SYNTHESIS AND REACTIONS OF SOME PYRIDINES AND THIENOPYRIDINES

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A thesis submitted in partial fulfilment of the requirements of the University of Abertay Dundee for the degree of Doctor of Philosophy

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I certify that this thesis is the true and accurate version of the thesis approved by the examiners.

Signed......[redacted]........... Date...26/10/05

DECLARATION

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

Signed ……………[redacted]…

Date ……………26/10/05……………

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Abstract

The overall aim of this research project is to investigate nucleophilic substitution reactions of the thiomethyl group of 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine. The multistep synthesis of this compound is reviewed and improvements described. The first step is the N-oxidation of ethyl 3-pyridylacetate, so reagents for the preparation of this and other 3-substituted pyridines were investigated and a novel workup procedure for oxidation with *m*-CPBA (*m*-chloroperbenzoic acid) is described. The preparation of ethyl 2-chloro-3-pyridylacetate and several polychlorinated pyridine derivatives are reported. Novel ketene dithioacetals were prepared from ethyl 5-chloro-3-pyridylacetate and 5-chloro-3-pyridylacetonitrile and some were converted to highly substituted thiophenes. Novel thieno[2,3-b]pyridines and [3,2-c]pyridines were prepared from ethyl 2-chloro-3-pyridylacetate, ethyl 4-chloro-3-pyridylacetate and their N-oxides. Preparation of the sulphoxide and sulphone of 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine was investigated and their relative susceptibility to substitution by some nitrogen nucleophiles examined. The conversion of benzylamine to benzaldehyde by the N-oxide group during the reaction of 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine N-oxide with benzylamine was studied in some detail. Attempts were made to develop a synthetic route to the potential agonist of serotonin, 3-(2-aminoethyl)-5-hydroxythieno[2,3-b]pyridine from 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine. Successful removal of the thiomethyl group at C-2 of 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine and progress made in development of the side chain at C-3 is reported. This thesis exhibits evidence of clear progress towards the development of a novel synthetic route to potential agonists of serotonin.

List of Abbreviations

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

°C	°Celcius
Δ	heat
ABCHC	1,1'-azo*bis*(cyclohexanecarbonitrile)
ADMA	acetoacetaldehyde dimethylacetal
bp	boiling point
m-CBA	*m*-chlorobenzoic acid
m-CPBA	*m*-chloroperbenzoic acid
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEMM (EMME)	diethyl ethoxymethylenemalonate
DEPC	diethylphosphorocyanidate
DMF	dimethylformamide
DMSO	dimethylsulphoxide
Et	ethyl
EWG	electron withdrawing group
[H]	reduction
h	hour
HMPT	hexamethylphosphoric triamide
IDBC	iodobenzene dichloride
J	Joule

K	Kelvin
MCH	morpholinocyclohexane
Me	methyl
mol	mole
mp	melting point
[O]	oxidation
Ph	phenyl
PPA	polyphosphoric acid
pmr	proton magnetic resonance
rt	room temperature
s	second
TBTH	tri-*n*-butyltin hydride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
tlc	thin layer chromatography
TMED	tetramethylethylenediamine
TMSCN	trimethylsilanocarbonitrile
TsCl	*p*-toluenesulphonylchloride

1 Introduction

1.1 Pyridine N-oxides

It would be unrealistic to give, in this introduction, a complete review of the chemistry of pyridine N-oxides. It is therefore an attempt to cover the main aspects of this subject including, as extensively as possible, preparation by direct oxidation as this was an important part of this project. There are several monographs[1-4] available which give a much more comprehensive overview of heterocyclic N-oxides. More recently a review[5] has been published covering the period 1990 to 2000 and focusing on the chemistry of pyridine N-oxides only. A brief review[6] of methods for the preparation of pyridine N-oxides by direct oxidation has also been published.

Pyridines are generally resistive to electrophilic substitution due to the uneven π electron distribution around the ring. The π-electron density is slightly higher at the 3-position than at the 2- and 4- positions because the nitrogen atom is more electrophilic than carbon causing a drift of electrons in its direction[7]. (A typical set of electron densities is shown in figure 1).

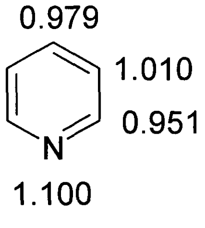


Figure 1

Therefore electrophilic aromatic substitution usually takes place at the 3-position under vigorous conditions. By the same arguments, nucleophilic substitution takes place readily at the 2- and 4-positions.

Pyridine N-oxides however, show greater susceptibility to both electrophilic and nucleophilic substitution. Examination of the dipole moment of pyridine N-oxide **1**, 4.24D[8], show that of the canonical structures **1–7**, structures **5–7** make significant contributions to the resonance hybrid. However, considering that **2–4** also make contributions to the resonance hybrid, these canonical structures are indicative of the versatility of the molecule [figure 2].

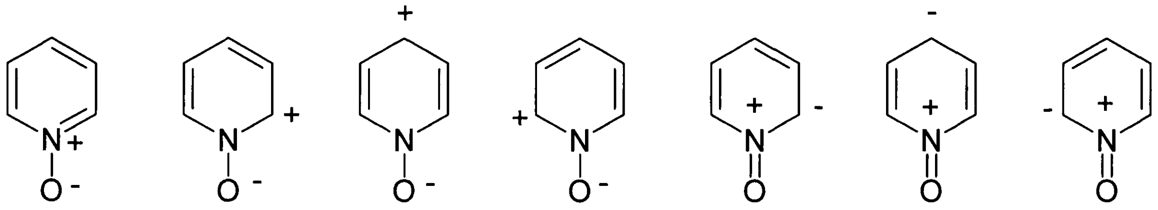


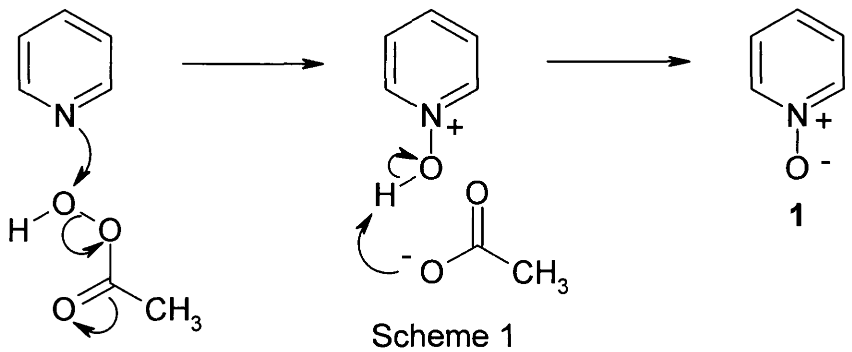
Figure 2

The N-oxide group acts as both an electron acceptor and an electron donor, facilitating both electrophilic and nucleophilic substitution at the 2- and 4-positions, depending on the reagents employed. It has been found[9] experimentally that both types of reactions occur.

1.1.1 Preparation of pyridine N-oxides

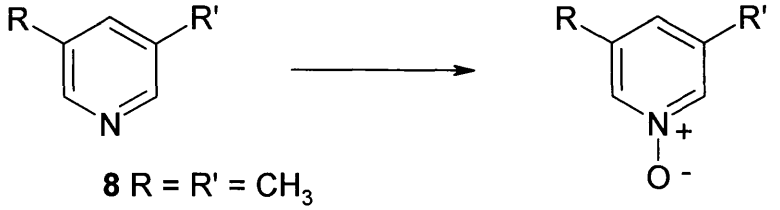
1.1.1.1 By direct oxidation with organic peracids

Pyridine N-oxide **1** was first prepared by Meisenheimer[10] using peroxybenzoic acid as the oxidising agent. Peracids are widely used as reagents in this transformation, the most common being peracetic acid[11-20] usually created *in situ* from glacial acetic acid and 30% hydrogen peroxide. The mechanism is shown in scheme 1. It involves reaction between the two neutral species, the pyridine and the peracid, with the latter acting as the electrophile.


Scheme 1

It is known[21] that sodium perborate and glacial acetic acid rapidly form peracetic acid under anhydrous conditions, and these have proved[22] to be effective reagents for the transformation of substituted pyridines to their corresponding N-oxides. No clear trends in steric or electronic effects have been reported, however while pyridine-3-carboxylic acid is N-oxidised in 63% yield, the 2- and 4- isomers have proved unreactive implying that electron-withdrawing groups in these positions inhibit oxidation.

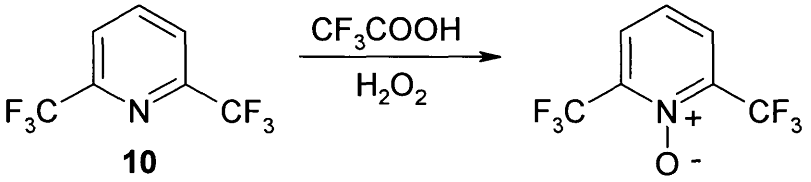
Nowadays, the most popular reagents for this transformation are *m*-chloroperbenzoic acid (*m*-CPBA)[23, 24] (commercially available with a 55% titre) and the equally effective[25] and safer magnesium monoperphthalate. Treatment of 3-trichloromethylpyridine with *m*-CPBA in dry chloroform[24] gives 3-trichloromethylpyridine N-oxide. The oxidation of heterocyclic compounds by *m*-CPBA/HCl/DMF has been reported; for example, 3,5-lutidine **8** and nicotinic acid **9** when treated with *m*-CPBA in DMF/methanol in the presence of hydrofluoric acid form their N-oxides in 85 and 87% yields[26] respectively [equation 1].



8 R = R' = CH_3
9 R = COOH R' = H

Equation 1

For difficult transformations such as the oxidation of 2,6-bis(trifluoromethyl)pyridine **10**, peroxytrifluoroacetic acid[27, 28] has been used [equation 2].



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Equation 2

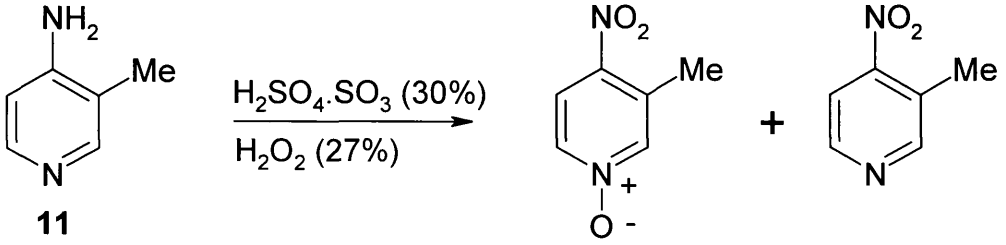
This reagent has also been used for the N-oxidation of 2,6-dibromopyridine, which has low basicity[29, 30] due to the inductive effect of the two α-bromine atoms of the molecule rendering the lone pair on the nitrogen less available for coordination. By using hydrogen peroxide in trifluoroacetic acid,[31] 2-pyridyl-2,4,5-trichlorophenyl sulphide has been converted into the corresponding sulphone N-oxide. N-Oxidation of pentachloropyridine with hydrogen peroxide (90%) and either acetic or trifluoroacetic acid in the presence of concentrated sulphuric acid[32] gives the desired product in 85% yield. It has been reported[33] that peroxymaleic acid has stronger oxidative powers than peroxybenzoic or peroxyphthalic acids and is more stable and well adapted as a reagent for N-oxidations.

1.1.1.2 Side reactions with organic peracids

N-oxidation is often accompanied by other oxidations especially when the reagents are hydrogen peroxide and glacial acetic acid. Hydrolysis by the acid, oxidation of functional groups on the pyridine or ring cleavage may occur.

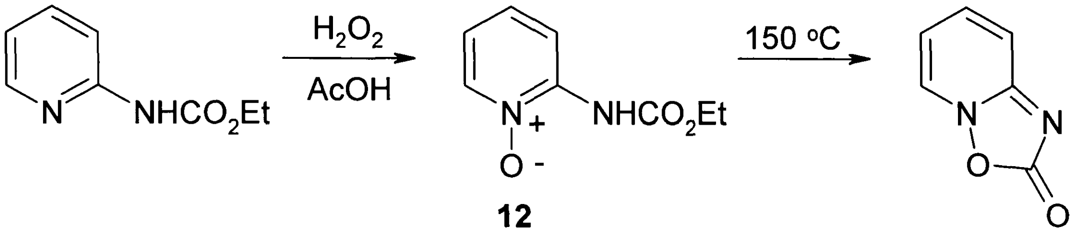
1.1.1.2.1 Oxidation of nitrogen substituents

The primary amine group of molecules such as 4-amino-3-methylpyridine **11** may be oxidised to a nitro group by peracids[34] or by a mixture of 30% fuming sulphuric acid and 27% hydrogen peroxide[35, 36] [equation 3].



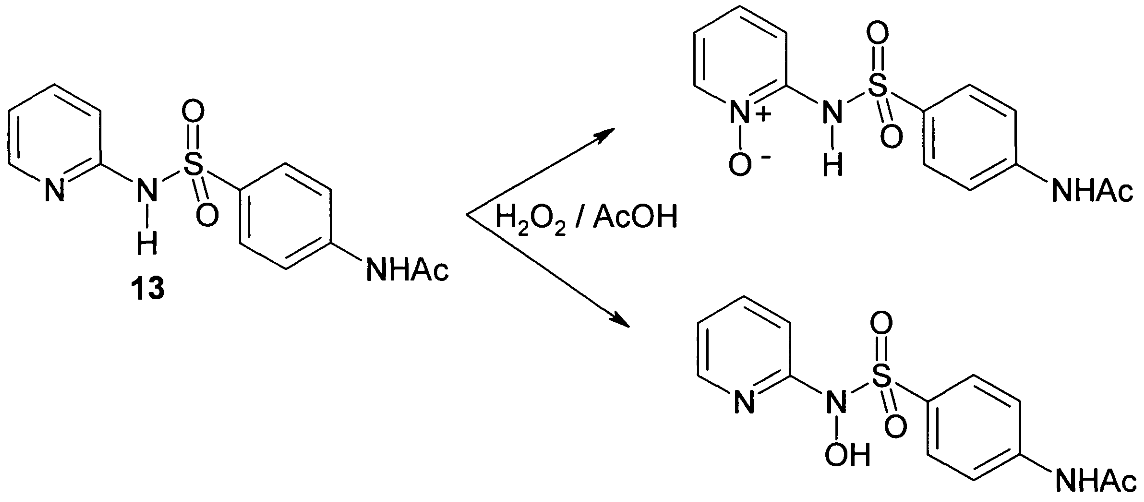
Equation 3

The amino group can be protected by acylation, then deprotected by hydrolysis after N-oxidation.[37] However urethane 1-oxide **12** tends to cyclise to a 1,2,4-oxadiazolone derivative [scheme 2].



Scheme 2

For tertiary amines the situation is complex in that the substituent nitrogen is preferentially oxidised in 2-dimethylaminopyridine, whereas in the 4-substituted isomer[38-41] it is the ring nitrogen. In the N-oxidation of the sulphonamide **13**, it is found[42] that part of the sulphonamide group is oxidised to a hydroxylamine [scheme 3].



Scheme 3

When compound **14** is treated with perbenzoic acid, the dimethylamino group is oxidised first, followed by the pyridine nitrogen[43] [figure 3].

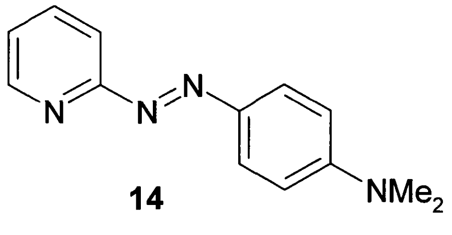


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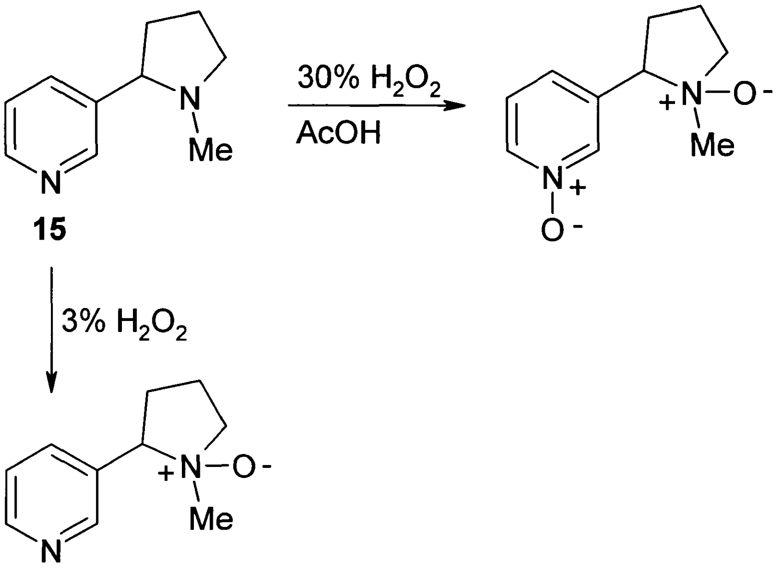
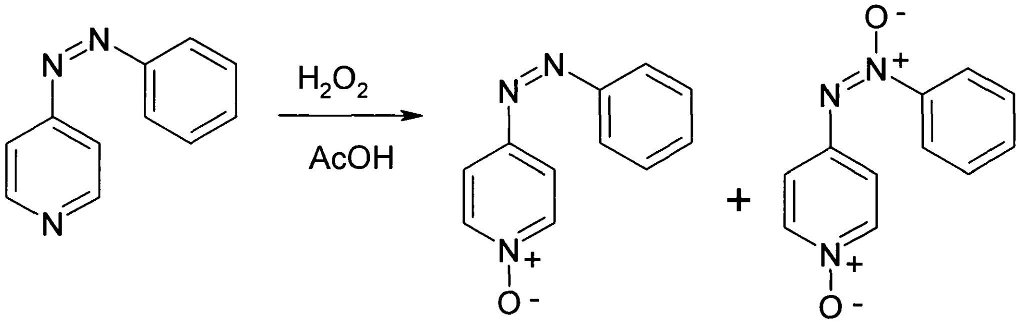
Figure 3

With nicotine **15**, which also contains an aliphatic tertiary amine and an aromatic tertiary amine, the formation of a double N-oxide is observed[44] when a peracid is used. However, if the original compound is oxidised under mild conditions e.g. standing in dilute aqueous acidic hydrogen peroxide at room temperature, only the aliphatic amine is oxidised [scheme 4].



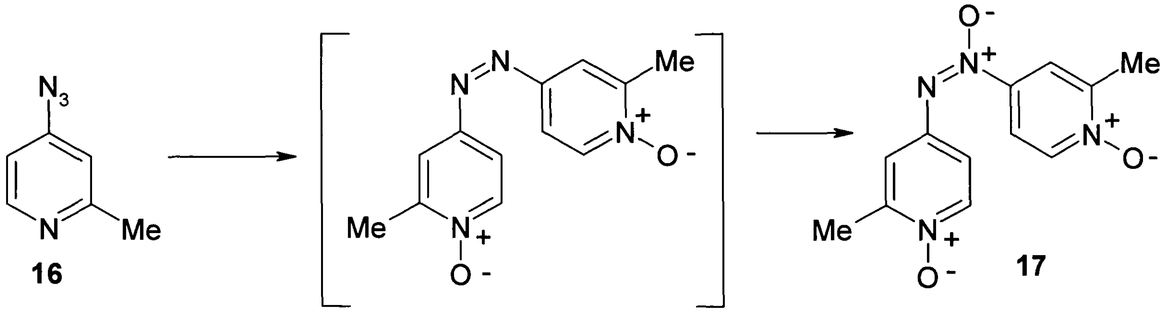
Scheme 4

Phenylazopyridines[45-47] are oxidised to give both azo and azoxy-1-oxides. The azo group is less readily oxidised than the ring nitrogen [equation 4].



Equation 4

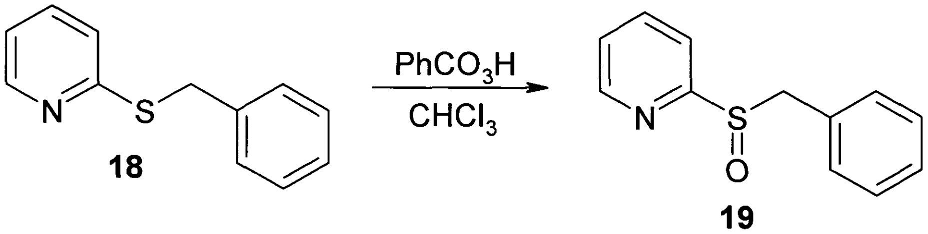
Decomposition of the azido group occurs during N-oxidation of 4-azido-2-picoline **16** and 4,4'-azoxy-2-picoline-1,1'-dioxide **17** is formed via the intermediate which contains an azo group[48] [scheme 5].



Scheme 5

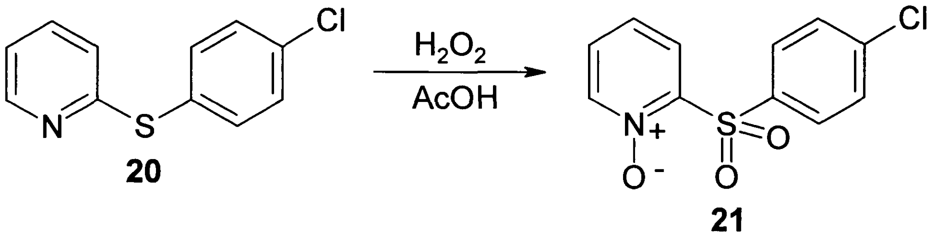
1.1.1.2.2 Oxidation of sulphur substituents

Alkylthio substituents, as in 2-alkylthio[49] and 3-alkylthio-2-chloro-pyidines[50] are oxidised preferentially by peracids to give the corresponding sulphoxides and sulphones with no reaction at the nitrogen. Stronger oxidising agents such as pertrifluoroacetic acid[31] or 3,5-dinitroperbenzoic acid[50] can oxidise the nitrogen atom. Pyridyl sulphides can be selectively oxidised depending on the reagents employed e.g. 2-pyridyl benzyl sulphide **18** is converted to the sulphoxide **19** with perbenzoic acid[51] [equation 5].



Equation 5

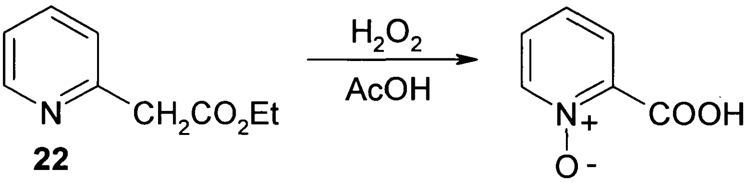
Alternatively 2-pyridyl-4-chlorophenyl sulphide **20** on reaction with hydrogen peroxide and acetic acid gives the corresponding sulphone N-oxide[31] **21** [equation 6].



Equation 6

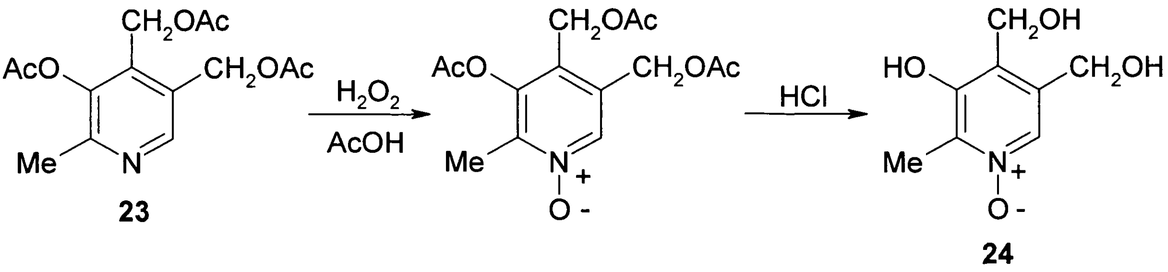
1.1.1.2.3 Oxidation of carbon substituents

When a side chain in the ring is activated, as with the groups CH2OH,[52] CHRCOOR' and CHRCOR'[53, 54] attack at the α-position of the chain occurs resulting in the formation of acyl or hydroxy derivatives. In the case of ethyl 2-pyridylacetate **22**, oxidation of the ester group accompanies N-oxidation[55] [equation 7].



Equation 7

The formation of pyridine N-oxide derivative **24**, without oxidation of the hydroxyl groups, was achieved[56] by reacting acylated pyridine **23** with hydrogen peroxide and acetic acid, followed by acid hydrolysis [scheme 6].

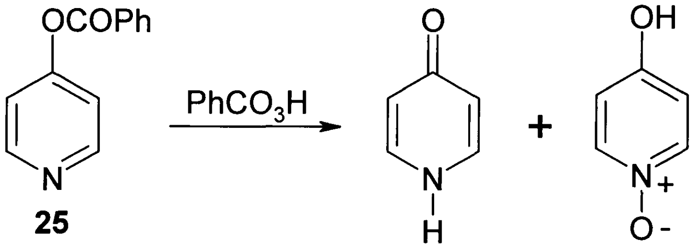


Scheme 6

The preparation of 2- and 4-epoxyethylenepyridine N-oxides by reaction[57] of 2- and 4-vinylpyridines with *m*-CPBA has been reported.

1.1.1.2.4 Other side reactions

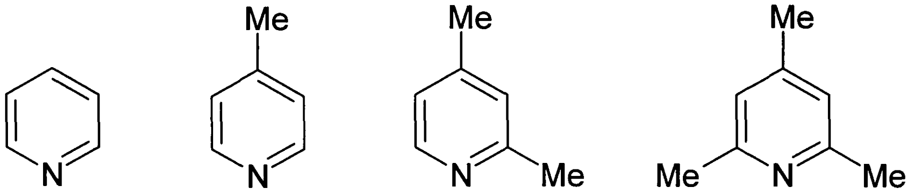
The use of hydrogen peroxide and acetic acid as reagents frequently causes hydrolysis of functional groups (acyloxy,[58] alkoxycarbonyl,[59] carboxyamido[60] or carbonitrile[61]) especially when heating is employed over long periods. It is possible to regard the reaction not merely as hydrolysis but as nucleophilic substitution[58, 59] by a peracid. This can usually be avoided by the use of aromatic peracids in nonpolar solvents[62] however, 4-benzoyloxypyridine **25** still undergoes hydrolysis even under these conditions[58] [equation 8].



Equation 8

1.1.1.2.5 Steric hindrance or electronic effects

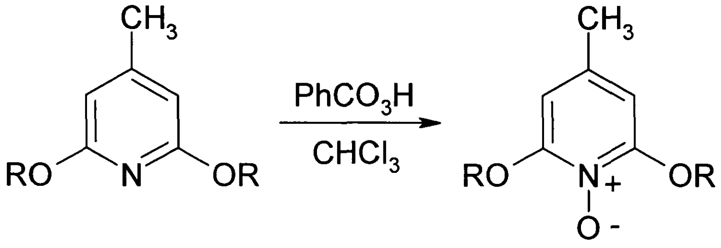
N-oxidation with a peracid is due to electrophilic attack by the peracid on the lone pair of the nitrogen. This is affected not only by the basicity of the nitrogen but also by steric or polar influences of adjacent or conjugated substituents. A study[63] of the N-oxidation of pyridine and some of its methyl homologues with perbenzoic acid has shown the reaction to be second order. Some typical rate constants are given below (25°C) [figure 4].



$Kx10^3 =$ 4.80 $s^{-1}mol^{-1}$ 7.25 $s^{-1}mol^{-1}$ 10.20 $s^{-1}mol^{-1}$ 10.20 $s^{-1}mol^{-1}$

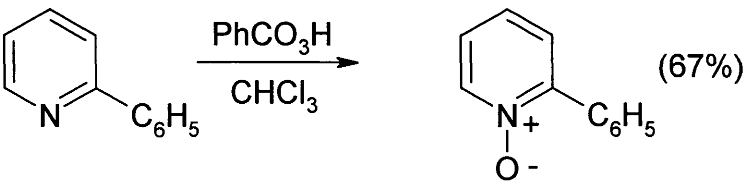
Figure 4

These figures indicate that the polar effects of methyl groups in the 2- and 4-positions increase the basicity of nitrogen and hence the ease of N-oxidation increases. The spatial hindrance of methyl groups in the 2- and 6- positions is only slight. Steric hindrance of an alkyl group becomes more pronounced within an alkoxyl group. In the following example the yield is low when R is methyl, but the reaction does not proceed at all when R is benzyl[64] [equation 9].

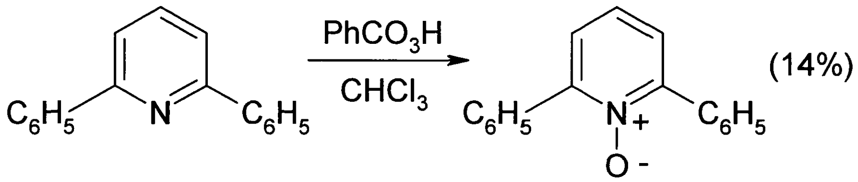


Equation 9

The steric hindrance of the methyl group is prevailed over by the polar effect in increasing the basicity of the nitrogen atom and promotes N-oxidation to a small degree. The basicity of the nitrogen is decreased by the introduction of a phenyl group into the 2-position [equation 10]. When phenyl groups occupy both the 2- and 6-positions the electronic effects becomes apparent[65] [equation 11]. When two of these groups are substituted in pyridine the availability of the unshared electron pair of the nitrogen for coordination with oxygen is sharply decreased.

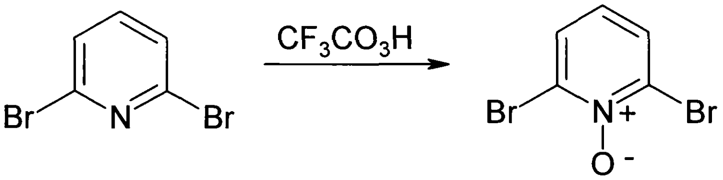


Equation 10



Equation 11

Halogens in the 2- and 6- positions strongly inhibit N-oxidation[29, 30] by polar effects. Such hindrance can be overcome[30] by the use of stronger oxidising agents, for example trifluoroperacetic acid [equation 12].

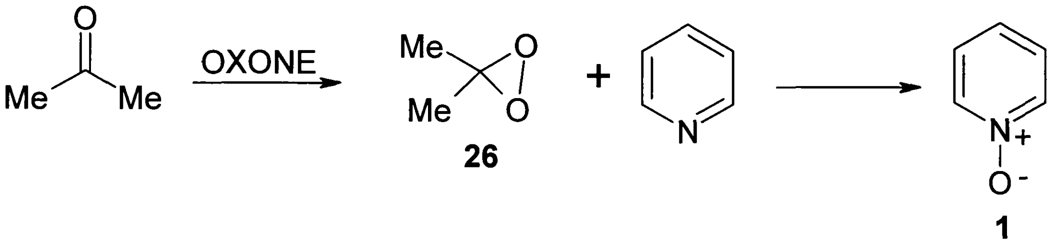


Equation 12

1.1.1.3 By direct oxidation with other reagents

Pyridine N-oxides have been obtained[66] by heating the pyridine and hydrogen peroxide alone in a sealed tube at 115-120 °C. Tris(2,2'-bipyridyl)iron(III) complexes were found[67] to disproportionate in basic solution to pyridine N-oxide iron(II) complexes.

Peroxymonosulphuric acid (Caro's acid[68]) has been found[69] to be effective in the N-oxidation of aminopyridines, removing the need for protection of the amino group and allowing the reaction to proceed under mild conditions. Potassium peroxomonosulphate (commercially available as OXONE[68]), when used in conjunction with acetone forms dimethyldioxirane **26**. This dioxirane when created *in situ* at a carefully controlled pH of between 7.5 and 9.0 affords pyridine N-oxide **1** in 96% yield[70, 71] [scheme 7].



Scheme 7

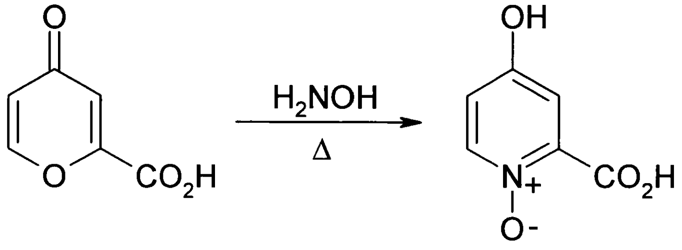
Addition of excess dimethyldioxirane **26** to a solution of a pyridine in ice cold dichloromethane[72] leads to quantitative yields of the corresponding pyridine N-oxide. When 4-dimethylaminopyridine is treated with dimethyldioxirane **26** the prepared N-oxide is partially deoxygenated[73] by excess dimethyldioxirane **26** in the reaction mixture. It is thought that nucleophilic attack by the N-oxide oxygen atom on the dioxirane peroxide bond takes place.

Pentachloropyridine when reacted[74] with sulphuric or polyphosphoric acid (PPA) and hydrogen peroxide (90%) only produced the N-oxide in 10% yield. A mixture of hydrogen peroxide and sodium tungstate[75,76] has been reported as effective and avoids some of the side reactions found when peracids are used. Hypochlorite under basic conditions[77], radiolysis[78] and photolysis[79] as methods for N-oxidation have also been mentioned in the literature. When hydrogen peroxide in the presence of catalytic amounts of methyltrioxorhenium[80] is used on 3- and 4-substituted pyridines, yields greater than 80% of the N-oxides were obtained. However, larger quantities of the catalyst were required for 2-substituted pyridines. The same group reported[81] the substitution of inorganic rhenium derivatives for methyltrioxorhenium and of bis(trimethylsilyl)peroxide for hydrogen peroxide in the N-oxidation of pyridines such as methyl isonicotinate. As well as being a useful reagent for N-oxidation, perfluoro-(cis-2,3-dialkyloxaziridine)[82] can also form N-aminides as a side reaction.

1.1.1.4 By synthesis of the heterocyclic ring

1.1.1.4.1 Intramolecular processes

γ-Pyrone and its derivatives have been used in the preparation of pyridine N-oxides. α,β-Unsaturated hydroxylamines are intermediates[83-87] in the synthesis of 4-hydroxylaminopyridine N-oxides from γ-pyrones. Heating coumaric acid with hydroxylamine gives 4-hydroxy-2-picolinic acid N-oxide[88] **27** [equation 13]. The same methodology has been utilized to prepare 5-ethoxy-4-hydroxy-2-picolinic acid N-oxide[89] and 2,6-diphenyl-4-hydroxypyridine N-oxide[90] from the corresponding appropriately substituted γ-pyrones.



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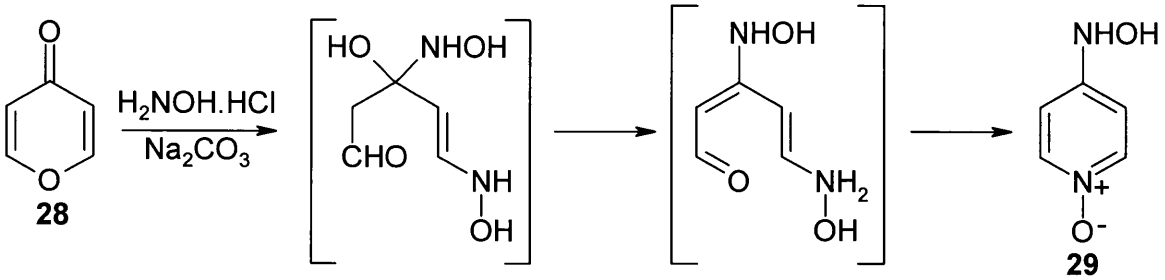
Equation 13

When γ-pyrone **28** and hydroxylamine hydrochloride in base were allowed to stand together at room temperature for a few days 4-hydroxyaminopyridine N-oxide **29** was produced in good yield[83] [scheme 8]. 4-Hydroxyamino-2,6-lutidine N-oxide **30** was prepared[84] by mixing the barium salt of the di-enol compound of diacetylacetone and hydroxylamine hydrochloride in ethanol and storing in a dark place. The same product was obtained from 2,6-dimethyl-γ-pyrone **31** by similar methodology[85] [scheme 9].



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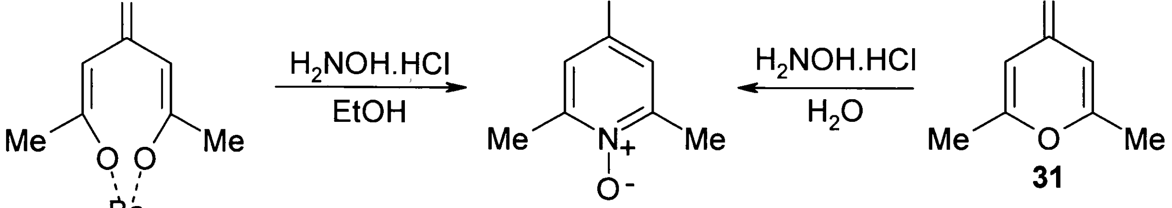
Scheme 8



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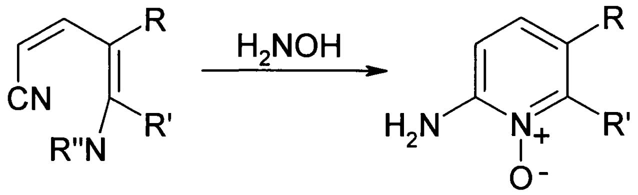
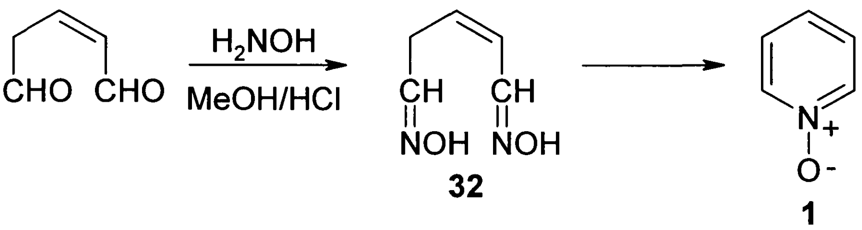
Scheme 9

Condensation of enaminonitriles with hydroxylamine leads to the formation of 2-aminopyridine N-oxides[91] [equation 14].



Equation 14

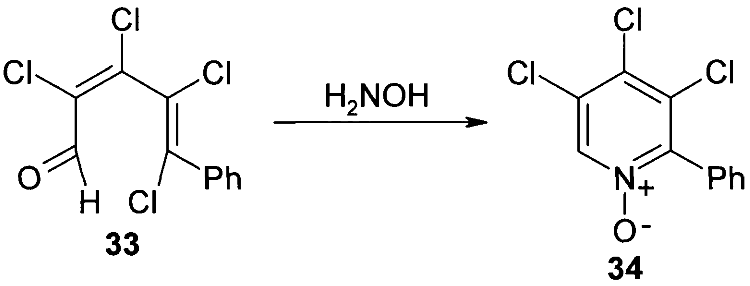
Reaction of glutaconaldehyde, a 1,5-dicarbonyl and hydroxylamine in acidic methanol leads[92] to the formation of **1**, via the dioxime **32** [scheme 10]. 4,4'-Azoxy-2,6-lutidine 1,1'-dioxide is likewise obtained[93] from diacetylacetone. This methodology is limited by poor availability of the required dicarbonyls. However 3-alkoxypyridine N-oxides have been prepared[94] from 6H-6-alkoxy-3-acyl-4,5-dihydro-1,2-oxazines via a nitrone intermediate.



32 **1**

Scheme 10

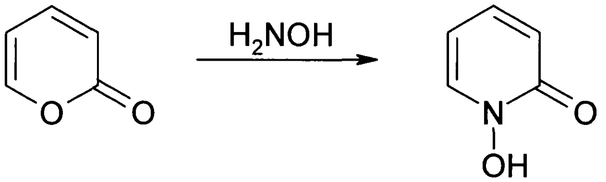
Ring closure via elimination may involve an unsaturated carbon and a heteroatom. Thus when 2,3,4,5-tetrachloro-5-phenyl-2,4,pentadienal **33** is treated with hydroxylamine, cyclisation with elimination of hydrochloric acid, gives 3,4,5-trichloro-2-phenylpyridine N-oxide[95] **34** [equation 15].



33 **34**

Equation 15

In a reaction course that is analogous to that seen with γ-pyrones, 2-pyrones are converted into 1-hydroxy-2-pyridone **35** by reaction with hydroxylamine[96, 97] [equation 16].

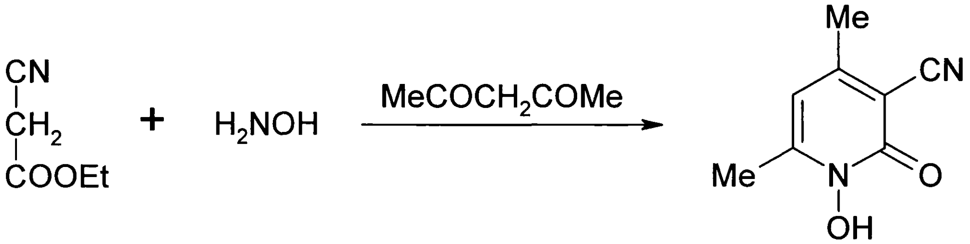


35

Equation 16

1.1.1.4.2 Intermolecular processes

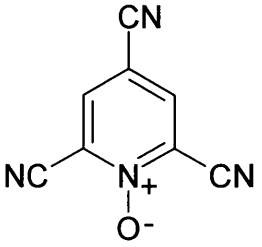
Ethyl cyanoacetate and hydroxylamine, react with acetylacetone in the presence of base, to give 1-hydroxy-3-cyano-4,6-dimethyl-2-pyridone[98] **36** [equation 17]. The yield is improved[99] when the preformed potassium salt of cyanoacetohydroxamic acid is used.



36

Equation 17

Cyclisation of aliphatic nitro compounds involves elimination of a leaving group, hence when the morpholino salt of 1,3,5-tricyano-1,3,5-trinitropentane dianion is reacted with sulphuric acid 2,4,6-tricyanopyridine N-oxide is formed[100] **37** [figure 5].



37

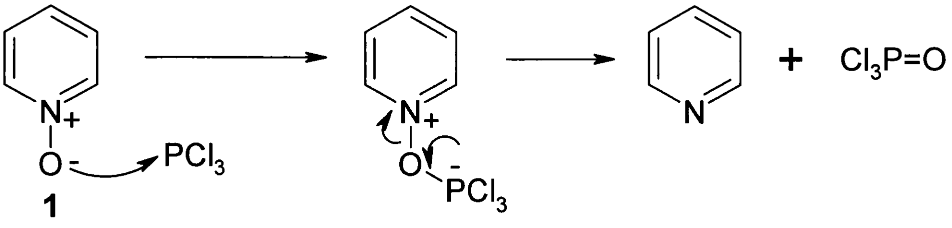
Figure 5

1.1.2 Reactions of pyridine N-oxides

1.1.2.1 Deoxygenation of pyridine N-oxides

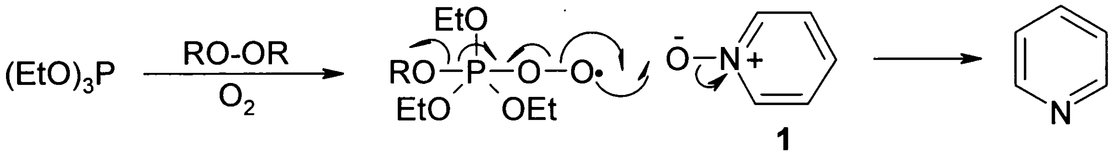
Deoxygenation of pyridine N-oxides has been effected by a variety of reducing agents. The reagent employed depends on the nature of any substituents on the pyridine ring, hence strong reducing agents should be avoided where easily reducible groups are present other than the N-oxide.

The most frequently used reducing agents are phosphorus (III) compounds particularly PX_3 (where X = Cl or Br). The mechanism is thought to involve nucleophilic attack on the electron deficient phosphorus atom followed by cleavage of the N-O bond[101-105] [equation 18].



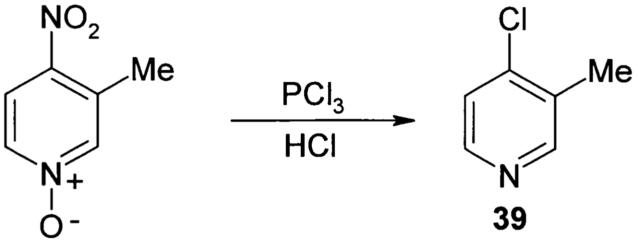
Equation 18

Triphenylphosphine[106] acts similarly although it is less reactive and heating is often required. The same reagent in the presence of catalytic amounts of molybdenum (IV) compounds has been found[107] to offer mild reaction conditions for deoxygenation. The use of triethylphosphite is facilitated[103, 108] by the presence of peroxide and oxygen and it is thought that a free radical mechanism is operating [scheme 11].



Scheme 11

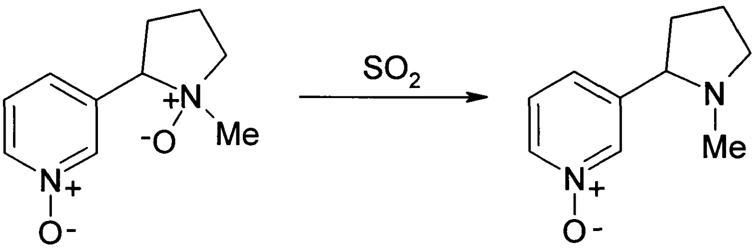
A nitro group in the α- or γ-positions is susceptible to substitution by a halogen when PX_3 is employed[108-111] however this is not the case[34] for the β position. While this may be desirable in some cases, deoxygenation alone[104] may be achieved by using lower temperatures and shorter reaction times. In the presence of hydrogen halide, substitution is highly favourable, hence if PCl_3 is reacted with 3-methyl-4-nitropyridine N-oxide **38** in hydrogen chloride saturated solvent[112] both deoxygenation and substitution of the nitro group take place to form 3-methyl-4-chloropyridine **39** [equation 19].



38 **39**

Equation 19

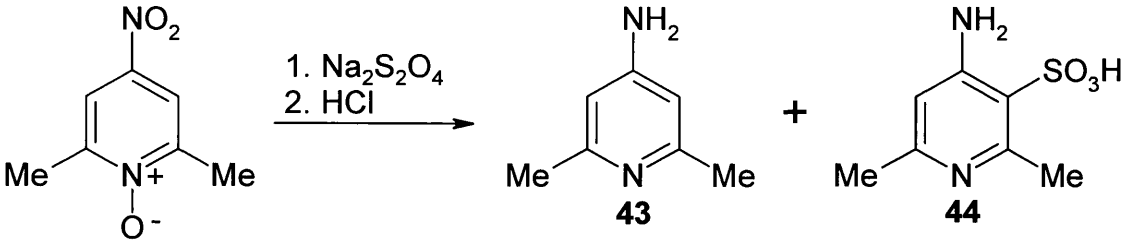
Heteroaromatic N-oxides are resistive[113] to reduction by sulphur dioxide or sodium sulphite at room temperature. This is useful for the selective deoxygenation[44] of, for example, nicotine 1,1'-dioxide **40** to nicotine 1-oxide **41** [equation 20], where the aliphatic tertiary amine oxide is exclusively reduced by sulphur dioxide.



40 **41**

Equation 20

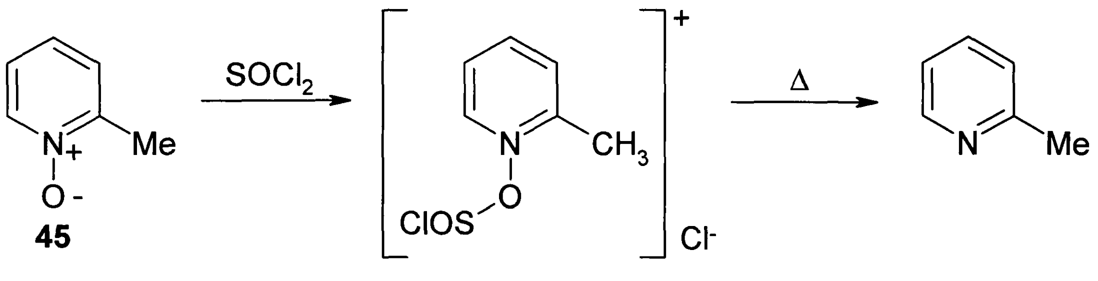
Although Relyea[114] reported that sulphur dioxide does not deoxygenate pyridine N-oxide **1**, it was subsequently shown that at higher temperatures[115] this reagent or a trimethyl(ethyl)amine sulphur dioxide complex[116] are effective. When reacted[117] with sodium hydrosulphite, sulphite or bisulphate, 4-nitro-2,6-lutidine N-oxide **42** is reduced to 4-amino-2,6-lutidine **43**. Additionally some 4-amino-2,6-lutidine-3-sulphonic acid **44** is formed in a side reaction [equation 21].



42 **43** **44**

Equation 21

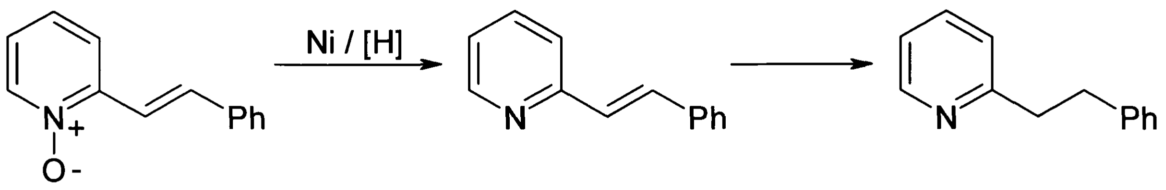
Arenesulphenyl and sulphinyl chloride[118-120] and thionyl chloride[121] all form quaternary salts with pyridine N-oxides which subsequently decompose on heating to give the free base. For example 2-picoline N-oxide **45** is reduced by thionyl chloride at reflux temperatures[121] in 92% yield [scheme 12].



Scheme 12

Sulpholenes[122] (2,5-dihydrothiophene-1,1-dioxides), as an alternative to sulphur dioxide, and trans-stilbene episulphoxide[123] (as an *in situ* source of sulphur monoxide), have both been reported as useful reagents for deoxygenation of pyridine N-oxides. Other notable reagents for this transformation in the pyridinic series include: dialkylsulphoxylates[129] (which react similarly to trialkylphosphites), dimethylsulphoxide (DMSO),[124] sulphur,[114, 125-127] mercaptans,[114, 128] thiophenol and thiourea[114] and diaryldisulphides.[129]

Catalytic reduction of the N-oxide group with reagents such as Raney[130-133] or Urushibara[134] nickel or palladium on charcoal[135] are relatively quick, high yield processes (although the last is by far the slowest). The reaction is slowed by α-substitution of the pyridine ring, such as in 2,6-lutidine N-oxide,[130] which is resistive due to steric effects. The formation of intramolecular hydrogen bonds in, for example, 2-hydroxypyridine N-oxide[130] also inhibits this reduction. 2-Styrylpyridine N-oxide **46** and similar compounds containing a conjugated carbon-carbon or nitrogen-nitrogen double bond when hydrogenated in the presence of nickel catalysts[133, 136] undergo deoxygenation prior to hydrogenation of the double bond [scheme 13].



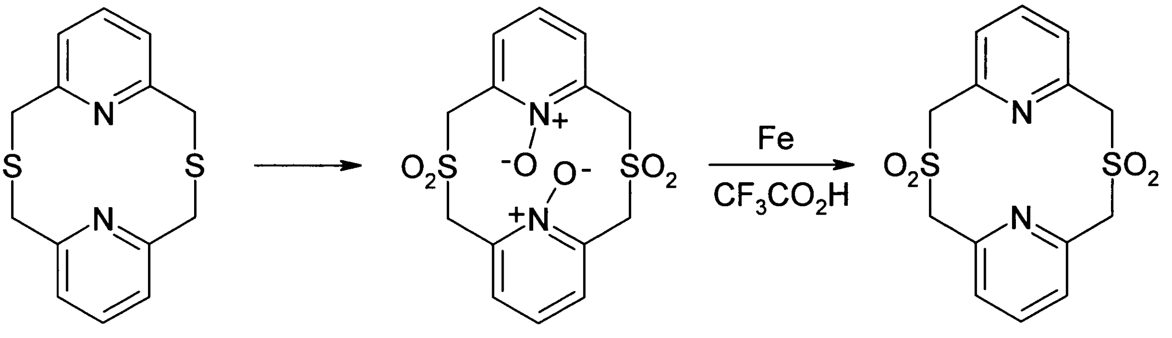
46

Scheme 13

Also known to occur subsequent to deoxygenation using these reagents are dehalogenation[132, 134] and hydrogenolysis of benzyloxyl[132-134] and acyloxymethyl[133] groups. This selectivity of Raney nickel is general and useful. When it is desirable to deoxygenate without reducing any other functional group present the reaction can be stopped after the absorption of one mole of hydrogen. Advantage can be taken of the relatively slow reduction of the N-oxide group by palladium on charcoal. Aminopyridine N-oxides can be prepared[133, 137-141] from their nitro precursors. Other catalytic hydrogenations of substituents preceding N-oxide reduction include azo to hydrazo and reduction of the azoxy group[136] and hydrogenolysis[133, 142] of alkoxy groups. Reduction of a nitro group to an amine with reduction of the N-oxide[117, 143-146] has been extensively reported.

Dissolving metals such as iron, zinc or tin under both acidic and basic conditions have been used widely[147-150] for the deoxygenation of pyridine N-oxides. Salts of iron (II) have also been reported[151, 152] for this reaction. Pyridine N-oxide **1** is completely reduced[153] to piperidine by nickel-aluminium alloy in sodium hydroxide solution. Nitro groups are reduced to amines under these conditions, and again, partial reduction of the nitro prior to deoxygenation of the N-O function[145, 154, 155] has been observed. Sulphones are resistive to these reagents[156, 157] hence it is expeditious, as in the case of pyridine derivative **47**, to oxidise to the disulphone

N,N'-dioxide then selectively N-deoxygenate[157] in this case using iron and trifluoroacetic acid [scheme 14].

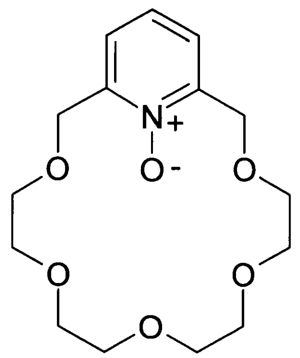


47

Scheme 14

Metal ions of low valency, molybdenum (III)[158] chromium (II)[159] and titanium (III)[160-162] typically, provide effective, mild conditions for deoxygenation. The products of hydride reduction of titanium (IV) chloride[163-166] or tungsten (VI) chloride[167] have also been reported for this reaction. Zinc in the presence of sodium iodide and trimethylsilylchloride[168] provide even milder conditions.

Pyridine N-oxides react with diborane and alkylboranes to give either a pyridine or a hexahydropyridine depending[169-172] on the choice of reagent employed. Tri(n-butyl)tin hydride and a free radical initiator have been reported[173] as effective in the deoxygenation of pyridine N-oxides. Pyridine N-oxide **1** has been reacted with mixed borohydrides[174, 175] with varying results. A single electron transfer (after complexation) mechanism has been proposed for the deoxygenation of crown ether **48** and its analog **49** [figure 6] on reaction[176] with potassium tri(*sec*-butyl)borohydride.



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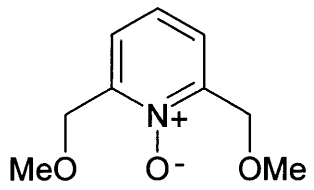


49

Figure 6

In the presence of fluorides[177] or methyllithium,[178] hexamethyldisilane and tetrabutyldichlorostannane[179] deoxygenate pyridine N-oxide **1**. Deoxygenation has also been reported[180] by heating with alcohols and sodium hydroxide. Thermal deoxygenation has been observed[181] in the case of 2-(2'-hydroxyphenyl)pyridine N-oxide. Deoxygenation is effected[182] by electrolysis at carefully controlled potential of pyridine N-oxide **1** in methanol solution using a mercury cathode. Enzymatic deoxygenation by xanthine oxidase[183] has also been reported.

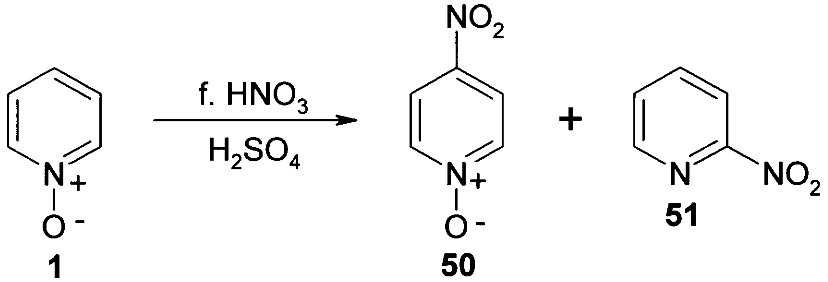
1.1.3.1 Electrophilic substitution

1.1.3.1.1 Hydrogen/deuterium exchange

Under neutral conditions, hydrogen/deuterium exchange, with D_2O at 180 °C, is observed in pyridine N-oxide **1** at the 2- and 6- positions[184] as the unprotonated N-O group is ortho/para directing. Similarly 3,5-dimethylpyridine N-oxide is deuterated at the 2-, 4- and 6- positions, while 2,6-dimethylpyridine N-oxide reacts at the 4-position under acidic conditions. At higher acidities 2,4,6-trimethylpyridine N-oxide and 2,6-dimethylpyridine N-oxide are deuterated[185] at the 3- and 5-positions.

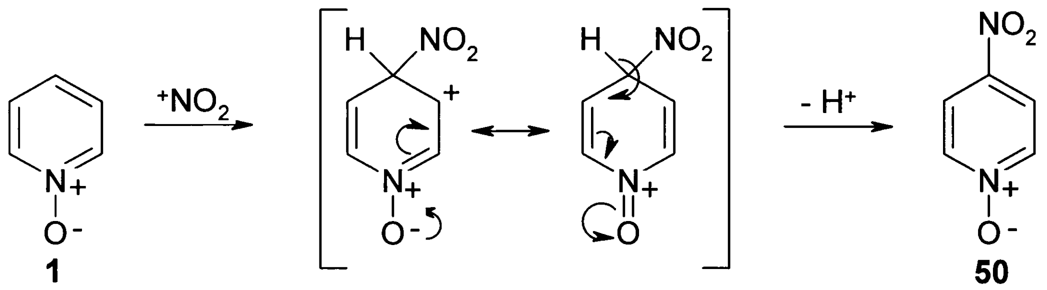
1.1.3.1.2 Nitration

This much studied reaction was first reported by Ochiai[186] and later by den Hertog[187] and produces 4-nitropyridine N-oxide **50** in yields up to 95% when pyridine N-oxide **1** is heated with a mixture of fuming nitric acid in sulphuric acid at 90 °C. Some 2-nitropyridine **51** is obtained as a by-product [equation 22].



Equation 22

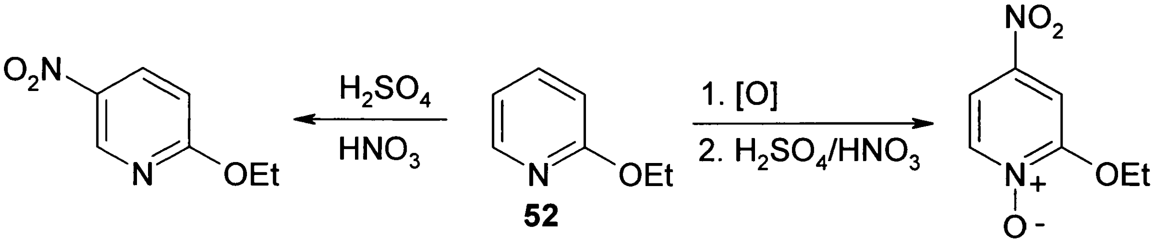
Nitration involves reaction between the nitronium ion and the non-protonated N-oxide function. As the N-oxide group is ortho/para directing, nitration takes place predominantly at the 4-position [scheme 15].



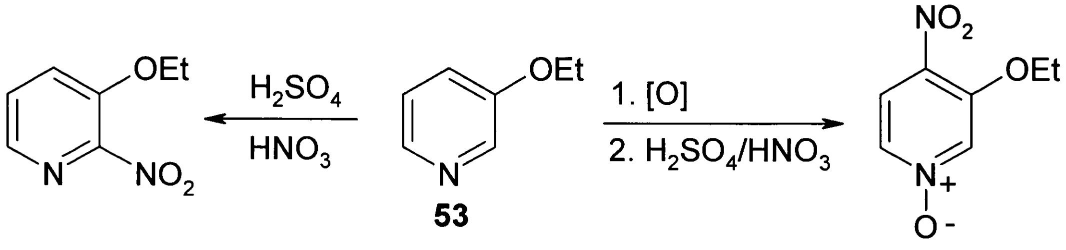
Scheme 15

4-Nitro derivatives of alkylpyridine N-oxides have been prepared[146, 188-190] by the same nitration reaction, however when the 4- position is occupied no reaction takes place[191] under these conditions. The presence of an alkyl group in the 2-

position, due to the inductive effect, increases the electron releasing effect of the N-O group and promotes nitration in the 4-position. An alkyl group in the 3-position causes slight steric hindrance. In the case of 3-*t*-butylpyridine N-oxide, nitration takes place at the positions α- to the nitrogen[190] and deoxygenated 3-*t*-butyl-2- or 3-*t*-butyl-6-nitropyridines that are formed. Steric hindrance is less for halogens, e.g. Cl or Br, as both 3,5- and 2,6-disubstituted pyridine N-oxides give 4-nitro derivatives[192-195] in good yield. The orientating effect of the N-oxide group is larger than that of an alkoxy group towards nitration. For example, 2-ethoxypyridine **52** gives[196-198] 5-nitro-2-ethoxypyridine while the corresponding N-oxide is nitrated[192] at the 4-position, and for 3-ethoxypyridine **53** nitration takes place[199-201] at the 2- position whereas for the N-oxide[192] the reaction is at the 4-position [schemes 16 and 17].

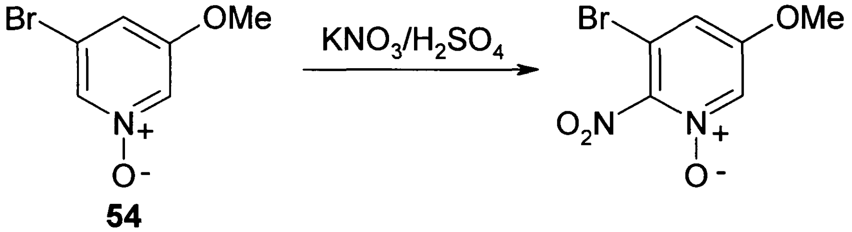


Scheme 16



Scheme 17

Similarly for 2- and 3-methoxypyridine N-oxides, nitration[202] is at the 4-position. It has been reported[195, 203-205] however that some substituted 3-alkoxypyridine N-oxides are nitrated in the 2- or 6-positions, for example, in the case of 3-bromo-5-methoxypyridine N-oxide **54**, reaction[202] is at the 2-position [equation 23].

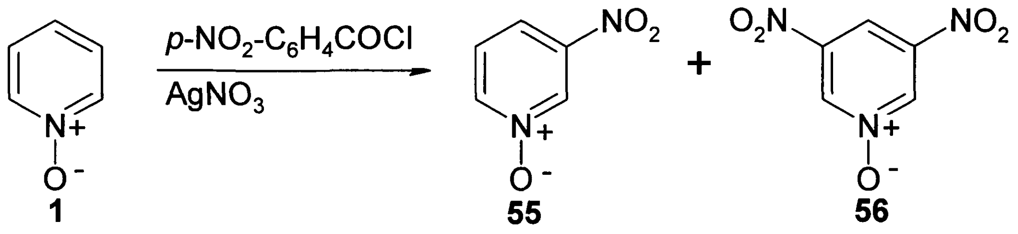


54

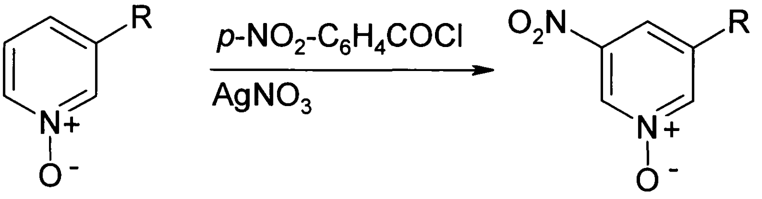
Equation 23

Hydroxyl groups have a predominating effect over that of the N-oxide so positions ortho and para to the hydroxyl are nitrated. Examples being: nitration in the 2-position[206] of 3-hydroxypyridine N-oxide, in the 3- and 5- positions of 4-hydroxypyridine N-oxide[207] and in the 5- position[208] of N-hydroxy-2-pyridone. Examination[209, 210] of the nitration of 2-, 3- and 4-phenylpyridine N-oxides shows that substitution only occurs in the phenyl rings and not at the 4-position of the pyridine ring. The site nitrated is dependant on the position of the phenyl group on the pyridine ring. The N-oxides of 2- and 4-phenylpyridine are substituted mainly at the meta position of the phenyl ring, while 3-phenylpyridine N-oxide is substituted almost exclusively at the para position. It has also been shown[209] that N-oxidation increases the rate of meta substitution and decreases para substitution when compared to the corresponding phenylpyridines.

If *p*-nitrobenzoylchloride and silver nitrate are employed, 3-nitropyridine N-oxide **55** and 3,5-dinitropyridine N-oxide **56** are each produced in approximately 10% yield[211] [equation 24]. The presence in the ring of a nitrile or ethyl ester group in the 3-position[212] increases the yields of the corresponding 5- nitro derivatives to 40–50% [equation 25].



Equation 24

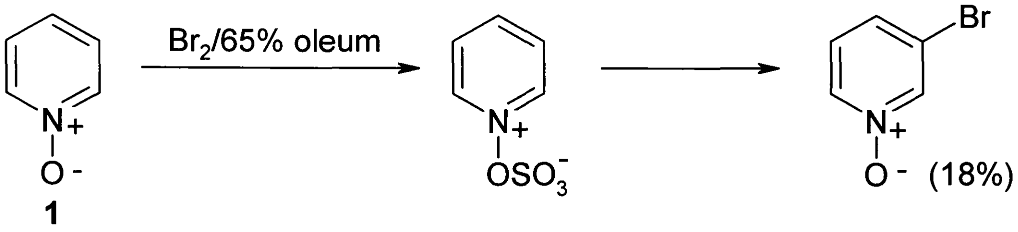


R = CO_2Et, CN

Equation 25

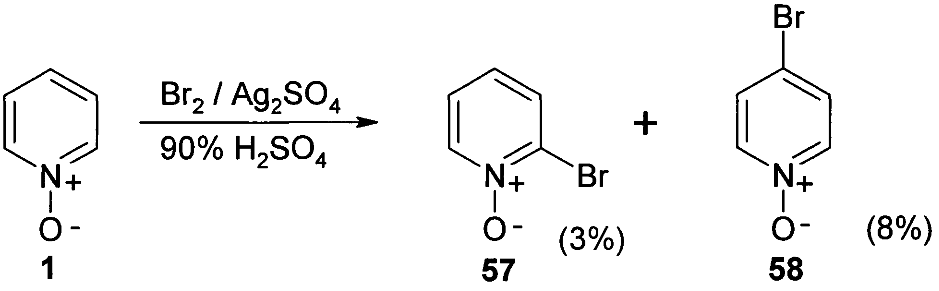
1.1.3.1.3 Bromination

Direct bromination[213] of pyridine N-oxide **1** takes place at the 3- position under acidic conditions via the N-O / SO_3 complex [scheme 18].



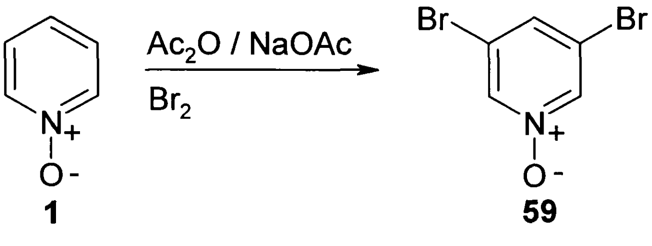
Scheme 18

However if bromine together with silver sulphate (a source of bromonium ions) in 90% sulphuric acid is used a mixture of 2-bromopyridine N-oxide **57** and 4-bromopyridine N-oxide **58** is formed[214] [equation 26].



Equation 26

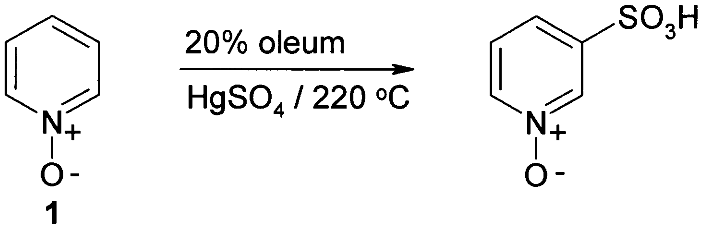
4-Bromination of 2,6-dimethylpyridine N-oxide has been achieved in 49% yield using bromine in the presence of thallium (III) acetate, however these conditions[215] will not brominate pyridine N-oxide **1** or 2-methylpyridine N-oxide. When a strongly electron-donating group such as an amino[216] or hydroxy[208, 217, 218] group is present, bromination is directed ortho or para to that group. Less activating species (alkoxy) only influence bromination[216] when there is correspondence with the effect of the N-oxide function, so the only methoxypyridine N-oxide that is reactive is the 3- isomer. Generally under acylating conditions bromination takes place in the 3- position however pyridine N-oxide **1** with bromine in the presence of acetic anhydride and sodium acetate is converted to 3,5-dibromopyridine N-oxide **59** in 35% yield[219] [equation 27].



Equation 27

1.1.3.1.4 Sulphonation

Sulphonation occurs with difficulty and at the 3- position[220-222] when pyridine N-oxide **1** is reacted with fuming sulphuric acid and mercuric sulphate at high temperatures [equation 28].



Equation 28

1.1.3.1.5 Other electrophilic substitutions

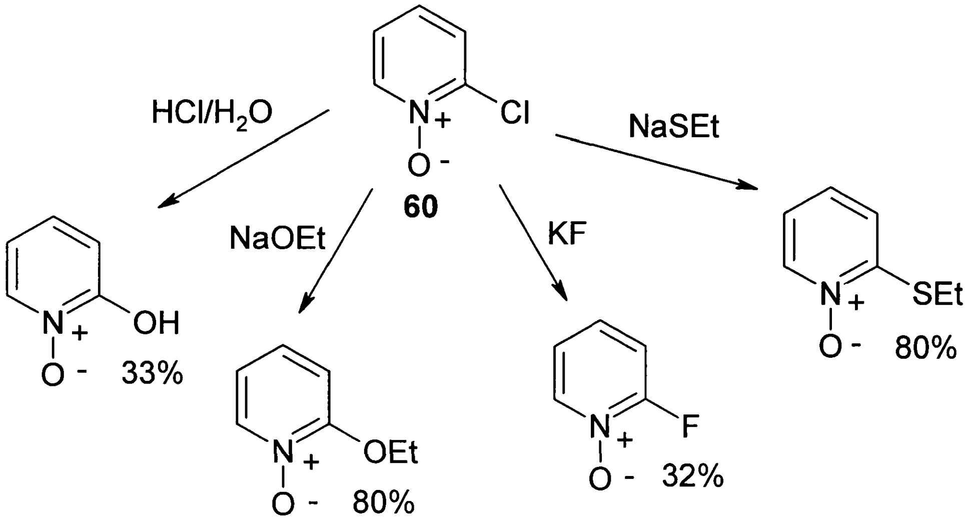
When mercury (II) acetate is employed, mercuration takes place predominantly at the 2-position of pyridine N-oxide **1** with some 3- isomer produced. The yield of the 3-isomer is improved[223] if mercuric sulphate in sulphuric acid is used. Benzylation in the 3-position is reported when pyridine N-oxide **1** is reacted with benzyl chloride and aluminium chloride[224] and nitrosation,[225, 226] coupling with diazonium salts[211] and aminomethylation[227-230] have all been reported on hydroxy- or amino- substituted pyridine N-oxides.

1.1.3.2 Nucleophilic substitution

Nucleophilic substitution generally occurs when there is a leaving group α– or γ– to the N-oxide function, usually through the addition-elimination mechanism. In some cases a leaving group in the β position is sufficiently activated towards nucleophiles. As the rate of reaction is notably increased, over the free base, it is often advantageous to carry out the substitution on the N-oxide and then deoxygenate. Direct substitution onto the ring with loss of H$^-$ is also possible, either with or without deoxygenation.

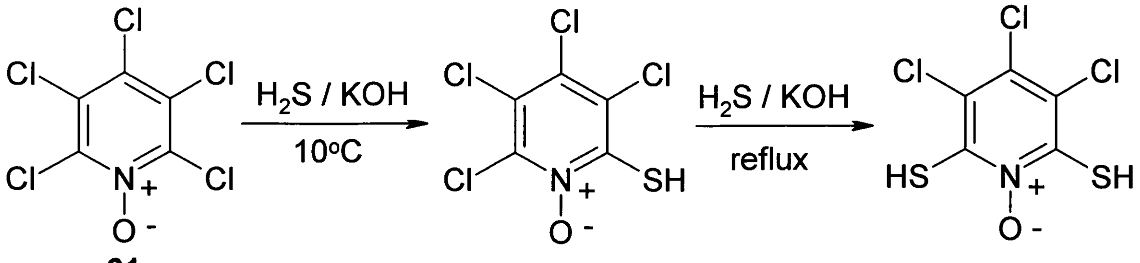
1.1.3.2.1 Substitution of a leaving group

Nucleophilic substitution is easier at the α– or γ-positions when a good leaving group in these positions is coupled with N-oxidation, which enhances the electron withdrawing effect of the ring nitrogen. Hence, 2-chloropyridine N-oxide **60** reacts readily with nucleophiles such as hydroxy,[219] ethoxy,[231] fluoride,[232] and ethylmercapto[219] [scheme 19].



Scheme 19

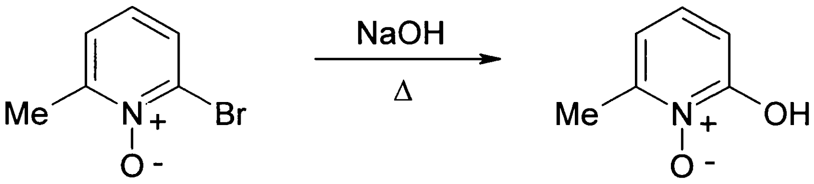
When pentachloropyridine N-oxide **61** is treated[233] with hydrogen sulphide and base, substitution only takes place at the 2-position. Further reaction at reflux leads to 2,6-disubstitution only [scheme 20].



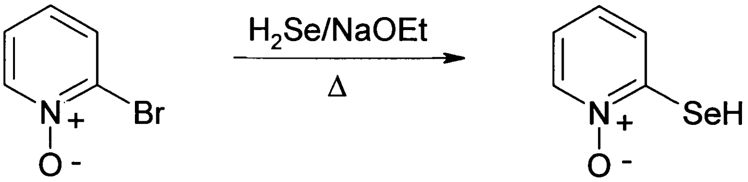
61

Scheme 20

Similar reactions take place when a bromo atom is in the 2-position. Substitution by hydroxy[234] [equation 29] or selenyl[235] [equation 30] groups is readily achieved under mild conditions.

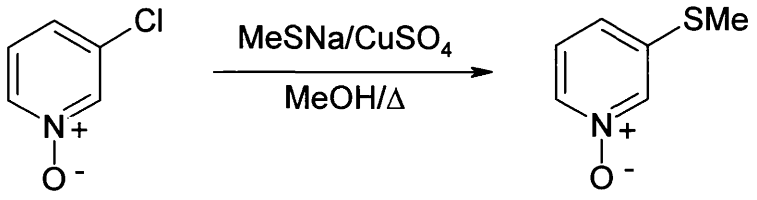


Equation 29



Equation 30

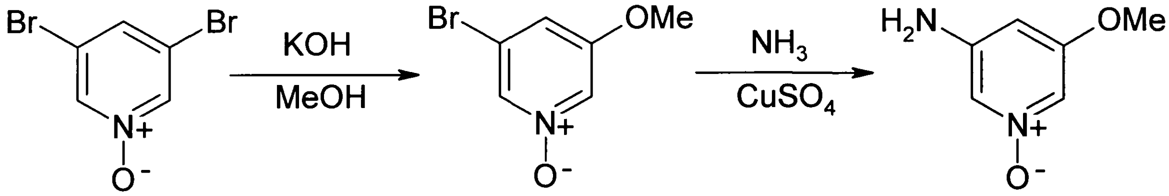
The β-position of the pyridine N-oxide is activated by the inductive effect of the N-oxide and so leaving groups at this position will be substituted by nucleophiles, although under more severe conditions than for the 2- or 4-positions. For example, 3-chloropyridine N-oxide **62**, when heated with sodium methylsulphide and copper sulphate[236] in methanol, produced 3-pyridylmethylsulphide N-oxide **63** in 60% yield [equation 31].



62 **63**

Equation 31

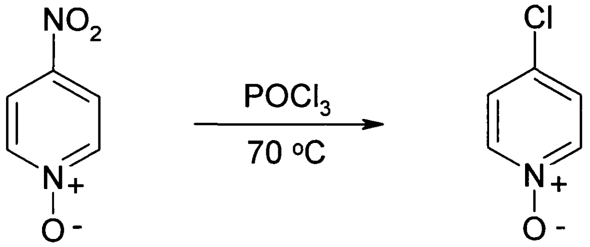
3,5-Dibromopyridine N-oxide **59** is transformed stepwise into 3-methoxy-5-aminopyridine N-oxide **64** by reaction first with potassium hydroxide in methanol, then with ammonia in the presence of copper sulphate[237] [scheme 21].



59 **64**

Scheme 21

4-Nitropyridine N-oxide **50** yields 4-chloropyridine N-oxide **65** on reaction with phosphorus oxychloride[238] at 70 °C [equation 32] (however, deoxidative chlorination is usually observed with this reagent).

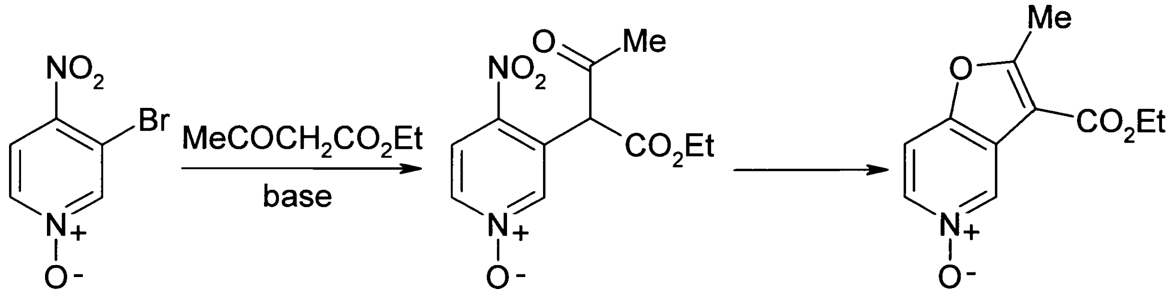


50 **65**

Equation 32

Substitution with other nucleophiles such as bromide[239] and ethoxide[240] also take place under mild conditions. Carbanions derived from compounds containing a methylene activated by adjacent electron withdrawing groups, such as phenylacetonitrile, nucleophilically substitute[241] the leaving group in 4-chloropyridine N-oxide **65** or 4-nitropyridine N-oxide **50**.

When there are two different leaving groups in the α- and γ-positions, substitution depends on the nature of the nucleophile employed. In one example, with 2-halo-4-nitropyridine N-oxides,[242] the halogen is replaced by amines and the nitro by alkoxides. In the case of 3-fluoro-4-nitropyridine N-oxide, oxygen, nitrogen and sulphur nucleophiles replace the fluoro group, while the nitro is replaced[243] by halides. Another example, in 3-halo-4-nitro-2,6-dimethylpyridine N-oxides it is the nitro proup that is substituted[244] by oxygen, nitrogen and sulphur nucleophiles. When 3-bromo-4-nitropyridine N-oxide **66** is treated[245, 246] with the carbanion of ethylacetoacetate, substitution of the bromo group takes place first, then a secondary intramolecular substitution by the enol leads to 3-ethyloxycarbonyl-2-methylfuro[3,2-c]pyridine N-oxide **67** [scheme 22].

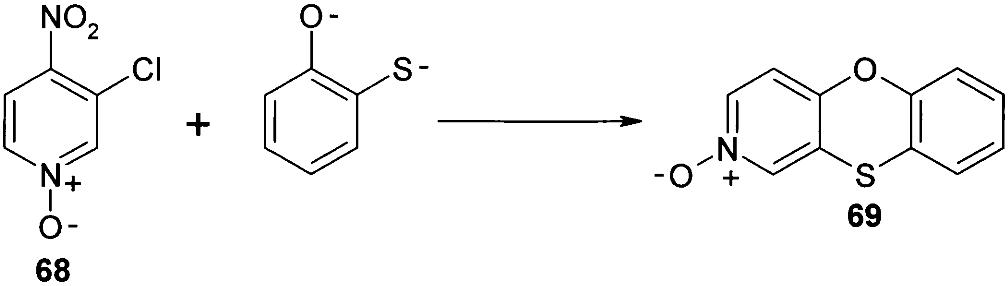


66

67

Scheme 22

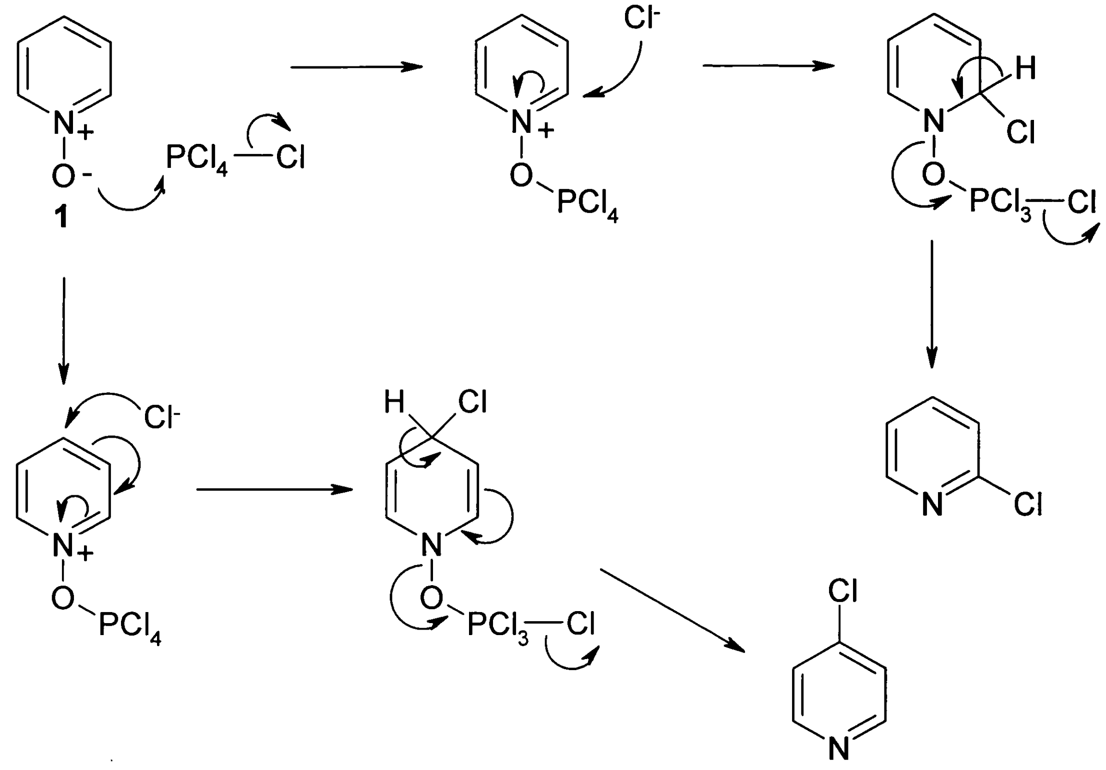
Condensation between aromatic or heterocyclic dianions with 3-chloro-4-nitropyridine N-oxide **68** allows entry to polyheterocycles. When the nucleophile[247-250] is the dianion of 2-hydroxythiophenol, the first substitution is of the chloro group by the sulphur anion then the oxygen anion replaces the nitro to form the N-oxide **69** [equation 33].



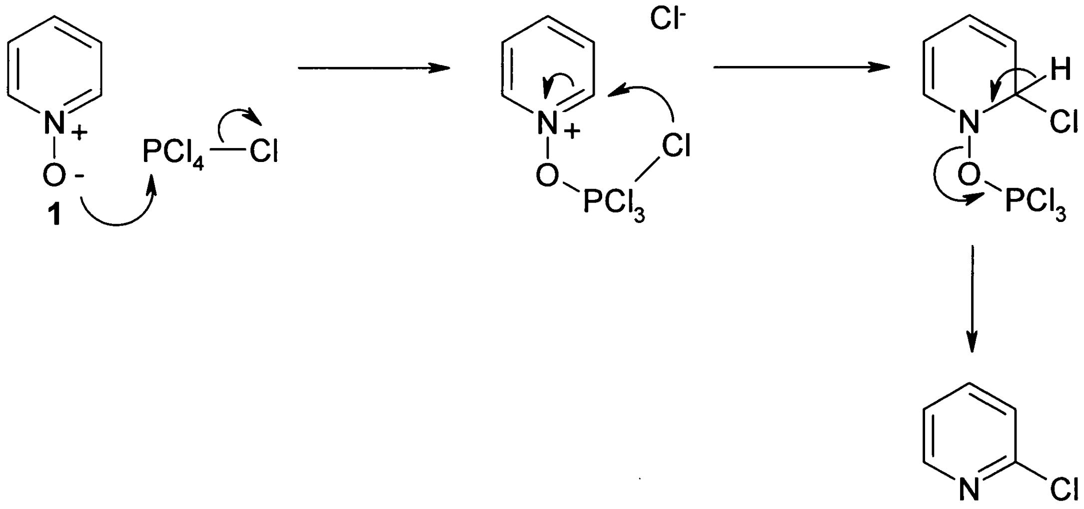
Equation 33

1.1.3.2.2 Halogenation

Treatment of pyridine N-oxide **1** with phosphorus (V) or sulphur (VI) halides such as phosphorus pentachloride, phosphorus oxychloride or sulphuryl chloride leads to the formation of halogenopyridines where the substitution takes place exclusively at the 2- and 4- positions and is known as the Meisenheimer[10] reaction. In the case of the halogenation of pyridine N-oxide **1** with phosphorus pentachloride the reaction proceeds by either an intermolecular mechanism, attack by a separated anion after electrophilic attack on the oxygen atom [scheme 4], or an intramoleclar mechanism involving concerted shift or recombination of the O-phosphorylated pyridine-chloride ion pair [scheme 23].



Scheme 23



Scheme 24

Choice of reagent is important as different product ratios[251, 252] are observed with different reagents on reaction with pyridine N-oxide **1** [table 1].

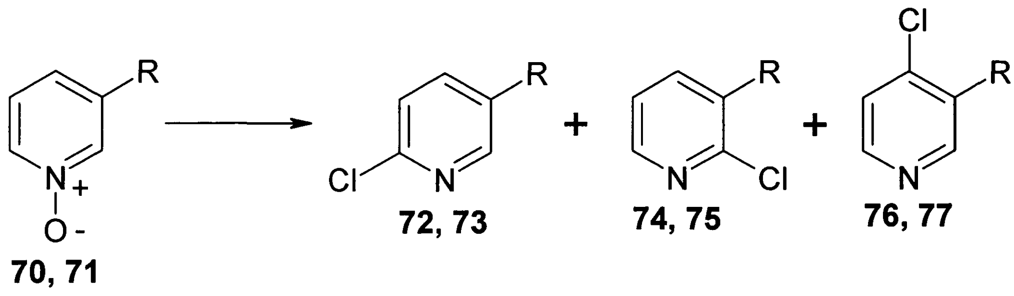
Reagent	2-Cl (%)	4-Cl (%)
SO_2Cl_2[252]	57	43
PCl_5[251]	41	58
$POCl_3$[251]	68	32

Table 1: Product Ratios by Reagent

When a stoichiometric amount of triethylamine is added to the reaction[253] of phosphorus oxychloride with pyridine N-oxide **1** chlorination is directed almost exclusively to the 2-position in 90% yield. With sulphur (VI) chlorides the same is observed although the yields are lower.

Substituents on the ring affect the regioselectivity of this reaction. 4-Substituted pyridine N-oxides are, for the most part, 2-halogenated. Notable exceptions include 4-cyanopyridine N-oxide[254] which gives 3-chloro-4-cyanopyridine, and 4-nitropyridine N-oxide[255, 256] which undergoes substitution at the 4-position. For groups at the 3-position, 2-halogenation usually[257-259] takes place exclusively.

In the cases of ethyl 3-pyridylacetate N-oxide **70** and pyridine-3-acetonitrile N-oxide **71**, competition between the inter- and intramolecular mechanisms leads to mixtures of the 2-, 4- and 6-chlorinated pyridines[260,261] [equation 34]. The ratio of isomers differs for each substituent at the 3-position [table 2].



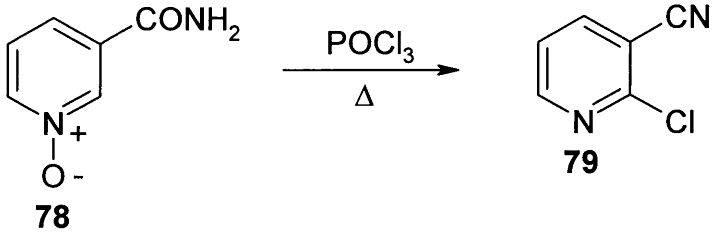
70, 72, 74, 76; R = CH_2CO_2Et and **71, 73, 75, 77**; R = CH_2CN

Equation 34

Substitution pattern	R = CH_2CN (%)	R = CH_2CO_2Et (%)
2,5- (**72**, **73**)	21	22
2,3- (**74**, **75**)	37	33
3,4- (**76**, **77**)	5	13

Table 2: Product Ratio by Substituent at C-3

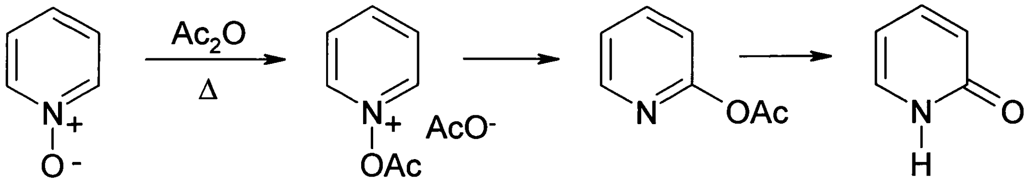
A phenyl[262] or methyl[263] group at the 2-position allows chlorination at the 4-position, but the 6-position is substituted when a chloro[219] or carboxy[264] is in the 2-position. When 2- or 4-hydroxypyridine N-oxides are reacted with phosphorus oxychloride substitution[265] of the hydroxy group takes place. An amide is dehydrated to a cyano group during chlorination, which takes place at the 2-position, as in the case of the chlorination[266] of nicotinamide N-oxide **78** which yields 2-chloro-3-cyanopyridine **79** [equation 35] and similarly[267] for isonicotinamide N-oxide which gives 2-chloro-4-cyanopyridine.



Equation 35

1.1.3.2.3 Formation of hydroxy or acyloxypyridines

Pyridine N-oxides are easily N-acylated by acetic anhydride to form acetate salts which rearrange to α-acetylypyridines and are then hydrolysed to the corresponding 2-pyridone derivative. This is known as the Katada[268] reaction and when it is applied to pyridine N-oxide **1**, 2-pyridone **35** is produced in 60% yield [scheme 25].



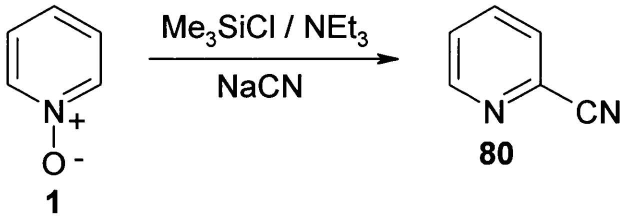
1 **35**

Scheme 25

Leaving groups such as chloro, ethoxy or phenoxy in the 2-position[219] are easily replaced, while 3-substituted pyridine N-oxides generally give[269] the corresponding 3-substituted-2-pyridones, but 3-methylpyridine N-oxide[270, 271] yields a mixture of 3- and 5-methyl-2-pyridones.

1.1.3.2.4 Cyanation

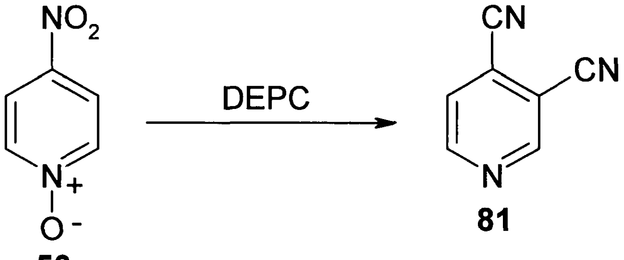
Cyanation is most conveniently carried out by a variation of the Reissert-Henze reaction, which employs silicon or phosphorus cyanides such as trimethylsilanocarbonitrile[272, 273] (TMSCN) or diethylphosphorocyanidate[274] (DEPC). Hence, pyridine N-oxide **1** is converted exclusively to 2-cyanopyridine **80** [equation 36], by TMSCN, which can be generated *in situ* from trimethylsilylchloride, sodium cyanide and triethylamine.



1 **80**

Equation 36

Exclusive 2-cyanation takes place when there is a halo, amino or alkoxy group in the 3-position, however when this position is occupied by an aryl, carbonyl or cyano group, either 2- or 6-substitution[275, 276] occurs. 4-Nitropyridine N-oxide **50** gives 3,4-dicyanopyridine **81** with DEPC[274] [equation 37].



50

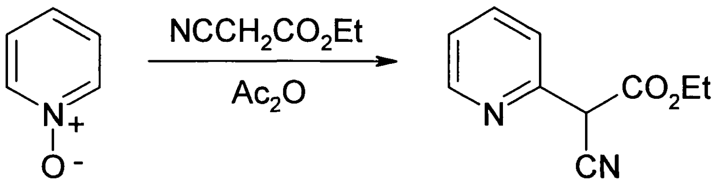
81

Equation 37

Cyanopyridines are also obtained by reaction of aqueous potassium cyanide on N-alkoxypyridines. Substituents in the 4-position lead to 2-cyanated pyridine derivatives[277, 278] while 3-alkylpyridine N-oxides give mixtures of 2-, 4-, and 6-cyanated pyridines[279, 280] and the ratios depend on both the substituent and the alkylating agent.

1.1.3.2.5 Alkylation

Pyridine N-oxides do not react directly with stabilised carbanions of the malonic ester type. However, in the presence of an acylating agent[281] such as acetic anhydride, which also acts as solvent, deoxidative alkylation takes place under mild conditions. For example, pyridine N-oxide **1** is deoxygenated and alkylated in the 2-position by ethyl cyanoacetate in the presence of acetic anhydride [equation 38].



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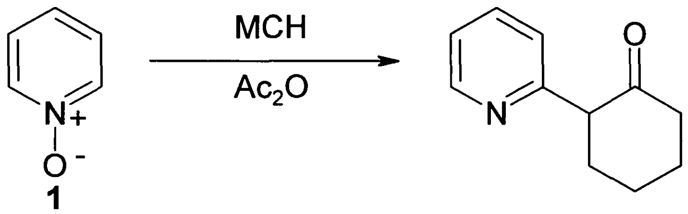
Equation 38

Enamines[282-286] also react with pyridine N-oxides, again in the presence of acylating reagents. Pyridine N-oxide **1** is alkylated at the 2-position[282] by morpholinocyclohexene (MCH) [equation 39], while for 2-methylpyridine N-oxide **45** the reaction takes place at the 6-position[283] [equation 40].



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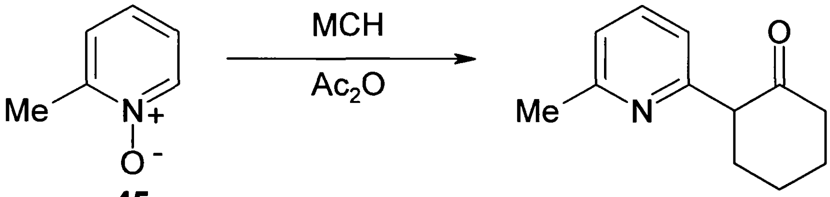
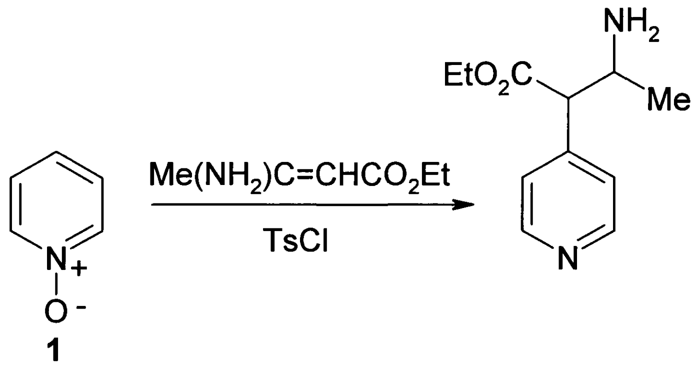
Equation 39



45

Equation 40

When pyridine N-oxide **1** is activated by *p*-toluenesulphonylchloride (TsCl), substitution[287] with ethyl 3-aminocrotonate takes place at the 4-position [equation 41].



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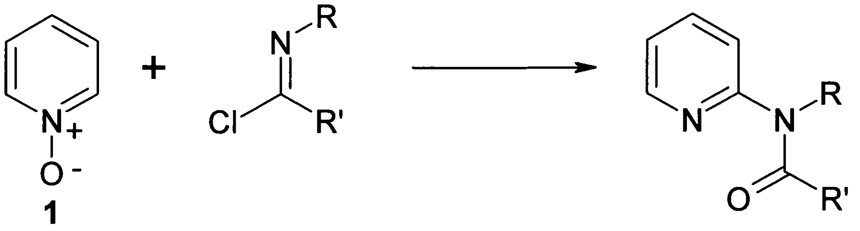
Equation 41

Grignard reagents, as strong nucleophiles, react[288] with N-alkoxypyridines to give a mixture of 2- and 4-alkylated pyridines. For N-alkoxycarboxypyridines,[289] prepared *in* siyu from the N-oxide and a chlorocarbonate, the reaction occurs exclusively at the 2-position. It has also been reported[290] that organozinc compounds react similarily.

1.1.3.2.6 Formation of carbon–heteroatom bonds

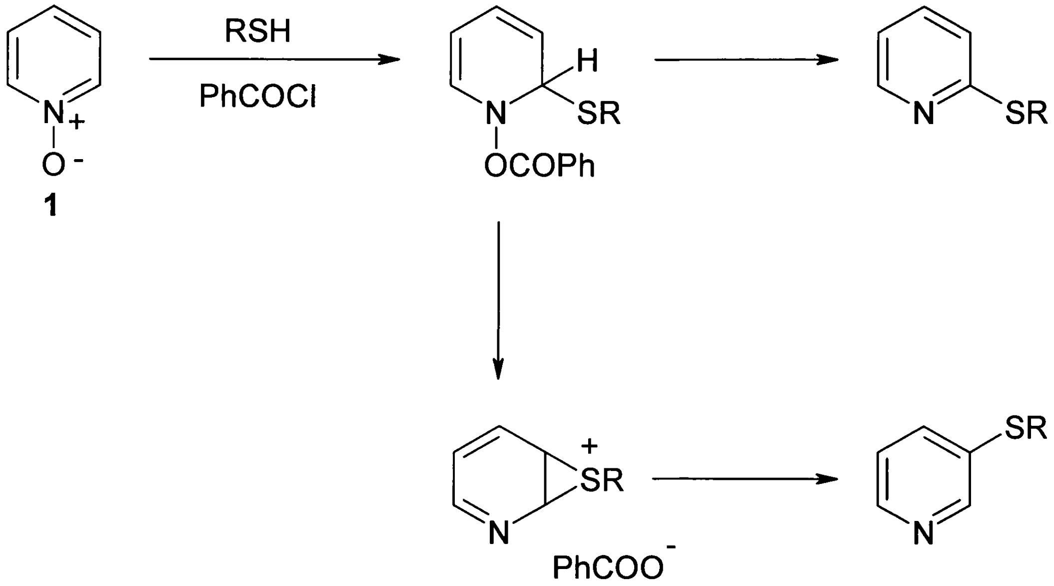
Amines are generally too weak nucleophiles for direct reaction but substitution can occur when good leaving groups are present and deoxygenation also usually occurs. Activation by tosyl or benzoylchlorides enhances deoxygenated amination for reagents such as ammonia,[291] amines[292, 293] and sulphonamides.[292] An example of a bifunctional reagent giving deoxidative substitution, rather than nucleophilic attack promoted by an auxiliary electrophilic reagent[294-297] is pyridine N-oxide **1** reacting with an imidoylchloride to give an acylaminopyridine [equation 42].



Equation 42

The nature of a substituent[297] in the 3-position has a directing effect on acylamination, hence for 3-methylpyridine N-oxide reaction takes place largely at the 2-position, while substitution occurs at the 6-position in 2-methoxypyridine N-oxide. Insufficiently basic N-oxides[294] such as 4-nitropyridine N-oxide **50** do not react.

Pyridine N-oxide **1** when reacted with thiols in the presence of auxiliary acylating agents[298] such as benzoylchloride or acetic anhydride, give 2- and 3-pyridylsulphides [scheme 26].

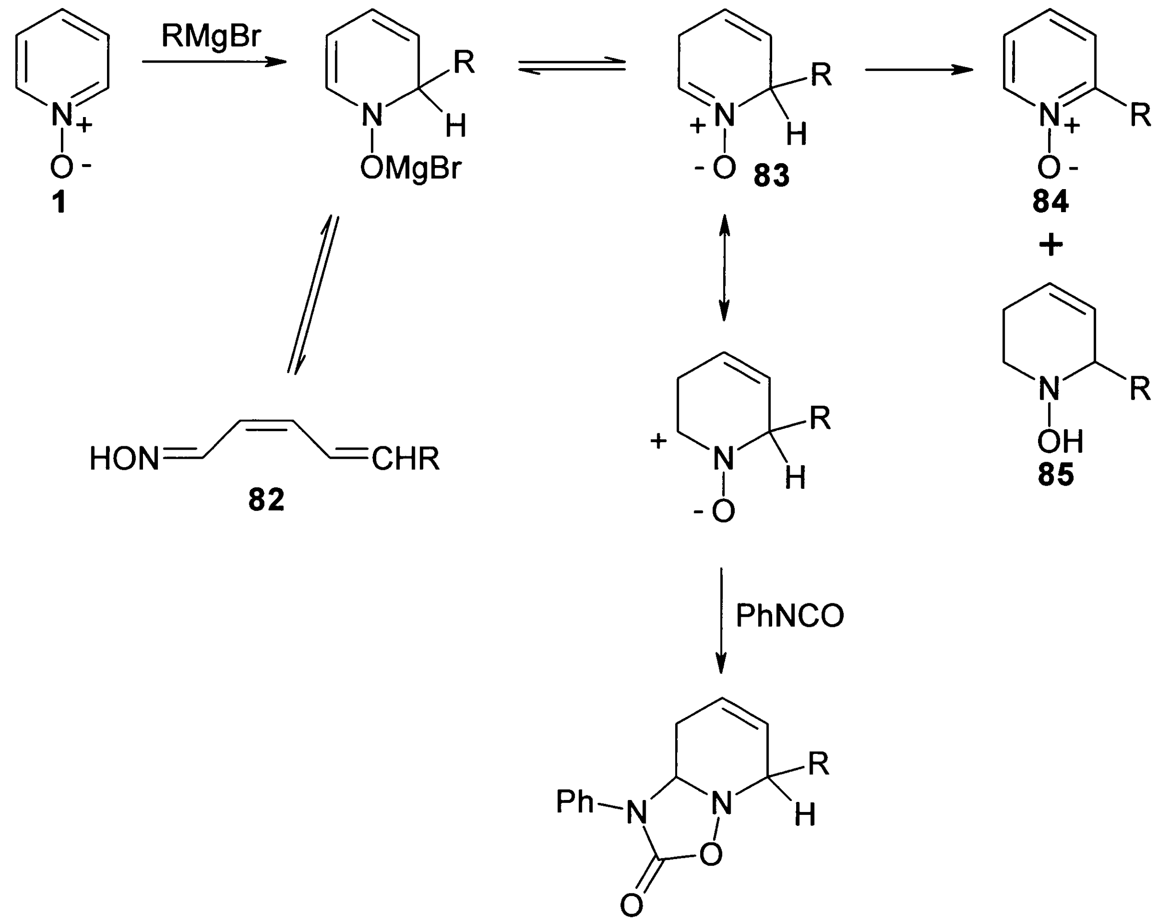


Scheme 26

If the 2-position is occupied, as in 2-methylpyridine N-oxide **45**, then substitution takes place[299] at the 5- and 6-positions. A mixture of 2-, 5- and 6-pyridylsulphides is obtained from 3-methylpyridine N-oxide[299] and with 4-methylpyridine N-oxide, substitution again occurs[299] at the 2- and 3- positions.

1.1.3.2.7 Ring cleavage

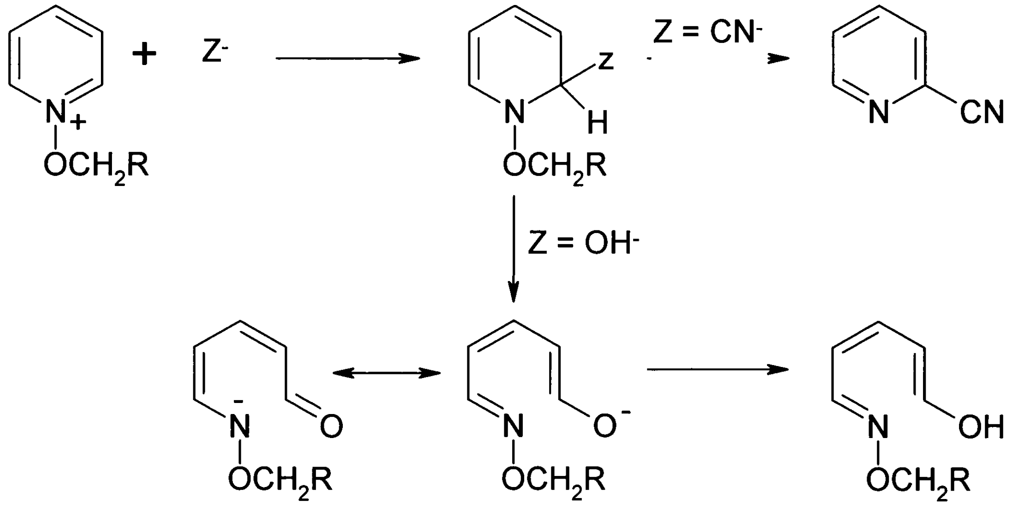
The reaction of pyridine N-oxide **1** with Grignard reagents, when carried out at -40 °C leads to the formation of an adduct that ring opens to a conjugated oxime **82**. However, protonation of the adduct gives a 2,5-dihydropyridine N-oxide **83** that can be either trapped with phenylisocyanate or allowed to disproportionate to a 2-substituted pyridine N-oxide **84** and its tetrahydro derivative **85**[300] [scheme 27].



R = Alkyl or Phenyl

Scheme 27

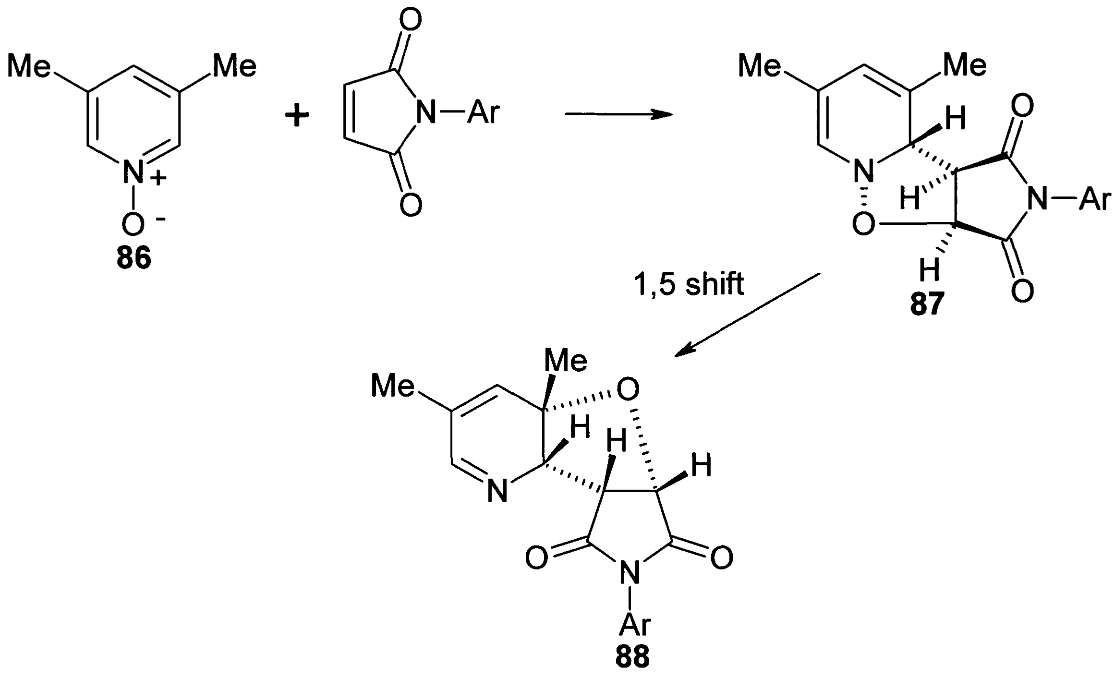
Reaction of N-alkoxypyridines with a base[301, 302] can lead to several different reactions. The base adds at the 2-position which leads to either ring opening (when the base is hydroxide), or deoxidative substitution (when the base is cyanide) [scheme 28].



Scheme 28

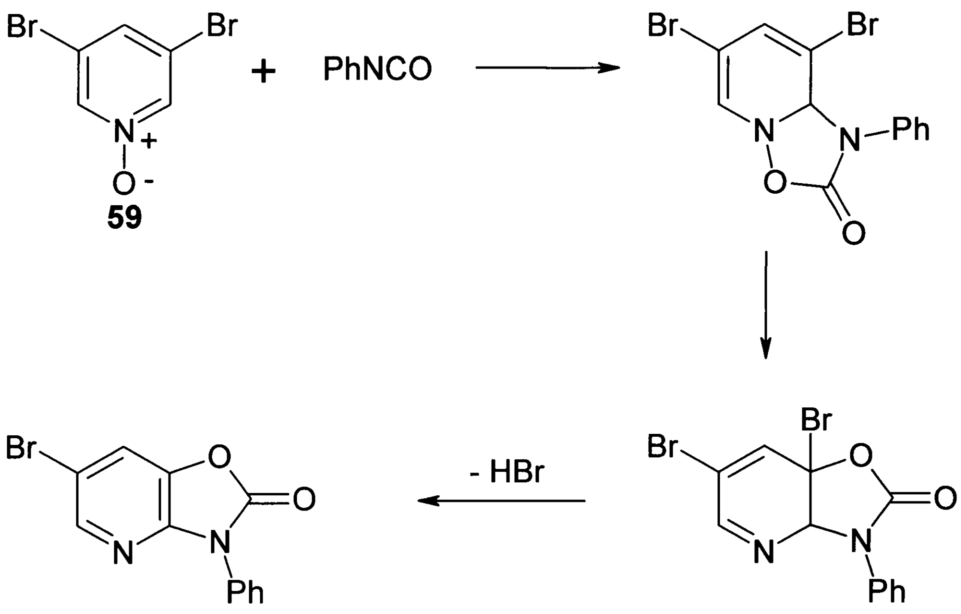
1.1.3.2.8 Cycloaddition

Pyridine N-oxide **1** reacts[303] with hexafluoropropene to form, after rearrangement of the postulated isoxazolidine intermediate, 2-(1,2,2,2-tetrafluoroethyl)pyridine. 3,5-Lutidine N-oxide **86** reacts stereospecifically with arylmaleimides to give products of type **88** after a 1,5-sigmatropic shift[304, 305] from adduct **87** [scheme 29].



Scheme 29

Reactions with alkynes can lead to N-ylides, 2- and 3-alkylpyridines or furanopyridines; the last are formed if suitable leaving groups are present on the pyridine. Thus, reaction of phenylpropionitrile with pyridine N-oxide **1** gives[306-309] mainly the 3-alkylated pyridine. A mixture of furano[3,2-b] and [3,2-c]pyridines is obtained[310] from 3,5-dichloropyridine N-oxide. Similar reactions have been reported[311] with benzyne. Pyridine N-oxides react[312-319] readily with phenylisocyanates to give oxazolo[4,5-b]pyridines after a 1,5 sigmatropic shift of the initially formed cycloadduct. In the case of 3,5-dibromopyridine N-oxide **59**, dehydrobromination yields a 2-oxazolo[4,5-b]pyridine[317] [scheme 30].

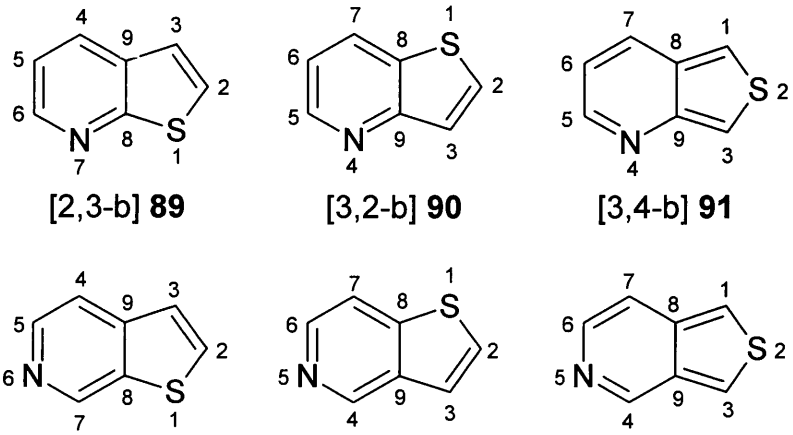


Scheme 30

1.2 Thieno[2,3-b]pyridines

1.2.1 Introduction

Thienopyridines can be considered in two ways: as analogues of quinoline, the [b] fused bicycles **89-91** or as analogues of isoquinoline, the [c] fused bicycles **92-94** [figure 7]. These compounds have attracted a lot of interest over the years as they consist of a π-excessive thiophene ring fused to a π-deficient pyridine ring and as analogues of quinoline and isoquinoline they have attracted attention as they have potential pharmacological value. In contrast to quinoline and isoquinoline, thienopyridines do not occur extensively in nature, in fact their only natural occurrence[320] is in shale oil of high sulphur content. The first reported preparation was by Steinkopf[321, 322] in 1912 in which the Skraup synthesis was carried out on 2-aminothiophene as the tin double salt to form thieno[2,3-b]pyridine **89**.



[2,3-b] **89** [3,2-b] **90** [3,4-b] **91**

[2,3-c] **92** [3,2-c] **93** [3,4-c] **94**

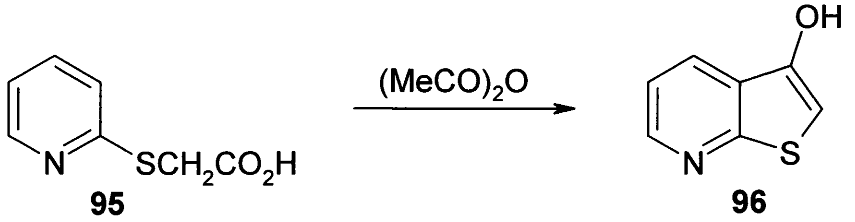
Figure 7

The current work has focused on thieno[2,3-b]pyridines and so it is the intention of this introduction to only cover the synthesis and reaction of these compounds. For a more comprehensive picture of the chemistry of all the thienopyridines several reviews[323-326] are available. From a synthetic point of view the preparative routes can be grouped together as those beginning from either a pre-formed pyridine ring or a pre-formed thiophene ring.

1.2.2 Preparation from a pre-formed pyridine

1.2.2.1 From thioacetic acids

Koenigs and Gesseler[327] claimed that treating 2-pyridylthioacetic acid **95** with acetic anhydride lead to the formation of 3-hydroxythieno[2,3-b]pyridine **96** [equation 43].



Equation 43

Chichibabin[328] challenged this when he prepared **96** from 3-methyloxycarbonyl-2-chloropyridine and found it to be different to Koenigs' product. The true structure was eventually established by Duffin and Kendall[329] [figure 8].

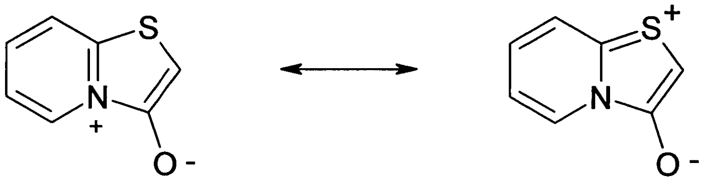
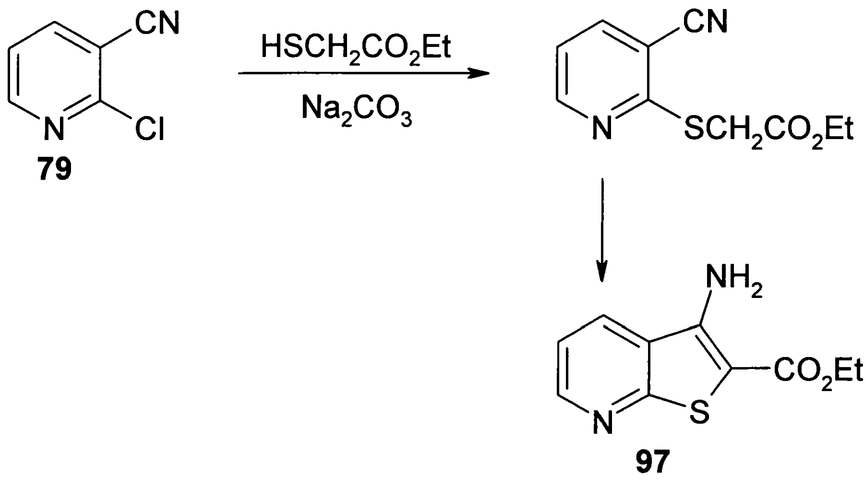


Figure 8

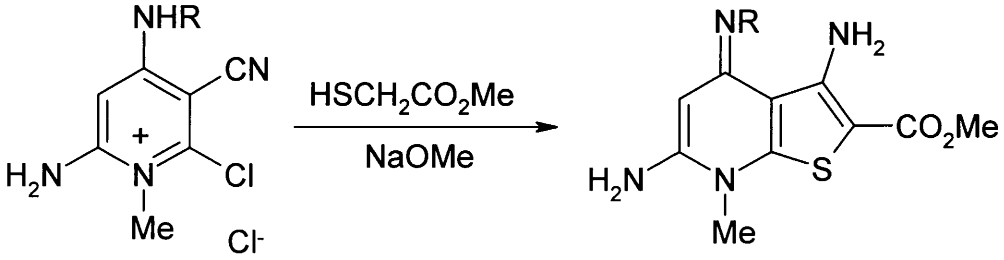
1.2.2.2 From 2-halo-3-cyanopyridines

3-Amino-2-ethyloxycarbonylthieno[2,3-b]pyridine **97**, has been prepared[330] by reacting 2-chloro-3-cyanopyridine **79** with ethyl mercaptoacetate. The nucleophilic substitution of the chlorine by the mercaptoacetate is followed by base promoted cyclisation [scheme 31].



Scheme 31

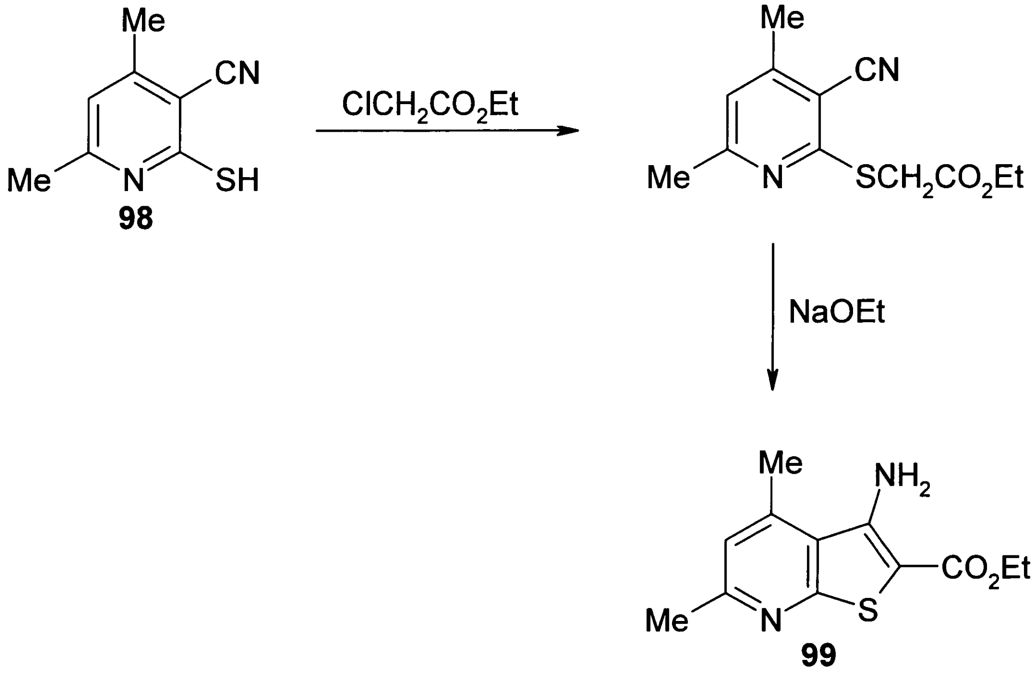
The same author[331] reported the formation of 2-acetamido-3-aminothieno[2,3-b]pyridine from 2-chloro-3-cyanopyridine **79** when the nucleophile was mercaptoacetamide. Highly substituted thieno[2,3-b]pyridines have also been prepared[332-335] by similar routes. In a related reaction 2-chloro-3-cyanopyridinium salts have been reacted[336] with methyl thioglycollate and sodium methoxide to form 4-iminothieno[2,3-b] pyridines [equation 44].



Equation 44

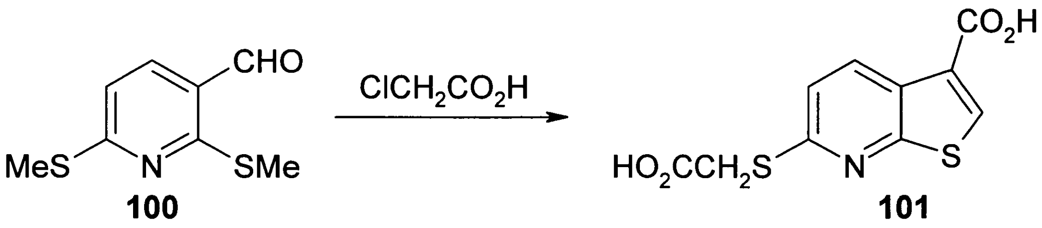
1.2.2.3 From pyridinethiol derivatives

Pyridine-2-thiol derivatives with a group such as a cyano or acid in the 3-position react[337-348] with halogen compounds containing a methylene group activated by an electron withdrawing group to form thieno[2,3-b]pyridines. A typical example[343] is the preparation of 3-amino-2-ethyloxycarbonyl-4,6-dimethylthieno[2,3-b]pyridine **98** by alkylation of 3-cyano-4,6-dimethylpyridine-2-thiol **99** with ethyl chloroacetate followed by base promoted cyclisation [scheme 32].



Scheme 32

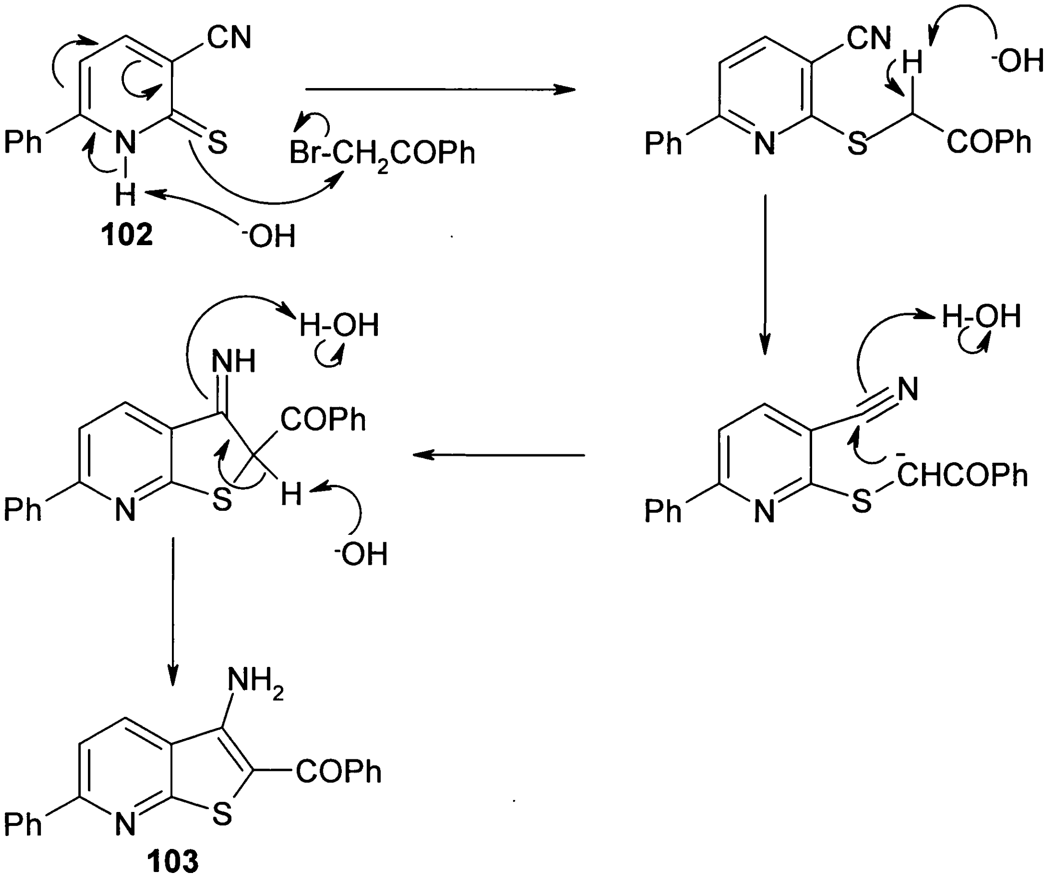
In a related reaction[349] the potential antiviral agent **101** is formed by reaction of chloroacetic acid with 2,6-dimethylthiopyridine-3-carboxaldehyde **100** [equation 45].



Equation 45

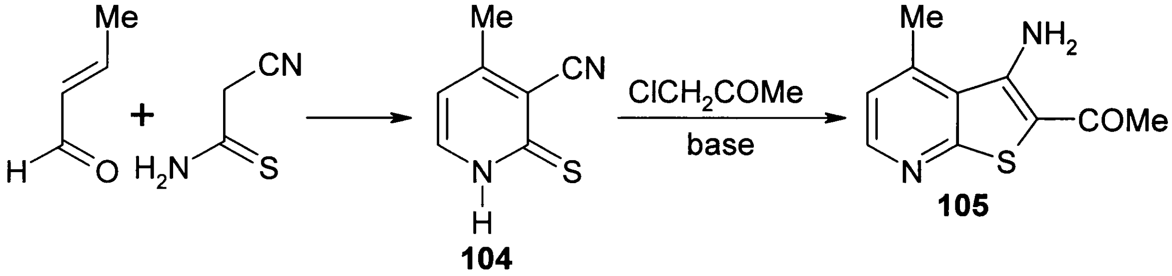
1.2.2.4 From pyridinethiones

Pyridinethiones have been extensively utilised by Russian workers[350-376] in the preparation of thieno[2,3-b]pyridines. Generally, the thione, in the form of a substituted 3-cyanopyridine-2(1H)-thione, is alkylated by a compound with a halogen adjacent to a methylene activated by an electron withdrawing group. These intermediates are then cyclised by the Zeigler method, in the presence of a base to thieno[2,3-b]pyridines. In a typical example[360] 3-cyano-6-phenylpyridine-2(1H)-thione **102** is alkylated by phenacylbromide in DMF with aqueous potassium hydroxide, followed by cyclisation to afford 3-amino-6-phenylthieno[2,3-b]pyridine **103** [scheme 33].



Scheme 33

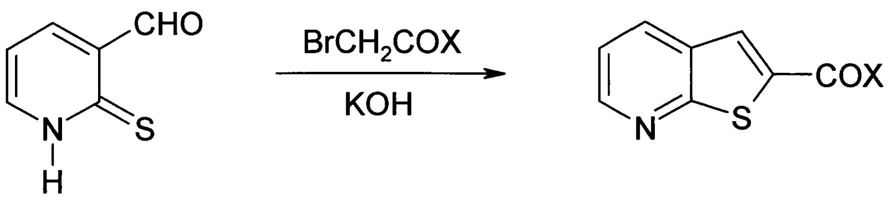
Attaby and co-workers have carried out considerable work with pyridine-2(1H)-thiones. In a series of papers[377-386] they report the formation of substituted 3-cyanopyridine-2(1H)-thiones from cyanothioacetamide and α,β-unsaturated carbonyl compounds. These were then reacted with active halogen compounds. Typically[385] cyanothioacetamide on reaction with but-2-enal yields 3-cyano-4-methylpyridine-2(1H)-thione **104**, which with 1-chloroacetone and base forms the 3-aminothieno[2,3-b]pyridine **105** [scheme34].



Scheme 34

Other synthetic routes to thieno[2,3-b]pyridines via 3-cyanopyridine-2(1H)-thiones, which were prepared from cyanothioacetamides reacting with enaminones[387-389] or diketones cyclised with thiocarboxamidocinnamonitriles[390-397] have been reported. In a similar manner[365, 366] the salts of pyridine-2-thiolates have been alkylated then cyclised to form thieno[2,3-b]pyridines.

3-Formylpyridine-2(1H)-thione **106** on reaction[375] with α-bromocarbonyl compounds and a base gives 2-substituted thieno[2,3-b]pyridines in good yield [equation 46].



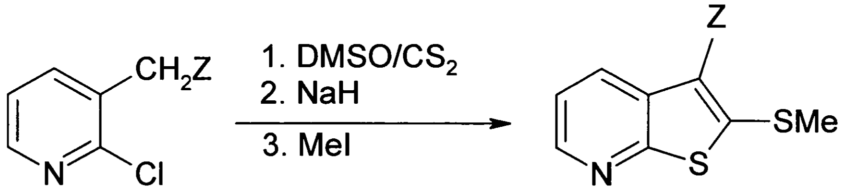
106

$X = OC_2H_5, C_6H_5, pBrC_6H_4$

Equation 46

1.2.2.5 From 2-chloropyridines containing an active methylene group

Thieno[2,3-b]pyridines have been prepared[260, 398, 399] by heating ethyl 2-chloro-3-pyridylacetate **74**, 2-chloro-3-cyanomethylpyridine **75** or methyl 2-chloro-3-pyridylacetate **107** with carbon disulphide and sodium hydride in dimethylsulphoxide (DMSO). On cooling, the addition of methyl iodide gave 2,3-disubstituted thieno[2,3-b]pyridines **108**, **109** and **110** [equation 47].

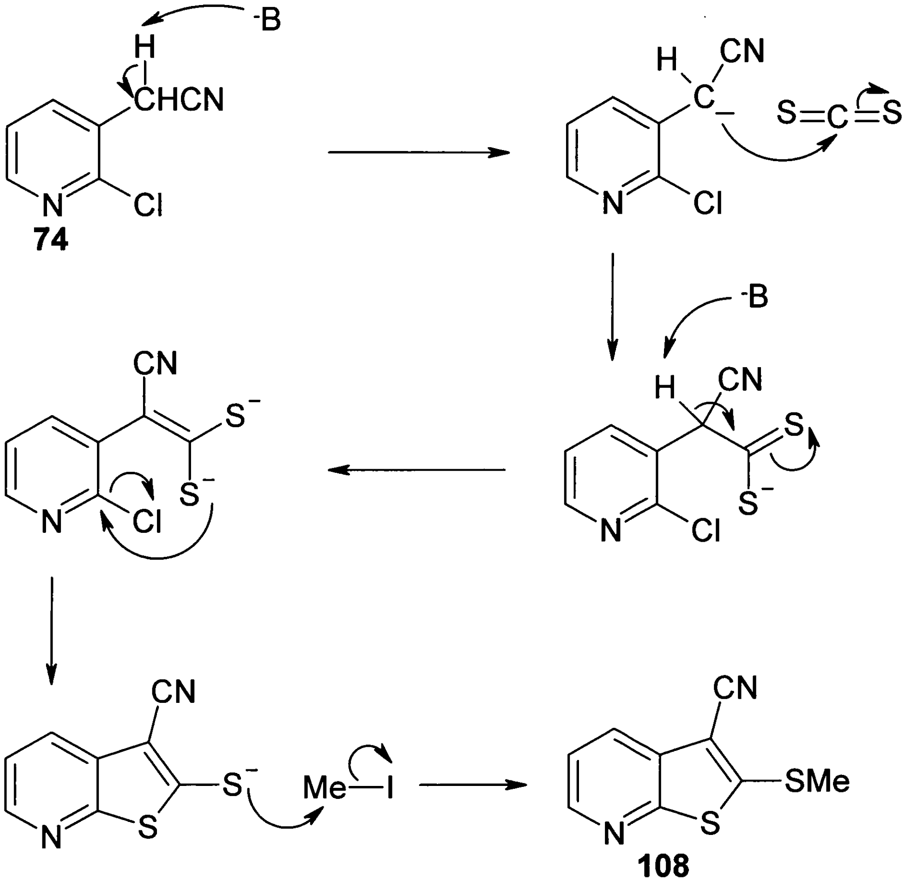


74, 75, 107 **108-110**

74, **108**; $Z=CO_2Et$, **75**, **109**; Z=CN, **107**, **110**; $Z=CO_2Me$

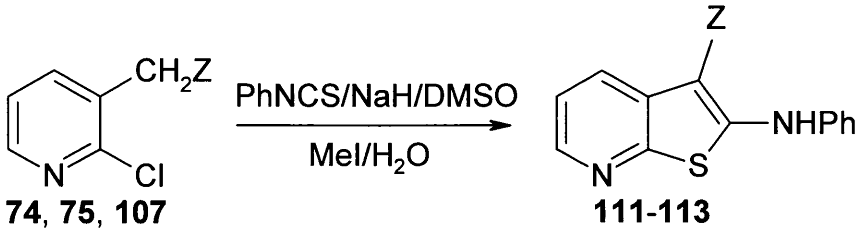
Equation 47

In each case the reaction is thought to proceed by base abstraction of the methylene protons and subsequent formation, with carbon disulphide, of a ketene dithioacetal dianion. On heating, one thiolate anion displaces the chlorine to form the bicycle and the other is alkylated by methyl iodide [scheme 35].



Scheme 35

A similar[260] alkylation step utilises ethyl chloroacetate. When the heterocumulene is phenylisothiocyanate, 2-anilinothieno[2,3-b]pyridines[400] **111-113** are produced. The alkylation step is not necessary and the products are formed via protonation by water [equation 48].

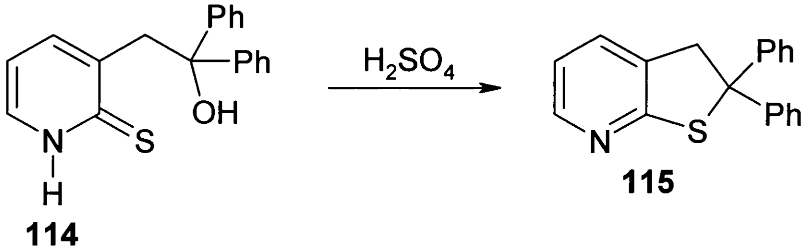


74, **111**; Z=CO_2Et, **75**, **112**; Z=CN, **107**, **113**; Z=CO_2Me

Equation 48

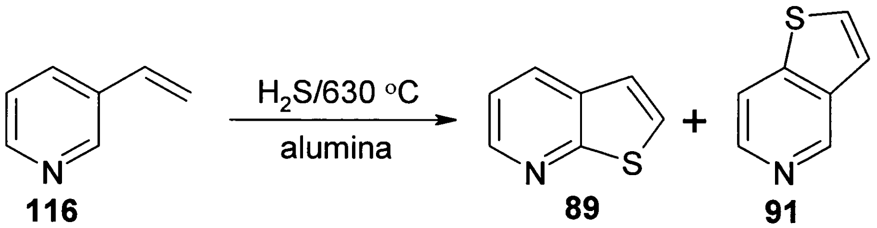
1.2.2.6 Miscellaneous preparations

2-Mercapto-3-(2-hydroxy-2,2-diphenylethyl)pyridine **114** undergoes cyclisation[401] with cold concentrated sulphuric acid to 2,2-diphenyl-2,3-dihydrothieno[2,3-b]pyridine **115** [equation 49].



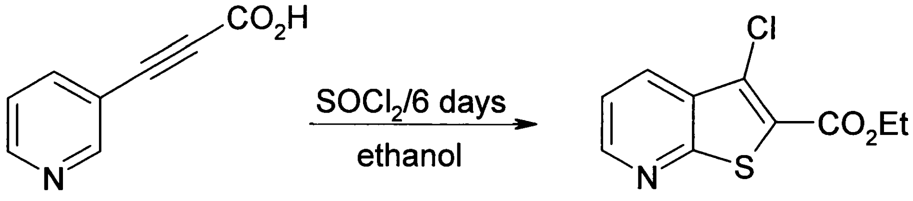
Equation 49

The reaction[402] of 3-vinylpyridine **116** with hydrogen sulphide at 630 °C with an alumina catalyst gives thieno[2,3-b]pyridine **89** in 6% yield together with some thieno[3,2-c]pyridine **91** [equation 50]. Under the same reaction conditions 2-methyl-5-vinylpyridine or 2-methyl-5-ethylpyridine gave 6-methylthieno[2,3-b]pyridine in 2% yield.



Equation 50

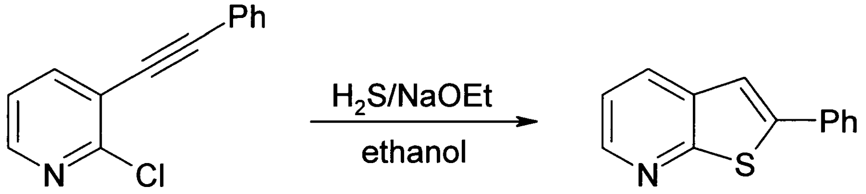
Treatment of pyridin-3-ylpropiolic acid **117** with thionyl chloride at reflux for six days followed by reaction with ethanol gives 2-ethyloxycarbonyl-3-chlorothieno[2,3-b]pyridine **118** in 4% yield[403] [equation 51].



117 **118**

Equation 51

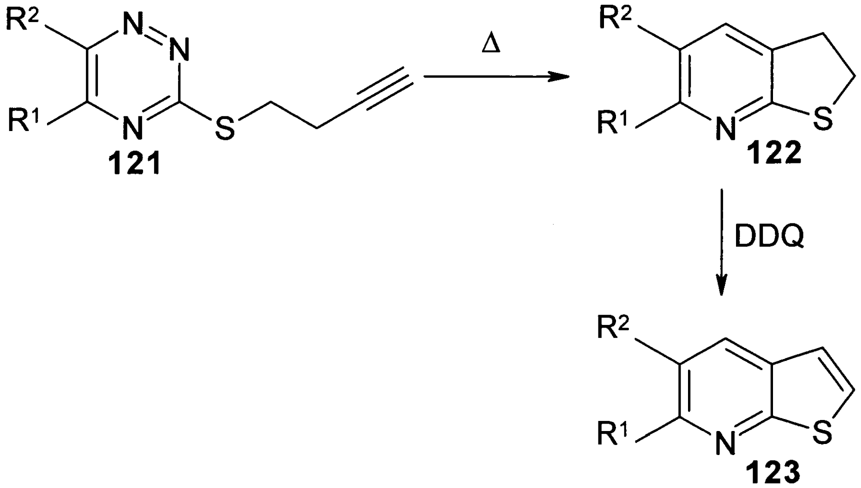
2-Phenylthieno[2,3-b]pyridine **120** was obtained in 69% yield from the reaction of 2-chloro-3-phenylethynylpyridine **119** with a hydrogen sulphide saturated solution of sodium ethoxide in ethanol[404] [equation 52].



119 **120**

Equation 52

An intramolecular Diels-Alder reaction to thienopyridines has been reported[405, 406] involving substituted 3-(3-butynylthio)-1,2,4-triazines **121** containing an electron rich dienophile. It forms a 2,3-dihydrothieno[2,3-b]pyridine **122**, which on refluxing with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), dehydrogenates to the thieno[2,3-b]pyridine **123** [scheme 36].

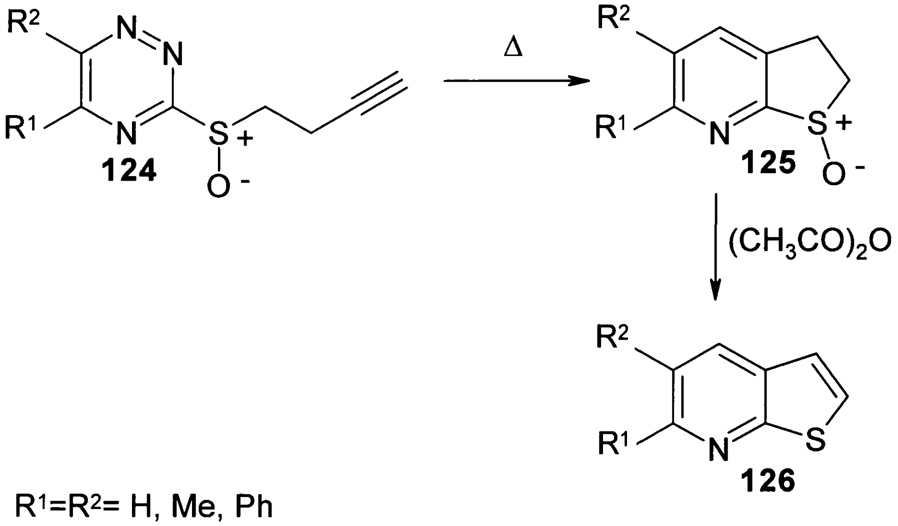


121 **122** **123**

R^1=R^2= H, Me, Ph

Scheme 36

It was discovered that oxidising the sulphur altered the reactivity with the rate of cyclisation in the order sulphoxide >> sulphone > sulphide. It is suggested that there is a correlation between C-S-C bond angle and rate of reaction. 2,3-Dihydrothieno[2,3-b]pyridine S-oxide **125** formed from triazine S-oxide **124** is dehydrated with refluxing acetic anhydride to thieno[2,3-b]pyridine **126** [scheme 37].

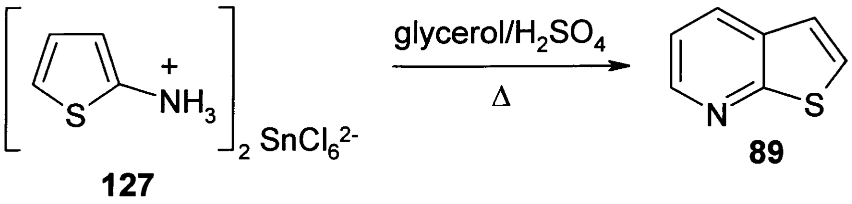


Scheme 37

1.2.3 Preparation from a pre-formed thiophene

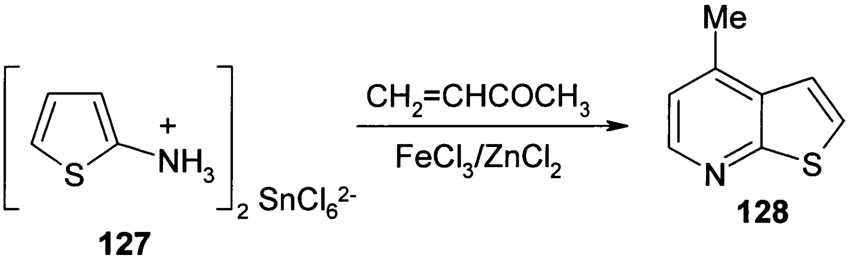
1.2.3.1 Skraup synthesis

Steinkopf[321, 322] used the stable tin double salt of 2-aminothiophene **127**, which was obtained directly from 2-nitrothiophene by reduction, with glycerol to give thieno[2,3-b]pyridine **89** [equation 53].



Equation 53

As an alternative to acrolein as an intermediate in the Skraup synthesis, the α,β-unsaturated carbonyl compound, methyl vinylketone, has been employed[407] to prepare 4-methylthieno[2,3-b]pyridine **128** [equation 54].

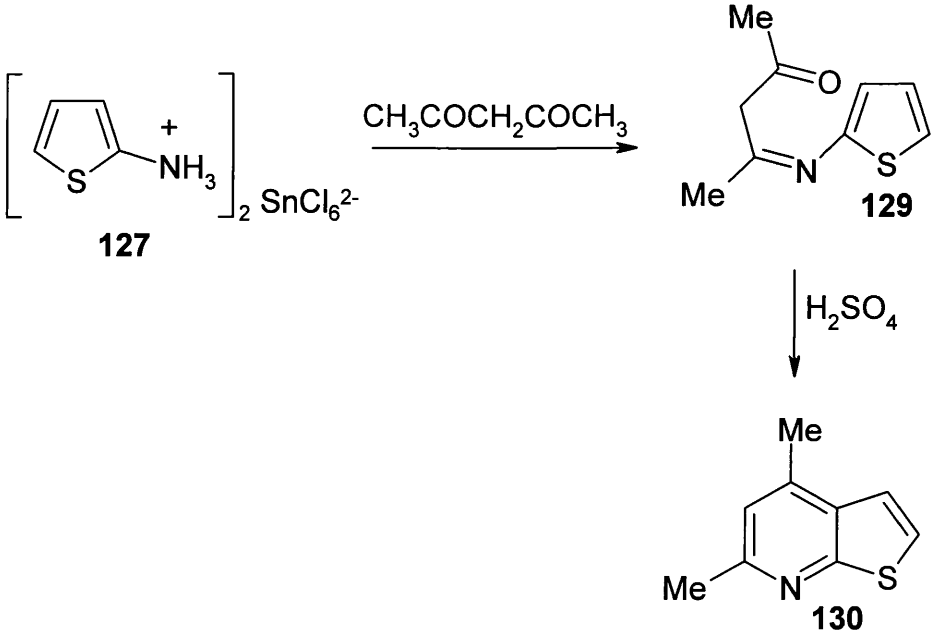


Equation 54

Klemm[408] reported however that some 6-methylthieno[2,3-b]pyridine is also produced in this reaction.

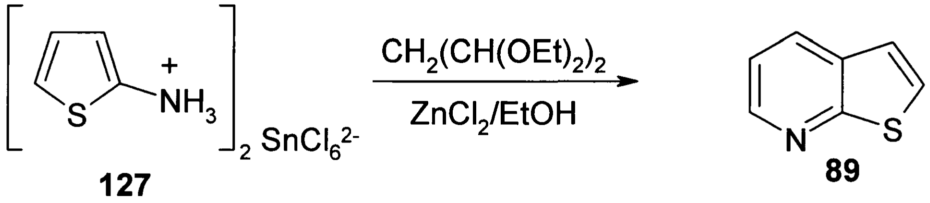
1.2.3.2 Aminothiophenes and 1,3-dicarbonyl compounds

The reaction of 2-aminothiophene double salt **127** with acetylacetone[409] gives 4,6-dimethylthieno[2,3-b]pyridine **130** via cyclisation of the formed Schiff base **129** [scheme 38].



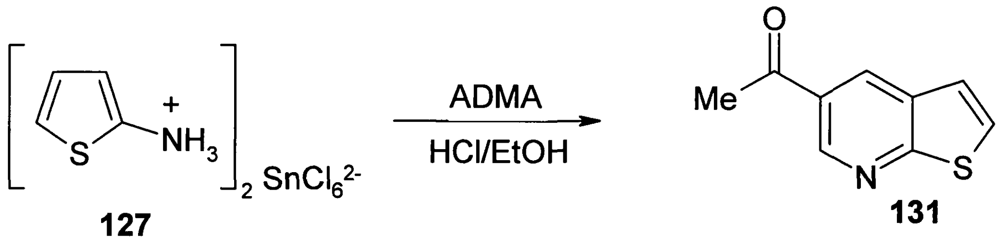
Scheme 38

Malondialdehyde tetraethylacetal, as a source for a 1,3-dicarbonyl, forms thieno[2,3-b]pyridine when treated[408] with zinc chloride and the double salt **127** [equation 55]. The proposed mechanism suggests a combination of, stepwise hydrolysis of the acetal plus a sequence of Schiff base formation with the amine salt then cyclodehydrative substitution into the thiophene ring.



Equation 55

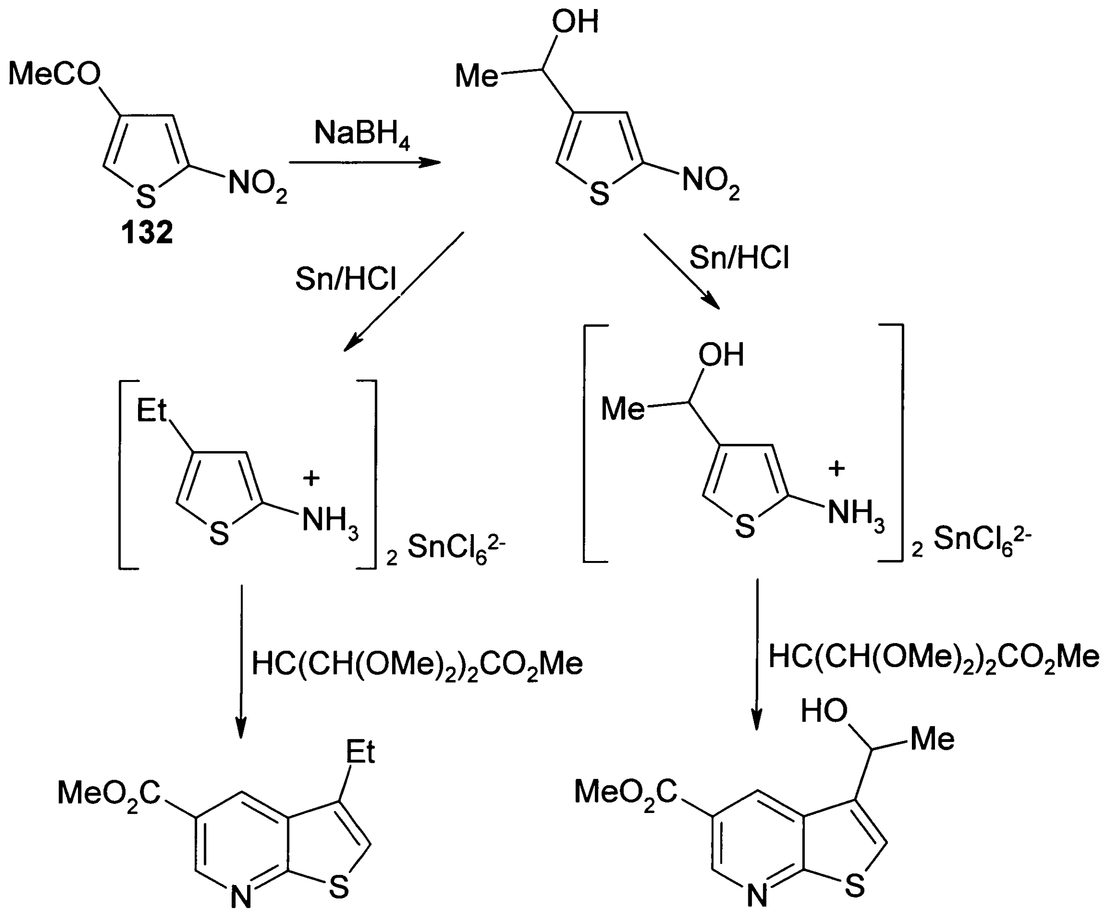
2-Aminothiophene double salt **127** was reacted[408] with acetylacetone and 3-methylpentane-2,4-dione to form 4,6-dimethylthieno[2,3-b]pyridine **130** and 4,5,6-trimethylthieno[2,3-b]pyridine respectively. Heating the tin salt **127** with acetoacetaldehyde dimethylacetal (ADMA) in ethanolic hydrochloric acid solution gave 5-acetylthieno[2,3-b]pyridine **131** in 32% yield[408] [equation 56].



Equation 56

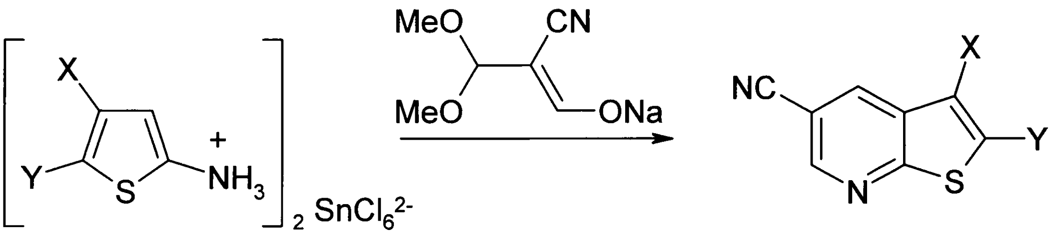
Trace amounts of 4-methylthieno[2,3-b]pyridine **128** and the 6-methyl isomer were also identified. It had been previously claimed[337] however, that the only product from this reaction was 6-methylthieno[2,3-b]pyridine.

The synthesis[410] of 3-substituted thieno[2,3-b]pyridines was attempted using 4-acetyl-2-nitrothiophene **132**. This proved difficult to reduce to the appropriate amine, so the acetyl function was reduced first. Subsequent formation of the amine tin salt lead to some further reduction of the carbinol and hence a mixture of thieno[2,3-b]pyridines **133** and **134** [scheme 39].



Scheme 39

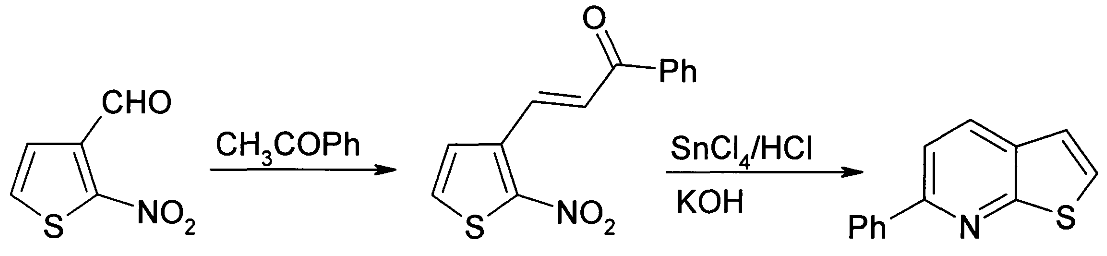
Thieno[2,3-b]pyridines were also prepared[410, 411] by reacting the sodium salt of 3,3-dimethoxy-2-formylpropionitrile with substituted 2-aminothiophene tin salts [equation 57].



Equation 57

1.2.3.3 From 2-amino-3-carbonylthiophenes

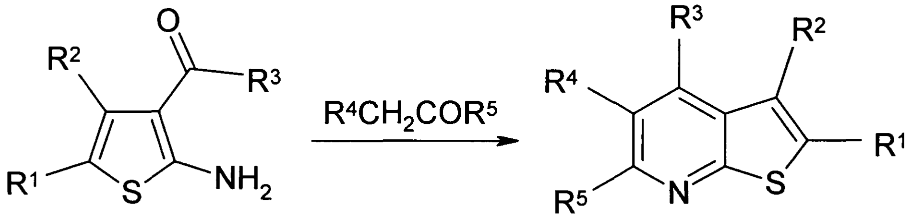
6-Phenylthieno[2,3-b]pyridine **136** was synthesised[412] from 2-nitrothiophene-3-carboxaldehyde **135** and acetophenone in a Friedländer type synthesis [scheme 40].



135 **136**

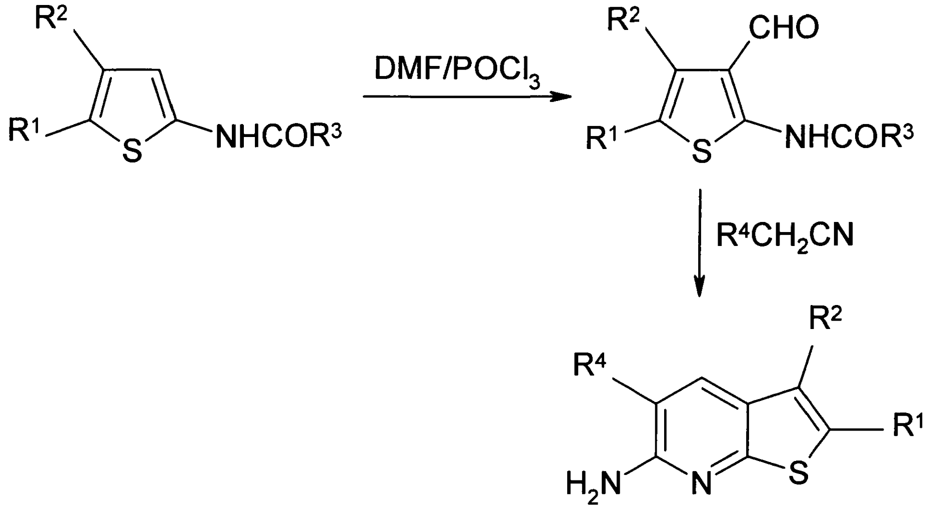
Scheme 40

Polysubstituted thieno[2,3-b]pyridines have been prepared[413] from 2-aminothiophenes and substituted ketones in a similar fashion [equation 58].



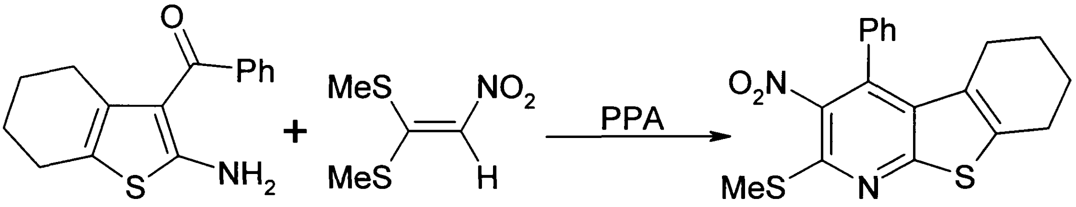
Equation 58

Formylation, by Vilsmeier's method, of substituted 5-acylaminothiophenes lead to their 3-formyl derivatives. Formation[414, 415] of thieno[2,3-b]pyridines followed cyclisation with compounds containing an active methylene group [scheme 41].



Scheme 41

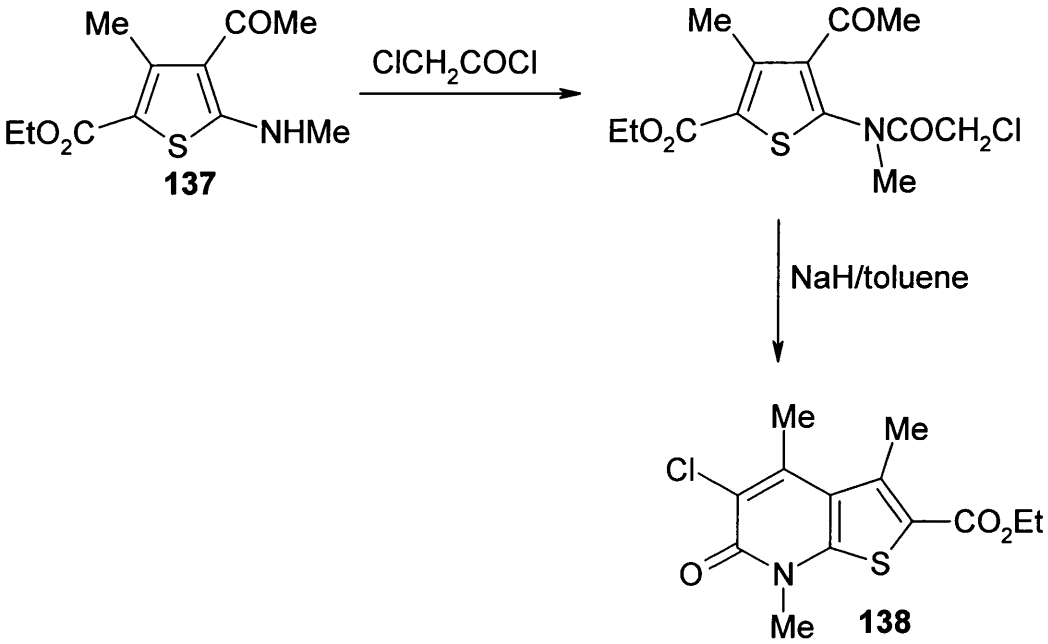
2-Amino-3-benzoylthiophenes on reaction[416] with ketones afford thieno[2,3-b]pyridines. Reaction[417] of these aminothiopenes with 1,1-dimethylthio-2-nitroethylene also leads to thieno[2,3-b]pyridines [equation 59].



Equation 59

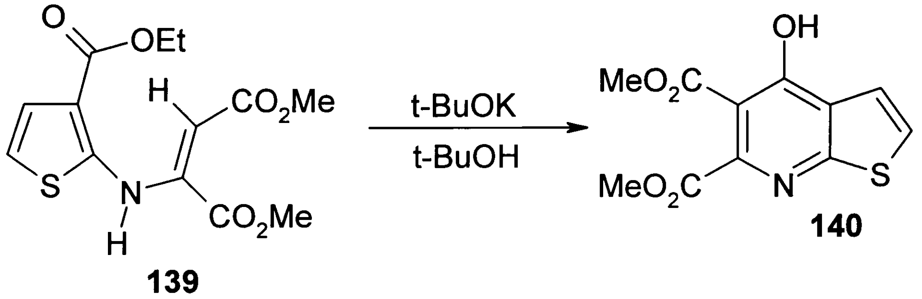
1.2.3.4 Base catalysed cyclisation of amides

Thiophene **137** was converted[418] to its chloroacetyl derivative and then cyclised to thieno[2,3-b]pyridine **138** by refluxing with sodium hydride in toluene [scheme 42].



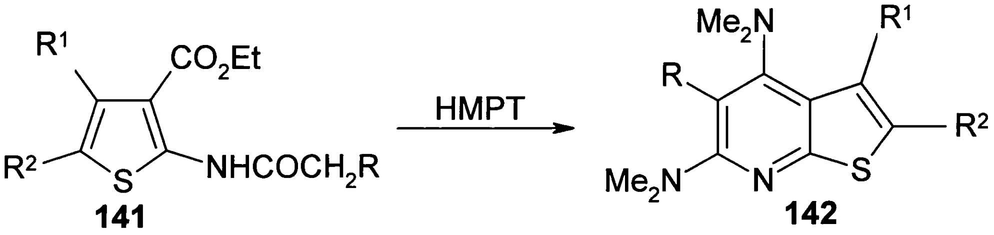
Scheme 42

Base catalysed intramolecular cyclisation of adduct **139** to thieno[2,3-b]pyridine **140** has been described[419] [equation 60].



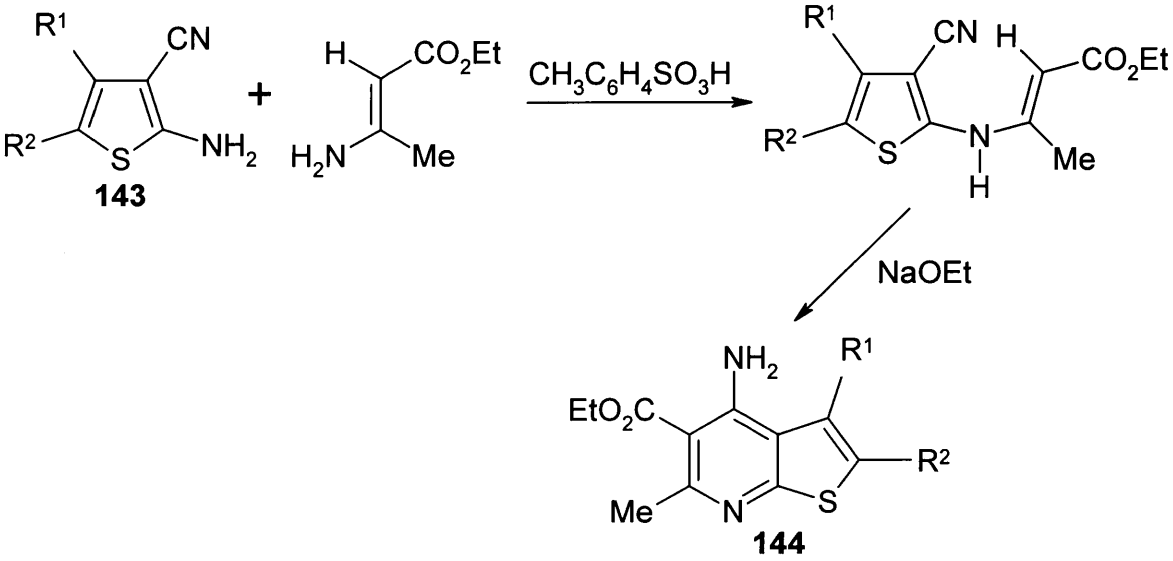
Equation 60

Ethyl 2-acetamido-3-thienocarboxylates **141** have been converted[420] to 4,6-bis(dimethylamino)thieno[2,3-b]pyridines **142** by refluxing in hexamethyl phosphoric triamide (HMPT) [equation 61]. When hydrogen is in the 4- position of **141** the yields obtained of **142** were between 30 and 40%. However when methyl or methylene groups are in this position the yields reduce to less than 10% and for a phenyl group no thienopyridine was isolated. Steric hindrance has been suggested[420] as a rationale for this.



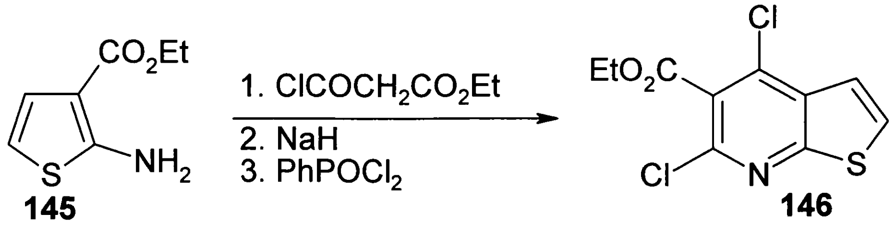
Equation 61

2-Amino-3-cyanothiophenes **143** were reacted[421] with ethyl aminocrotonate together with p-toluenesulphonic acid as a catalyst to form 2-[N-(3'-ethyloxycarbonyl)-2'-propenylamino]-3-cyanothiophenes which are readily cyclised by sodium ethoxide to the corresponding thieno[2,3-b]pyridines **144** with yields greater than 80% [scheme 43].



Scheme 43

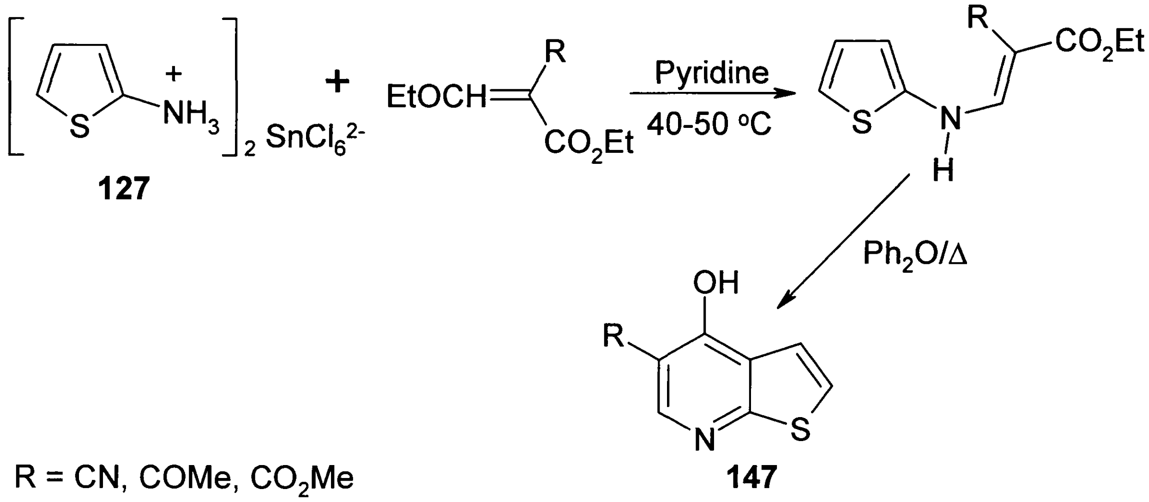
4,6-Dichloro-5-ethyloxycarbonylthieno[2,3-b]pyridine **146** was prepared[422] from ethyl 2-aminothiophene-3-carboxylate **145** in three steps as shown in equation 62.



Equation 62

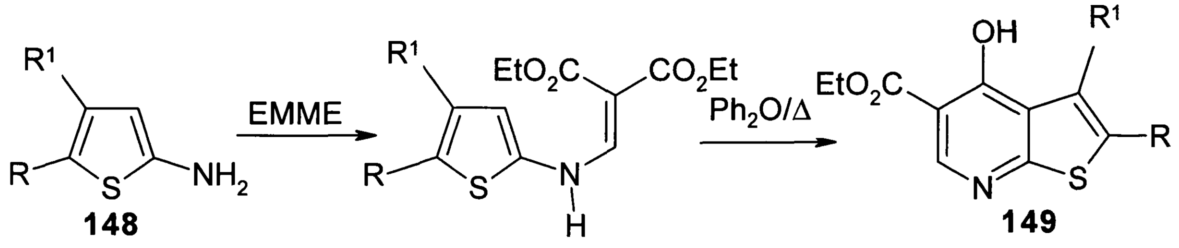
1.2.3.5 Gould-Jacobs synthesis

The Gould-Jacobs synthesis was first utilised[423] for the preparation of thienopyridines by heating 2-aminothiophene tin double salt **127** with ethoxymethylene derivatives of active methylene compounds at 40–50 °C in pyridine for 24 hours. The resulting aminoacrylate intermediate was cyclised to the corresponding thieno[2,3-b]pyridine **147** by refluxing in diphenyl ether [scheme 44].



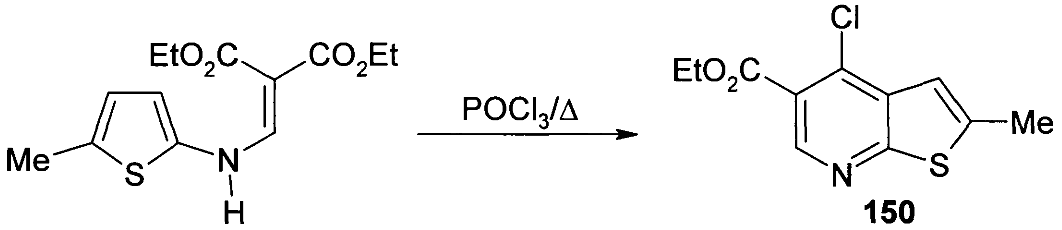
Scheme 44

The Gould-Jacobs synthesis was applied[424] to 4,5-disubstituted 2-aminothiophenes **148**. Condensation with diethylethoxymethylenemalonate (EMME) gave a diethyl-(2-thienyl)aminomethylenemalonate which, when refluxed in diphenyl ether, cyclised to the 5-ethyloxycarbonyl-4-hydroxythieno[2,3-b]pyridine **149** [scheme 45].



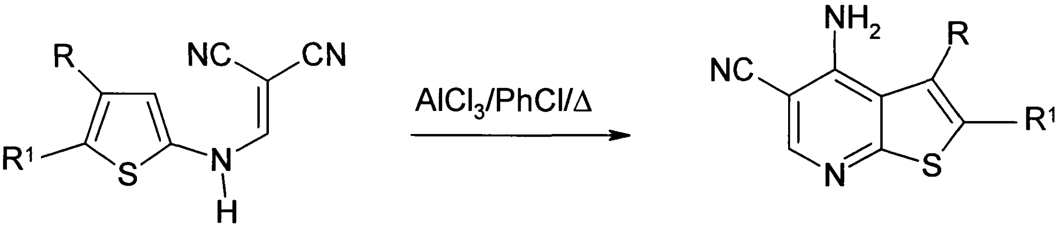
Scheme 45

Alternatively[425] if the cyclisation step is carried out in refluxing phosphorus oxychloride, chlorination takes place at the thienopyridine 4- position to give **150** in 55% yield [equation 63].



Equation 63

Similarily, 4-aminothieno[2,3-b]pyridine derivatives have been prepared[426] via cyclisation of a 2-(1,1-dicyanovinylamino)thiophene by refluxing in chlorobenzene in the presence of aluminium chloride [equation 64].

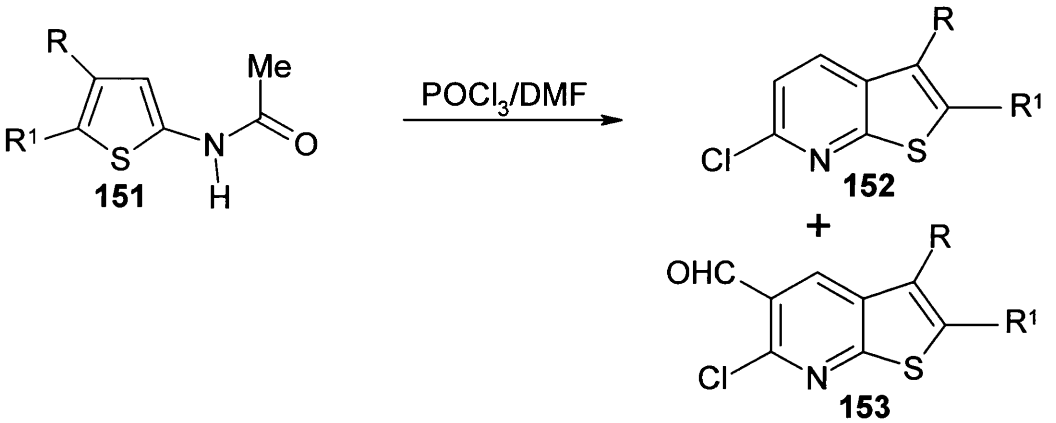


Equation 64

1.2.3.6 Vilsmeier synthesis

Meth-Cohn[427] found that by using 4- and 5- substituted 2-acetamidothiophenes **151**, 6-chlorothieno[2,3-b]pyridines **152** and 6-chloro-5-formylthieno[2,3-

b]pyridines **153** could be prepared by the Vilsmeier-Haack reaction [equation 65]. In a study[428] of these reactions it was discovered that altering the ratio of the Vilsmieier reagents phosphorus oxychloride and DMF profoundly changed the ratio of products formed. Using them in the ratio $POCl_3$:DMF; 3:1, gave **152** in 80% yield. When the ratio was $POCl_3$:DMF; 7:3, the major product was **153** produced in 88% yield.

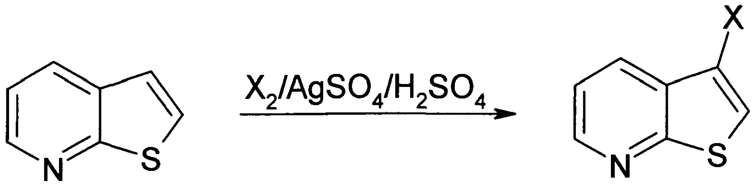


Equation 65

1.2.4 Reactions of thieno[2,3-b]pyridines

1.2.4.1 Electrophilic substitution

Klemm[408] observed, based on quantum chemical reactivity indices, that electrophilic substitution into thieno[2,3-b]pyridine **89** should occur predominantly at the 3- position rather than the 2- position. Reaction of **89** with elemental halogen in concentrated sulphuric acid and silver sulphate gave[429] 3-halothieno[2,3-b]pyridine **154-156** in yields of 27-40% [equation 66].

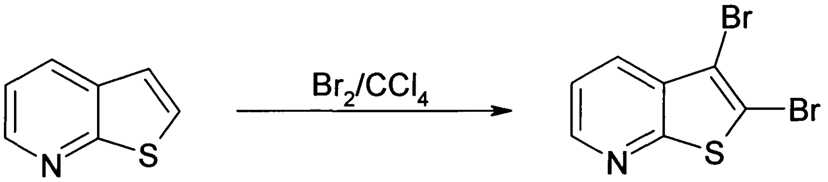


89 **154-156**

154; X=Cl, **155**; X=Br, **156**; X=I

Equation 66

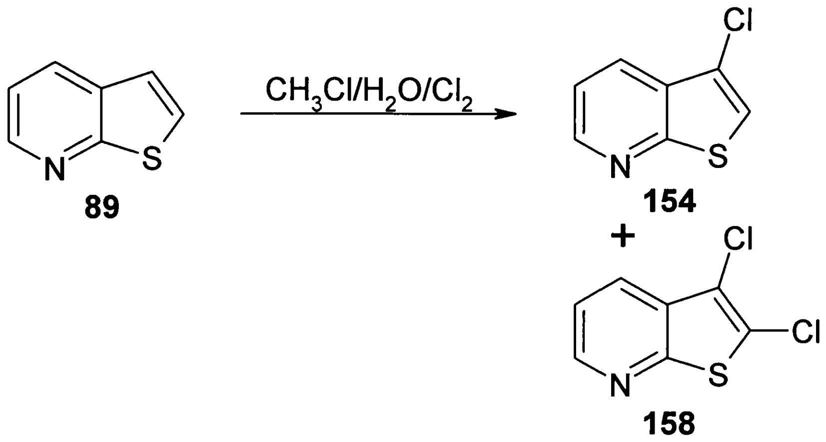
Reaction of **89** with deuterosulphuric acid at 98.5 °C gave faster deuterodeprotonation[408, 430] at the 3- position. Treatment[408] of **89** with bromine in carbon tetrachloride however led to 2,3-dibromothieno[2,3-b]pyridine **157** in 17% yield [equation 67].



89 **157**

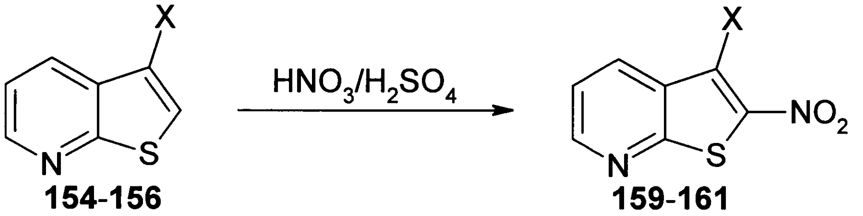
Equation 67

When **89** was treated[429] with bromine in carbon tetrachloride and a phosphate buffer, 3-bromothieno[2,3-b]pyridine **155** was produced in 57% yield. Refluxing **89** in chloroform/water mixture with the introduction of chlorine gas gave a mixture of 3-chlorothieno[2,3-b]pyridine **154** and 2,3-dichlorothieno[2,3-b]pyridine **158** [equation 68].



Equation 68

3-Halothieno[2,3-b]pyridines **154-156** were nitrated[429] with nitric and sulphuric acids to give the corresponding 2-nitro-3-halothieno[2,3-b]pyridines **159-161** in 22-47% yields [equation 69].

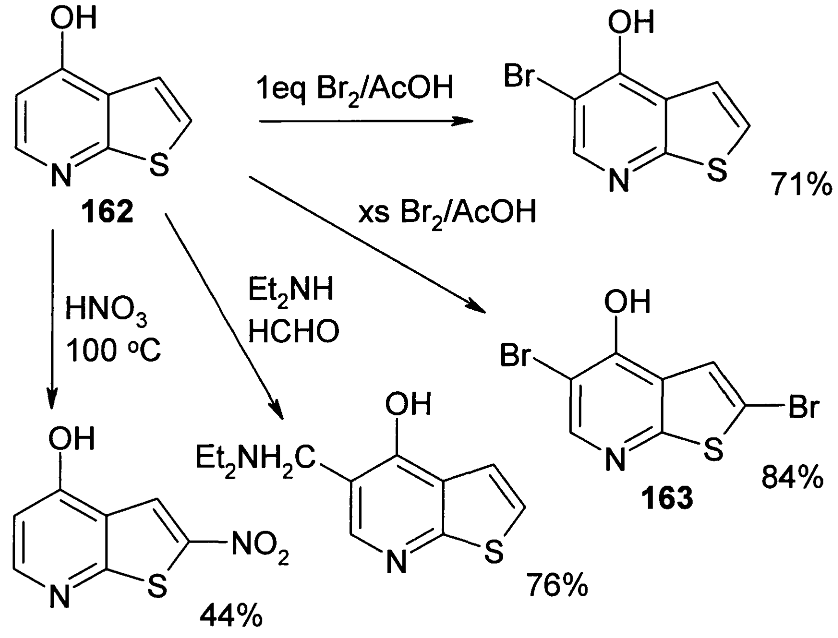


154, **159**; X=Cl, **155**, **160**; X=Br, **156**, **161**; X=I

Equation 69

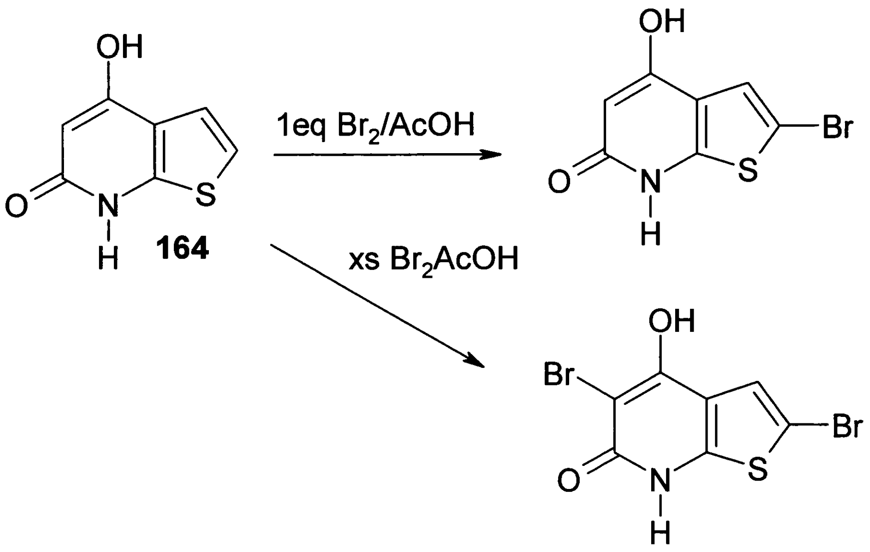
Mixed acids were also used[431] to nitrate thieno[2,3-b]pyridine **89** in the 3- position and to produce[432] 5-ethyl-3-nitrothieno[2,3-b]pyridine. Nitration[427] of 2-bromo-6-chlorothieno[2,3-b]pyridine gives 2-bromo-3-nitro-6-chlorothieno[2,3-b]pyridine in 96% yield.

Barker[433] has reported on the electrophilic substitution reactions of some hydroxythienopyridines and thienopyridones. When 4-hydroxythieno[2,3-b]pyridine **162** is treated with one equivalent of bromine in acetic acid 5-bromination takes place while 2,5-dibromo-4-hydroxythieno[2,3-b]pyridine **163** is formed with excess bromine. Substitution at C-5 also takes place when the reagents are diethylamine and formaldehyde. Nitration with nitric acid takes place at the 2-position [scheme 46].



Scheme 46

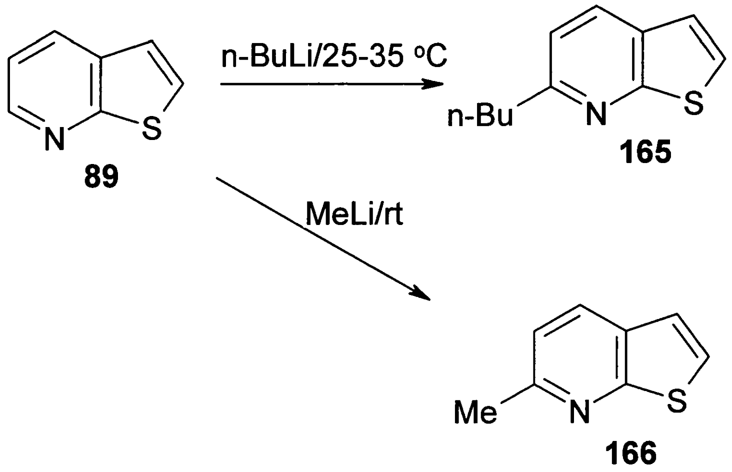
The same reactions[433] were carried out on 7-methylthieno[2,3-b]pyridin-4(7H)-one with similar results except the bromination was slower and the Mannich base could not be formed. The only electrophilic substitution reactions reported[433] on 4-hydroxythieno[2,3-b]pyridin-6(7H)-one **164** were brominations [scheme 47].



Scheme 47

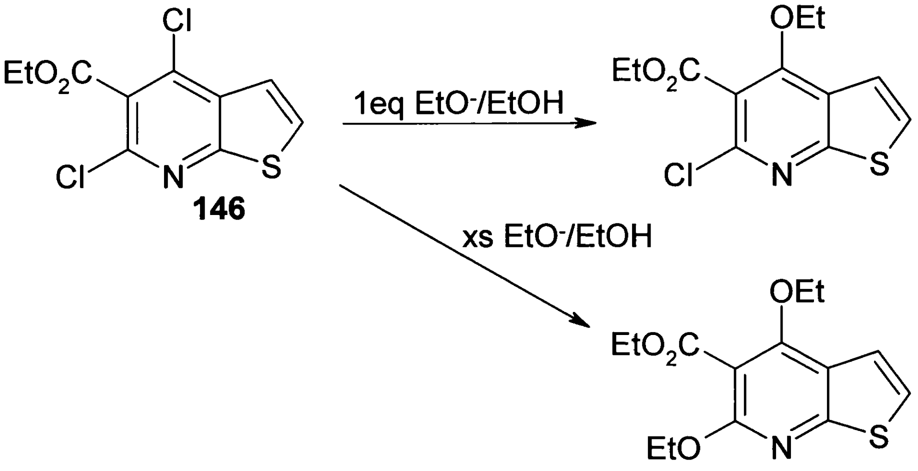
1.2.4.2 Nuceophilic substitution

Treatment[408] of thieno[2,3-b]pyridine **89** with n-butyllithium gave 6-n-butylthieno[2,3-b]pyridine **165** in 47% yield, while methyllithium gave 25% of 6-methylthieno[2,3-b]pyridine **166** [scheme 48]. At –25 °C, reaction with methyllithium followed by hydrolysis, first with D_2O, then water gives **166** in 11% yield and 2-deuterothieno[2,3-]pyridine apparently[408] formed from metalation at the 2- position of **89** which competes with the nucleophilic attack.



Scheme 48

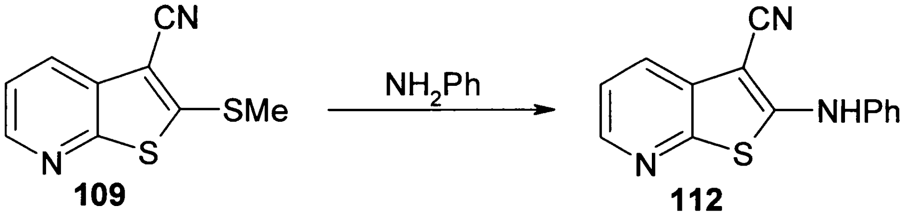
Reaction[429] of 3-bromothieno[2,3-b]pyridine **155** with cuprous chloride in DMF gave 3-chlorothieno[2,3-b]pyridine in 45% yield. Similarily the 5-bromo isomer was converted[434] to the corresponding cyanothienopyridine in 29% yield. Treatment[435] of 6-chlorothieno[2,3-b]pyridine with γ-diethylaminopropylamine and copper powder gave 6-(γ-diethylamino)propylaminothieno[2,3-b]pyridine in 58% yield. The chlorine in 2-bromo-6-chlorothieno[2,3-b]pyridine is readily replaced[436] by piperidine or thiophenol. 4,6-Dichloro-5-ethyloxycarbonylthieno[2,3-b]pyridine **146** when reacted[422] with 1 equivalent of ethoxide is substituted in the 4-position while excess ethoxide causes 4,6-disubstitution to occur [scheme 49].



Scheme 49

A similar substitution pattern was found[422] when 4,6-dichlorothieno[2,3-b]pyridine was treated with methoxide.

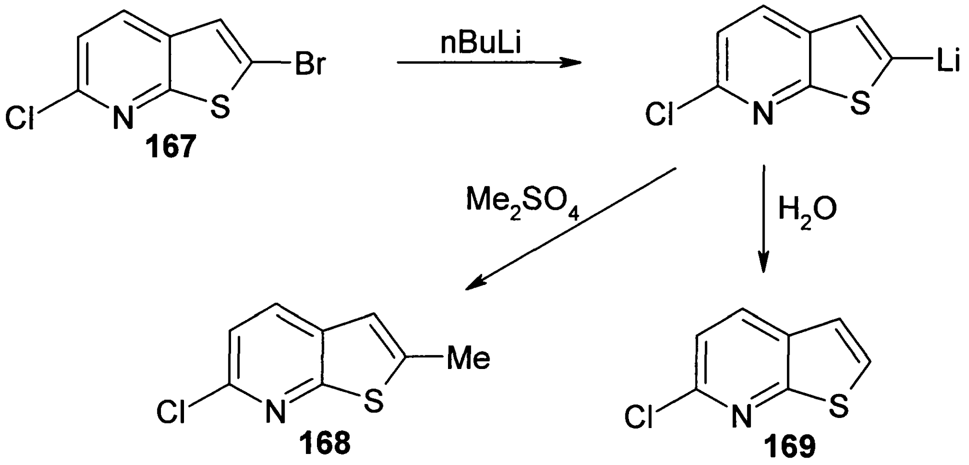
3-Cyano-2-methylthiothieno[2,3-b]pyridine **109** is substituted[260] in the 2-position by some nitrogen nucleophiles but not oxygen nucleophiles [equation 70]. Oxidation of the thiomethyl group of **109** gave the corresponding sulphoxide and sulphone. Reaction with the anion of diethylmalonate showed the sulphone[260] to be most reactive followed by the sulphoxide while the sulphide did not react.



Equation 70

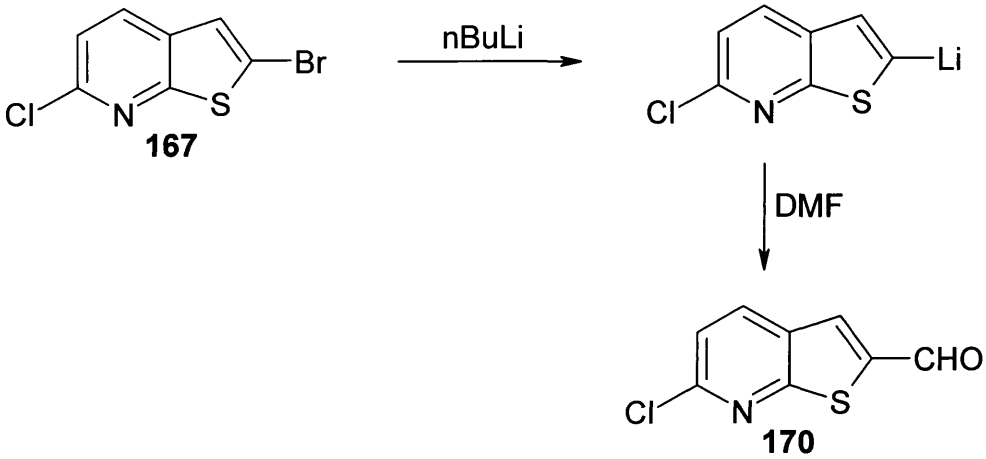
1.2.4.3 Metalation of thieno[2,3-b]pyridines

Reaction[427] of 2-bromo-6-chlorothieno[2,3-b]pyridine **167** with n-butyllithium followed by either dimethylsulphate or water gives 2-methyl-6-chlorothieno[2,3-b]pyridine **168** or 6-chlorothieno[2,3-b]pyridine **169** respectively [scheme 50].



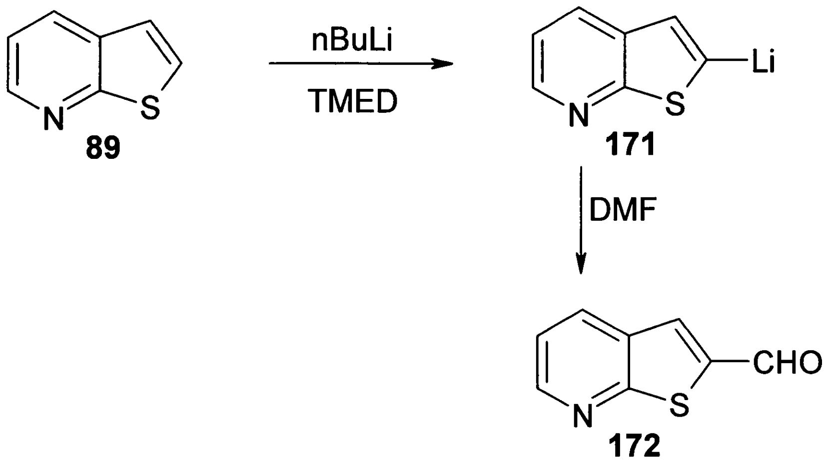
Scheme 50

In a related reaction[436] **167**, when treated with n-butyllithium followed by DMF, gave 2-formyl-6-chlorothieno[2,3-b]pyridine **170** [scheme 51].



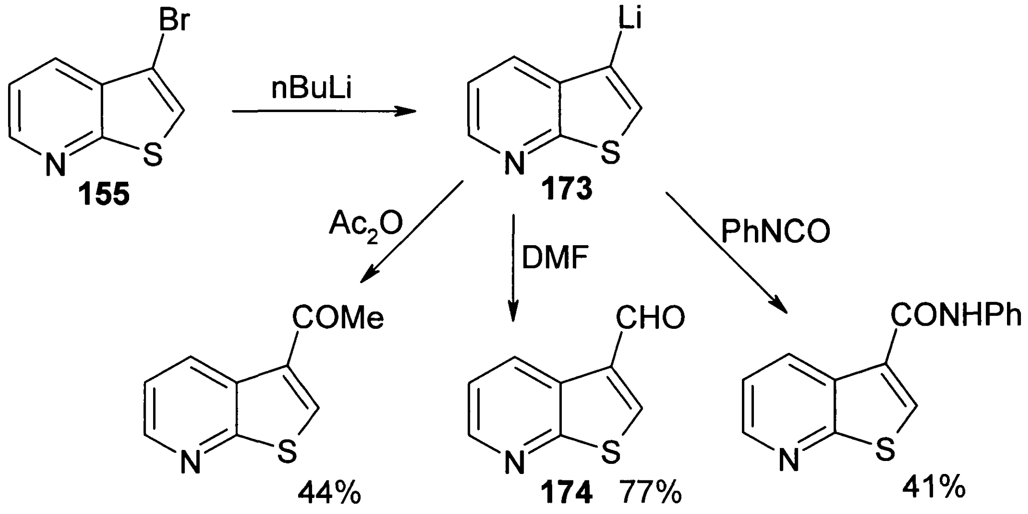
Scheme 51

Treatment[437] of thieno[2,3-b]pyridine **89** with n-butyllithium and tetramethylethylenediamine (TMED) at –70 °C gave 2-lithiothieno[2,3-b]pyridine **171** which in turn reacts with DMF to give 2-formylthieno[2,3-b]pyridine **172** in 66% yield [scheme 52].



Scheme 52

3-Lithiothieno[2,3-b]pyridine **173** was prepared[437] by halogen-metal exchange between 3-bromothieno[2,3-b]pyridine **155** and n-butyllithium at –70 °C. Subsequently **173** was reacted *in situ* with various carbonyl compounds. The 3-formyl derivative **174** was produced in 77% yield however other products were obtained in only moderate yields [scheme 53].

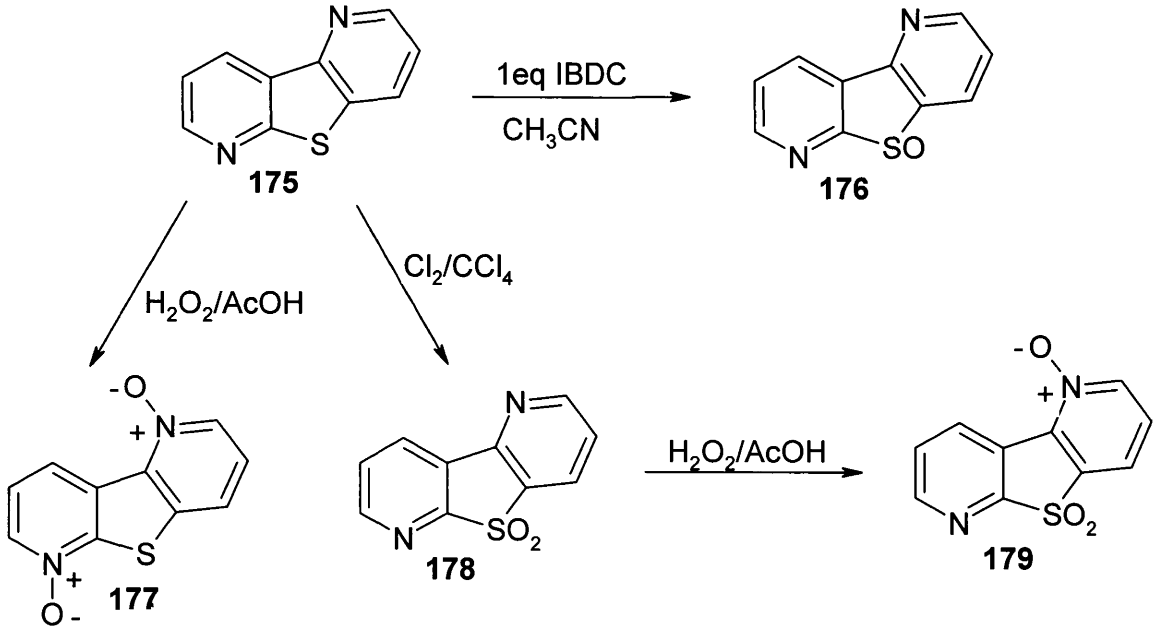


Scheme 53

1.2.4.4 Oxidation of thieno[2,3-b]pyridines

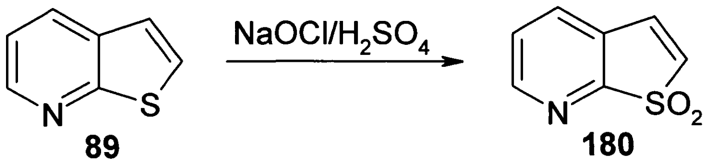
Thieno[2,3-b]pyridines have been converted to their N-oxides using hydrogen peroxide and glacial acetic acid,[429, 438] *m*-chloroperoxybenzoic acid[425, 439] and magnesium monoperoxyphthalate[440, 441] by methods similar to those used for pyridines.

Treatment[442] of thieno[2,3-b;4,5-b]dipyridine **175** with one equivalent of iodobenzene dichloride (IBDC) gave the corresponding sulphoxide **176**. Reaction of **175** in carbon tetrachloride with chlorine gas followed by hydrolysis gave sulphone **178**. Hydrogen peroxide in glacial acetic acid converted **175** to N,N'-dioxide **177**, and **178** to the 1,1,5-trioxide **179** [scheme 54].



Scheme 54

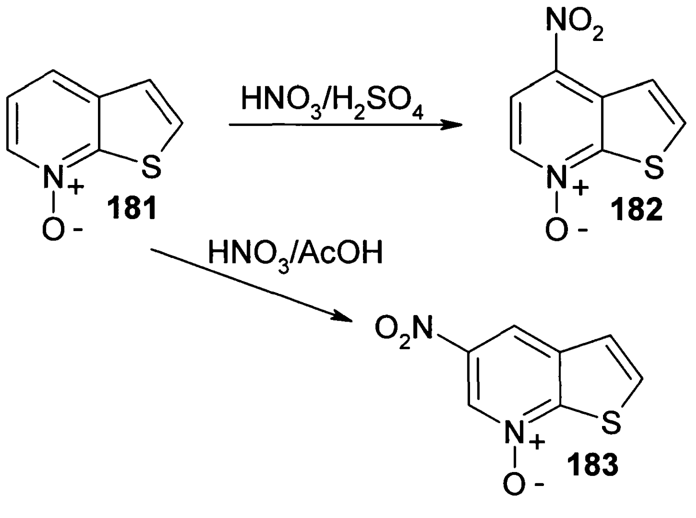
Sodium hypochlorite and dilute sulphuric acid were employed[443] to convert thieno[2,3-b]pyridine **89** to its sulphone **180** in 37% yield [equation 71]. Similar reagents, sodium hypochlorite and dilute hydrochloric acid, transform benzothieno[2,3-b]pyridine to the sulphone in 73% yield.



equation 71

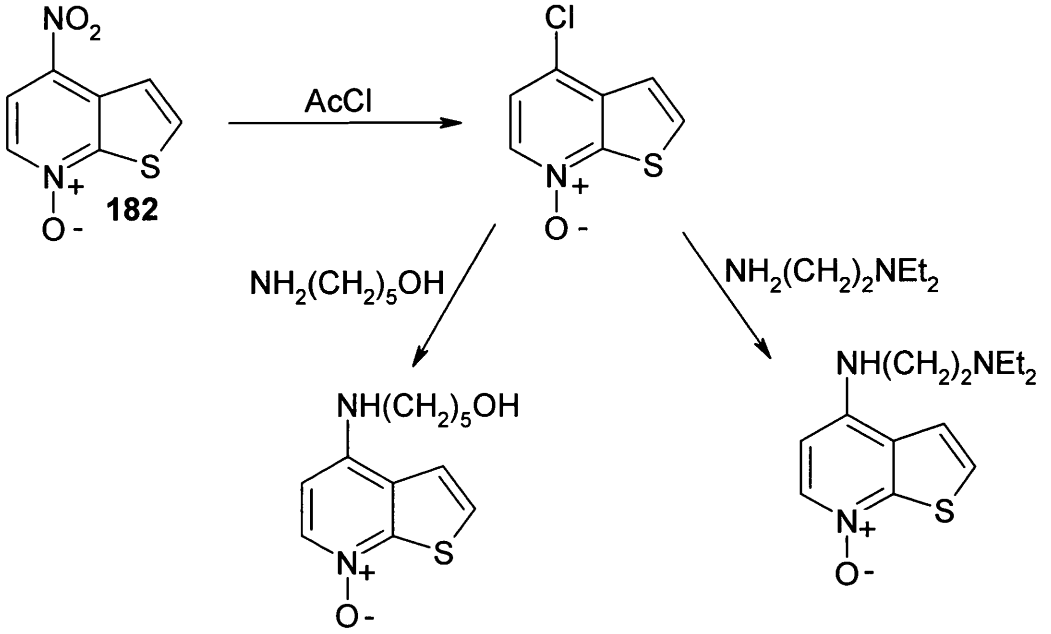
1.2.4.5 Reactions of thieno[2,3-b]pyridine oxides

Thieno[2,3-b]pyridine N-oxide **181**, when treated[438] with a mixture of nitric and sulphuric acids at 90-120 °C, nitrates in the 4-position to give **182** in 50% yield. Alternatively with nitric and acetic acids 5-nitrothieno[2,3-b]pyridine N-oxide **183** is formed in 56% yield [scheme 55]. **182** is thought[438] to form by electrophilic substitution by the nitronium ion while 1,3-dipolar addition to the nitrone followed by electrophilic substitution accounts for **183**.



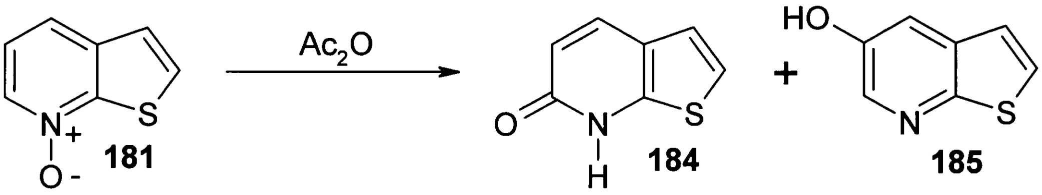
Scheme 55

Reaction[438] of **182** with acetyl chloride replaces the nitro group with a chloro which then undergoes further substitution by nitrogen nucleophiles [scheme 56].



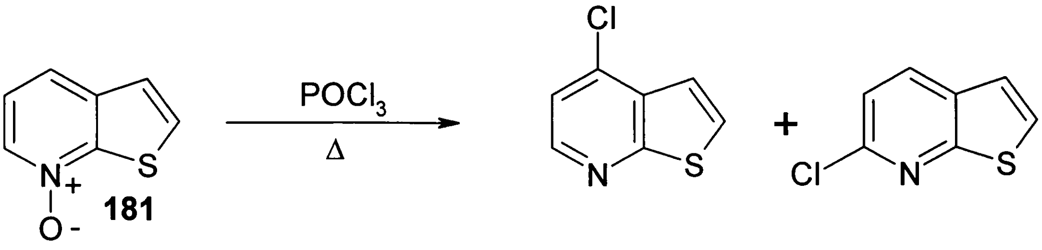
Scheme 56

Refluxing[444] **181** with acetic anhydride followed by hydrolysis gives thieno[2,3-b]pyrid-6(7H)-one **184** in 13% yield together with 4% of 5-hydroxythieno[2,3-b]pyridine **185** [equation 72].



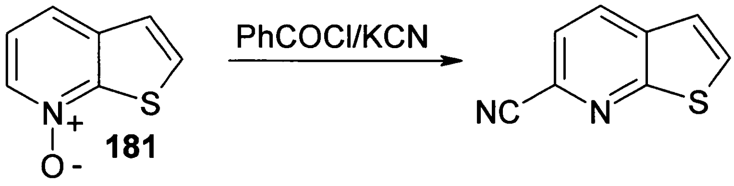
Equation 72

Chlorination[444] takes place at either the 4-position (54%) or the 6-position (31%) on reaction of **181** with phosphorus oxychloride by the S_NA mechanism (see section 1.1.3.2.2) [equation 73].

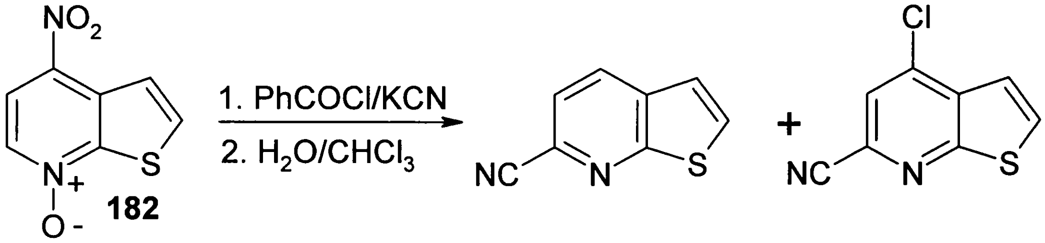


Equation 73

Reissert-Henze reactions successfully[445] introduce a cyano group into the 6-position of **181**. For 4-substituted thieno[2,3-b]pyridines, the functional group at C-4 is retained [equation 74], but[445] when this group is nitro it is replaced by either hydrogen or chloride when subsequently refluxed in water/chloroform [equation 75].

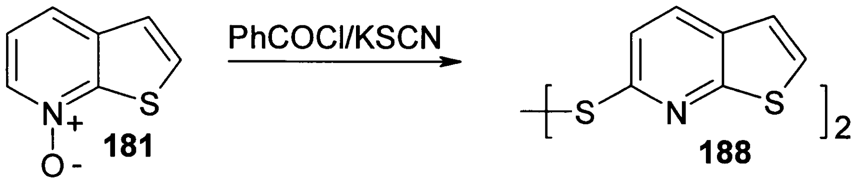


Equation 74



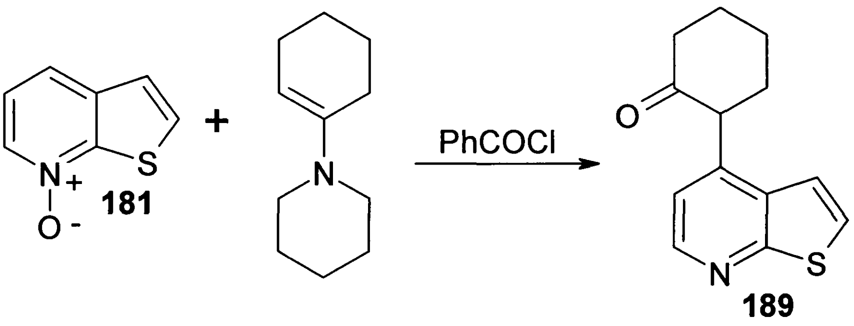
Equation 75

An extension[440] to the Reissert-Henze reaction involves potassium thiocyanate, however only dimer **188** was formed in 2% yield [equation 76].

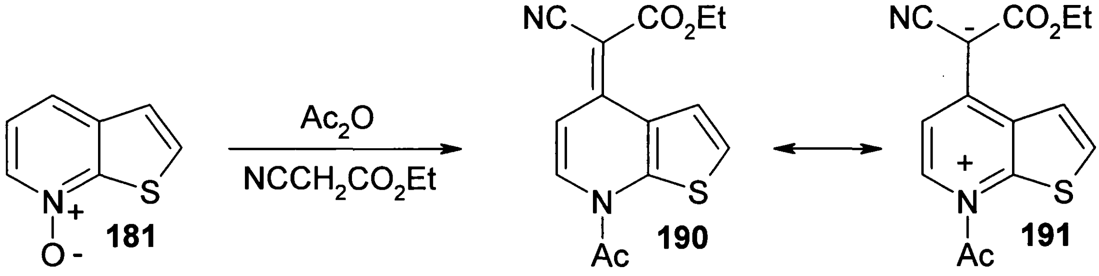


Equation 76

Reaction[446] of **181** with carbon nucleophiles gives substitution at C-4 with loss of the N-oxide function. Benzoyl chloride and enamines of cyclohexanone give the 4-cyclohexanonyl derivative **189** [equation 77]. When **181** is treated with acetic anhydride and ethyl cyanoacetate a product forms which on analysis contains an acetyl group in addition to the expected ethylcyanoacetate. It is thought[446] that this compound exists as two tautomeric forms **190** and **191** [scheme 56].

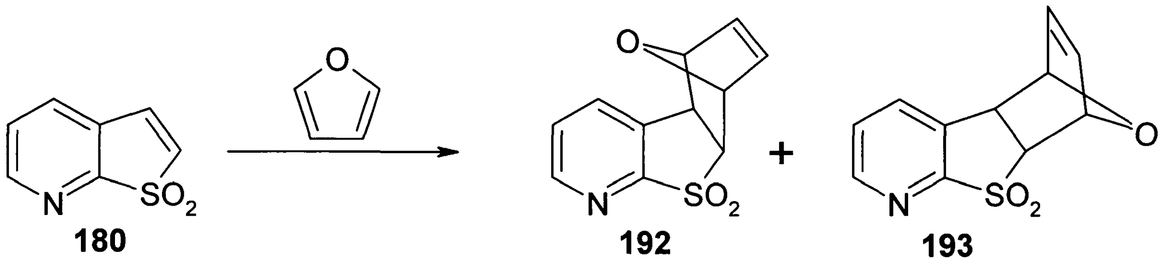


Equation 77



Scheme 56

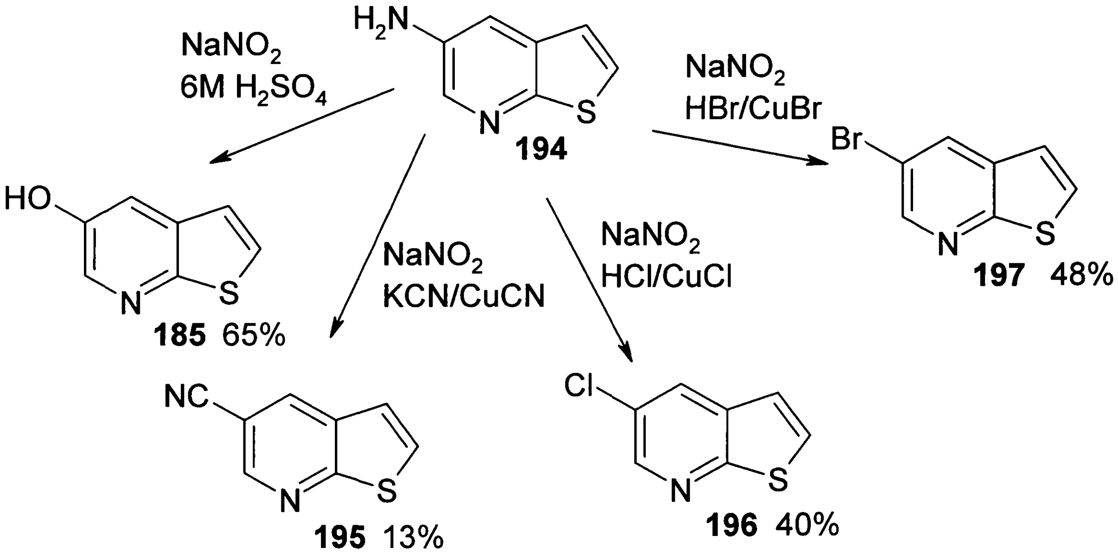
Thieno[2,3-b]pyridine sulphones are known to act as dienophiles and undergo Diels-Alder reactions[443, 447] with anthracene, cyclopentadiene and other dienes. For example[443] **180** condenses with furan to form two products; the exo adduct **192** and the endo **193** [equation 78].



Equation 78

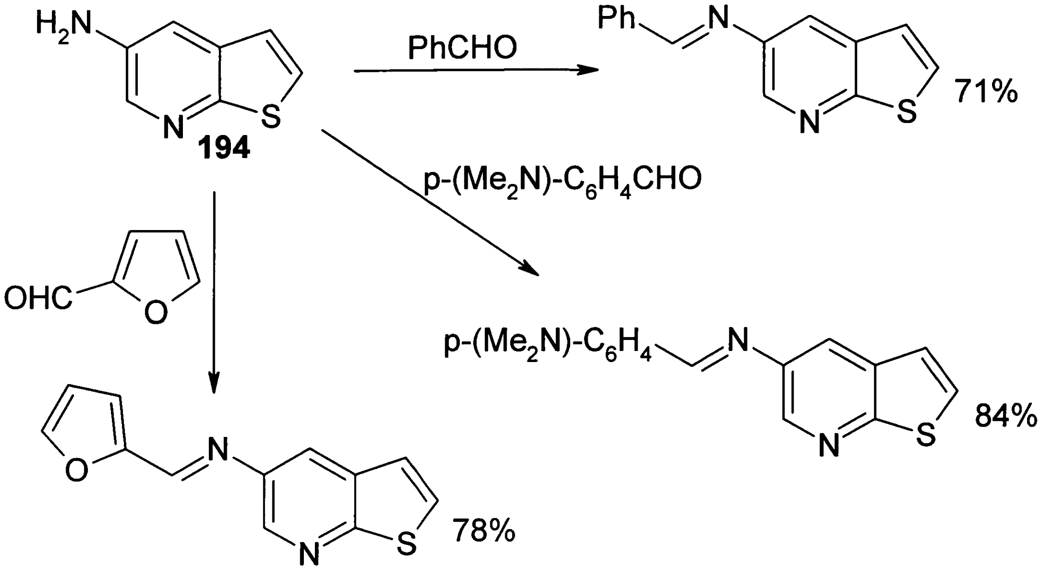
1.2.4.6 Reactions of aminothieno[2,3-b]pyridines

5-Aminothieno[2,3-b]pyridine **194** shows[434] two kinds of reaction typical of primary aryl amines. Firstly, when **194** is diazotised with sodium nitrite and concentrated sulphuric acid, the resulting salt can be converted by Sandmeyer reactions to the 5-hydroxy **185**, 5-cyano **195**, 5-chloro **196**, and 5-bromo **197** thieno[2,3-b]pyridines [scheme 58].



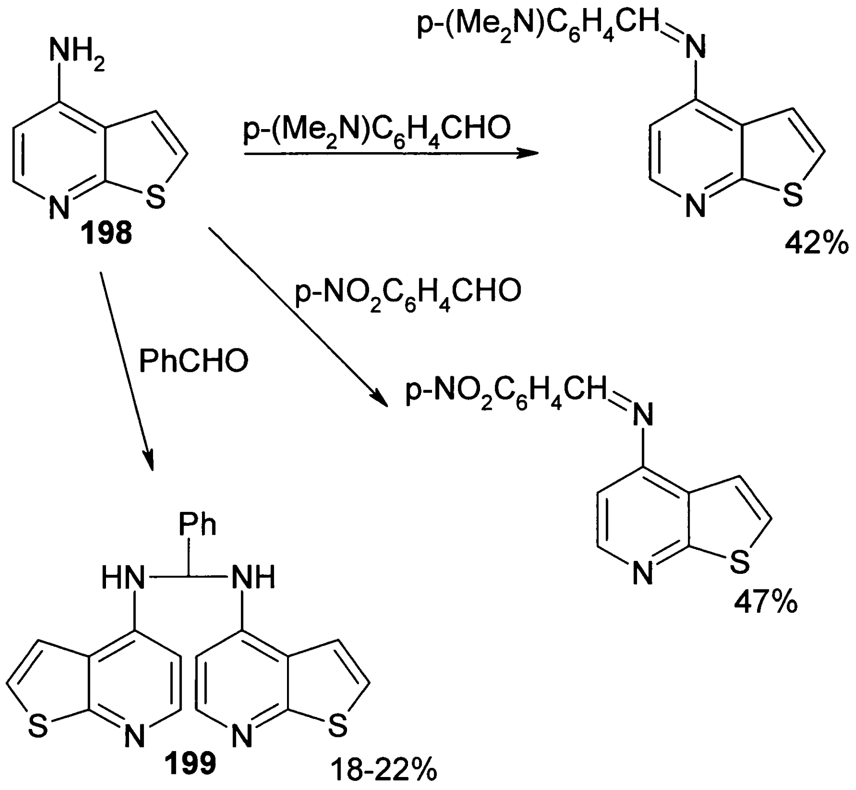
Scheme 58

Secondly condensation[434] of **194** with benzaldehyde, dimethylaminobenzaldehyde and fufuraldehyde gives the corresponding imines in good yield [scheme 59].



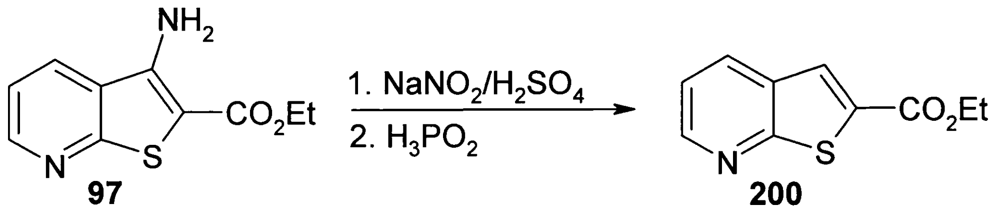
Scheme 59

Reaction[438] of 4-aminothieno[2,3-b]pyridine **198** with p-dimethylamino benzaldehyde or p-nitrobenzaldehyde, molecular sieve and a catalytic amount of acetic acid in refluxing xylene led to the formation of the corresponding imines. Benzaldehyde likewise reacted under these conditions but gave the 2:1 condensate **199** [scheme 60].



Scheme 60

Diazotisation[448] of 3-amino-2-ethyloxycarbonylthieno[2,3-b]pyridine **97** followed by hypophosphorus acid mediated reduction of the intermediate diazonium salt produced 2-ethyloxycarbonylthieno[2,3-b]pyridine **200** in 38% yield [equation 79].

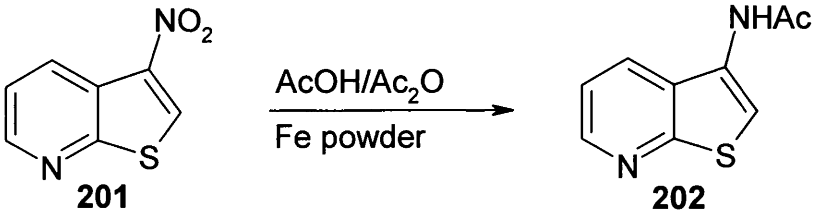


Equation 79

1.2.4.7 Miscellaneous reactions

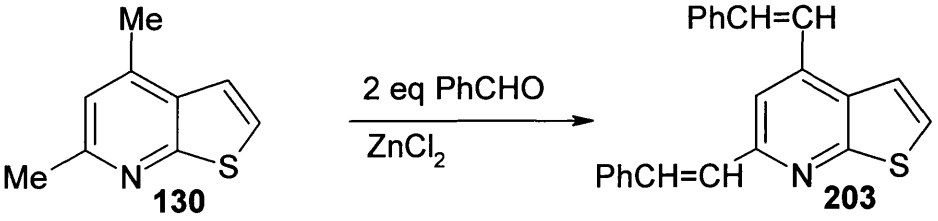
Heating 3-nitrothieno[2,3-b]pyridine **201** with acetic acid, acetic anhydride and iron produced[449] 3-acetamidothieno[2,3-b]pyridine **202** [equation 80]. In the case of 2-

nitro-3-bromothieno[2,3-b]pyridine **160** the reaction is accompanied by some debromination.



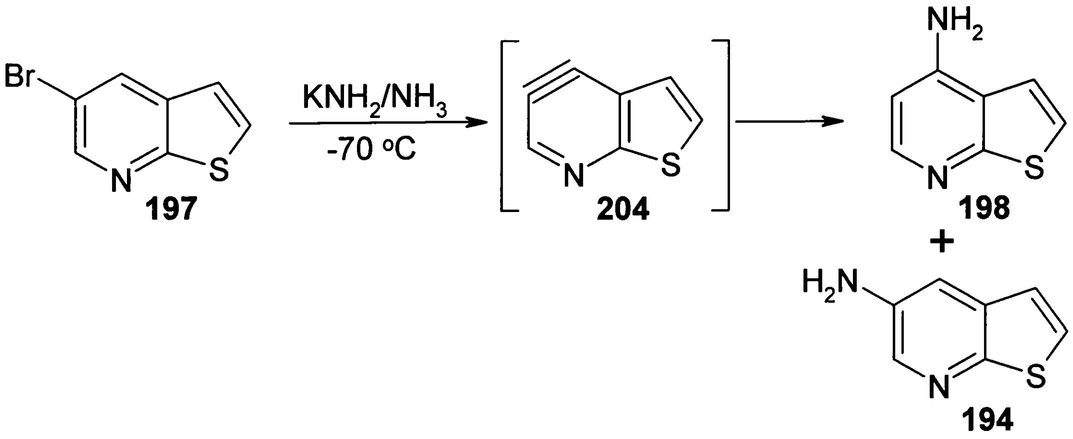
Equation 80

The methyl groups of 4,6-dimethylthieno[2,3-b]pyridine **130**, being relatively acidic, readily condense[409] with two equivalents of benzaldehyde to form 4,6-distyrylthieno[2,3-b]pyridine **203**, when mixed with zinc chloride [equation 81].



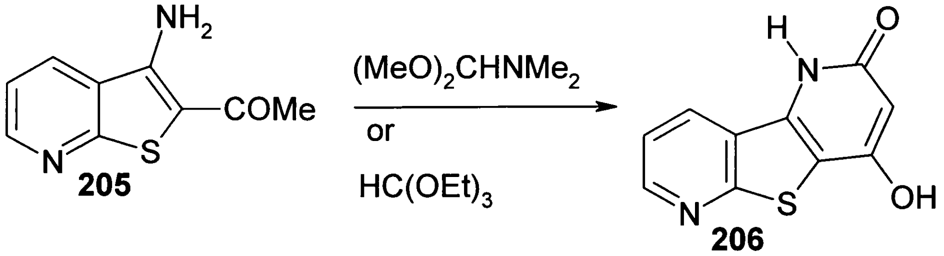
Equation 81

Treatment[434] of 5-bromothieno[2,3-b]pyridine **197** with potassium amide in liquid ammonia at –70 °C gave 4-aminothieno[2,3-b]pyridine **198** in 40% yield together with 0-13% of **194**. The reaction is thought to proceed via the thienopyridyne **204** [scheme 61].



Scheme 61

There has been considerable interest in thieno[2,3-b]pyridines as precursors to tricycles and other polycyclic compounds. It is not feasible to review this topic here as it is outside the scope of this investigation, however a recent review[450] covers the subject in considerable detail. Most cyclisation reactions take place on polysubstituted 3-aminothienopyridines containing a carbonyl or nitrile in the 2-position. For example[338] the cyclocondensation of 2-acetyl-3-aminothieno[2,3-b]pyridine **205** with N,N-dimethylformamide dimethylacetal or triethyl orthoformate gave 4-hydroxypyrido[2',3':4,5]thieno[2,3-b]pyridin-2(1H)-one **206** [equation 82].

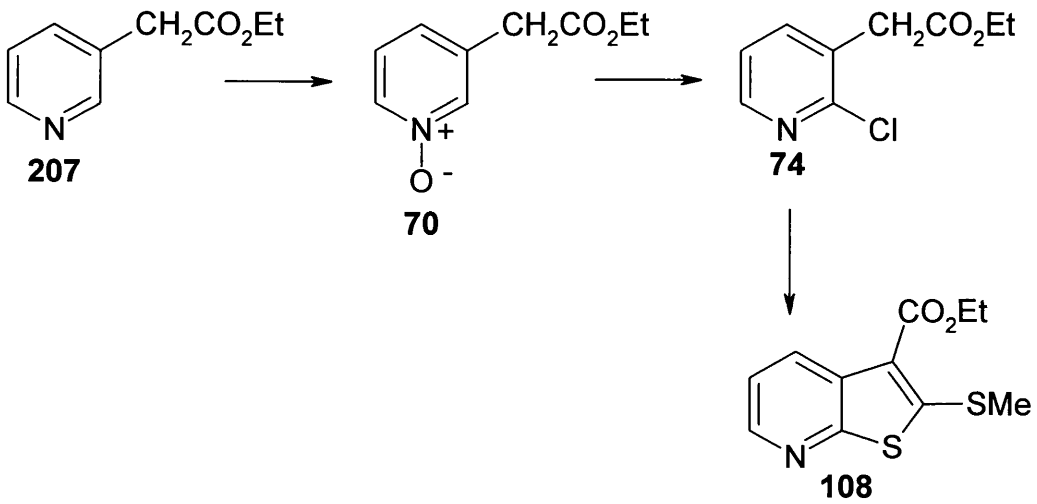


Equation 82

2 Discussion

2.1 Overview

The overall aim of this research project was to investigate nucleophilic substitution of the thiomethyl group of 3-ethyloxycarbonyl-2-thiomethylthieno[2,3-b]pyridine **108** with various nitrogen, carbon and oxygen nucleophiles in an attempt to produce novel thienopyridines and gain entry into polycyclic systems. The synthetic route to **108** is in three steps: oxidation of ethyl 3-pyridylacetate **207** to its N-oxide **70**, followed by chlorination of **70** to obtain ethyl 2-chloro-3-pyridylacetate **74**, then reaction of **74** with carbon disulphide and subsequent cyclisation to **108** [scheme 63]. Each step in this route is examined and any improvements discussed.

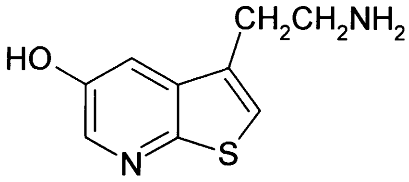


Scheme 63

During the attempted nucleophilic substitution reactions of **108**, an interesting reaction was observed, the conversion of benzylamine to benzaldehyde by action of an N-oxide group. This transformation was investigated to see whether it was a general reaction of pyridine N-oxides and if optimum reaction conditions could be found.

Additionally, the preparation of other chloropyridines, thieno[2,3-b] and [3,2-c]pyridines, ketene dithioacetals and thiophenes, arising from byproducts of the preparation of **74**, are described.

Molecular modelling studies, undertaken previously[399] within the research group, identified a possible thieno[2,3-b]pyridine agonist of serotonin (5-hydroxytryptophan, 5-HT) **208** [figure 9]. A synthetic route to this compound starting with thieno[2,3-b]pyridine **108** was investigated.



208

Figure 9

The final section concerns the position of the carbonyl stretching absorbance observed in the infrared spectra of prepared compounds containing an ethyl ester group. Other functional groups in these molecules influence this vibration and these observations are discussed.

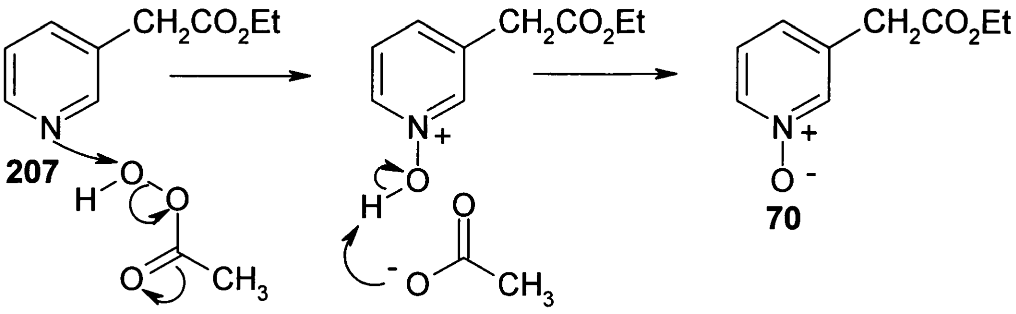
This discussion is therefore divided into the following sections:

- Preparation of pyridine N-oxides
- Preparation of chloropyridines
- Preparation of thienopyridines
- Preparation of ketenedithioacetals and thiophenes
- Reactions of thienopyridines
- Route to an agonist of serotonin

- Reaction of benzylamine with pyridine N-oxides
- Ester carbonyl stretching absorbances.

2.2 Preparation of pyridine N-oxides

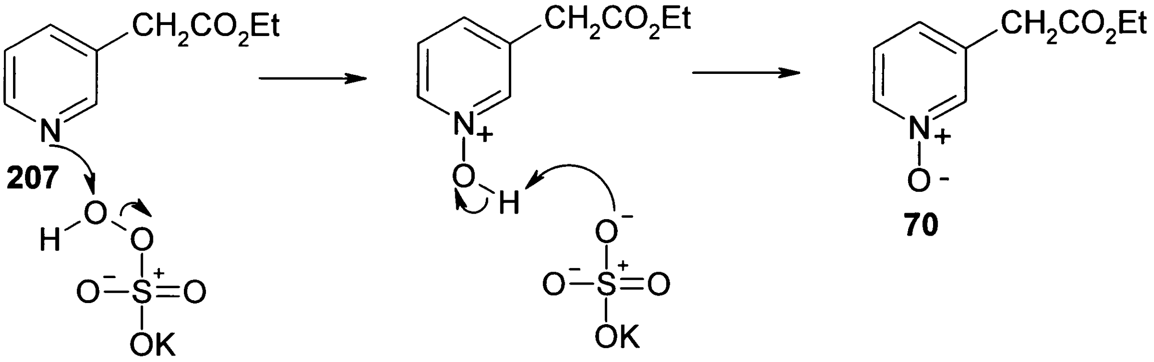
The preparation of ethyl 3-pyridylacetate N-oxide was carried out using peracetic acid generated *in situ* from hydrogen peroxide and glacial acetic acid. Hence, ethyl 3-pyridylacetate **207** was dissolved in glacial acetic acid and a slight stoichiometric excess of hydrogen peroxide (30% v/v) was added. The mixture was heated at 70 °C for seven days with the addition of more hydrogen peroxide as required (section 5.1). The presence of excess peroxide in the reaction mixture was determined by moist starch/iodide paper. The workup procedure involved destruction of any excess peroxide by the addition of activated carbon, filtration, and the removal of the solvent *in vacuo*, to give a brown oil which consisted of ethyl 3-pyridylacetate N-oxide **70**, some unreacted ethyl 3-pyridylacetate **207**, residual acetic acid and some dark coloured decomposition products. Separation by column chromatography was time consuming and did not fully separate ethyl 3-pyridylacetate N-oxide **70** from the coloured material. Further purification by recrystallisation led to an overall yield of 69%, based on the starting material. The reaction proceeds by nucleophilic attack by the nitrogen lone pair on the peracid [scheme 64].



Scheme 64

As this was the first of a multistep reaction sequence it was important to maximise the yield and so this resulted in other oxidising agents being investigated.

Potassium peroxymonosulphate, commercially available as OXONE,[68] was the first reagent employed using the method, describing the preparation of sulphoxides and sulphones, published[451] by Greehalgh. OXONE consists of a mixture of two parts potassium peroxymonosulphate, one part potassium bisulphate and one part potassium sulphate, and is considered a powerful, more stable alternative to Caro's acid (peroxysulphuric acid). Ethyl 3-pyridylacetate **207**, together with OXONE (1.1 equivalents) and wet alumina, present as a surface catalyst, were refluxed in dichloromethane for four hours. Filtration, evaporation of the solvent, and recrystallisation of the resulting solid led to production of the ethyl 3-pyridylacetate N-oxide **70** in 50% yield, with unreacted ethyl 3-pyridylacetate **207** recovered quantitatively (section 5.2). Attempts were made to improve the yield. Increasing the quantity of OXONE used proved unsuccessful, and refluxing in a higher boiling solvent led to degradation of the starting pyridine, while the application of ultrasound to the reaction mixture had no marked effect. This oxidation was consistently incomplete (according to tlc). It was thought the problem lay in the solubility of ethyl 3-pyridylacetate **207** in water, which was present as a requirement of this method. Eliminating water entirely from the reaction however led to a further reduction in yield. The mechanism is similar to that for oxidation by an organic peracid, with nucleophilic attack by the nitrogen lone pair as the first step, followed by proton abstraction by the sulphate anion [scheme 65].



Scheme 65

Sodium perborate monohydrate has been reported[22] as an oxidising agent for the preparation of pyridine N-oxides. The structure of sodium perborate has been shown[452] to be a six-membered heterocyclic bisanion [figure 10].

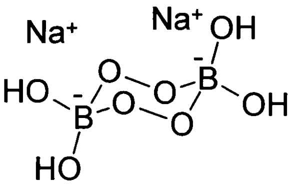
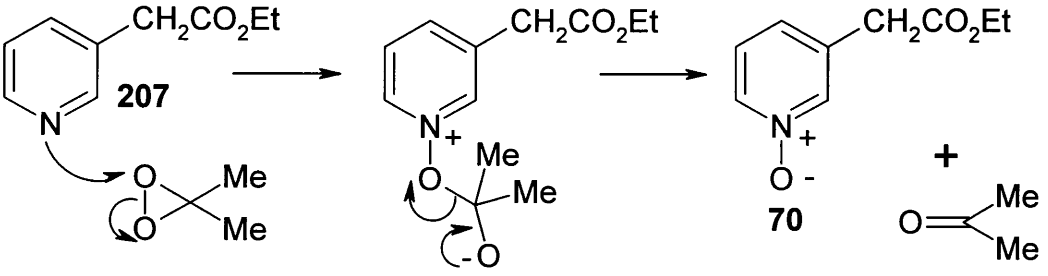


Figure 10

It is considered a "dry carrier" of hydrogen peroxide and releases hydrogen peroxide spontaneously[453] in water. Oxidation of acetic acid to peracetic acid by sodium perborate has been demonstrated[454] and is thought to be the reagent responsible for the production of pyridine N-oxides in this reaction. Thus, sodium perborate monohydrate and ethyl 3-pyridylacetate **207** were stirred in glacial acetic acid at 60 °C for 24 hours. The solution was then filtered and the solvent removed *in vacuo*. Acetone was added and the solution filtered and concentrated.

Purification by column chromatography and recrystallisation gave ethyl 3-pyridylacetate N-oxide **70** in 73% yield (section 5.3).

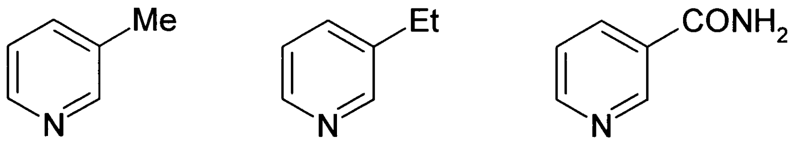
N-oxidation of pyridine with dimethyldioxirane **26**, formed *in situ* from acetone and OXONE, has also been described[71] and hence investigated. An aqueous solution of OXONE was added dropwise to a mixture of acetone and ethyl 3-pyridylacetate **207** in a phosphate buffer, kept at pH 7.5-8.0 by the constant addition of 1M potassium hydroxide. After stirring at room temperature for 2 hours the mixture was extracted with four portions of dichloromethane. The solvent was removed *in vacuo* and the resulting solid purified by recrystallisation to give ethyl 3-pyridylacetate N-oxide **70** in 57% yield (section 5.4). The mechanism of N-oxidation is by nucleophilic attack of the nitrogen lone pair on the peroxide bond, followed by regeneration of acetone [scheme 66]. The reaction medium is held at neutral pH to avoid the side reaction involving Baeyer-Villiger oxidation of the ketone, known[455] to take place at low pH.



Scheme 66

The final reagent[23] investigated was *m*-chloroperbenzoic acid. Initially the method reported by Paquett and Barrett[456] was followed. Ethyl 3-pyridylacetate **207** and *m*-CPBA (1.1 equivalents) were stirred together in chloroform for 1 hour at room temperature. The chloroform solution was then washed, first with sodium metabisulphite solution, to destroy excess *m*-CPBA, then with sodium bicarbonate solution to neutralise the *m*-chlorobenzoic acid (*m*-CBA) formed. The solvent was removed *in vacuo* to give ethyl 3-pyridylacetate N-oxide **70** in 66% yield. The aqueous washings were combined and extracted repeatedly with chloroform to give a further 8% of product (section 5.5). This process was inefficient and time consuming; therefore an improved method was developed. It was found that if solid reagents were added directly to the chloroform solution, i.e. sodium metabisulphite to destroy excess oxidising agent, potassium carbonate to neutralise *m*-CBA, followed by the usual workup, ethyl 3-pyridylacetate N-oxide **70** was isolated in 93% yield (section 5.6). The mechanism is thought to be essentially the same as for other organic peracids.

It was decided to study these reagents with other 3-substituted pyridines in order to gauge their effectiveness in the general preparation of N-oxides. The readily available pyridines chosen were 3-methylpyridine **209**, 3-ethylpyridine **210**, and nicotinamide **211** [figure 11].



209 **210** **211**

Figure 11

Each pyridine was oxidised using the methods already described and the yields obtained are detailed [table 3].

Pyridine	CH_3CO_3H	*m*-CPBA	OXONE	$NaBO_3$	Dioxirane
207	69%	93%	50%	73%	57%
209	94%	84%	50%	77%	23%
210	64%	83%	52%	69%	52%
211	74%	70%	52%	52%	1%

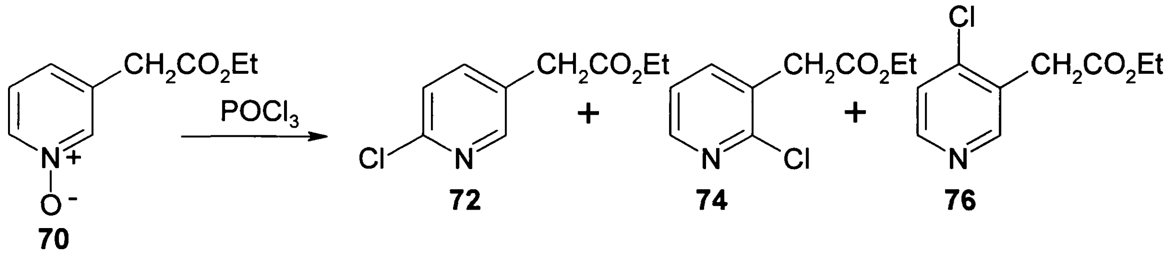
Table 3: Yields of N-oxides by Oxidising Agent.

Although reasonable yields were obtained in some individual cases, we concluded[457] that *m*-CPBA, using the improved procedure described, gave the greatest yield. This involved the utilisation of solid reagents in the work-up and provided the most efficient method for the transformation of these pyridines to their N-oxides.

2.3 Preparation of chloropyridines

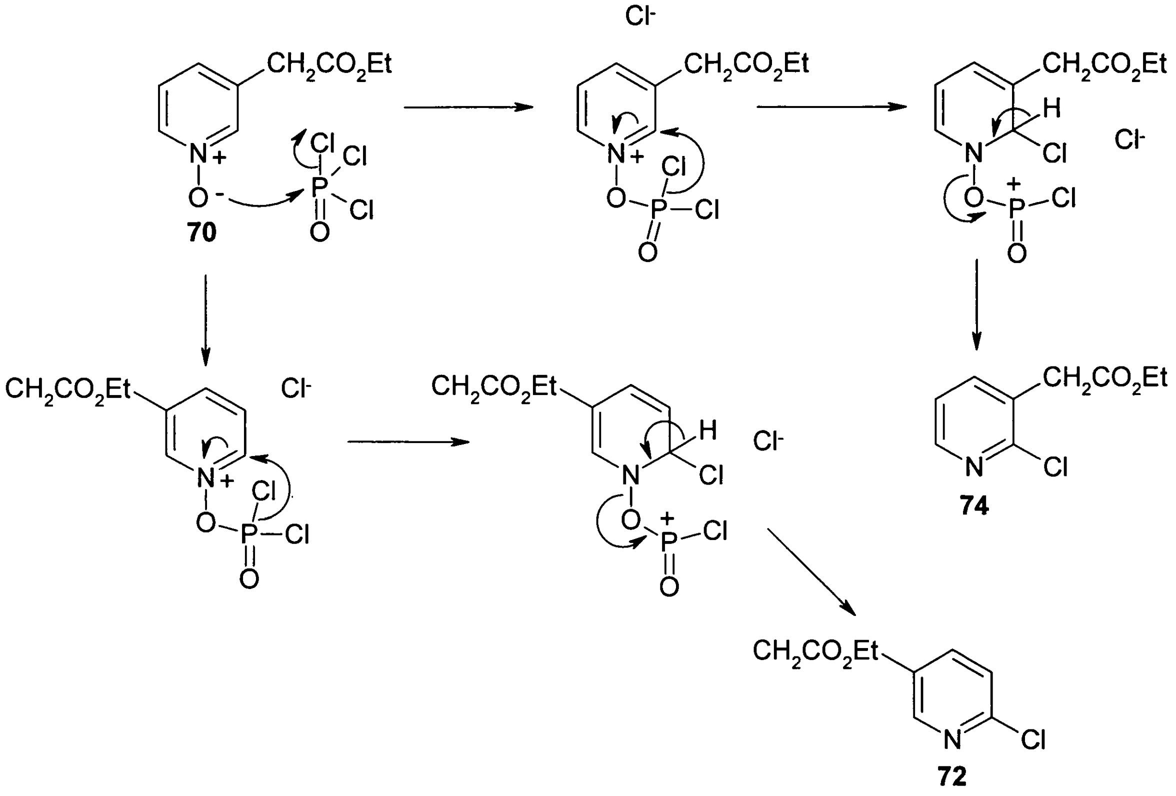
See appendix 1 for a summary of the reactions discussed in this section.

The method used in this programme for the preparation of ethyl 2-chloro-3-pyridylacetate **74** was developed[260,261] in this laboratory, and was in turn based on the procedure reported by Okuda and Robison[259] for the preparation of chloro-3-cyanomethylpyridine. Ethyl 3-pyridylacetate N-oxide **70** was added slowly to phosphorus oxychloride and the mixture refluxed for 3 hours. Excess phosphorus oxychloride was removed by distillation and the residue poured onto ice, basified with ammonia solution and extracted with ethyl acetate (section 5.7). Evaporation of the solvent gave a brown oil which when examined by tlc was seen to consist of two products with very similar Rf's and one more polar component. Column chromatography resulted in poor separation of ethyl 2-chloro-5-pyridylacetate **72** and ethyl 2-chloro-3-pyridylacetate **74**, only affording small quantities of the pure substances both of which were identified by comparison[260,261] of their infrared and pmr spectra with those reported. The more polar third isomer ethyl 4-chloro-3-pyridylacetate **76** was readily separated and was isolated in 13% yield [equation 83]. Again the structure was confirmed[260,261] by comparison of spectroscopic data with the literature.

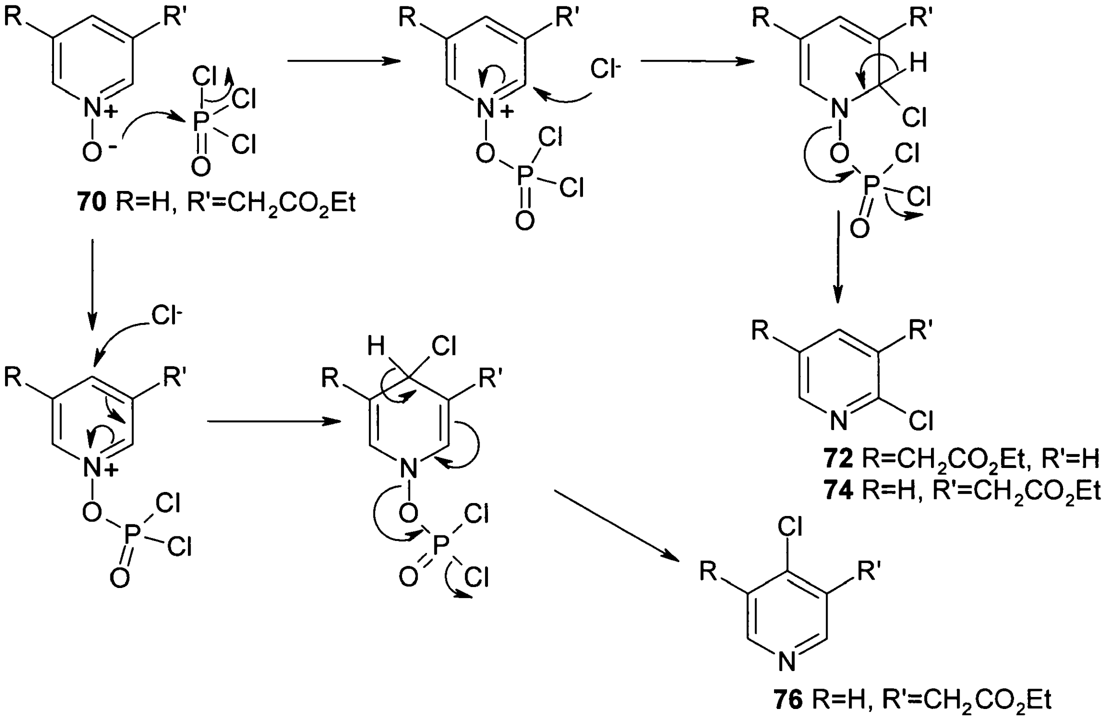


Equation 83

There are two mechanistic routes that this reaction can take, an intramolecular mechanism involving concerted shift or recombination of the O-phosphorylated pyridine-chloride ion pair [scheme 67], or an intermolecular mechanism via attack by a separated anion after electrophilic attack on the oxygen atom [scheme 68]. The intermolecular mechanism accounts for the formation of all three isomers **72**, **74** and **76**, while the intramolecular mechanism also explains the formation of **72** and **74**.

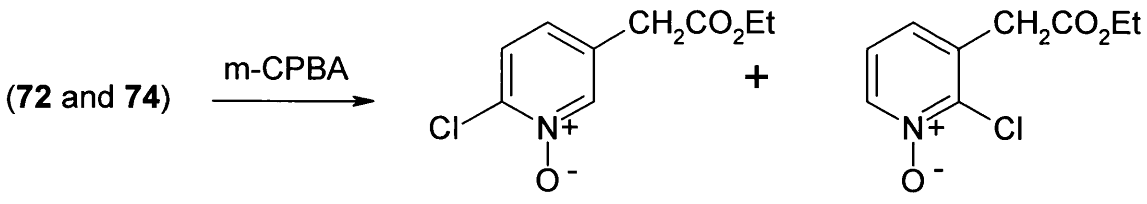


Scheme 67



Scheme 68

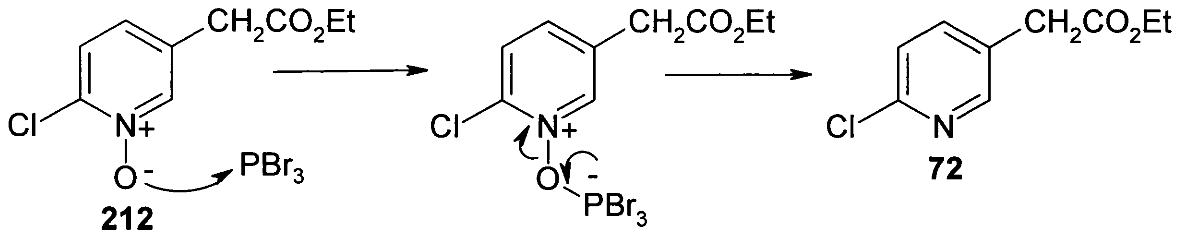
As ethyl 2-chloro-3-pyridylacetate **74** was the required isomer for further reaction a good separation was essential. It was envisaged that conversion of ethyl 2-chloro-5-pyridylacetate **72** and ethyl 2-chloro-3-pyridylacetate **74** to their N-oxides may lead to differences in Rf and allow separation; therefore they were treated with *m*-CPBA using the method previously described (section 2.2). Examination of the reaction by tlc indicated that a better separation had been achieved, however it also showed a significant amount of unreacted ethyl 2-chloro-5-pyridylacetate **72** and ethyl 2-chloro-3-pyridylacetate **74** remaining (section 5.8). This was thought to be due to the presence of a chlorine atom α to the nitrogen atom. Not only does it sterically hinder the nitrogen site but the chlorides inductive effect, which predominates over it's mesomeric effect, reduces the susceptibility[29, 63] of the nitrogen to N-oxidation by making it less basic. It has been reported[32] that the addition of a mineral acid improves the oxidising ability of an organic peracid; therefore the oxidation was repeated in the presence of a little concentrated sulphuric acid (section 5.9). Again some unoxidised ethyl 2-chloro-5-pyridylacetate **72** and ethyl 2-chloro-3-pyridylacetate **74** were found in the reaction mixture, however there appeared to be substantially less than before. Separation by column chromatography gave unreacted ethyl 2-chloro-5-pyridylacetate **72** and ethyl 2-chloro-3-pyridylacetate **74**, recovered in 28% yield as a mixture. Further elution gave, firstly, a white solid after recrystallisation from ethyl acetate. Examination of the infrared spectrum showed a strong absorbance at 1735cm^{-1} characteristic of an ester group, a strong absorbance at 1250cm^{-1} from an N-oxide group and both aromatic (3075, 3010cm^{-1}) and aliphatic (2950, 2960cm^{-1}) C-H stretching absorbances. (For convenience, peaks in the infrared spectra around 1700cm^{-1} are assigned to ester carbonyls, where appropriate. A more comprehensive discussion of these absorbances is in section 2.9). The pmr spectrum showed a triplet at 1.24δ and a quartet at 4.14δ characteristic of an ethyl ester and there was the expected singlet for a methylene function at 3.74δ. The singlets observed at 7.08δ, 7.14δ and 8.18δ were indicative of a 2,5-disubstituted pyridine N-oxide. As a result the compound was assigned the structure ethyl 2-chloro-5-pyridylacetate N-oxide[261] (**212**, 30%). This structure was supported[458] by mass spectometry and elemental analysis. Further elution gave a second white solid after recrystallisation from toluene. The infrared spectrum showed aliphatic and aromatic C-H stretching at 2980 and 3060cm^{-1} respectively, a strong absorbance at 1734cm^{-1} due to an ester function and a further strong signal at 1275cm^{-1} characteristic of an N-oxide group. The pmr spectrum again showed a triplet at 1.20δ and a quartet at 4.03δ characteristic of an ethyl ester and there was the expected singlet for methylene protons at 3.47δ. The pattern observed for the pyridine protons, i.e. a doublet of doublets at 6.99δ, a doublet at 7.25δ and a doublet of doublets at 8.07δ, is of the type expected for a 2,3-disubstituted pyridine N-oxide and hence this product was assigned the structure ethyl 2-chloro-3-pyridylacetate N-oxide[261] (**213**, 31%). Elemental analysis[458] coupled with mass spectrometry corroborated this structure, [equation 84].



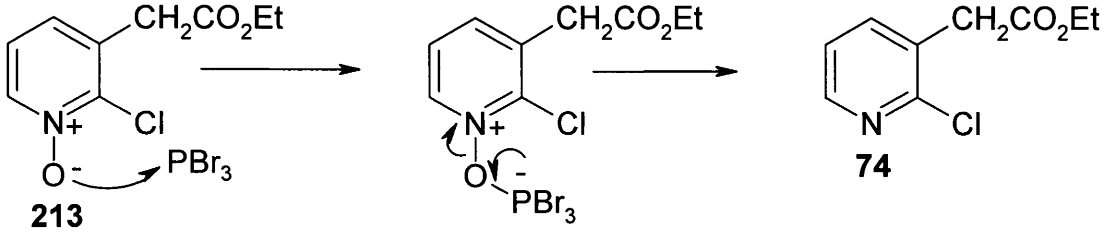
212 **213**

Equation 84

Deoxygenation of ethyl 2-chloro-5-pyridylacetate N-oxide **212** and ethyl 2-chloro-3-pyridylacetate N-oxide **213** to their parent compounds ethyl 5-chloro-3-pyridylacetate **72** and ethyl 2-chloro-3-pyridylacetate **74** was achieved with phosphorus tribromide (see section 1.1.2.1). The method used in this work was based on that described[105] by Hamana. The pyridine N-oxide was dissolved in DMF at 0 °C and treated with phosphorus tribromide. After one hour the mixture was poured onto saturated sodium bicarbonate solution and extracted with ethyl acetate. The solvent was dried and removed *in vacuo* to give chloropyridines **72** and **74** as, in each case, a colourless oil, which were positively identified[260,261] by comparison (infrared, pmr and tlc) with the literature (section 5.10 and 5.11). The mechanism involves nucleophilic attack on the electron deficient phosphorus atom of phosphorus tribromide, followed by cleavage of the N-O bond [schemes 69 and 70].

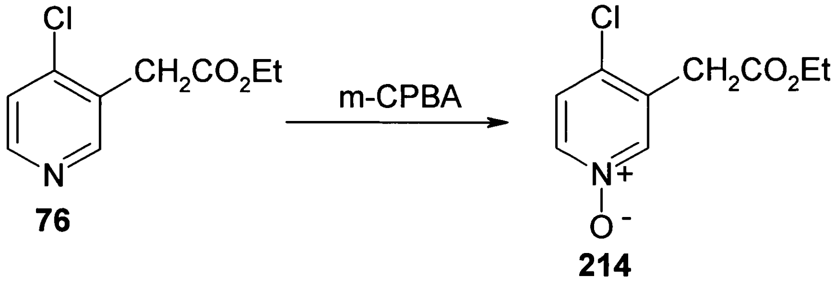


Scheme 69



Scheme 70

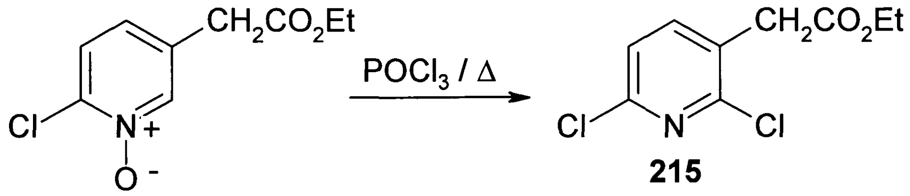
Ethyl 4-chloro-3-pyridylacetate **76**, also a colourless oil, was found to decompose rapidly in the atmosphere and even storage as a dilute solution at low temperatures was not effective. It was anticipated, based on previous observations, that the N-oxide of this pyridine would be a solid and hence, hopefully, more stable. Oxidation of ethyl 4-chloro-3-pyridylacetate **76** with *m*-CPBA gave after recrystallisation from ethyl acetate a white crystalline solid (section 5.12). The infrared spectrum showed the expected absorbance at 1734cm^{-1} for an ester group, at 1245cm^{-1} for an N-oxide function and at 2990cm^{-1} (aliphatic) and 3040cm^{-1} (aromatic) C-H bonds. The pmr spectrum showed a triplet at 1.25δ and a quartet at 4.20δ characteristic of an ethyl ester and there was the expected singlet at 3.60δ for a methylene function adjacent to an ester group. A doublet at 7.25δ, a doublet of doublets at 8.03δ and a doublet at 8.15δ were indicative of a 3,4-disubstituted pyridine N-oxide. The compound was therefore assigned the structure ethyl 4-chloro-3-pyridylacetate N-oxide[261] **214** and was obtained in 70% yield. This structure was supported by elemental analysis[458] and mass spectrometry, [equation 85]. Ethyl 4-chloro-3-pyridylacetate N-oxide **214** proved to be stable under normal storage conditions over long time periods.



Equation 85

As there was a significant amount of ethyl 2-chloro-5-pyridylacetate N-oxide **212** obtained from these reactions this was further chlorinated to produce novel polychlorinated pyridines. Theoretically there could be two dichloropyridines formed, as the nucleophilic chlorination of pyridine N-oxides usually proceeds by two mechanistic routes (see section 1.1.3.2.2): via a complex of the N-oxide function and the inorganic acid halide.

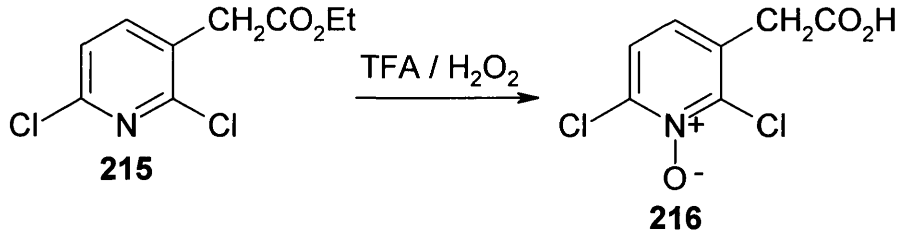
Ethyl 2-chloro-5-pyridylacetate N-oxide **212** was added to phosphorus oxychloride and the mixture refluxed for three hours, then the solvent removed *in vacuo*. The resulting brown oil was poured onto ice, basified with ammonia solution and extracted with ethyl acetate. Examination by tlc indicated that only one product had been formed. The solvent was evaporated and the oil distilled under reduced pressure (section 5.13). The infrared spectrum confirmed the presence of an ester group (1736cm^{-1}) while the pmr spectrum showed the characteristic peak pattern for a 2,3,6-trisubstituted pyridine, two doublets at 7.18δ and 7.58δ (for both J=7.2Hz) for protons C-5 and C-4 respectively. A triplet at 1.25δ and a quartet at 4.15δ were characteristic of an ethyl ester and there was the expected singlet at 3.69δ for a methylene function adjacent to an ester group. As a result the compound was assigned the structure ethyl 2,6-dichloro-3-pyridylacetate **215** obtained in 58% yield [equation 86]. This structure was supported by mass spectrometry[458] and elemental analysis.



Equation 86

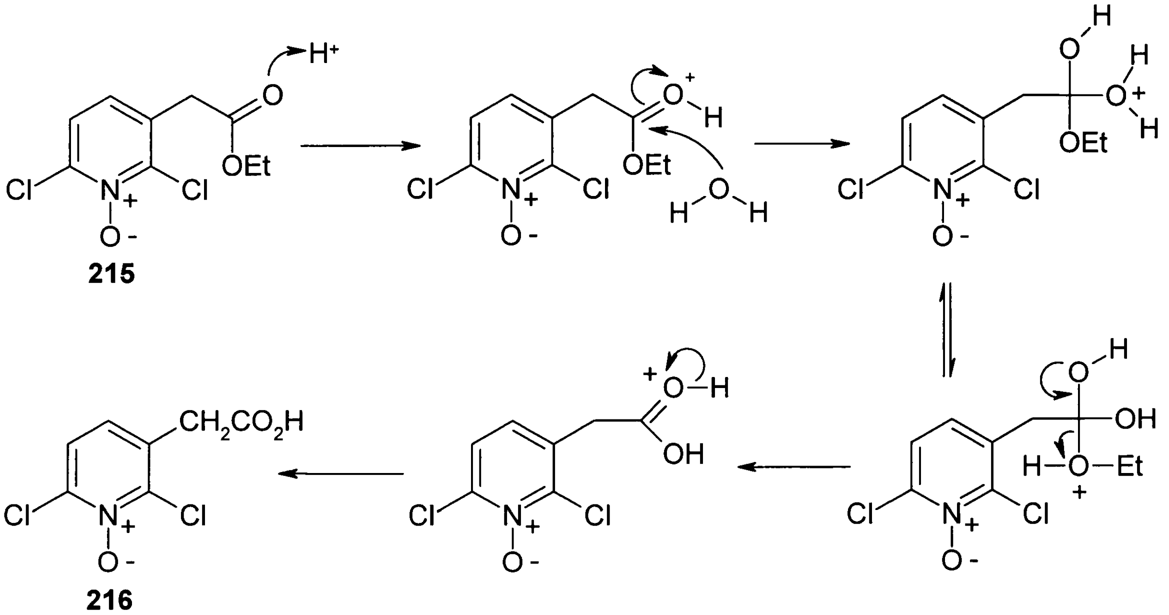
As no other product was isolated from this reaction it would appear that the intramolecular mechanism [scheme 67] overwhelmingly predominates in this case, and if any other isomer had formed, it was in a quantity too small to be detected.

An attempt to produce the 2,4,6-trichloropyridine derivative from ethyl 2,6-dichloro-3-pyridylacetate **215** was now undertaken to allow the later preparation of more novel thienopyridines. As has been described earlier, chlorine atoms α- to the nitrogen reduce the susceptibility of pyridines to N-oxidation. Ethyl 2,6-dichloro-3-pyridylacetate **215** was treated with *m*-CPBA and a little concentrated sulphuric acid. After stirring for four days tlc indicated a substantial amount of **215** remaining in the reaction mixture. Following work up the only compound isolated was the starting material **215** (section 5.14). It has been reported[27,28,30] that peroxytrifluoroacetic acid, which contains a powerful electron attracting group (CF_3) and offers a more highly reactive electrophilic peracid, was effective in the N-oxidation of less basic pyridines. Thus, ethyl 2,6-dichloro-3-pyridylacetate **215** was dissolved in trifluoroacetic acid and 30% hydrogen peroxide added. The mixture was stirred for four days at room temperature then examined by tlc which showed mostly starting material in the reaction mixture. A further portion of hydrogen peroxide was added and the reaction was heated to 90 °C for sixteen hours when tlc indicated that no starting material remained. The mixture was cooled and carbon added to destroy any remaining peroxide. The solution was filtered and concentrated *in vacuo* to leave a brown solid, which on recrystallisation from methanol gave colourless crystals (section 5.15). The infrared spectrum showed a strong carbonyl absorbance (1715cm^{-1}) while the pmr spectrum again showed characteristic peak patterns for a 2,3,6-trisubstituted pyridine N-oxide; two doublets at 7.28δ and 7.67δ (for both J=7.2Hz) for protons C-4 and C-5 respectively. Surprisingly there were no characteristic signals for an ethyl ester group, but a singlet at 3.74δ confirmed the presence of a methylene function downfield shifted by an electron-withdrawing group. A further broad singlet, which integrated for one proton, was observed at 10.91δ indicating the molecule was an organic acid. Based on these observations the product was assigned the structure 2,6-dichloro-3-pyridylacetic acid N-oxide (**216**, 56%). Elemental analysis[459] corroborated the structure; although the analytical figure found for carbon was slightly high [equation 88].



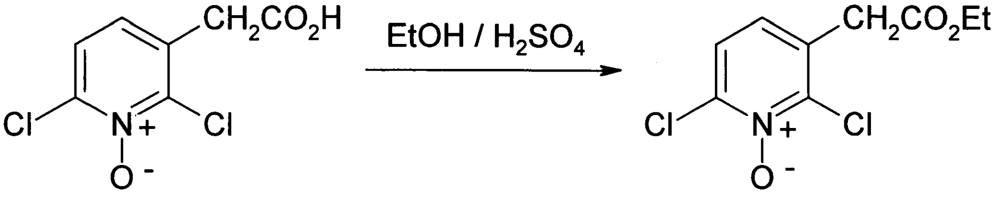
Equation 88

Acid catalysed hydrolysis of an ester usually requires heating with an excess of water present. The use of 30% hydrogen peroxide would appear to provide sufficient water for this reaction to take place [scheme 71].



Scheme 71

The ethyl ester of 2,6-dichloro-3-pyridylacetic acid N-oxide **216** was required as a precursor to thienopyridines, so **216** was refluxed in ethanol together with a drop concentrated sulphuric acid for 7 hours. Following work-up, white needles were obtained after recrystallisation from ethyl acetate [equation 89] (section 5.16). The infrared spectrum contained absorbances for a carbonyl (1721 cm^{-1}), aromatic C-H stretching (3048 and 3087cm^{-1}) and aliphatic C-H stretching (2932 and 2985cm^{-1}). The pmr spectrum showed a triplet at 1.30δ and a quartet at 4.24δ, characteristic of an ethyl ester together with a singlet at 3.81δ for the methylene protons shifted downfield by the ester group. There were doublets at 7.18 and 7.47δ (for both J = 8.3 Hz) which were assigned to H-4 and H-5 respectively. Microanalysis[459] corroborated the structure as ethyl 2,6-dichloro-3-pyridylacetate N-oxide **217**, isolated in 64% yield.

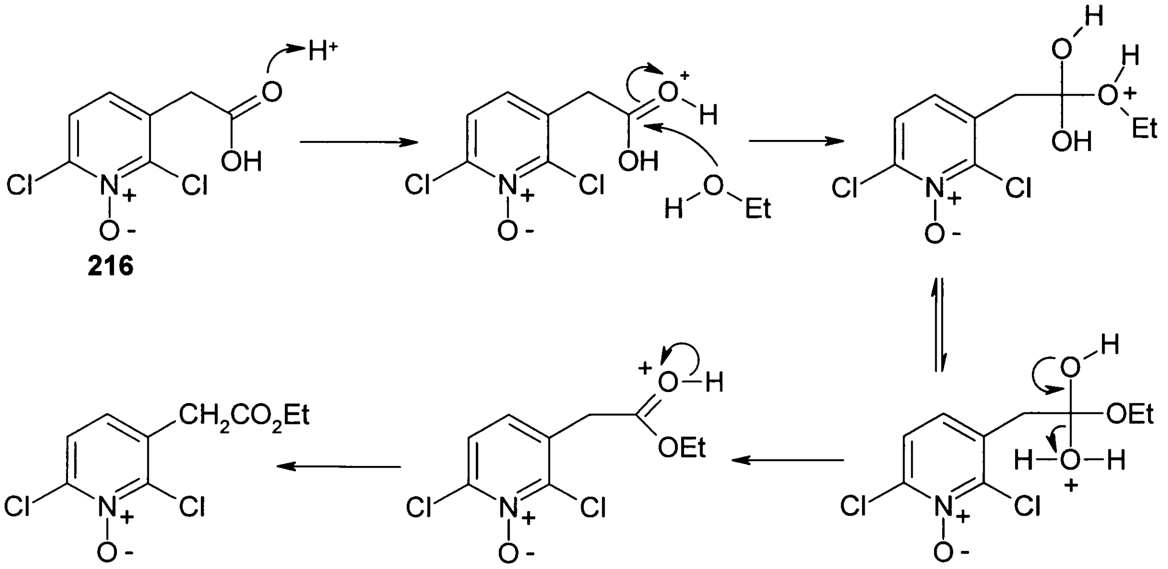


216

217

Equation 89

Acid catalysed esterification usually takes place in the presence of excess alcohol via an acid catalysed nucleophilic substitution mechanism [scheme 72].

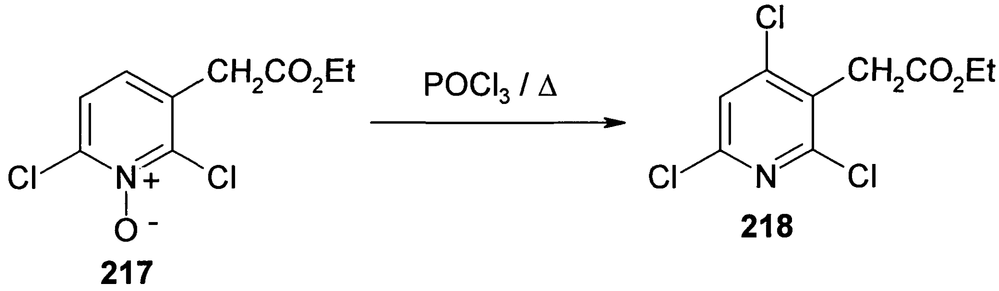


216

217

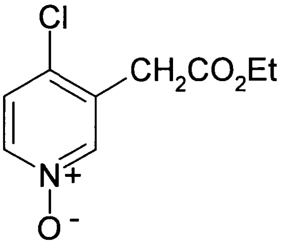
Scheme 72

Ethyl 2,6-dichloro-3-pyridylacetate N-oxide **217** was added to phosphorus oxychloride and the mixture refluxed for three hours, and after work-up a pink oil was obtained (section 5.17). The infrared spectrum showed an absorbance for an alkyl ester group (1732cm^{-1}). The pmr spectrum revealed a three proton triplet at 1.27δ, a 2 proton singlet at 3.93δ and a two proton quartet at 4.20δ: the expected pattern for the acetate moiety. A singlet at 7.38δ was assigned to H-5. The compound formed in 82% yield was assigned the structure ethyl 2,4,6-trichloro-3-pyridylacetate **218** based on these data [equation 90]. This oil was unstable and decomposed rapidly on storing and so no elemental analysis was obtained.



Equation 90

Having previously prepared ethyl 4-chloro-3-pyridylacetate N-oxide **214** [figure 12], it was again decided to attempt further chlorination of this compound.



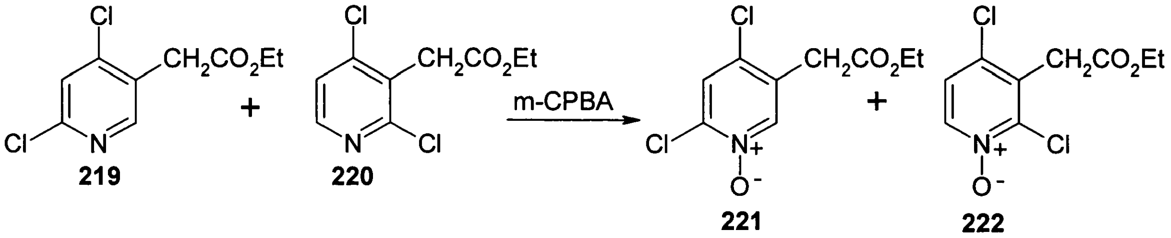
214

Figure 12

As the only available sites for chlorination are those α- to the nitrogen atom, any reaction should lead to the formation of two products. Ethyl 4-chloro-3-pyridylacetate N-oxide **214** was added to phosphorus oxychloride and the mixture refluxed for three hours. The solvent was removed *in vacuo* and the residue poured onto ice, made basic with dilute ammonia solution then extracted with ethyl acetate (section 5.18). Examination by tlc surprisingly indicated only one product had been formed. The solution was concentrated and the resulting oil distilled under reduced pressure to give a colourless oil. The infrared spectrum confirmed the presence of an ester group (1733cm^{-1}) while the pmr spectrum showed what appeared to be the overlaid spectra of two similar compounds. There were two sets of signals for an ethyl ester group and two signals for methylene groups. The patterns for the ring protons suggested that there was as a mixture a 2,4,5-

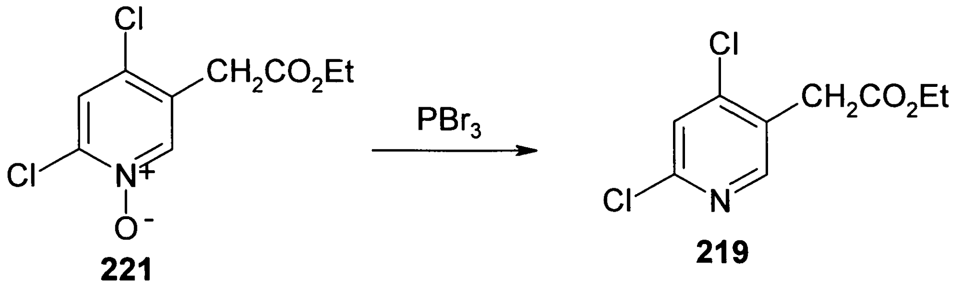
trisubstituted pyridine and a 2,3,4-trisubstituted pyridine, therefore they were tentatively assigned the structures ethyl 2,4-dichloro-5-pyridylacetate **219** and ethyl 2,4-dichloro-3-pyridylacetate **220**. N-oxidation was again employed to effect separation. The pyridine mixture was dissolved in chloroform and *m*-CPBA and a little concentrated sulphuric acid added. The reaction was monitored by tlc and continued for four days until there appeared to be no further reaction. Sodium metabisulphite, followed by potassium carbonate were added and the resulting solids removed at the pump. The solution was concentrated *in vacuo* to give a pale yellow oil which was separated by column chromatography (section 5.19). Elution with ethyl acetate gave first, after recrystallisation from ethyl acetate, white needles. The infrared spectrum showed the expected absorbance at 1732cm^{-1} for an ester group and at 1273cm^{-1} for an N-oxide function. The pmr spectrum showed a triplet at 1.28δ and a quartet at 4.18δ characteristic of an ethyl ester and there was the expected singlet at 3.65δ for a methylene group adjacent to the ester. Singlets at 7.52δ and 8.28δ were assigned to H-3 and H-6 respectively. Elemental analysis[459] verified the structure as ethyl 2,4-dichloro-5-pyridylacetate (**221**, 23%). Further elution gave as a colourless crystalline solid after recrystallisation from ethyl acetate. The infrared spectrum showed the expected absorbances for an ester (1733cm^{-1}) and an N-oxide (1282cm^{-1}). The pmr spectrum showed a triplet at 1.35δ and a quartet at 4.30δ characteristic of an ethyl ester and there was the expected singlet at 4.09δ for a methylene group adjacent to the ester. Two sets of doublets were observed at 7.37δ and 8.35δ (for both J=7.2Hz), which were assigned to the protons H-5 and H-6 respectively.

Elemental analysis[459] supported the structure as ethyl 2,4-dichloro-3-pyridylacetate N-oxide (**222**, 26%) [equation 91].



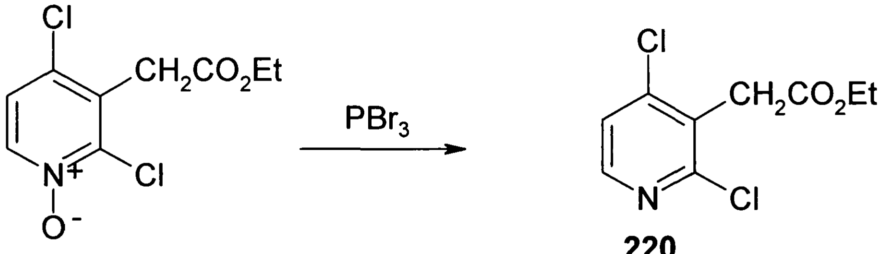
Equation 91

In order to regenerate ethyl 2,4-dichloro-5-pyridylacetate **219**, deoxygenation with phosphorus tribromide was employed, to give after distillation, a colourless oil (section 5.20). The infrared spectrum confirmed the presence of an ester group (1737cm^{-1}), aliphatic (2932, 2982cm^{-1}) and aromatic (3087cm^{-1}) C-H stretching, while the pmr spectrum showed characteristic peak patterns for a 2,4,5-trisubstituted pyridine, two singlets at 7.56δ and 8.36δ for protons H-3 and H-6 respectively. A triplet at 1.24δ and a quartet at 4.10δ characteristic of an ethyl ester were also present and there was the expected singlet at 3.84δ for methylene protons adjacent to an ester group. Corroboration of the structure as ethyl 2,4-dichloro-5-pyridylacetate **219**, obtained in 41% yield, was from the elemental analysis[459] [equation 92].



Equation 92

Ethyl 2,4-dichloro-3-pyridylacetate N-oxide **222** was deoxygenated with phosphorus tribromide in a similar manner and a colourless oil was obtained after distillation (section 5.21). The infrared spectrum showed the expected absorbance at $1715cm^{-1}$ for an ester group and aliphatic (2936 and $2982cm^{-1}$) and aromatic ($3077cm^{-1}$) C-H stretching. The pmr spectrum contained a triplet at 1.22δ and a quartet at 4.20δ characteristic of an ethyl ester and there was the expected singlet at 4.00δ for a methylene function adjacent to an ester group. Two sets of doublets were observed at 7.46δ and 8.25δ (for both J=4.8Hz), which were assigned to the protons H-5 and H-6 respectively. Elemental analysis[459] supported the structure as ethyl 2,4-dichloro-3-pyridylacetate (**220**, 77%) [equation 93].



Equation 93

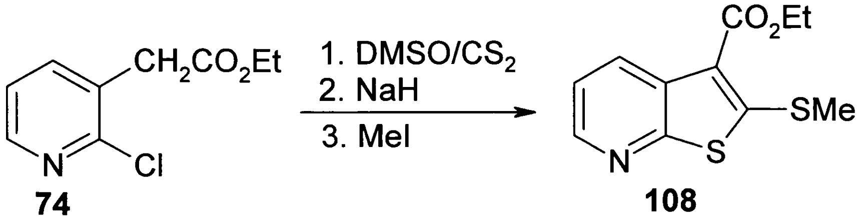
Overall the preparation of pyridine N-oxides and chloropyridines was easily achieved in moderate to good yields. The use of *m*-CPBA in the presence of sulphuric acid appears to have been a strong enough reagent to N-oxidise the mixture of ethyl 2,4-dichloro-5-pyridylacetate **219** and ethyl 2,4-dichloro-3-pyridylacetate **220**. Although both have chlorine atoms α and γ to the nitrogen in the ring the combined inductive effect does not seem to reduce the basicity enough to prevent N-oxidation occuring under these conditions. The reduced basicity of ethyl 2,6-dichloro-3-pyridylacetate **215**, due to electronic effects of the two α- chlorine atoms requires the use of the much stronger oxidising agent pertrifluoroacetic acid to effect N-oxidation. With these chloropyridines in hand, the next stage in the project was their convertion to thienopyridines.

2.4 Preparation of thienopyridines

2.4.1 Thieno[2,3-b]pyridines

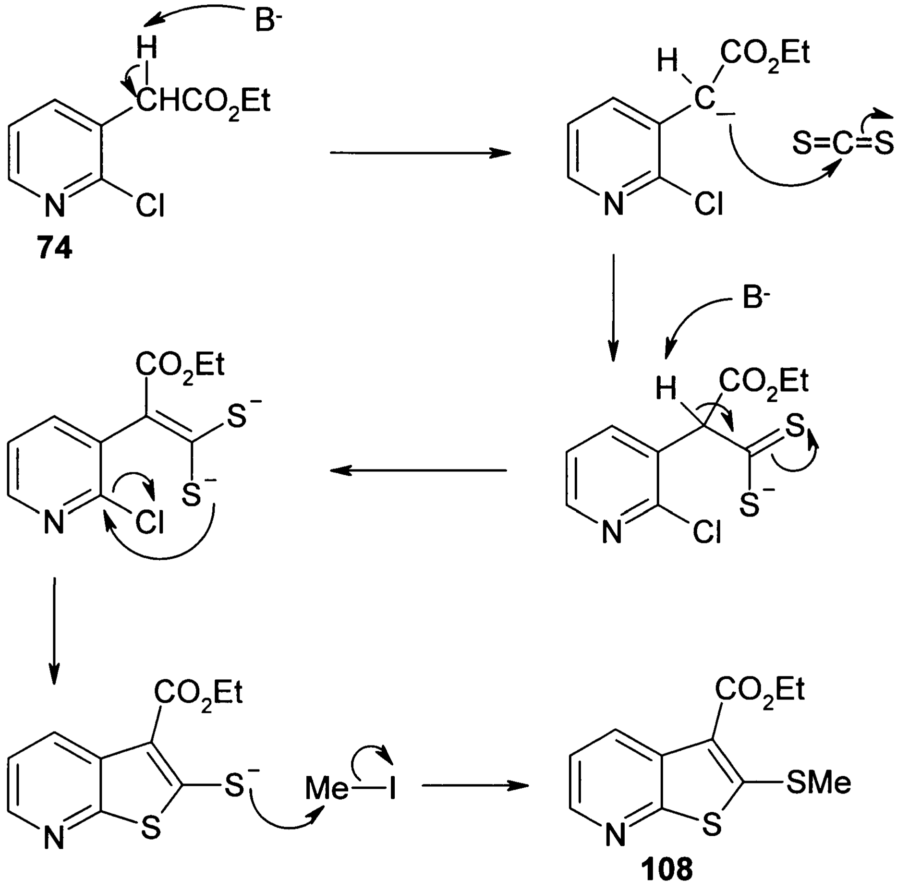
See appendix 1 for a summary of the reactions described in this section.

3-Ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** was prepared using the method of Wilson, who reported[260,261] a yield of 36%. Ethyl-2-chloro-3-pyridylacetate **74** and carbon disulphide were dissolved in DMSO under dry nitrogen and sodium hydride added in portions with constant stirring. The reaction was heated for 1.5 hours, cooled and methyl iodide added. After a further 1 hour at room temperature the mixture was poured onto ice and extracted with ethyl acetate. The solvent was removed *in vacuo* and the resulting solid recrystallised from ethyl acetate to give pale yellow crystals of **108** in 40% yield [equation 94] (section 5.22).



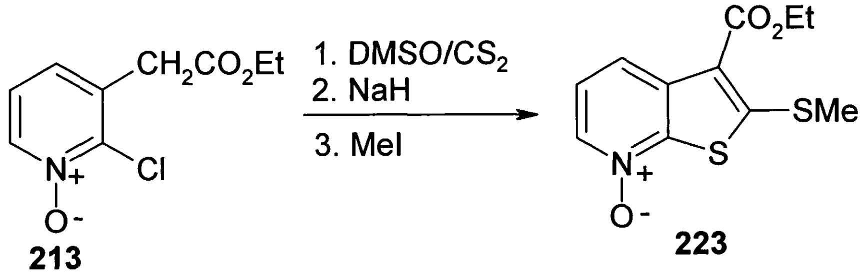
Equation 94

This reaction proceeds by base catalysed abstraction of the methylene protons and subsequent formation, with carbon disulphide, of a ketenedithioacetal dianion. Heating displaces the chlorine with one thiolate anion to form the bicycle, while the other anion is alkylated by methyl iodide [scheme 73].



Scheme 73

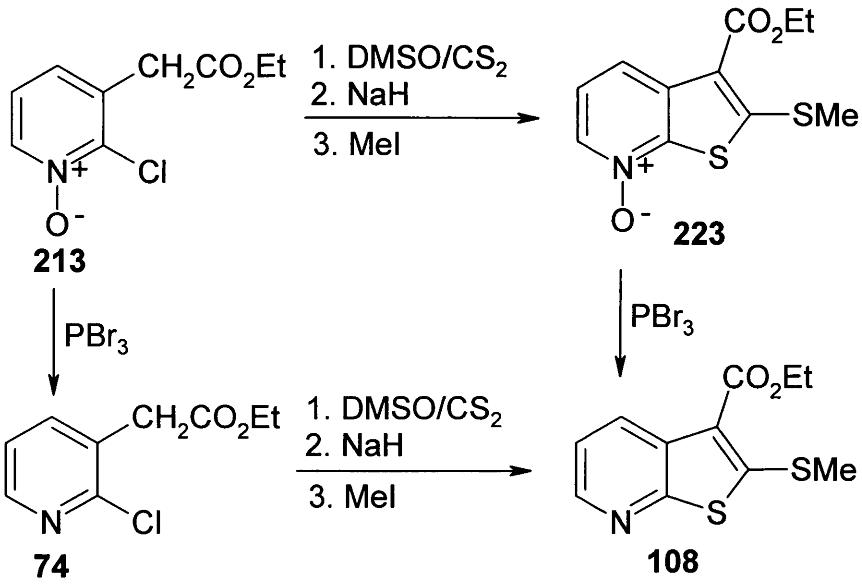
It was of interest to see whether ethyl 2-chloro-3-pyridylacetate N-oxide **213** would undergo the same reaction to form the corresponding thienopyridine N-oxide and if the N-oxide group had any influence on the yield of the reaction. Hence, ethyl 2-chloro-3-pyridylacetate N-oxide **213** was similarly treated to produce pale yellow needles after recrystallisation from ethyl acetate (section 5.23). The infrared spectrum of this compound showed the expected absorbances for an ester (1675cm^{-1}) and for an N-oxide group (1240cm^{-1}). The pmr spectrum showed a triplet at 1.48δ and a quartet at 4.46δ characteristic of an ethyl ester and there was the expected singlet at 2.70δ for the thiomethyl protons. A doublet of doublets at 7.36δ (J= 8.0 and 6.3Hz) for the H-4 proton was observed together with a multiplet at 8.22δ, which integrated for two protons and was assigned to the H-5 and H-6 protons. This data together with the elemental analysis[458] and mass spectrometry corroborated the structure as 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine N-oxide[261] (**223**, 65%) [equation 95].



Equation 95

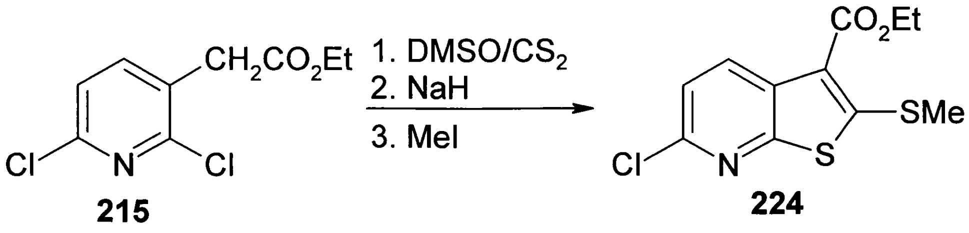
Conversion of **223** to 3-ethyloxycarbonyl-2-methyl thiothieno[2,3-b]pyridine **108** in 72% yield was achieved with phosphorus tribromide (section 5.24).

The route from ethyl 2-chloro-3-pyridylacetate N-oxide **213** to ethyl 2-chloro-3-pyridylacetate **74** and hence to 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** has an overall yield of 33% [scheme 74]. This route is somewhat cumbersome, involving the N-oxidation and subsequent deoxygenation of **72** and **74** to effect their separation before conversion of **74** to **108**. If ethyl 2-chloro-3-pyridylacetate N-oxide **213** however is converted to 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine N-oxide **223** prior to deoxygenation to **108**, an overall yield of 47% is obtained. Additionally this conversion appeared to produce fewer by-products in the final step and those formed were more soluble in ethyl acetate than the desired compound allowing purification by recrystallisation. This route[261] was found to be the better of the two in terms of yield and overall simplicity.



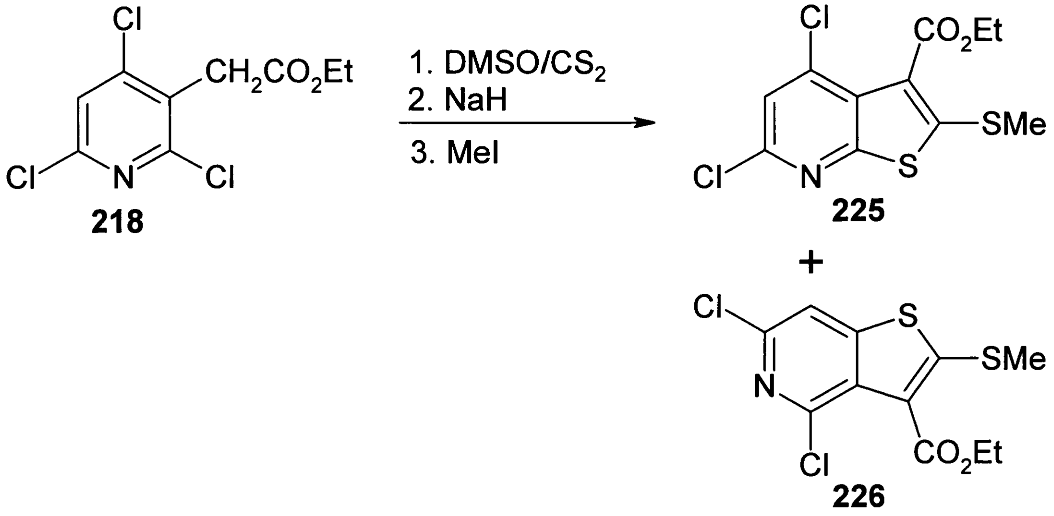
Scheme 74

When ethyl 2,6-dichloro-3-pyridylacetate **215** was reacted with carbon disulphide and sodium hydride followed by quenching with methyl iodide, a white solid was obtained, after recrystallisation from ethyl acetate (section 5.25). The pmr spectrum had the expected pattern for an ethyl ester (a triplet at 1.41δ and a quartet at 4.40δ), and a singlet at 2.63δ for the thiomethyl protons. Doublets at 7.20δ and at 8.38δ, J=8.0Hz for both, were the expected pattern for a 2,3,6-trisubstituted pyridine. The infrared spectrum indicated the presence of an ester group (1670cm^{-1}). Elemental analysis[458] and the mass spectrometry supported the structure of the product as 6-chloro-3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **224**, obtained in 13% yield [equation 96].



Equation 96

Reaction of ethyl 2,4,6-trichloro-3-pyridylacetate **218** with carbon disulphide and sodium hydride followed by alkylation with methyl iodide led to the formation of a mixture of two products, as shown by tlc. This mixture was separated by column chromatography on silica gel using petroleum ether / diethyl ether as eluant (section 5.26). First separated was a white crystalline solid. The pmr spectrum showed a three-proton triplet at 1.43δ and a two-proton quartet at 4.45δ, indicative of an ethyl ester group and the expected three-proton singlet at 2.65δ for a thiomethyl group. There was also a one-proton singlet at 7.38δ for the lone pyridine hydrogen. The infrared spectrum showed an absorbance for an ester at 1694cm^{-1}. The more polar compound, obtained as colourless crystals, showed an absorbance for an ester group at 1726cm^{-1} in the infrared spectrum. The pmr spectrum contained an ethyl ester group: a triplet at 1.45δ and a quartet at 4.48δ. There was also a singlet at 2.62δ due to the thiomethyl group and a singlet at 7.61δ for the pyridine hydrogen. As the spectroscopic data for these two compounds were very similar it was not considered possible to differentiate between them. Microanalysis would not have provided any further clarification as the molecular formulae of the compounds were the same and hence was not sought. It is postulated, based on the available data, that the structures of these products were 4,6-dichloro-3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **225** (38% yield) and 4,6-dichloro-3-ethyloxycarbonyl-2-methylthiothieno[3,2-c]pyridine **226** (58% yield) [equation 97]. This reaction was carried out with the assistance of Claire Milne, as part of an Honours degree project[460] under my supervision.



Equation 97

2.4.2 Thieno[3,2-c]pyridines

See appendix 1 for a summary of the reactions described in this section.

The preparation and reactions of 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** was the main aim of this research programme. However, ethyl 4-chloro-3-pyridylacetate **76** and ethyl 4-chloro-3-pyridylacetate N-oxide **214** [figure 13] were isolated as byproducts of the preparative route to ethyl 2-chloro-3-pyridylacetate **74**. This presented an opportunity to prepare some novel thieno[3,2-c]pyridines.

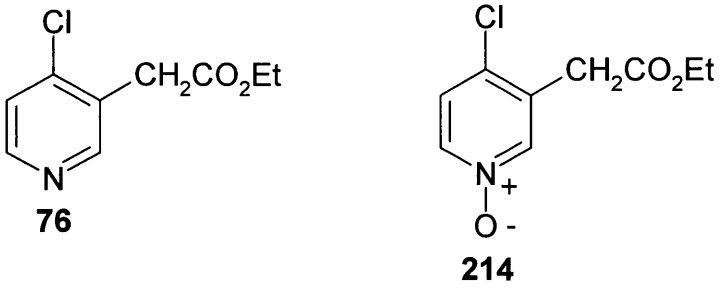
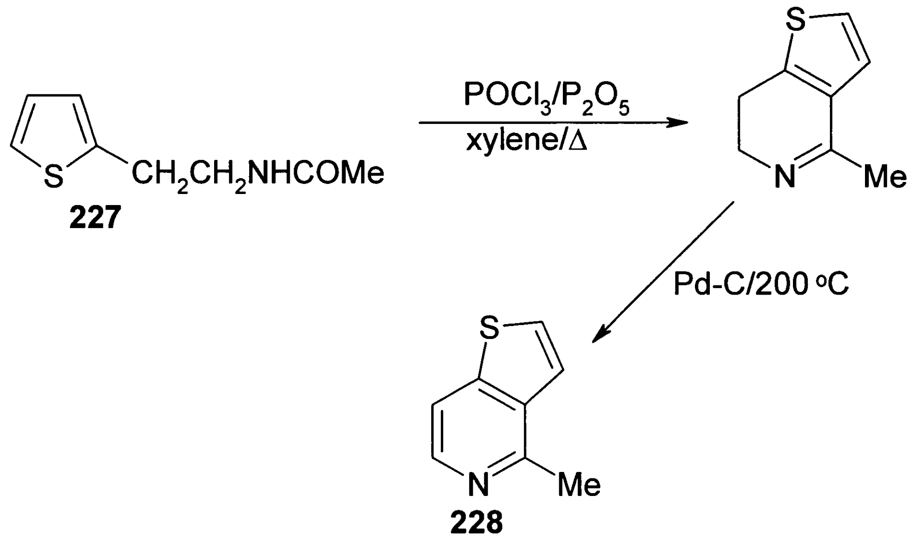


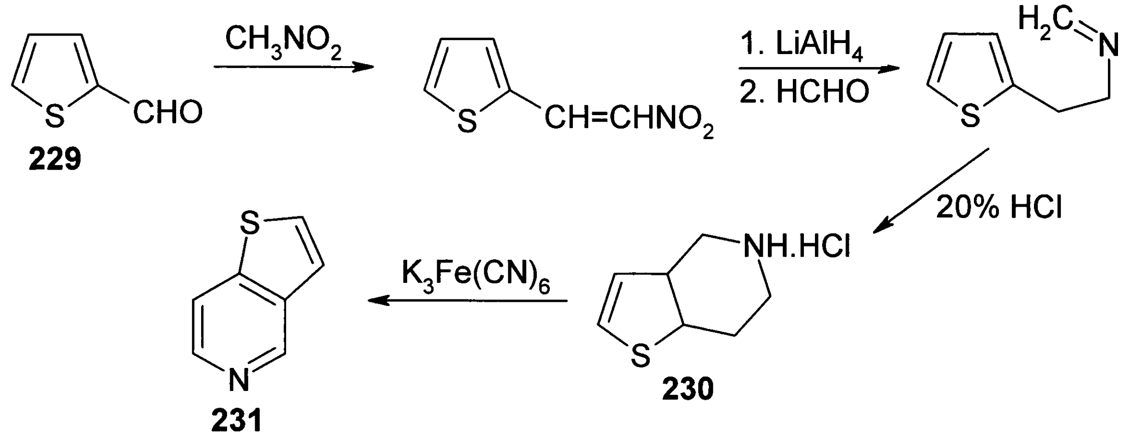
Figure 13

Thieno[3,2-c]pyridines, as isosters of isoquinoline, have been prepared by adaptations of many of the common synthetic routes to isquinolines. The Bischler-Napieralski[461-465] synthesis has been used on 2-thienylethylamides. Reaction with phosphoryl chloride and phosphorus pentoxide causes cyclisation usually to a 6,7-dihydrothieno[3,2-c]pyridine. In the case[461] of N-acyl-β-2-thienylethylamine **227** the intermediate 6,7-dihydro derivative is oxidised to 4-methylthieno[3,2-c]pyridine **228** [scheme 75].



Scheme 75

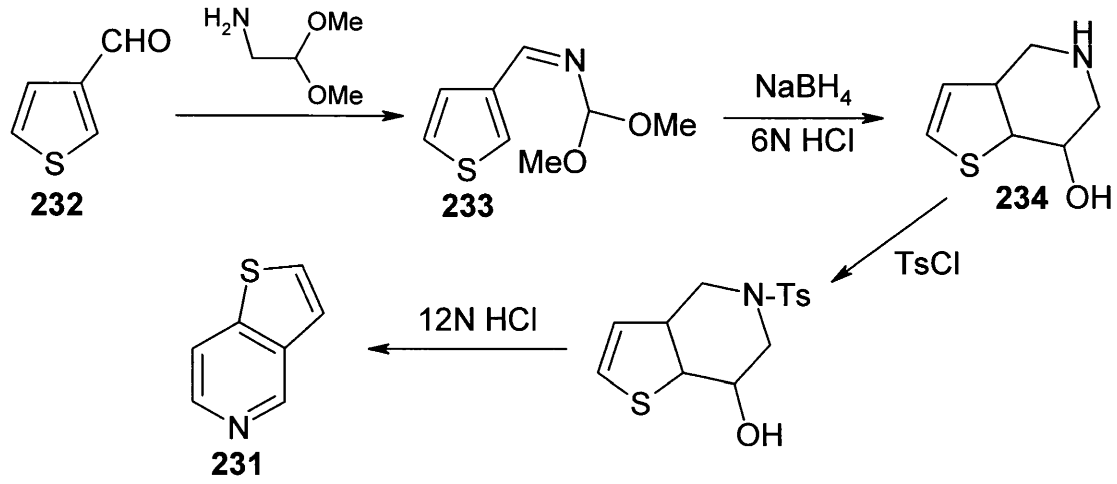
Variations on the Bischler-Napieralski reaction are also reported. The Pictet-Spengler synthesis[466] is used to condense thiophene 2-aldehyde **229** with nitromethane. The ω-nitrovinylthiophene formed is reduced then condensed with formaldehyde to give an imine which cyclises in acid to **230**. Oxidation with potassium ferricyanide gave **231** [scheme 76].



Scheme 76

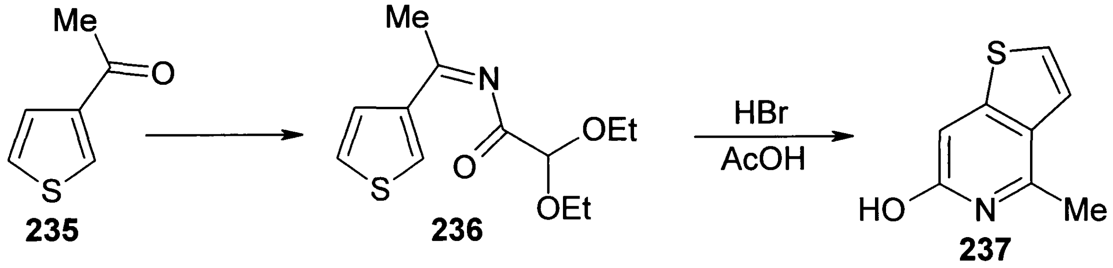
The Pictet-Gams modification[462] has been used on 5-methoxythiophene derivatives. Cyclisation in this case was accompanied by demethylation of the methoxy group.

A modification[467] of the Pomeranz-Fritch reaction was employed to transform thiophene 3-aldehyde **232** via the imine **233** to the tetrahydrothieno[3,2-c]pyridine **234**. Treatment first by tosyl chloride then acid gave **231** in 54% yield [scheme 77].



Scheme 77

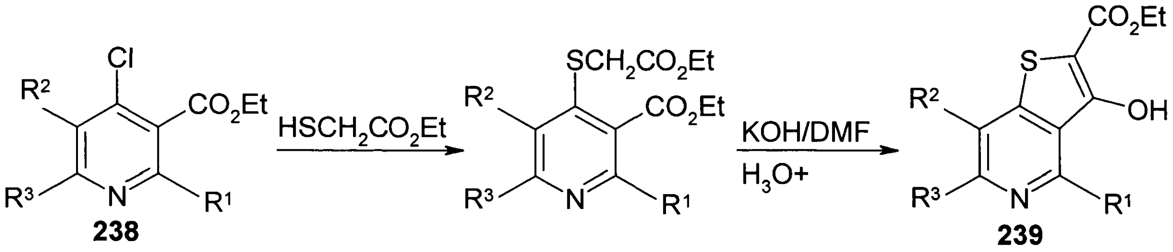
In a variation,[468] 3-acetylthiophene **235** was converted in several steps to the amide **236**. Heating with hydrobromic and acetic acids gave 6-hydroxy-4-methylthieno[3,2-c]pyridine **237** [scheme 78].



Scheme 78

Thieno[3,2-c]pyridines have also been formed from thiophenevinyl isocyanates[469] and isothiocyanates,[470] treatment[471] of pyrillium salts with ethanolic ammonia, 2(2-chloroethyl)thiophene and nitrile/tin IV complexes,[472] thermolysis of azides,[473] the Beckman rearrangement[474] and acid induced cyclisation[475-477] of 2[(3-methylamino)thienyl]propanal diacetals.

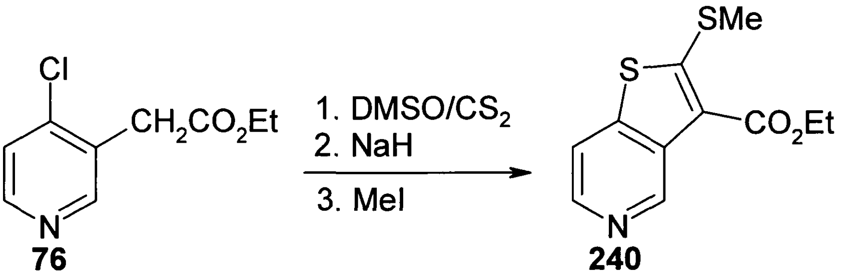
Pyridinethioacetic acid derivatives have been prepared[478] by nucleophilic displacement of a chlorine in the 4- position of **238** by ethyl mercaptoacetate followed by a Dieckmann type condensation of the intermediate to form thieno[3,2-c]pyridine **239** [scheme 79].



Scheme 79

Other reactions involve the high temperature catalytic (Cu/Cr) cyclisation by PPA of pyridinethioacetic acids[479-481] and cyclisation[404] of a 3-phenylethynylpyridine with sodium hydrosulphide. Thieno[3,2-c]pyridines have also been prepared by methodology developed in this laboratory[260,261] as described previously (sections 1.2.2.5 and 2.4.1).

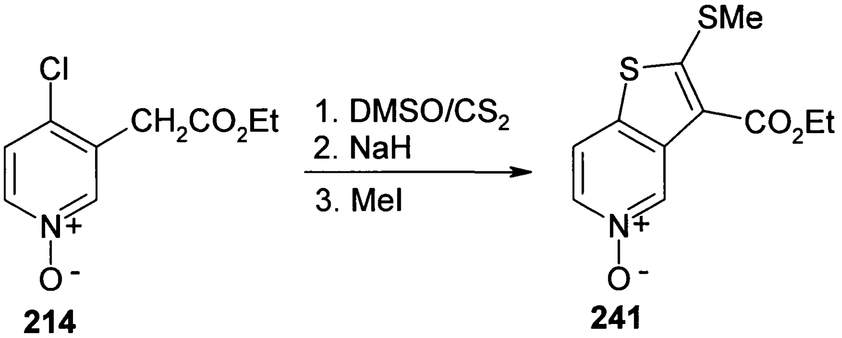
Ethyl 4-chloro-3-pyridylacetate **76** was found to be relatively unstable and decomposed rapidly in the atmosphere (see section 2.1) and hence had to be reacted timeously. Conversion[260,261] to 3-ethyloxycarbonyl-2-methylthiothieno[3,2-c]pyridine **240**, however, was only achieved in 37% yield [equation 99] (section 5.27).



Equation 99

So that full use could be made of all the chloro-3-pyridylacetates prepared, ethyl 4-chloro-3-pyridylacetate N-oxide **214** was reacted with carbon disulphide in the presence of base then cyclised and alkylated with methyl iodide to give colourless needles after recrystallisation from ethyl acetate (section 5.28). Examination of the infrared spectrum showed the expected absorbances for an ester (1681cm^{-1}) and for an N-oxide (1221cm^{-1}). The pmr spectrum showed a triplet at 1.38δ and a quartet at 4.38δ characteristic of an ethyl ester and there was the expected singlet at 2.71δ for the thiomethyl protons. Three doublets of doublets at 8.02δ (J= 6.9 and 0.66Hz), 8.12δ (J=6.9 and 1.8Hz) and 8.88δ (J=1.8 and 0.66Hz) were assigned to the protons H-7, H-6 and H-4 respectively. The structure 3-

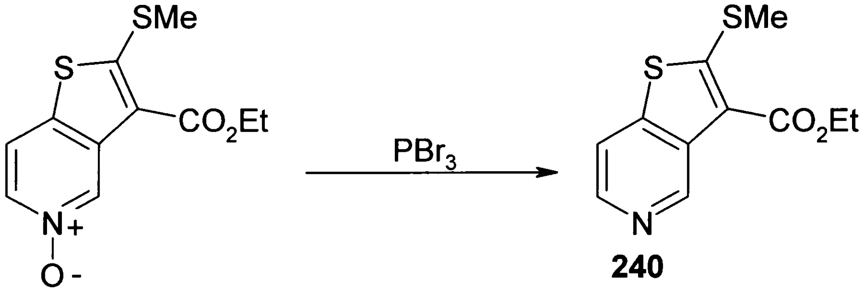
ethyloxycarbonyl-2-methylthiothieno[3,2-c]pyridine N-oxide[261] (**241**, 79%) was supported[459] by elemental analysis [equation 100].



Equation 100

While measuring the melting point of this product **241**, it was noticed that there was some evolution of gas as the compound melted (221-224°C). A larger sample was therefore heated in a Woods Metal bath to its melting point until gas evolution could no longer be observed. Tlc indicated that the compound was no longer 3-ethyloxycarbonyl-2-methylthiothieno[3,2-c]pyridine N-oxide **241**. The infrared spectrum of this substance was found to be identical to that of 3-ethyloxycarbonyl-2-methylthiothieno[3,2-c]pyridine **240** showing that deoxygenation had taken place. It is known[30, 482, 483] that for some heterocyclic N-oxides, varying degrees of deoxygenation takes place at elevated temperatures (see section 1.1.2.1). This observation was further tested by heating 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine N-oxide **223** to it's melting point. While no gas evolution was evident and the melting point took place over approximately one degree Celsius, comparison with pure samples of 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine N-oxide **223** and 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** by tlc showed that some thermally induced deoxygenation had in fact taken place. The gas evolved was therefore presumed to be oxygen. Although this was not novel for N-oxides, it was however, quite an interesting phenomenon. No mention could be found in the literature for this occurring in the thienopyridine series, and as no other thienopyridines prepared in this work, exhibited this behaviour, no further attempts were made to examine these transformations.

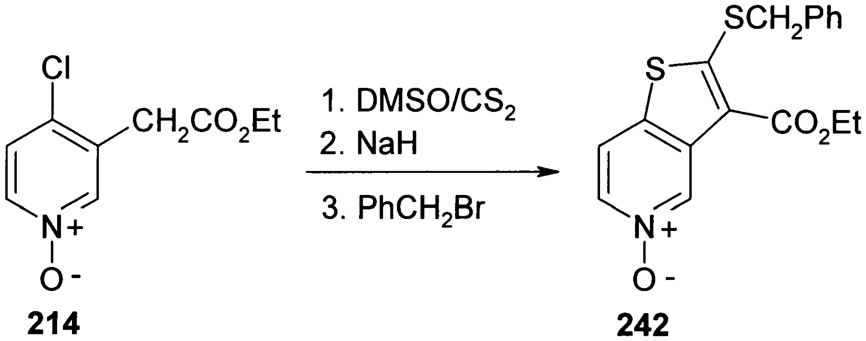
3-Ethyloxycarbonyl-2-methylthiothieno[3,2-c]pyridine N-oxide **241** was successfully deoxygenated with phosphorus tribromide to 3-ethyloxycarbonyl-2-methylthiothieno[3,2-c]pyridine[260,261] **240** in 83% yield [equation 101] (section 5.29). This was confirmed by comparing[260,261] the melting point and infrared spectrum with the literature.



241 **240**

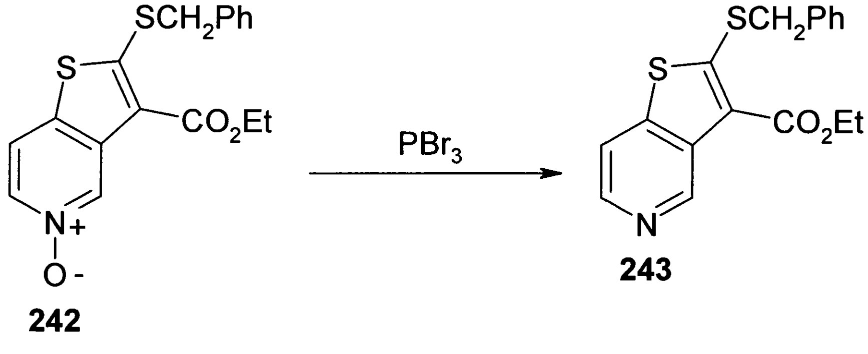
Equation 101

In an attempt to produce more novel thieno[3,2-c]pyridines, ethyl 4-chloro-3-pyridylacetate N-oxide **214** was treated with carbon disulphide and sodium hydride then alkylated with benzyl bromide [equation 102] (section 5.30). 3-Ethyloxycarbonyl-2-benzylthiothieno[3,2-c]pyridine N-oxide **242**, produced in 79% yield, was identified from spectroscopic data. The infrared spectrum showed the expected absorbances for an ester (1690cm^{-1}), an N-oxide (1223cm^{-1}) and aliphatic (2978cm^{-1}) and aromatic (3131cm^{-1}) C-H stretching. The pmr spectrum showed a triplet at 1.40δ and a quartet at 4.34δ characteristic of an ethyl ester and there was the expected singlet at 4.36δ for the methylene protons of the benzyl group. Three signals at 7.74δ (J= 7.2Hz), 8.02δ (J=7.2 and 2.4Hz) and 8.94δ (J=2.4Hz) were assigned to the protons H-7, H-6 and H-4 respectively. A multiplet at 7.34δ, which integrated for 5 protons, was assigned to the phenyl ring. The proposed structure was supported[459] by elemental analysis.



Equation 102

Deoxygenation of 3-ethyloxycarbonyl-2-benzylthiothieno[3,2-c]pyridine N-oxide **242** with phosphorus tribromide, (section 5.31), gave 3-ethyloxycarbonyl-2-benzylthiothieno[3,2-c]pyridine **243** as expected, although in a disappointingly low yield of 42% [equation 103].



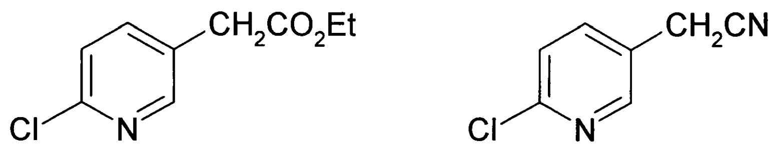
Equation 103

Analysis of the pmr spectrum revealed: a triplet at 1.44δ and a quartet at 4.40δ for the ethyl ester group, a singlet at 4.24δ for the methylene protons of the benzyl group and a five-proton multiplet centred at 7.26δ characteristic of a benzene ring. The presence of a 3,4-disubstituted pyridine was concluded from the chemical shifts and coupling constants of the signals at 7.46δ, 8.30δ and 9.44δ and assigned to H-7, H-6 and H-4 respectively. The infrared spectrum had the expected absorbances for aromatic (3070, 3026cm^{-1}) and aliphatic (2972, 2934 and 2902cm^{-1}) C-H stretching, an ester (1683cm^{-1}). Microanalysis[459] supported the structure.

2.5 Preparation of ketenedithioacetals and thiophenes

See appendix 1 for a summary of the reactions described in this section.

Over a number of years, Shell and other companies have showed interest in novel heterocyclic compounds as potential agrochemicals and pharmaceuticals, and many synthesised[260] at the University of Abertay Dundee have been evaluated for bioactivity including ketenedithioacetals prepared from substituted pyridines. Ethyl 2-chloro-5-pyridylacetate **72** was a major by-product in the preparation ethyl 2-chloro-3-pyridylacetate **74** (section 2.3), and was therefore readily available. The related compound 2-chloro-5-cyanomethyl pyridine **73** was also to hand arising from work[260] previously carried out in this laboratory [figure 14]. **73** was used initially in this reaction so that experience could be gained in the synthetic methodology used to prepare thienopyridines.

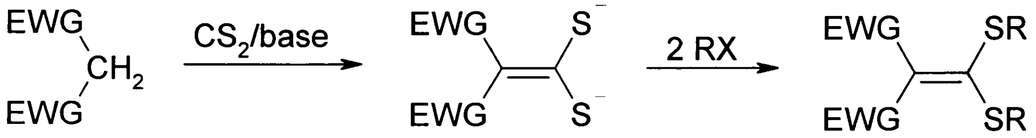


72 **73**

Figure 14

The chlorine atom is not α to the active methylene group in these molecules, so no cyclisation can take place when reacted with CS_2 and base, hence they should lead to novel ketene dithioacetals.

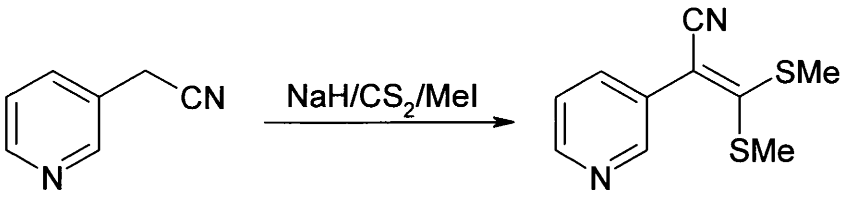
It is known[484-494] that polyfunctionalised ketene dithioacetals are available from reaction of carbon disulphide with appropriately functionalised carbanionic species followed by alkylation of the sulphur anions [scheme 80].



EWG = COR, CO_2R, CN, NO_2, halogen, OR, SR, S(O)R, $S(O)_2R$
X = halogen
R = alkyl, aryl

Scheme 80

Ketene dimethyldithioacetals have been prepared[490] from 2-, 3-, and 4-cyanomethylpyridines. For example 3-cyanomethylpyridine **244** was added to a suspension of sodium hydride in THF at 0 °C, followed by addition of carbon disulphide then methyl iodide to produce cyano(3-pyridyl)ketene dimethyl dithioacetal **245** [equation **104**].

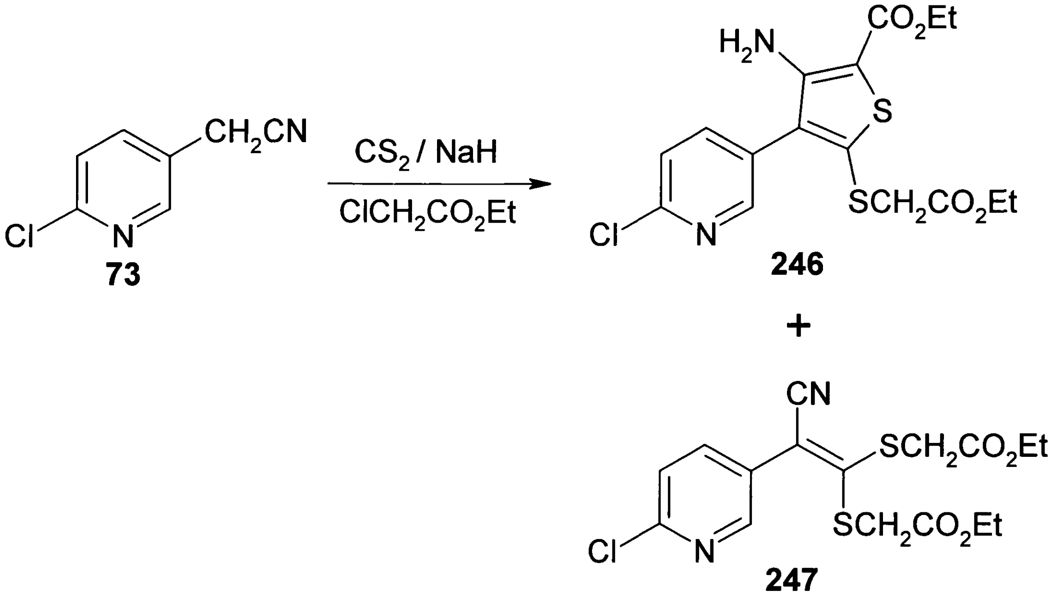


244 **245**

Equation 104

The preparation of some ketene dithioacetals was attempted using available alkyating agents containing an active methylene group. Hence, 2-chloro-5-cyanomethylpyridine **73** and carbon disulphide were dissolved in DMSO under dry nitrogen and sodium hydride added in portions with constant stirring. The reaction was stirred for 1.5 hours and ethyl chloroacetate added. After a further one hour stirring, the mixture was poured onto ice and extracted with ethyl acetate. Tlc indicated that there was one major product and a small but significant amount of a second less polar compound but no starting material **73**. The solution was then dried and the solvent removed *in vacuo* and the resulting solid chromatographed on silica gel using petroleum ether / ethyl acetate as eluant (section 5.32). Separated first was a white crystalline solid. The infrared spectrum showed the presence of a primary amine (3447 and 3343 cm^{-1}) and two ester groups (1724, 1661cm^{-1}). The pmr spectrum showed two triplets, 1.17 and 1.26δ, which integrated for three protons each and two quartets at 4.02 and 4.18δ, which integrated for two protons each, indicating two ethyl ester groups in the molecule. A singlet was found at 3.46δ, which integrated for two protons, typical of a methylene group. The expected pattern for a 2,5-disubstituted pyridine was observed, a doublet at 7.30δ (J = 8.4 Hz), a doublet of doublets at 7.64δ (J = 8.4 and 2.4 Hz) and a doublet at 8.26δ (J = 2.4 Hz), all integrating for one proton each, for H-3, H-4 and H-6 respectively. There was also a broad singlet at 5.36δ that integrated for two protons and was most likely a primary amino group. The structure was therefore considered to be 2-chloro-5-(3-amino-2-ethyloxycarbonyl-5-ethyloxycarbonylmethylthio-4-thienyl) pyridine **246**. This was supported by elemental analysis[458] and mass spectrometry (401).

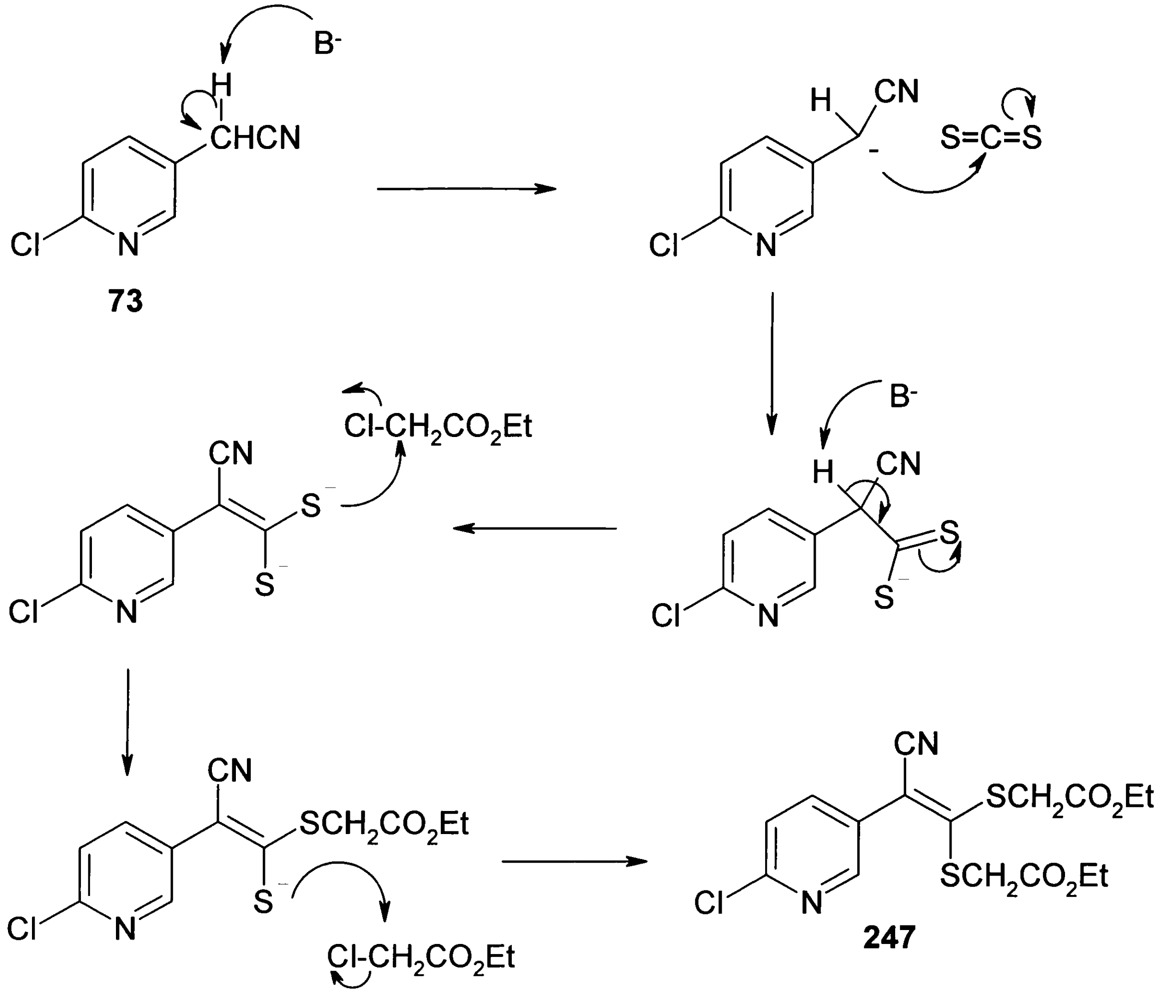
Eluted second was a pale yellow oil. The infrared spectrum showed the molecule to contain a nitrile group (2209cm^{-1}) and an ester (1736cm^{-1}). The pmr spectrum revealed three-proton triplets at 1.28δ and 1.32δ and two-proton quartets at 4.16δ and 4.20δ indicating two ethyl ester groups. A pair of two-proton singlets were found at 3.72δ and 3.80δ, which were assigned the methylene protons of the ethyl thioacetate groups. A doublet at 7.33δ (J = 8.4 Hz), a doublet of doublets at 7.85δ (J = 8.4 and 2.4 Hz) and a doublet at 8.52δ (J = 2.4 Hz), all integrated for one proton each, were assigned to H-3, H-4 and H-6 of the pyridine ring respectively. This compound was assigned the structure 2-chloro-5-(1-cyano-2,2-di(ethyloxycarbonylmethylthio)-1-vinyl)pyridine (**247**, 58%), which was supported[458] by microanalysis [equation 105].



73 **246** **247**

Equation 105

The mechanism for the formation of **247** is similar to that of the thienopyridine series. It proceeds by base catalysed abstraction of the methylene protons and subsequent formation, with carbon disulphide, of a ketenedithioacetal dianion. These anions are then alkylated with ethyl chloroacetate [scheme 81].

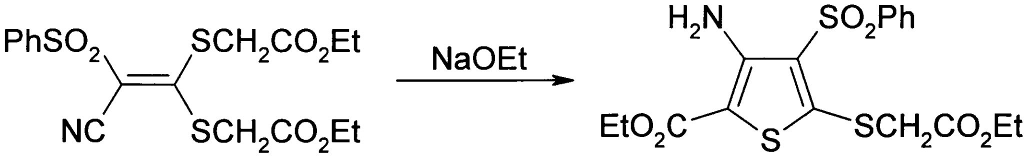


73

247

Scheme 81

The minor product formed in this reaction appears to arise from the base catalysed cyclisation of **247**. It is well known[484, 486, 488, 489, 492, 494] that polyfunctional ketene dithioacetals containing an active methylene on a sulphur will cyclise onto a nitrile or ester group. For example[488] ketenedithioacetal **248** treated with sodium ethoxide affords thiophene **249** [equation 106].

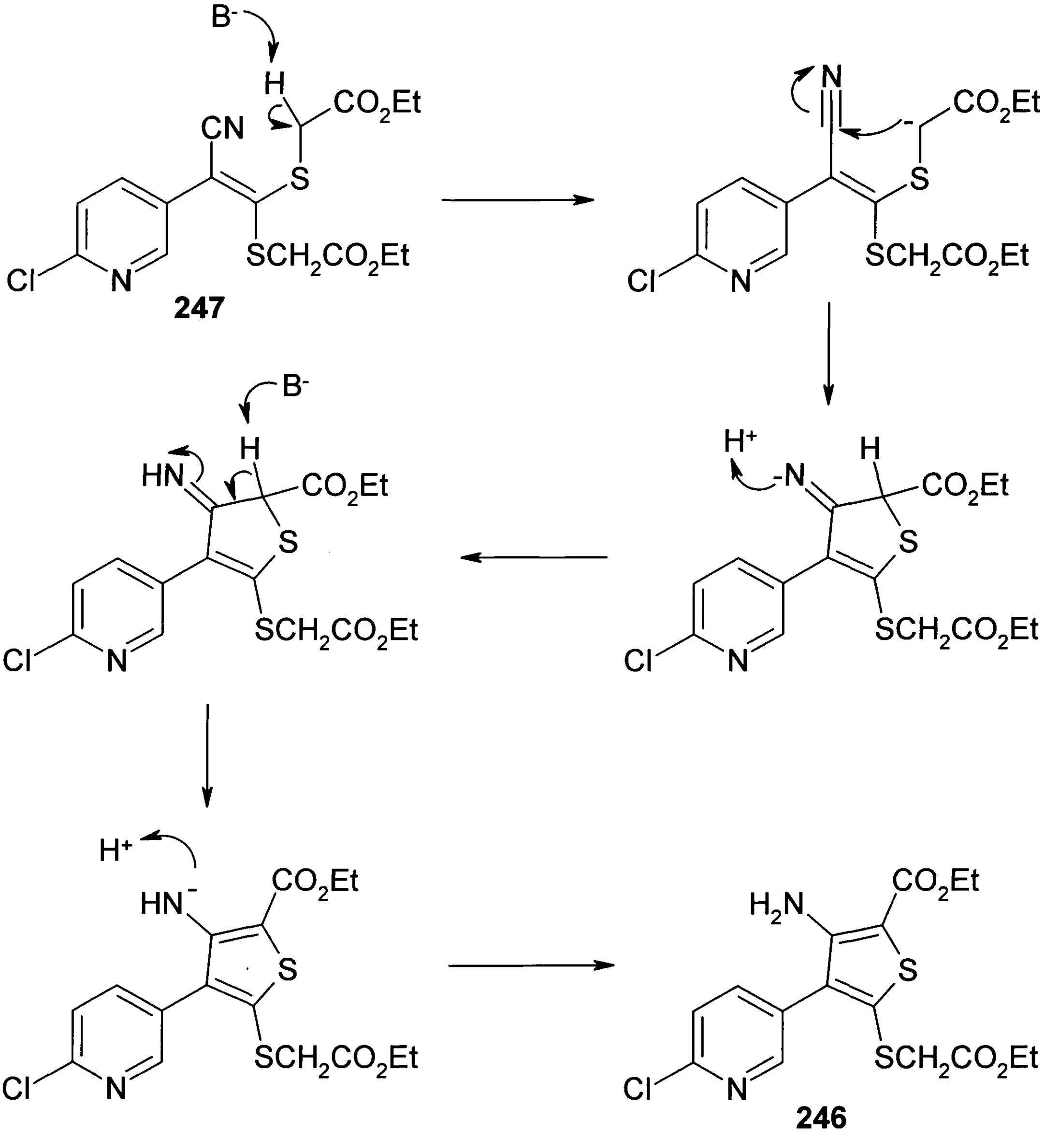


248

249

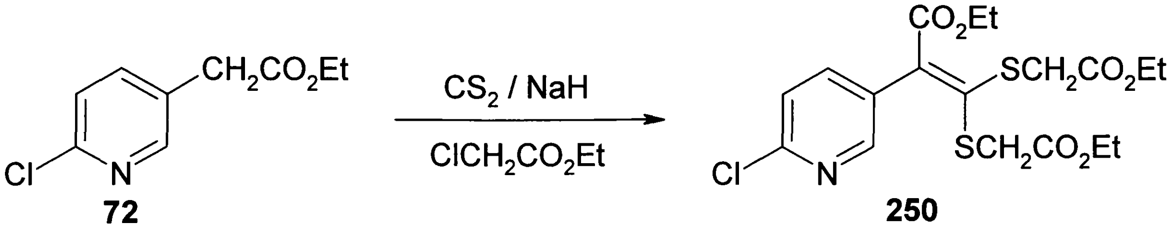
Equation 106

The mechanism for the preparation of 2-chloro-5-(3-amino-2-ethyloxycarbonyl-5-ethyloxycarbonylmethylthio-4-thienyl)pyridine **246** involves firstly the sequential abstraction of the active methylene protons of **247** followed by nucleophilic attack on the nitrile carbon to form the thiophene ring. The nitrogen anion picks up two protons to form the amine [scheme 82].



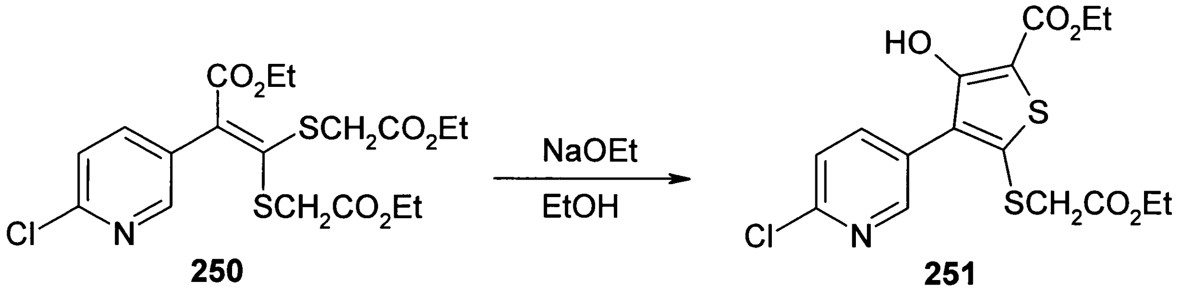
Scheme 82

To further investigate these reactions, ethyl 2-chloro-5-pyridylacetate **72**, (available from the chlorination of ethyl 3-pyridylacetate N-oxide **70**; section 2.3), and carbon disulphide were dissolved in DMSO under dry nitrogen and sodium hydride added in portions with constant stirring. The reaction was stirred for 1.5 hours then quenched with ethyl chloroacetate and stirred for a further one hour. The mixture was poured onto ice and extracted with ethyl acetate. Tlc indicated that the reaction mixture contained one major product and small amounts of impurities. Hence the solution was dried and the solvent removed *in vacuo* and the resulting oil was collected after distillation at reduced pressure (section 5.33). The infrared spectrum of this compound showed an ester group (1736cm^{-1}) to be present. The pmr spectrum contained a three-proton triplet at 1.24δ and a six-proton triplet at 1.28δ. These, together with a four-proton quartet at 4.08δ and a two-proton quartet at 4.14δ, (J = 7.2 Hz for all), signified three ethyl ester groups, two almost identical and in a different environment from the third. Two 2-proton singlets were observed at 3.56 and 3.68δ and assigned to the methylene protons of ethyl thioacetate groups. A doublet at 7.28δ (J = 8.4 Hz), a doublet of doublets at 7.72δ (J = 8.4 and 2.4 Hz) and a doublet at 8.34δ (J = 2.4 Hz), integrating for 1 proton each, were assigned to H-3, H-4 and H-6 respectively. The compound was therefore 2-chloro-5-(1-ethyloxy carbonyl-2,2-di(ethyloxycarbonylmethylthio)-1-vinyl)pyridine (**250**, 43%) [equation 107]. This structure was supported by microanalysis[458] and mass spectrometry.



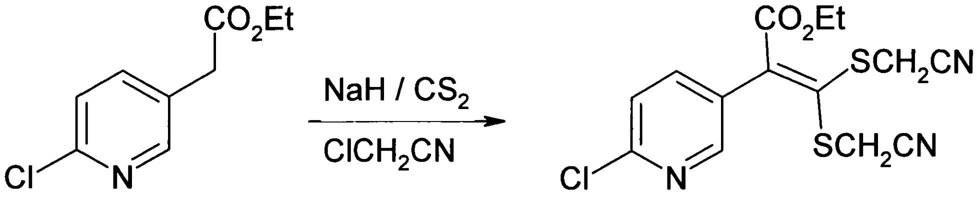
Equation 107

Further reaction of 2-chloro-5-(1-ethyloxycarbonyl-2,2-di(ethyloxycarbonylmethylthio)-1-vinyl)pyridine **250** with base was attempted. The keteneditioacetal was dissolved in ethanol, sodium ethoxide added, and stirred at room temperature for 24 hours. The mixture was then flooded with water and extracted with ethyl acetate. The extracts were dried and the solvent removed *in vacuo* to give a pale yellow solid after recrystallisation from diethyl ether (section 5.34). The infrared spectrum revealed the presence of two ester groups (1748, 1666cm^{-1}). The pmr spectrum contained two triplets (1.20 and 1.32δ), both integrated for three protons and two quartets (4.02 and 4.24δ), that integrated for two protons each, indicating two discrete ethyl ester groups. A methylene group was also in evidence as a singlet at 3.48δ. The expected pattern for a 2,5-disubstituted pyridine was also found: a doublet at 7.22δ (J = 8.4 Hz), a doublet of doublets at 7.66δ (J = 8.4 and 2.4 Hz) and a doublet at 8.34δ (J = 2.4 Hz), for H-3, H-4 and H-6 respectively. There was also a broad singlet at 9.70δ, that integrated for one proton, for a hydroxy group. The position of this signal is typical of salicylate type ester, where hydrogen bonding is occurring between the hydroxy hydrogen and the ester carbonyl oxygen. The compound was therefore assigned the structure 2-chloro-5-(2-ethyloxycarbonyl-5-ethyloxycarbonyl methylthio-3-hydroxy-4-thienyl)pyridine **251**, obtained in 33% yield [equation 108]. Elemental analysis[459] supported this assignment.



Equation 108

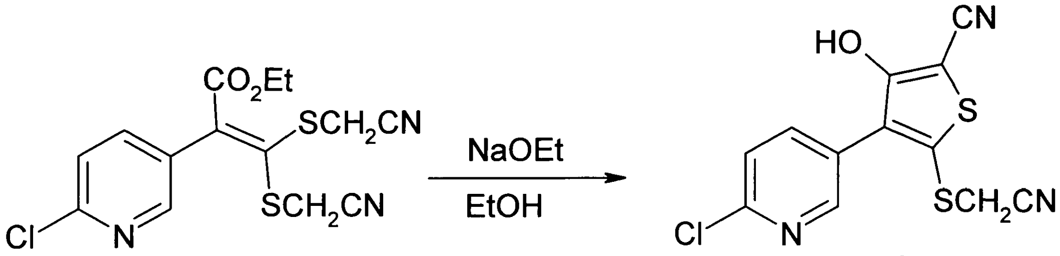
This reaction sequence was repeated using chloroacetonitrile as the alkylating agent. Ethyl 2-chloro-5-pyridylacetate **72** and carbon disulphide were dissolved in DMSO under dry nitrogen and sodium hydride added in portions with constant stirring. The reaction was allowed to stir for 1.5 hours then chloroacetonitrile added and stirring continued for a further one hour. The mixture was poured onto ice and extracted with ethyl acetate. Tlc indicated the presence of only one product, so the solution was dried and the solvent removed *in vacuo* to give white needles after recrystallisation from ethanol (section 5.35). The infrared spectrum showed that the molecule contained a nitrile function (2246cm^{-1}) and an ester group (1720cm^{-1}). The pmr spectrum revealed a three-proton triplet at 1.25δ and a two-proton quartet at 4.24δ, (J = 7.2 Hz for both), typical of an ethyl ester group. Two singlets at 3.56δ and 3.68δ, each integrating for two protons, were assigned to the methylene hydrogens of the acetonitrile groups. A doublet at 7.24δ (J = 8.4 Hz), a doublet of doublets at 7.58δ (J = 8.4 and 2.4 Hz) and a doublet at 8.24 (J = 2.4 Hz), each integrating for one proton, were assigned to H-3, H-4 and H-6 of the pyridine ring respectively. Elemental analysis[459] corroborated the structure as 2-chloro-5-(1-ethyloxycarbonyl-2,2-di(cyanomethylthio)-1-vinyl)pyridine **252**, obtained in 57% yield [equation 109].



72 **252**

Equation 109

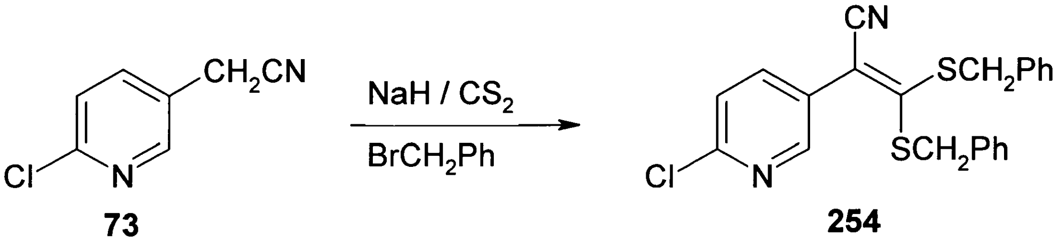
To promote cyclisation to a thiophene, **252** was dissolved in ethanol and sodium ethoxide added with stirring. The reaction was stirred for 24 hours when tlc indicated no starting material remained. The mixture was then poured onto ice and the resulting solid collected by filtration, dried and recrystallised from ethyl acetate to give pale yellow needles (section 5.36). The infrared spectrum showed a nitrile group (2211cm^{-1}) and a hydroxy group (3452cm^{-1}) present in the molecule. The pmr spectrum contained a two-proton singlet at 4.04δ which was assigned to the methylene hydrogens of an acetonitrile group and the expected pattern for a 2,5-disubstituted pyridine i.e. a doublet at 7.58δ (J = 8.4 Hz), a doublet of doublets at 7.86δ (J = 8.4 and 2.4 Hz) and a doublet at 8.42δ (J = 2.4 Hz), each integrating for one proton, for H-3, H-4 and H-6 respectively. The compound was therefore named 2-chloro-5-(2-cyano-5-cyanomethylthio-3-hydroxy-4-thienyl)pyridine (**253**, 46%). Elemental analysis[459] supported this structure [equation 110].



252 **253**

Equation 110

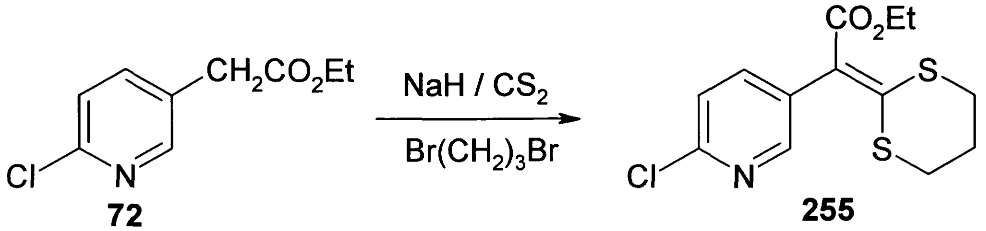
Ethyl 2-chloro-5-cyanomethylpyridine **73** was dissolved, together with carbon disulphide, in DMSO under dry nitrogen and sodium hydride added in portions with stirring. The mixture was stirred for 1.5 hours and then benzylbromide was added. After a further one hour stirring the mixture was poured onto ice and extracted with ethyl acetate. Tlc indicated the presence of one major product, so the solution was dried and the solvent removed *in vacuo* to give a white crystalline solid after recrystallisation from ethyl acetate / petroleum ether mixture (section 5.37). The infrared spectrum showed the molecule to contain a nitrile group (2202cm^{-1}). The pmr spectrum showed two singlets at 3.92 and 4.20δ due to the methylene hydrogens of the benzyl groups. A multiplet was observed at 7.24δ that integrated for 12 protons and was considered to be for two phenyl groups and H-3 and H-4 of the pyridine. A one-proton doublet at 7.96δ was assigned to H-6 of the pyridine. From this spectroscopic data the compound was given the structure 2-chloro-5-(1-cyano-2,2-di(benzylthio)-1-vinyl)pyridine (**254**, 54%) [equation 111]. Microanalysis was in agreement[459] with the proposed molecular formula.



Equation 111

To effect cyclisation of 2-chloro-5-(1-cyano-2,2-di(benzylthio)-1-vinyl)pyridine **254** to a thiophene, it was dissolved in ethanol and sodium ethoxide added. After 24 hours tlc indicated that there was only starting material in the reaction mixture. So the mixture was poured onto ice and the resulting solid collected by filtration (section 5.38). It was positively identified as unreacted **254** (tlc, ir). It would appear that the benzene rings in the molecule are insufficiently electron withdrawing to allow abstraction of the adjacent methylene protons and hence the cyclisation could not proceed.

Ethyl 2-chloro-5-pyridylacetate **72** was reacted with carbon disulphide in the presence of base and alkylated with 1,3-dibromopropane (section 5.39). The mixture was poured onto ice and extracted with ethyl acetate. The solution was dried and the solvent removed *in vacuo* to give pale yellow needles after recrystallisation from diethyl ether / petroleum ether [equation 112]. The infrared spectrum revealed the presence of an ester group (1684cm^{-1}). Furthermore, the pmr spectrum showed the expected patterns for an ethyl ester and a 2,5-disubstituted pyridine. Also observed was a two-proton triplet at 2.16δ and a four-proton triplet at 3.90δ (J = 6.0 Hz for both). These were assigned to a propyl chain, linking the sulphur atoms of a dithiane, hence explaining the chemical shift of the signal at 3.90δ. The structure assigned therefore, was (2'-[3-(5-chloropyridyl)]-2'-ethyloxycarbonyl)-1'-vinyl-1,3-dithiane (**255**, 53%), which was verified by elemental analysis[458] and mass spectrometry.



Equation 112

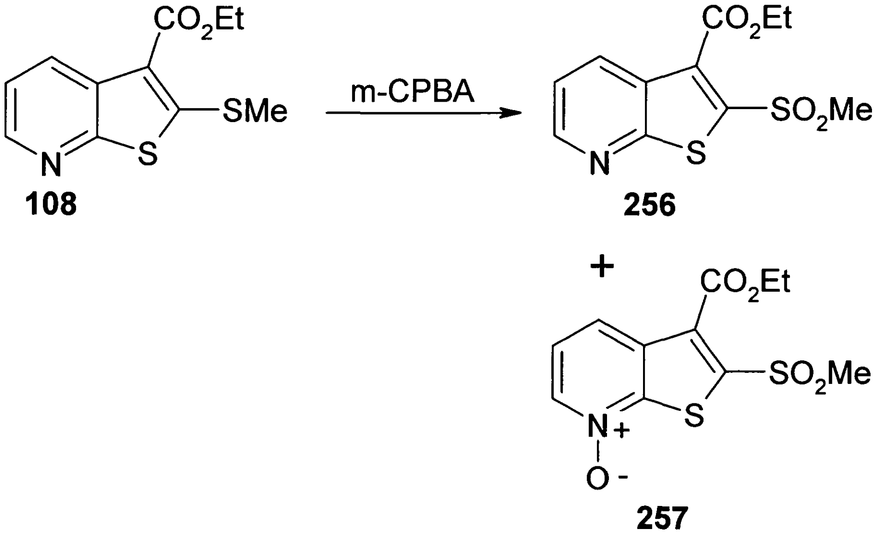
The preparation of ketene dithioacetals and highly substituted thiophenes served two purposes: they provided experience for the later preparation of thienopyridines and produced new compounds for evaluation as potential agrochemicals. Several compounds were tested by Shell but no bioactivity was observed. Use of a wider range of functionalised alkylating agents could allow entry into novel polycyclic compounds but no further attempt was made to expand upon this line of work in this programme.

2.6 Reactions of thieno[2,3-b]pyridines

See appendix 1 for a summary of the reactions described in this section.

In an attempt to prepare novel substituted thieno[2,3-b]pyridines and possibly tricyclic compounds, nucleophilic substitution reactions at C-2 of 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** were investigated. Previously reported[260] attempts to replace the thiomethyl group were largely unsuccessful and it was suggested[260] that reactions with nitrogen nucleophiles would be more efficient if the thiomethyl were converted to its sulphone derivative.

Reaction of 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** with excess *m*-CPBA was therefore employed to try and effect this conversion [equation 113]. After workup, tlc indicated the product was a mixture of two components (section 5.40). Column chromatography, using ethyl acetate as eluent, gave as a white crystalline solid. The infrared spectrum indicated the presence of an ester group ($1724cm^{-1}$). The pmr spectrum showed a triplet at 1.49δ and a quartet at 4.48δ expected for an ethyl ester and there was a singlet at 3.51δ characteristic of the methyl protons of the sulphone. A doublet of doublets at 7.36δ (J= 8.0 and 4.0Hz) for the H-5 proton was observed together with a doublet of doublets at 8.40δ (J=8.0 and 2.0Hz) for H-4 and a doublet of doublets at 8.57δ (J=4.0 and 2.0Hz) for H-6. This data together with the elemental analysis[458] and molecular ion (286) verified the structure as 3-ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine (**256**,15%). Further elution gave a pale yellow solid. The pmr spectrum contained the usual pattern expected for an ethyl ester and a singlet for the sulphone. The signal pattern typical of a 2,3-disubstituted pyridine N-oxide: a doublet of doublets at 7.36δ (J=8.4 and 6.0Hz) for H-5, a doublet at 8.04δ (J=8.4Hz) for H-4 and a doublet at 8.28δ (J=6.0Hz) for H-6, was also found. The structure 3-ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine N-oxide (**257**, 71%) was corroborated by elemental analysis[458] and mass spectrometry.



108

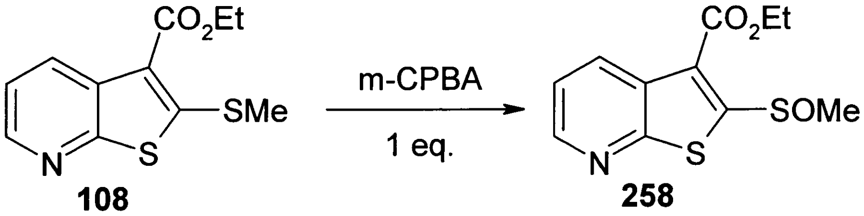
256

257

Equation 113

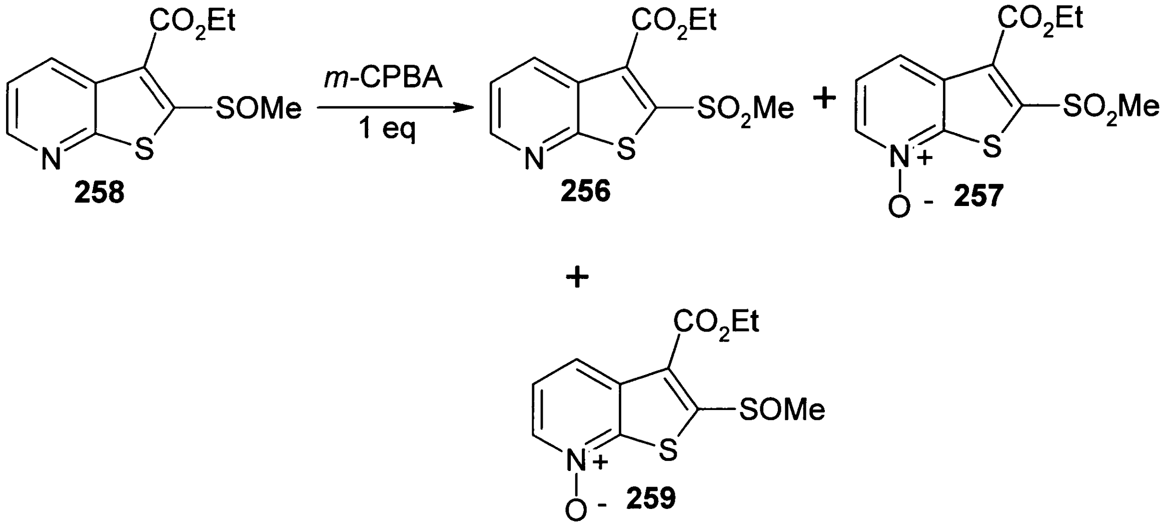
It would appear that oxidation at the pyridine nitrogen and thiomethyl sulphur atoms takes place sequentially, so it was of interest to investigate these reactions to attempt to determine that sequence. When this reaction was repeated using one equivalent of *m*-CPBA [equation 114] a single product was isolated (section 5.41). The pmr was essentially that expected for 3-ethyloxycarbonyl-2-

methylthiothieno[2,3-b]pyridine **108** except the singlet for the thiomethyl group in the 2- position had shifted to 3.04δ indicating that the sulphide had been oxidised to a sulphoxide. The infrared spectrum indicated the presence of an ester group (1697cm^{-1}). This compound was assigned the structure 3-ethyloxycarbonyl-2-methylsulphinylthieno[2,3-b]pyridine **258**, obtained in 96% yield, based on the spectroscopic data, the elemental analysis[458] and mass spectrometry.



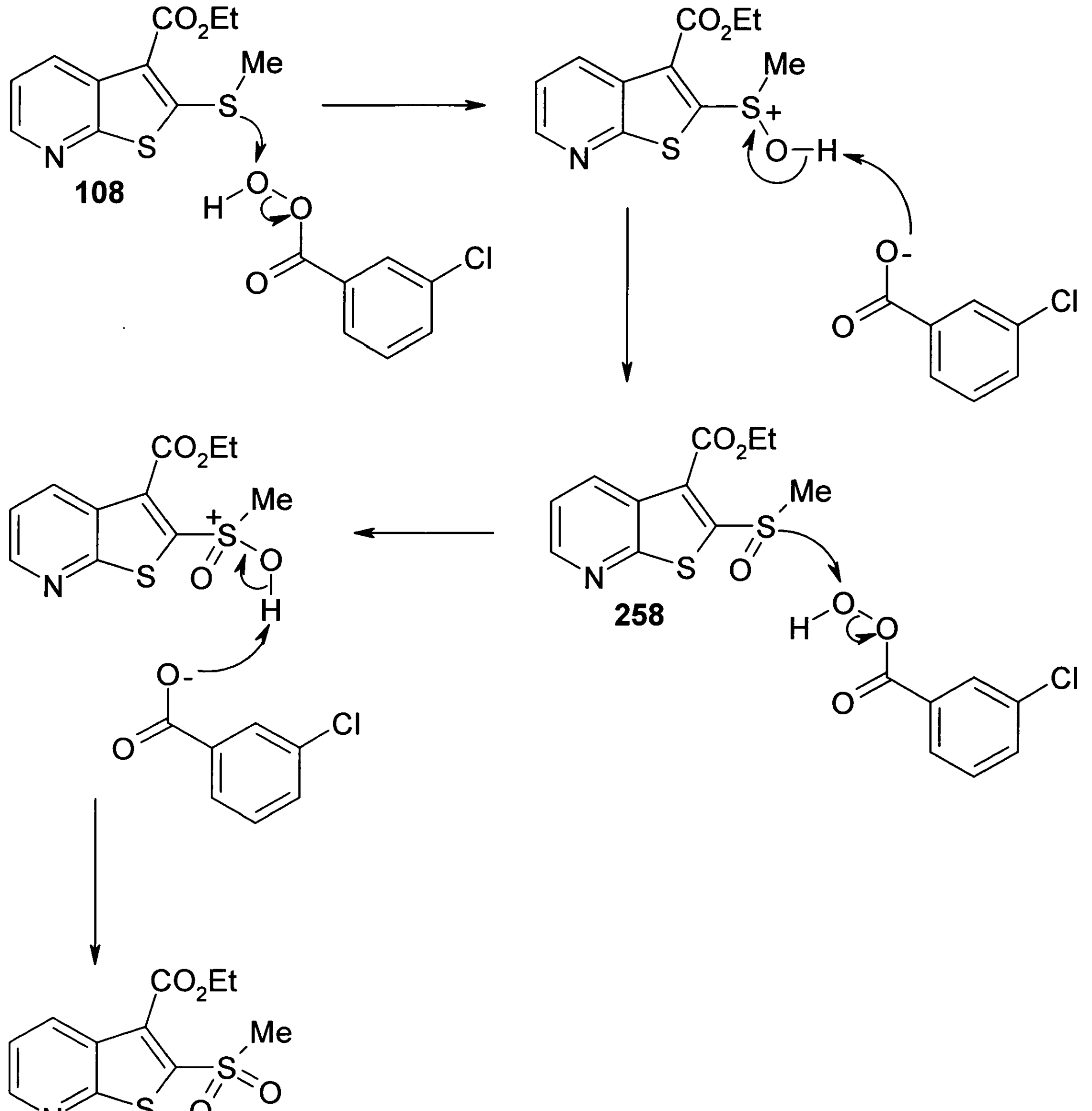
Equation 114

Next **258** was treated with a further one equivalent of *m*-CPBA in the usual manner. Examination by tlc after workup showed the presence of four compounds [equation 115]. This mixture was separated by column chromatography using ethyl acetate as eluent (section 5.42). The first compound isolated, proved, on examination of the infrared spectrum, to be unreacted 3-ethyloxycarbonyl-2-methyl sulphinylthieno[2,3-b]pyridine **258**, collected in 10% yield. The second compound was found from the infrared spectrum to be identical to a pure sample of 3-ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine **256** and was obtained in 55% yield. Further elution gave 3-ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine N-oxide **257** in 12.5% yield, evidenced again by comparison of the infrared spectrum with that of a pure sample. The final product was obtained after recrystallisation from ethyl acetate. The infrared spectrum showed an ester group (1694cm^{-1}) and an N-oxide function (1261cm^{-1}). The pmr spectrum showed a triplet at 1.49δ and a quartet at 4.48δ expected for an ethyl ester and there was a singlet at 3.06δ characteristic of the methyl protons of the sulphoxide. A doublet of doublets at 7.39δ, a doublet at 8.17δ and a doublet at 8.24δ were also observed indicating the presence of a 2,3-disubstituted pyridine N-oxide. The product was therefore assigned the structure 3-ethyloxycarbonyl-2-methylsulphinylthieno[2,3-b]pyridine N-oxide (**259**, 22%). This structure was further supported by elemental analysis[458] and mass spectrometry.



Equation 115

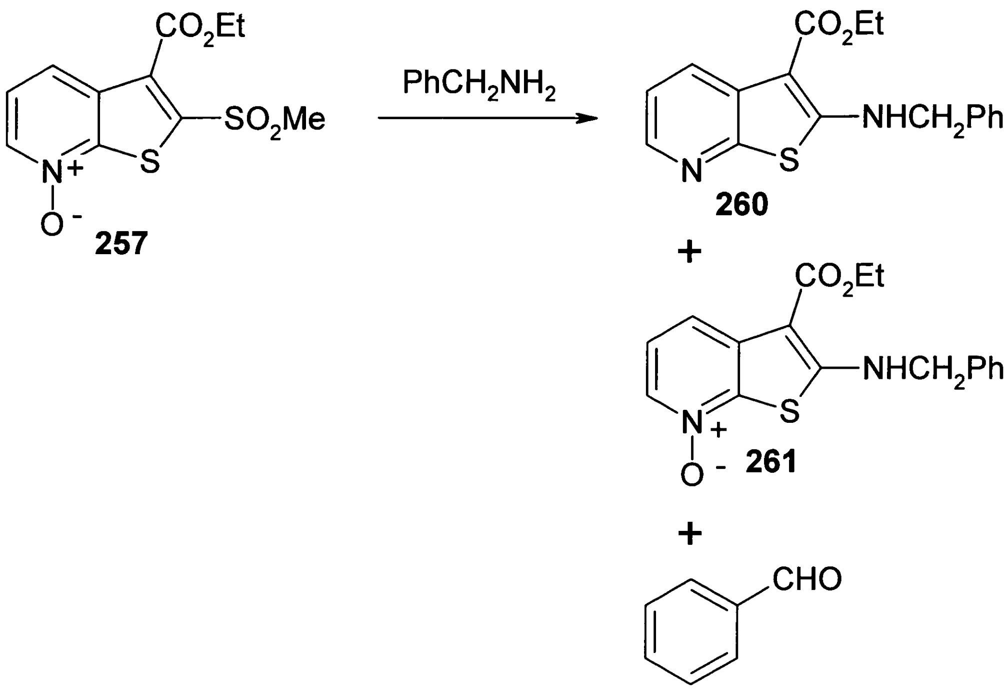
Oxidation of 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** with one equivalent of *m*-CPBA yields exclusively 3-ethyloxycarbonyl-2-methylsulphinylthieno[2,3-b]pyridine **258**. On reaction of **258** with a further one equivalent of oxidising agent there appears to be competition between the formation of a methylsulphonyl group and an N-oxide. The relative abundances of derivatives **256** and **257**, 45% and 13.5% respectively, over derivative **259**, 23%, suggest that oxidation of the methylsulphinyl to the methylsulphonyl moiety predominates over the formation of the N-oxide function. However the latter does offer some competition. The mechanism for the production of sulphoxides and sulphones with *m*-CPBA involves, initial nucleophilic attack by the sulphide sulphur on the peracid to form the sulphoxide, followed by a second reaction to form the sulphone [scheme 83].



Scheme 83

The major product from these reactions was the, inadvertently, over-oxidised 3-ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine N-oxide **257**, however it contained the desired sulphone function. It was decided to attempt nucleophilic substitutions at C-2 as it was not envisaged that the N-oxide group would interfere as there was no leaving group at the α- or γ- positions of the pyridine N-oxide ring that would facilitate nucleophilc substitution at these positions.

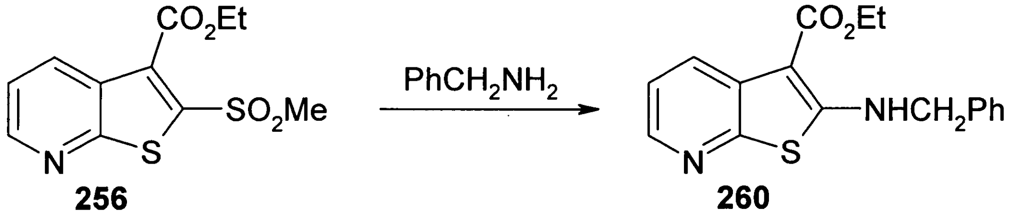
3-Ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine N-oxide **257** was refluxed together with one molar equivalent of benzylamine for three hours in chloroform, when tlc indicated that only starting material was present in the reaction mixture. The chloroform solution was washed with dilute hydrochloric acid and the solvent removed *in vacuo* after drying with magnesium sulphate (section 5.43). The infrared spectrum of the resulting solid, showed it to be unreacted starting material. The reaction was attempted again this time refluxing **257** in neat benzylamine for three hours. As tlc indicated that all the starting material had reacted, the mixture was cooled, then poured onto ice and neutralised with dilute hydrochloric acid. The aqueous solution was extracted with ethyl acetate, dried with magnesium sulphate, and the solvent removed *in vacuo* to give a brown oil (section 5.44). Column chromatography, eluting with ethyl acetate:petrol, 1:1, gave, first a pale yellow oil that had a characteristic almond odour and examination by infrared spectroscopy revealed it to be substantially benzaldehyde, though at the time of analysis a considerable amount had aerially oxidised to benzoic acid and therefore it could not be accurately quantified. Further elution gave a white solid. The infrared spectrum had a sharp peak at 3318cm^{-1} indicative of a secondary amine and the expected absorbance of an ester (1650cm^{-1}). The pmr spectrum showed a triplet at 1.40δ and a quartet at 4.32δ characteristic of an ethyl ester. A doublet at 4.48δ (J=6.0Hz) that integrated for two protons and a one-proton triplet at 8.80δ (J=6.0Hz) were strong evidence of a secondary amine attached to a methylene group. An unresolved multiplet at 7.12δ (six protons) was thought to correspond to the phenyl ring protons and H-5, while an unresolved two-proton multiplet at 8.12δ accounted for the remaining protons H-4 and H-6. The elemental analysis[459] corroborated the structure assignation as 3-ethyloxycarbonyl-2-benzyl aminothieno[2,3-b]pyridine **260**, obtained in 64% yield. The more polar compound was collected as a white solid. The infrared spectrum contained absorbances for a secondary amine (3317cm^{-1}), an ester (1649cm^{-1}) and an N-oxide group (1244cm^{-1}). The pmr spectrum again showed a triplet at 1.44δ and a quartet at 4.38δ for the ethyl ester group. A doublet at 4.57δ and a triplet at 8.95δ for the secondary amine attached to a methylene carbon were also observed. The phenyl protons gave an unresolved multiplet at 7.36δ and the expected pattern for a 2,3-disubstituted pyridine N-oxide was also found. Based on this evidence the compound was assigned the structure 3-ethyloxycarbonyl-2-benzylamino thieno[2,3-b]pyridine N-oxide (**261**, 28%). Elemental analysis[459] supported this structure [equation 116].



Equation 116

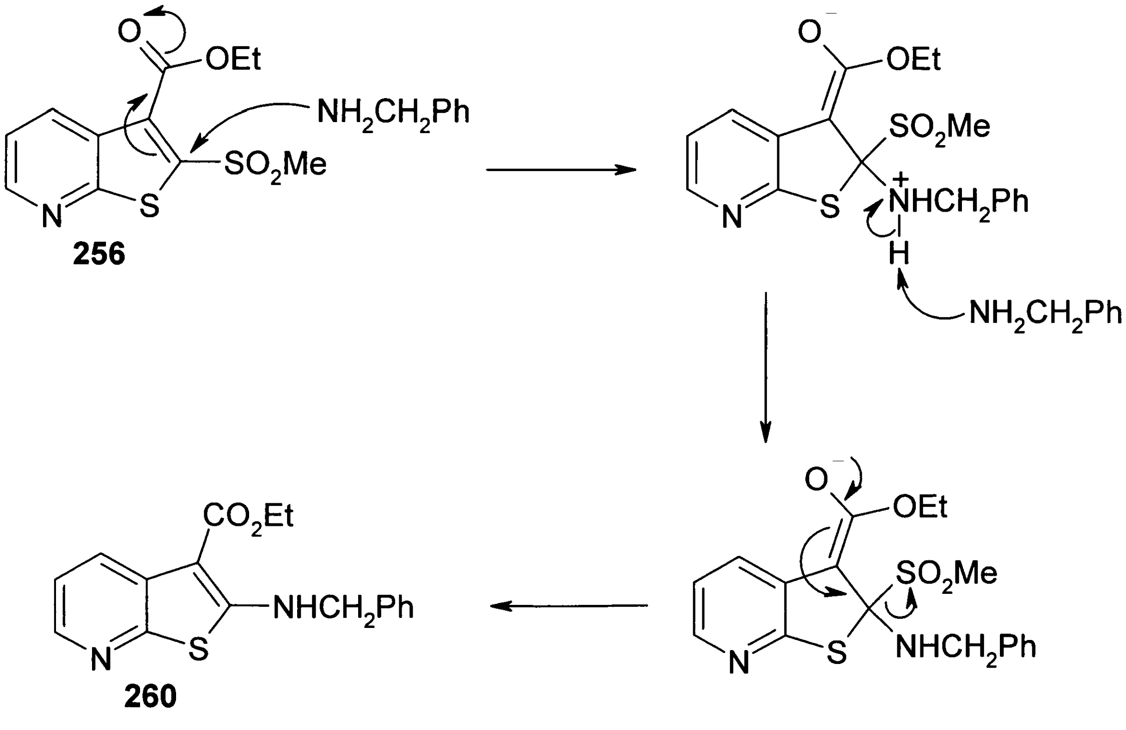
The production of benzaldehyde in this reaction was unexpected and was considered to arise from the oxidation of benzylamine by either the sulphone or the N-oxide function. Examination of the literature revealed that heterocyclic N-oxides are well known as oxidising agents. Typical examples include dehydrogenation[495] of diphenylethanes to stilbene derivatives, aromatisation of hydroaromatics[496] and the conversion[497] of aromatic alcohols to ketones. The conversion of halogen derivatives to carbonyl compounds[498-503] by N-oxides has also been reported. Sulphones are not known to participate in these reactions.

To investigate, experimentally, which functional group was responsible for this transformation, 3-ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine **256** was refluxed in neat benzylamine for three hours then worked up as previously described (section 5.45). There was no evidence of benzaldehyde present and the solid obtained in 22% yield after recrystallisation from ethyl acetate, was found, from its infrared and pmr spectra, to be identical to 3-ethyloxycarbonyl-2-benzylamino thieno[2,3-b]pyridine **260** [equation 117]. From this it would appear that the methylsulphonyl group plays no part in the production of benzaldehyde.



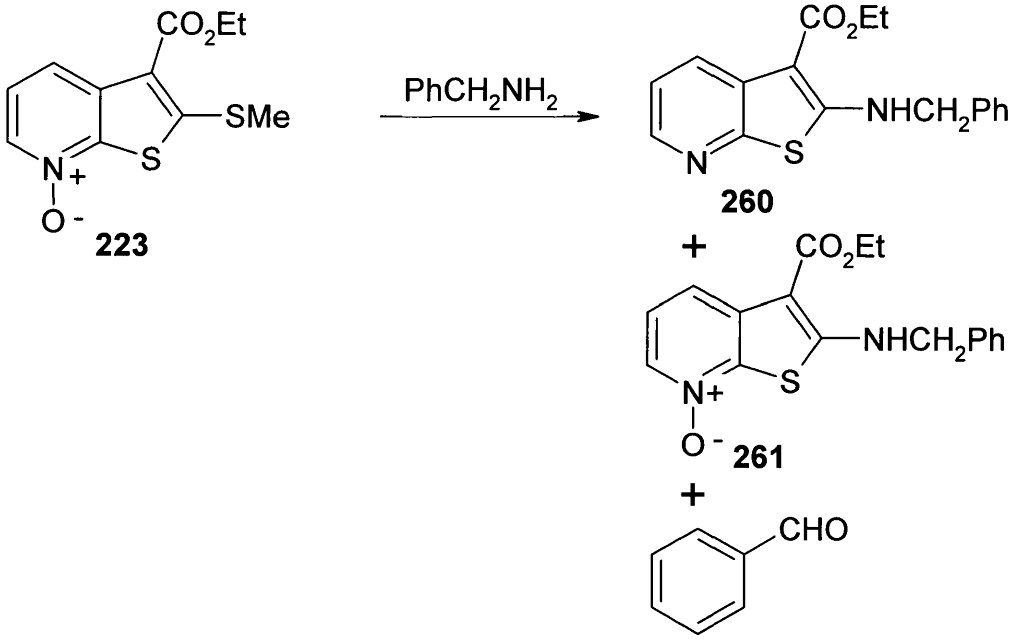
Equation 117

The nucleophilic substitution of the sulphone at C-2 is thought to take place by an addition/elimination mechanism. The nitrogen lone pair of benzylamine attacks the carbon and the electrons of the double bond are delocalised into the ester at C-3. A second benzylamine molecule abstracts a proton from the tertiary ammonium cation and the double bond reforms with elimination of the sulphone [scheme 84] as methanesulphenic acid after protonation.



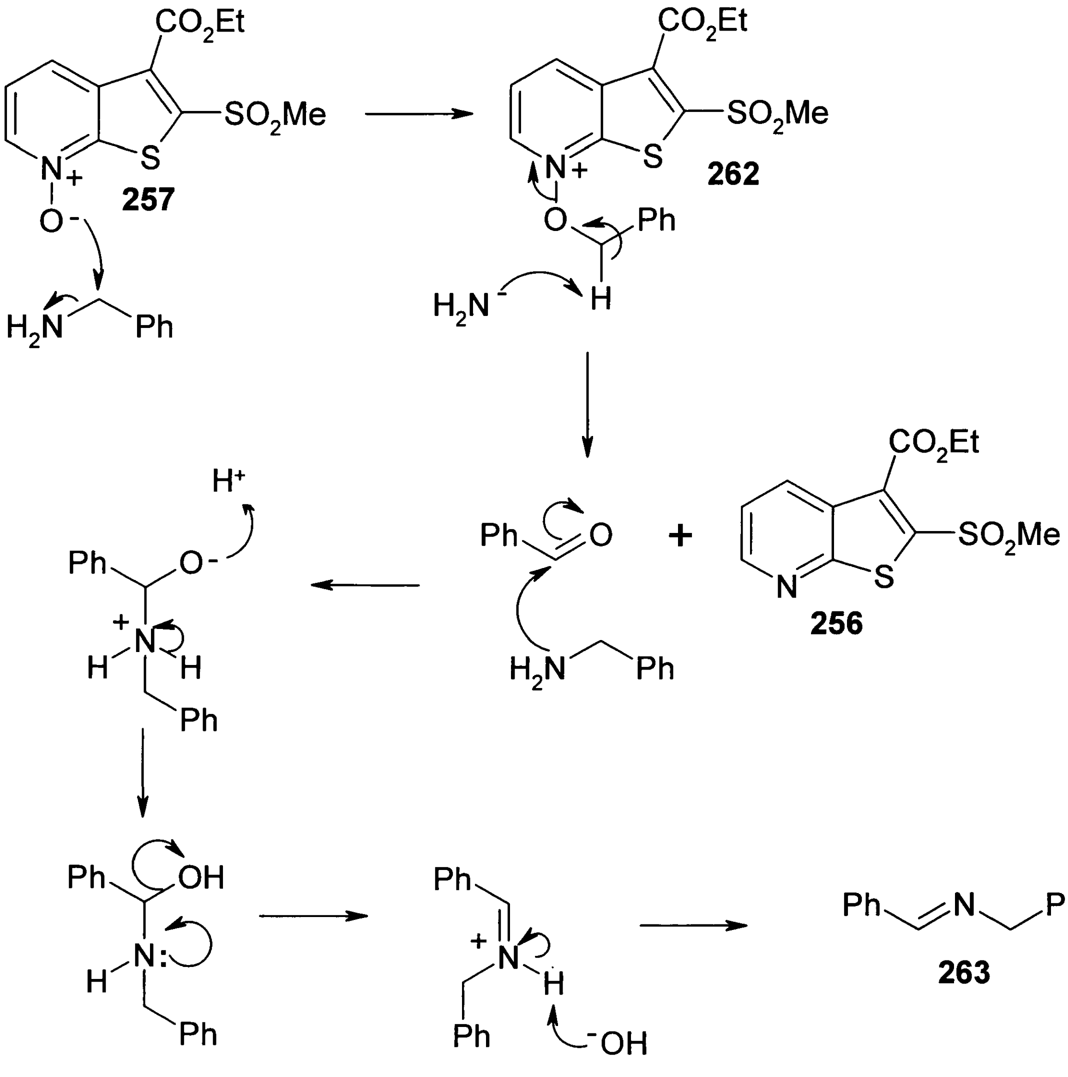
Scheme 84

Furthermore, 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine N-oxide **223** was treated with benzylamine in the same fashion (section 5.46). Tlc indicated three major products together with some baseline material. The mixture was separated by column chromatography using ethyl acetate / petrol mixture as eluent. Separated first was a pale yellow oil (50mg) which from it's characteristic odour, infrared and pmr spectra was found to be benzaldehyde. Eluted next was a white crystalline solid, the infrared and pmr spectra of which were identical to a pure sample of 3-ethyloxycarbonyl-2-benzylaminothieno[2,3-b]pyridine **260**, with a yield of 64%. Eluted last was 3-ethyloxycarbonyl-2-benzylaminothieno[2,3-b]pyridine N-oxide **261**, which was also identified by comparison with a pure sample [equation 118].



Equation 118

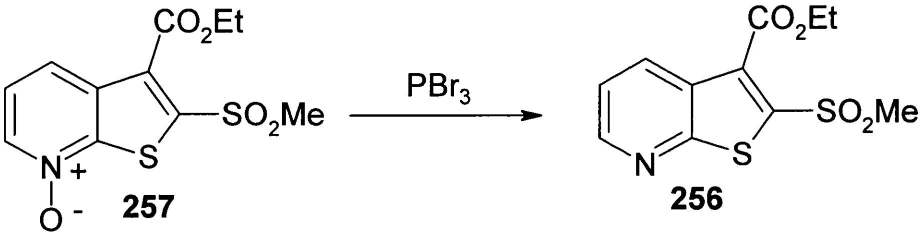
These reactions confirmed that the conversion of benzylamine to benzaldehyde was due to the N-oxide rather than the methylsulphonyl group. It is believed that the reaction proceeds via attack by the oxygen of the N-oxide on the benzylic position of benzylamine. At refluxing temperatures the amine anion is displaced and picks up a proton from intermediate **262**, to then form benzaldehyde. Since there was excess benzylamine present, this now reacts with benzaldehye to give the corresponding imine **263**, which reacts no further [scheme 85]. The imine **263** then decomposes to benzaldehyde during the aqueous work up.



Scheme 85

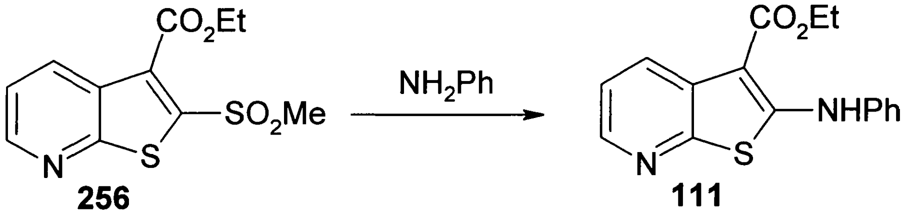
To establish whether this is a general reaction of pyridine N-oxides, a series of N-oxides were reacted with benzylamine. These reactions are discussed in section 2.8.

To try and avoid further unexpected side reactions during this work, the N-oxide function of 3-ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine N-oxide **257** was reduced with phosphorus tribromide under the usual conditions to give 3-ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine **256** in 95% yield [equation 119] (section 5.47).



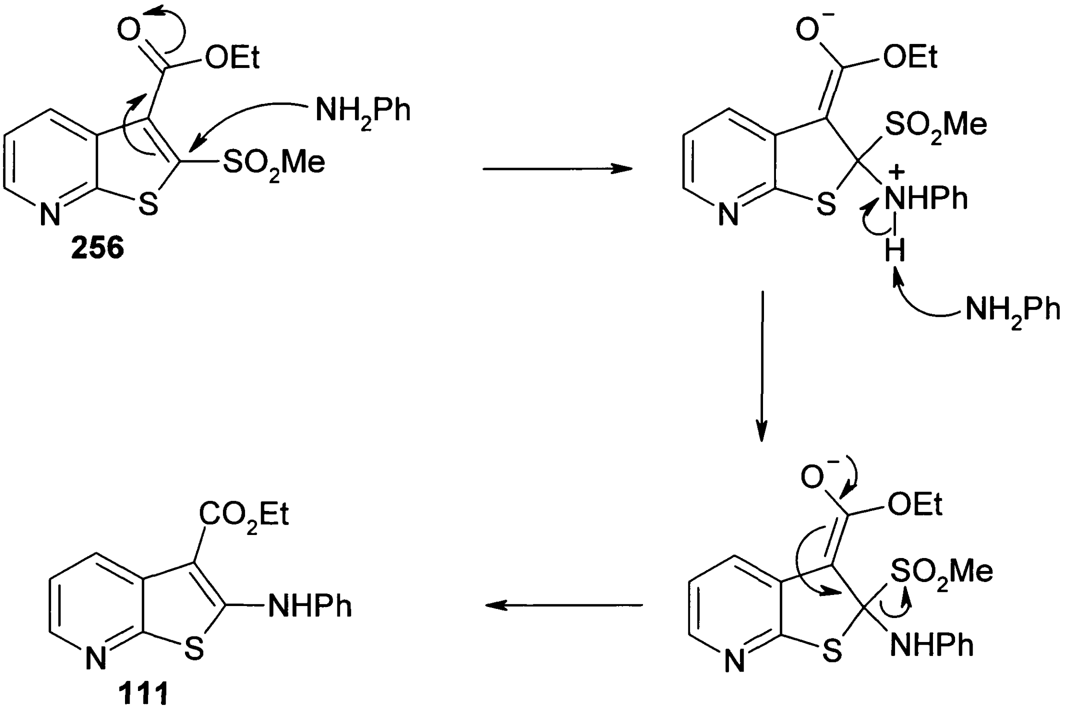
Equation 119

Nucleophilic substitution at C-2 was then attempted with aniline. 3-Ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine **256** was refluxed in neat aniline for three hours, cooled, diluted with ethyl acetate and washed with dilute hydrochloric acid. The organic solution was dried and the solvent removed *in vacuo*. Tlc of the resulting solid indicated that there was no starting material remaining and that there was one major product and some baseline material. The mixture was chromatographed on silica gel with ethyl acetate/petrol as eluant, and gave a white crystalline solid (section 5.48). The infrared spectrum contained absorbances at 3437cm^{-1} (primary amine) and 1653cm^{-1} (ester). The pmr spectrum had the expected pattern for an ethyl ester: a triplet at 1.52δ and a quartet at 4.49δ. There was no signal at about 3.50δ for the methylsulphonyl group, however a multiplet at 7.20δ (five protons) and a singlet at 10.67δ (one proton) were indicative of the anilino group. There was the expected pattern for a 2,3-disubstituted pyridine also present. The compound was therefore assigned the structure 3-ethyloxycarbonyl-2-anilinothieno[2,3-b]pyridine **111**, obtained in 45% yield. Elemental analysis[459] and comparison of the melting point with the reported[260,400] value, supported this structure assignation [equation 120].



Equation 120

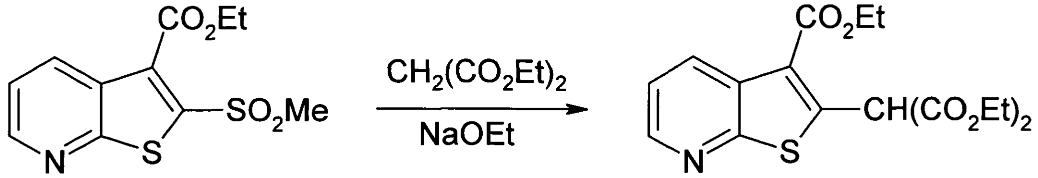
The mechanism for the preparation of **111** was thought to be similar to that for the reaction of **256** with benzylamine. Nucleophilic attack at C-2 by aniline, followed by elimination of the sulphone [scheme 86].



Scheme 86

This reaction was repeated under identical conditions with 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** (section 5.49). A white crystalline solid, obtained after purification by column chromatography in 36% yield, was identified from spectroscopic data as recovered starting material.

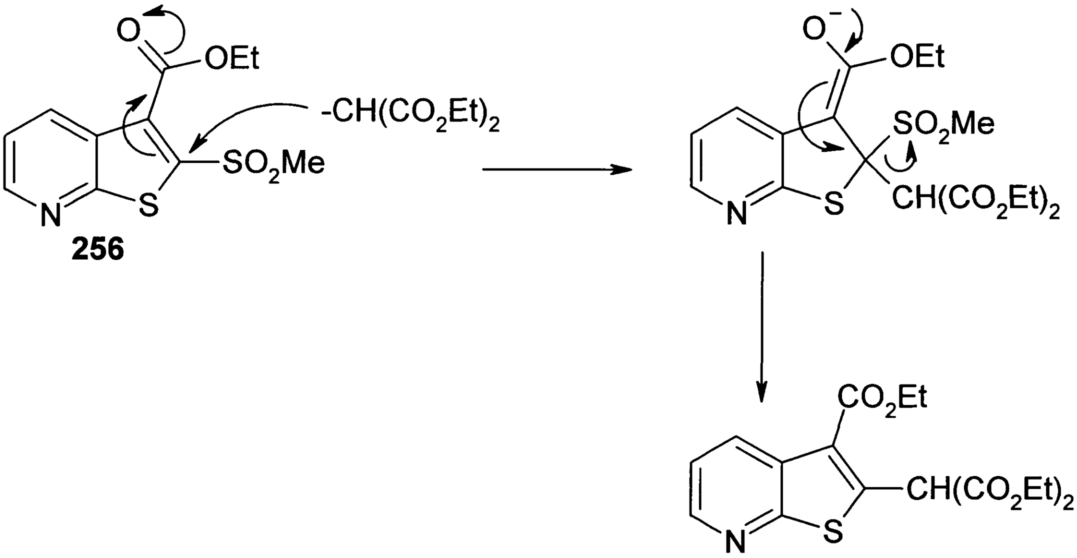
In a further attempt to expand the scope of these nucleophilic substitutions, 3-ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine **256** was treated with sodium ethoxide and diethyl malonate at 100 °C for three hours [equation 121]. Tlc showed no starting material, one major product and some baseline material. Separation by column chromatography with petrol/ethyl acetate as eluent gave a pale yellow oil (section 5.50). The infrared spectrum showed the presence of more than one ester group (1736 and 1708cm^{-1}) and aliphatic C-H stretching (2983cm^{-1}). The pmr spectrum showed a triplet at 1.41δ (three protons) and a quartet at 4.36δ (2 protons), typical of an ester group at the 3- position of the thienopyridine system, based on previous observations. There was a triplet at 1.28δ, which integrated for six protons and a quartet at 4.22δ, which integrated for four protons. These together with a singlet at 6.07δ, which integrated for one proton, were assigned to a diethylmalonyl group. As there was no three-proton singlet in the region of 3.5δ, which would be evidence for the presence of a methylsulphonyl group in the molecule, it was considered that nucleophilic substitution of this group by a diethylmalonyl function had taken place. There was also the expected pattern for a 2,3-disubstituted pyridine present. However attempted purification by distillation at reduced pressure led to substantial decomposition and it was therefore not possible to obtain any analytical data for this compound. Based solely on the spectroscopic evidence, the structure 3-ethyloxycarbonyl-2-diethylmalonyl thieno[2,3-b]pyridine **264** was assigned to this compound.


256

264

Equation 121

In this reaction, an ethoxide ion abstracts an acidic proton from diethylmalonate to form the anion, which nucleophilically attacks the thienopyridine **256** at C-2. The sulphone group is then eliminated [scheme 87].


256

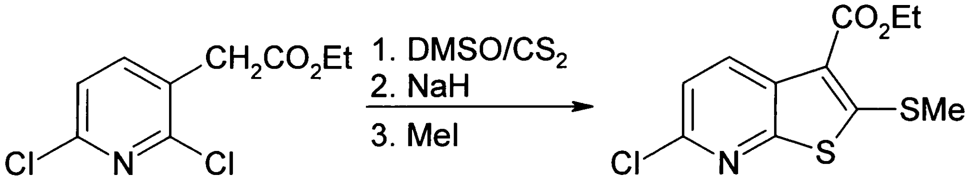
264

Scheme 87

An attempt was made to replace the methylsulphonyl group of 3-ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine **256** with an ethoxide group in the form of the ethoxide anion. 3-Ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine **256** was refluxed with sodium ethoxide using ethanol as solvent for three hours. The solvent was removed *in vacuo* and the resulting solid washed with water. Redissolving in ethyl acetate followed by drying and evaporation of the solvent gave a white solid which was identical by tlc and spectroscopic analysis to the starting material 3-ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine **256**, in 37% yield (section 5.51).

This reaction was again repeated using 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** under the same conditions. After workup the only isolable compound obtained was unreacted **108** in 70% yield (section 5.52).

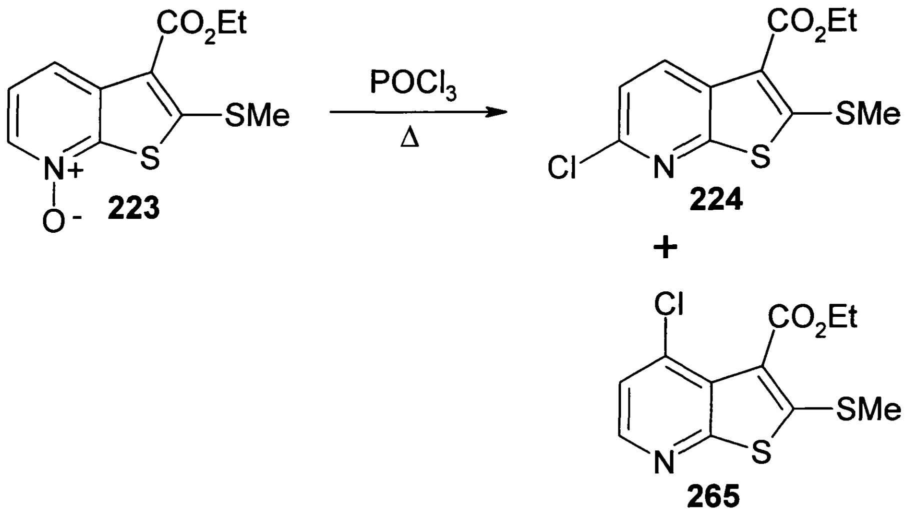
Previously, (section 2.3), the preparation of 6-chloro-3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **224** was achieved by reaction of ethyl 2,6-dichloro-3-pyridylacetate **215** [equation 97].



215 **224**

Equation 97

Alternatively **224** and the isomeric 4-chloro-3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **265** should be formed by chlorination of 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine N-oxide **223**. The brown oil obtained from the reaction of **223** with phosphorus oxychloride was chromatographed on silica gel to give **224** in 52% yield. Also obtained was a pale pink oil [equation 122] (section 5.53). The expected pattern for an ethyl ester was found in the pmr spectrum along with a three-proton singlet at 2.60δ for a thiomethyl group. Doublets at 7.19 and 8.21δ (J=5.0 Hz) were assigned to H-5 and H-6 respectively. The infrared spectrum showed absorbances for an ester (1695cm^{-1}) and aliphatic C-H bonds (2880 and 2940cm^{-1}). Microanalysis[458] and the mass spectrometry supported the structure assignation as 4-chloro-3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **265**, collected in 34% yield.



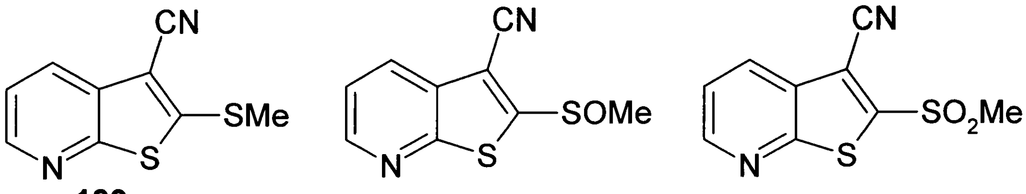
Equation 122

Overall the nucleophilic substitution reactions had not proved to be particularly successful. It is interesting that in these reactions, it was found that the methylsulphonyl group in the 2- position of the thienopyridine was more labile than the thiomethyl group, with both aniline and diethylmalonate [table 4].

Group at C-2	Nucleophile		
	Benzylamine	Aniline	Diethylmalonate
-SMe	64%	0%	0%
-SO_2Me	22%	45%	8%

Table 4: Yields by Nucleophile Employed

This appears to corroborate the findings of other workers[260] in this laboratory, however, that work centred on 3-cyano-2-methylthiothieno[2,3-b]pyridine **109**, its sulphoxide and sulphone [figure 16]. Conversely when the nucleophile employed was benzylamine, the order of reactivity appears to be reversed, with the thiomethyl group as the more labile substituent.



109

Figure 16

The oxidation of benzylamine to benzaldehyde was unexpected and further work was carried out to investigate this more fully (see section 2.8). It was decided therefore to abandon this line of work in favour of an investigation into a synthetic route from prepared thienopyridine 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** to a possible agonist for serotonin (5-hydroxytryptophan).

2.7 Route to a potential agonist for serotonin

See appendix 1 for a summary of the reactions described in this section.

Serotonin was first isolated in 1948 by Rapport[504] from blood serum and later Erspamer[505, 506] found enteramine in the gastrointestinal tract. Both substances were found to be identical to synthetically prepared[507] 5-hydroxytryptamine (5-HT) [figure 17]. Serotonin has been suggested as a neurohormone[508] after its discovery in the mammalian central nervous system[509] and has been implicated in several processes including migraine,[510] anxiety,[511] schizophrenia,[512] sleep[513] and obesity.[514]

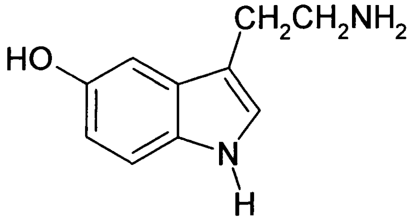
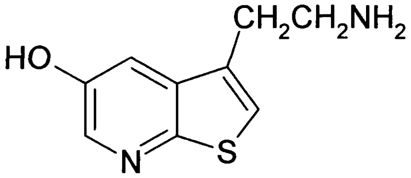


Figure 17

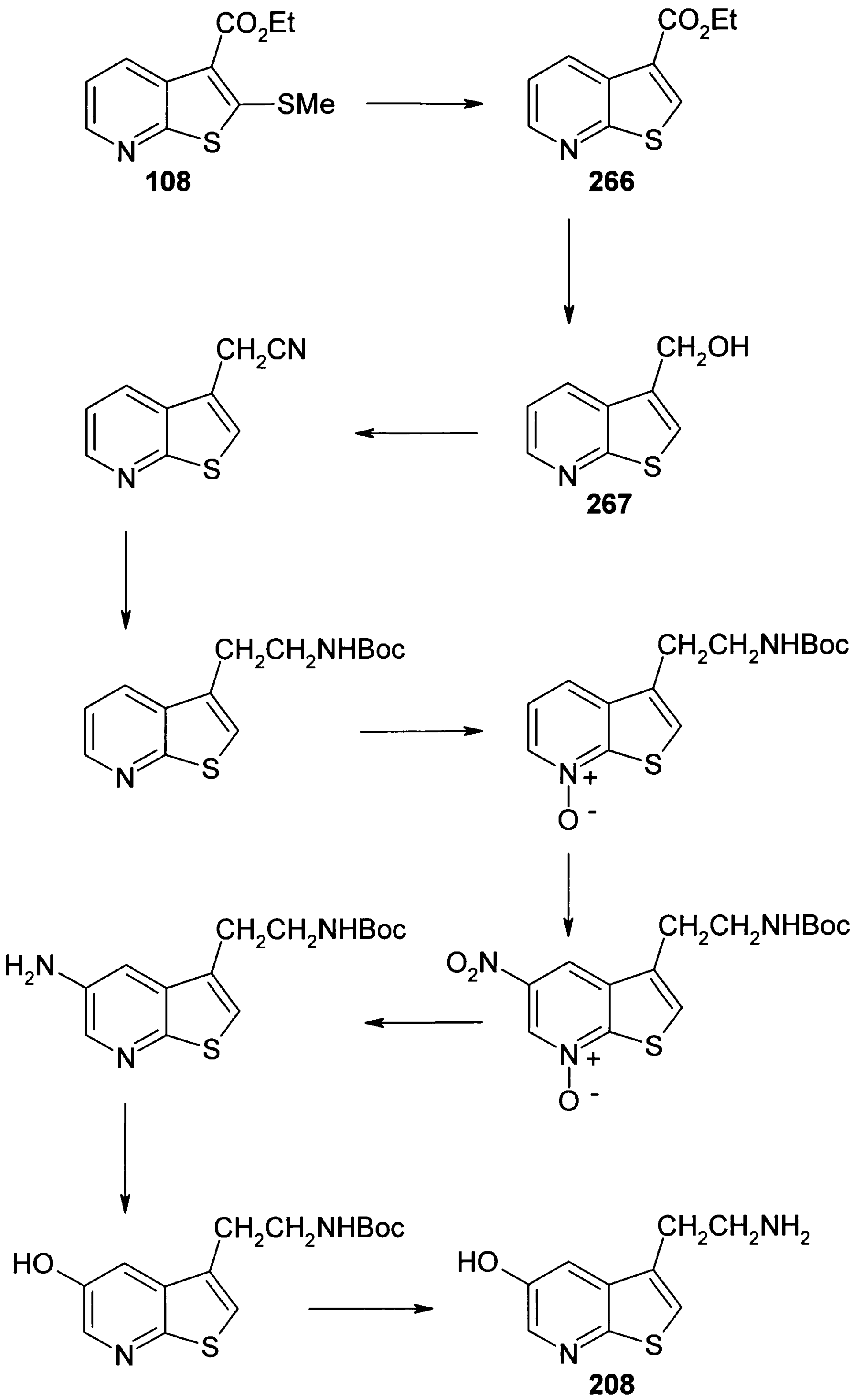
Previous work[399] in this laboratory centred on the molecular modelling of 5-hydroxytryptamine receptors that may be involved in migraine headaches[510] and an agonist binding site identified. As a potential thieno[2,3-b]pyridine analog of 5-HT, 3-aminoethyl-5-hydroxythieno[2,3-b]pyridine **208** [figure 9], had been modelled, synthetic routes to this compound were studied.



208

Figure 9

In parallel to that synthetic programme[399] it was proposed that an alternative route to 3-aminoethyl-5-hydroxythieno[2,3-b]pyridine **208** would be investigated. Starting from 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108**, removal of the thiomethyl group at C-2 would be a priority. This would then be followed by reduction of the ethyl ester function of **266** to the corresponding alcohol **267** then conversion of this to the nitrile, which on reduction would yield the desired ethylamine moiety at C-3 (protection would be necessary). Introduction of a nitro group at C-5 would result in, via diazotisation, the required hydroxy group [scheme 88]. Although not shown in scheme 88, it is possible to introduce a nitro group at C-5 at an earlier stage in the reaction scheme.

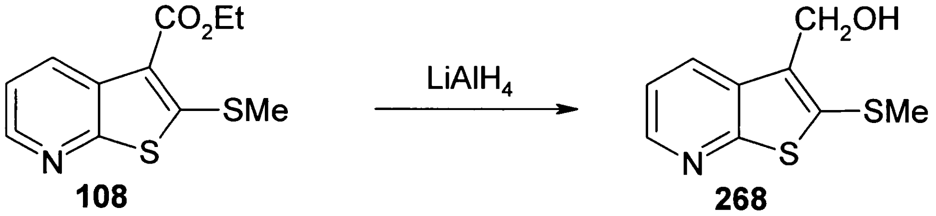

CO2Et
SMe
N
S
108
CO2Et
N
S
266
CH2OH
N
S
267
CH2CN
N
S
CH2CH2NHBoc
N
S
CH2CH2NHBoc
N+
O -
S
CH2CH2NHBoc
O2N
N+
O -
S
CH2CH2NHBoc
H2N
N
S
CH2CH2NHBoc
HO
N
S
CH2CH2NH2
HO
N
S
208

Scheme 88

2.7.1 Removal of thiomethyl group at C-2

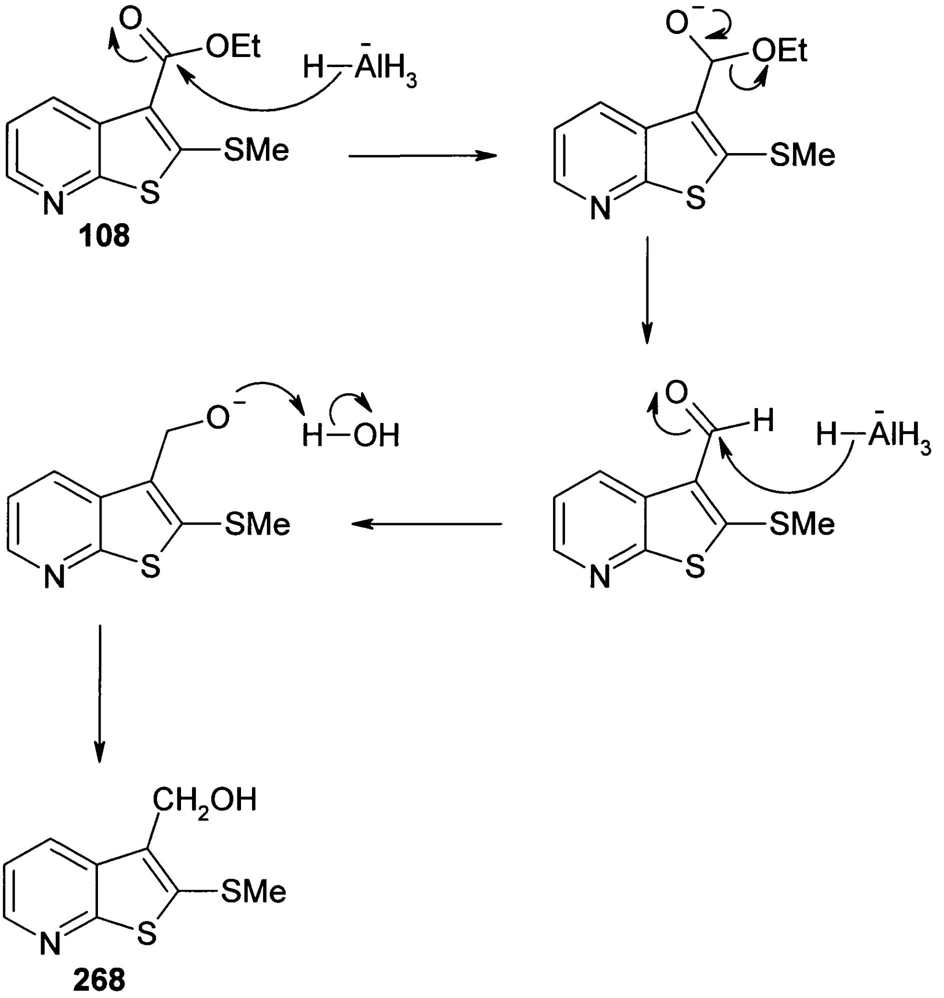
It has been reported[515] that Raney Ni in acetone provides an effective method of desulphurisation and it has been further reported[399] that this reagent was successfully used in the removal of the thiomethyl group from 3-cyano-2-methylthiothieno[2,3-b]pyridine **109** but it was found that the outcome was variable and the one good yield obtained was unrepeatable. Milder conditions were described[516] where Raney Ni in methanol was utilised. Thus, 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** in a methanol solution was added dropwise to a stirred suspension of Raney Ni in dry methanol under dry nitrogen gas and the mixture stirred for six hours. The solids were filtered and washed with hot methanol. The combined organic solutions were concentrated to give a brown solid, which was recrystallised from diethyl ether (section 5.54). Spectroscopic examination showed the product to be unreacted 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108**.

It was postulated that perhaps the bulky ethyl ester group at C-3 was inhibiting this reaction either by virtue of its electron withdrawing properties or by steric effects. Reduction of the ester to the corresponding hydroxymethyl function with lithium aluminium hydride ($LiAlH_4$) was attempted. A solution of 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** in dry diethyl ether was added dropwise to a stirred suspension of $LiAlH_4$ in dry diethyl ether and the mixture was refluxed for forty-eight hours (additional portions of the ether were added occasionally to prevent the reaction mixture drying out). The reaction was cooled and a portion of ethyl acetate added to destroy any unreacted $LiAlH_4$, followed by dilute sulphuric acid. The layers were separated and the aqueous phase washed with diethyl ether. The organic solution was combined with the washes, dried and the solvent removed *in vacuo* to give a white crystalline solid after recrystallisation from ethyl acetate/hexane (section 5.55). Examination of the infrared spectrum revealed an aliphatic C-H stretching absorbance at 2911cm^{-1} and a broad peak at 3204cm^{-1} indicative of a hydroxy group, but no peak for an ester in the region of 1700cm^{-1}. The pmr spectrum contained a singlet at 2.55δ, expected for thiomethyl protons. Also observed were a one-proton singlet at 3.05δ, together with a two-proton singlet at 4.93δ, strongly suggestive of a benzylic hydroxymethyl group. A doublet of doublets at 7.24δ (J=8 & 4 Hz) for H-5, a doublet of doublets at 8.08δ (J=8 & 2 Hz) for H-4 and a doublet of doublets at 8.40δ (J=4 & 2 Hz) for H-6 formed the expected pattern for a 2,3-disubstituted pyridine. This agrees with previous data[399] for 3-hydroxymethyl-2-methylthiothieno[2,3-b]pyridine **268**, obtained in 60% yield [equation 123].



Equation 123

Reduction with $LiAlH_4$ of an ester to an alcohol is in two steps, first reduction to an aldehyde by hydride transfer and elimination of ethoxide, then to an alcohol, again by hydride transfer followed by protonation with water [scheme 89].



Scheme 89

3-Hydroxymethyl-2-methylthiothieno[2,3-b]pyridine **268** was stirred for 24 hours with Raney Ni in dry methanol. Examination of the reaction mixture showed there to be only starting material present so the mixture was refluxed for two hours. The solids were filtered under vacuum and washed with methanol. The combined filtrates were evaporated *in vacuo* to give a solid which was purified by recrystallisation from diethyl ether. Examination (tlc, ir, pmr) confirmed that the product was unreacted starting material (section 5.56).

Hypophosphorous acid and various salts of this acid are known[517,518] to be facile radical reducing agents for organic halides, thionoesters and isocyanides affording the corresponding hydrocarbons. It was envisaged that this reagent could effect the desired transformation. Hence, a solution of 3-ethyloxycarbonyl-2-methyl thiothieno[2,3-b]pyridine **108** and sodium hypophosphite in dry dioxane was refluxed under dry argon. The radical initiator 1,1'-azo*bis*(cyclohexane carbonitrile) (ABCHC) was added in portions every 30 minutes over 4 hours. The solution was cooled, diluted with water and dioxane removed by evaporation. The aqueous residue was extracted with ethyl acetate. After drying and removal of solvent unreacted **108**, as confirmed by comparison with a pure sample, was recovered (section 5.57).

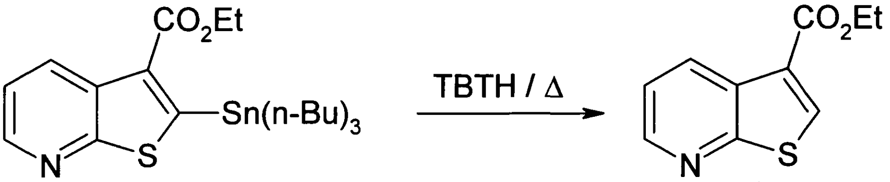
A similar method[518] was then employed using an organic salt of hypophosphorous acid. 3-Ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** together with hypophosphorous acid, triethylamine and the radical initiator, ABCHC, were refluxed in dry dioxane under nitrogen for five hours. During this time further portions of ABCHC were added at hourly intervals. Examination of the reaction by tlc showed only one major spot which had the same Rf as starting material. The reaction mixture was then concentrated, diluted with water and extracted with ethyl acetate. The extracts were dried, filtered and the solvent removed *in vacuo* to give a solid, which was identical (tlc, ir) to a pure sample of starting material **108** (section 5.58).

Organo-tin reagents, mainly tri-*n*-butyltin hydride (TBTH), have been used in a variety[519] of reactions of organic compounds. Principally, replacement of substituents such as halide, nitro, amino or hydroxy groups with hydrogen; addition to carbon carbon and carbon heteroatom multiple bonds; and generating carbon radicals for carbon to carbon inter- or intra-molecular coupling. They have also been reported[520] as powerful and selective reagents for free radical desulphurisation of unsymmetrical sulphides. The cleavage of thioethers by stannyl radicals follows the S_H2 mechanism and the sequence of removal is:

$$\text{Phenyl} \ll \text{methyl} < \text{sec. Alkyl} < \text{tert. Alkyl} < \text{allyl} \approx \text{benzyl}$$

i.e. the rate of reaction increases with increasing stability of the radical cleaved. It has been postulated that stannylation occurs when one equivalent of TBTH, in the presence of a free radical initiator, is used. Protonolysis is achieved by reaction with a second equivalent of TBTH. Consequently, the method published[520] for the cleavage of unsymmetrical sulphides was adapted and it involved refluxing the sulphide together with TBTH and an initiator in a hydrocarbon solvent such as benzene or cyclohexane.

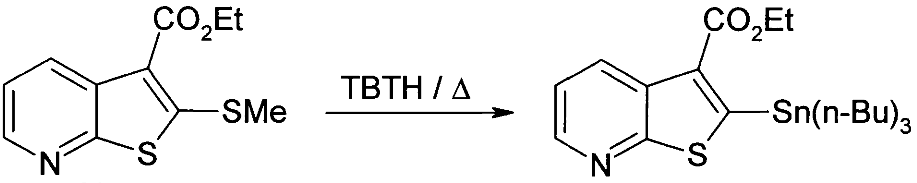
The first attempts at this reaction were undertaken under mild conditions, so 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** and TBTH were refluxed together with free radical initiator ABCHC in dry cyclohexane for 24 hours. A strong smell of methanethiol accompanied this procedure. The resulting oil, obtained after removal of solvent, was chromatographed on silica gel using petroleum ether / ethyl acetate as eluant (section 5.59). First separated was a colourless oil that when examined by pmr spectroscopy, appeared to contain only alkyl groups as unresolved multiplets between 0.85δ and 1.60δ. These signals integrated for about 43 protons and were thought to be tri-*n*-butyltin byproducts. Eluted second was a colourless oil. The pmr spectrum showed the usual pattern for a 2,3-disubstituted pyridine and a 2-proton quartet at 4.38δ, usually associated with an ethyl ester group. There was no signal in the region of 2.60δ that would signify a thiomethyl group. There was again an unresolved multiplet between 0.83δ and 1.66δ. This signal integrated for 35 protons which was more than was required had the compound been the expected 3-ethyloxycarbonyl-2-(tri-*n*-butylstannyl)thieno[2,3-b]pyridine **269**. The infrared spectrum showed the molecule to contain an ester at 1703cm^{-1}. No further attempt was made to purify this compound as further reaction with a second equivalent of TBTH should give the desired dethiomethylated thienopyridine derivative. The oil, obtained from this second reaction with TBTH under the same conditions, was dissolved in acetonitrile and washed with *n*-hexane. It had been reported[521] that by-products of reactions involving TBTH tend to be soluble in hydrocarbons while the desired products are not and remain dissolved in acetonitrile. The resulting oil, after removal of solvent *in vacuo*, was stored in a stoppered flask at room temperature while other work was undertaken. Re-examination of this oil revealed the formation of a solid, which was collected by filtration and recrystallised from *n*-hexane to give a white crystals (section 5.60). The pmr spectrum contained the expected signal pattern for an ethyl ester and a 2,3-disubstituted pyridine. There was also a one-proton singlet at 8.46δ that was characteristic of the hydrogen at the 2-position of a thiophene. The infrared spectrum showed an absorption at 1703cm^{-1} (ester) and both aromatic (3087cm^{-1}) and aliphatic (2983cm^{-1}) carbon-hydrogen bonds. Elemental analysis[459] supported the structure as 3-ethyloxycarbonylthieno[2,3-b]pyridine **266** in 50% yield [equation 124].



269 **266**

Equation 124

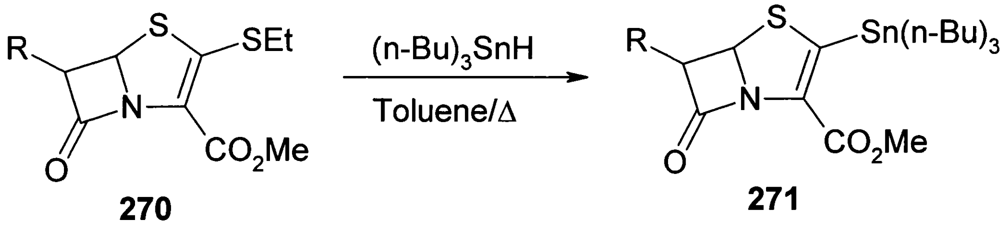
In order to confirm that the precursor to **266** was in fact the postulated 3-ethyloxycarbonyl-2-(tri-*n*-butylstannyl)thieno[2,3-b]pyridine **269**, the reaction of 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** with one equivalent of TBTH was repeated (section 5.61). The product mixture, an oil, was chromatographed on silica gel to give a pale yellow powder after recrystallisation from ethyl acetate [equation 125]. The infrared spectrum contained strong absorbances due to aliphatic carbon-hydrogen bonds (2956 and 2924cm^{-1}) and an ester group (1696cm^{-1}). The pmr spectrum showed a triplet at 0.88δ and a multiplet centred at 1.45δ, which together were due to the *n*-butyl hydrogens and the methyl hydrogens of the ester group. The presence of an ethyl ester was confirmed by the two-proton quartet at 4.47δ. The expected pattern for a 2,3-disubstituted pyridine was also observed. The structure was supported by microanalysis[459] as 3-ethyloxycarbonyl-2-(tri-*n*-butylstannyl)thieno[2,3-b]pyridine (**269**, 66%).



108 **269**

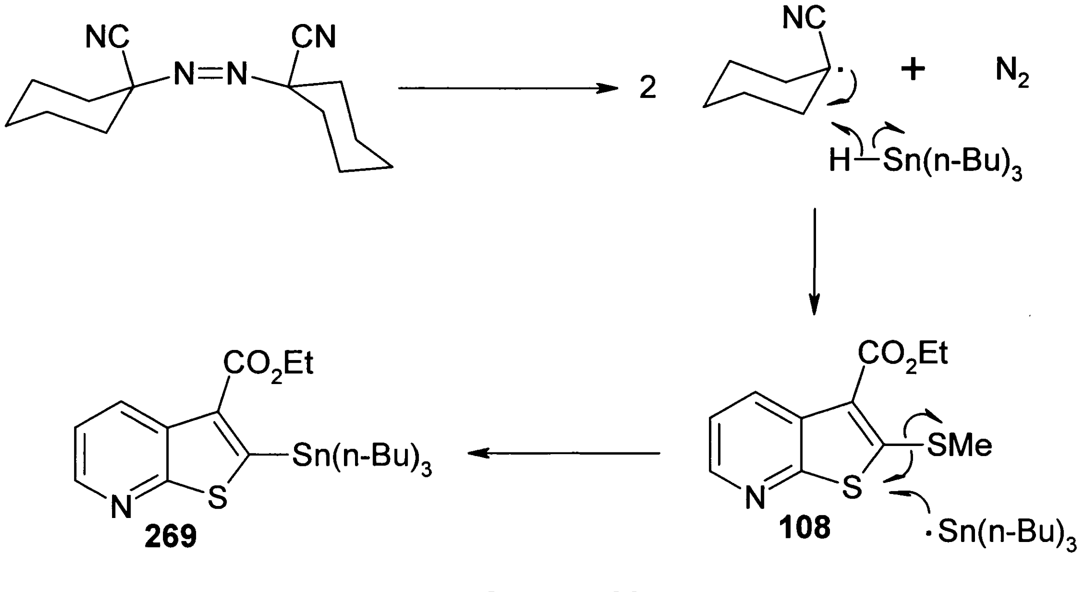
Equation 125

It is known[522] that for the ethylthiopenem **270**, reaction with TBTH, in refluxing toluene with an initiator, affords the 2-stannyl derivative **271** in 96% yield although no mechanism is proposed [equation 126].



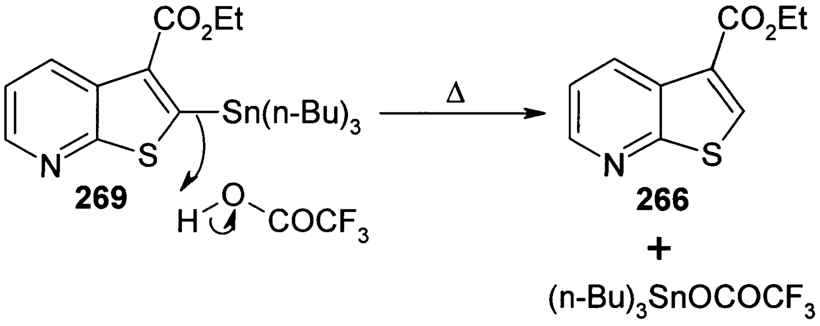
Equation 126

In the cleavage[519] of unsymmetrical sulphides with TBTH, a methyl group is less readily cleaved than a secondary alkyl group. In this transformation, **108** with the thiomethyl at C-2, is acting more like a ketenedithioacetal than a thiophene, i.e. more like an aliphatic system than an aromatic one. Hence, the production of stannylated derivative **269** by the S$_H$2 mechanism [scheme 90].



Scheme 90

Protonolysis of stannylated compounds can be achieved by treatment with acids such as trifluoroacetic acid[523] or benzoic acid[524] and is considered[525] to be electrophilic substitution at the carbon of the C-Sn bond. So, 50% trifluoroacetic acid was investigated for the protonolysis of the tri-*n*-butylstannyl derivative **269**. Hence, 3-ethyloxy carbonyl-2-(tri-*n*-butylstannyl)thieno[2,3-b]pyridine **269** was dissolved in ethanol, trifluoroacetic acid (50%) added and the mixture refluxed for 16 hours (section 5.62). Removal of solvent, then column chromatography gave 3-ethyloxycarbonyl thieno[2,3-b]pyridine **266** in 73% yield [equation 127].



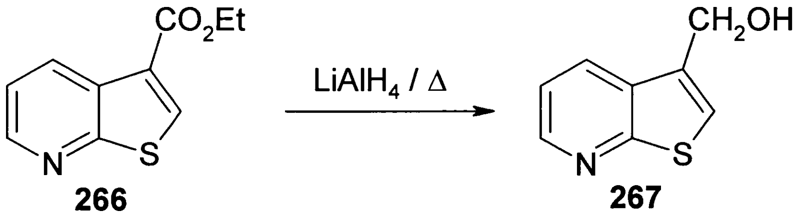
Equation 127

This method was used therefore, in place of the second treatment with TBTH, in subsequent reactions of this nature as an inexpensive and simple alternative for the formation of **266** from **269**.

Overall the dethiomethylation sequence is relatively straight forward, although care must be taken in the purification of **269** as tin byproducts are not always easy to remove, especially when the reaction is carried out on a larger scale. However, the desired product **266** was obtained, which allowed further transformations to be attempted on the side chain at C-3.

2.7.2 Manipulation of the side chain at the C-3

Having prepared 3-ethyloxycarbonylthieno[2,3-b]pyridine **266**, the next step was to reduce the ester at the 3-position to the corresponding primary alcohol. A solution of 3-ethyloxycarbonylthieno[2,3-b]pyridine **266** in dry diethyl ether was added dropwise to a stirred suspension of $LiAlH_4$ in dry diethyl ether and the mixture refluxed for 48 hours. Excess $LiAlH_4$ was destroyed by careful addition of ethyl acetate, followed by dilute sulphuric acid. Extraction with diethyl ether and removal of the solvent *in vacuo* gave white needles, after recrystallisation from diethyl ether [equation 128] (section 5.63). There was a broad O-H stretch absorption (3216cm^{-1}) but no peak for an ester in the infrared spectrum. The pmr spectrum showed a one-proton singlet at 3.29δ and a two-proton singlet at 4.91δ. These signals were comparable to those in the pmr spectrum of 3-hydroxymethyl-2-methylthiothieno[2,3-b]pyridine **268**, so were assigned to the hydroxyl hydrogen and the methylene hydrogens respectively. Also present were the expected peak pattern for a 2,3-disubstituted pyridine ring and a one proton singlet at 7.43δ for the hydrogen at C-2. Microanalysis[459] supported the structure 3-hydroxymethylthieno[2,3-b]pyridine (**267**, 50%).



Equation 128

The transformation of a primary alcohol to a nitrile is well documented in the literature and usually involves conversion of the hydroxyl group to a halide or tosylate before nucleophilic substitution by a nitrile anion takes place. There are several methods for the direct conversion, with the simplest[526] of them being refluxing the alcohol with sodium cyanide in DMF. So, 3-hydroxymethylthieno[2,3-b]pyridine **267** and sodium cyanide were refluxed in DMF for 20 hours. The mixture was then basified with solid sodium hydroxide and the solvent replaced with water. Neutralisation, followed by extraction with dichloromethane and removal of solvent *in vacuo* gave a pale yellow solid which was identified as unreacted 3-hydroxymethylthieno[2,3-b]pyridine **267** (section 5.64)

The reaction of primary alcohols with 2 equivalents each of sodium cyanide and trimethylsilylchloride, together with acetonitrile, in the presence of a catalytic amount of sodium iodide has been reported[527] to produce the corresponding nitriles in good yield. It is proposed that the reaction proceeds via the *in situ* generation of a trimethylsilyl ether of the alcohol and then reaction of this with the complex formed between acetonitrile and trimethylsilyliodide to form an oxonium ion, which is nucleophilically diplaced, by a cyanide anion. In the absence of sodium iodide no reaction takes place. An acetonitrile solution of 3-hydroxymethylthieno[2,3-b]pyridine **267** was therefore added to a suspension of sodium cyanide and a catalytic amount of sodium iodide in DMF. To this was added trimethylsilylchloride and the mixture heated to 60 °C for 6 hours. Tlc indicated at this point that starting material remained largely unreacted. After workup a solid was obtained which indeed proved to be unreacted 3-hydroxymethylthieno[2,3-b]pyridine **267** and so the reaction was discontinued (section 5.65).

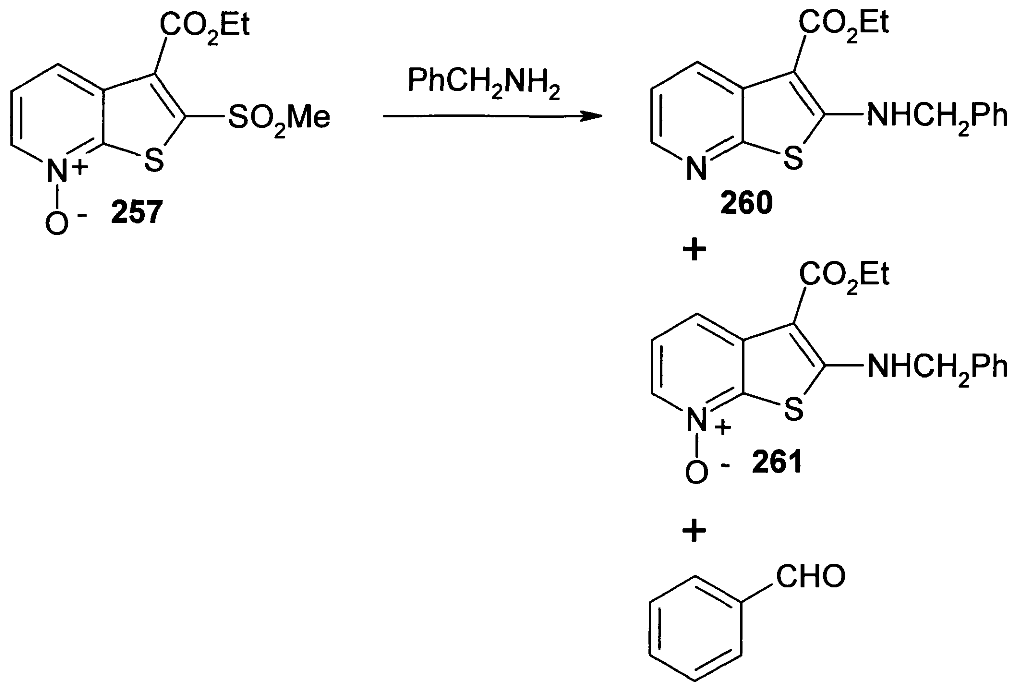
Nitriles have been produced in good yields[528] by the treatment of primary alcohols with a mixture of tri-n-butylphosphine, carbon tetrachloride and potassium cyanide in acetonitrile in the presence of 18-crown-6 ether. 18-Crown-6 ether is vital to the reaction as it complexes with potassium ions allowing unsolvated nitrile ions to become available for reaction. No nitrile was produced in the absence of 18-crown-6, however it was reported that benzyl chloride was synthesised from benzyl alcohol under these conditions. 15-Crown-5 ether was available in the laboratory and it has been reported[490] that this smaller crown ether, in conjunction with sodium cyanide, would complex with sodium ions allowing the nitrile anions to react. 3-Hydroxymethylthieno[2,3-b]pyridine **267**, sodium cyanide and 15-crown-5 in acetonitrile were stirred at room temperature under dry nitrogen gas. A solution of tri-n-butylphosphine in acetonitrile was added followed by the dropwise addition of an acetonitrile solution of carbon tetrachloride at 0 °C. The mixture was stirred at room temperature for 5 hours, when tlc showed that the starting material was largely unreacted. The reaction was then heated at reflux for 16 hours cooled, diluted with diethyl ether and washed with citric acid solution. After workup the residue was chromatographed on silica gel using petroleum ether / ethyl acetate as eluant. The only compound isolated was unreacted 3-hydroxymethylthieno[2,3-b]pyridine **267** (section 5.66). This was disappointing as even if the desired nitrile had not been formed, it was hoped that 3-chloromethylthieno[2,3-b]pyridine may have been produced as an alternative.

As the hydroxyl group was proving to be unreactive, it was decided to attempt to increase its lability by converting it to its tosylate. Generally[529] tosylation of an alcohol takes place in the presence of a base and usually requires an excess of both *p*-toluenesulphonylchloride and base. However there are problems encountered with this reaction, for example, the formation of pyridinium salts (when the base is pyridine) that reduce the overall yield of the reaction. In spite of these reservations the method described by Kabalka[530] was followed. The thienopyridine **267** was dissolved in chloroform at 0 °C and pyridine added followed by *p*-toluenesulphonyl chloride in portions with constant stirring. Examination by tlc showed significant amounts of starting material remained after 3 hours at 0 °C, so the mixture was allowed to warm to room temperature and stirring was continued for a further 24 hours. The reaction mixture was diluted with diethyl ether and washed with dilute hydrochloric acid, sodium bicarbonate solution and water. Removal of diethyl ether *in vacuo* resulted in recovery of unreacted *p*-toluenesulphonyl chloride. The aqueous solution was made strongly basic with solid potassium hydroxide and extracted with ethyl acetate. The solvent was dried and removed *in vacuo* to give unreacted 3-hydroxymethylthieno[2,3-b]pyridine **267** (section 5.67). It is possible, as the p-toluenesulphonyl chloride used was not absolutely fresh, that it contained sufficient tosic acid to render it ineffective. This, coupled with the known problem of formation of pyridinium salts in the reaction mixture, may have caused the reaction to fail.

Due to time constraints no further work on this was carried out. However some progress has been made towards the goal of synthesising a potential agonist of serotonin. Having prepared the hydroxythienopyridine **267**, it is now possible that other reactions to replace the hydroxy group with a nitrile can be investigated.

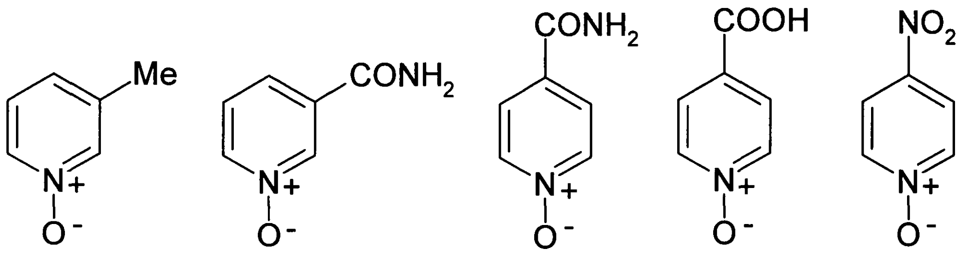
2.8 Oxidation of benzylamine to benzaldehyde with pyridine N-oxides

The nucleophilic substitution reaction at the 2-position of 3-ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine N-oxide **257** with benzylamine led to the production of benzaldehyde by a side reaction (section 2.4) [equation 116].



Equation 116

It was postulated that the formation of benzaldehyde was due to either the sulphone or the N-oxide function. This was tested by also reacting benzylamine with 3-ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine **256** and 3-ethyloxy carbonyl-2-thiomethylthieno[2,3-b]pyridine N-oxide **223**. As benzaldehyde was only isolated from the reaction involving the latter, it appears that the N-oxide function was responsible for this transformation. In order to further explore the involvement of the N-oxide group, the readily available pyridine N-oxides 3-methylpyridine N-oxide **272**, 3-amidopyridine N-oxide **78**, 4-amidopyridine N-oxide **273**, isonicotinic acid N-oxide **274** and 4-nitropyridine N-oxide **50** [figure 18] were investigated as potential oxidising agents for this transformation.



272 **78** **273** **274** **50**

Figure 18

Firstly, 3-methylpyridine N-oxide **272** was refluxed in neat benzylamine for three hours, cooled, acidified with dilute hydrochloric acid and extracted with diethyl ether. The extracts were combined, dried with magnesium sulphate and the solvent removed *in vacuo* to give benzaldehyde, confirmed by comparison with the ir spectrum of a genuine sample, as a pale yellow liquid in 39% yield (section 5.68). In an attempt to improve this yield, 3-methylpyridine N-oxide **272** was purified by distillation and the reaction repeated. This however led to a reduction in yield to 10%. As anhydrous conditions were unsuccessful, the reaction was again repeated with the addition of a few drops of water. In this case the yield was further reduced to 3%. There seems to be no clear trend to these observations so the other pyridine N-oxides were used with no further purification and are listed together with the yields of benzaldehyde obtained [table 5]. The yields are the best found, as repeatability proved difficult under these reaction conditions.

N-oxide	Yield (%)
3-methylpyridine **272**	39
3-amidopyridine **78**	6
4-amidopyridine **273**	4
isonicotinic acid **274**	32
4-nitropyridine **50**	93

Table 5: Yields of Benzaldehyde

Initially, when 4-nitropyridine N-oxide **50** was heated in neat benzylamine, a violent reaction occurred when the temperature exceeded 120 °C, which precluded the collection of any benzaldehyde. However, when the reaction was stopped just below this temperature, benzaldehyde was isolated in 93% yield. It proved on repetition to be very difficult to predict at exactly what temperature the reaction could be stopped to maximise the yield and hence it was not studied further.

The problem of variable yields was thought to be largely due to the volatility and reactivity in air of benzaldehyde, so it was decided to collect the product as its 2,4-dinitrophenylhydrazone. 3-Methylpyridine N-oxide **272** was refluxed with benzylamine and after cooling, neutralisation with dilute hydrochloric acid and extraction of benzaldehyde into diethyl ether, an acidic solution of 2,4-dinitrophenylhydrazine (DNP) in methanol was added. The reaction mixture was concentrated, refrigerated for two hours and the resulting precipitate collected by filtration to give a 40% yield of benzaldehyde-2,4-dinitrophenylhydrazone, identified by comparison (mp, tlc, ir) with a genuine sample (section 5.69). When this procedure was extended to the pyridine N-oxides listed in table 3, the yields obtained, although not markedly improved upon, did become repeatable. In the hands of co-workers[531] reproducibility was confirmed [table 6].

N-oxide	Yield (%)
3-methylpyridine **272**	40
3-amidopyridine **78**	9
4-amidopyridine **273**	6
isonicotinic acid **274**	28

Table 6: Yields of Benzaldehyde as the 2,4-Dinitrophenylhydrazone

The reaction of 4-nitropyridine N-oxide **50** with benzylamine was revisited as, although unreliable, it did produce the highest yield of benzaldehyde. Mechanistically, the transformation of benzylamine to benzaldehyde involves two moles of benzylamine for each mole of pyridine N-oxide employed, so **50** was refluxed together with two equivalents of benzylamine in o-xylene (25 ml). It was considered that o-xylene would not only act as a diluant but as it boils at 118 °C would reduce the possibility of explosive decomposition. The reaction was monitored by tlc and after seven hours 4-nitropyridine N-oxide **50** was still in evidence, so the reaction mixture was cooled and neutralised with dilute hydrochloric acid. An acidic solution of 2,4-dinitrophenylhydrazine in methanol was added, and the reaction worked up as previously described to give benzaldehyde-2,4-dinitrophenylhydrazone in 22% yield. Lengthening the reaction time improved the yield, however it became apparent after refluxing for 96 hours, that to achieve a maximum yield would require an unfeasibly long reaction time. Reducing the amount of solvent employed was then investigated as a possible way to improve the yield without causing the reaction to become unstable. 4-Nitropyridine N-oxide **50** and benzylamine were refluxed in *o*-xylene (15 ml) for 7 hours and the reaction mixture treated as previously described to give benzaldehyde-2,4-dinitrophenylhydrazone in 45% yield. Increasing the reaction time improved the yield, however times beyond 24 hours led to marked reductions in the yield [table 7].

o-xylene volume (ml)	Reaction time (h)	Yield (%)
25	7	22
25	17	45
25	24	62
25	96	67
15	7	45
15	16	64
15	24	78
15	48	62
15	96	54

Table 7: Variation in Yield by Time and Solvent Volume

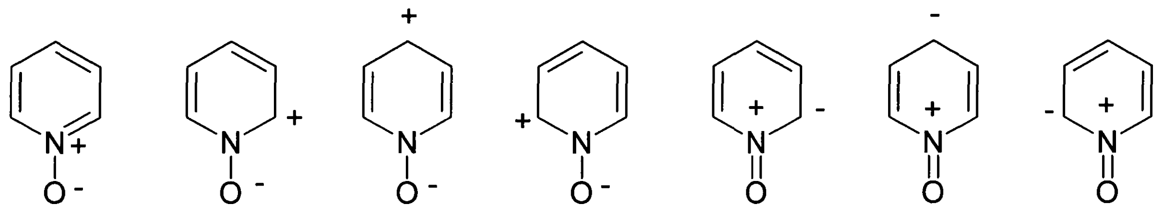
It can be seen from the above table that the most productive conditions for the transformation of benzylamine to benzaldehyde using **50** are when the reagents are in the molar ratio of amine : N-oxide; 2 : 1 and are refluxed in *o*-xylene (15 ml) for 24 hours (section 5.70).

It was decided to extend this methodology to the other pyridine N-oxides used in this investigation. Each was, in turn, refluxed in *o*-xylene (15 ml) with 2 equivalents of benzylamine for 24 hours, then subjected to the usual work-up and benzaldehyde collected as its 2,4-diphenylhydrazone. The yields found [table 8], although reproducible were not a significant improvement on those obtained when neat reagents were used and hence this particular methodology appears to be most useful for 4-nitropyridine N-oxide **50**.

N-oxide	Yield (%)
3-methylpyridine **272**	8
3-amidopyridine **78**	13
4-amidopyridine **273**	4
isonicotinic acid **274**	54

Table 5: Yield from Reaction in *o*-xylene

An alternative mechanism to that shown in scheme 85 has been proposed (personal communication from Dr P N Preston). It was pointed out that, as an amino group is not a particularly good leaving group, an alternative mechanistic route could involve a pyridine N-oxide reacting in one of its canonical forms **5**, **6** or **7** [figure 2].

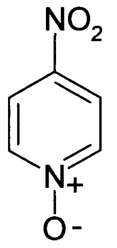


1 **2** **3** **4** **5** **6** **7**

Figure 2

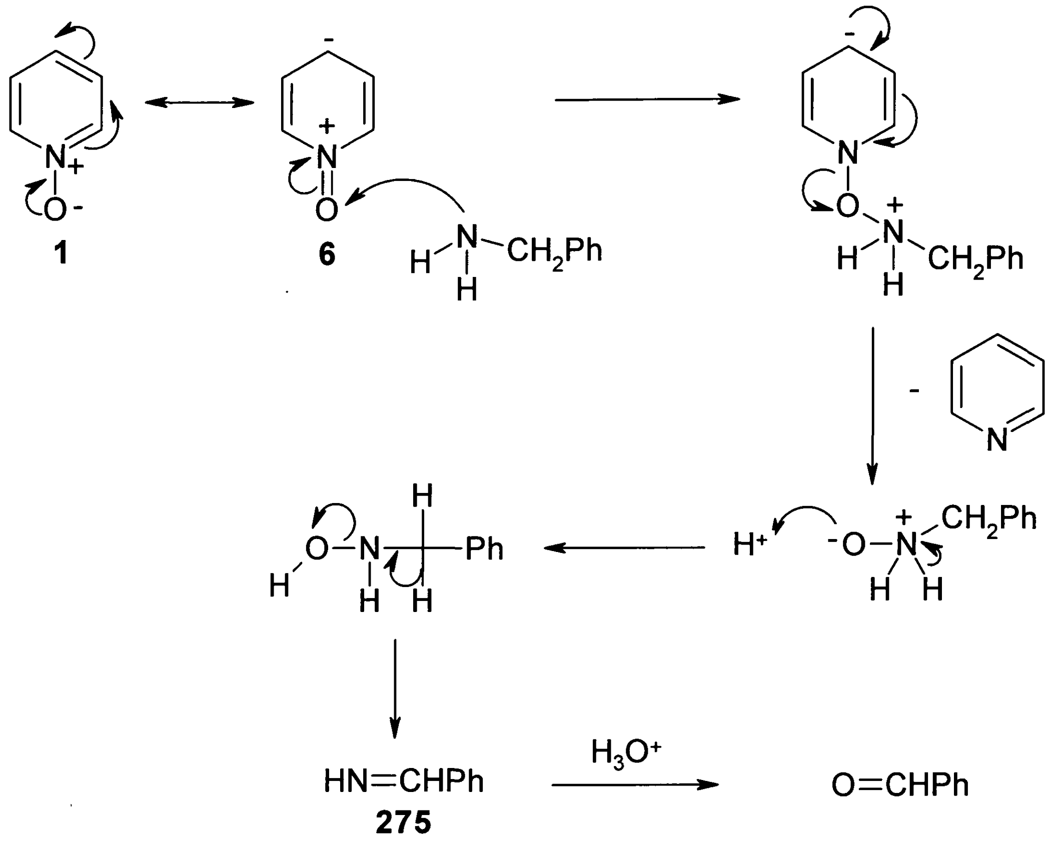
In these forms the oxygen atom is relatively electron deficient and hence susceptible to nucleophilic attack by the nitrogen atom of benzylamine. The hydroxylamine thus formed could lose water to form the imine **275** that would hydrolyse during work up to produce benzaldehyde [scheme 91].

Supporting evidence for this is the reactivity of 4-nitropyridine N-oxide **50** [figure 19]. The nitro group being strongly electron withdrawing will enhance this effect and render the N-oxide oxygen more susceptible to nucleophilic attack.



50

Figure 19



Scheme 91

This interesting reaction is worthy of further investigation into its scope and limitations in order to develop a general procedure for the conversion of primary amines to aldehydes. It was not, in terms of the objectives of this project, considered worth devoting more resources to and was satisfactorily concluded at this point.

2.9 Ester carbonyl stretching absorbances

A number of different types of compound were prepared in this programme, the majority of which contain an ethyl ester group. Other groups in these molecules influence the position, in the infrared spectra, of the ester carbonyl stretching absorbance.

For the chloropyridine derivatives **72**, **74**, **76**, **215**, **218**, **219** and **220**, [figure 20], all the ester groups are aliphatic and the expected[532] absorbance range for carbonyl stretching for this type of ester is 1750-1720cm^{-1}.

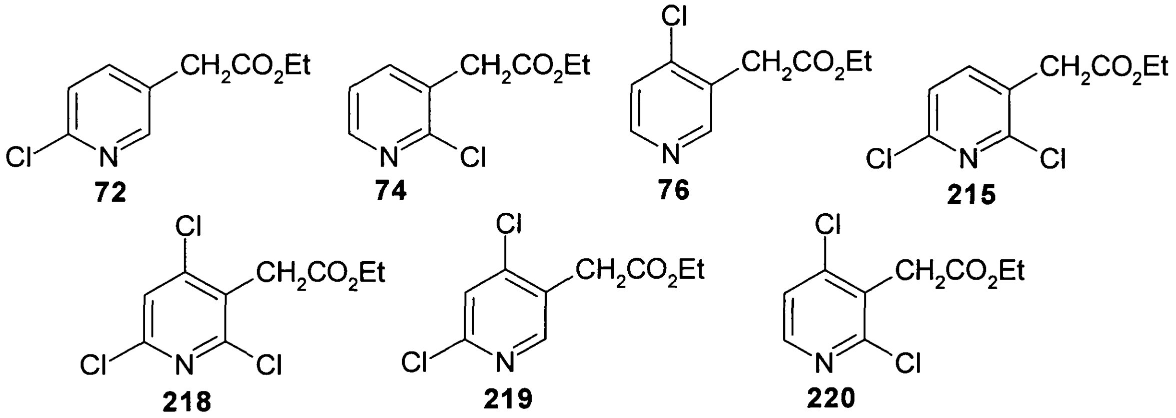


Figure 20

As can be seen in Table 9, the carbonyl stretching absorbances for these compounds all fall within the expected range.

Pyridine	Absorbance (cm^{-1})
72	1732
74	1735
76	1737
215	1736
218	1732
219	1737
220	1738

Table 9. Carbonyl Stretching Absorbances for Chloropyridines

Chloropyridine N-oxide derivatives **212**, **213**, **214**, **217**, **221** and **222** also have aliphatic ester groups in their structure. Chloropyridine N-oxide **216** contains an aliphatic acid group [figure 21].

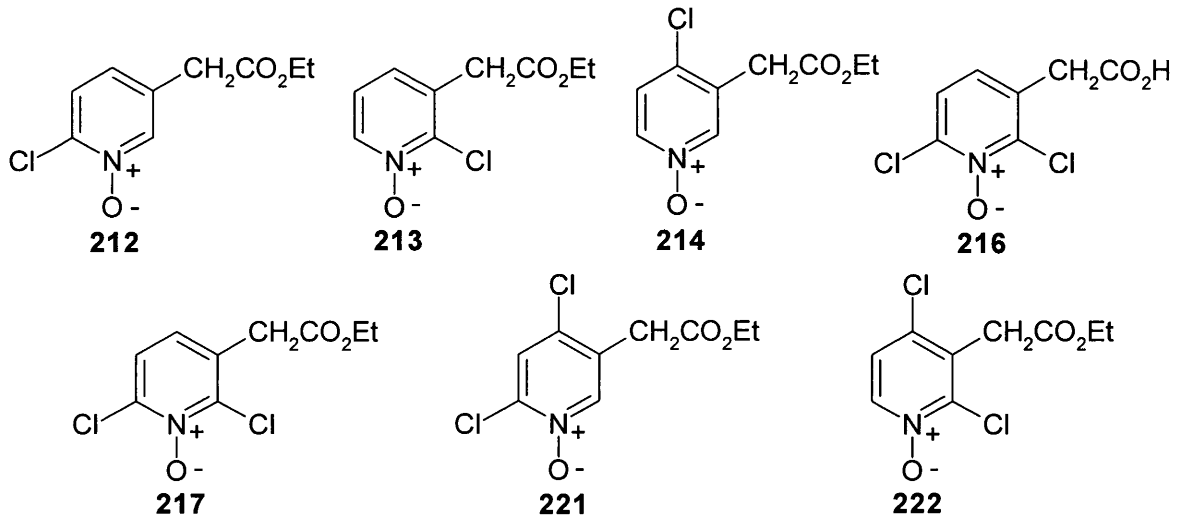


Figure 21

The stretching vibration for the carbonyl of the aliphatic ester groups, again, all fall within the expected range[532] for this type of compound, although for **217** the wavenumber is slightly lower than the others. The aliphatic acid group of **216** shows an absorbance within the range[532] for this type of group (1725-1700cm^{-1}) [table 10].

Pyridine N-oxide	Absorbance (cm^{-1})
212	1735
213	1734
213	1734
216	1715
217	1721
221	1732
222	1733

Table 10. Carbonyl Stretching Absorbances for Chloropyridine N-oxides.

Thienopyridines containing a thiomethyl group at C-2, **108**, **223**, **224**, **225**, **226**, **240**, **241**, **242**, **243** and **265**, [figure 22], have an aromatic ethyl ester group at C-3.

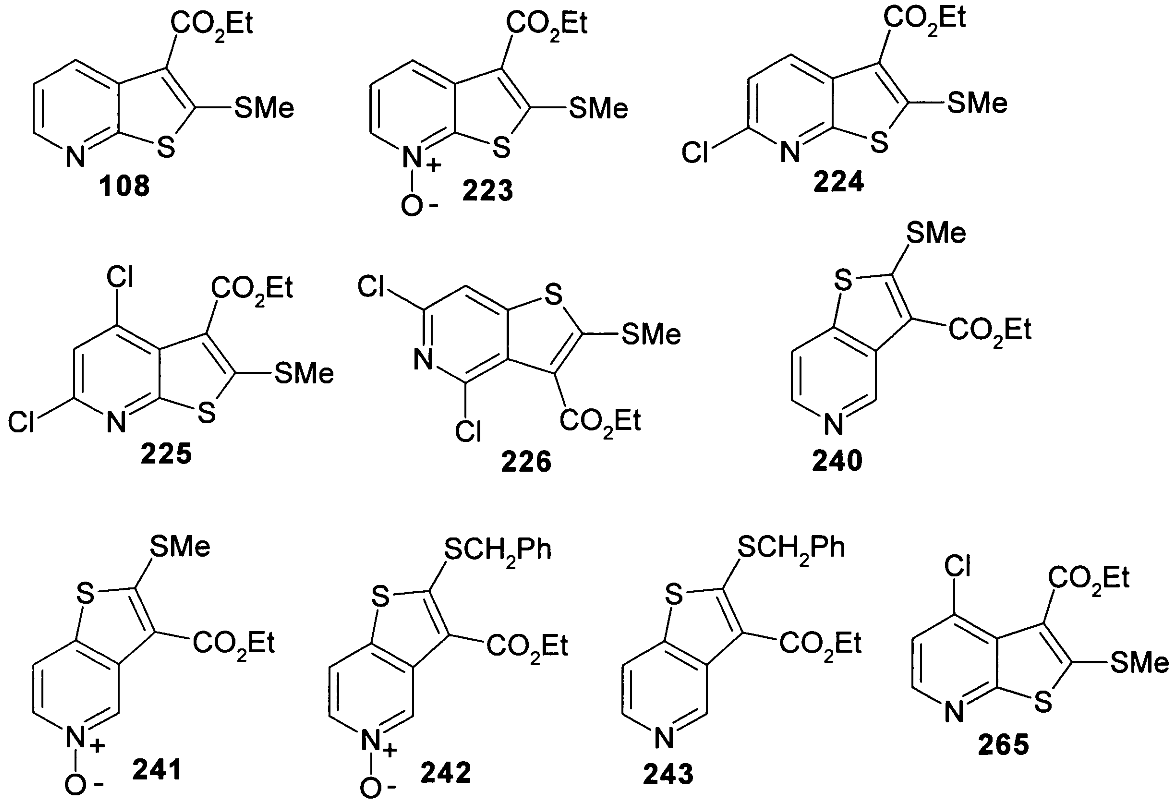


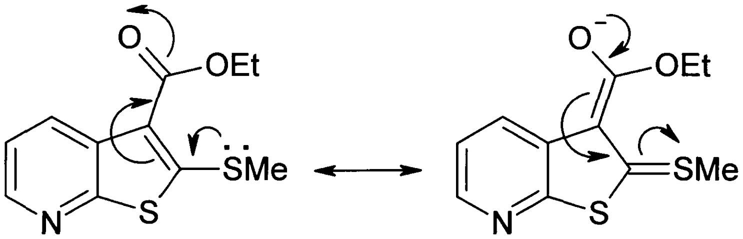
Figure 22

This type of ester would be expected[532] to have a carbonyl stretching absorbance between 1730 and 1705cm^{-1}. The actual absorbances recorded are at lower wavenumbers [table 11].

Thienopyridine	Absorbance (cm^{-1})
108	1695
223	1675
224	1670
225	1690
226	1726
240	1690
241	1681
242	1690
242	1683
265	1695

Table 11. Carbonyl Stretching Absorbances for Thienopyridines.

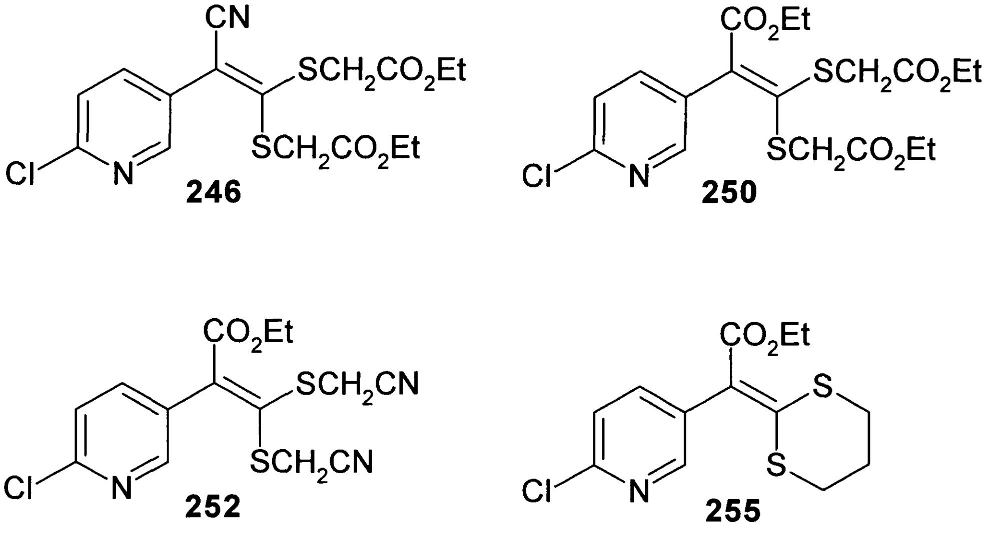
This can be explained by the presence of the thiomethyl group at C-2. A lone pair of electrons of the sulphur can delocalise into the conjugated system leading to a reduction in double bond character of the ester carbonyl [figure 23]. It is known[532] that esters of salicylic or anthranilic acids show this behaviour and their carbonyl stretching absorbances are normally within the range 1690-1670cm^{-1}. However, **226** does not appear to exhibit this phenomenon.



108

Figure 23

Prepared ketenedithioacetals with ester groups in their structures are shown in figure 24.



246 **250** **252** **255**

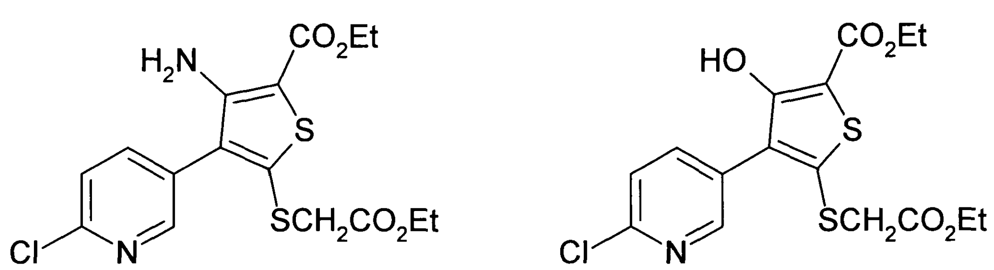
Figure 24

The infrared spectra for **246** and **250** show a carbonyl stretching absorbance in the expected region for aliphatic esters [table 12]. This was unexpected for **250**, as it also contains α,β-unsaturated ethyl ester group and a second peak should have been observed at a lower wavenumber, typically[532] 1730-1705cm^{-1}. The carbonyl absorbance in the spectrum of **252** is in the correct region for an α,β-unsaturated ester group, but for the corresponding group in **255** a lower wavenumber was found.

Ketene dithioacetals	Absorbance (cm^{-1})
246	1736
250	1736
252	1720
255	1684

Table 12. Carbonyl Stretching Absorbances for ketene dithioacetals.

The substituted thiophenes **247** and **251**, [figure 25], both show two carbonyl stretching absorbances. One, in each spectrum, can be interpreted as due to the aliphatic ethyl ester. The second, at lower wavenumbers, would be for the esters directly attached to the thiophene rings, behaving in a similar manner to salicylate or anthranilate esters [table 13]. There will also be some hydrogen bonding between the ester carbonyl and the amino hydrogens **247** or the hydroxy hydrogen **251**. This phenomenon is known[532] to move the absorbance to a lower wavenumber.



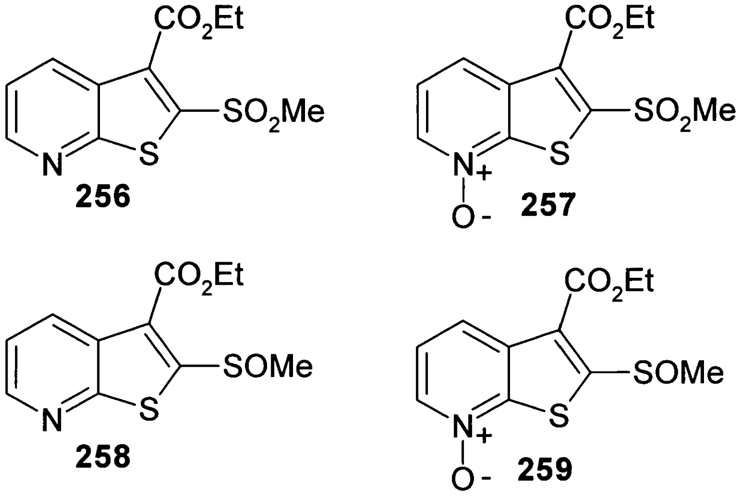
247 **251**

Figure 25

Thiophene	Absorbance (cm^{-1})
247	1724, 1661
251	1748, 1666

Table 13. Carbonyl Stretching Absorbances for Thiophenes.

Thieno[2,3-b]pyridine sulphoxides and sulphones **256**, **257**, **258** and **259** are shown in figure 26.



256 **257** **258** **259**

Figure 26

For **256** and **257,** the carbonyl stretching absorbances are typical of aromatic ester groups. Those for **258** and **259**, are as expected for salicylate type esters, where again the lone pair of electrons of the sulphoxide sulphur at C-2 is delocalising into the conjugated system leading to a reduction in double bond character of the ester carbonyl [table 14].

Sulphoxide, Sulphone	Absorbance (cm^{-1})
256	1724
257	1718
258	1697
259	1694

Table 14. Carbonyl Stretching Absorbances for Thieno[2,3-b]pyridine sulphoxides and sulphones.

The other thieno[2,3-b]pyridines, prepared by substitution of the thiomethyl at C-2 of **108** are listed in figure 27.

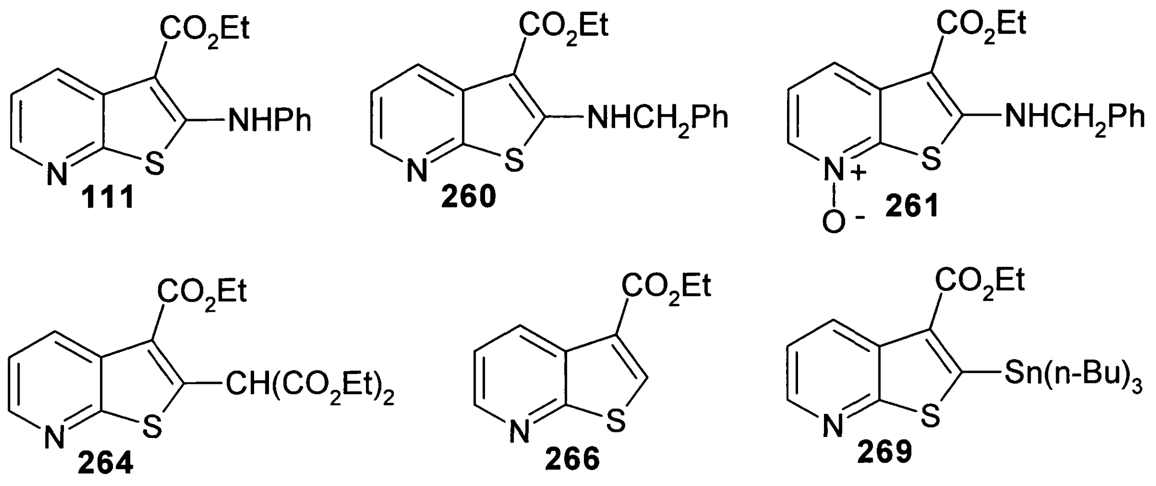


Figure 27

For the thieno[2,3-b]pyridines with secondary amino groups at C-2, **111**, **260** and **261**, the carbonyl stretching absorbances are all at wavenumbers much lower than normally seen for this vibration in aromatic esters [table 15]. This may be due to the influence of the amine on the conjugated system, coupled with hydrogen bonding between the amine hydrogen and the carbonyl. Thieno[2,3-b]pyridine **264** shows two peaks for carbonyl stretching; at 1736cm^{-1} for the aliphatic ester groups and at 1708cm^{-1} for the aromatic ethyl ester group at C-3. The absorbance seen in the spectrum of **266** is typical of an aromatic ethyl ester group. The stannylated derivative **269** has a carbonyl stretching absorbance in a position slightly lower than for an aromatic ethyl ester group, therefore it would appear that the tin atom at C-2 is contributing electrons to the conjugated system by a +I effect, but this influence is not as pronounced as for the amines where electrons can be delocalised.

Thienopyridine	Absorbance (cm^{-1})
111	1653
260	1650
261	1649
264	1736, 1708
266	1703
269	1696

Table 15. Carbonyl Stretching Absorbances for substituted thieno[2,3-b]pyridines. Interpretation of the positions of these signals is useful in confirming the structure of the prepared compounds. It should be noted that not all compounds gave absorbances exactly in the expected regions, hence, the predictive power of this type of analysis is limited.

3 Conclusions

The preparation of 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** is the result of a multi-step reaction sequence. Improving the yield of ethyl 3-pyridylacetate N-oxide **213**, using *m*-CPBA with the improved procedure[457] described, together with the more effective separation of ethyl 2-chloro-3-pyridylacetate **74** allowed the desired thienopyridine **108** to be synthesized in greater yield[261] than that reported[260] previously. Additionally, N-oxidation of the unstable ethyl 4-chloro-3-pyridylacetate **76** gave the opportunity to prepare some novel thieno[3,2-c]pyridines [figure 28].

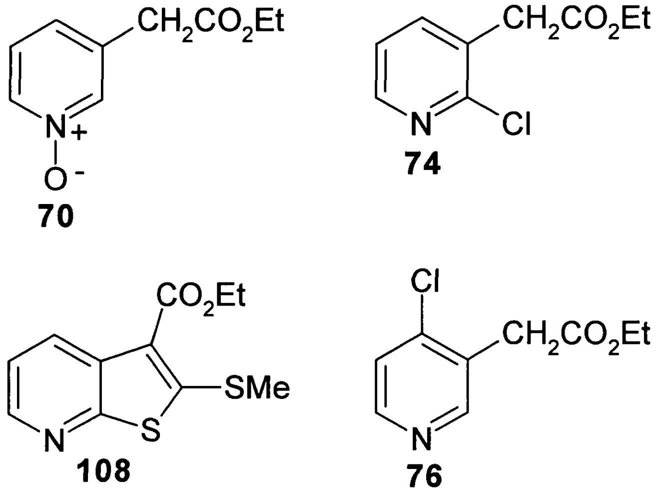

70 **74** **108** **76**

Figure 28

The preparation of other pyridine N-oxides was easily achieved in moderate to good yields. Separation of the mixture of ethyl 2,4-dichloro-5-pyridylacetate **219** and ethyl 2,4-dichloro-3-pyridylacetate **220** was accomplished by conversion to the N-oxides by the use of *m*-CPBA with concentrated sulphuric acid. Pertrifluoroacetic acid was necessary to convert the less basic ethyl 2,6-dichloro-3-pyridylacetate **215** to the N-oxide. It was found that the ester was hydrolysed during this process; however, esterification of the acid **216** was easily achieved [figure 29]. Chlorination of these compounds with phosphorus oxychloride gave polychlorinated pyridines that were converted to novel thienopyridines.

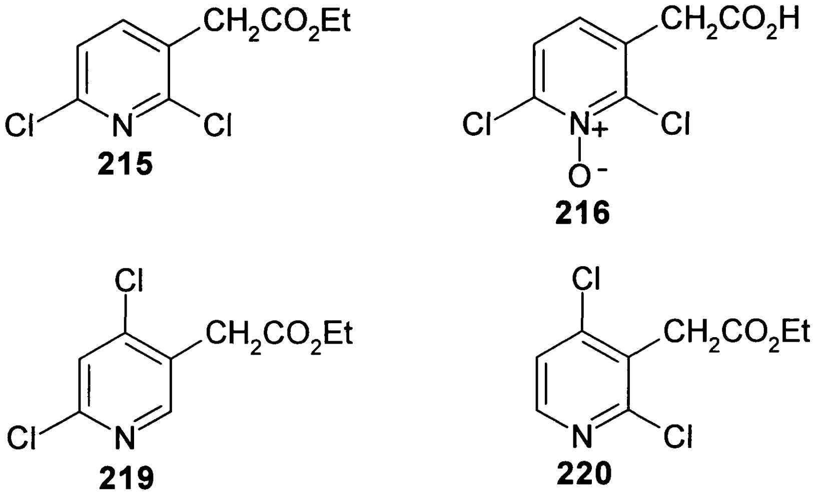
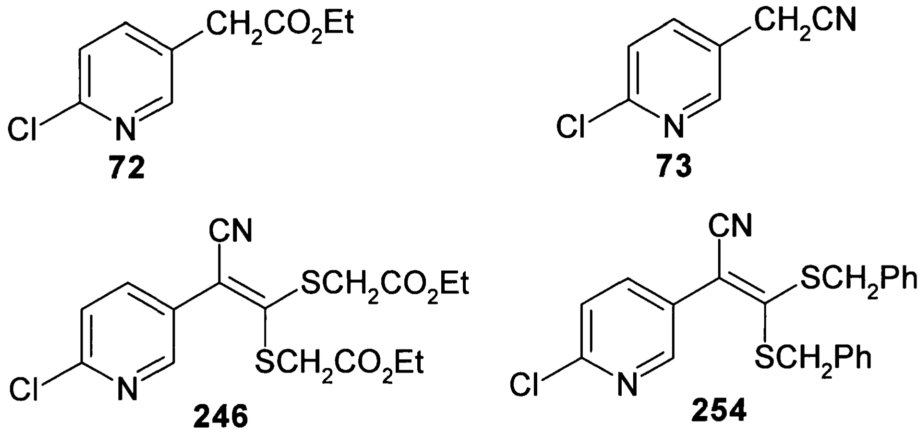


Figure 29

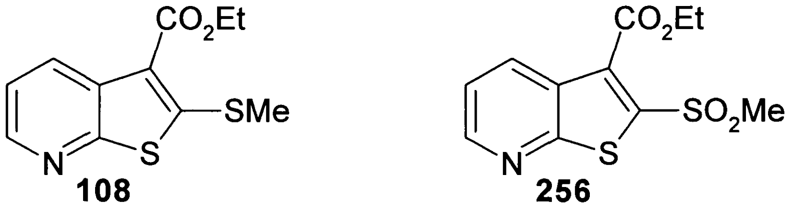
The initial preparation of ketene dithioacetal **246** from 2-chloro-5-pyridylacetonitrile **73** was carried out to gain experience of the synthetic methodology to be used in the formation of thienopyridines. The subsequent cyclisation to highly substituted thiophenes proved to be very interesting, although not unknown and extension of this work to 2-chloro-5-pyridylacate **72** proved fruitful as more novel thiophenes were synthesized. It was seen however, that for the ketene dithioacetal **254**, the phenyl groups were insufficiently electron withdrawing to allow abstraction of the methylene protons and hence no cyclisation occurred [figure 30].



72 **73** **246** **254**

Figure 30

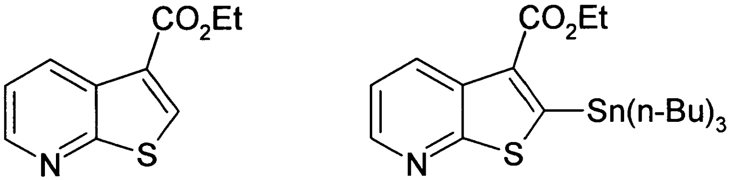
The nucleophilic substitution reactions carried out on thieno[2,3-b]pyridines **108** and **256** with nitrogen, and carbon nucleophiles did not prove to be particularly successful [figure 31]. Interestingly, it was found that the methylsulphonyl group in the 2- position was more labile than the thiomethyl group, with both aniline and the diethylmalonate anion. Conversely when the nucleophile employed was benzylamine, the order of reactivity appears to be reversed, with the thiomethyl group as the more labile substituent.



108 **256**

Figure 31

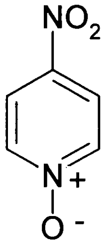
Overall the dethiomethylation sequence, using TBTH followed by protonolysis, is relatively straightforward, although care must be taken in the purification of **269** as tin byproducts are not always easy to remove, especially when the reaction is carried out on a larger scale. However, the desired product **266** was obtained, which allowed further transformations to be attempted on the side chain at C-3 [figure 32]. This allowed some progress to be made towards the goal of synthesising a potential agonist of serotonin.



266 **269**

Figure 32

Investigation into the optimum conditions for the conversion of benzylamine to benzaldehyde, by pyridine N-oxides, concluded that 4-nitropyridine N-oxide **50**, [figure 19], refluxed in *o*-xylene for 24 hours, offered the best yield. Other N-oxides investigated gave lower yields and there did not appear to be any distinct trend in effects due to substituents on the ring.

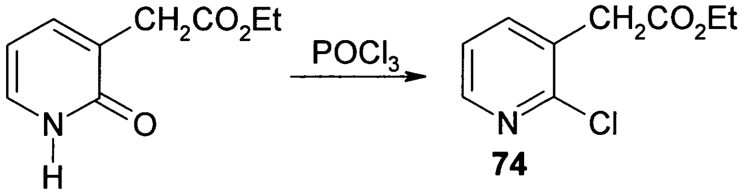


50

Figure 19

4 Future work

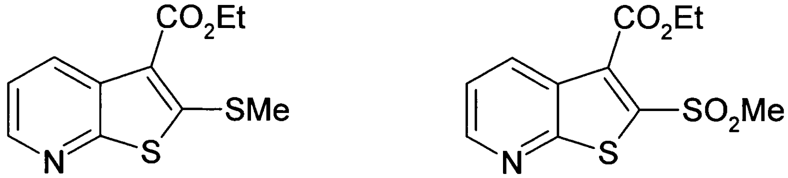
As 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** is the thienopyridine required for the desired reaction sequence to a potential agonist of 5-HT, it may be of some value to explore other routes to ethyl 2-chloro-3-pyridylacetate **74** involving methodology that reduces the number of byproducts. Perhaps chlorination of a suitable pyrid-2(1H)-one[268] may prove productive [equation 129].



74

Equation 129

The nucleophilic substitution of the thiomethyl group of **108** and the methylsulphonyl group of **256**, [figure 33], proved largely unsuccessful, so it would be worth attempting to expand upon this reaction by using other nitrogen nucleophiles, such as hydrazine, acetamidine or guanidine. This may allow entry into novel tricycles. The methodology for substitution with carbon nucleophiles requires further exploration in order to develop suitable reaction conditions. The scope could then be expanded to other reagents; for example, ethyl acetoacetate or malononitrile.

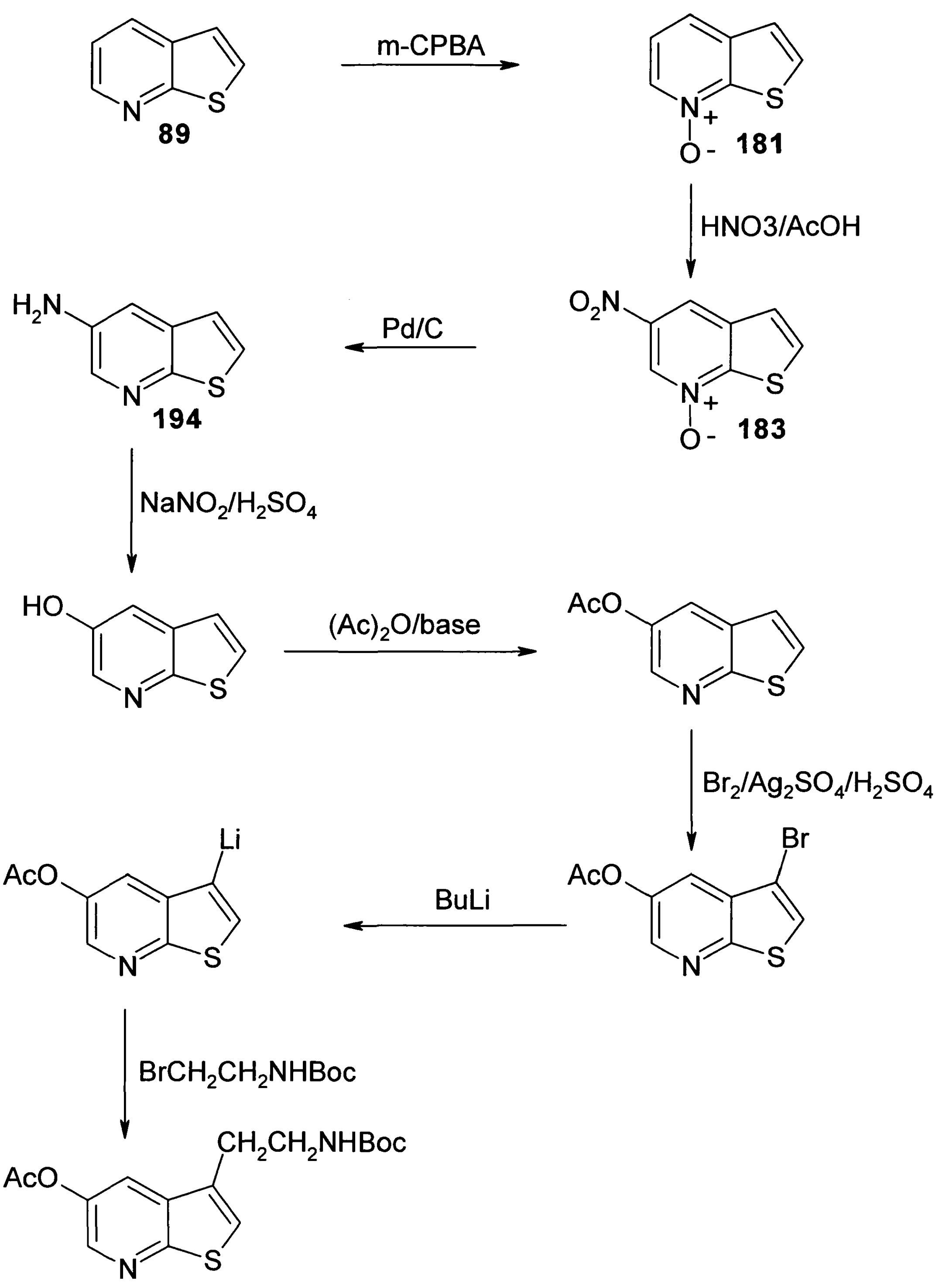


108 **256**

Figure 33

It is disappointing that a thieno[2,3-b]pyridine analogue of 5-HT could not be synthesised. Nevertheless a number of novel thieno[2,3-b]pyridines were prepared on route. Although the thiomethyl group has been successfully removed from **108**, with TBTH, the toxicity of organostannanes necessitates special handling in their disposal, and problems with product purification were found. Other reagents, such as chlorodiphenylsilane,[533] tris(trimethylsilyl)silane,[534] and silylated cyclohexadienes[535] are now becoming available as replacements for tin hydrides in many transformations and it would be useful to investigate the effectiveness of these reagents. Further reactions of the side chain at C-3 to convert it into the required aminoethyl moiety need to be explored. Direct halogenation prior to reaction with cyanide is a possibility, and the tosylation reactions require further study. Mesylation or triflation of the alcohol could also be investigated. There is also the matter of the introduction of a hydroxy group at C-5 that should theoretically be possible as nitration[446] at this position has been reported. Subsequent reduction of the nitro group and diazotisation followed by replacement with a hydroxy group should achieve this.

Alternatively, other routes are possible as there are many preparative routes to thieno[2,3-b]pyridine **89**. One possible scheme, starting with thieno[2,3-b]pyridine **89** would be, N-oxidation, followed by nitration in acetic acid leading to substitution at C-5. This could be readily converted to a hydroxy group, by reduction, diazotisation and hydrolysis. After protection of the OH, bromination at C-3 followed by lithiation would allow substitution with suitably protected 2-bromoethylamine [scheme 92].



Scheme 92

The conversion of benzylamine to benzaldehyde facilitated by a pyridine N-oxide is ripe for further exploration. The scope of this reaction could be expanded upon in terms of both the N-oxides and amines employed and may prove a useful new method of affecting this transformation. Not only substituted benzylamines but also some aliphatic amines should be considered, particularily in the presence of other reactive functional groups to gauge the selectivity of the reaction.

5 Experimental

Melting points were determined using an Electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded on either a Perkin-Elmer 1600 FT-IR or a Perkin-Elmer Paragon spectrophotometer. Pmr spectra were recorded on a Jeol PMX 60i or a Bruker AMX 360 spectrometer. Column chromatography was performed using pressurised short path columns with Kieselgel 60, particle size < 0.063 mm (Merck No. 7729) and reactions were monitored with Merck DC-Alufoilien 60 F_{254} (Merck No. 5554) which were visualised by ultraviolet irradiation. Glaxo of Montrose and Warwick Analytical Services provided microanalysis. All chemicals, except where otherwise stated were purchased from Aldrich Chemical Company and were used without further purification.

5.1 N-oxidation of pyridines **207, 209-211** with peracetic acid; general procedure, ethyl 3-pyridylacetate **207** as an example

Ethyl 3-pyridylacetate **207** (1 g) was dissolved in glacial acetic acid (30 ml) and 30% hydrogen peroxide (3 ml) added. The reaction was stirred at 70 °C for 7 days. Activated charcoal (0.5 g) was added to destroy any excess peroxide (tested with starch/iodide paper) and the solution was filtered through Celite before removing the solvent *in vacuo*. The resulting oil was chromatographed on silica gel with ethyl acetate as eluant to afford ethyl 3-pyridylacetate N-oxide **70**; (0.76 g, 69%), mp 96-98 °C (literature[11] 97-98 °C). From 3-methylpyridine **209**, 3-methylpyridine N-oxide **272**; (1.10 g, 94%), bp 120 °C / 4 mm Hg (literature[536] 146-149 °C / 15 mm Hg). From 3-ethylpyridine**210**, 3-ethylpyridine N-oxide; (0.74 g, 64%), bp 100 °C / 4 mm Hg (literature[190] 125-126 °C / 15 mm Hg). From nicotinamide **211**, nicotinamide N-oxide **78**; (0.84 g, 74%), mp 291-292 °C (literature[537] 291-293 °C).

5.2 N-oxidation of pyridines 207, 209-211 with OXONE[451]; general procedure, ethyl 3-pyridylacetate 207 as an example

Ethyl 3-pyridylacetate **207** (1 g) was added to a vigorously stirred suspension of wet alumina (2 g), (prepared[451] by adding 10 ml of water to 50 g of Brockman grade alumina [200 mesh] and shaking until a free flowing powder was obtained) and Oxone (1 eq.) in dichloromethane (20 ml). The reaction mixture was refluxed for 3 hours, cooled and the solids filtered and washed with dichloromethane. The filtrate was evaporated to afford an oil which was chromatographed on silica gel with ethyl acetate as eluant to afford ethyl 3-pyridylacetate N-oxide **70**; (0.55 g, 50%), mp 96-98 °C (literature[11] 97-98 °C). From 3-methylpyridine **209**, 3-methylpyridine N-oxide **272**; (0.58 g, 50%), bp 120 °C / 4 mm Hg (literature[536] 146-149 °C / 15 mm Hg). From 3-ethylpyridine **210**, 3-ethylpyridine N-oxide; (0.60 g, 52%), bp 100 °C / 4 mm Hg (literature[190] 125-126 °C / 15 mm Hg). From nicotinamide **211**, nicotinamide N-oxide **78**; (0.59 g, 52%), mp 290-292 °C (literature[537] 291-293 °C).

5.3 N-oxidation of pyridines **207**, **209-211** with sodium perborate monohydrate[22]; general procedure, ethyl 3-pyridylacetate **207** as an example

Ethyl 3-pyridylacetate **207** (1 g) was dissolved in glacial acetic acid (20 ml) and sodium perborate monohydrate (1.5 eq.) added. The reaction mixture was heated at 60 °C for 24 hours, filtered and the solvent removed *in vacuo*. The resulting oil was flooded with acetone and filtered once more. The solution was dried over magnesium sulphate, filtered and the solvent evaporated to give a crude product. Chromatography on silica gel eluting with ethyl acetate gave ethyl 3-pyridylacetate N-oxide **70**; (0.80 g, 73%), mp 96-97 °C (literature[11] 97-98 °C). From 3-methylpyridine **209**, 3-methylpyridine N-oxide **272**; (0.90 g, 77%), bp 120 °C / 4 mm Hg (literature[536] 146-149 °C / 15 mm Hg). From 3-ethylpyridine **210**, 3-ethylpyridine N-oxide; (0.79 g, 69%), bp 100 °C / 4 mm Hg (literature[190] 125-126 °C / 15 mm Hg). From nicotinamide **211**, nicotinamide N-oxide **78**; (0.59 g, 52%), mp 291-293 °C (literature[537] 291-293 °C).

5.4 N-oxidation of pyridines **207**, **209-211** with OXONE and acetone (dimethyl dioxirane **26**)[71]; general procedure, ethyl 3-pyridylacetate **207** as an example

Oxone (30 mmol) in water (100 ml) was added dropwise, with constant stirring, to a mixture of ethyl 3-pyridylacetate **207** (12.6 mmol), acetone (5 ml) and phosphate buffer (50 ml). Potassium hydroxide solution (1 M) was added as required to maintain the pH at 7.5 – 8.0. The mixture was stirred for 2 hours, extracted with dichloromethane, dried over magnesium sulphate and the solvent removed *in* *vacuo*. Chromatography on silica gel, eluting with ethyl acetate afforded ethyl 3-pyridylacetate N-oxide **70**; (7.12 mmol, 57%), mp 96-98 °C (literature[11] 97-98 °C). From 3-methylpyridine **209**, 3-methylpyridine N-oxide **272**; (2.93 mmol, 23%), bp 120 °C / 4 mm Hg (literature[536] 146-149 °C / 15 mm Hg). From 3-ethylpyridine **210** 3-ethylpyridine N-oxide; (6.50 mmol, 52%), bp 100 °C / 4 mm Hg (literature[190] 125-126 °C / 15 mm Hg). From nicotinamide **211**, nicotinamide N-oxide **78**; (0.07 mmol, 1%), mp 291-292 °C (literature[537] 291-293 °C).

5.5 N-oxidation of ethyl 3-pyridylacetate **207** with m-CPBA; method A[456]

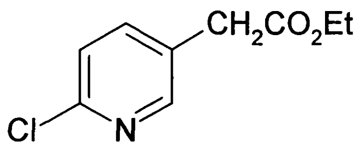
Ethyl 3-pyridylacetate **207** (0.50 g, 3 mmol) was stirred in dichloromethane at room temperature and *m*-CPBA (70%, 3.3 mmol) was added portionwise. The reaction mixture was stirred for 1 hour and extracted with aqueous sodium metabisulphite (10% w/v). The organic phase was then washed with saturated sodium bicarbonate followed by brine. The aqueous washings were combined and extracted with dichloromethane. All organic fractions were combined, dried with magnesium sulphate and concentrated. Chromatography on silica gel, eluting with ethyl acetate, afforded Ethyl 3-pyridylacetate N-oxide **70**; (0.37 g, 68%), mp 96-98 °C (literature[11] 97-98 °C).

5.6 N-oxidation of pyridines 207, 209-211 with m-CPBA[457]; method B general procedure, ethyl 3-pyridylacetate 207 as an example

Ethyl 3-pyridylacetate **207** (1.0 g) was stirred in dichloromethane at room temperature and *m*-CPBA acid (70%; 1.1 eq.) was added portionwise. The reaction mixture was stirred for 1 hour and the excess oxidising agent was destroyed by the careful addition of solid sodium metabisulphite. The mixture was filtered and solid potassium carbonate was added to neutralise *m*-CBA, subsequently dried over magnesium sulphate and all solids removed by filtration. The solvent was removed *in vacuo* to give a solid that on recrystallisation from toluene gave ethyl 3-pyridylacetate N-oxide **70**; (1.03 g, 93%), mp 96-98 °C (literature[11] 97-98 °C). From 3-methylpyridine **209**, 3-methylpyridine N-oxide **272**; (0.98 g, 84%), bp 120 °C / 4 mm Hg (literature[536] 146-149 °C / 15 mm Hg). From 3-ethylpyridine **210**, 3-ethylpyridine N-oxide; (0.95 g, 83%), bp 100 °C / 4 mm Hg (literature[190] 125-126 °C / 15 mm Hg). From nicotinamide **211**, nicotinamide N-oxide **78**; (0.79 g,70%), mp 291-292 °C (literature[537] 291-293 °C).

5.7 Reaction of ethyl 3-pyridylacetate N-oxide 70 with phosphorus oxychloride[260]

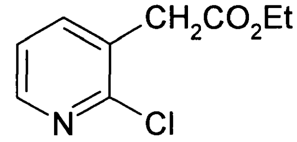
Ethyl 3-pyridylacetate N-oxide **70** (20 g, 110 mmol) was added in portions with constant stirring to phosphorus oxychloride (100 ml) in a round bottom flask. The solution was refluxed for 3 hours and the phosphorus oxychloride removed *in vacuo*. The residue was poured onto ice (100 g) and cautiously made alkaline with ammonium hydroxide solution (2M) then extracted with ethyl acetate (3 x 50



72

ml). The extracts were combined, dried over magnesium sulphate and the solvent evaporated to give a brown oil (11.7 g) that was chromatographed on silica gel using petroleum ether/ethyl acetate as eluant. The first compound obtained as a pale yellow oil was ethyl 2-chloro-5-pyridylacetate **72**; (1.25 g, 5.7%), bp 135 °C / 4 mm Hg (literature[260] 75 °C / 0.2 mbar); ν_{max}(film)/cm^{-1} 2982, 1732; δ_H($CDCl_3$) 1.24(3H, t, J=7.2 Hz, CH_3), 3.58(2H, s, CH_2CO_2), 4.14(2H, q, J=7.2 Hz, CO_2CH_2), 7.30(1H, d, J=8.0 Hz, H-4), 7.58(1H, dd, J=8.0 & 2.4 Hz, H-3), 8.26(1H, d, J=2.4 Hz, H-6).

Next eluted was the remaining ethyl 2-chloro-5-pyridylacetate **72** together with ethyl 2-chloro-3-pyridylacetate **74** as an inseparable mixture (6.06 g).



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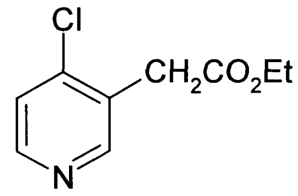
Third was the remaining ethyl 2-chloro-3-pyridylacetate **74** (1.81 g, 8.3%), bp. 135 °C / 4 mm Hg (literature[260] 85 °C / 0.5 mbar); ν_{max}(film)/cm^{-1} 2983, 1735; δ_H($CDCl_3$) 1.26(3H, t, J=7.2 Hz, CH_3), 3.72(2H, s, CH_2CO_2), 4.16(2H, q, J=7.2 Hz, CO_2CH_2), 7.16(1H, dd, J=7.2 & 4.8 Hz, H-5), 7.62(1H, dd, J=7.2 & 2.4 Hz, H-4), 8.26(1H, dd, J=4.8 & 2.4 Hz, H-6).



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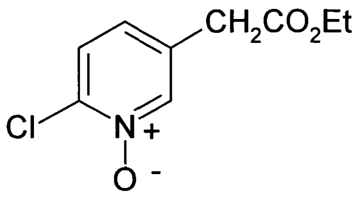
Finally ethyl 4-chloro-3-pyridylacetate **76** (2.28 g, 10.4%), No boiling point was obtained due to decomposition[260]; ν_{max}(film)/cm^{-1} 2982, 1737; δ_H($CDCl_3$) 1.24(3H, t, J=7.2 Hz, CH_3), 3.72(2H, s,

CH_2CO_2), 4.14(2H, q, J=7.2 Hz, CO_2CH_2), 7.26(1H, d, J=4.8 Hz, H-5), 8.38(1H, d, J=4.8 Hz, H-6), 8.54(1H, s, H-2).

5.8 N-oxidation of mixture of ethyl 2-chloro-5-pyridylacetate **72** and ethyl 2-chloro-3-pyridylacetate **74**[457]

m-CPBA (50%) (5.07g, 20 mmol) was added to a solution of ethyl 2-chloro-5-pyridylacetate **72** and ethyl 2-chloro-3-pyridylacetate **74** (2.93 g, 17 mmol) in chloroform (50 ml). The reaction mixture was stirred at room temperature for 18 hours. Excess oxidising agent was destroyed by the addition of solid sodium metabisulphite (monitored by starch/iodide paper). Solid potassium carbonate was then added and insoluble materials removed at the pump. The filtrate was dried over magnesium sulphate and the solvent removed *in vacuo* to give a yellow oil which was chromatographed on silica gel. Elution with petroleum ether/ethyl acetate gave first unreacted starting materials ethyl 2-chloro-5-pyridylacetate **72** and ethyl 2-chloro-3-pyridylacetate **74** (0.83 g, 28%).



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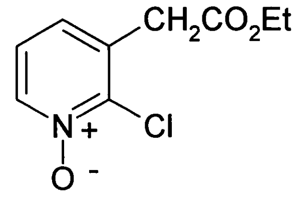
Further elution gave ethyl 2-chloro-5-pyridylacetate N-oxide[261] **212** (0.84 g, 23%) as a white solid, mp 59-60 °C; ν_{max}(KBr)/cm^{-1} 3075, 3010, 2950, 1735, 1250; δ_H($CDCl_3$) 1.24(3H, t, J=6 Hz, CH_3), 3.74(2H, s, CH_2CO_2), 4.14(2H, q, J=6 Hz, CO_2CH_2), 7.08(1H, s, H-4), 7.14(1H, s, H-3), 8.18 (1H, s, H-6); (Found[458]: C, 49.8;H, 4.8; N, 6.5. $C_9H_{10}ClNO_3$ requires C, 50.1; H, 4.7; N, 6.5%), MS m/z 216/218 (M+H).

Finally eluted was 2-chloro-3-pyridylacetate N-oxide[261] **213** (0.90 g, 24%) as a white solid, mp 104-105 °C; ν_{max}(KBr)/cm^{-1} 3050, 2975, 1734, 1205; δ_H($CDCl_3$) 1.2(3H, t, J=6 Hz, CH_3), 3.47(2H, s, CH_2CO_2), 4.03(2H, q, J=6 Hz, CO_2CH_2), 6.99(1H, dd, J=8&2 Hz, H-4), 7.25(1H, d, J=8 Hz, H-5), 8.07(1H, dd, J=8&2 Hz, H-6); (Found[458]: C, 49.8; H, 4.5; N, 6.4. $C_9H_{10}ClNO_3$ requires C, 50.1; H, 4.7; N, 6.5%), MS m/z 216/218 (M+H).



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5.9 N-oxidation of mixture of ethyl 2-chloro-5-pyridylacetate **72** and ethyl 2-chloro-3-pyridylacetate **74** in the presence of sulphuric acid[32]

m-CPBA (50%) (12.3 g, 50 mmol) was added to a solution of ethyl 2-chloro-5-pyridylacetate **72** and ethyl 2-chloro-3-pyridylacetate **74**, (9.58g, 48 mmol) and concentrated sulphuric acid (1 ml) in chloroform (100 ml). The reaction mixture was stirred at room temperature for 18 hours. Excess oxidising agent was destroyed by the addition of solid sodium metabisulphite (monitored by starch/iodide paper). Solid potassium carbonate was then added and insoluble materials removed at the pump. The filtrate was dried over magnesium sulphate and the solvent removed *in vacuo* to give a yellow oil which was chromatographed on silica gel. Elution with petroleum ether/ethyl acetate gave first unreacted starting materials ethyl 2-chloro-5-pyridylacetate **72** and ethyl 2-chloro-3-pyridylacetate **74** (1.3 g, 12.5%).

Further elution gave ethyl 2-chloro-5-pyridylacetate N-oxide **212** (3.09 g, 30%) as a white solid, identical (ir, mp) to an authentic sample previously prepared.

Finally eluted was 2-chloro-3-pyridylacetate N-oxide **213** (3.20 g, 31%) as a white solid, again identical (ir, mp) to an authentic sample prepared previously.

5.10 Reaction of ethyl 2-chloro-5-pyridylacetate N-oxide **212** with phosphorus tribromide[105]

Phosphorus tribromide (2 ml, 21 mmol) was added dropwise to a solution of ethyl 2-chloro-5-pyridylacetate N-oxide **212** (2.88 g, 13 mmol) in DMF (25 ml) at 0 °C. The reaction mixture was stirred for 1 hour then poured into ice cold saturated sodium bicarbinate solution (25 ml) and extracted with ethyl acetate (3 x 25 ml). The combined organic extracts were washed with brine then dried over magnesium sulphate. The solvent was removed *in vacuo* to give ethyl 2-chloro-5-pyridylacetate **72** as a colourless oil (2.78 g, 96%), which was identical (ir, tlc) with a genuine sample prepared previously.

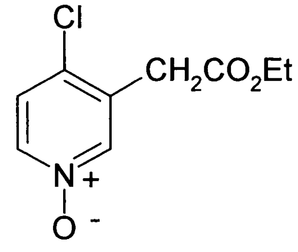
5.11 Reaction of ethyl 2-chloro-3-pyridylacetate N-oxide **213** with phosporus tribromide[105]

Phosphorus tribromide (0.6 ml, 6.4 mmol) was added dropwise to a solution of ethyl 2-chloro-3-pyridylacetate N-oxide **213** (1.17 g, 5.4 mmol) in DMF (25 ml) at 0 °C. The reaction mixture was stirred for 1 hour then poured into saturated sodium bicarbonate solution (25 ml) and extracted with ethyl acetate (3 x 25 ml). The combined organic extracts were washed with brine then dried over magnesium sulphate. The solvent was removed *in vacuo* to give ethyl 2-chloro-3-

pyridylacetate **74** as a colourless oil (0.86 g, 74%) that was identical (ir, tlc) to a genuine sample prepared previously.

5.12 N-oxidation of ethyl 4-chloro-3-pyridylacetate **76**[457]

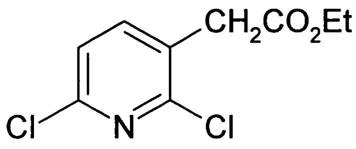
m-CPBA (50%) (5.9 g, 34 mmol) was added to a solution of ethyl 4-chloro-3-pyridylacetate **76** (1.7 g, 8.5 mmol) in chloroform (50 ml). The solution was stirred at room temperature for 4 hours. Excess oxidising agent was destroyed by the addition of solid sodium metabisulphite (monitored by starch/iodide paper). Solid potassium carbonate was then added and insoluble materials removed at the pump. The filtrate was dried over magnesium sulphate and the solvent removed *in vacuo* to give ethyl 4-chloro-3-pyridylacetate[261] **214** (1.28 g, 70%) as a white solid after recrystallisation from ethyl acetate. Mp 110-112 °C; ν_{max}(KBr)/cm^{-1} 3040, 2955, 1734, 1245; δ_H(CDCl$_3$) 1.25(3H, t, J=7 Hz, CH$_3$), 3.60(2H, s, CH$_2$CO$_2$), 4.20(2H, q, J=7 Hz, CO$_2$CH$_2$), 7.25(1H, d, J=6 Hz, H-5), 8.03(1H, dd, J=6&2 Hz, H-6), 8.15(1H, d, J=2 Hz, H-2); (Found[458]: C, 50.0; H, 4.9; N, 6.5. C$_9$H$_{10}$ClNO$_3$ requires C, 50.1; H, 4.7; N, 6.5%), MS m/z 216/218 (M+H).



214

5.13 Reaction of ethyl 2-chloro-5-pyridylacetate N-oxide **212** with phosphorus oxychloride

Ethyl 2-chloro-5-pyridylacetate N-oxide **72** (4.78 g, 22 mmol) was added in portions with constant stirring to phosphorus oxychloride (75 ml) in a round bottom flask. The solution was refluxed for 3 hours and the phosphorus oxychloride removed *in vacuo*. The residue was poured onto ice (100 g) and cautiously made alkaline with ammonium hydroxide solution (2M) and extracted with ethyl acetate (3 x 50 ml). The extracts were combined, dried over magnesium sulphate and the solvent evaporated to give ethyl 2,6-dichloro-3-pyridylacetate **215** (3.02 g, 58%) as a colourless oil after distillation at reduced pressure. Bp 140 °C at 3 mbar; ν_{max}(film)/cm^{-1} 2983, 1736; δ_H($CDCl_3$) 1.25 (3H, t, J=7.2 Hz, CH_3), 3.69(2H, s, CH_2CO_2), 4.15(2H, q, J=7.2 Hz, CO_2CH_2), 7.18(1H, d, J=8 Hz, H-5), 7.58(1H, d, J=8 Hz, H-4); (Found[458]: C, 46.1; H, 3.8; N, 6.2. $C_9H_9Cl_2NO_2$ requires C, 46.2; H, 3.9; N, 6.0%), MS m/z 234/236 (M+H).



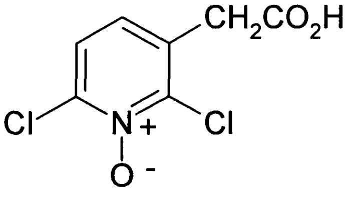
215

5.14 N-Oxidation of ethyl 2,6-dichloro-3-pyridylacetate **215** with *m*-CPBA and sulphuric acid

m-CPBA (70%) (2.2 g, 9 mmol) was added to a solution of ethyl 2,6-dichloro-3-pyridylacetate **215** (2.0 g, 8.5 mmol) and concentrated sulphuric acid (1 ml) in chloroform (50 ml). The reaction mixture was stirred at room temperature for 18 hours. Excess oxidising agent was destroyed by the addition of solid sodium metabisulphite (monitored by starch/iodide paper). Solid potassium carbonate was then added and insoluble materials removed at the pump. The filtrate was dried over magnesium sulphate and the solvent removed *in vacuo* to give a yellow oil (1.80 g, 90.1% recovered) which was identical, (tlc ir), to the starting material ethyl 2,6-dichloro-3-pyridylacetate **215**.

5.15 N-Oxidation of ethyl 2,6-dichloro-3-pyridylacetate 215 with trifluoroperacetic acid

A mixture of ethyl 2,6-dichloro-3-pyridylacetate **215** (2.0 g, 8.5 mmol) and hydrogen peroxide (30%) (5 ml) in trifluoroacetic acid (25 ml) were heated at 90 °C for 16 hours with stirring. Carbon was added to destroy any excess oxidising agent (monitored with starch/iodide paper). The suspension was filtered and the solvent removed *in vacuo* to give 2,6-dichloro-3-pyridylacetic acid N-oxide **216** (1.05 g, 56%) as a white solid after recrystallisation from methanol. Mp 140-142 °C; ν_{max} (KBr) /cm^{-1} 2926, 1710, 1262; δ_H($CDCl_3$) 3.74(2H, s, CH_2CO_2), 7.28(1H, d, J=8 Hz, H-5), 7.67(1H, d, J=8 Hz, H-4), 10.91(1H, s, CO_2H); (Found[459]: C, 40.1; H, 2.4; N, 6.5. $C_7H_5Cl_2NO_3$ requires C, 37.9; H, 2.3; N, 6.3%).

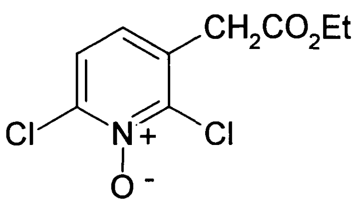


216

5.16 Esterification of 2,6-dichloro-3-pyridylacetic acid N-oxide 216

2,6-Dichloro-3-pyridylacetic acid N-oxide **216** (0.56 g, 2.5 mmol) was dissolved in ethanol (10 ml) and one drop of concentrated sulphuric acid added. The mixture was refluxed for 7 hours, then the solvent removed *in vacuo*. The residue was dissolved in ethyl acetate and washed with saturated sodium bicarbonate solution, water then brine. The organic solution was dried over magnesium sulphate and the solvent removed to give ethyl 2,6-dichloro-3-pyridylacetate N-oxide **217** (0.40 g, 64.5%) as white needles after recrystallisation from ethyl acetate. Mp 123-125

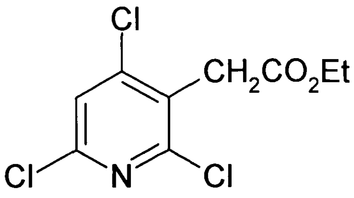
°C, ν_{max}(KBr)/cm^{-1} 3087, 3048, 2985, 2932, 1721, 1280; δ_H(CDCl$_3$) 1.30(3H, t, J=7.12 Hz, CH$_3$), 3.81(2H, s, CH$_2$CO$_2$), 4.24(2H, q, J=7.12 Hz, CO$_2$CH$_2$), 7.18(1H, d, J=8.3 Hz, H-4), 7.47(1H, d, J=8.3 Hz, H-5); (Found[459]: C, 43.1; H, 3.6; N, 5.5. $C_9H_9Cl_2NO_3$ requires C, 43.2; H, 3.6; N, 5.6%).



217

5.17 Reaction of ethyl 2,6-dichloro-3-pyridylacetate N-oxide 217 with phosphorus oxychloride

Ethyl 2,6-dichloro-3-pyridylacetate N-oxide **217** (0.5 g, 2 mmol) was added in portions to phosphorus oxychloride (25 ml) in a 50 ml round bottom flask fitted with a condenser. The solution was refluxed for 3 hours and the excess phosphorus oxychloride removed *in vacuo*. The resulting oil was poured onto ice (100 g), neutralised with dilute ammonia solution and extracted with ethyl acetate (3 x 50 ml). The extracts were combined, dried with magnesium sulphate and the solvent evaporated to give ethyl 2,4,6-trichloro-3-pyridylacetate **218** as a pale pink oil (0.44 g, 82%). No boiling point or microanalysis was recorded due to decomposition. γ_{MAX}(film)/cm^{-1} 3057, 2968, 1732; δ_H(CDCl$_3$) 1.27(3H, t, J=7.2 Hz, CH$_3$), 3.93(2H, s, CH$_2$CO$_2$), 4.20(2H, q, J=7.2 Hz, CO$_2$CH$_2$), 7.38(1H, s, H-5).



218

5.18 Reaction of ethyl 4-chloro-3-pyridylacetate N-oxide **76** with phosphorus oxychloride

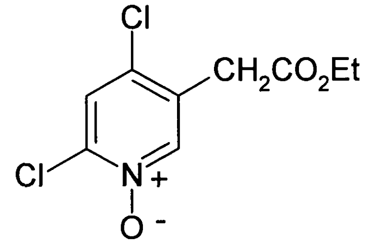
Ethyl 4-chloro-3-pyridylacetate N-oxide **76** (2.7 g, 12.5 mmol) was added in portions with constant stirring to phosphorus oxychloride (75 ml) in a round bottom flask. The solution was refluxed for 3 hours and the phosphorus oxychloride removed *in vacuo*. The residue was poured onto ice (100 g) and cautiously made alkaline with ammonium hydroxide solution (2M) and extracted with ethyl acetate (3 x 50 ml). The extracts were combined, dried over magnesium sulphate and the solvent evaporated to give a colourless oil (1.8 g) after distillation at reduced pressure (112-115 °C at 2 mbar). ν_{max}(film)/cm^{-1} 2983, 1738; δ_H(CDCl$_3$) 1.19(6H, t, J=7.2 Hz, CH$_3$), 3.68(2H, s, CH$_2$CO$_2$), 3.93(2H, s, CH$_2$CO$_2$), 4.11(2H, q, J=7.2 Hz, CO$_2$CH$_2$), 4.13(2H, q, J=7.2 Hz, CO$_2$CH$_2$), 7.25(1H, d, J=7.1 Hz, H-5$^\#$), 7.34(1H, s, H-3*), 8.15(1H, d, J=7.1 Hz, H-6$^\#$), 8.21(1H, s, H-6*).

(The symols * and # are used to indicate signals due to different isomers which were inseparable).

Therefore:

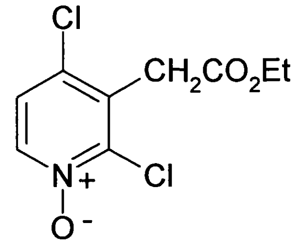
5.19 N-oxidation of inseparable mixture with *m*-CPBA and sulphuric acid

The oil (1.25 g) was dissolved in chloroform and *m*-CPBA (50%) (2.02 g, 5.9 mmol) added in portions followed by concentrated sulphuric acid (1 ml). The reaction mixture was stirred at room temperature for 4 days. Excess oxidising agent was destroyed by the addition of solid sodium metabisulphite (monitored by starch/iodide paper). Solid potassium carbonate was then added and insoluble materials removed at the pump. The filtrate was dried over magnesium sulphate and the solvent removed *in vacuo* to give a yellow oil (1.14 g) that was chromatographed on silica gel. Elution with petroleum ether/ethyl acetate gave ethyl 2,4-dichloro-5-pyridylacetate N-oxide **221** (0.31 g, 23%) after recrystallisation from ethyl acetate. Mp 88-90 °C; ν_{max}(KBr)/cm^{-1} 3094, 3033, 2992, 2933,1732, 1273; δ_H(CDCl$_3$) 1.28(3H, t, J=7.2 Hz, CH$_3$), 3.65(2H, s, CH$_2$CO$_2$), 4.18(2H, q, J=7.2 Hz, CO$_2$CH$_2$), 7.52(1H, s, H-3), 8.28(1H,s, H-6); (Found[459]: C, 43.1; H, 3.6; N, 5.5. $C_9H_9Cl_2NO_3$ requires C, 43.2; H, 3.6; N, 5.6%).



221

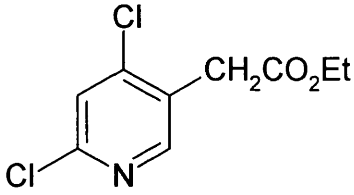
Further elution afforded ethyl 2,4-dichloro-3-pyridylacetate N-oxide **222** (0.35 g, 26%) as a white crystalline solid after recrystallisation with ethyl acetate. Mp 77-78 °C, ν_{max}(KBr)/cm^{-1} 3050, 2985, 1733, 1282; δ_H(CDCl$_3$) 1.35(3H, t, J=7.1 Hz, CH$_3$), 4.09(2H, s, CH$_2$CO$_2$), 4.30(2H, q, J=7.1 Hz, CO$_2$CH$_2$), 7.37(1H, d, J=7.1 Hz, H-5), 8.35(1H, d, J=7.1 Hz, H-6); (Found[459]: C, 43.1; H, 3.5; N, 5.4. $C_9H_9Cl_2NO_3$ requires C, 43.2; H, 3.6; N, 5.6%).



222

5.20 Reaction of ethyl 2,4-dichloro-5-pyridylacetate N-oxide 221 with phosphorus tribromide

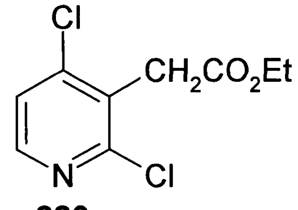
Phosphorus tribromide (0.2 ml, 6.4 mmol) was added dropwise to a solution of ethyl 2,4-dichloro-5-pyridylacetate N-oxide **221** (0.16 g, 0.6 mmol) in DMF (25 ml) at 0 °C. The reaction mixture was stirred for 1 hour then poured into saturated sodium bicarbonate solution (25 ml) and extracted with ethyl acetate (3 x 25 ml). The combined organic extracts were washed with brine then dried over magnesium sulphate. The solvent was removed *in vacuo* to give ethyl 2,4-dichloro-5-pyridylacetate **219** (0.06g, 41%) as a colourless oil after distillation at reduced pressure. Bp 105 °C at 2 mbar, ν_{max}(film)/cm^{-1} 3087, 2982, 2932, 1737; δ_H($CDCl_3$) 1.24(3H, t, J=7.2 Hz, CH_3), 3.84(2H, s, CH_2CO_2), 4.10(2H, q, J=7.2 Hz, CO_2CH_2), 7.56(1H, s, H-3), 8.36(1H, s, H-6); (Found[459]: C, 46.1; H, 3.9; N, 5.8. $C_9H_9Cl_2NO_2$ requires C, 46.2; H, 3.9; N, 6.0%).



219

5.21 Reaction of ethyl 2,4-dichloro-3-pyridylacetate N-oxide **222** with phosphorus tribromide

Phosphorus tribromide (0.2 ml, 6.4 mmol) was added dropwise to a solution of ethyl 2,4-dichloro-3-pyridylacetate N-oxide **222** (0.20 g, 0.8 mmol) in DMF (25 ml) at 0 °C. The reaction mixture was stirred for 1 hour then poured into saturated sodium bicarbonate solution (25 ml) and extracted with ethyl acetate (3 x 25 ml). The combined organic extracts were washed with brine then dried over magnesium sulphate. The solvent was removed *in vacuo* to give ethyl 2,4-dichloro-3-pyridylacetate **220** (0.14g, 77%) as a colourless oil after distillation at reduced pressure. Bp 110 °C at 2 mbar, ν_{max}(film)/cm^{-1} 3077, 2982, 2936, 1738;

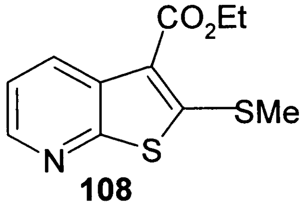


220

$\delta_H(CDCl_3)$ 1.22(3H, t, J=7.2 Hz, CH_3), 4.0(2H, s, CH_2CO_2), 4.2(2H, q, J=7.2 Hz, CO_2CH_2), 7.46(1H, d, J=4.8 Hz, H-5), 8.25(1H, d, J=4.8 Hz, H-6); (Found[459]: C, 46.3; H, 3.9; N, 5.8. $C_9H_9Cl_2NO_2$ requires C, 46.2; H, 3.9; N, 6.0%).

5.22 Preparation of 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine 108[260]

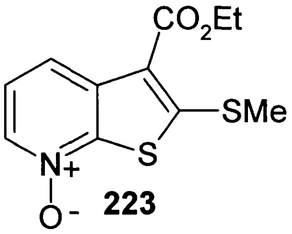
Sodium hydride (0.63 g, 26.4 mmol) was added in portions to a stirred solution of ethyl 2-chloro-3-pyridylacetate **74** (2.33 g, 12 mmol) and carbon disulphide (1.0 g, 13.2 mmol) in DMSO (50 ml) under dry nitrogen in a 3-necked round bottom flask. The reaction mixture was stirred at room temperature for 1 hour then heated on an oil bath at 70 °C for 1.5 hours. After cooling to room temperature, methyl iodide (3.75 g, 26.4 mmol) was added and stirring continued for a further hour. The reaction mixture was poured onto ice/water (200 ml) and extracted with ethyl acetate (3 x 50 ml). The combined extracts were dried over magnesium sulphate and the solvent removed *in vacuo* to give 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** (1.21 g, 40%) as a pale yellow solid after recrystallisation from diethyl ether. Mp 109-110 °C (literature[260, 261] 109-110 °C); $\nu_{max}(KBr)/cm^{-1}$ 1695; $\delta_H(CDCl_3)$ 1.46(3H, t, J=7.1 Hz, CH_3), 2.66(3H, s, SCH_3), 4.44(2H, q, J=7.1 Hz, CO_2CH_2), 7.29(1H, dd, J=8.26 & 4.65 Hz, H-5), 8.41 (1H, dd, J=4.65 & 1.65 Hz, H-4), 8.51(1H, dd, J=8.26 & 1.65 Hz, H-6).



108

5.23 Preparation of 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine N-oxide 223

Sodium hydride (0.24 g, 10 mmol) was added in portions to a stirred solution of ethyl 2-chloro-3-pyridylacetate N-oxide **213** (1.0 g, 4.6 mmol) and carbon disulphide (0.39 g, 5.1 mmol) in DMSO (25 ml) under dry nitrogen in a 3-necked round bottom flask. The reaction mixture was stirred at room temperature for 1 hour then heated on an oil bath at 70 °C for 1.5 hours. After cooling to room temperature, methyl iodide (1.42 g, 10 mmol) was added and stirring continued for a further hour. The reaction mixture was poured onto ice/water (200 ml) and extracted with ethyl acetate (3 x 50 ml). The combined extracts were dried over magnesium sulphate and the solvent removed *in vacuo* to give 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine N-oxide **223** (0.81 g, 65%) as a white solid after recrystallisation from ethyl acetate. Mp 158-159 °C; ν_{max}(KBr)/cm^{-1} 3030, 1675, 1240; δ_H($CDCl_3$) 1.48(3H, t, J=7.2 Hz, CH_3), 2.70(3H, s, SCH_3), 4.46(2H, q, J=7.2 Hz, CO_2CH_2), 7.36(1H, dd, J=8.0&6.5 Hz, H-4), 8.22(2H, m, H-5 &H-6); (Found[458]: C, 48.8; H, 4.4; N, 5.2. $C_{11}H_{11}NO_3S_2$ requires C, 49.0; H, 4.1; N, 5.2%); MS m/z 270 (M+H).



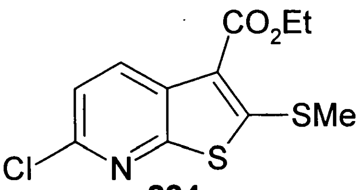
223

5.24 Reaction of 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine N-oxide **223** with phosphorus tribromide

Phosphorus tribromide (0.2 ml, 6.4 mmol) was added dropwise to a solution of 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine N-oxide **223** (0.10 g, 0.37 mmol) in DMF (25 ml) at 0 °C. The reaction mixture was stirred for 1 hour then poured into saturated sodium bicarbonate solution (25 ml) and extracted with ethyl acetate (3 x 25 ml). The combined organic extracts were washed with brine then dried over magnesium sulphate. The solvent was removed *in vacuo* to give 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** (0.09 g, 96%) after recrystallisation from diethyl ether, which was identical (tlc, ir, pmr) to a previously prepared sample.

5.25 Preparation of 6-chloro-3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine 224

Sodium hydride (0.11 g, 4.7 mmol) was added in portions to a stirred solution of ethyl 2,6-dichloro-3-pyridylacetate **215** (0.5 g, 2.1 mmol) and carbon disulphide (0.18 g, 2.4 mmol) in DMSO (30 ml) under dry nitrogen in a 3-necked round bottom flask. The reaction mixture was stirred at room temperature for 1 hour then heated on an oil bath at 70 °C for 1.5 hours. After cooling to room temperature, methyl iodide (0.67 g, 4.7 mmol) was added and stirring continued for a further hour. The reaction mixture was poured onto ice/water (150 ml) and extracted with ethyl acetate (3 x 50 ml). The combined extracts were dried over magnesium sulphate and the solvent removed *in vacuo* to give 6-chloro-3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **224** (0.08 g, 13%) after recrystallisation from ethyl acetate. Mp 103-104 °C; ν_{max}(KBr)/cm^{-1} 2940, 1670; δ_H(CDCl$_3$) 1.41(3H, t, J=7.2 Hz, CH$_3$), 2.63(3H, s, SCH$_3$), 4.40(2H, q, J=7.2 Hz, CO$_2$CH$_2$), 7.20(1H, d, J=8.0 Hz, H-5), 8.38(1H, d, J=8.0 Hz, H-4); (Found[458]: C, 45.6; H, 3.6; N, 4.8. $C_{11}H_{10}ClNO_2S_2$ requires C, 45.9; H, 3.5; N, 4.9%); MS m/z 288/290 (M+H).



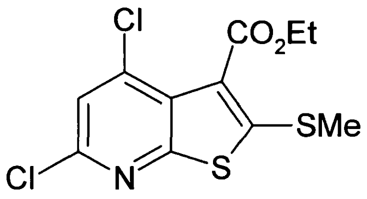
224

5.26 Reaction of ethyl 2,4,6-trichloro-3-pyridylacetate **218** with carbon disulphide, sodium hydride and methyl iodide

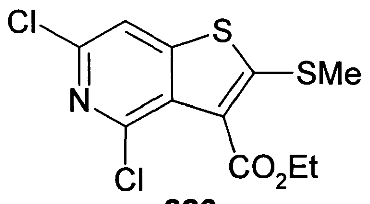
Ethyl 2,4,6-trichloro-3-pyridylacetate **218** (0.25 g, 0.74 mmol) and carbon disulphide (0.06 g, 0.8 mmol) were stirred in DMSO (20 ml) in a round bottom flask fitted with a gas inlet tube under dry nitrogen. Sodium hydride (0.04 g, 1.6 mmol) was added in portions and the mixture stirred at room temperature for 1 hour, then at 70 °C for 1.5 hours. The solution was cooled and methyl iodide (0.23 g, 1.6 mmol) added and stirring continued for a further 1 hour at room temperature. The mixture was poured onto ice (75 g) and extracted with ethyl acetate (3 x 25 ml). The extracts were combined, dried with magnesium sulphate, filtered and the solvent evaporated to give a brown solid (0.26 g) that was chromatographed on silica gel using petroleum ether / diethyl ether as eluant. Separated first was a white crystalline solid (0.09 g, 37.8%); mp 75-78 °C; γ_{MAX}(KBr)/cm^{-1} 2990, 1694; δ_H(CDCl$_3$) 1.43(3H, t, J=7.14 Hz, CH$_3$), 2.65(3H, s, SCH$_3$), 4.45(2H, q, J=7.14 Hz, CO$_2$CH$_2$), 7.38(1H, s, H-5).

Also isolated was a colourless crystalline solid (0.14 g, 58.1%); mp 85-87 °C; γ_{MAX}(KBr)/cm^{-1} 2989, 1726; δ_H(CDCl$_3$) 1.45(3H, t, J=7.16 Hz, CH$_3$), 2.62(3H, s, SCH$_3$), 4.48(2H, q, J=7.16 Hz, CO$_2$CH$_2$), 7.61(1H, s, H-5).

Spectroscopic analysis could not differentiate between 4,6-dichloro-3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **225** and 4,6-dichloro-3-ethyloxycarbonyl-2-methylthiothieno[3,2-c]pyridine **226**. Microanalysis was not sought, as it would not clarify the situation.



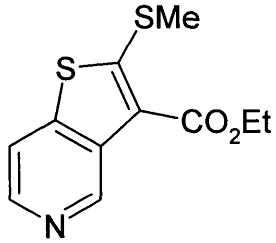
225



226

5.27 Preparation 3-ethyloxycarbonyl-2-methylthiothieno[3,2-c]pyridine **240**

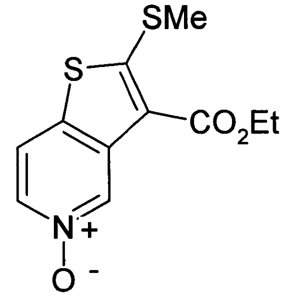
Sodium hydride (0.32 g, 13.2 mmol) was added in portions to a stirred solution of ethyl 4-chloro-3-pyridylacetate **76** (1.2 g, 6.6 mmol) and carbon disulphide (0.50 g, 6.6 mmol) in DMSO (30 ml) under dry nitrogen in a 3-necked round bottom flask. The reaction mixture was stirred at room temperature for 1 hour then heated on an oil bath at 70 °C for 1.5 hours. After cooling to room temperature, methyl iodide (1.87 g, 13.2 mmol) was added and stirring continued for a further hour. The reaction mixture was poured onto ice/water (150 ml) and extracted with ethyl acetate (3 x 50 ml). The combined extracts were dried over magnesium sulphate, filtered and the solvent removed *in vacuo* to give 3-ethyloxycarbonyl-2-methylthiothieno[3,2-c]pyridine **240** (0.49 g, 37%) after recrystallisation from ethyl acetate. Mp 119-120 °C (literature[260, 261] 119-120 °C); ν_{max}(KBr)/cm^{-1} 1681, 1218; δ_H($CDCl_3$) 1.40(3H, t, J=7.2 Hz, CH_3), 2.70 (3H, s, SCH_3), 4.36(2H, q, J=7.2 Hz, CO_2CH_2), 7.90(1H, d, J=4.8 Hz, H-7), 8.36(1H, d, J=4.8 Hz, H-6), 9.36(1H, s, H-4).



240

5.28 Preparation 3-ethyloxycarbonyl-2-methylthiothieno[3,2-c]pyridine N-oxide **241**

Sodium hydride (0.48 g, 20 mmol) was added in portions to a stirred solution of ethyl 4-chloro-3-pyridylacetate N-oxide **214** (2.0 g, 9.3 mmol) and carbon disulphide (0.78 g, 10 mmol) in DMSO (30 ml) under dry nitrogen in a 3-necked round bottom flask. The reaction mixture was stirred at room temperature for 1 hour then heated on an oil bath at 70 °C for 1.5 hours. After cooling to room temperature, methyl iodide (2.84 g, 20 mmol) was added and stirring continued for a further hour. The reaction mixture was poured onto ice/water (150 ml) and extracted with ethyl acetate (3 x 50 ml). The combined extracts were dried over magnesium sulphate, filtered and the solvent removed *in vacuo* to give 3-ethyloxycarbonyl-2-methylthiotieno[3,2-c]pyridine N-oxide **241** (1.98 g, 79%) after



241

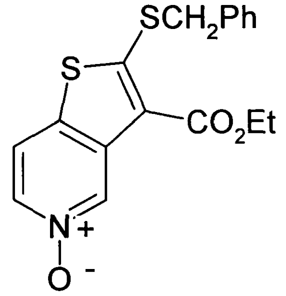
methanol. Mp 221-224 °C; ν_{max}(KBr) 3067, 3033, 2969, 1681, 1221; δ_H($CDCl_3$) 1.38(3H, t, J=7.1 Hz, CH_3), 2.71(3H, s, SCH_3), 4.38(2H, q, J=7.1 Hz, CO_2CH_2), 8.02(1H, dd, J=6.9 & 0.66 Hz, H-7), 8.12(1H, dd, J=6.9 & 1.8 Hz, H-6), 8.88(1H, dd, J=1.8 & 0.66 Hz, H-4); (Found[459]: C, 48.7; H, 4.2; N, 5.0. $C_{11}H_{11}NO_3S_2$ requires C, 49.0; H, 4.1; N, 5.2%).

5.29 Reaction of 3-ethyloxycarbonyl-2-methylthiothieno[3,2-c]pyridine N-oxide **241** with phosphorus tribromide

Phosphorus tribromide (0.2 ml, 2.1 mmol) was added dropwise to a solution of 3-ethyloxycarbonyl-2-methylthiothien[3,2-c]pyridine N-oxide **241** (0.2 g, 0.74 mmol) in DMF (25 ml) at 0 °C. The reaction mixture was stirred for 1 hour then poured into saturated sodium bicarbonate solution (25 ml) and extracted with ethyl acetate (3 x 25 ml). The combined organic extracts were washed with brine, dried over magnesium sulphate and filtered. The solvent was removed *in vacuo* to give 3-ethyloxycarbonyl-2-methylthiothieno[3,2-b]pyridine **240** (0.16 g, 83%) as a white solid after recrystallisation from ethyl acetate, which was identical (mp, ir, pmr) to a previously prepared sample.

5.30 Preparation of 3-ethyloxycarbonyl-2-benzylthiothieno[3,2-c]pyridine N-oxide **242**

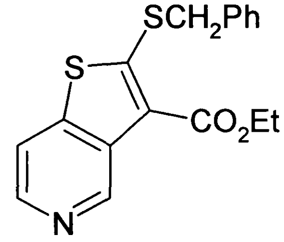
Sodium hydride (0.24 g, 10 mmol) was added in portions to a stirred solution of ethyl 4-chloro-3-pyridylacetate N-oxide **214** (1.0 g, 4.6 mmol) and carbon disulphide (0.38 g, 5 mmol) in DMSO (30 ml) under dry nitrogen in a 3-necked round bottom flask. The reaction mixture was stirred at room temperature for 1 hour then heated on an oil bath at 70 °C for 1.5 hours. After cooling to room temperature, benzyl bromide (1.71 g, 10 mmol) was added and stirring continued for a further hour. The reaction mixture was poured onto ice/water (150 ml) and extracted with ethyl acetate (3 x 50 ml). The combined extracts were dried over magnesium sulphate, filtered and the solvent removed *in vacuo* to give 3-ethyloxycarbonyl-2-benzylthiothieno[3,2-c]pyridine N-oxide **242** (1.26 g, 79%) after recrystallisation from methanol. Mp 169-170 °C; ν_{max}(KBr) 3131, 2978,1690,1223; δ_H($CDCl_3$) 1.40(3H, t, J=7.2 Hz, CH_3), 4.34(2H, q, J=7.2 Hz, CO_2CH_2), 4.36(2H, s, SCH_2), 7.34(5H, s, C_6H_5), 7.74(1H, d, J=7.2 Hz, H-7), 8.02(1H, dd, J=7.2 & 2.4 Hz, H-6), 8.94(1H, d, J=2.4 Hz, H-4); (Found[459]: C, 58.0; H, 4.3; N, 3.9. $C_{17}H_{15}NO_3S_2$ requires C, 59.1; H, 4.4; N, 4.1%).



242

5.31 Reaction of 3-ethyloxycarbonyl-2-benzylthiothieno[3,2-c]pyridine N-oxide **242** with phosphorus tribromide

Phosphorus tribromide (0.6 ml, 6.4 mmol) was added dropwise to a solution of 3-ethyloxycarbonyl-2-benzylylthiothien[3,2-c]pyridine N-oxide **242** (0.2 g, 0.58 mmol) in DMF (25 ml) at 0 °C. The reaction mixture was stirred for 1 hour then poured into saturated sodium bicarbonate solution (25 ml) and extracted with ethyl acetate (3 x 25 ml). The combined organic extracts were washed with brine, dried over magnesium sulphate and filtered. The solvent was removed *in vacuo* to give 3-ethyloxycarbonyl-2-benzylthiothieno[3,2-c]pyridine **243** (0.08 g, 42%) as a white solid after recrystallisation from ethyl acetate. Mp 99-101 °C; ν_{max}(KBr)/cm^{-1} 3070, 2972, 1683;δ_H(CDCl$_3$) 1.44(3H, t, J=7.2 Hz, CH$_3$), 4.24(2H, s, SCH$_3$), 4.40(2H, q, J=7.2 Hz, CO$_2$CH$_2$), 7.26(5H, m, C$_6$H$_5$), 7.46(1H, d, J=6.0 Hz, H-7), 8.30(1H, d, J=6.0 Hz, H-6), 9.44(1H, s, H-4); (Found[459]: C, 61.9; H, 4.6; N, 4.2. $C_{17}H_{15}NO_2S_2$ requires C, 62.0; H, 4.6; N, 4.2%).

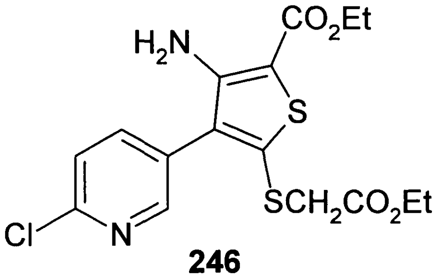


243

5.32 Reaction of 2-chloro-5-cyanomethylpyridine **73** with carbon disulphide and ethyl chloroacetate

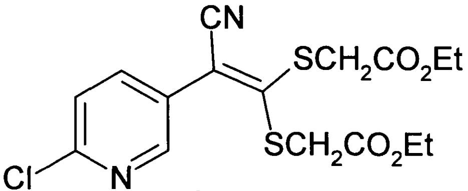
2-Chloro-5-cyanomethylpyridine **73** (2.0 g, 13.1 mmol) and carbon disulphide (1.1 g, 14.4 mmol) were dissolved in DMSO (40 ml) in a 2-neck round bottom flask fitted with a gas inlet tube under dry nitrogen and sodium hydride (0.66 g, 27.5

mmol) added in portions with constant stirring. The mixture was stirred for 2 hours then ethyl chloroacetate (3.38 g, 27.5 mmol) added and stirring continued for another hour, then poured onto ice (100 g) and extracted with ethyl acetate (3 x 50 ml). The extracts were combined, dried with magnesium sulphate, filtered and the solvent evaporated to give a pale yellow oil (4.46 g). The oil was chromatographed on silica gel using petroleum ether / ethyl acetate to give first 2-chloro-5-(3-amino-2-ethyloxycarbonyl-5-ethyloxycarbonylmethylthio-4-thienyl) pyridine **246** (0.26 g, 5%) as a pale yellow solid. Mp 101-102 °C; γ_{max}(KBr)/cm^{-1} 3447, 3343, 2967, 1724, 1661; δ_H($CDCl_3$) 1.17(3H, t, J=7.2 Hz, CH_3), 1.26(3H, t, J=7.2 Hz, CH_3), 3.46(2H, s, SCH_2), 4.02(2H, q, J=7.2 Hz, CO_2CH_2), 4.18(2H, q, J=7.2 Hz, CO_2CH_2), 5.36(2H, s, NH_2), 7.30(1H, d, J=8.4 Hz, H-5), 7.64(1H, dd, J=8.4 & 2.4 Hz, H-4), 8.26(1H, d, J=2.4 Hz, H-2); (Found[458]: C, 48.1; H, 4.2; N, 6.9. $C_{16}H_{17}ClN_2O_4S_2$ requires C, 47.9; H, 4,3; N, 7.0%); MS m/z 401/403 (M+H).



246

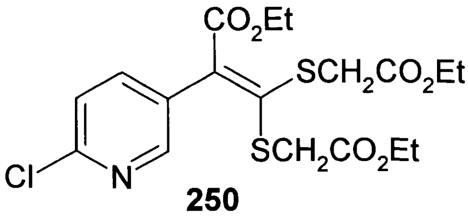
Eluted second was 2-chloro-5-(1-cyano-2,2-di[ethyloxycarbonylmethylthio]-1-vinyl)pyridine **247** (3.07 g, 58.4%) as a colourless oil. Bp (decomp); γ_{max}(film)/cm^{-1} 2982, 2209, 1736; δ_H($CDCl_3$) 1.28(3H, t, J=7.2 Hz, CH_3), 1.32(3H, t, J=7.2 Hz, CH_3), 3.72(2H, s, SCH_2), 3.80(2H, s, SCH_2), 4.16(2H, q, J=7.2 Hz, CO_2CH_2), 4.20(2H, q, J=7.2 Hz, CO_2CH_2), 7.33(1H, d, J=8.4 Hz, H-5), 7.85(1H, dd, J=8.4 & 2.4 Hz, H-4), 8.52(1H, d, J=2.4 Hz, H-2); (Found[458]: C, 48.0; H, 4.4; N, 7.1. $C_{16}H_{17}ClN_2O_4S_2$ requires C, 47.9; H, 4.3; N, 7.0%); MS m/z 401/403 (M+H).



247

5.33 Reaction of ethyl 2-chloro-5-pyridylacetate 72 with carbon disulphide and ethyl chloroacetate

Ethyl 2-chloro-5-pyridylacetate **72** (1.0 g, 5 mmol) and carbon disulphide (0.42 g, 5.5 mmol) were dissolved in DMSO (25 ml) in a 2-neck round bottom flask fitted with a gas inlet tube under dry nitrogen and sodium hydride (0.24 g, 10 mmol) added in portions with constant stirring. The mixture was stirred for 2 hours then ethyl chloroacetate (1.23 g, 10 mmol) added and stirring continued for another hour, then poured onto ice (100 g) and extracted with ethyl acetate (3 x 50 ml). The extracts were combined, dried with magnesium sulphate, filtered and the solvent evaporated to give a pale yellow oil (2.21 g). The oil was chromatographed on silica gel using petroleum ether / ethyl acetate to give 2-chloro-5-(1-ethyloxycarbonyl-2,2-[diethyloxycarbonylmethylthio]-1-vinyl)pyridine **250** (0.97 g, 43%); bp 190 °C at 0.4 mm Hg; γ_{max}(film)/cm^{-1} 2982, 2937, 1736; δ_H($CDCl_3$)1.24(3H, t, J=7.2 Hz, CH_3), 1.28(6H, t, J=7.2 Hz, CH_3), 3.56(2H, s,

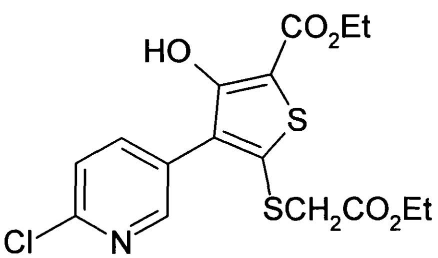


250

SCH_2), 3.68(2H, s, SCH_2), 4.08(4H, q, J=7.2 Hz, CO_2CH_2), 4.14(2H, q, J=7.2 Hz, CO_2CH_2), 7.28(1H, d, J=8.4 Hz, H-3), 7.72(1H, dd, J=8.4 & 2.4 Hz, H-4), 8.34(!H, d, J=2.4 Hz, H-6); (Found[458]: C, 49.6; H, 4.8; N, 3.3. $C_{18}H_{22}ClNO_6S_2$ requires C, 48.3; H, 4.9; N, 3.1%); MS m/z 448/450 (M+H).

5.34 Reaction of 2-chloro-5-(1-ethyloxycarbonyl-2,2-[diethyloxycarbonylmethylthio] -1-vinyl)pyridine **250** with sodium ethoxide

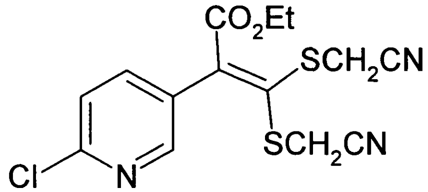
2-Chloro-5-(1-ethyloxycarbonyl-2,2-[diethyloxycarbonylmethylthio]-1-vinyl)pyridine **250** (0.5 g, 1.1 mmol) was dissolved in ethanol (20 ml) in a 50 ml round bottom flask and sodium ethoxide (0.16 g, 2.4 mmol) added. The mixture was stirred at room temperature for 24 hours. The solvent was removed *in vacuo*, the residue flooded with water and extracted with ethyl acetate (3 x 25 ml). The combined extracts were dried with magnesium sulphate, filtered and the solvent removed to give 2-chloro-5-(2-ethyloxycarbonyl-5-ethyloxycarbonylmethylthio-3-hydroxy-4-thienyl) pyridine **251** (0.14 g, 33%) after recrystallisation from diethyl ether. Mp 74-75 °C; γ_{max}(KBr)/cm^{-1} 2978, 2914, 1748, 1666; δ_H($CDCl_3$) 1.20(3H, t, J=7.2 Hz, CH_3), 1.32(3H, t, J=7.2 Hz, CH_3), 3.48(2H, s, SCH_2), 4.02(2H, q, J=7.2 Hz, CO_2CH_2), 4.24(2H, q, J=7.2 Hz, CO_2CH_2), 7.22(1H, d, J=8.4 Hz, H-3), 7.66(1H, dd, J=8.4 & 2.4 Hz, H-4), 8.34(1H, d, J=2.4 Hz, H-6), 9.70(1H, s, OH); (Found[459]: C, 47.8; H, 3.7; N, 3.3. $C_{16}H_{16}ClNO_5S_2$ requires C; 47.8; H, 4.0; N, 3.4%).



251

5.35 Reaction of ethyl 2-chloro-5-pyridylacetate **72** with carbon disulphide and chloroacetonitrile

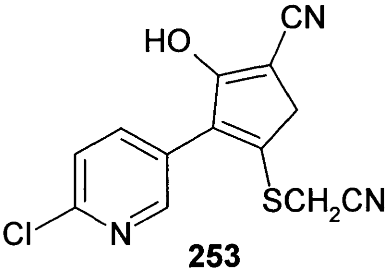
To a stirred solution of ethyl 2-chloro-5-pyridylacetate **72** (2.11 g, 10.6 mmol) and DMSO (20 ml) under dry nitrogen in a 2-neck round bottom flask fitted with a gas inlet tube was added carbon disulphide (0.89 g, 11.6 mmol) followed by sodium hydride (0.51 g, 21.2 mmol) in portions. The reaction was stirred for 2 hours at room temperature then chloroacetonitrile (1.75 g, 23.2 mmol) added and stirring continued for 1 hour. The mixture was poured onto ice (100 g) and extracted with ethyl acetate (3 x 25 ml). The combined extracts were dried with magnesium sulphate, filtered and the solvent evaporated to give 2-chloro-5-(2,2-di[cyanomethylthio]-1-ethyloxycarbonyl-1-ethenyl)pyridine **252** (2.15 g, 57%) after recrystallisation from ethanol. Mp 98-99 °C; γ_{max}(KBr)/cm^{-1} 2976, 2246, 1720; δ_H($CDCl_3$) 1.25(3H, t, J=7.2 Hz, CH_3), 3.56(2H, s, SCH_2), 3.68(2H, s, SCH_2),4.24(2H, q, J=7.2 Hz, CO_2CH_2), 7.24(1H, d, J=8.4 Hz, H-3), 7.58(1H, dd, J=8.4 & 2.4 Hz, H-4), 8.24(1H, d, J=2.4 Hz, H-6); (Found[459]: C, 47.4; H, 3.0; N, 11.7. $C_{14}H_{12}ClN_3O_2S_2$ requires C, 47.5; H, 3.4; N, 11.9%).



252

5.36 Reaction 2-chloro-5-(2,2-di[cyanomethylthio]-1-ethyloxycarbonyl-1-vinyl) pyridine **252** with sodium ethoxide

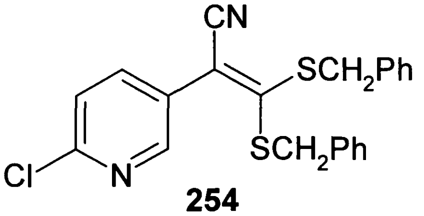
2-Chloro-5-(2,2-di[cyanomethylthio]-1-ethyloxycarbonyl-1-vinyl)pyridine **252** (0.5 g, 1.4 mmol) was dissolved in ethanol (25 ml) in a 50 ml round bottom flask and sodium ethoxide (0.20 g, 3.0 mmol) added. The reaction was stirred at room temperature for 16 hours. The solvent was evaporated, replaced with water and extracted with ethyl acetate (3 x 25 ml). The combined extracts were dried with magnesium sulphate, filtered and the solvent removed *in vacuo* to give 2-chloro-5-(2-cyano-3-hydroxy-5-cyanomethylthio-4-thienyl)pyridine (AY) (0.20 g, 46%) as pale yellow prisms after recrystallisation from ethyl acetate. Mp 101-102 °C; γ_{max}(KBr)/cm^{-1} 3452, 2975, 2926, 2211; δ_H(CDCl$_3$) 4.04(2H, s, SCH$_2$),7.58(1H, d, J=8.4 Hz, H-3), 7.86(1H, dd, J=8.4 & 2.4 Hz, H-4), 8.42(1H, d, J=2.4 Hz, H-6); (Found[459]: C, 46.9; H, 1.7; N, 13.5. $C_{12}H_6ClN_3OS_2$ requires C, 46.8; H, 46.8; H, 1.9; N, 13.6%).



253

5.37 Reaction of 2-chloro-5-cyanomethylpyridine **73** with carbon disulphide and benzyl bromide

2-Chloro-5-cyanomethylpyridine **73** (2.0 g, 13.1 mmol) and carbon disulphide (1.1 g, 14.4 mmol) were dissolved in DMSO (50 ml) under dry nitrogen in a 2-neck round bottom flask fitted, with a gas inlet tube and sodium hydride (0.66 g, 27.5 mmol) added in portions with constant stirring. The mixture was stirred for 2 hours then benzylbromide (4.7 g, 27.5 mmol) added and stirring continued for another hour, then poured onto ice (100 g) and extracted with ethyl acetate (3 x 100 ml). The extracts were combined, dried with magnesium sulphate, filtered and the solvent evaporated to give 2-chloro-5-(2,2-di[benzylthio]-1-cyano-1-vinyl)pyridine **254** as pale yellow needles (2.87 g, 54%). Mp 83-84 °C; γ_{max}(KBr)/cm^{-1} 3027, 2202, 696; δ_H($CDCl_3$) 3.92(2H, s, SCH_2), 4.20(2H, s, SCH_2), 7.24(12H, m, Ph & H-3 & H-4), 7.96(1H, d, J=2.4 Hz, H-6); (Found[459]: C, 64.6; H, 4.2; N, 6.7. $C_{22}H_{17}ClN_2S_2$ requires C, 64.6; H, 4.2; N, 6.9%).



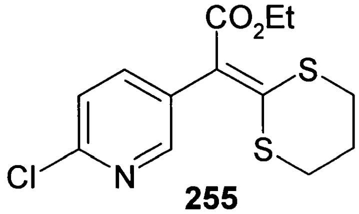
254

5.38 Reaction of 2-chloro-5-(2,2-di[benzylthio]-1-cyano-1-vinyl)pyridine **254** with sodium ethoxide

To 2-chloro-5-(2,2-di[benzylthio]-1-cyano-1-vinyl)pyridine **254** (0.2 g, 0.5 mmol) and ethanol (25 ml) in a 50 ml round bottom flask was added sodium ethoxide (0.67 g, 1 mmol) and the mixture stirred at room temperature for 16 hours. The solution was poured onto ice (100 g) and extracted with ethyl acetate (3 x 25 ml). The extracts were combined, dried with magnesium sulphate, filtered and the solvent removed *in vacuo* to give unreacted starting material 2-chloro-5-(2,2-di[benzylthio]-1-cyano-1-vinyl)pyridine **254** (0.19 g, 95%). This was confirmed by comparison with a pure sample.

5.39 Reaction of ethyl 2-chloro-5-pyridylacetate **72** with carbon disulphide and 1,3-dibromopropane

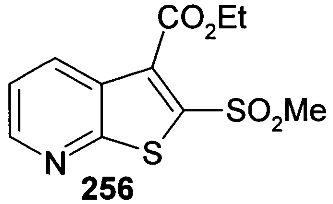
To a stirred solution of ethyl 2-chloro-5-pyridylacetate **72** (1.0 g, 5.0 mmol) and DMSO (20 ml) under dry nitrogen in a 2-neck round bottom flask fitted with a gas inlet tube was added carbon disulphide (0.42 g, 5.5 mmol) followed by sodium hydride (0.26 g, 11 mmol) in portions. The reaction was stirred for 2 hours at room temperature then 1,3-dibromopropane (2.22 g, 11 mmol) added and stirring continued for 1 hour. The mixture was poured onto ice (100 g) and extracted with ethyl acetate (3 x 75 ml). The combined extracts were dried with magnesium sulphate, filtered and the solvent evaporated to give (2'-[3-(5-chloropyridyl)]-2'-ethyloxycarbonyl)-1'-vinyl-1,3-dithiane **255** (0.84 g, 53%) as pale yellow needles after recrystallisation from diethyl ether/petroleum ether. Mp 92-93 °C; γ_{max}(KBr)/cm^{-1} 2980, 2922, 1684; δ_H(CDCl$_3$) 1.14(3H, t, J=7.2 Hz, CH$_3$), 2.16(2H, t, J=6.0 Hz, CH$_2$), 3.90(4H, t, J=6.0 Hz, SCH$_2$), 4.08(2H, q, J=7.2 Hz, CO$_2$CH$_2$), 7.18(1H, d, J=8.4 Hz, H-3), 7.40(1H, dd, J=8.4 & 2.4 Hz, H-4),8.10(1H, d, J=2.4 Hz, H-6); (Found[458]: C, 49.2; H, 4.4; N, 4.4. $C_{13}H_{14}ClNO_2S_2$ requires C, 49.3; H, 4.8; N, 4.4%); MS m/z 316/318 (M+H).



255

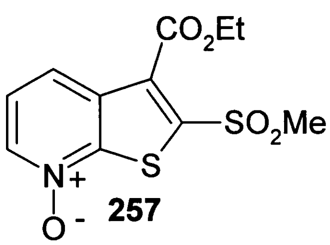
5.40 Reaction of 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** with excess *m*-CPBA

3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** (5.0g, 0.02 moles) was dissolved in chloroform (100 ml) and in a round bottom flask. *m*-CPBA (50%, 13.8g, 0.04 moles) was added in portions and the mixture stirred at room temperature for 2 hours. Excess oxidising agent was destroyed by the addition of solid sodium metabisulphite (monitored by starch/iodide paper). Solid potassium carbonate was then added and insoluble materials removed at the pump. The filtrate was dried over magnesium sulphate, filtered and the solvent removed *in vacuo* to give a yellow solid (5.9 g) that was chromatographed on silica gel using methanol/dichloromethane as eluant. The first compound obtained as a white solid was 3-ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine **256**; (0.86 g, 15%), mp 99-100 °C; γ_{max}(KBr)/cm^{-1} 2982, 2930, 1724; δ_H($CDCl_3$) 1.49(3H, t, J=7.2 Hz, CH_3), 3.51(3H, s, SO_2CH_3), 4.48(2H, q, J=7.2 Hz, CH_2), 7.36(1H, dd, J=8.0 & 4.0 Hz, H-5), 8.40(1H, dd, J=8.0 & 2.0 Hz, H-4), 8.57(1H, dd, J=4.0 & 2.0 Hz, H-6); (Found[458]: C, 46.0; H, 3.8; N, 4.9. $C_{11}H_{11}NO_4S_2$ requires C, 46.3; H, 3.9; N, 4.9%); MS m/z 286 (M+H).



256

Also eluted was 3-ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine N-oxide **257** as a pale yellow solid; (4.28 g, 71%), mp 174-176 °C; γ_{max}(KBr)/cm^{-1}

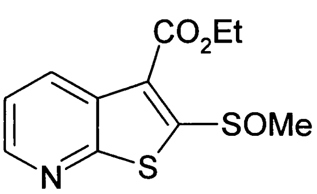


257

3050, 2950, 1718, 1256; δ_H(CDCl$_3$) 1.48(3H, t, J=7.2 Hz, CH$_3$), 3.52(3H, s, SO$_2$CH$_3$), 4.48(2H, q, J=7.2 Hz, CO$_2$CH$_2$), 7.36(1H, dd, J=8.4 & 6.0 Hz, H-5), 8.04(1H, d, J=8.4 Hz, H-4), 8.28(1H, d, J=6.0 Hz, H-6); (Found[458]: C, 44.4; H, 3.7; N, 4.8. $C_{11}H_{11}NO_5S_2$ requires C, 43.8; H, 3.7; N, 4.7%); MS m/z 302 (M+H).

5.41 Reaction of 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** with 1 equivalent of *m*-CPBA

3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** (0.5 g, 2 mmoles) was dissolved in chloroform (20 ml) in a round bottom flask. *m*-CPBA (50%, 0.68g, 2 mmoles) was added in portions and the mixture stirred at room temperature for 2 hours. Excess oxidising agent was destroyed by the addition of solid sodium metabisulphite (monitored by starch/iodide paper). Solid potassium carbonate was then added and insoluble materials removed at the pump. The filtrate was dried over magnesium sulphate, filtered and the solvent removed *in vacuo* to give 3-ethyloxycarbonyl-2-methylsulphinylthieno[2,3-b]pyridine **258** (0.52 g, 96%) as a white solid after recrystallisation from ethyl acetate. Mp 132-133° C;



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γ_{max}(KBr)/cm^{-1} 2979, 2925, 1697; δ_H(CDCl$_3$) 2.48(3H, t, J=7.2 Hz, CH$_3$), 3.04(3H, s, SOCH$_3$), 4.24(2H, q, J=7.2 Hz, CH$_2$), 7.34(1H, dd, J=8.0 & 4.0 Hz, H-5), 8.48(1H, dd, J=8.0 & 2.0 Hz, H-4), 8.60(1H, dd, J=4.0

& 2.0 Hz, H-6); (Found[459]: C, 49.1; H, 4.1; N, 5.1. $C_{11}H_{11}NO_3S_2$ requires C, 49.1; H, 4.1; N, 5.2%).

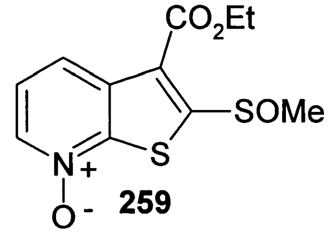
5.42 Reaction of 3-ethyloxycarbonyl-2-methylsulphinylthieno[2,3-b]pyridine **258** with 1 equivalent *m*-CPBA

To a solution of 3-ethyloxycarbonyl-2-methylsulphinylthieno[2,3-b]pyridine **258** (0.42 g, 1.6 mmol) in chloroform (20 ml), in a round bottom flask, was added *m*-CPBA (50%, 0.54 g, 1.6 mmol) in portions. The reaction mixture was stirred at room temperature for 2 hours then excess oxidising agent was destroyed by the addition of solid sodium metabisulphite (monitored by starch/iodide paper). Solid potassium carbonate was then added and insoluble materials removed at the pump. The filtrate was dried over magnesium sulphate, filtered and the solvent removed *in vacuo* to give a yellow solid (0.42 g) that was chromatographed on silica gel using methanol/dichloromethane as eluant. Obtained first was 3-ethyloxycarbonyl-2-methylsulphinylthieno[2,3-b]pyridine **258** (0.04 g, 10%), identified by comparison (mp, ir, pmr) with an authentic sample.

Secondly 3-ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine **256** (0.23 g, 45%), which was identical (mp, ir, pmr) to a previously prepared sample.

The third compound eluted was 3-ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine N-oxide **257** (0.05 g, 13%), again identified by comparison (mp, ir, pmr) with a previously prepared sample.

Finally eluted was 3-ethyloxycarbonyl-2-methylsulphinylthieno[2,3-b]pyridine N-oxide **259** (0.09 g, 23%), mp 188-189 °C; γ_{max}(KBr)/cm^{-1} 3059, 2983, 1694, 1261; δ_H(CDCl$_3$) 1.49(3H, t, J=7.2 Hz, CH$_3$), 3.06(3H, s, SOCH$_3$), 4.47(2H, q, J=7.2 Hz, CH$_2$), 7.39(1H, dd, J=8.0 & 6.0 Hz, H-4), 8.17(1H, d, J=8.0 Hz, H-5), 8.24(1H, d, J=6.0 Hz, H-6); (Found[459]: C, 46.3; H, 3.9; N, 4.8. $C_{11}H_{11}NO_4S_2$requires C, 46.3; H, 3.9; N, 4.9%).



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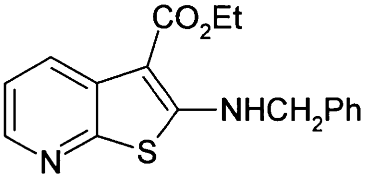
5.43 Reaction of 3-ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine N-oxide 257 with benzylamine in chloroform

3-ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine N-oxide **257** (0.30 g, 0.99 mmol) and benzylamine (0.11 g, 0.99 mmol) were dissolved in chloroform (25 ml) and refluxed together for 3 hours. The mixture was cooled to room temperature and washed with a dilute solution of hydrochloric acid (3 x 10 ml). The organic phase was dried over magnesium sulphate, filtered and the solvent removed *in vacuo* to give a pale yellow solid (0.28 g, 93%) which was identical (mp, ir) to the starting material 3-ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine N-oxide **257**.

5.44 Reaction of 3-ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine N-oxide 257 with neat benzylamine

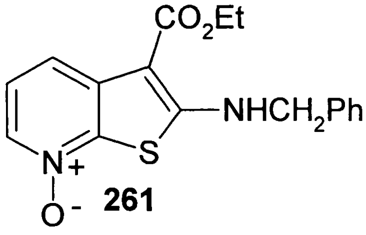
3-ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine N-oxide **257** (0.30 g, 0.99 mmol) and benzylamine (5 ml) were refluxed together in a round bottom flask for 3 hours. The mixture was cooled, poured onto ice/water (50 ml) neutralised with a dilute solution of hydrochloric acid and extracted with ethyl acetate (3 x 25 ml). The organic solution was dried with magnesium sulphate, filtered and the solvent removed *in vacuo* to give a brown oil (0.96 g). The oil was chromatographed on silica gel with ethyl acetate/petrol to give firstly a colourless oil (unquantified due to aerial oxidation) which was determined to be substantially benzaldehyde when compared (ir) to a sample purchased from Aldrich Chemical Co.



260

Secondly 3-ethyloxycarbonyl-2-benzylaminothieno[2,3-b]pyridine **260** (0.21g, 68%), mp 114-115 °C; γ_{MAX}(KBr)/cm^{-1} 3318, 2984, 1650; δ_H(CDCl$_3$) 1.40(3H, t, J=7.2 Hz, CH$_3$), 4.32(2H, q, J=7.2 Hz, CO$_2$CH$_2$), 4.48 (2H, d, J=6.0 Hz, NCH$_2$), 7.12(6H, m, unresolved, H-5 & C$_6$H$_5$), 8.12(2H, m, unresolved, H-4 & H-6), 8.80(1H, t, J=6.0 Hz, NH); (Found[459]: C, 65.4; H, 5.2; N, 8.9. $C_{17}H_{16}N_2O_2S$ requires C, 65.4; H, 5.2; N, 9.0%).

Eluted last was 3-ethyloxycarbonyl-2-benzylaminothieno[2,3-b]pyridine N-oxide **261** (0.09 g, 28%). mp 202-203 °C; γ_{MAX}(KBr)/cm^{-1} 3317, 3057, 1649, 1244;



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δ_H(CDCl$_3$) 1.44(3H, t, J=8.0 Hz, CH$_3$), 4.38(2H, q, J=8.0 Hz, CO$_2$CH$_2$), 4.57(2H, d, J=6.0 Hz, NCH$_2$), 7.20(1H, dd, J=8.0 & 6.0 Hz, H-4), 7.36(5H, m, unresolved, C$_6$H$_5$), 7.87(1H, dd, J=8.0 & 7.0 Hz, H-5), 8.00(1H, dd, J=7.0 & 6.0 Hz, H-6), 8.95(1H, t, J=6.0 Hz, NH); (Found[459]: C, 62.1; H, 4.9; N, 8.4. $C_{17}H_{16}N_2O_3S$ requires C, 62.2; H, 4.9; N, 8.5%).

5.45 Reaction of 3-ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine **256** with neat benzylamine

3-ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine **256** (0.30 g, 1.05 mmol) and benzylamine (5 ml) were refluxed together in a round bottom flask for 3 hours. The mixture was cooled, poured onto ice/water (50 ml) neutralised with a dilute solution of hydrochloric acid and extracted with ethyl acetate (3 x 25 ml). The organic solution was dried with magnesium sulphate, filtered and the solvent removed *in vacuo* to give 3-ethyloxycarbonyl-2-benzylaminothieno[2,3-b]pyridine **260** (0.20 g, 61%) after recrystallisation from ethyl acetate. The compound was identified by comparison (tlc, ir, pmr) with a genuine sample.

5.46 Reaction of 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine N-oxide **223** with neat benzylamine

3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine N-oxide **223** (0.30 g, 1.1 mmol) and benzylamine (5 ml) were refluxed together in a round bottom flask for 3 hours. The mixture was cooled, poured onto ice/water (50 ml) neutralised with a dilute solution of hydrochloric acid and extracted with ethyl acetate (3 x 25 ml). The organic solution was dried with magnesium sulphate, filtered and the solvent removed *in vacuo* to give a brown oil (0.29 g) which was chromatographed on silica gel with ethyl acetate/petrol as eluant to give, first, a yellow oil (0.03 g) which was identified as benzaldehyde by comparison (ir) with a genuine sample.

Second to be eluted was 3-ethyloxycarbonyl-2-benzylaminothieno[2,3-b]pyridine **260** (0.12 g, 34%) which was identical, (tlc, ir, pmr), to a previously prepared sample.

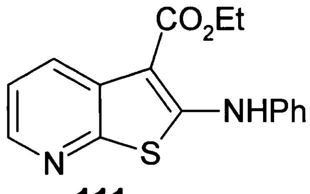
Finally, 3-ethyloxycarbonyl-2-benzylaminothieno[2,3-b]pyridine N-oxide **261** (0.10 g, 28%) was obtained, which was also identical, (tlc, ir, pmr), to a previously prepared sample.

5.47 Reaction of 3-ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine N-oxide **257** with phosphorus tribromide

Phosphorus tribromide (0.2 ml, 6.4 mmol) was added dropwise to an ice cold solution of 3-ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine N-oxide **257** (1.0 g, 3.3 mmol) in DMF (20 ml). The reaction mixture was stirred for 1 hour then poured into saturated sodium bicarbonate solution (25 ml) and extracted with ethyl acetate (3 x 25 ml). The combined organic extracts were washed with brine then dried over magnesium sulphate. The solvent was removed *in vacuo*, to give after recrystallisation from ethyl acetate, 3-ethyloxycarbonyl-2-methylsulphonyl thieno[2,3-b]pyridine **256** (0.9 g, 95%), which was identical, (mp, ir, pmr), to a previously prepared sample.

5.48 Reaction of 3-ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine **256** with neat aniline

3-ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine **256** (0.3 g, 1.05 mmol) and aniline (5 ml) were refluxed in a round bottom flask for 3 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and washed with a dilute solution of hydrochloric acid (3 x 25 ml). The organic phase was dried over magnesium sulphate, filtered and the solvent remove *in vacuo* to give a brown oil (0.25 g). The oil was chromatographed on silica gel with ethyl acetate/petrol as eluant to give 3-ethyloxycarbonyl-2-anilinothieno[2,3-b]pyridine **111** (0.17 g, 54%). Mp 115-116 °C (literature[260, 400] 115-116.5 °C; γ_{MAX}(KBr)/cm^{-1} 3437, 1653; δ_H($CDCl_3$) 1.52(3H, t, J=7.12 Hz, CH_3), 4.49(2H, q, J=7.12 Hz, CH_2), 7.20(6H, m(unresolyed), C_6H_5 & H-5), 8.03(1H, s, H-4), 8.13(1H, s, H-6), 10.40(1H, s, NH); (Found[459]: C, 64.3; H, 4.7; N, 9.4. $C_{16}H_{14}N_2O_2S$ requires C, 64.4; H, 4.7; N, 9.4%).



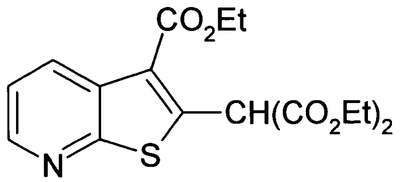
111

5.49 Reaction of 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** with neat aniline

3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** (0.34 g, 1.3 mmol) and aniline (5 ml) were refluxed in a round bottom flask for 3 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and washed with a dilute solution of hydrochloric acid (3 x 25 ml). The organic phase was dried over magnesium sulphate, filtered and the solvent remove *in vacuo* to give a brown oil (0.28 g). 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** (0.14 g, 36%) was the only compound isolated after column chromatography using petrol/ethyl acetate as eluant. It was identified by comparison, (tlc, ir, pmr), with a pure sample.

5.50 Reaction of 3-ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine **256** with diethylmalonate

3-ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine **256** (0.3 g, 1.05 mmol), sodium ethoxide (0.15 g, 2.2 mmol) and diethyl malonate (0.37 g, 2.3 mmol) were heated together on an oil bath at 100 °C in a round bottom flask for 3 hours. The reaction mixture was cooled, poured onto ice (20 g) and extracted with ethyl acetate (3 x 25 ml). The combined extracts were dried over magnesium sulphate, filtered and the solvent removed *in vacuo* to give a pale yellow oil (0.57 g). The oil was chromatographed on silica gel with petrol/ethyl acetate as eluant to give firstly 3-ethyloxycarbonyl-2-diethyl malonylthieno[2,3-b]pyridine **264** (0.03 g, 8%); γ_{MAX}(neat)/cm^{-1} 1736, 1708; δ_H($CDCl_3$) 1.28(6H, t, J=7.0 Hz, CH_3 (malonate)), 1.41(3H, t, J=7.2 Hz, CH_3), 4.22(4H, q, J=7.0 Hz, CH_2 (malonate)), 4.36(2H, q, J=7.2 Hz, CH_2), 6.07(1H, s, CH (malonate)), 7.23(1H, dd, J=8.0 & 4.0 Hz, H-5), 8.50(1H, dd, J=8.0 & 2.0 Hz, H-4), 8.63(1H, dd, J=4.0 & 2.0 Hz, H-6). No boiling point could be measured due to decomposition and hence no elemental analysis was obtained.



264

Also eluted was 3-ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine **256** (0.03 g, 10 %). The structure was confirmed by comparison (tlc, ir, pmr) with an authentic sample.

5.51 Reaction of 3-ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine **256** with sodium ethoxide

3-Ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine **256** (0.3 g, 1.05 mmol), sodium ethoxide (0.71 g, 10.5 mmol) and ethanol (25 ml) were refluxed together in a round bottom flask for 3 hours. The mixture was cooled and the solvent evaporated and replaced with water then extracted with ethyl acetate (3 x 25 ml). The solution was dried with magnesium sulphate, filtered and the solvent removed *in vacuo* to give after recrystallisation from ethyl acetate 3-ethyloxycarbonyl-2-methylsulphonylthieno[2,3-b]pyridine **256** (0.11 g, 37%). This was confirmed by comparison (tlc, ir, pmr) with a genuine sample.

5.52 Reaction of 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** with sodium ethoxide

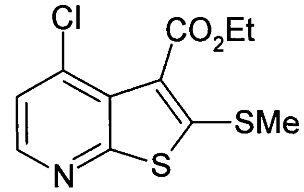
3-Ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** (0.2 g, 0.79 mmol), sodium ethoxide (0.53 g, 7.9 mmol) and ethanol (25 ml) were refluxed together in a round bottom flask for 3 hours. The mixture was cooled and the solvent evaporated and replaced with water then extracted with ethyl acetate (3 x 25 ml). The solvent was dried with magnesium sulphate, filtered and the solvent removed *in vacuo* to give after recrystallisation from ethyl acetate, starting material 3-

ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** (0.14 g, 70 %). This was confirmed by comparison (tlc, ir, pmr) with a genuine sample.

5.53 Reaction of 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine N-oxide **223** with phosphorus oxychloride

3-Ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine N-oxide **223** (0.32 g, 1.2 mmol) was added in portions with constant stirring to phosphorus oxychloride (25 ml) in a 50 ml round bottom flask fitted with a condenser. The solution was refluxed for 3 hours then the phosphorus oxychloride removed *in vacuo*. The residue was poured onto ice (100 g) and cautiously made alkaline with ammonium hydroxide solution (2M) and extracted with ethyl acetate (3 x 50 ml). The extracts were combined, dried over magnesium sulphate, filtered and the solvent evaporated to give a brown solid (0.31 g) that was chromatographed on silica gel using petroleum ether / diethyl ether as eluant. Obtained first was 6-chloro-3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **224** (0.16 g, 52%). Confirmed by comparison (ir, mp) with a genuine sample.

Eluted second was 4-chloro-3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **265** as a pale pink oil (0.10 g, 34%). Bp 120 °C / 4mm Hg; γ_{MAX}(film)/cm^{-1} 2940, 2880, 1695; δ_H($CDCl_3$) 1.40(3H, t, J=7.0 Hz, CH_3), 2.60(3H, s, SCH_3), 4.35(2H, q, J=7.0 Hz, CO_2CH_2), 7.19(1H, d, J=5.0 Hz, H-5), 8.21(1H, d, J=5.0 Hz, H-6); (Found[458]: C, 46.0; H, 3.3; N, 4.9. $C_{11}H_{10}ClNO_2S_2$ requires C, 45.9; H, 3.5; N, 4.9%); MS m/z 288/290 (M+H).



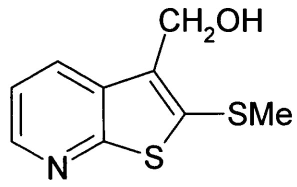
265

5.54 Reaction of 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** with Raney Nickel in methanol

3-Ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** (0.1 g, 0.39 mmol) was added to a stirred suspension of raney-Ni (1 g) in dry methanol under a blanket of dry nitrogen in a 2-necked round bottom flask. The mixture was stirred at room temperature for 6 hours, then the solids were removed at the pump and washed with hot methanol. The solvent was removed *in vacuo* to give unreacted 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** (0.09 g, 90%) (tlc,ir,pmr).

5.55 Reaction of 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** with Lithium Aluminium Hydride

A solution of 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** (0.5 g, 2 mmol) in dry diethyl ether (20 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (0.1 g, 2.6 mmol) in dry diethyl ether (30 ml) under dry nitrogen in a 2-necked round bottom flask fitted with a constant pressure dropping funnel and a gas inlet tube. The dropping funnel was replaced with a water condenser and the mixture refluxed for 48 hours (with the occasional addition of more dry diethyl ether). Excess hydride was then destroyed by the careful addition of ethyl acetate (2 ml) followed by water (10 ml) and dilute sulphuric acid (2 ml, 1M) with constant stirring. The layers were separated and the aqueous phase extracted with diethyl ether (3 x 25 ml). The organic extracts were combined, dried with magnesium sulphate, filtered and the solvent removed *in vacuo* to give after recrystallisation from ethyl acetate / hexane, 3-hydroxymethyl-2-methylthiothieno[2,3-b]pyridine **268** (0.25 g, 59%); mp 92-93 °C (literature[399] 92-93 °C); γ_{MAX}(KBr)/cm^{-1} 3204, 2911; δ_H($CDCl_3$) 2.55(3H, s, SCH_3), 3.05(1H, s, OH), 4.93(2H, s,CH_2), 7.24(1H, dd, J=8.0 & 4.0 Hz, H-5), 8.08(1H, dd, J=8.0 & 2.0 Hz, H-4), 8.40(1H, dd, J=4.0 & 2.0 Hz, H-6).



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5.56 Reaction of 3-hydroxymethyl-2-methylthiothieno[2,3-b]pyridine 268 with Raney Nickel in methanol

3-Hydroxymethyl-2-methylthiothieno[2,3-b]pyridine **268** (0.1 g, 0.47 mmol), Raney-Ni (1.0 g) and dry methanol were stirred together in a 2-necked round bottom flask under dry nitrogen. After 24 hours examination by tlc indicated that only starting material was present. The mixture was then refluxed for 2 hours. Re-examination by tlc again showed only starting material present, so the solids were removed by filtration and washed with hot methanol (2 x 25 ml). The combined filtrates were evaporated to give a pale yellow solid (0.09 g, 90%) which was identical, (tlc, ir, pmr), to a genuine sample of 3-hydroxymethyl-2-methyl thiothieno[2,3-b]pyridine **268**.

5.57 Reaction of 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** with sodium hypophosphite[518]

A solution of 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** (0.1 g, 0.39 mmol) and sodium hypophosphite (0.42 g, 0.39 mmol) in dry dioxane (3 ml) was refluxed under a blanket of dry nitrogen in a 2-necked round bottom flask fitted with a condenser and a constant pressure dropping funnel. To this was added a solution of ABCHC in dry dioxane (0.217 g in 3 ml) at a rate of 150 µl every 30 minutes. After 4 hours the solvent was replaced with ethyl acetate (20 ml) and extracted with water (3 x 10 ml). The organic phase was dried with magnesium sulphate, filtered and the solvent removed *in vacuo* to give 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** (0.09 g, 90%), identified by comparison, (tlc, ir, pmr), with a pure sample.

5.58 Reaction of 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** with hypophosphorus acid and triethylamine[517]

3-Ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** (0.5 g, 1.97 mmol), hypophosphorus acid (50%, 1.3 g, 9.9 mmol), triethylamine (1.01 g, 10 mmol) and dry dioxane (5 ml) were refluxed under a blanket of dry nitrogen in a 2-necked round bottom flask fitted with a condenser and a constant pressure dropping funnel. To this was added a solution of ABCHC in dry dioxane, (0.5 g in 5 ml), at a rate of 500 µl every 30 minutes. After 5 hours the solvent was replaced with ethyl acetate and washed with water (3 x 10 ml). The ethyl acetate solution was dried with magnesium sulphate, filtered and the solvent removed *in vacuo* to give a pale yellow solid which was identical, (tlc, ir, pmr), to a pure sample of 3-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108**.

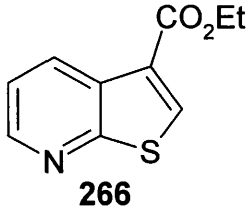
5.59 Reaction of 2-ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** with TBTH[520]

3-Ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** (0.5 g, 1.97 mmol), TBTH (0.57 g, 1.97 mmol) and ABCHC (0.01 g, 2 mol %) were dissolved in dry cyclohexane (20 ml) in a 50 ml round bottom flask fitted with a condenser. The mixture was refluxed for 24 hours and the solvent removed *in vacuo*. The resulting oil (1.3 g) was chromatographed on silica gel using petroleum ether / diethyl ether as eluant to give first tri-*n*-butyltin by-products as a pale yellow oil; (0.34 g); $\delta_H(CDCl_3)$ 0.85 – 1.60(43H, m(unresolved), alkyl).

Eluted second was a colourless oil; (0.9 g); $\delta_H(CDCl_3)$ 0.83 – 1.66(35H, m(unresolved), alkyl), 4.38(2H, q, J=7.2 Hz, CO_2CH_2), 7.42(1H, dd, J=8.2 & 4.5 Hz, H-5), 8.49(1H, dd, J=4.5 & 1.3 Hz, H-4), 8.70(1H, dd, J=8.2 & 4.5 Hz, H-6). Spectral data indicated that this was 3-ethyloxycarbonyl-2-(tri-*n*-butylstannyl)thieno[2,3-b]pyridine **269** contaminated with *n*-butyltin residues, therefore:

5.60 Reaction of contaminated 3-ethyloxycarbonyl-2-(tri-*n*-butylstannyl)thieno[2,3-b]pyridine **269** with TBTH

The contaminated thienopyridine **269** (0.8 g, 1.6 mmol), TBTH (0.44 g, 1.6 mmol) and ABCHC (0.008 g, 2 mole %) were dissolved in dry cyclohexane (20 ml) in a 50 ml round bottom flask fitted with a condenser. The mixture was refluxed for 24 hours and the solvent removed *in vacuo*. The resulting oil was dissolved in acetonitrile and extracted with *n*-hexane (3 x 25 ml). The acetonitrile solution was dried with magnesium sulphate, filtered and removed *in vacuo* to give an oil from which colourless needles crystallised on standing. The crystals were collected by filtration and recrystallised from *n*-hexane to give 3-ethyloxycarbonylthieno[2,3-b]pyridine **266** (0.16 g, 50%); mp 72-73 °C; γ_{max}(KBr)/cm^{-1} 3087, 2983, 2900, 1703; δ_H($CDCl_3$) 1.43(3H, t, J=7.2 Hz, CH_3), 4.42(2H, q, J=7.2 Hz, CO_2CH_2), 7.38(1H, dd, J=8.2 & 4.5 Hz, H-5), 8.46(1H, s, H-2), 8.60(1H, dd, J=4.5 & 1.3 Hz, H-4), 8.79(1H, dd, J=8.2 & 1.3 Hz, H-6); (Found[459]: C, 57.9; H, 4.4; N, 6.7. $C_{10}H_9NO_2S$ requires C, 57.9; H, 4.4; N, 6.7%).



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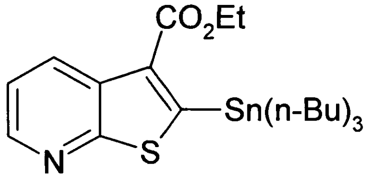
5.61 Preparation of 3-ethyloxycarbonyl-2-(tri-*n*-butylstannyl)thieno[2,3-b]pyridine **269**

3-Ethyloxycarbonyl-2-methylthiothieno[2,3-b]pyridine **108** (0.34 g, 1.3 mmol), TBTH (0.38 g, 1.3 mmol) and ABCHC (0.006 g, 2 mole %) were dissolved in dry cyclohexane (20 ml) in a 50 ml round bottom flask fitted with a condenser. The mixture was refluxed for 24 hours and the solvent removed *in vacuo*. The resulting oil (0.72 g) was chromatographed on silica gel using petroleum ether / diethyl ether as eluant to give 3-ethyloxycarbonyl-2-(tri-*n*-butylstannyl)thieno[2,3-b]pyridine **269** after recrystallisation from ethyl acetate. (0.42 g, 64.6%); mp 112-113 °C, γ_{max}(KBr)/cm^{-1} 2956, 2924, 1696; δ_H($CDCl_3$) 0.88(9H, t, J=7.26 Hz, CH_3(*n*-butyl)),1.03-1.47(18H, m(unresolved), CH_2 (*n*-butyl) & CH_3 (ester)), 4.47(2H, q, J=7.1 Hz,CO_2CH_2), 7.35(1H, dd, J=8.2 & 4.5 Hz, H-5), 8.55(1H, dd, J=4.5 & 1.3 Hz, H-4), 8.73(1H, dd, J=8.2 & 1.3 Hz, H-6); (Found[459]: C, 53.2; H, 7.0; N, 2.4. $C_{22}H_{35}NO_2SSn$ requires C, 53.2; H, 7.1; N, 2.8%).



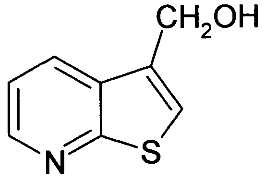
269

5.62 Protodestannylation of 3-ethyloxycarbonyl-2-(tri-*n*-butyltin)thieno[2,3-b] pyridine **269** with 50% trifluoroacetic acid

3-Ethyloxycarbonyl-2-(tri-*n*-butyltin)thieno[2,3-b]pyridine **269** (270 mg, 0.54 mmol) was dissolved in ethanol (20 ml) in a 50 ml round bottom flask fitted with a condenser. Trifluoroacetic acid (50%, 1 ml) was added and the mixture refluxed for 3 hours. The solvent was removed *in vacuo* and 3-ethyloxycarbonylthieno[2,3-b]pyridine **266** obtained by column chromatography on silica gel using petroleum ether / diethyl ether as eluant. (0.08 g, 73%). Identical, (ir, mp), to a genuine sample.

5.63 Reaction of 3-ethyloxycarbonylthieno[2,3-b]pyridine **266** with lithium aluminium hydride

A stirred suspension of lithium aluminium hydride (0.35 g, 9.2 mmol) in dry diethyl ether (20 ml) was prepared in a 2-neck 100 ml round bottom flask, fitted with a constant pressure dropping funnel and a gas inlet tube. To it was added a solution of 3-ethyloxycarbonylthieno[2,3-b]pyridine **266** (1.52 g, 7.3 mmol) in dry ether (30 ml) over 30 minutes under dry nitrogen. The dropping funnel was replaced with a condenser and the reaction refluxed for 48 hours under dry nitrogen with the addition of portions of dry diethyl ether to maintain the solution volume. Excess hydride was then destroyed by the careful addition of ethyl acetate (2 ml) followed by dilute sulphuric acid (2 ml, 1M) with constant stirring. The layers separated and the aqueous phase extracted with diethyl ether (3 x 25 ml). The combined organic solutions were dried with magnesium sulphate and filtered. The solvent was removed *in vacuo* and after recrystallisation from diethyl ether 3-hydroxymethylthieno[2,3-b]pyridine **267** (0.60 g, 50%) was isolated. Mp 94-96 °C; γ_{max}(KBr)/cm^{-1} 3216, 2842; δ_H(CDCl$_3$) 3.29(1H, s, OH), 4.91 2H, s, CH$_2$), 7.30(1H,dd, J=8.0 & 4.4 Hz, H-5), 7.43(1H, s, H-2), 8.15(1H, d, J=8.0 Hz, H-4), 8.50(1H, d, J=4.4 Hz, H-6); (Found[459]: C, 58.5; H, 4.3; N, 8.6. C_8H_7NOS requires C, 58.2; H, 4.3; N, 8.5%).



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5.64 Reaction of 3-hydroxymethylthieno[2,3-b]pyridine **267** with sodium cyanide in DMF

3-Hydroxymethylthieno[2,3-b]pyridine **267** (0.20 g, 1.2 mmol) and sodium cyanide (0.07 g, 1.46 mmol) were added to DMF (25 ml) in a 50 ml round bottom flask fitted with a condenser. The mixture was heated to reflux on an oil bath under dry nitrogen for 24 hours with constant stirring. The solution was cooled, diluted with water (5 ml), and made strongly basic with solid sodium hydroxide. The solvent was removed *in vacuo*, water added (20 ml) and the pH adjusted to 7 with glacial acetic acid then extracted with DCM (3 x 20 ml). The organic extracts were combined, washed with water, dried with magnesium sulphate, filtered and the solvent removed *in vacuo* to give a pale yellow solid (0.18 g, 90%) which was identified as unreacted 3-hydroxymethylthieno[2,3-b]pyridine **267** by comparison, (tlc, ir), with a pure sample.

5.65 Reaction of 3-hydroxymethylthieno[2,3-b]pyridine **267** with sodium cyanide and trimethylsilyliodide

3-Hydroxymethylthieno[2,3-b]pyridine **267** (0.18 g, 1.1 mmol) was dissolved in acetonitrile (10 ml) and added to a suspension of sodium cyanide (0.11 g, 2.2 mmol) and sodium iodide (5 mg) in DMF (10 ml) in a 50 ml 3-neck round bottom flask fitted with a gas inlet tube. The mixture was de-aerated with dry nitrogen for 30 minutes then trimethyl silylchloride (0.28 ml, 2.2 mmol) added quickly and the solution heated to 60 °C for 6 hours under dry nitrogen. After cooling the solution was poured into water and extracted with diethyl ether (3 x 25 ml). The combined extracts were washed with water then brine, dried with magnesium sulphate, filtered and the solvent removed *in vacuo* to give unreacted 3-hydroxymethylthieno[2,3-b]pyridine **267** (0.07 g, 39%). Confirmed by tlc and infrared spectroscopy.

5.66 Reaction of 3-hydroxymethylthieno[2,3-b]pyridine **267** with sodium cyanide, tri-*n*-butylphosphine and 15-crown-5 ether

A mixture of 3-hydroxymethylthieno[2,3-b]pyridine **267** (0.12 g, 0.73 mmol), sodium cyanide (0.071 g, 1.45 mmol) and 15-crown-5 (16 mg, 0.073 mmol) in acetonitrile (10 ml) were stirred in a 2-neck round bottom flask fitted with a gas inlet tube and a constant pressure dropping funnel for 15 minutes under dry nitrogen. A solution of tri-*n*-butylphosphine (0.16 g, 0.79 mmol) in acetonitrile (5 ml) was added followed by the dropwise addition of a solution of carbon tetrachloride (0.12 g, 0.79 mmol) in acetonitrile (5 ml) at 0 °C. The reaction mixture was stirred for 3 hours when tlc indicated that the reaction had not proceeded, so the flask was equipped with a condenser and heated to reflux for 24 hours. The solution was cooled, diluted with diethyl ether (100 ml) and washed with citric acid solution (50 ml, 10%). After the addition of carbon tetrachloride (5 ml), the mixture was washed with water then brine, dried over magnesium sulphate and filtered. The solvent was evaporated to give 3-hydroxy methylthieno[2,3-b]pyridine **267** (0.10 g, 80%). Spectroscopic analysis confirmed this finding.

5.67 Reaction of 3-hydroxymethylthieno[2,3-b]pyridine **267** with *p*-toluene sulphonyl chloride

3-Hydroxymethylthieno[2,3-b]pyridine **267** (0.14 g, 0.85 mmol) pyridine (0.134 g, 1.7 mmol) and DCM (10 ml) were stirred in a 25 ml round bottom flask at 0 °C. *p*-Toluenesulphonylchloride (0.24 g, 1.27 mmol) was added in portions and the mixture stirred for 24 hours at room temperature. Tlc indicated substantial amounts of starting material remained, so the flask was fitted with a condenser and the solution refluxed for 24 hours. The mixture was cooled, diluted with diethyl ether (30 ml) and water (7 ml) added. The organic layer was washed with dilute hydrochloric acid, saturated sodium bicarbonate and water, dried with magnesium sulphate, filtered and the solvent evaporated to give *p*-toluenesulphonyl chloride (0.20 g, 83%). The aqueous washes were combine, made strongly basic with solid potassium hydroxide and extracted with ethyl acetate (3 x 25 ml). The solution was dried with magnesium sulphate, filtered and the solvent removed *in vacuo* to give 3-hydroxymethylthieno[2,3-b]pyridine **267** (0.08 g, 57%), confirmed by comparison with a genuine sample.

5.68 Reaction of Pyridine N-oxides **50**, **78**, **272**, **273** and **274** with benzylamine; general procedure, 3-picoline N-oxide **272** as an example

3-Picoline N-oxide **272** (5g) and benzylamine (10ml) were refluxed together in a round bottom flask fitted with a water condenser for 4 hours. On cooling the mixture was acidified with 2M hydrochloric acid (50ml) and extracted with diethyl ether (3 x 50ml). The organic extracts were combined, dried over magnesium sulphate, filtered and the solvent removed *in vacuo* to afford benzaldehyde as a colourless oil (1.93g, 39%); bp 45 °C at 3mm Hg (literature[538] 62 °C at 10mm Hg). From 3-amidopyridine N-oxide **78**; (0.23 g, 6%), 4-amidopyridine **273**; (0.15g, 4%), isonicotinic acid N-oxide **274**; (1.22g, 32%). For 4-nitropyridine N-oxide **50**, the reaction was stopped when the temperature reached 118°C, rapidly cooled then worked up to give benzaldehyde (3.52 g, 93%).

5.69 Reaction of pyridine N-oxides **78**, **272**, **273** and **274** with benzylamine; benzaldehyde collected as the 2,4-dinitrophenylhydrazone, 3-picoline N-oxide **272** as an example

3-Picoline N-oxide **272** (5g) and benzylamine (10 ml) were refluxed together in a round bottom flask fitted with a water condenser for 4 hours. On cooling the mixture was acidified with 2M hydrochloric acid (100 ml) and extracted with diethyl ether (3 x 50 ml). To the extracts was added a solution of 2,4-dinitrophenylhydrazine (1 mole equivalent per mole pyridine N-oxide employed) in methanol (50 ml) and concentrated sulphuric acid (2 ml). The diethyl ether was evaporated and the solution cooled at 4 °C for 2 hours. Benzaldehyde-2,4-dinitrophenylhydrazone was collected by filtration as an orange solid (5.25 g, 40%), mp 234-236 °C (literature[538] 237 °C). From 3-amidopyridine N-oxide **78**; (0.93 g, 9%), 4-amidopyridine N-oxide **273**; (0.62 g, 6%), isonicotinic acid **274**; (2.88 g, 28%).

5.70 Reaction of pyridine N-oxides **50**, **78**, **272**, **273** and **274** with benzylamine in *o*-xylene; typical procedure, 4-nitropyridine N-oxide **50** as an example

4-Nitropyridine N-oxide **50** (1 g, 7.14 mmol) and benzylamine (1.53 g, 14.3 mmol) were dissolved in *o*-xylene (15 ml) in a 25 ml round bottom flask fitted with a condenser. The mixture was refluxed for 24 hours, cooled, poured onto dilute hydrochloric acid (100 ml) and extracted with diethyl ether (3 x 50 ml). To the diethyl ether solution was added a solution of 2,4-dinitrophenylhydrazine (1 mole equivalent per mole pyridine N-oxide employed) in methanol (50 ml) and concentrated sulphuric acid (2 ml). The diethyl ether was evaporated and the solution cooled at 4 °C for 2 hours. Benzaldehyde-2,4-dinitrophenylhydrazone (1.59 g, 78%) was collected by filtration as an orange solid; mp 234-236 °C (literature[538] 237 °C). From 3-picoline N-oxide **272**; (0.21 g, 8%), 3-amidopyridine N-oxide **78**; (0.27 g, 13%), 4-amidopyridine N-oxide **273**; (0.08 g, 4%), isonicotinic acid N-oxide **274**; (1.11 g, 54%).

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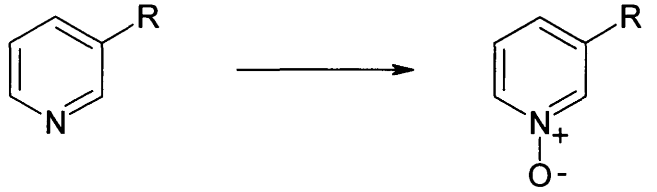
7 Appendices

7.1 Appendix 1

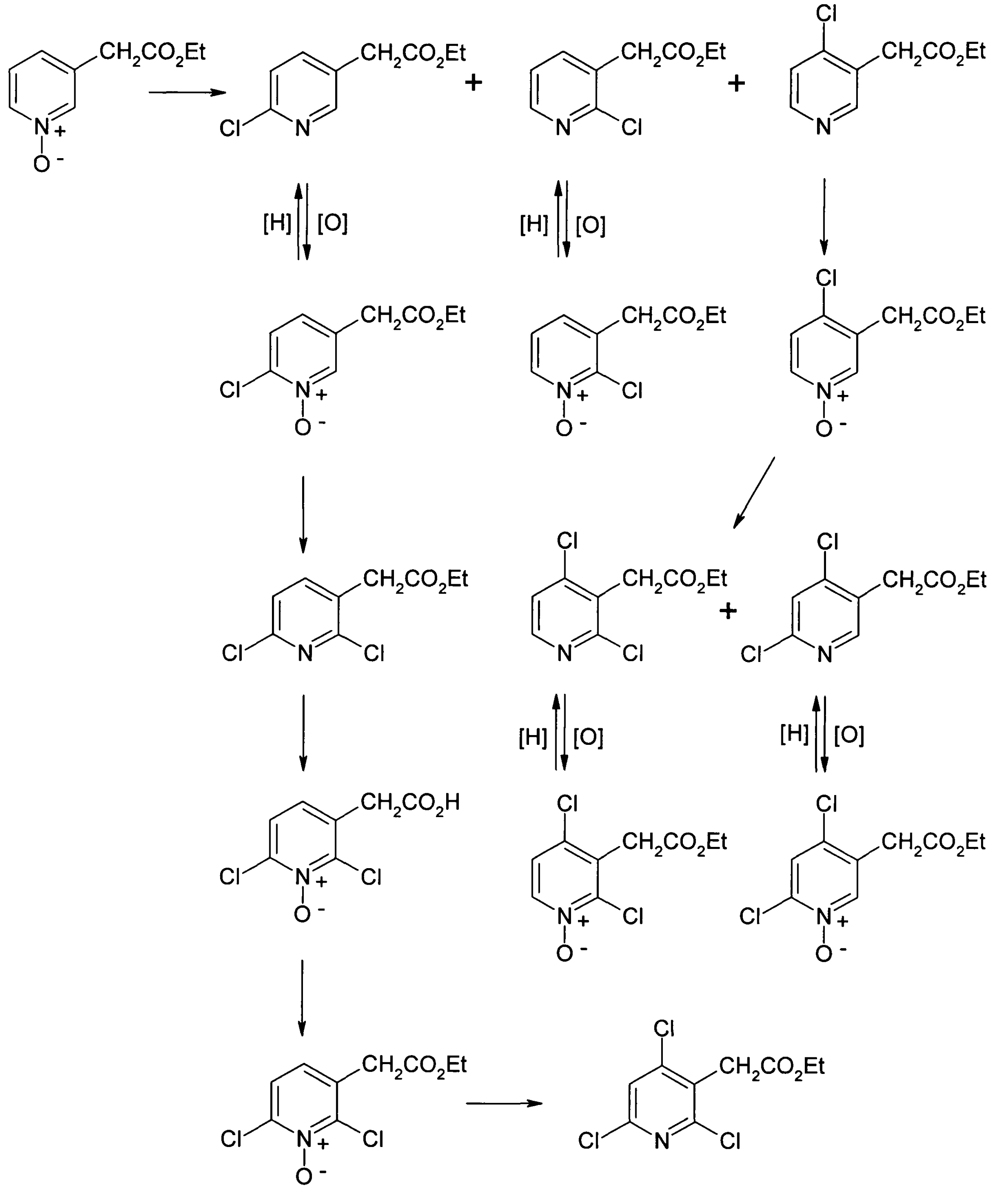
Reaction summaries by section

Preparation of pyridine N-oxides (section 2.2)



207; R=CH_2CO_2Et, **209**; R=Me, **210**; R=Et, **211**; R=$CONH_2$

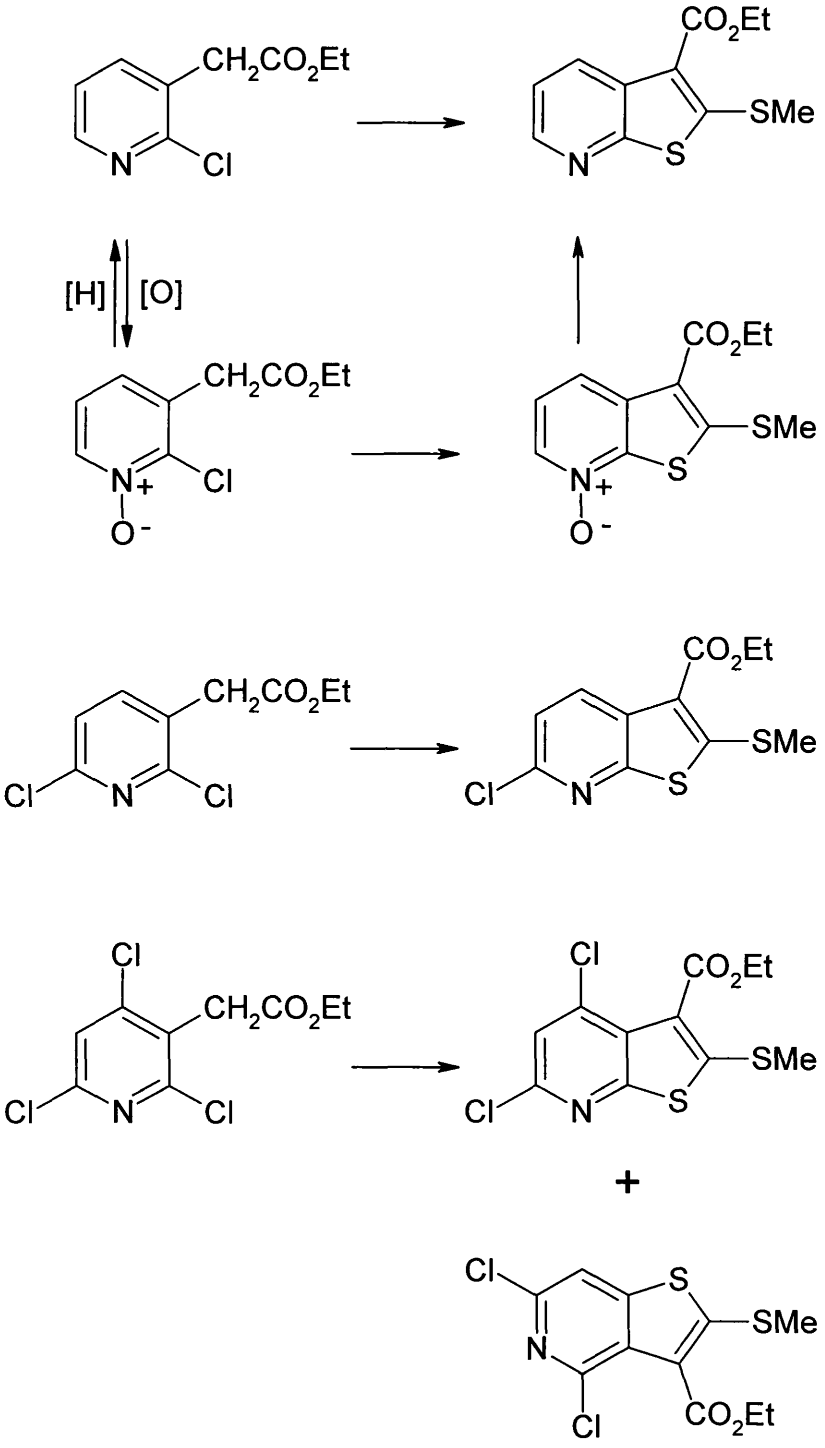
Preparation of chloropyridines (section 2.3)



Key: the arrows $\rightleftharpoons$ indicate interconversion between the compounds

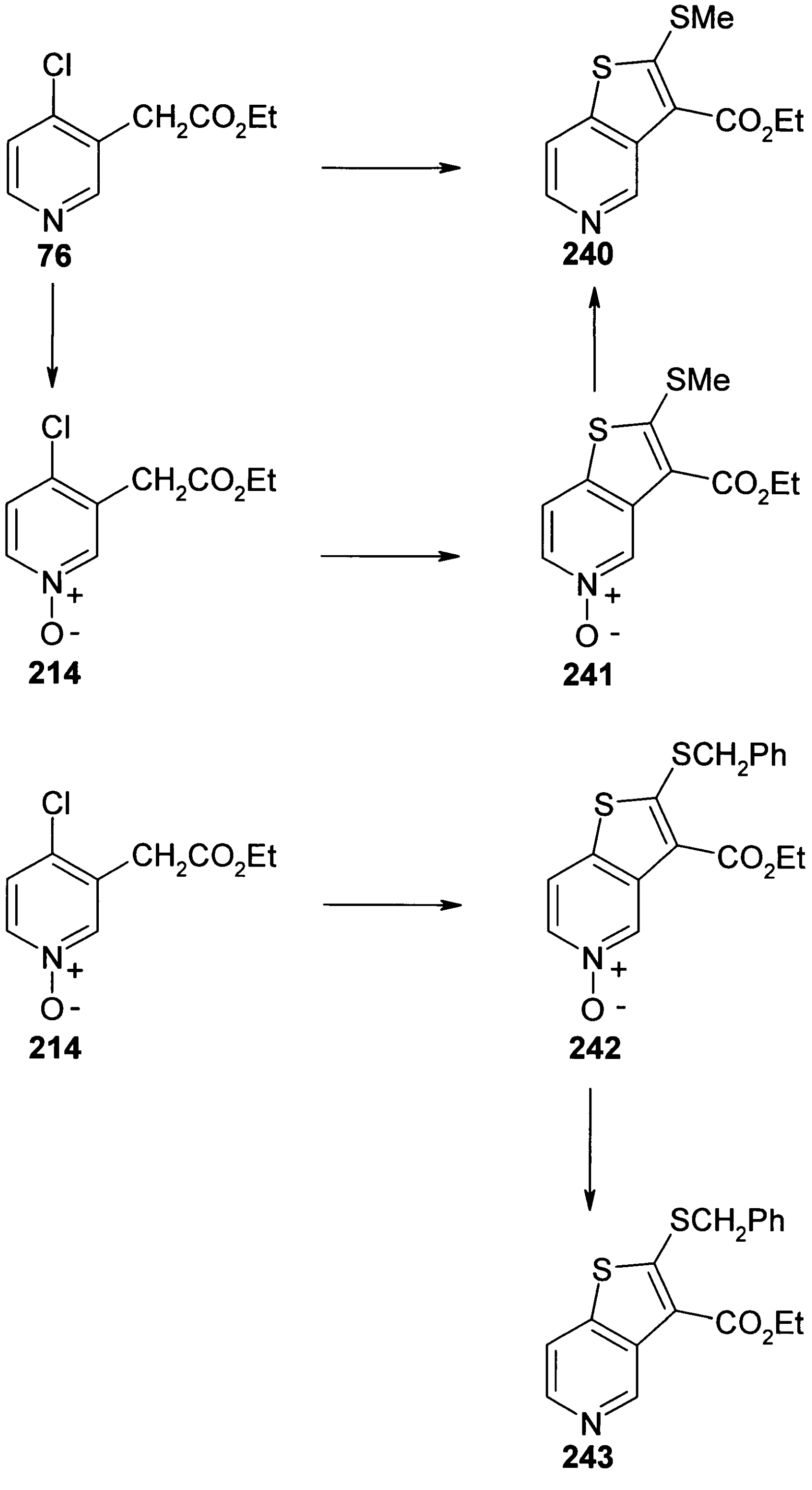
Preparation of thienopyridines (section 2.4)

Thieno[2,3-b]pyridines (section 2.4.1)

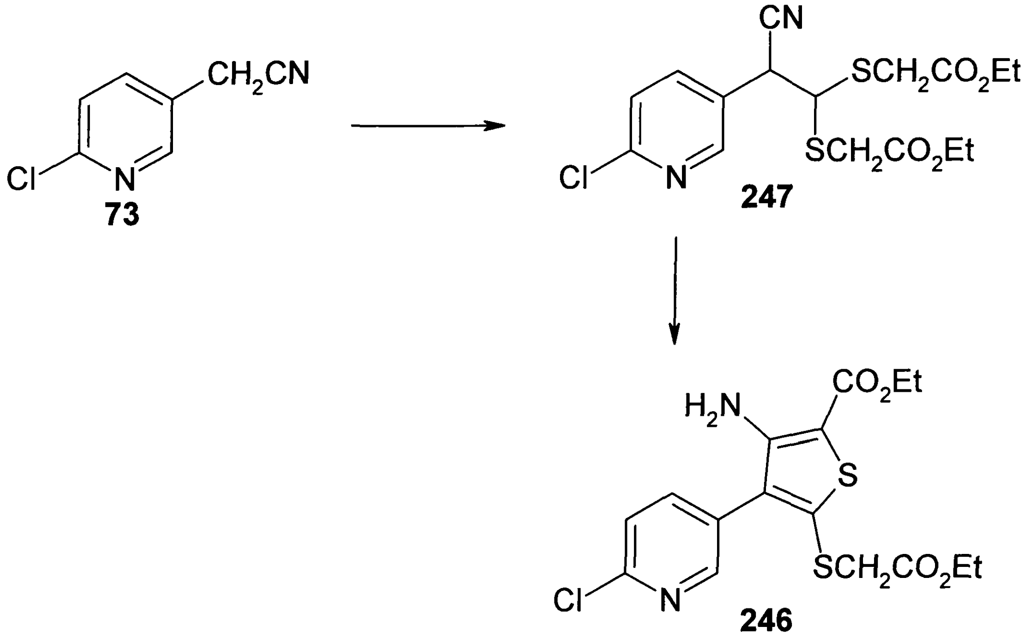


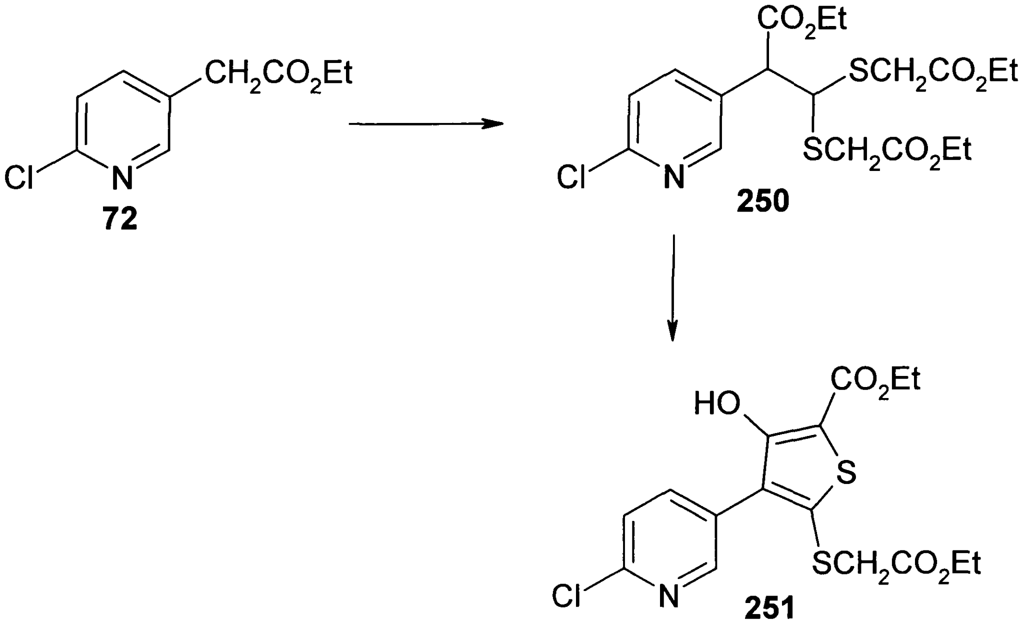
Key: the arrows ⇄ indicate interconversion between the compounds

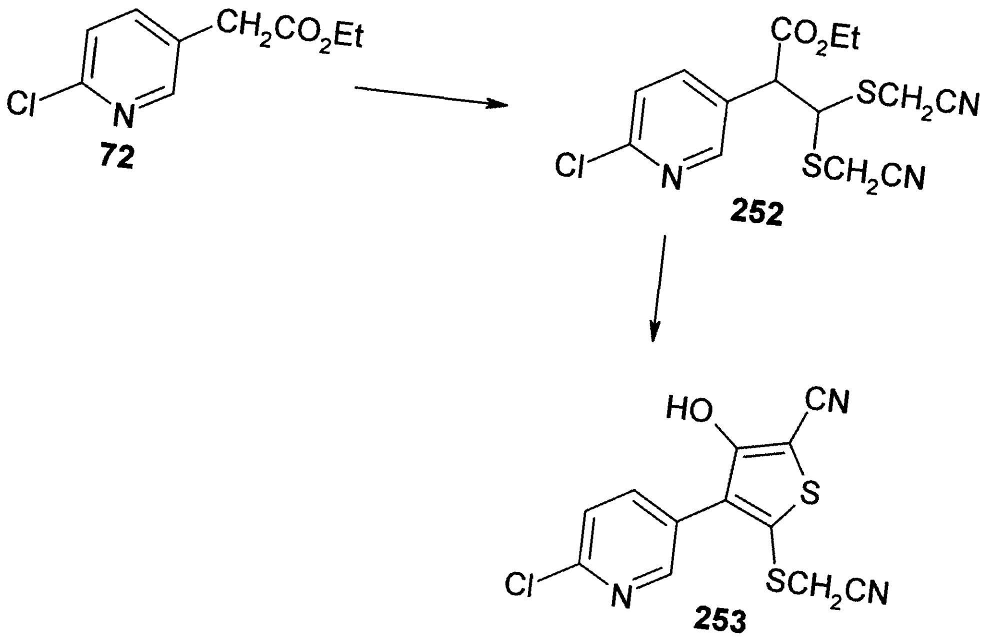
Thieno[3,2-c]pyridines (section 2.4.2)



Preparation of ketenedithioacetals and thiophenes (section 2.5)



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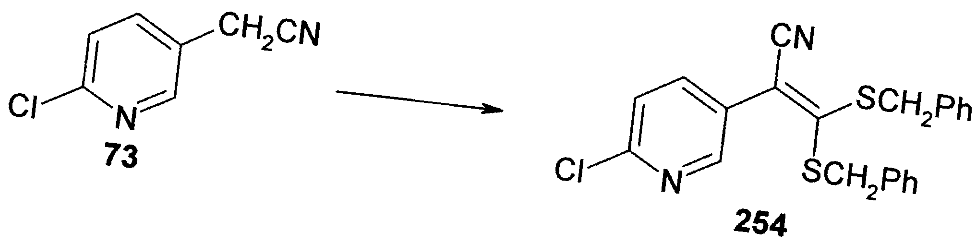
CO2Et
SCH2CN
SCH2CN
Cl
N
252
HO
CN
S
Cl
N
SCH2CN
253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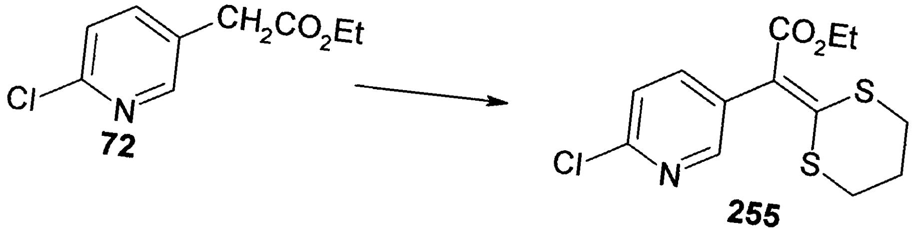
Cl
N
73
CN
SCH2Ph
SCH2Ph
Cl
N
254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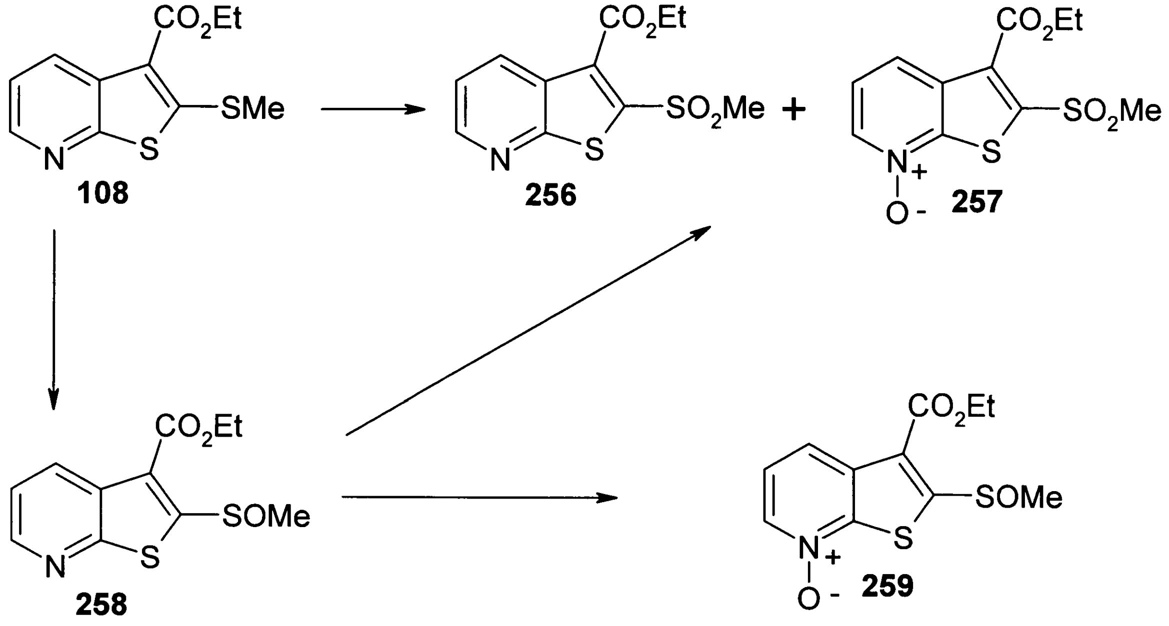
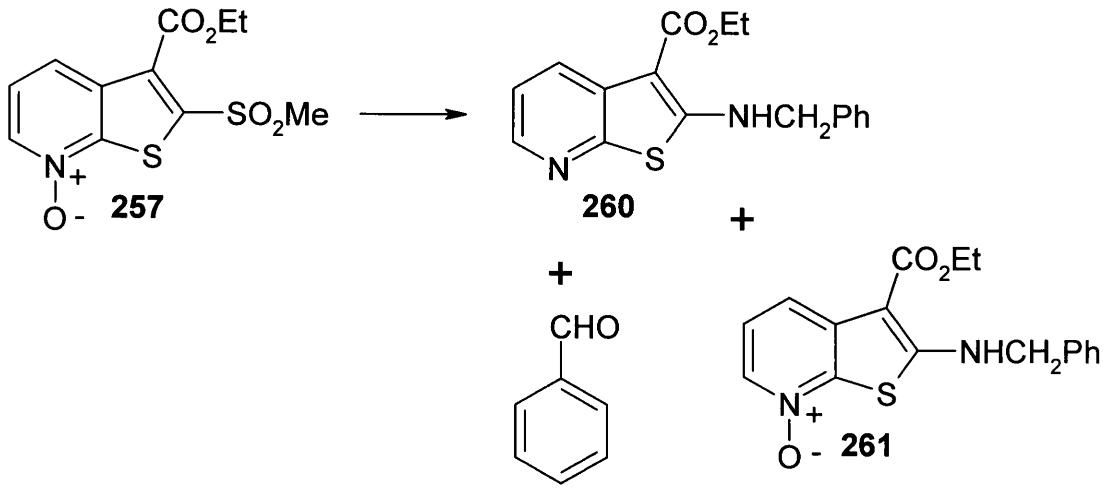
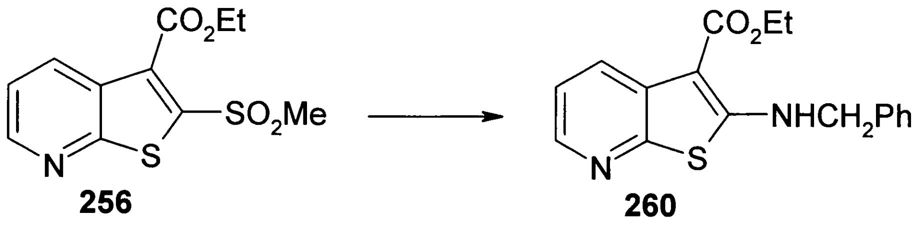
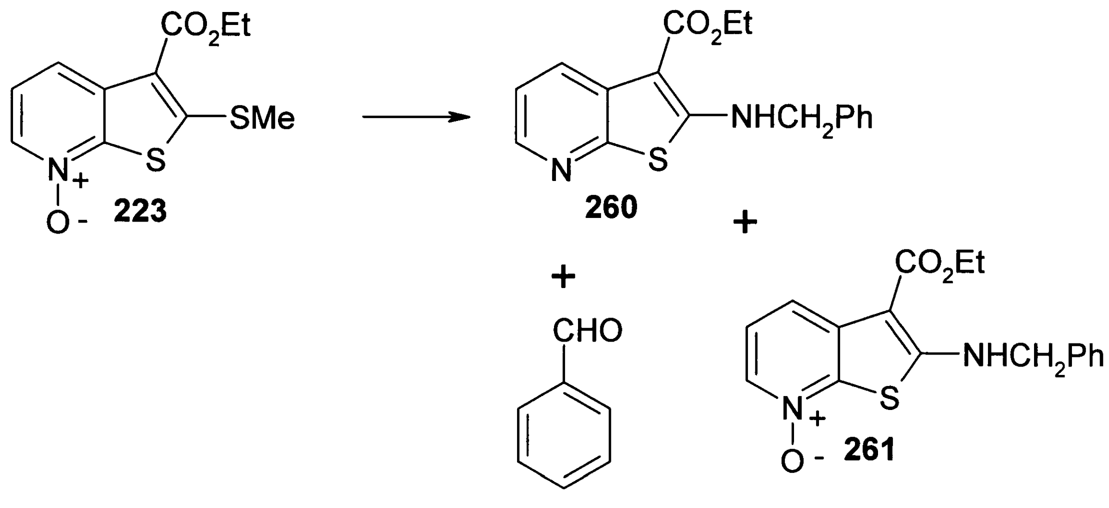
CO2Et
S
S
Cl
N
255

Reactions of thieno[2,3-b]pyridines (section 2.6)





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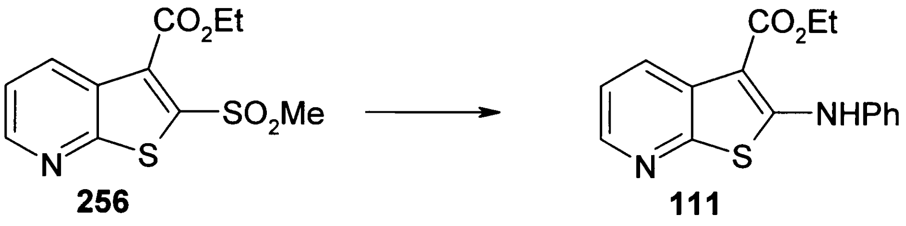
260
261
CO2Et
SMe
NHCH2Ph
CHO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111
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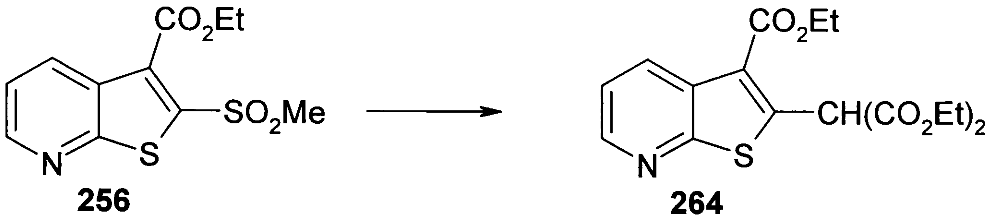
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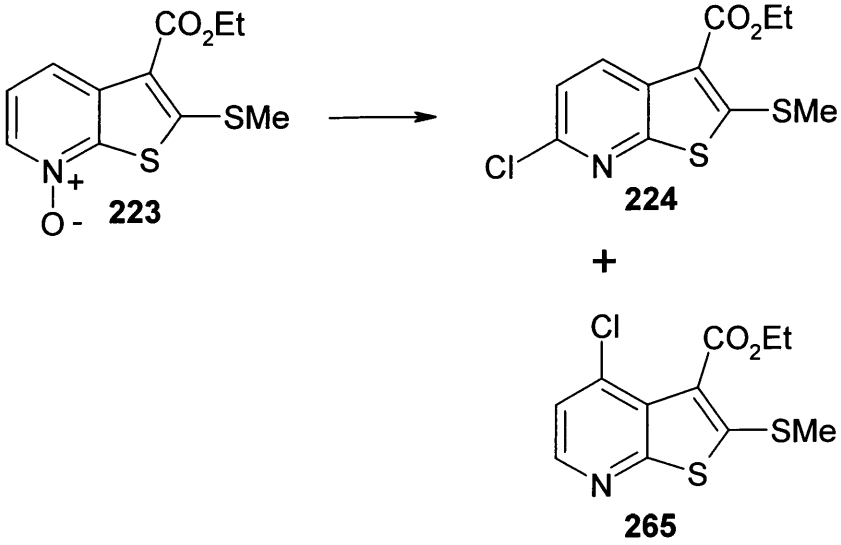
264
CO2Et
SO2Me
CH(CO2Et)2

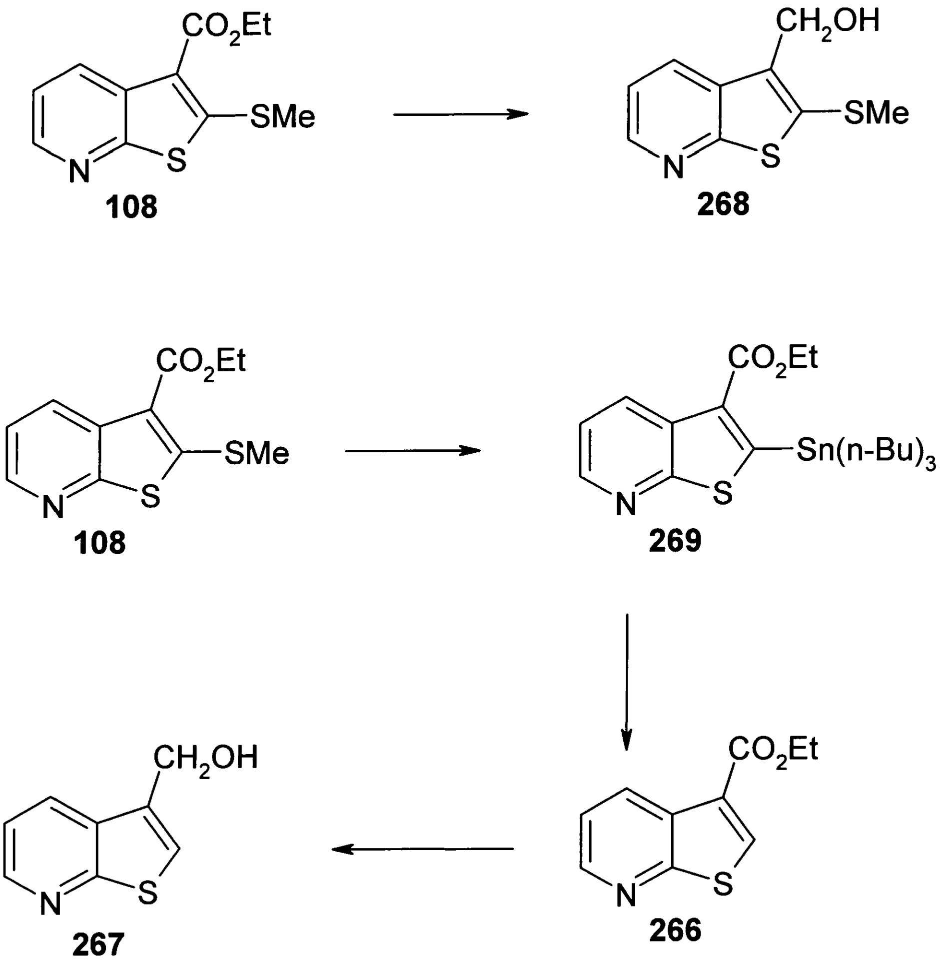


223

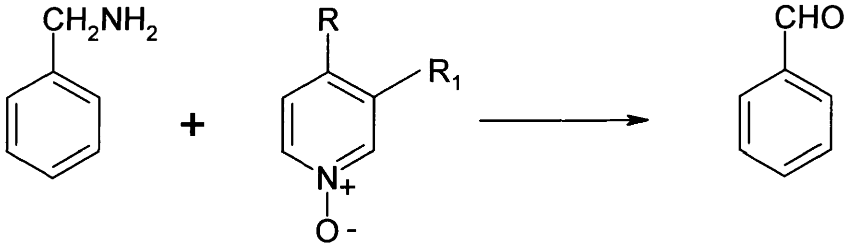
224

265

Route to a potential agonist of serotonin (section 2.7)



Benzylamine to benzaldehyde with pyridine N-oxides (section 2.8)



272; R=H and R_1=Me,
78; R=H and R_1=$CONH_2$
273; R=$CONH_2$ and R_1=H,
274; R=COOH and R_1=H
50; R=NO_2 and R_1=H

The three published articles cited below have been removed from the e-thesis due to copyright restrictions:

D H Bremner, K R Sturrock, G Wishart, S Mitschell, S M Nichol and G Jones (1997). A comparison of methods for n-oxidation of some 3-substituted pyridines. In *Synthetic Commununications*, 27(9), 1535-1542.

D H Bremner, A D Dunn, K A Wilson, K R Sturrock and G Wishart (1997) The synthesis of thienopyridines from ortho-halogenated pyridine derivatives; part 2. In *Synthesis*, 8, 949-952.

D H Bremner, A D Dunn, K A Wilson, K R Sturrock and G Wishart (1998). The synthesis of thienopyridines from ortho-halogenated pyridine derivatives; part 3. In *Synthesis*, 1095-1097.

7.2 Appendix 2

Published papers arising from this PhD programme

D H Bremner, K R Sturrock, G Wishart, S Mitschell, S M Nichol and G Jones, *Synth. Commun.*, 1997, **27**, 1535-1542.

D H Bremner, A D Dunn, K A Wilson, K R Sturrock and G Wishart, *Synthesis*, 1997, 949-952.

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