.0; Cl,17.8%). No bp obtained due to decomposition.

3-Cyano-2-methylthiothieno[2,3-b]pyridine (262).

Carbon disulfide (4.5g, 0.059mol) was added to a stirred solution of 2-chloro-3-cyanomethylpyridine (238) (7.5g, 0.049mol) in dimethyl sulfoxide

(150mL), under nitrogen. Sodium hydride (2.6g, 0.108mol) was added portionwise and the reaction mixture was stirred for 1 hour at room temperature, warmed to 70°C for 1 hour, allowed to cool to room temperature and iodomethane (15.3g, 0.108mol) added. The reaction mixture was stirred for a further 1 hour at room temperature, poured onto ice (750g), and the crude product was obtained by filtration. This product was dissolved in ethyl acetate, dried over magnesium sulfate, decolourised with charcoal, filtered and solvent removed *in vacuo*.

Recrystallisation from ethyl acetate afforded 3-cyano-2-methylthiothieno[2,3-b]pyridine (262) (9.1g, 80%) as a pale yellow crystalline solid. mp 143-143.5°C. ν_{max} (KBr) 2996, 2924, 2213cm⁻¹. δ_{H} (CDCl₃) 2.79 (s, 3H, CH₃), 7.41 (dd, 1H, J=4.6 & 8.1Hz, H-5), 8.03 (dd, 1H, J=1.5 & 8.1Hz, H-4), 8.54 (dd, 1H, J=1.5 & 4.6Hz, H-6). (Found: C,52.4; H,3.0; N,13.8; S,31.4. C₉H₆N₂S₂ requires C,52.4; H,2.9; N,13.6; S,31.05%). m/e(%) 206(M⁺,100), 191(47), 173(23), 147(32).

3-Cyano-2-methylthiothieno[3,2-c]pyridine (264).

Carbon disulfide (157mg, 2.06mmol) was added to a stirred solution of 4-chloro-3-cyanomethylpyridine (239) (250mg, 1.64mol) in dimethyl sulfoxide (10mL), under nitrogen. Sodium hydride (85mg, 3.54mmol) was added portionwise and the reaction mixture was stirred for 1 hour at room temperature, warmed to 70°C for 1 hour and allowed to cool to room temperature before the addition of iodomethane (465mg, 3.28mmol). The reaction mixture was stirred for a further 1 hour at room temperature, poured onto ice (75g), and the crude product was obtained by filtration. This product was dissolved in ethyl acetate, dried over magnesium sulfate, decolourised with charcoal, filtered and solvent removed *in vacuo*. Recrystallisation from ethyl acetate afforded 3-cyano-2-methylthiothieno[3,2-c]pyridine (264) (140mg, 54%) as a pale yellow crystalline solid. mp 145.5-146°C. ν_{max} (KBr) 3050, 2960, 2217cm⁻¹. δ_{H} (CDCl₃) 2.79 (s, 3H, CH₃), 7.70 (d, 1H, J=5.7Hz, H-5), 8.53 (d, 1H, J=5.7Hz, H-6), 9.09 (s, 1H, H-2). (Found:

C,52.1; H,2.8; N,13.9; S,31.2. $C_9H_6N_2S_2$ requires C,52.4; H,2.9; N,13.6; S,31.05%. $m/e(\%)$ 206(M^+ ,100), 191(58), 173(20), 147(16).

3-Cyano-2-methylthiothieno[2,3-c]pyridine (265).

Sodium hydride (260mg, 10.95mmol) was added portionwise to a stirred solution of 3-bromo-4-cyanomethylpyridine (**240**) (1.0g, 5.08mmol), dimethyl sulfoxide (20mL) and carbon disulfide (480mg, 6.34mmol), under nitrogen. The reaction mixture was stirred for 1 hour at room temperature, warmed to 70°C for 1 hour, allowed to cool to room temperature and iodomethane (1.44g, 10.15mmol) added. The reaction mixture was stirred for a further 1 hour at room temperature, poured onto ice (150g), and the crude product was obtained by filtration. This product was dissolved in ethyl acetate, dried over magnesium sulfate, decolourised with charcoal, filtered and solvent removed *in vacuo*. Recrystallisation from ethyl acetate afforded 3-cyano-2-methylthiothieno[2,3-c]pyridine (265) (450mg,43%) as a pale yellow crystalline solid. mp 137-138°C. $\nu_{\max}(\text{KBr})$ 3060, 2922, 2214 cm^{-1} . δ_{H} (CDCl_3) 2.89 (s, 3H, CH_3), 7.66 (d, 1H, $J=5.7\text{Hz}$, H-5), 8.57 (d, 1H, $J=5.7\text{Hz}$, H-6), 9.25 (s, 1H, H-2). (Found: C,52.6; H,3.1; N,13.3; S,31.4. $C_9H_6N_2S_2$ requires C,52.4; H,2.9; N,13.6; S,31.05%). $m/e(\%)$ 206(M^+ ,100), 191(19), 173(34), 147(19).

3-Cyano-2-methylthiothieno[3,2-b]pyridine (266).

Sodium hydride (260mg, 10.95mmol) was added portionwise to a stirred solution of 3-bromo-2-cyanomethylpyridine (**241**) (1.0g, 5.08mmol), dimethyl sulfoxide (20mL) and carbon disulfide (480mg, 6.34mmol), under nitrogen. The reaction mixture was stirred for 1 hour at room temperature, warmed to 70°C for 1 hour and then allowed to cool to room temperature followed by the addition of iodomethane (1.44g, 10.15mmol). The reaction mixture was stirred for a further 1 hour at room temperature, poured onto ice (150g), and the crude product was obtained by

filtration. This product was dissolved in ethyl acetate, dried over magnesium sulfate, decolourised with charcoal, filtered and solvent removed *in vacuo*.

Recrystallisation from ethyl acetate afforded 3-cyano-2-methylthiothieno[3,2-b]-pyridine (266) (400mg, 38%) as a pale yellow crystalline solid. mp 125-126°C. ν_{max} (KBr) 3057, 2936, 2213cm⁻¹. δ_{H} (CDCl₃) 2.79 (s, 3H, CH₃), 7.28 (dd, 1H, J=4.8 & 8.3Hz, H-5), 8.03 (dd, 1H, J=1.3 & 8.3Hz, H-4), 8.74 (dd, 1H, J=1.3 & 4.8Hz, H-6). (Found: C,52.2; H,2.9; N,13.8; S,31.3. C₉H₆N₂S₂ requires C,52.4; H,2.9; N,13.6; S,31.05%). m/e(%) 206(M⁺,100), 191(28), 161(17), 147(27), 136(54).

2-Carboethoxymethylthio-3-cyanothieno[2,3-b]pyridine (267).

Carbon disulfide (1.2g, 0.016mol) was added to a stirred solution of 2-chloro-3-cyanomethylpyridine (238) (2.0g, 0.013mol) in dimethyl sulfoxide (40mL), under nitrogen. Sodium hydride (750mg, 0.031mol) was added portionwise and the reaction mixture was stirred for 1 hour at room temperature, warmed to 80°C for 1 hour, allowed to cool to room temperature and ethyl chloroacetate (3.9g, 0.031mol) added. The reaction mixture was stirred for a further 1 hour at room temperature, poured onto ice (300g), and the crude product was obtained by filtration. The solid was dissolved in ethyl acetate, dried over magnesium sulfate, decolourised with charcoal, filtered and solvent removed *in vacuo*. Recrystallisation from ethyl acetate afforded 2-carboethoxymethylthio-3-cyanothieno[2,3-b]pyridine (267) (1.89g, 52%) as a white crystalline solid. mp 81-81.5°C. ν_{max} (KBr) 3049, 2994, 2910, 2218, 1725cm⁻¹. δ_{H} (CDCl₃) 1.24 (t, 3H, J=12.0Hz, CH₃), 3.84 (s, 2H, SCH₂), 4.18 (q, 2H, J=12.0Hz, CH₂), 7.34 (dd, 1H, J=6.0 & 14.0Hz, H-5), 8.01 (dd, 1H, J=2.0 & 14.0Hz, H-4), 8.50 (dd, 1H, J=2.0 & 6.0Hz, H-6). (Found: C,51.8; H,3.5; N,10.0; S,23.0. C₁₂H₁₀N₂O₂S₂ requires C,51.8; H,3.6; N,10.1; S,23.0%).

2-Carboethoxymethylthio-3-cyanothieno[3,2-c]pyridine (268).

Sodium hydride (346mg, 14.41mmol) was added portionwise to a stirred solution of 4-chloro-3-cyanomethylpyridine (**239**) (1.0g, 6.55mol), dimethyl sulfoxide (20mL) and carbon disulfide (550mg, 7.21mmol). The reaction mixture was stirred for 1 hour at room temperature, warmed to 80°C for 1 hour and allowed to cool to room temperature, followed by the addition of ethyl chloroacetate (1.76g, 14.41mmol). The reaction mixture was stirred for a further 1 hour at room temperature, poured onto ice (150g), and an oil was obtained. The aqueous mixture was extracted with ethyl acetate, dried over magnesium sulfate, decolourised with charcoal, filtered and the solvent was removed *in vacuo* to give an oil. The oil was chromatographed on silica gel (10g) and elution with light petroleum ether / diethyl ether (10-50%) afforded 2-carboethoxymethylthio-3-cyanothieno[3,2-c]pyridine (268) (780mg, 43%) as a white crystalline solid. mp 85-86°C. $\nu_{\max}(\text{KBr})$ 2994, 2217, 1725 cm^{-1} . $\delta_{\text{H}}(\text{CDCl}_3)$ 1.24 (t, 3H, $J=12.0\text{Hz}$, CH_3), 3.84 (s, 2H, SCH_2), 4.18 (q, 2H, $J=12.0\text{Hz}$, CH_2), 7.72 (d, 1H, $J=5.9\text{Hz}$, H-5), 8.54 (d, 1H, $J=5.9\text{Hz}$, H-6), 9.08 (s, 1H, H-2). (Found: C,51.7; H,3.6; N,10.0; S,23.2. $\text{C}_{12}\text{H}_{10}\text{N}_2\text{O}_2\text{S}_2$ requires C,51.8; H,3.6; N,10.1; S,23.0%).

2-Anilino-3-cyanothieno[3,2-c]pyridine (269).

Phenyl isothiocyanate (680mg, 5.05mmol) was added to a stirred solution of 4-chloro-3-cyanomethylpyridine (**239**) (700mg, 4.59mmol) in dimethyl sulfoxide (15mL), under nitrogen. Sodium hydride (130mg, 5.50mmol) was added portionwise and the reaction mixture was stirred for 1 hour at room temperature, warmed to 70°C for 1 hour, allowed to cool to room temperature and iodomethane (780mg, 5.50mmol) added. The reaction mixture was stirred for a further 1 hour at room temperature, poured onto ice (150g), and the crude product obtained by filtration. This product was dissolved in ethyl acetate dried over magnesium sulfate, decolourised with charcoal, filtered and solvent removed *in vacuo*.

Recrystallisation from ethyl acetate afforded 2-anilino-3-cyanothieno[3,2-c]-pyridine (269) (419mg, 36%) as a white crystalline solid. mp 247.5-248°C.

ν_{max} (KBr) 3175, 2960, 2210 cm^{-1} . δ_{H} (d_6 -DMSO) 7.18-7.52 (m, 5H, C_6H_5), 7.83(d, 1H, $J=6.3\text{Hz}$, H-5), 8.34 (d, 1H, $J=6.3\text{Hz}$, H-6), 8.34 (d, 1H, $J=6.3\text{Hz}$, H-2), 8.67 (s, 1H, NH). (Found: C,66.9; H,3.5; N,16.7; S,13.0. $\text{C}_{14}\text{H}_9\text{N}_3\text{S}$ requires C,66.9; H,3.6; N,16.7; S,12.8%). $m/e(\%)$ 252(17), 251(100), 250(11), 77(11), 57(18), 44(40).

Reaction of 2-Chloro-3-cyanomethylpyridine (238) with Phenyl Isothiocyanate at 70°C.

Sodium hydride (190mg, 7.86mmol) was added portionwise to a stirred solution of 2-chloro-3-cyanomethylpyridine (238) (1.0g, 6.55mmol) and phenyl isothiocyanate (970mg, 7.21mmol) in dimethyl sulfoxide (20mL), under nitrogen. The reaction mixture was stirred for 1 hour at room temperature, warmed to 70°C for 1 hour, allowed to cool to room temperature and iodomethane (1.12g, 7.86mmol) added. The reaction mixture was stirred for a further 1 hour at room temperature, poured onto ice (150g), and the crude product was obtained by filtration. The solid was dissolved in ethyl acetate, dried over magnesium sulfate, decolourised with charcoal, filtered and solvent removed *in vacuo*. Recrystallisation from ethyl acetate afforded 3-(2'-anilino-1'-cyano-2'-methylthio)ethenyl-2-chloropyridine (271) (700mg, 37%) as a yellow crystalline material. mp 174.5-175°C. ν_{max} (KBr) 3172, 3053, 2938, 2192 cm^{-1} . δ_{H} (d_6 -DMSO) 3.31 (s, 3H, CH_3), 6.86-7.26 (m, 6H, C_6H_5 & H-5), 7.90 (unresolved, 1H, H-4), 8.18 (unresolved, 1H, H-6), 9.29 (s, 1H, NH). (Found: C,59.7; H,4.0; N,13.9; Cl,11.7; S,10.7. $\text{C}_{15}\text{H}_{12}\text{N}_3\text{ClS}$ requires C,59.7; H,4.0; N,13.9; Cl,11.7; S,10.7%). $m/e(\%)$ 303(6), 301(16), 97(30), 85(31), 83(33), 71(43), 69(29), 57(100).

Reaction of 2-Chloro-3-cyanomethylpyridine (238) with Phenyl Isothiocyanate at 100°C.

Phenyl isothiocyanate (970mg, 7.21mmol) was added to a stirred solution of 2-chloro-3-cyanomethylpyridine (238) (1.0g, 6.55mmol) in dimethyl sulfoxide (20mL), under nitrogen. Sodium hydride (190mg, 7.86mmol) was added portionwise and the reaction mixture stirred for 1 hour at room temperature, warmed to 100°C for 2 hours and cooled to room temperature before the addition of iodomethane (1.12g, 7.86mmol). The reaction mixture was stirred for a further 1 hour at room temperature, poured onto ice (150g), and the crude product was obtained by filtration. This product was dissolved in ethyl acetate dried over magnesium sulfate, decolourised with charcoal, filtered and solvent removed *in vacuo*. Recrystallisation from ethyl acetate afforded 2-anilino-3-cyanothieno-[2,3-b]pyridine (272) (330mg, 20%) as a white crystalline solid. mp 153-154.5°C. ν_{\max} (KBr) 3190, 3053, 2993, 2198cm⁻¹. δ_{H} (CDCl₃) 7.27 (dd, 1H, J=5.4 & 8.8Hz, H-5), 7.22-7.48 (m, 5H, C₆H₅), 7.70 (s, 1H, NH), 7.80 (dd, 1H, J=1.5 & 8.8Hz, H-4), 8.34 (dd, 1H, J=1.5 & 5.4Hz, H-6). (Found: C,66.9; H,3.6; N,16.5; S,12.8. C₁₄H₉N₃S requires C,66.9; H,3.6; N,16.7; S,12.8%). m/e(%) 252(18), 251(100), 250(15), 147(10), 77(18).

Reaction of 3-Bromo-4-cyanomethylpyridine (240) with Phenyl Isothiocyanate at 100°C.

Phenyl isothiocyanate (754mg, 5.58mmol) was added to a stirred solution of 3-bromo-4-cyanomethylpyridine (240) (1.0g, 5.07mmol) in dimethyl sulfoxide (20mL), under nitrogen. Sodium hydride (146mg, 6.09mmol) was added portionwise and the reaction mixture stirred for 1 hour at room temperature, warmed to 100°C for 1 hour and allowed to cool to room temperature before the addition of iodomethane (864mg, 6.09mmol). The reaction mixture was stirred for a further 1 hour at room temperature, poured onto ice (150g), and the crude product

obtained by filtration. This product was dissolved in ethyl acetate, dried over magnesium sulfate, decolourised with charcoal, filtered and solvent removed *in vacuo*. Recrystallisation from ethyl acetate afforded 4-(2'-anilino-1'-cyano-2'-methylthio)ethenyl-3-bromopyridine (273) (540mg, 32%) as a yellow crystalline solid. mp 188.5-189°C. ν_{\max} (KBr) 3175, 3054, 2999, 2192cm⁻¹. δ_{H} (d₆-DMSO) 3.33 (s, 3H, CH₃), 6.86-7.24 (m, 6H, C₆H₅ & H-5), 8.34 (unresolved, 1H, H-6), 8.52 (unresolved, 1H, H-2), 9.47 (s, 1H, NH). (Found: C,52.0; H,3.6; N,12.0; Br,23.0; S,9.2. C₁₅H₁₂N₃BrS requires C,52.0; H,3.5; N,12.1; Br,23.1; S,9.25%). m/e(%) 347(45), 345(M⁺,44), 266(74), 251(70), 150(78), 77(100).

Reaction of 3-Bromo-2-cyanomethylpyridine (241) with Phenyl Isothiocyanate at 100°C.

Phenyl isothiocyanate (754mg, 5.58mmol) was added to a stirred solution of 3-bromo-2-cyanomethylpyridine (**241**) (1.0g, 5.07mmol) in dimethyl sulfoxide (20mL), under nitrogen. Sodium hydride (146mg, 6.09mmol) was added portionwise and the reaction mixture stirred at room temperature for 1 hour, warmed to 100°C for 1 hour, allowed to cool to room temperature and iodomethane (864mg, 6.09mmol) was added. The reaction mixture was stirred for a further 1 hour at room temperature, poured onto ice (150g), and the crude product was obtained by filtration. This product was dissolved in ethyl acetate, dried over magnesium sulfate, decolourised with charcoal, filtered and solvent removed *in vacuo*. Recrystallisation from ethyl acetate afforded 2-(2'-anilino-1'-cyano-2'-methylthio)ethenyl-3-bromopyridine (274) (1.22g, 69%) as a yellow crystalline solid. mp 135.5-136°C. ν_{\max} (KBr) 3179, 3032, 2929, 2189cm⁻¹. δ_{H} (d₆-DMSO) 2.25 (s, 3H, CH₃), 7.04 (dd, 1H, J=5.4 & 8.8Hz, H-5), 7.02-7.38 (m, 5H, C₆H₅), 7.94 (dd, 1H, J=1.4 & 5.4Hz, H-4), 8.45 (dd, 1H, J=1.5 & 8.8Hz, H-6), 11.08 (s, 1H, NH). (Found: C,51.9; H,3.4; N,12.1; Br,23.1; S,8.9. C₁₅H₁₂N₃BrS requires C,52.0; H,3.6; N,12.1; Br,23.1; S,9.3%). m/e(%) 347(24), 345(21), 300(97),

299(30), 298(100), 297(12), 266(29).

Reaction of 3-Bromo-4-cyanomethylpyridine (240) with Phenyl Isothiocyanate at 110°C.

Phenyl isothiocyanate (658mg, 4.87mmol) was added to a stirred solution of 3-bromo-4-cyanomethylpyridine (240) (800mg, 4.06mmol) in dimethyl sulfoxide (15mL), under nitrogen. Sodium hydride (117mg, 4.87mmol) was added portionwise and the reaction mixture stirred for 1 hour at room temperature, warmed to 110°C for 2 hours and allowed to cool to room temperature before the addition of iodomethane (692mg, 4.87mmol). The reaction mixture was stirred for a further 1 hour at room temperature, poured onto ice (100g), and the crude product was obtained by filtration. The solid was dissolved in ethyl acetate, dried over magnesium sulfate, decolourised with charcoal, filtered and solvent removed *in vacuo*. Tlc (petrol/ethyl acetate 1:1) indicated that the product was impure so it was chromatographed on silica gel (20g). Elution with light petroleum ether / diethyl ether (10-50%) afforded 2-anilino-3-cyanothieno[2,3-c]pyridine (275) (193mg, 19%) as a white crystalline solid. mp 178-179°C. $\nu_{\max}(\text{KBr})$ 3180, 2983, 2217cm⁻¹. δ_{H} (d₆-DMSO) 7.28-7.51 (m, 6H, H-5 & C₆H₅), 8.57 (d, 1H, J=4.8Hz, H-4), 9.02 (s, 1H, H-2), 11.06 (s, 1H, NH). (Found: C,66.9; H,3.6; N,16.7; S12.8. C₁₄H₉N₃S requires C,66.9; H,3.6; N,16.7; S,12.8%).

Reaction of 3-Bromo-2-cyanomethylpyridine (241) with Phenyl Isothiocyanate at 110°C.

Sodium hydride (70mg, 2.74mmol) was added portionwise to a stirred solution of 3-bromo-2-cyanomethylpyridine (241) (450mg, 2.28mmol) and phenyl isothiocyanate (370mg, 2.74mmol) in dimethyl sulfoxide (10mL), under nitrogen. The reaction mixture was stirred for 1 hour at room temperature, warmed to 110°C for 2 hours and allowed to cool to room temperature before the addition of

iodomethane (400mg, 2.74mmol). The reaction mixture was stirred for a further 1 hour at room temperature, poured onto ice (150g), and the crude product obtained by filtration. Tlc (petrol/ethyl acetate 1:1) indicated that the crude product was impure so the solid was dissolved in toluene and chromatographed on silica gel (10g). Gradient elution with light petroleum ether / diethyl ether (10-50%) afforded 2-anilino-3-cyanothien[3,2-b]pyridine (276) (160mg, 28%) as a white crystalline solid. mp 195-196°C. ν_{\max} (KBr) 3195, 3052, 2983, 2220cm⁻¹. δ_{H} (d₆-DMSO) 7.08 (dd, 1H, J=6.0 & 14.0Hz, H-5), 7.00-7.44 (m, 5H, C₆H₅), 8.03 (dd, 1H, J=2.0 & 14.0Hz, H-4), 8.40 (dd, 1H, J=2.0 & 6.0Hz, H-6), 10.60 (s, 1H, NH). (Found: C,66.8; H,3.6; N,16.8; S12.8. C₁₄H₉N₃S requires C,66.9; H,3.6; N,16.7; S,12.8%).

3-Carbomethoxy-2-methylthiothien[2,3-b]pyridine (279).

Carbon disulfide (453mg, 5.95mmol) was added to a stirred solution of methyl 2-chloro-3-pyridylacetate (**246**) (920mg, 4.96mmol) in dimethyl sulfoxide (20mL), under nitrogen. Sodium hydride (261mg, 10.89mmol) was added portionwise and the reaction mixture was stirred for 1 hour at room temperature, warmed to 90°C for 1.5 hours and allowed to cool to room temperature before the addition of iodomethane (1.5g, 10.89mmol). The reaction mixture was stirred for a further 1 hour at room temperature, poured onto ice (150g), and the crude product obtained by filtration. The solid was dissolved in ethyl acetate, dried over magnesium sulfate, decolourised with charcoal, filtered and the solvent was removed *in vacuo*. Recrystallisation from ethyl acetate afforded 3-carbomethoxy-2-methylthiothieno-[2,3-b]pyridine (279) (490mg, 41%) as a white crystalline solid. mp 118-118.5°C. ν_{\max} (KBr) 3051, 2951, 1688cm⁻¹. δ_{H} (CDCl₃) 2.66 (s, 3H, SCH₃), 3.98 (s, 3H, CO₂CH₃), 7.23 (dd, 1H, J=8.0 & 14.0Hz, H-5), 8.34 (dd, 1H, J=4.0 & 8.0Hz, H-4), 8.51 (dd, 1H, J=4.0 & 14.0Hz, H-6). (Found: C,50.1; H,3.9; N,5.8; S,26.9. C₁₀H₉NO₂S₂ requires C,50.2; H,3.8; N,5.85; S,26.8%).

3-Carboethoxy-2-methylthiothieno[2,3-b]pyridine (280).

Carbon disulfide (412mg, 5.41mmol) was added to a stirred solution of ethyl 2-chloro-3-pyridylacetate (**242**) (900mg, 4.51mmol) in dimethyl sulfoxide (20mL), under nitrogen. Sodium hydride (238mg, 9.92mmol) was added portionwise and the reaction mixture stirred at room temperature for 1 hour, warmed to 90°C for 1.5 hours and then allowed to cool to room temperature before the addition of iodomethane (1.4g, 9.92mmol). The reaction mixture was stirred for a further 1 hour at room temperature, poured onto ice (150g), and an oil was obtained. This aqueous mixture was extracted with ethyl acetate, dried over magnesium sulphate and solvent removed *in vacuo* to afford an oil. The oil was dissolved in toluene and chromatographed on silica gel (10g). Elution with light petroleum ether / diethyl ether 10-50% afforded 3-Carboethoxy-2-methylthiothieno[2,3-b]pyridine (280) (182mg, 36%) as a white crystalline solid. mp 109-110°C. $\nu_{\max}(\text{KBr})$ 3175, 2946, 1682 cm^{-1} . δ_{H} (CDCl_3) 1.48 (t, 3H, $J=12.0\text{Hz}$, CH_3), 4.50 (q, 2H, $J=12.0\text{Hz}$, CH_2), 7.56 (dd, 1H, $J=8.0$ & 12.0Hz , H-5), 8.24 (dd, 1H, $J=8.0$ & 2.0Hz , H-4), 8.63 (dd, 1H, $J=2.0$ & 12.0Hz , H-6). (Found: C,52.1; H,4.3; N,5.5; S,25.4. $\text{C}_{11}\text{H}_{11}\text{NO}_2\text{S}_2$ requires C,52.1; H,4.4; N,5.5; S,25.3%).

Reaction of Ethyl 4-Chloro-3-pyridylacetate (243) with Carbon Disulfide at 100°C.

Carbon disulfide (587mg, 7.71mmol) was added to a stirred solution of ethyl 4-chloro-3-pyridylacetate (**243**) (1.4g, 7.01mmol) in dimethyl sulfoxide (20mL), under nitrogen. Sodium hydride (370mg, 15.42mmol) was added portionwise and the reaction mixture was stirred for 1 hour at room temperature, followed by warming to 100°C for 1.5 hours, allowed to cool to room temperature and iodomethane (2.2g, 15.42mmol) added. The reaction mixture was stirred for a further 1 hour at room temperature, poured onto ice (150g), and the crude product

obtained by filtration. The solid was dissolved in methanol, dried over magnesium sulfate, decolourised with charcoal and solvent removed *in vacuo*.

Recrystallisation from methanol gave a highly polar product (640mg). $\nu_{\max}(\text{KBr})$ 3449, 3028, 2978, 1682 cm^{-1} . (Found: C,37.1; H,3.8; N,3.6%). No NMR spectrum was obtained due to solubility problems and from the data obtained, no structure assigned for the product

3-Carboethoxy-2-methylthiothieno[3,2-c]pyridine (281)

Sodium hydride (185mg, 7.72mmol) was added portionwise to a stirred solution of ethyl 4-chloro-3-pyridylacetate (**243**) (700mg, 3.51mmol) and carbon disulfide (321mg, 4.21mmol) in dimethyl sulfoxide (15mL), under nitrogen. The reaction mixture was stirred for 1 hour at room temperature, warmed to 70°C for 1.5 hours and allowed to cool to room temperature before the addition of iodomethane (1.1g, 7.72mmol). The reaction mixture was stirred for a further 1 hour at room temperature, poured onto ice (100g), and the crude product obtained by filtration. The solid was dissolved in ethyl acetate, dried over magnesium sulfate, decolourised with charcoal and the solvent was removed *in vacuo* to afford 3-carboethoxy-2-methylthiothieno-[3,2-c]pyridine(281) (150mg, 17%) after recrystallisation from ethyl acetate. mp 119.5-120°C. $\nu_{\max}(\text{KBr})$ 2984, 2908, 1681 cm^{-1} . δ_{H} (CDCl_3) 1.40 (t, 3H, $J=12.0\text{Hz}$, CH_3), 2.70 (s, 3H, SCH_3), 4.35 (q, 2H, $J=12.0\text{Hz}$, CH_2), 7.90 (d, 1H, $J=8.0\text{Hz}$, H-5), 8.34 (d, 1H, $J=8.0\text{Hz}$, H-6), 9.34 (s, 1H, H-2). (Found: C,52.1; H,4.4; N,5.5; S,25.3. $\text{C}_{11}\text{H}_{11}\text{NO}_2\text{S}_2$ requires C,52.1; H,4.4; N,5.5; S,25.3%).

3-Carboethoxy-2-methylthiothieno[2,3-c]pyridine (282).

Carbon disulfide (748mg, 9.83mmol) was added to a stirred solution of ethyl 3-bromo-4-pyridylacetate (**244**) (2.0g, 8.19mmol) in dimethyl sulfoxide (40mL), under nitrogen. Sodium hydride (433mg, 18.02mmol) was added portionwise and

the reaction mixture was stirred for 1 hour at room temperature, warmed to 90°C for 1.5 hours, allowed to cool to room temperature and iodomethane (2.6g, 18.02mmol) added. The reaction mixture was stirred for a further 1 hour at room temperature, poured onto ice (300g), and the crude product was obtained by filtration. The solid was dissolved in ethyl acetate and some insoluble material was filtered. The organic extracts were dried over magnesium sulfate, decolourised with charcoal, filtered and solvent removed *in vacuo*.

Recrystallisation from ethyl acetate afforded 3-carboethoxy-2-methylthiothieno-[2,3-c]pyridine (282) (882mg, 42%). mp 138.5-139°C. ν_{\max} (KBr) 2980, 1681cm⁻¹. δ_{H} (CDCl₃) 1.38 (t, 3H, J=12.0Hz, CH₃), 2.70 (s, 3H, SCH₃), 4.32 (q, 2H, J=12.0Hz, CH₂), 7.95 (d, 1H, J=8.0Hz, H-5), 8.36 (d, 1H, J=8.0Hz, H-6), 9.00 (s, 1H, H-2). (Found: C,51.9; H,4.4; N,5.6; S,25.4. C₁₁H₁₁NO₂S₂ requires C,52.1; H,4.4; N,5.5; S,25.3%).

3-Carboethoxy-2-methylthiothieno[3,2-b]pyridine (283).

Carbon disulfide (748mg, 9.83mmol) was added to a stirred solution of ethyl 3-bromo-2-pyridylacetate (**245**) (2.0g, 8.19mmol) in dimethyl sulfoxide (40mL), under nitrogen. Sodium hydride (433mg, 18.02mmol) was added portionwise and the reaction mixture was stirred for 1 hour at room temperature, followed by warming to 90°C for 1.5 hours and then allowed to cool to room temperature before the addition of iodomethane (2.6g, 18.02mmol). The reaction mixture was stirred for a further 1 hour at room temperature, poured onto ice (300g), and the crude product obtained by filtration. The solid was dissolved in ethyl acetate, dried over magnesium sulfate, decolourised with charcoal, filtered and the solvent was removed *in vacuo* to afford 3-carboethoxy-2-methylthiothieno[3,2-b]pyridine (283) (1.02g, 50%) as a white crystalline solid after recrystallisation from ethyl acetate. mp 85.5-86°C. ν_{\max} (KBr) 2977, 1680cm⁻¹. δ_{H} (CDCl₃) 1.44 (t, 3H, J=12.0Hz, CH₃), 1.62 (s, 3H, SCH₃), 4.44 (q, 2H, J=12.0Hz, CH₂), 7.08 (dd, 1H,

J=8.0 & 14.0Hz, H-5), 7.93 (dd, 1H, J=1.5 & 14.0Hz, H-4), 8.68 (dd, 1H, J=1.5 & 8.0Hz, H-6). (Found: C,51.8; H,4.6; N,5.4; S,25.5. $C_{11}H_{11}NO_2S_2$ requires C,52.1; H,4.4; N,5.5; S,25.3%).

2-Carboethoxymethylthio-3-carboethoxythieno[3,2-b]pyridine (284).

Sodium hydride (216mg, 9.01mmol) was added portionwise to a stirred solution of ethyl 3-bromo-2-pyridylacetate (**245**) (1.0g, 4.10mmol) and carbon disulfide (374mg, 4.92mmol) in dimethyl sulfoxide (10mL), under nitrogen. The reaction mixture was stirred for 1 hour at room temperature, warmed to 100°C for 1.5 hours, allowed to cool to room temperature and ethyl chloroacetate (1.10g, 9.01mmol) was added. The reaction mixture was stirred for a further 1 hour at room temperature, poured onto ice (100g), and the crude product obtained by filtration. The solid was dissolved in ethyl acetate, dried over magnesium sulfate, decolourised with charcoal, filtered and solvent removed *in vacuo*.

Recrystallisation from ethyl acetate afforded 2-carboethoxymethylthio-3-carboethoxythieno[3,2-b]pyridine (284) (900mg, 67%) as a white crystalline solid. mp 128-128.5°C. $\nu_{\max}(\text{KBr})$ 2985, 1725, 1678 cm^{-1} . δ_{H} (d_6 -DMSO) 1.22 (t, 3H, J=12.0Hz, CH_3), 1.38 (t, 3H, J=12.0Hz, CH_3), 4.00-4.58 (m, 6H, $\text{SCH}_2\text{CO}_2\text{CH}_2$, CO_2CH_2), 7.33 (dd, 1H, J=8.0 & 14.0Hz, H-5), 8.41 (dd, 1H, J=4.0 & 14.0Hz, H-4), 8.56 (dd, 1H, J=4.0 & 8.0Hz, H-6). (Found: C,52.0; H,4.8; N,4.3; S,19.8. $C_{14}H_{15}NO_4S_2$ requires C,51.7; H,4.6; N,4.3; S,19.7%).

2-Carboethoxymethylthio-3-carbomethoxythieno[2,3-b]pyridine (285).

Carbon disulfide (345mg, 4.53mmol) was added to a stirred solution of methyl 2-chloro-3-pyridylacetate (**246**) (700mg, 3.77mmol) in dimethyl sulfoxide (15mL), under nitrogen. Sodium hydride (199mg, 8.29mmol) was added portionwise and the reaction mixture was stirred at room temperature for 1 hour, warmed to 100°C for 1.5 hours and then allowed to cool to room temperature before the addition of

ethyl chloroacetate (1.02g, 8.29mmol). The reaction mixture was stirred for a further 1 hour at room temperature, poured onto ice (100g), and the crude product obtained by filtration. The solid was dissolved in ethyl acetate, dried over magnesium sulfate, decolourised with charcoal, filtered and solvent removed *in vacuo*. Recrystallisation from ethyl acetate afforded 2-carboethoxymethylthio-3-carbomethoxythieno[2,3-b]pyridine (285) (650mg, 56%). mp 104.5-105°C.

ν_{\max} (KBr) 2986, 1725, 1678 cm^{-1} . δ_{H} (d_6 -DMSO) 1.26 (t, 3H, $J=12.0\text{Hz}$, CH_2), 3.94 (s, 3H, CO_2CH_3), 4.20 (q, 2H, $J=12.0\text{Hz}$, CH_2), 4.22 (s, 2H, SCH_2), 7.26 (d, 1H, $J=8.0\text{Hz}$, H-5), 8.22 (s, 1H, H-4), 8.34 (s, 1H, H-6); (Found C,50.0; H,4.3; N,4.4; S,20.3. $\text{C}_{13}\text{H}_{13}\text{NO}_4\text{S}_2$ requires C,50.1; H,4.2; N,4.5; S,20.6%).

2-Anilino-3-carbomethoxythieno[2,3-b]pyridine (286).

Phenyl isothiocyanate (480mg, 3.56mmol) was added to a stirred solution of methyl 2-chloro-3-pyridylacetate (**246**) (600mg, 3.24mmol) in dimethyl sulfoxide (10mL), under nitrogen. Sodium hydride (90mg, 3.89mmol) was added portionwise and the reaction mixture was stirred for 1 hour at room temperature, warmed to 100°C for 2 hour, allowed to cool to room temperature and iodomethane (550mg, 3.89mmol) added. The reaction mixture was stirred for a further 1 hour at room temperature, poured onto ice (100g), and the crude product obtained by filtration. The solid was dissolved in ethyl acetate, dried over magnesium sulfate, decolourised with charcoal, filtered and solvent removed *in vacuo* to afford 2-anilino-3-carbomethoxythieno[2,3-b]pyridine(286) (200mg, 22%) as a white crystalline solid after recrystallisation from ethyl acetate. mp 103-104°C. ν_{\max} (KBr) 3192, 2942, 1666 cm^{-1} . δ_{H} (CDCl_3) 3.94 (s, 3H, CH_3), 6.90-7.38 (m, 6H, C_6H_5 & H-5), 8.10 (d, 1H, $J=4.0\text{Hz}$, H-4), 8.22 (d, 1H, $J=1.5\text{Hz}$, H-6), 11.70 (s, 1H, NH). (Found: C,63.4; H,4.2; N,9.7; S,11.3. $\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_2\text{S}$ requires C,63.4; H,4.2; N,9.8; S,11.3%).

2-Anilino-3-carboethoxythieno[2,3-b]pyridine (287).

Sodium hydride (132mg, 5.50mmol) was added portionwise to a stirred solution of ethyl 2-chloro-3-pyridylacetate (**242**) (500mg, 2.50mmol) and phenyl isothiocyanate (405mg, 3.00mmol) in dimethyl sulfoxide (10mL), under nitrogen. The reaction mixture was stirred for 1 hour at room temperature, followed by warming to 100°C for 2 hours, allowed to cool to room temperature and iodomethane (426mg, 3.00mmol) added. The reaction mixture was stirred for a further 1 hour at room temperature, poured onto ice (100g), and an oil was obtained. This aqueous mixture was extracted with ethyl acetate (3 x 100mL) and the organic extracts were dried over magnesium sulfate, decolourised with charcoal and solvent removed *in vacuo* to afford an oil. The oil was chromatographed on silica gel (10g) and elution with light petroleum ether / ethyl acetate (10-50%) afforded 2-anilino-3-carboethoxythieno[2,3-b]pyridine(287) (268mg, 36%) as a white crystalline solid. mp 115-116.5°C. $\nu_{\max}(\text{KBr})$ 3193, 1668 cm^{-1} . δ_{H} (CDCl_3) 1.42 (t, 3H, $J=12.0\text{Hz}$, CH_3), 4.48 (q, 2H, $J=12.0\text{Hz}$, CH_2), 7.06-7.42 (m, 6H, C_6H_5 & H-5), 8.04 (dd, 1H, $J=2.0$ & 8.0Hz, H-4), 8.73 (dd, 1H, $J=2.0$ & 4.6Hz, H-6), 9.63 (s, 1H, NH). (Found: C,64.4; H,4.2; N,9.5; S,10.9. $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$ requires C,64.4; H,4.7; N,9.4; S,10.7%).

2-Anilino-3-carboethoxythieno[3,2-c]pyridine (288).

Phenyl isothiocyanate (744mg, 5.51mmol) was added to a stirred solution of ethyl 4-chloro-3-pyridylacetate (**243**) (1.0g, 5.00mmol) in dimethyl sulfoxide (20mL), under nitrogen. Sodium hydride (144mg, 6.00mmol) was added portionwise and the reaction mixture stirred at room temperature for 1 hour, followed by warming to 80°C for 1.5 hours, followed by the addition of iodomethane (852mg, 6.00mmol) at room temperature. The reaction mixture was stirred for a further 1 hour at room temperature, poured onto ice (150g), and an oil obtained. The aqueous mixture was extracted with ethyl acetate, the organic portion dried over

magnesium sulfate, decolourised with charcoal, filtered and solvent removed *in vacuo*. Recrystallisation from ethyl acetate afforded 2-anilino-3-carboethoxy-thieno[3,2-c]-pyridine (288) (1.01g, 67%) as a white crystalline solid. mp 83-83.5°C. $\nu_{\max}(\text{KBr})$ 3195, 3094, 2977, 1646 cm^{-1} . $\delta_{\text{H}}(\text{CDCl}_3)$ 1.48 (t, 3H, $J=12.0\text{Hz}$, CH_3), 4.46 (q, 2H, $J=12.0\text{Hz}$, CH_2), 7.23-7.47 (m, 6H, C_6H_5 & H-5), 8.00 (d, 1H, $J=10.0\text{Hz}$, H-6), 9.24 (s, 1H, H-2), 9.52 (s, 1H, NH). (Found: C,64.3; H,4.7; N,9.3; S,10.9. $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$ requires C64.4, H4.7, N9.4, S10.7%).

2-Anilino-3-carboethoxythieno[2,3-c]pyridine (289).

Phenyl isothiocyanate (610mg, 4.51mmol) was added to a stirred solution of ethyl 3-bromo-4-pyridylacetate (**244**) (1.0g, 4.10mmol) in dimethyl sulfoxide (20mL), under nitrogen. Sodium hydride (118mg, 4.92mmol) was added portionwise and the reaction mixture stirred for 1 hour at room temperature, warmed to 110°C for 2 hours, allowed to cool to room temperature and iodomethane (698mg, 4.92mmol) added. The reaction mixture was stirred for a further 1 hour at room temperature, poured onto ice (150g), and the crude product obtained by filtration. The solid was dissolved in ethyl acetate, some insoluble material was filtered, the filtrate was dried over magnesium sulfate, decolourised with charcoal, filtered and the solvent was removed *in vacuo*. Recrystallisation from ethyl acetate to afford 2-anilino-3-carboethoxythieno[2,3-c]pyridine (289) (90mg, 8%). mp 122-122.5°C. $\nu_{\max}(\text{KBr})$ 3175, 2985, 1652 cm^{-1} . $\delta_{\text{H}}(\text{CDCl}_3)$ 1.46 (t, 3H, $J=12.0\text{Hz}$, CH_3), 4.40 (q, 2H, $J=12.0\text{Hz}$, CH_2), 7.06-7.42 (m, 6H, C_6H_5 & H-5), 8.29 (d, 1H, $J=8.0\text{Hz}$, H-6), 8.60 (s, 1H, H-2), 11.84 (s, 1H, NH). (Found: C,64.4; H,4.7; N,9.4; S,10.3. $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$ requires C64.4, H4.7, N9.4, S10.7%).

Also isolated from this reaction was a very polar product which was insoluble in ethyl acetate. This polar compound was recrystallised from methanol to give (300mg) of the by-product. mp 250°C with decomposition. $\nu_{\max}(\text{KBr})$ 3028, 2978,

1685cm⁻¹. (Found: C,37.1; H,3.8; N3.6). No NMR was recorded due to solubility problems.

2-Anilino-3-carboethoxythieno[3,2-b]pyridine (290).

Phenyl isothiocyanate (665mg, 4.92mmol) was added to a stirred solution of ethyl 3-bromo-2-pyridylacetate (**245**) (1.0g, 4.10mmol) in dimethyl sulfoxide (20mL), under nitrogen. Sodium hydride (216mg, 9.02mmol) was added portionwise and the reaction mixture stirred for 1 hour at room temperature, warmed to 110°C for 2 hours and then allowed to cool to room temperature before the addition of iodomethane (1.28g, 9.02mmol). The reaction mixture was stirred for a further 1 hour at room temperature, poured onto ice (150g), and a semi-solid was obtained. The aqueous mixture was extracted with ethyl acetate and the organic phase dried over magnesium sulfate, decolourised with charcoal, filtered and solvent removed *in vacuo* to afford an oil. The oil was chromatographed on silica gel (20g) and elution with light petroleum ether / diethyl ether (10-50%) afforded 2-anilino-3-carboethoxythieno[3,2-b]-pyridine (290) (170mg, 14.2%). mp 120.5-121 °C.

ν_{\max} (KBr) 2975, 1635cm⁻¹. δ_{H} (d₆-DMSO) 1.36 (t, 3H, J=12.0Hz, CH₃), 4.38 (q, 2H, J=12.0Hz, CH₂), 7.08 (dd, 1H, J=8.0 & 14.0Hz, H-5), 7.26-7.52 (m, 5H, C₆H₅), 8.07 (dd, 1H, J=2.0 & 14.0Hz, H-4), 8.19 (dd, 1H, J=2.0 & 8.0Hz, H-6), 10.52 (s, 1H, NH). (Found: C,64.5; H,4.8; N,9.4; S10.5. C₁₆H₁₄N₂O₂S requires C64.4, H4.7, N9.4, S10.7%).

Also isolated from this reaction was a very polar product which was filtered from the ethyl acetate phase before chromatography. The solid was recrystallised from methanol to give the pure product (60mg). mp 250°C with decomposition.

ν_{\max} (KBr) 2915, 1674cm⁻¹. (Found: C,37.1; H,3.8; N3.6). No NMR was recorded due to solubility problems.

3-Amino-2-cyanothieno[2,3-b]pyridine (293).

3-Cyano-2(1H)-pyridinethione²⁴⁸ (**291**) (1.0g, 7.48mmol) was added to an ice cold stirred mixture of DMF (20mL) and sodium methoxide (890mg, 16.46mmol). The reaction mixture was stirred for 5 minutes at ice temperature and chloroacetonitrile (621mg, 8.23mmol) added dropwise. The reaction mixture was stirred for a further 10 minutes at ice temperature, for 2 hours at room temperature, poured onto ice (150g) and the crude product obtained by filtration. The solid was dissolved in ethyl acetate, dried over magnesium sulfate, decolourised with charcoal and solvent removed *in vacuo*. Recrystallisation from ethyl acetate afforded 3-amino-2-cyanothieno[2,3-b]pyridine²³¹ (**293**) (965mg, 72%) as a yellow crystalline solid. mp 218-220°C (literature mp²³¹ 218-220°C).

3-Amino-2-phenylthieno[2,3-b]pyridine (294).

Addition of the thione (**291**) (500mg, 3.67mmol) to an ice cold stirred mixture of DMF (10mL) and sodium ethoxide (550mg, 8.03mmol) was followed by stirring for 5 minutes at ice temperature before the addition of benzyl bromide (650mg, 3.67mmol). The reaction mixture was stirred for a further 10 minutes at ice temperature, for 2 hours at room temperature, poured onto ice (100g) and the crude product obtained by filtration. The solid was dissolved in ethyl acetate, dried over magnesium sulfate, decolourised with charcoal and solvent removed *in vacuo*. Recrystallisation from ethyl acetate afforded 3-amino-2-phenylthieno-[2,3-b]-pyridine (**294**) (210mg, 24%) as a yellow crystalline solid. mp 195-196.5°C. $\nu_{\max}(\text{KBr})$ 3340, 3221, 3085, 2946cm⁻¹. δ_{H} (CDCl₃) 7.07 (dd, 1H, J=8.0 & 14.0Hz, H-5), 7.10-7.38 (m, 5H, C₆H₅), 7.80 (dd, 1H, J=2.0 & 14.0Hz, H-4), 8.56 (dd, 1H, J=2.0 & 8.0Hz, H-6). (Found: C,70.9; H,3.4; N,11.8; S,13.7. C₁₄H₈N₂S requires C,71.2; H,3.4; N,11.8; S,13.6%).

Reaction of 3-Cyano-2(1H)-pyridinethione (291) and Allyl Bromide.

Thione (292) (2.0g, 0.0147mol) was added to an ice cold stirred mixture of DMF (20mL) and sodium methoxide (1.75g, 0.0323mol). The reaction mixture was stirred for 5 minutes at ice temperature and allyl bromide (2.0g, 0.0162mol) was added dropwise. The reaction mixture was stirred for a further 10 minutes at ice temperature, for 1 hour at room temperature, poured onto ice (150g) and the crude product was obtained by filtration. The solid was dissolved in ethyl acetate, dried over magnesium sulfate, decolourised with charcoal and solvent removed *in vacuo* to afford 3-cyano-2-(propen-1'-yl-3'-thio)pyridine (295) (1.8g, 70%) as a pale yellow crystalline solid after recrystallisation from ethyl acetate. mp 34-35°C. $\nu_{\max}(\text{KBr})$ 3059, 2932, 2224 cm^{-1} . $\delta_{\text{H}}(\text{CDCl}_3)$ 3.92 (d, 2H, $J=12.0\text{Hz}$, SCH_2), 5.00-6.28 (m, 3H, $\text{CH}=\text{CH}_2$), 7.02 (dd, 1H, $J=8.0$ & 14.0Hz , H-5), 7.73 (dd, 1H, $J=4.0$ & 14.0Hz), 8.32 (dd, 1H, $J=4.0$ & 8.0Hz). (Found: C,61.2; H,4.5; N,15.7; S,18.5. $\text{C}_9\text{H}_8\text{N}_2\text{S}$ requires C,61.3; H,4.6; N,15.9; S,18.2%).

Reaction of (291) with Propargyl Chloride.

Propargyl chloride (600mg, 8.00mmol) was added dropwise to an ice cold stirred mixture of the thione (291) (1.0g, 7.34mmol) and sodium methoxide (793mg, 14.69mmol) in DMF (20mL). The reaction mixture was stirred for 10 minutes at ice temperature, for 1 hour at room temperature, poured onto ice (150g) and the crude product obtained by filtration. The solid was dissolved in ethyl acetate, dried over magnesium sulfate, decolourised with charcoal and the solvent was removed *in vacuo*. Recrystallisation from petrol / diethyl ether afforded 3-cyano-2-(propyn-1'-yl-3'-thio)pyridine (296) (1.2g, 93%) as a white crystalline solid. mp 108-109°C. $\nu_{\max}(\text{KBr})$ 3245, 3068, 2969, 2226 cm^{-1} . $\delta_{\text{H}}(\text{CDCl}_3)$ 2.18 (t, 1H, $J=4.0\text{Hz}$, CH), 4.01 (d, 2H, $J=4.0\text{Hz}$, SCH_2), 7.09 (dd, 1H, $J=8.0$ & 14.0Hz , H-5), 7.80 (dd, 1H, $J=2.0$ & 14.0Hz , H-4), 8.57 (dd, 1H, $J=2.0$ & 8.0Hz , H-6). (Found: C,62.1; H,3.5; N,16.1; S,18.4. $\text{C}_9\text{H}_6\text{N}_2\text{S}$ requires C,62.0; H,3.5; N,16.1; S,18.4%).

Reaction of (291) with Methyl 4-Bromocrotonate.

The thione (291) (1.0g, 7.34mmol) was added to an ice cold stirred mixture of DMF (20mL) and sodium methoxide (793mg, 14.69mmol). The reaction mixture was stirred for 5 minutes at ice temperature and methyl 4-bromocrotonate (1.6g, 8.08mmol) was added dropwise. The reaction mixture was stirred for a further 10 minutes at ice temperature, for 2 hours at room temperature, poured onto ice (150g) and the crude product was obtained by filtration. The solid was dissolved in ethyl acetate, dried over magnesium sulfate, decolourised with charcoal and the solvent was removed *in vacuo*. Recrystallisation from petrol / diethyl ether afforded methyl 4-(3'-cyanopyridyl-2'-thio)crotonate (297) (1.05g, 65%) as a yellow crystalline solid. mp 75-76°C. $\nu_{\max}(\text{KBr})$ 3063, 2952, 2220, 1727 cm^{-1} . $\delta_{\text{H}}(\text{CDCl}_3)$ 3.68 (s, 3H, CO_2CH_3), 4.00 (dd, 2H, $J=2.0$ & 10.0Hz, SCH_2), 6.00 (dd, 1H, $J=2.0$ & 24.0Hz, CH=), 6.96 (m, 2H, H-5 & $=\text{CHCO}_2\text{Me}$), 7.70 (dd, 1H, $J=2.0$ & 12.0Hz, H-4), 8.52 (dd, 1H, $J=2.0$ & 8.0Hz, H-6). (Found: C,56.2; H,4.3; N,12.1; S,13.8. $\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}_2\text{S}$ requires C,56.3; H,4.3; N,12.0; S,13.7%).

Reaction of (291) with Chloroacetone.

Addition of the thione (291) to an ice cold stirred mixture of DMF (20mL) and sodium methoxide (793mg, 14.69mmol) was followed by stirring for 5 minutes at ice temperature before the dropwise addition of ethyl chloroacetone (750mg, 8.10mmol). The reaction mixture was stirred for a 10 minutes at ice temperature, for 2 hours at room temperature, poured onto ice (150g) and the crude product obtained by filtration. The solid was dissolved in ethyl acetate, dried over magnesium sulfate, decolourised with charcoal and solvent removed *in vacuo* to afford 2-acetyl-3-aminothieno[2,3-b]pyridine (298) (400mg, 25%) as a yellow crystalline solid after recrystallisation from ethyl acetate. mp 192-193°C. $\nu_{\max}(\text{KBr})$ 3440, 3328, 1607 cm^{-1} . $\delta_{\text{H}}(\text{d}_6\text{-DMSO})$ 2.38 (s, 3H, COMe), 7.26 (dd,

1H, J=8.0 & 12.0Hz, H-5), 7.78 (s, 2H, NH₂), (dd, 1H, J=2.0 & 12.0Hz, H-4), (dd, 1H, J=2.0 & 8.0Hz, H-6). (Found: C,56.3; H,4.3; N,14.8; S,16.5. C₉H₈N₂OS requires C,56.2; H,4.2; N,14.6; S,16.7%).

Reaction of (291) with Chloroacetophenone.

The thione (291) (1.0g, 7.34mmol) was added to an ice cold stirred mixture of DMF (20mL) and sodium ethoxide (1.0g, 14.68mmol). The reaction mixture was stirred for 5 minutes at ice temperature and chloroacetophenone (1.36g, 8.81mmol) was added portionwise. The reaction mixture was stirred for a further 10 minutes at ice temperature, for 2 hours at room temperature, poured onto ice (150g) and the crude product was obtained by filtration. The solid was dissolved in ethyl acetate, dried over magnesium sulfate, decolourised with charcoal and the solvent was removed *in vacuo*. Recrystallisation from ethyl acetate afforded 3-amino-2-benzoylthieno[2,3-b]pyridine (299) (750mg, 35%) as a yellow crystalline solid. mp 180-182°C (literature²³¹ mp 181-182°C).

Reaction of (291) with Ethyl Chloroacetate.

Ethyl chloroacetate (1.01g, 8.23mmol) was added dropwise to an ice cold stirred mixture of the thione (291) (1.0g, 7.48mmol) and sodium hydride (395mg, 16.46mmol) in DMF (20mL). The reaction mixture was stirred for a further 10 minutes at ice temperature, for 2 hours at room temperature, poured onto ice (150g) and the crude product was obtained by filtration. The solid was dissolved in ethyl acetate, dried over magnesium sulfate, decolourised with charcoal and the solvent was removed *in vacuo*. Recrystallisation from ethyl acetate afforded 3-amino-2-carboethoxythieno[2,3-b]pyridine (300) (850mg, 56%) as a bright yellow crystalline solid. mp 184-185°C (literature²³¹ mp 185-186°C). ν_{\max} (KBr) 3414, 3312, 3205, 2984, 1673cm⁻¹. δ_{H} (CDCl₃) 1.32 (t, 3H, J=12.0Hz, CH₃), 4.28 (q, 2H, J=12.0Hz, CO₂CH₂), 7.20 (s, 2H, NH₂), 7.58 (dd, 1H, J=8.0 & 12.0Hz,

H-5), 8.30 (dd, 1H, J=2.0 & 12.0Hz, H-4), 8.62 (dd, 1H, J=2.0 & 8.0Hz, H-6).

Reaction of (291) with Diethyl Bromomalonate.

The thione (291) (1.0g, 7.34mmol) was added to an ice cold stirred mixture of DMF (20mL) and sodium ethoxide (1.09g, 16.15mmol). The reaction mixture was stirred for 5 minutes at ice temperature before diethyl bromomalonate (2.11g, 8.81mmol) was added dropwise. The reaction mixture was stirred for a further 10 minutes at ice temperature, for 2 hours at room temperature, poured onto ice (150g) and a crude product was isolated by filtration. The solid was dissolved in ethyl acetate, dried over magnesium sulfate, decolourised with charcoal and solvent removed *in vacuo*. Recrystallisation from ethyl acetate afforded a product which was identical (tlc, mp, ir and nmr) to 3-amino-2-carboethoxythieno-[2,3-b]pyridine (300) (690mg, 42%).

Reaction of (291) with Ethyl 2-Chloroacetoacetate.

The thione (291) (500mg, 3.67mmol) was added to an ice cold stirred mixture of DMF (10mL) and sodium ethoxide (525mg, 7.71mmol). The reaction mixture was stirred for 5 minutes at ice temperature before ethyl 2-chloroacetoacetate (664mg, 4.04mmol) was added dropwise. The reaction mixture was stirred for a further 10 minutes at ice temperature followed by a further 2 hours at room temperature, poured onto ice (100g) and the crude product obtained by filtration. The solid was dissolved in ethyl acetate, dried over magnesium sulfate, decolourised with charcoal and solvent removed *in vacuo* to afford a product which was identical (tlc, mp, ir and nmr) to 3-amino-2-carboethoxythieno-[2,3-b]pyridine(300) (520mg, 63%).

Attempted Reaction of (291) with Ethyl 2-Bromopropionate.

The thione (291) (500mg, 3.67mmol) was added to an ice cold stirred mixture of DMF (10mL) and sodium ethoxide (525mg, 7.71mmol). The reaction mixture was stirred for 5 minutes at ice temperature and ethyl 2-bromopropionate (731mg, 4.04mmol) was added dropwise. The reaction mixture was stirred for a further 10 minutes at ice temperature followed by a further 2 hours at room temperature, poured onto ice (100g) and an oil was obtained. The aqueous mixture was extracted with ethyl acetate and these extracts were dried over magnesium sulfate, decolourised with charcoal, and solvent removed *in vacuo* to afford an oil. The oil was dissolved in toluene and chromatographed on silica gel (10g) but elution with petrol / ethyl acetate afforded no homogeneous product.

Reaction of (291) with Ethyl 4-Chloroacetoacetate.

Ethyl 4-chloroacetoacetate (1.3g, 8.07mmol) was added dropwise to a stirred mixture of the thione (291) (1.0g, 7.34mmol) and sodium ethoxide (1.05g, 15.42mmol) in DMF (20mL). The reaction mixture was stirred for 10 minutes at ice temperature followed by a further 2 hours at room temperature, poured onto ice (150g) to afford an oil. The aqueous mixture was extracted with ethyl acetate and these extracts were dried over magnesium sulfate, decolourised with charcoal and solvent removed *in vacuo* to afford a yellow solid. Recrystallisation from ethyl acetate gave 3-amino-2-(ethylacetoacetyl)thieno[2,3-b]pyridine (304) (200mg, 10%) as a pale yellow crystalline material. mp 92-94°C. ν_{max} (KBr) 3410, 3308, 2992, 1740, 1720cm⁻¹. δ_{H} (CDCl₃) 1.31 (t, 3H, J=12.0Hz, CH₃), 3.80 (s, 2H, COCH₂CO₂), 4.26 (q, 2H, J=12.0Hz, CO₂CH₂), 6.90 (s, 2H, NH₂), 7.31 (dd, 1H, J=8.0 & 14.0Hz, H-5), 8.00 (dd, 1H, J=2.0 & 14.0Hz, H-4), 8.70 (dd, 1H, J=2.0 & 8.0Hz, H-6). (Found: C,54.4; H,4.7; N,10.7; S,12.2. C₁₂H₁₂N₂O₃S requires C,54.5; H,4.6; N,10.6; S,12.1%).

The aqueous layer was acidified with glacial acetic acid and a solid precipitated out of solution. The solid was filtered, dissolved in ethanol, dried over magnesium sulfate, decolourised with charcoal and solvent removed *in vacuo*.

Recrystallisation from ethanol afforded 3,2-(3'-hydroxypyridin-2'(1'H)-one)-thieno[2,3-b]pyridine(305) (600mg, 38%) as a yellow solid. mp >345°C.

ν_{\max} (KBr) broad 3500-3000, 1620cm⁻¹. δ_{H} (d₆-DMSO) 5.91 (s, 1H, H), 7.55 (dd, 1H, J= 8.0 & 14.0Hz, H-5), 8.72 (multiplet, 2H, H-4 & H-6), 13.5 (s, very broad, 2H, NH & OH). (Found: C,55.2; H,2.7; N,12.7; S,14.5. C₁₀H₆N₂O₂S requires C,55.1; H,2.8; N,12.8; S,14.7%).

3-Cyano-2-morpholinothieno[2,3-b]pyridine (306).

3-Cyano-2-methylthiothieno[2,3-b]pyridine (262) (300mg, 1.45mmol) and morpholine (1.00g, 11.5mmol) were heated at 100°C for 24 hours. The solvent was removed *in vacuo* to afford a solid which was dissolved in ethyl acetate, dried over magnesium sulfate solvent removed *in vacuo* and recrystallisation from ethyl acetate to affords 3-cyano-2-morpholinothieno[2,3-b]pyridine (306) as a pale orange crystalline solid (160mg, 45%). mp 208-208.5°C. ν_{\max} (KBr) 2980, 2909, 2199cm⁻¹. δ_{H} (CDCl₃) 3.66-4.00 (m, 8H, CH₂), 7.30 (dd, 1H, J=6.0 & 10.0Hz, H-5), 7.81 (dd, 1H, J=2.0 & 10.0Hz, H-4), 8.34 (dd, 1H, J=2.0 & 6.0Hz, H-4). (Found: C,59.0; H,4.7; N,16.9; S,13.3. C₁₂H₁₁N₃OS requires C,58.8; H,4.5; N,17.1; S,13.1%).

3-Cyano-2-benzylaminothieno[2,3-b]pyridine (307).

3-Cyano-2-methylthiothieno[2,3-b]pyridine (262) (900mg, 4.36mmol) and benzylamine (4.7g, 43.6mmol) were refluxed for 5 hours. The solvent was removed *in vacuo* to afford an oil which was dissolved in toluene and chromatographed on silica gel (20g). Elution with light petroleum ether / diethyl

ether (10-50%) afforded a solid which was recrystallised from ethyl acetate to afford 3-cyano-2-benzylaminothieno[2,3-b]pyridine (307) (530mg, 45%) as a pale orange crystalline solid. mp 152-153°C. $\nu_{\max}(\text{KBr})$ 3290, 2925, 2201 cm^{-1} . δ_{H} (CDCl_3) 4.56 (d, 2H, CH_2), 6.25 (s, 1H, NH), 7.37 (m, 6H, H-5 & C_6H_5), 7.70 (dd, 1H, $J=2.0$ & 12.0Hz, H-4), 8.26 (dd, 1H, $J=2.0$ & 8.0Hz, H-6). (Found: C,67.5; H,4.1; N,15.6; S,11.8. $\text{C}_{15}\text{H}_{11}\text{N}_3\text{S}$ requires C,67.9; H,4.2; N,15.8; S,12.1%).

Attempted Reactions of (262) with Oxygen Nucleophiles.

a) Methanol. - The thienopyridine (262) (300mg, 1.45mmol) was refluxed with methanol (20mL) for 5 hours. Tlc indicated that no reaction had occurred so the reaction mixture refluxed for a further 10 hours. Solvent was removed *in vacuo*, water was added to the residue and the aqueous mixture extracted with ethyl acetate. The organic extracts were dried over magnesium sulfate and the solvent was removed *in vacuo* to afford a solid which was identical (tlc and nmr) to unreacted (262).

The reaction of (262) in refluxing butanol and refluxing pentanol also failed to displace the thiomethyl group.

b) with Sodium Methoxide. - The thienopyridine (262) (300mg, 1.45mmol) and sodium (123mg, 5.33mmol) were stirred in methanol (20mL) for 5 hours but no reaction occurred (tlc). The reaction mixture was heated at reflux for 5 hours, then solvent removed *in vacuo* and water added to the residue. The aqueous mixture was extracted with ethyl acetate, and the organic phase dried over magnesium sulfate and solvent removed *in vacuo* to afford a solid which was identical (tlc and nmr) to unreacted (262).

c) with Sodium Pentoxide. - Thienopyridine (**262**) (300mg, 1.45mmol) and sodium (123mg, 5.33mmol) were heated in pentanol (20mL) at 100°C for one hour.

Solvent was removed *in vacuo*, water added to the residue and the aqueous mixture extracted with ethyl acetate. No compounds were isolated from the organic extracts and therefore the solvent from the aqueous mixture was removed *in vacuo*. The solid obtained was insoluble in organic solvent but soluble in water and therefore it was believed to be a salt, possibly due to decomposition.

Attempted Synthesis of (308) from (262).

a) From the Reaction of (262) and Ammonia Under Pressure - Thienopyridine (**262**) (300mg, 1.45mmol) and a saturated solution of ammonia in methanol were reacted in a Berghorf pressure vessel (Teflon lined) at 160°C / 10bars. for 18 hours. Tlc indicated that no reaction had occurred so the reaction was repeated at 200°C / 20bars. Tlc indicated a number of components but no homogeneous product could be isolated from column chromatography.

b) Gabriel Synthesis. - Thienopyridine (**262**) (500mg, 2.42mmol) and potassium phthalimide (490mg, 2.67mmol) were refluxed in DMF for 5 hours. The reaction mixture was added to water and the aqueous mixture extracted with ethyl acetate. The organic extracts were dried over magnesium sulfate and solvent removed *in vacuo* to afford a solid which was identical (tlc and nmr) to unreacted (**262**). The use of a variety of reaction conditions such as varying temperature and solvent systems resulted in similar results.

c) Modified Gabriel Synthesis. - Thienopyridine (**262**) (500mg, 2.42mmol) and sodium diformylamide (300mg, 2.91mmol) were refluxed in ethanol for 12 hours. The solvent was removed *in vacuo*, water was added to the residue and the aqueous

mixture extracted with ethyl acetate. The organic extracts were dried over magnesium sulfate and solvent removed *in vacuo* to afford a solid which was identical (tlc and nmr) to unreacted (262).

d) Reaction with Sodium Amide. - Thienopyridine (262) (500mg, 2.42mmol) and sodium amide (113mg, 2.9mmol) were stirred in DMF (20mL) at 100°C for 10 hours. The reaction mixture was added to water and the aqueous mixture extracted with ethyl acetate. The organic extracts were dried over magnesium sulfate and solvent removed *in vacuo* to afford a solid which was identical (tlc and nmr) to unreacted (262).

3-Cyano-2-methylsulfinylthieno[2,3-b]pyridine (309).

The thienopyridine (262) (500mg, 2.48mmol) was dissolved in dichloromethane (10mL), cooled to ice temperature and *m*-chloroperbenzoic acid (approximately 50% pure, 800mg, 4.86mmol) was added portionwise. Once all of the *m*-CPBA had been added, the reaction mixture was stirred at ice temperature for 2 hours. The reaction mixture was diluted with dichloromethane (50mL), washed with a 10% aqueous solution of sodium metabisulfite, brine, sodium hydrogen carbonate, brine, dried over magnesium sulfate and solvent removed *in vacuo* to afford a white crystalline solid. Recrystallisation from ethyl acetate afforded

3-cyano-2-methylsulfinylthieno[2,3-b]pyridine (309) (390mg, 71%). mp 139-139.5°C. ν_{max} (KBr) 2984, 2220cm⁻¹. δ_{H} (CDCl₃) 3.20 (s, 3H, SMe), 7.56 (dd, 1H, J=8.0 & 12.0Hz, H-5), 8.26 (dd, 1H, J=2.0 & 12.0Hz, H-4), 8.64 (dd, 1H, J=2.0 & 8.0Hz, H-6). (Found: C,48.8; H,2.9; N,12.6; S,28.6. C₉H₆N₂OS₂ requires C,48.6; H,2.7; N,12.6; S,28.8%).

3-Cyano-2-methylsulfonylthieno[2,3-b]pyridine (310).

The thienopyridine (**262**) (500mg, 2.48mmol) was dissolved in dichloromethane (10mL), cooled to ice temperature and *m*-chloroperbenzoic acid (approximately 50% pure, 1.67g, 9.7mmol) was added portionwise. Once all of the *m*-CPBA had been added, the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with dichloromethane (50mL), washed with a 10% solution of sodium metabisulfite, brine, aqueous sodium hydrogen carbonate, brine; dried over magnesium sulfate and solvent removed *in vacuo* to afford a solid. Recrystallisation from ethyl acetate afforded 3-cyano-2-methylsulfonyl-thieno[2,3-b]pyridine (310) (410mg, 70%) as a white crystalline solid. mp 192-192.5°C. ν_{max} (KBr) 3026, 2922, 2225cm⁻¹. δ_{H} (CDCl₃) 3.62 (s, 3H, SO₂Me), 7.68 (dd, 1H, J=8.0 & 12.0Hz, H-5), 8.46 (dd, 1H, J=2.0 & 12.0Hz, H-4), 8.82 (dd, 1H, J=2.0 & 8.0Hz, H-6). (Found: C,45.6; H,2.7; N,11.8; S,26.7. C₉H₆N₂O₂S₂ requires C,45.4; H,2.5; N,11.8; S,26.9%).

Attempted Reaction of Sulfide (262) with Diethyl Malonate.

Thienopyridine (**262**) (300mg, 1.45mmol), sodium ethoxide (197mg, 2.9mmol) and diethyl malonate (465mg, 2.9mmol) were heated at 100°C for 3 hours. The cooled reaction mixture was poured onto ice (75g) and extracted with ethyl acetate. The organic extracts were dried over magnesium sulfate and solvent removed *in vacuo* to afford a liquid, which was chromatographed on silica gel and elution with petroleum ether / ethyl acetate (10%) afforded diethyl malonate. Further elution (10-30%) afforded a solid which was identical (tlc and nmr) to unreacted (**262**).

Reaction of Sulfoxide (309) with Diethyl Malonate.

The sulfoxide (**309**) (300mg, 1.35mmol), sodium ethoxide (184mg, 2.7mmol) and diethyl malonate (465mg, 2.9mmol) were heated at 100°C for 3 hours. The cooled

reaction mixture was poured onto ice (75g) and extracted with ethyl acetate. The organic extracts were dried over magnesium sulfate and solvent removed *in vacuo* to afford a liquid which was chromatographed on silica gel and elution with petroleum ether / ethyl acetate (10%) afforded diethyl malonate.

Further elution (10-30%) afforded 3-cyano-2-dicarboethoxymethylthieno-[2,3-b]-pyridine (311) (240mg, 56%) as a clear oil. $\nu_{\max}(\text{KBr})$ 2983, 2226, 1740 cm^{-1} . δ_{H} (CDCl_3) 1.18 (t, 6H, $J=12.0\text{Hz}$, 2CH_3), 3.26 (s, 1H, CH), 4.00 (q, 4H, $J=12.0\text{Hz}$, $2\text{CO}_2\text{CH}_2$), 7.10 (dd, 1H, $J=8.0$ & 12.0Hz , H-5), 7.48 (dd, 1H, $J=2.0$ & 12.0Hz , H-4), 8.06 (dd, 1H, $J=2.0$ & 8.0Hz , H-6). (Found: C,56.7; H,4.4; N,8.6; S,10.2. $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_4\text{S}$ requires C,56.6; H,4.4; N,8.8; S,10.1%).

Reaction of Sulfone (310) with Diethyl Malonate.

The sulfone (310) (300mg, 1.26mmol), sodium ethoxide (188mg, 2.8mmol) and diethyl malonate (465mg, 2.9mmol) were heated at 100°C for 3 hours. The cooled reaction mixture was poured onto ice (75g) and extracted with ethyl acetate. The organic extracts were dried over magnesium sulfate and solvent removed *in vacuo* to afford a liquid which was chromatographed on silica gel and elution with petroleum ether / ethyl acetate (10-30%) afforded diethyl malonate, followed by 3-cyano-2-dicarboethoxymethylthieno[2,3-b]pyridine (311) obtained as a colourless oil (430mg, 83%), identical (tlc, ir and nmr) to an authentic sample.

Reaction of (310) with Nucleophiles.

a) Sodium Methoxide - The sulfone (310) (500mg, 2.1mmol) and sodium methoxide (113mg, 21.0mmol) were stirred in DMF (10mL) for 24 hours. The reaction mixture was poured onto water (75mL) and a solid obtained by filtration which was identical (tlc and nmr) to unreacted (310).

b) Sodium Amide - The sulfone (**310**) (300mg, 1.35mmol) and sodium amide (526mg, 13.5mmol) were stirred in DMF (10mL) for 24 hours. The reaction mixture was poured onto water (75mL) and a solid obtained by filtration which was identical (tlc and nmr) to unreacted (**310**).

c) Urea - The sulfone (500mg, 2.1mmol) and urea (265mg, 4.41mmol) were heated in DMF at 100°C for 5 hours. The reaction mixture was poured onto water (75mL) and a solid obtained by filtration which was identical (tlc and nmr) to unreacted (**310**).

Cyclisation of (**267**) with Sodium Ethoxide.

The thienopyridine (**267**) (500mg, 1.79mmol) was added to an ice cold mixture of sodium ethoxide (269mg, 3.95mmol) in DMF (10mL). The reaction mixture was stirred for 10 minutes at ice temperature, followed by a further 2 hours at room temperature and then poured onto ice/water (100mL). The crude product was obtained by filtration, then dissolved in ethyl acetate, dried over magnesium sulfate and solvent removed *in vacuo*. Recrystallisation from ethyl acetate afforded 3-amino-2-carboethoxythieno[2,3-b]thieno[2,3-b]pyridine (**313**) (130mg, 26%) as a white crystalline solid. mp 162-164°C. ν_{\max} (KBr) 3377, 3294, 2988, 1673cm⁻¹. δ_{H} (CDCl₃) (t, 3H, J=12.0Hz, CH₃), (q, 2H, J=12.0Hz, CO₂CH₂), (dd, 1H, J=8.0 & 14.0Hz, H-5), (dd, 1H, J=2.0 & 14.0Hz, H-4), (dd, 1H, J=2.0 & 8.0Hz, H-6). (Found: C,52.0; H,3.6; N,10.0; S,23.2. C₁₂H₁₀N₂O₂S₂ requires C,51.8; H,3.6; N,10.1; S,23.0%).

Attempted Cyclisation of (**285**) with a Sodium Ethoxide.

The thienopyridine (**285**) (500mg, 1.79mmol) was added to an ice cold mixture of sodium ethoxide (269mg, 3.95mmol) in DMF (10mL). The reaction mixture was stirred for 10 minutes at ice temperature, followed by a further 2 hours at room

temperature and then poured onto ice/water (100mL). The crude product was obtained by filtration, then dissolved in ethyl acetate, dried over magnesium sulfate and solvent removed *in vacuo* to afford a solid which was identical (tlc, ir and nmr) to unreacted (285).

5-(2',2'-Bisthiomethyl-1'-cyanoethenyl)2-chloropyridine (315).

Carbon disulfide (620mg, 8.19mmol) was added to a stirred solution of 2-chloro-5-cyanomethylpyridine (248) (1.0g, 6.55mmol) in dimethyl sulfoxide (20mL), under nitrogen. Sodium hydride (350mg, 14.14mol) was added portionwise and the reaction mixture stirred for 1 hour at room temperature. Iodomethane (2.0g, 14.14mmol) was added and the reaction mixture was stirred for a further 1 hour at room temperature, poured onto ice (150g), and the crude product obtained by filtration. This product was dissolved in ethyl acetate, dried over magnesium sulfate, decolourised with charcoal, filtered and solvent removed *in vacuo*. Recrystallisation from ethyl acetate afforded 5-(2',2'-Bisthiomethyl-1'-cyanoethenyl)2-chloropyridine (315) (860mg, 51%) as a yellow crystalline solid. mp 78-79°C. ν_{\max} (KBr) 2930, 2206cm⁻¹. δ_{H} (CDCl₃) 2.34 (s, 3H, SCH₃), 2.60 (s, 3H, SCH₃), 7.27 (d, 1H, J=14.0Hz, H-3), 7.68 (dd, 1H, J=4.0 & 14.0Hz, H-4), 8.42 (d, 1H, J=4.0Hz, H-6). (Found: C,46.8; H,3.5; N,10.8; Cl,14.2; S,25.0. C₁₀H₉N₂ClS₂ requires C,46.8; H,3.5; N,10.8; Cl,13.8; S,31.05%).

2-Chloro-5-(1'cyano-2'-(1'',3''-dithiocyclopent-2''-yl)ethenyl)pyridine (316).

Carbon disulfide (620mg, 8.19mmol) was added to a stirred solution of 2-chloro-5-cyanomethylpyridine (248) (1.0g, 6.55mmol) in dimethyl sulfoxide (20mL), under nitrogen. Sodium hydride (350mg, 14.14mol) was added portionwise and the reaction mixture stirred for 1 hour at room temperature. 1,2-Dibromoethane (2.7g, 14.14mol) was added and the reaction mixture was stirred for a further 1 hour at room temperature, poured onto ice (150g), and the

crude product obtained by filtration. This product was dissolved in ethyl acetate dried over magnesium sulfate, decolourised with charcoal, filtered and solvent removed *in vacuo*. Recrystallisation from ethyl acetate afforded 2-chloro-5-(1'cyano-2'-(1'',3''-dithiocyclopent-2''-yl)ethenyl)pyridine (316) (900mg, 54%) as a white crystalline solid. mp 171-172°C. $\nu_{\max}(\text{KBr})$ 2930, 2225 cm^{-1} . δ_{H} (CDCl_3) 3.76 (s, 4H, $\text{SCH}_2\text{CH}_2\text{S}$), 7.55 (d, 1H, $J=14.0\text{Hz}$, H-3), 7.91 (dd, 1H, $J=4.0$ & 14.0Hz , H-4), 8.47 (d, 1H, $J=4.0\text{Hz}$, H-6). (Found: C,47.1; H,2.7; N,11.0; Cl,14.2; S,25.2. $\text{C}_{10}\text{H}_7\text{N}_2\text{ClS}_2$ requires C,47.2; H,2.8; N,11.0; Cl,13.9; S,25.2%).

2-Chloro-5-(1'cyano-2'-(1'',3''-dithiocyclohex-2''-yl)ethenyl)pyridine (317).

Carbon disulfide (598mg, 7.86mmol) was added to a stirred solution of 2-chloro-5-cyanomethylpyridine (**248**) (1.0g, 6.55mmol) in dimethyl sulfoxide (20mL), under nitrogen. Sodium hydride (350mg, 14.14mol) was added portionwise and the reaction mixture stirred for 1 hour at room temperature followed by addition of 1,3-dibromopropane (2.9g, 14.14mol). The reaction mixture was stirred for a further 1 hour at room temperature, poured onto ice (150g), and the crude product was obtained by filtration. This product was dissolved in ethyl acetate dried over magnesium sulfate, decolourised with charcoal, filtered and solvent removed *in vacuo*. Recrystallisation from ethyl acetate afforded 2-Chloro-5-(1'cyano-2'-(1'',3''-dithiocyclohex-2''-yl)ethenyl)-pyridine (317) (950mg, 54%) as a white crystalline solid. mp 120-122°C. $\nu_{\max}(\text{KBr})$ 2923, 2194 cm^{-1} . δ_{H} (CDCl_3) 2.32 (q, 2H, $J=12.0\text{Hz}$, CH_2), 3.10 3.10 (q, 1H, $J=12.0\text{Hz}$, 2SCH_3), 7.12 (d, 1H, $J=14.0\text{Hz}$, H-3), 7.76 (dd, 1H, $J=4.0$ & 14.0Hz , H-4), 8.46 (d, 1H, $J=4.0\text{Hz}$, H-6). (Found: C,49.2; H,3.4; N,10.4; Cl,13.0; S,24.1. $\text{C}_{11}\text{H}_9\text{N}_2\text{ClS}_2$ requires C,49.1; H,3.4; N,10.4; Cl,13.2; S,23.9%).

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